

Rheumatology

Rheumatology

VOLUME 1

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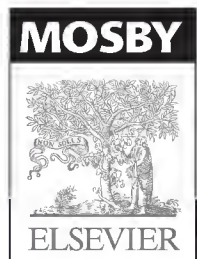
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In this new edition of *Rheumatology*, the editors have again attempted to bring together a large group of world-renowned authors to provide essential information on the scientific basis of rheumatology and the definition, epidemiology, pathophysiology, clinical features, and management of all arthritic, musculoskeletal, and rheumatic disorders.

Rheumatology, Sixth Edition, builds on the success of the previous editions. As stated by Professor Jan Dequeker in his review of the fourth edition, “*Rheumatology* is the most comprehensive, authoritative rheumatology text designed to meet the complete needs of all practicing and academic rheumatologists as well as arthritis-related health care professionals and scientists interested in disorders of the musculoskeletal system. The edition is firmly grounded on modern medical science, integrating the relevant basic biology with current clinical practice, easily accessible, user-friendly, and a beautifully illustrated color publication.”

For this edition, every chapter has either been substantially revised or, in many cases, entirely rewritten, following a rigorous editorial policy to ensure that the content and format of the book remain consistent and meet the highest possible standards. Each chapter has been updated to incorporate a broad range of new information. Fourteen completely new chapters cover biomedical and translational science, disease and outcome

assessment, including new imaging modalities and early emerging disease, clinical therapeutics, and patient management and rehabilitation. The text has been streamlined, ensuring that each chapter contains the most critical and current information in the field, while supplemental materials (including extra tables, figures, and bonus text) are conveniently located online. The index has also been improved, making it easier for the reader to find topics of interest.

The production of this edition of *Rheumatology* has been a greatly enjoyable team effort. We would like to thank the authors who have contributed to this and previous editions of the book, as well as the excellent team at Elsevier, including Michael Houston, Kelly McGowan, and Louise King, among others. We look forward to bringing you a seventh edition in another 4 years.

Marc C. Hochberg
Alan J. Silman
Josef S. Smolen
Michael E. Weinblatt
Michael H. Weisman

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Marc C. Hochberg
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THE SCIENTIFIC BASIS OF RHEUMATIC DISEASE

1

Epidemiologic concepts and classification of rheumatic and musculoskeletal conditions

■ DEBORAH P.M. SYMMONS

- Musculoskeletal epidemiology is concerned with the determinants and distribution of rheumatic and musculoskeletal conditions in different populations.
- The frequency of disease in a population can be expressed in terms of incidence (the number of new cases) and prevalence (the proportion of the population with the disease).
- Most rheumatic and musculoskeletal diseases are defined by using sets of classification criteria.
- Classification criteria are powerful tools for identifying and distinguishing patients with a target disease from those without the condition.
- The frequency and severity of rheumatic and musculoskeletal diseases vary with age, gender, ethnic origin, and country.
- Differences in disease or outcome frequency can be explored to yield hypotheses about demographic, genetic, hormonal, environmental, and psychosocial risk factors for the development or severity of disease.
- Such hypotheses are best tested in case-control or cohort studies that involve the use of a comparison group.

INTRODUCTION

Epidemiology is the clinical science that studies the distribution and determinants of disease in populations. It involves describing the frequency of diseases and their consequences (including morbidity and mortality) and understanding the risk factors for development of a disease or its complications. Two basic types of epidemiologic study can be performed:

- *Descriptive* epidemiology describes the number of people in whom the disease develops in a particular period or who currently have the disease, what type of people are susceptible (in terms of, e.g., age, gender, or ethnic background), and where and when the disease occurs (geographic variations on a large or small scale, secular trends).¹
- *Analytic* epidemiology tests hypotheses of causation and involves using a comparison group (Fig. 1.1). By comparing the frequency of a disease in people who have particular characteristics (e.g., exposure to certain drugs, pregnancy, or certain genotypes) or by comparing exposure characteristics in people with and without a particular disease or outcome, it is possible to identify risk factors for development of the disease or attributes that affect outcome or disease severity. In cohort studies, subjects are selected on the basis of their exposure status or being disease free and are observed to see in how many the disease develops. Cohort studies may be prospective, if the outcome

has not occurred when the study begins, or retrospective, if the outcome has already happened. In case-control studies, groups are selected on the basis of their disease status, those with the disease being the *cases* and those without being the *controls*. All the subjects are then studied to see how many in each group have been exposed to the risk factor or factors of interest. Each design has advantages and disadvantages, and the choice is often dictated by the relative prevalence of the disease and the exposure.²

This chapter introduces the fundamental concepts of epidemiology and describes how these concepts have been used to study the frequency of rheumatic and musculoskeletal disorders (RMDs) and their burden worldwide. It also discusses how hypotheses concerning risk factors for the development of RMDs or particular outcomes can be generated and tested.

DESCRIPTIVE EPIDEMIOLOGY—HOW MANY PEOPLE HAVE THE DISEASE?

The two most common measures of disease frequency are prevalence and incidence (Table 1.1).¹

Prevalence

Prevalence relates to existing cases of disease. *Point* prevalence is the proportion of the population who have the disorder at a particular point in time. This measure is useful for chronic persistent disorders such as rheumatoid arthritis (RA) and osteoarthritis (OA). For intermittent conditions such as back pain and gout, it is more appropriate to measure *period* prevalence—the proportion of the population who have the disorder at any time during a given period (usually 1 year). Finally, *cumulative* prevalence is the proportion of the population who have had or now have the disorder up to a specified time point (e.g., by 60 years of age) or up to the time of the study.

Prevalence in the population setting is commonly determined by conducting a survey via questionnaires, clinical evaluation, or a combination of both. Such questionnaires may be self-completed or administered by an interviewer. In the hospital or primary care setting, prevalence is often assessed by identifying diagnosed cases and relating them to the appropriate population base. Though practical for uncommon conditions,³ cases identified in this way are often skewed toward the more severe end of the spectrum. Increasingly, information on disease prevalence is derived from electronic health care record databases, with the denominator being the relevant proportion of the population covered by the database.

Incidence

The term *incidence* relates to the number of individuals in a defined population in whom the disorder first develops in a given period, typically 1 year.

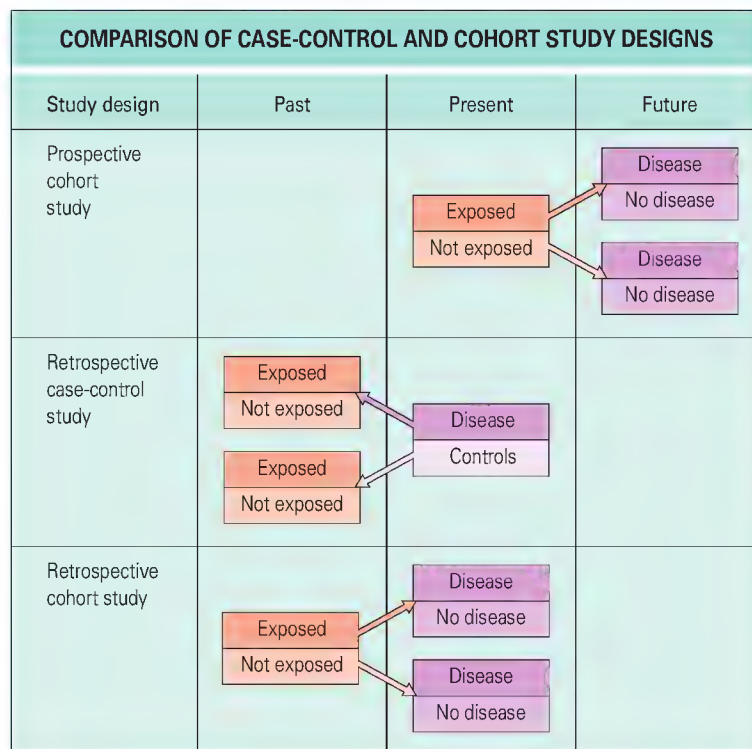


Fig. 1.1 Comparison of case-control and cohort study designs.

TABLE 1.1
Measures of disease frequency

Term	Denominator	Numerator
Prevalence (relates to existing disease)	Number of people in the population	Point prevalence (number who have the disorder at a given time point) Period prevalence (number who have the disorder at some time during a given period) Cumulative prevalence (number who have the disorder at some time up to a given time point)
Incidence (relates to disease onset)	Total person-time of observation	First incidence (number who have their first onset of the disorder in a given period) Episode incidence (number of episodes of the disorder in a given period) Cumulative incidence (number who have their first onset up to a given time point)

This is known as the incidence rate or the *first incidence rate*. *Episode incidence* is the total number of episodes of a disorder in the defined population in a given period. The episode incidence of back pain is higher than the first incidence rate because it counts those who have repeated episodes during the time frame of interest. *Cumulative incidence* is the number of individuals who have ever had an episode up to a particular time.

Incidence is measured either by monitoring for new cases as they are diagnosed or by conducting two cross-sectional surveys some time apart and identifying new cases that have developed between the two surveys. Disease incidence and prevalence are related by the following formula:

$$\text{Incidence} \times \text{Duration} = \text{Prevalence}$$

Individuals may leave the prevalent pool of cases through either recovery or death. RA has a relatively low incidence but a long duration, so its prevalence is relatively high. The rate of death may be expressed as the *mortality rate* (the number of deaths from a disease in a given period divided by the total population) or the *case fatality rate* (the number of deaths from a disease in a given period divided by the number of cases of the disease).

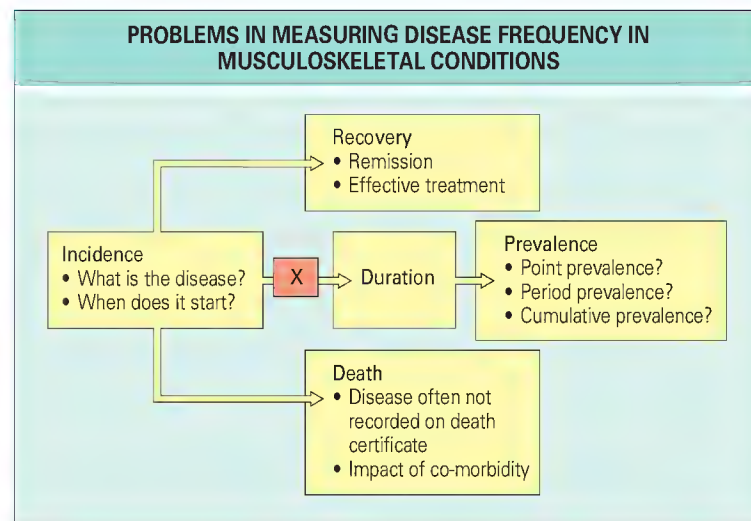


Fig. 1.2 Problems in measuring disease frequency in patients with rheumatic and musculoskeletal conditions.

Practical issues in measuring disease frequency

Issues related to measuring disease frequency can be divided into those related to the numerator and those related to the denominator (Fig. 1.2).

Numerator

Case definition

Accurate estimation of incidence and prevalence depends on using standard nomenclature, a reliable case definition, and complete case ascertainment. The nomenclature in most widespread use is that adopted by the International Classification of Diseases (ICD).⁴ The ICD names diseases and groups them in a hierarchy on the basis of the body system. ICD10 is the version in current use.

Most RMDs do not have a specific diagnostic test, so sets of classification criteria (Table 1.2) have been developed to identify homogeneous patient populations for epidemiologic studies and clinical trials. These sets of classification criteria combine different types of information, including symptoms, signs, laboratory findings, imaging, genetic factors, and etiologic agents. Classification criteria have two purposes: first, to separate patients with the target disorder from normal subjects, and second, to distinguish patients with the target disorder from those with other similar disorders. In the majority of conditions, classification criteria should not be used for the diagnosis of individual patients.

Historically, most sets of classification criteria in rheumatology were developed by consensus and use of the physician's opinion as the "gold standard." A panel of experts compiled a list of candidate variables and then assessed their ability, either alone or in combination, to distinguish subjects who were judged by their physician to be cases from those judged not to be cases (either normal subjects or subjects with similar conditions). The assessment was done by determining the sensitivity and specificity of the criteria (Table 1.3). In more recent times, statistical techniques such as receiver operating characteristic curves, discriminant analysis, and logistic regression have been used to eliminate redundant variables and weight the individual characteristics to give maximum sensitivity and specificity. Classification and regression tree methodology enables the substitution of one variable for another (which helps when some data are missing) and enables attributes to be used more than once in different parts of the tree. In the recent development of new classification criteria for RA,⁴³ the decision to prescribe methotrexate to a patient with recent-onset synovitis was used as the gold standard, and a decision analysis software program⁴⁴ using discrete pairwise choices was used to assign weights to the categories within the selected criteria.

Many problems are encountered when interpreting and applying classification criteria. For example, early or mild cases may not meet the criteria. Furthermore, some criteria require expensive, invasive, or nonroutine investigations such as radiography or immunochemical tests. This makes it difficult to apply the criteria retrospectively using patients' medical records or to use them unaltered in population surveys.

For inflammatory conditions such as RA or systemic lupus erythematosus (SLE), the criteria were developed by studying patients with active disease. A population survey of the prevalence of RA will therefore identify individuals who currently have active disease plus those who in the past have had disease that was sufficiently severe to leave stigmata such as joint

TABLE 1.2

Classification criteria for rheumatic diseases

Name of disease	Name of classification criteria
Ankylosing spondylitis	New York criteria ⁵ Modified New York Criteria ⁶ ASAS criteria for axial spondyloarthritis ⁷
Antiphospholipid syndrome	Sapporo classification ⁸ Revised Sapporo criteria ⁹
Behçet syndrome	Preliminary classification criteria for Behçet disease ¹⁰
Benign joint hypermobility syndrome	Revised (Brighton 1998) criteria ¹¹
Churg-Strauss syndrome	ACR 1990 criteria for CSS ¹² Algorithm for diagnosing ANCA-associated vasculitides ¹³
Dermatomyositis and polymyositis	Bohan and Peter criteria ¹⁴ Classification criteria for DM and PM ¹⁵ Inclusion criteria for DM/PM trials ¹⁶
Fibromyalgia	ACR 1990 classification criteria for fibromyalgia ¹⁷
Giant cell (temporal) arteritis	ACR 1990 criteria for GCA ¹⁸
Gout	Preliminary ARA criteria ¹⁹
Granulomatosis with polyangiitis	ACR 1990 criteria for Wegener granulomatosis ²⁰ Algorithm for diagnosing ANCA-associated vasculitides ¹³
Henoch-Schönlein purpura	
Adults	ACR 1990 criteria for HSP ²¹
Children	EULAR/PRINTO/PRES criteria for HSP, childhood polyarteritis nodosa, childhood Wegener granulomatosis, and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria ²²
Hypersensitivity vasculitis	ACR 1990 criteria for hypersensitivity vasculitis ²³
Juvenile idiopathic arthritis	ILAR classification criteria for JIA ^{24,25}
Kawasaki syndrome	EULAR/PRES criteria for childhood vasculitides ²⁶
Osteoarthritis of the hand	ACR classification criteria for hand OA ²⁷
Osteoarthritis of the hip	ACR classification criteria for hip OA ²⁸
Osteoarthritis of the knee	ACR classification criteria for knee OA ²⁹
Polyarteritis nodosa	ACR 1990 criteria for PAN ³⁰ Classification of ANCA-associated vasculitides and PAN ¹³
Polymyalgia rheumatica	ACR/EULAR 2012 provisional classification criteria for polymyalgia rheumatica ³¹
Psoriatic arthritis	Moll and Wright ³² CASPAR criteria ³³
Rheumatic fever	Jones criteria (updated) ³⁴
Rheumatoid arthritis	ACR/EULAR 2010 classification criteria for rheumatoid arthritis ³⁵
Sjögren syndrome	ACR 2012 classification criteria for Sjögren syndrome ³⁶
Systemic lupus erythematosus	Systemic Lupus International Collaborating Clinics criteria for SLE (a revision and validation of the ACR criteria for SLE) ³⁷
Spondyloarthritis	ESSG criteria ³⁸
Systemic sclerosis	
Adult	ARA criteria ³⁹
Childhood	PRES/ACR/EULAR provisional criteria for juvenile SSC ⁴⁰
Takayasu arteritis	
Adult	ACR 1990 criteria for TA ⁴¹
Childhood	EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis, and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria ²²
Vasculitis	ACR 1990 criteria for vasculitis ⁴²

ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibody; ARA, American Rheumatism Association; ASAS, Assessment of SpondyloArthritis International Society; CASPAR, Classification Criteria for the Study of Psoriatic Arthritis; ESSG, European Spondylarthropathy Study Group; EULAR, European League Against Rheumatism; ILAR, International League of Associations for Rheumatology; PRES, Pediatric Rheumatology European Society; PRINTO, Pediatric Rheumatology International Trials Organization.

deformities. People who had mild disease that is now in natural or drug-induced remission will not be detected. Thus, the resultant estimate is a cross between point prevalence and cumulative prevalence.

Finally, although prevalence does not affect the sensitivity and specificity of the classification criteria, it does affect their positive predictive value (see Table 1.3). In the example given in Table 1.4, the proportion of positives that are falsely positive is 2% in the clinic setting and 66% in the population setting.

Determining the date of onset

Determining the time of disease onset is problematic for some RMDs. If OA is defined in terms of radiologic change, it is usually impossible to say when it first appeared. For conditions such as SLE the onset date is often defined as the (arbitrary) date on which the classification criteria were first met. In RA the onset date may be defined as the date of first symptoms, but this may be difficult for patients to recall. When comparing studies it is important to take note of any different definitions of onset date.

Completeness of ascertainment

Finally, all cases of the disease within the population should be identified. Disease in the population has a continuum of severity (Fig. 1.3) and ascertainment may not be complete, depending on where it is carried out. Clinic-based studies rely on the patient having sought medical care, the condition being diagnosed (more or less) correctly, and the patient being referred to the appropriate specialist. To maximize ascertainment, several approaches may be used simultaneously (e.g., ascertaining SLE cases from hospital clinics, self-help groups, and laboratory records of antinuclear antibody screening) in an attempt to capture all cases.

Denominator

The size of the population from which the cases have been identified is difficult to determine when cases are identified only from the hospital or from clinic attenders and there is no defined catchment population. Many factors determine whether an individual case is referred to a particular center (referral bias).

The denominator population should consist of only individuals at risk for development of the disease. Thus, the incidence of juvenile idiopathic arthritis should be expressed per 100,000 children 16 years and younger. A frequently encountered error is to apply the prevalence rate (e.g., for RA) measured in the adult population to the total population for estimating the total number of cases in the population. This assumes that the prevalence of RA is the same in children as in adults (which is not the case).

Sources of data for estimating disease occurrence

Routinely collected data may prove useful in building a picture of the epidemiology of RMDs, although assessment of the diagnostic accuracy and level of completeness of these data is essential. Examples are included in the following sections.

Death certificates

Mortality records have, with few exceptions, been of little use in RMD epidemiology because RMDs are an infrequent cause of death. RMDs are often

not recorded on the death certificate, and thus estimating, for example, how many people with RA die each year is impossible. However, death certificates will provide valuable information on the number and causes of death in an identified RA cohort. Using the ICD, comparisons of the attributed causes of death among RA cohorts in different locations and between RA cohorts and the general population are possible.

Morbidity registers

Even though many countries have cancer registers, the same is not generally true for RMDs. Some Scandinavian countries have registers of people who are admitted to hospital or seen in a clinic with a particular diagnosis or who can claim reimbursable medication, and by using a unique personal identity number, investigators are able to link information on these registers with, for example, mortality data. The Mayo Clinic in Rochester, Minnesota, has developed a record linkage system whereby the health care records of all residents in Olmsted County are maintained in a central database.⁴⁵ Information from this database, which dates back to 1910, has been used to generate incidence estimates for a number of RMDs. However, the population of Olmsted County is only about 100,000 and the majority of the population is of Scandinavian descent. The former limits the reliability of estimates for rare diseases and the latter, the generalizability of all estimates because the residents of Olmsted County are not representative of the general U.S. population.

Health care provider databases

In some countries, health care that is reimbursed by the government or insurance companies is linked to diagnostic codes on large computerized e-health databases. Such databases have provided a rich source of data on the frequency of rare events (e.g., drug toxicity or major complications of orthopedic surgery). Examples from the United States include Medicare and data from health maintenance organizations such as Kaiser Permanente. In the United Kingdom, the General Practice Research Database (now part of the Clinical Practice Research Database, www.cprd.com) and The Health

TABLE 1.3

Sensitivity, specificity, and positive and negative predictive values of criteria sets

		Disease—by “gold standard”	
		Yes	No
Criterion or criteria set	Positive	a (true positive)	b (false positive)
	Negative	c (false negative)	d (true negative)
Sensitivity: proportion of cases identified correctly		$\frac{a}{a+c}$	
Specificity: proportion of noncases identified correctly		$\frac{d}{b+d}$	
Positive predictive value: proportion with a positive test who have the disease		$\frac{a}{a+b}$	
Negative predictive value: proportion with a negative test who do not have the disease		$\frac{d}{c+d}$	

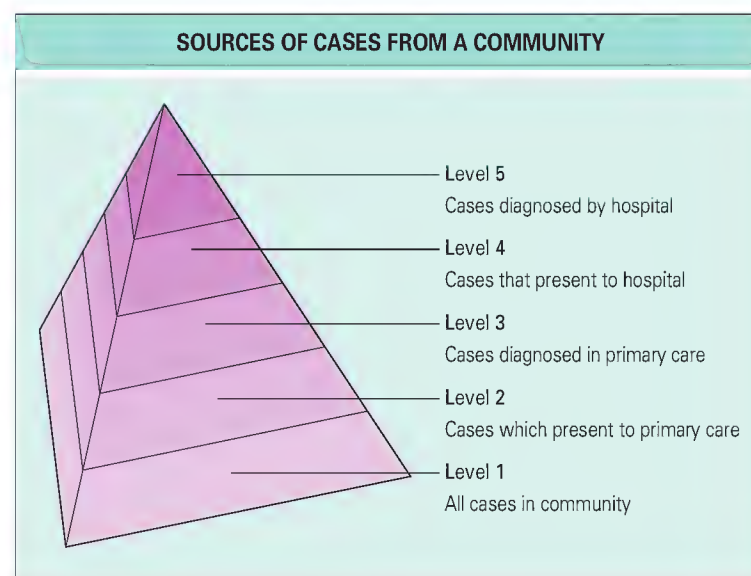


Fig. 1.3 Sources of cases from a community.

TABLE 1.4

Influence of prevalence on positive predictive value

		Clinic setting			Population setting		
		Prevalence of target disease—50%			Prevalence of target disease—1%		
		Gold standard			Gold standard		
Criteria		Yes	No		Yes	No	
	Positive	490	10	500	98	188	286
	Negative	10	490	500	2	9702	9704
		500	500		100	9900	
		Positive predictive value—98%			Positive predictive value—34%		
		% False positives—2%			% False positives—66%		

Improvement Network (www.thin-uk.com) provide pooled anonymous patient data from a large number of practices of general practitioners. In all these situations, information about the denominator—the number of people covered by the registers—is known, but standard disease definitions are not generally used.

Work absenteeism records

In some countries, information on the reason for and duration of absence from work for sickness is recorded and can be used to examine the profile of musculoskeletal complaints in the workforce.

Population health surveys

Many countries have regular population surveys (called *health interview surveys*) that examine social and demographic trends. These surveys may include health-related information such as the number of visits to a physician, self-reported illness, and disability. Examples include the General Lifestyle Survey (formerly the General Household Survey) in the United Kingdom. Sometimes an examination phase is included (a *health examination survey*). Examples include the National Health and Nutrition Examination Surveys in the United States (www.cdc.gov/nchs/nhanes.htm). There is a move to try to standardize the questions used in health interview surveys across countries to facilitate comparisons.

ANALYTIC EPIDEMIOLOGY—WHO IS SUSCEPTIBLE TO THE DISEASE?

Differences in disease occurrence arising from descriptive epidemiology (e.g., the twofold greater incidence of RA in females⁴⁶ and the rare onset of ankylosing spondylitis after the age of 55⁴⁷) may hint at causes. It is important to account for population differences in age (e.g., 10-year age bands) and gender before making inferences. This can be done by applying the age- and sex-specific incidence rates from one population (the *standard*, often the national population) to the age and sex distribution of another population (the *index*) to calculate an overall rate in the latter, assuming that the age and gender distributions are identical.

Increased frequency or adverse outcomes may also be found in specific ethnic groups (e.g., SLE in people of African ancestry),⁴⁸ occupations (e.g., hip OA in farmers),⁴⁹ and socioeconomic groups (e.g., back pain in lower socioeconomic groups).⁵⁰ It can be difficult, however, to determine the relative contributions of these factors because they are often interrelated.

WHERE DOES THE DISEASE OCCUR?

Differences in disease rates between countries or regions may be due to genetic, other host-related, or environmental factors (or any combination of such factors). Possible environmental factors include macroenvironmental variables such as air and water pollution, microenvironmental factors such as diet and smoking, and socioeconomic factors. Migration studies may suggest whether geographic differences in disease frequency are predominantly due to genetic or environmental factors. If a migrating population has the same frequency of disease in its native and newly adopted countries, this suggests that genetic factors are more important. If the disease frequency changes, especially if it changes within one or two generations, this suggests a change in environment or lifestyle as being important.

There are hints of geographic patterns for a number of RMDs, which are still being unraveled (Table 1.5). First, RA occurs with similar frequency in most white populations. However, it has a higher prevalence in some Native Americans such as the Pima and a lower prevalence in West Africa, China, and Indonesia.⁵¹ Second, most of the geographic variation in the frequency of ankylosing spondylitis can be explained by the varying prevalence of HLA-B27 in different racial groups. By contrast, it is more difficult to explain the ethnic variation in SLE, although investigation of the frequency and clinical characteristics of SLE in people of African origin can yield important etiologic clues. The frequency of SLE is high in African American and African Caribbean populations but lower in West Africans.⁴⁸ Although this suggests an environmental cause of SLE, it is possible that genetic admixture⁵² may play a part in the changing incidence of SLE in this group of people.

WHEN DOES THE DISEASE OCCUR?

Time trends in disease occurrence may also provide important etiologic clues. Clusters of incident cases in a particular season of the year or sporadic time-space clusters suggest that all or most of the cases in the cluster may

TABLE 1.5
Variations in rheumatic and musculoskeletal disease frequency versus European whites

	Increased frequency	Decreased frequency
Rheumatoid arthritis	Native American (Pima, Chippewa, Yakima)	Rural African Chinese Indonesian
Juvenile idiopathic arthritis	Canadian Inuit	African Americans
Ankylosing spondylitis	Haida people	Australian aboriginals African Americans
Gout	Polynesians Filipinos	Africans
Systemic lupus erythematosus	African Americans African Caribbeans Asian Indians Chinese	West Africans
Scleroderma	Southern United States	Australian aboriginals
Polymyalgia rheumatica	Northern European whites	African Americans
Osteoarthritis of the knee	African American women	
Osteoarthritis of the hip		Chinese Japanese Asian Indians Africans
Osteoporosis	Northern Europeans	Africans

have been exposed to an etiologic agent from a common source. Lyme disease provides a good example of a disease identified because of clustering of cases of juvenile and adult inflammatory arthritis in place and time.⁵³ A rise or fall in disease incidence annually may suggest a change in the level of exposure to risk factors. Between around 1970 and 1985 the incidence of RA in women fell in the United States and United Kingdom. This coincided with increasing use of oral contraceptive pills, and some evidence suggests that the two phenomena are linked.⁵⁴ Changes in disease prevalence with time are more difficult to interpret because they may be caused by alterations in disease incidence, recovery rates, survival, or a combination of all three. Health care planners must take into account trends in incidence and prevalence, both of which may be affected by increasing life expectancy. For instance, the number of new cases of hip and knee OA in most Western countries is rising steeply. This is due more to the aging population than to any change in age-specific incidence.

WHY DOES THE DISEASE OCCUR?

Descriptive epidemiologic studies can generate hypotheses about disease causation, but they cannot test these hypotheses. Analytic studies are required to investigate the relationship between exposure to a risk factor (environmental or genetic) and development of disease. As discussed earlier, such studies may be retrospective or prospective (see Fig. 1.1). In a prospective study, individuals are identified and classified according to their exposure status before development of the disease. However, it is sometimes possible to assemble such cohorts retrospectively after development of the disease, for example, by using records of occupational exposure (e.g., to vinyl chloride) or immunization (e.g., rubella vaccine).

A cohort study is more efficient when investigating a rare exposure, whereas a case-control design is more efficient when investigating a rare disease (Table 1.6). A case-control study is best for investigating multiple risk factors simultaneously. Incident cases are usually preferred over prevalent cases because any risk factors identified are markers for disease susceptibility rather than persistence. For example, clinic attenders with RA have a much higher frequency of the *shared epitope* than the general population does. Furthermore, combinations of shared epitope alleles (e.g., 0404 homozygosity) are associated with a particularly poor outcome of RA. However, in studies that are confined to incident cases of RA, the association with the shared epitope is only modest.

The most difficult aspect of a case-control study is selection of appropriate controls. Controls should be individuals who would have been included among the cases if the disease had developed and hence should be selected from the same catchment population.

TABLE 1.6
Advantages and disadvantages of various epidemiologic study designs

Study design	Advantages	Disadvantages
Prospective cohort	Good exposure data Accurate timing of exposure and disease onset Little recall bias	Expensive May be long delay before disease onset Large numbers needed Only suitable for frequent outcomes
Case-control	Relatively inexpensive Quick to perform Useful for rare diseases	Subject to recall bias Cases may not be representative Controls difficult to select and ascertain Exposure data may be unreliable Time of exposure and disease onset may be imprecise
Cross-sectional	Generalizable Quick to perform	Difficult to distinguish cause and effect Biased toward inclusion of chronic cases

The results from longitudinal studies are usually expressed as a relative risk or risk ratio (i.e., risk for [or incidence of] the disease in the exposed cohort $\frac{a}{a+b}$ divided by risk for disease in the unexposed cohort [$\frac{c}{c+d}$; see Table 1.3]). In a case-control study, however, the relative frequency of risk factors is compared between the cases and controls, and thus in this situation the odds ratio is calculated (i.e., the odds of exposure given disease $\frac{a}{c}$ divided by the odds of exposure given no disease $\frac{b}{d}$). The relative risk or odds ratio indicates the strength of the association between the risk factor and the disease. In a case-control study, causality cannot be assumed because information about disease state and exposure status is collected cross-sectionally or retrospectively. It is therefore impossible to be certain which came first. In a longitudinal study, the higher the relative risk, the more likely the exposure and the outcome to be linked in a causal chain. Box 1.1 shows the other factors that should be considered when examining causality.

CLINICAL EPIDEMIOLOGY—WHAT HAPPENS TO PEOPLE WITH THE DISEASE?

Investigation of prognosis is analogous to investigation of development of the disease and can be assessed with either cohort or case-control studies. In prognosis studies, all the individuals studied have the disease in question. In longitudinal studies, patients are selected on the basis of exposure to a predictor variable (e.g., anti-citrullinated peptide antibody positive in RA) and then monitored for the incidence, in those with and without the

TABLE 1.7
Some etiologic, protective, and prognostic environmental factors in rheumatic and musculoskeletal disease

Condition	Etiologic factors	Protective factors	Risk factors for a poor prognosis
Rheumatoid arthritis	Smoking Periodontitis Obesity Exposure to silica dust Breastfeeding Female gender	Oral contraceptive use Alcohol consumption High fruit intake	Rheumatoid factor Anti-citrullinated protein antibodies HLA-DR4
Ankylosing spondylitis	HLA-B27 Male gender		
Gout	Hyperuricemia Thiazide diuretics Fructose Lead exposure	Low-fat dairy products Regular heavy coffee consumption	
Systemic lupus erythematosus	Complement deficiency African origin Some drugs (e.g., hydralazine) Female gender Ultraviolet light		Lower socioeconomic status
Scleroderma	Silica exposure Organic solvents Some drugs (e.g., bleomycin) Female gender		
Osteoarthritis of the knee	Obesity Joint malalignment Trauma Certain occupations Female gender	Smoking	Obesity
Osteoarthritis of the hip	Childhood hip disease (e.g., Perthes) Trauma Certain occupations (e.g., farming) Hip dysplasia		
Back pain	Obesity Certain occupations Driving		Previous back pain Psychological factors
Osteoporosis	Early menopause Low body mass index Smoking Excessive alcohol intake Physical inactivity Corticosteroid use	Obesity African origin Exercise	Falls

BOX 1.1 ASSESSING CAUSALITY BETWEEN A RISK FACTOR AND A DISEASE OR OUTCOME

An association between an exposure and an outcome may be due to

- Direct causation
- Chance
- Bias
- Confounding

Causality is more likely if

- Exposure precedes the outcome of interest
- Association is biologically plausible
- Association is strong (high relative risk)
- Association is consistent between studies
- Association is supported by experimental evidence

predictor, of the outcome of interest (e.g., death). Longitudinal observational studies may be subject to left or right censorship.

- Left censorship, a bias in recruitment, occurs when, for example, subjects are recruited as consecutive prevalent cases from a hospital clinic. Patients with mild disease who have been discharged from follow-up and those who have severe disease and have died will be underrepresented in the cohort.
- Right censorship, a bias in follow-up, occurs, for example, in a follow-up study when subjects have been lost to follow-up.

In a case-control study of outcome, patients are selected on the basis of whether a particular complication of their disease has developed (e.g.,

lymphoma in RA or vertebral fracture in osteoporosis) and then compared with patients without this outcome for predictors such as corticosteroid use.

A summary of some of the etiologic, protective, and prognostic factors for selected rheumatic diseases is shown in Table 1.7. The evidence for some of these factors is more definitive than for others.

Determining absolute risk, attributable risk, and population attributable risk fraction

The size of the relative risk indicates the strength of association between an exposure and outcome but not the relative importance of the exposure to the overall prevalence. Patients with Sjögren syndrome have a relative risk of 44 for the development of non-Hodgkin lymphoma with respect to the general population.⁵⁵ However, non-Hodgkin lymphoma develops in few patients with Sjögren syndrome given the former's rarity in the general population.

From a patient's perspective, it is the absolute risk for development of a disease or outcome that is key. From a public health perspective, two other measures are more important: attributable risk and the population attributable risk fraction.

- Attributable risk is the difference between risk for the outcome in the exposed and in the unexposed. It gives an estimate of the number of cases in an exposed population that can be attributed to the exposure.
- The population attributable risk fraction is the proportion of cases of the disease in the population that can be attributed to the risk factor (and thus could be prevented if the risk factor were eliminated). For example, it has been estimated that 35% of cases of seropositive RA are attributable to smoking.⁵⁶

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2

Principles of clinical outcome assessment

■ NICHOLAS BELLAMY

- Measurements of symptom severity, disease activity and consequence, and adverse effects of treatment as well as global assessments are all commonly used.
- Outcome measures must be valid, reliable, responsive, and feasible, and should be brief, simple, and easy to score, particularly for use in routine clinical care.
- The choice of outcome measures depends on disease state, the therapeutic repertoire of the intervention(s) exhibited, and whether they are to be used for research or routine practice.
- Core sets of outcome measures have been recommended for use in clinical trials for several rheumatic diseases.
- Clinical benchmarks are emerging against which the treatment response can be interpreted at the individual patient level.

INTRODUCTION

Measurement forms an essential component of health care at all levels, from the treatment of individual patients to policy development. The measurements may provide descriptive information or play a role in evaluation of response to treatment or in prognostication. The focus of this chapter is on evaluating clinical health status in individual patients and groups of patients; that is, aspects of the condition that can be appreciated through questioning and clinical examination. In addition to allowing evaluation of individuals and groups of patients, clinical outcome measures find important applications in making formal assessments of the impact of health care decisions on health care costs, quality of care, quality of life, and burden of disease, as measured by morbidity and mortality in the population. Such assessments are an integral part of health care delivery systems. A list of abbreviations related to clinical measurement that are used in this chapter can be found in [Box 2.1](#).

CLINICAL OUTCOME ASSESSMENT:
A CONCEPTUAL FRAMEWORK

Clinical outcome measures examine the clinical consequences of a disease or disorder in terms of mortality (survivorship) and morbidity (symptom severity, impact of the condition on various aspects of health-related quality of life, negative consequences of treatment). In painful musculoskeletal conditions the impact on function is particularly important, as is the bidirectional relationship between perceived pain and emotional well-being. The paradigm of the “5 Ds”—death, disability, discomfort, drug (or other iatrogenic) reactions, and dollar (or economic) costs—advanced by Fries encompasses outcomes that are relevant to all patients because they are discernible at the individual patient level, represent the key consequences of disease and its treatment, and are the ultimate outcomes of the disease process.¹ The components of health and the consequences of arthritis and musculoskeletal conditions are many and diverse. It is possible to measure multiple aspects of a patient's condition with evaluation procedures that are relevant to specific clinical conditions and assessment and measurement environments, and are aligned with assessment objectives.

It is important to appreciate that in the discipline of clinical measurement (synonym: clinical metrology) there is variable use of common terminology.

The terms *endpoint* and *outcome* are used interchangeably. However, the terms *instrument* and *tool* can refer not only to electromechanical devices but also to questionnaires and other assessment techniques. The questionnaires, in turn, are variably referred to as *health status questionnaires*, *health status measures*, or *health status instruments*. The terms *subjective* (soft) and *objective* (hard) are best avoided, and instead the measurement technique should be referred to according to its qualitative (e.g., type of measure, purpose of measurement) and quantitative (e.g., reliability, validity, responsiveness) measurement characteristics.

Outcome measures may be divided into two broad categories: observer dependent (or assessor rated) and observer independent (or self-rated). In general, observer-independent clinical measures are based on self-administered questionnaires, usually referred to as *patient-reported outcome measures* (PROMs). In contrast, observer-dependent clinical measures include interviewer-scored questionnaires, physical examination findings, and tests of performance rated using technical instruments (e.g., grip strength, walk time). Certain techniques, such as face-to-face interview, walk time, grip strength, and articular index, involve an interaction between the assessor and the patient, which on occasion may bias the result obtained.

A fundamental aspect of measurement is whether all patients will be asked the same questions on every occasion, or whether the questions asked should be adapted to individual patients or the response patients give to initial questions should determine the nature of subsequent questions, using computer adaptive testing. The National Institutes of Health are currently exploring aspects of this issue in the Patient-Reported Outcomes Measurement Information Systems (PROMIS) initiative.²⁻⁴ This initiative has resulted in the development of item banks that form the basis of an alternative approach to index construction and presentation.

FUNDAMENTAL PRINCIPLES OF CLINICAL
OUTCOME ASSESSMENT

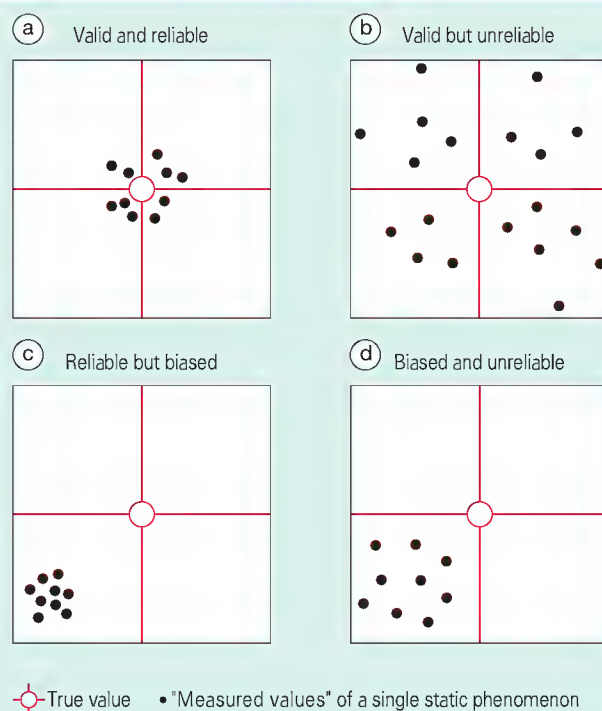
Outcome measurement procedures should fulfill three major criteria that are encompassed by those proposed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group, as the OMERACT filter.¹ The three components of the filter are “truth,” “discrimination,” and “feasibility.” Truth concerns issues of validity, discrimination addresses issues of both reliability and responsiveness, and feasibility encompasses ease, time, cost, interpretability and arguably ethics. Measurement processes that are potentially hazardous to patients raise ethical issues that must be explained to and understood and accepted by patients and study participants. The importance and necessity of acquiring new information should be weighed against any attendant risks.

Validity

Validity is a measure of the extent to which an instrument specifically measures the phenomenon of interest. In contrast, reliability defines the extent to which the measurement procedure yields the same result on repeated determinations. Validity and reliability are separate clinimetric issues, and it does not follow that because a measure is reliable it is also valid or vice versa ([Fig. 2.1](#)). More specifically, validity is concerned with sources of nonrandom error (i.e., systemic error or bias), whereas reliability is concerned with sources of random error, also known as *noise*. Systemic error or bias may prevent an instrument from truly measuring what is intended, which results in inaccuracy. A number of different strategies may be employed to determine validity, each conceptually different and relying on different methods of assessment. There are four types of validity: face, content, construct, and criterion.

BOX 2.1 LIST OF ABBREVIATIONS

ACR	American College of Rheumatology	LAI-P	Lupus Activity Index in Pregnancy
AIMS	Arthritis Impact Measurement Scales	MCII	Minimum clinically important improvement
AIMS2	Arthritis Impact Measurement Scales 2	MDI	Myositis Damage Index
AS	Ankylosing spondylitis	MHAQ	Modified Health Assessment Questionnaire
ASAS	Assessment in Ankylosing Spondylitis	MITAX	Myositis Intention to Treat Activity Index
ASDAS	Ankylosing Spondylitis Disease Activity Score	m-SLAM	Modified Systemic Lupus Activity Measure
AUSCAN	Australian-Canadian Hand Osteoarthritis Index	MYOACT	Myositis Disease Activity Assessment Visual Analogue Scale
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index	NHP	Nottingham Health Profile
BASFI	Bath Ankylosing Spondylitis Functional Index	OA	Osteoarthritis
BDAI	Behçet's Disease Activity Index	OAKHQOL	Osteoarthritis Knee and Hip Quality of Life
BD-QoL	Behçet's Disease Quality of Life	OARSI	Osteoarthritis Research Society International
BILAG	British Isles Lupus Assessment Group	OMERACT	Outcome Measures in Rheumatology Clinical Trials
BLISS	Bellamy Low-Intensity Symptom State-Attainment Index	PASS	Patient-acceptable symptom state
BVAS/WG	Birmingham Vasculitis Activity Score/Wegener's Granulomatosis	PROMIS	Patient-Reported Outcomes Measurement Information Systems
CDA	Combined Damage Assessment	PROMs	Patient-reported outcome measures
CDAI	Clinical Disease Activity Index	PsA	Psoriatic arthritis
DAS	Disease Activity Score	RA	Rheumatoid arthritis
DFI	Dougados Functional Index	RIFLE	Responder Index for Lupus Erythematosus
DRP	Disease Repercussion Profile	RLDQ	Revised Leeds Disability Questionnaire
ECLAM	European Consensus Lupus Activity Measurement	SDAI	Simplified Disease Activity Index
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index	SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus National Assessment Modification of the Systemic Lupus Erythematosus Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index	SF-36	Short Form-36 Health Survey
EULAR	European League Against Rheumatism	SHAQ	Scleroderma Health Assessment Questionnaire
EuroQoL	European Health-Related Quality of Life	SLAM	Systemic Lupus Activity Measure
FDA	U.S. Food and Drug Administration	SLE	Systemic Lupus Erythematosus
FIHOA	Functional Index for Hand Osteoarthritis	SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
FIQ	Fibromyalgia Impact Questionnaire	SLEPDAI	Systemic Lupus Erythematosus in Pregnancy Disease Activity Index
HAQ	Health Assessment Questionnaire	SSDAI	Sjögren's Syndrome Disease Activity Index
HAQ-DI	Health Assessment Questionnaire Disability Index	SSDDI	Sjögren's Syndrome Disease Damage Index
HAQ-S	Health Assessment Questionnaire for the Spondyloarthropathies	TRI	Therapeutic Responder Index
HUI	Health Utilities Index	VDI	Vasculitis Damage Index
ICAF	Combined Index of Severity of Fibromyalgia	WHO	World Health Organization
ICF	International Classification of Functioning, Disability, and Health	WOMAC	Western Ontario and McMaster Osteoarthritis Index
ICS	Indices of Clinical Severity		
LAI	Lupus Activity Index		

SCHEMATIC REPRESENTATION OF SYSTEMIC ERROR (BIAS) AND RANDOM ERROR (NOISE)**Fig. 2.1** Differentiation of systemic error (bias) and random error (noise).**Face validity**

A measure has face validity if experts judge that it measures at least part of the defined phenomenon. In many instances this is self-evident, whereas in others, particularly in questionnaire-based measures of functional status, it may not be entirely obvious whether the measurement reflects physical, social, or emotional function.

Content validity

An instrument can have face validity but fail to capture in its entirety the dimension of interest. Content validity, therefore, is a measure of comprehensiveness—the extent to which the measure encompasses all relevant aspects of the defined attribute. Content validity is generally determined by group consensus (e.g., nominal or Delphi techniques). The decision regarding which items should be included in a questionnaire-based instrument and which should be excluded is critical, because it defines the nature of the instrument and its future applicability. Any subsequent addition or deletion results in an instrument that requires further validation.

Given the variability in symptom expression by patients, one of two approaches can be employed to achieve comprehensiveness in questionnaire-based measures. The first is to include a standard battery of measures that probes frequently occurring symptoms that are clinically important to the majority of patients. In the second approach, the measurement process is tailored to the individual by measuring only those items that are important to that particular person. The issue of importance can be decided by patients, who rate the importance of their symptoms, or by clinical assessors, whose decision is based on their perception of the patient's symptoms.

Construct validity

Construct validity is of two types: convergent and discriminant. Both are tested by demonstrating relationships between measurement scores and a theoretical manifestation (i.e., construct or consequences of an attribute) of the disease. Convergent construct validity is assessed by the statistical

correlation between scores on a single health component, as measured by two different instruments. If the correlation coefficient is positive and appreciably above zero, the new measure is said to have convergent construct validity. In contrast, discriminant construct validity testing compares correlation coefficients between scores on the same health component, as measured by two different instruments (e.g., separate measures of physical function) and between scores on that health component and each of several other health components (e.g., measures of social and emotional function). A measure has discriminant construct validity if the proposed measure correlates better with a second measure, accepted as more closely related to the construct, than it does with a third, more distantly related measure.

Criterion validity

Criterion validity is assessed by statistically testing a new measurement technique against an independent criterion or standard (concurrent validity) or against a future standard (predictive validity). Criterion validity is an estimate of the extent to which a measure agrees with a gold standard (i.e., an external criterion of the phenomenon being measured). The major problem in criterion validity testing, for questionnaire-based measures, is the general lack of gold standards. Indeed, some purported gold standards may not themselves provide completely accurate estimates of the true value of a phenomenon. In contrast, electromechanical devices such as those evaluating strength, resistance, and range of movement can more often be validated using standard calibration techniques found in the engineering literature.

Reliability

Consistency, reproducibility, repeatability, and agreement are synonyms for *reliability*. Reliability is the extent to which a measurement procedure yields the same result on repeated determinations (see Fig. 2.1). These determinations may be either different measurements performed at the same time (internal consistency) or the same measurements performed at different times (stability). Repeated measurements are rarely exactly the same, because there is usually some random error, noise, or degree of inconsistency. There are various methods of calculating reliability, each method reflecting a different aspect of instrument performance, so that different coefficients are derived using different methods. Defined sources of measurement error include the subject, the assessor, and the measuring instrument. Patient variability often arises from normal variation in symptoms or from fatigue or inattention. When observers are involved in capturing information, both interobserver and intraobserver reliability are important. Observer variability may be the result of inadequate standardization, the necessity for complex judgments, perceptual elements, or fatigue. When technical instruments are involved in the measurement process, variation in, for example, the cuff configuration of a modified sphygmomanometer or in the mechanical resistance of a dynamometer or dolorimeter may be important sources of error.

Responsiveness (sensitivity to change)

The primary goal of outcome assessment in evaluative research is to detect clinically important changes in some aspect of a condition. To detect change, a measurement technique needs to be targeted to aspects of the disease amenable to change, using content and scaling methods that allow detection of change, and be applied at a point in time when change might have occurred. Validity and reliability are important aspects of all measurement techniques, but the capacity to detect change is the quintessential requirement of a successful outcome measure for evaluating change over time and the patient's response to treatment. An assessment technique may fail to record any clinical improvement for a number of reasons (e.g., patient lacks response potential, lacks compliance with the treatment program, or has received inefficacious treatment; the outcome measure is insensitive; or a type II error occurs due to inadequate sample size).

STATISTICAL ISSUES

It is necessary to have a basic understanding of the statistics used in the development and validation of health status measures. Although correlation coefficients are frequently used, they are a measure of the strength of association, not a measure of agreement, so that it is possible to have perfect correlation but zero agreement between two measurements. In evaluating construct validity using correlation coefficients, both strength and direction should be considered *a priori*; otherwise, data interpretation can become complex and biased.

The following are commonly used statistical tests for evaluating reliability, validity, and responsiveness:

- Bland and Altman scatter plots permit the distribution of pairwise data to be appreciated.
- The Cohen κ statistic, a metric reflecting agreement beyond chance, can be weighted or unweighted and adjustments made for bias and prevalence.
- Intraclass correlation coefficients are often used in intrarater and interrater agreement analyses, based on continuous data.
- The Cronbach α statistic, a measure of average interitem correlation, is used to evaluate internal consistency.
- Factor analysis is a useful procedure for evaluating structure provided the sample is sufficiently large and is also representative. Repeated factor analyses on the same instrument using different data sets may yield conflicting results.
- Rasch analysis is increasingly being employed to test outcome scales against mathematical models using a probabilistic form of hierarchical or Guttman scaling. The Rasch model attempts to scale variables along a continuum, but not all Rasch analyses of the same instrument necessarily agree with one another. Although, in general, individuals who can perform tasks of a particular degree of difficulty should be able to perform all tasks of lesser difficulty, this is not always the case.
- A number of techniques, including interperiod correlation matrix analysis, may be used to estimate measurement error, which can in turn be used to evaluate change beyond measurement error.
- ANOVA (analysis of variance) and Student's *t*-test are commonly used to evaluate responsiveness.
- Effect size (change score/baseline standard deviation) is used to evaluate responsiveness.
- Standardized response mean (change score/change score standard deviation) is used to evaluate responsiveness. Responsiveness, whether evaluated by ANOVA, Student's *t*-test, effect size or standardized response mean may differ between outcome measures used to evaluate different variables or even the same variable and may differ even within an outcome measure when it is presented in different scaling formats.
- Relative efficiency (square of the ratio of two *t* or *z* statistics) is used to evaluate relative responsiveness.

OUTCOME ASSESSMENT MEASURES FOR MUSCULOSKELETAL DISORDERS

There are numerous techniques for assessing the beneficial and adverse outcomes of treatment. Some health status instruments have been developed specifically to assess certain conditions (condition-specific measures), whereas others have been developed to permit measurement across several or many diseases (generic measures). Readers interested in specific measurement issues should consult standard measurement texts. In this section a review is presented of the measurement of pain, impairment, ability/disability, and participation/handicap; patient and physician global assessments; multidimensional health status instruments (quality of life, utility); and measures of adverse drug reactions. Readers should refer to other sections of this textbook for information on laboratory-based and imaging-based measurement procedures.

Pain

Pain is an entirely subjective phenomenon, the perception of which is modulated by a variety of influences, and results in pain behaviors that may be observed. The severity of perceived pain can be rated only by the sufferer. In contrast, pain behavior can be rated by a trained assessor. Complex bidirectional interactions occur between pain and other factors, including personal factors unique to the individual. Pain can be assessed using a variety of techniques (Fig. 2.2), including the following:

- Likert or adjectival scales
- Visual analogue scales
- Ladder scales, numerical rating scales
- Chromatic continuous analogue scales
- Pain faces scales
- McGill Pain Questionnaire
- Behavioral observation techniques

Comparative studies of pain rating scales in rheumatoid arthritis (RA) and osteoarthritis (OA) suggest that there is a positive relationship between

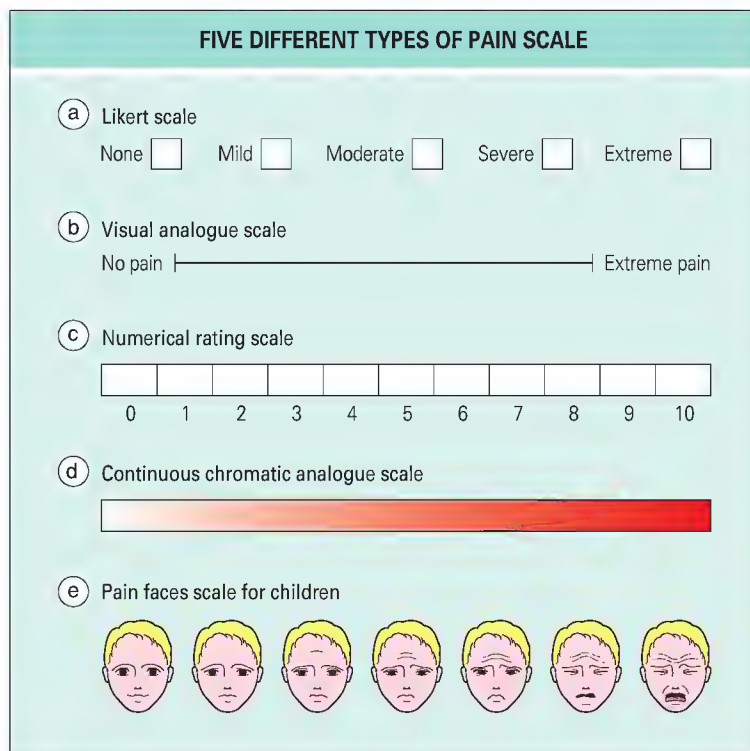


Fig. 2.2 Adjectival, numerical, and visual scales for rating pain.

initial pain rating and subsequent pain relief scores and that all the aforementioned types of scales are responsive. Likert and visual analogue scales are the most frequently applied types of scales. Likert scales usually employ an odd number of descriptors (3, 5, 7, or 9), whereas visual analogue scales are most often 100 mm long and horizontal in orientation, with terminal descriptors. The numerical rating scale is often scaled from 0 to 10, displayed in linked boxes, and has terminal descriptors. The focus, phraseology, descriptors, and time frames for recall used in such scales often vary among different questionnaires. In comparative studies in RA and OA, the single-item global numerical rating pain scale appears comparable in responsiveness to the same question presented on a visual analogue scale and is slightly more responsive than the corresponding five-point Likert scale.

When pain scales are applied, it is important to specify either the global nature of the question or the specific aspect of pain that is being assessed (e.g., while stair climbing, while walking, at rest, during the night, overall) and clearly indicate the time interval over which pain is being evaluated (e.g., previous 48 hours, 1 week). Several of the standard established segregated multidimensional health status instruments, including the Health Assessment Questionnaire (HAQ),⁵ Arthritis Impact Measurement Scales (AIMS) and AIMS2,^{6,7} Western Ontario and McMaster (WOMAC) Osteoarthritis Index,⁸ and Australian-Canadian (AUSCAN) Hand Osteoarthritis Index,⁹ contain distinct pain subscales. These contrast with other instruments that either contain no pain subscale (e.g., Functional Index for Hand Osteoarthritis [FIHOA],¹⁰ Cochin index¹¹) or in which pain is an integral part of an aggregated scoring system combining scores on several different dimensions (e.g., Indices of Clinical Severity [ICS]).¹² It should be noted that the recall period differs among measures. A short recall period may offer advantage when the intervals between repeat assessments are short.

Impairment, ability/disability, and participation/handicap

The terms *impairment*, *disability*, and *handicap* may be confused in everyday usage, even though the World Health Organization (WHO) has previously characterized these three different entities.¹³ *Impairment* is defined as any loss or abnormality of psychological, physiologic, or anatomic structure or function. It signifies that a pathologic state has reached a stage of detectability. In contrast, *disability* includes any restriction or lack of ability to perform an activity in the manner considered normal. Such disabilities include alteration in behavior and interactive processes such as communication, as well as strictly physical function. A *handicap* is manifest as a disadvantage experienced by an individual as a result of an impairment or

disability, such that it limits or prevents the fulfillment of a role considered normal for that individual. In essence, therefore, impairment occurs at an organ level (intellectual, sensory, visceral, musculoskeletal), disability occurs at a personal level (behavior, self-care, locomotion, dexterity), and handicap occurs at a social level (independence, geographic mobility, employability, social integration).¹³ The concepts of disability and handicap, in particular, are considered unipolar; and partly for this reason the newer WHO International Classification of Functioning, Disability, and Health (ICF) is to be preferred, because it considers these same concepts in a bipolar framework of ability and participation.¹⁴ The ICF framework proposed by the WHO is particularly useful in conceptualizing the functional impact of many of the conditions described in other chapters of this text. The ICF framework considers a hierarchy of impairments, activities, and participation, modulated by contextual factors (environmental and personal), and extends the original WHO classification of impairment, disability, and handicap to incorporate positive aspects of health, including physical activity and participation in society.¹⁴ Several more modern outcome measures have been mapped to the ICF framework.¹ The ICF framework may also provide a construct on which to base instrument development.

Impairment

In clinically based musculoskeletal applications in research and practice, measurement is often directed at the assessment of abnormalities in structure (e.g., swelling, tenderness). The most important examination-based measurement procedure is the separate enumeration of swollen and tender joints in patients with inflammatory polyarthritis.¹ The usual method employs separate counts of the number of swollen and tender joints using either the American College of Rheumatology (ACR) 68-joint count or the European League Against Rheumatism (EULAR) 28-joint count. The 28-joint count is often conducted as part of determining the 28-joint Disease Activity Score (DAS28).

It is convenient to chart individual joint involvement on a homunculus or mannequin (Fig. 2.3), as is the practice with the DAS28. Other methods have been developed for scoring joint involvement in OA, enthesopathy in ankylosing spondylitis (AS), and tender points in fibromyalgia.¹ Methods for assessing other clinical signs, such as heat, erythema, and crepitus, have been less rigorously studied. All such procedures are liable to interrater and intrarater error and are best performed by skilled standardized assessors. Nevertheless, various impairment assessments can be conducted at acceptable levels of reliability by trained assessors.

The American Medical Association *Guides to the Evaluation of Permanent Impairment*^{14a} provides a standardized method to rate impairment at maximum medical improvement. However, the guides are primarily employed in compensation/litigation applications, and different jurisdictions may use different versions of the guides.¹⁵

Ability/Disability

Functional measures can be subdivided into those based on observed tests of performance and questionnaires that assess functional capacity.

Performance-based measures

Performance-based measures might at first seem the most direct way to assess the patient's function. However, such measures often involve an interaction between the assessor and subject that may augment or diminish the true performance and raise concern regarding intra-assessor and inter-assessor consistency and the need for assessor standardization. Furthermore, change in performance on the performance test may not correspond to a comparable change in the performance of relevant activities of daily living. The relevance of the change to the patient may therefore require interpretation. Nevertheless, some measures, such as the modified Schober test in AS, grip strength in RA, and range of movement in knee OA, remain in common usage in clinical rheumatology. In health disciplines such as orthopedic surgery and physiotherapy extensive use is made of performance-based measures in the routine management of patients with bone and joint diseases.¹ Interrater and intrarater reliability have been quantified and standard procedures developed to train assessors and perform the evaluations.

Capacity-based measurement

Patients with musculoskeletal disorders may experience three types of functional disability: physical, emotional, and social. All three forms are amenable to outcome assessment using valid, reliable, and responsive questionnaires. Physical disability, in particular, has received considerable attention, and some techniques have been designed for a specific purpose whereas others have multipurpose applications.¹ Physical disability is one

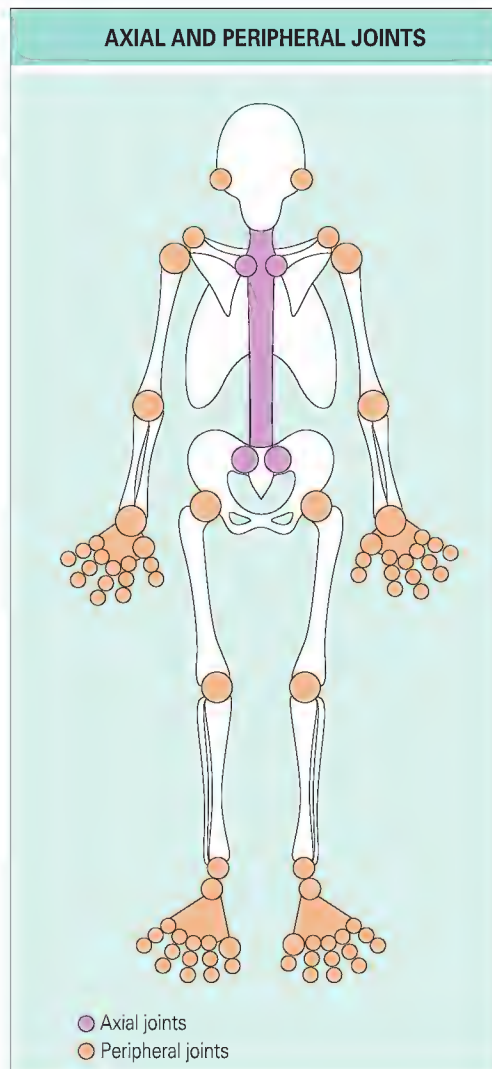


Fig. 2.3 Homunculus for recording joint involvement by arthritis in routine clinical care.

of the two most important and immediate consequences of many musculoskeletal conditions. The capacity to measure this aspect of the disease, both in clinical trials and clinical practice, is paramount. Fully validated health status instruments including separate measures of pain and function are to be preferred over ad-hoc scales. Examples of disease-specific measures of function include the following:

- WOMAC Osteoarthritis Hip/Knee Index⁸
- AUSCAN Osteoarthritis Hand Index⁹
- Cochin hand index¹¹
- FIHOA¹⁰
- Bath Ankylosing Spondylitis Functional Index (BASFI)¹
- Fibromyalgia Impact Questionnaire (FIQ)¹

In contrast, measures such as the HAQ,⁵ AIMS,⁶ and AIMS2⁷ have multipurpose musculoskeletal applications and generic quality-of-life measures such as the Short Form-36 Health Survey (SF-36) and the European Health-Related Quality of Life (EuroQol) instrument can be used across a wide variety of diverse medical conditions.¹⁶ The SF-36 is available in different several formats. In recent years, there have been an increasing number of comparative studies of the performance of different health status measures. Different measures are underpinned by different constructs, vary in their responsiveness, and may impose different sample size requirements when used in clinical research applications.

The measurement of emotional disability in musculoskeletal disease is important because considerable psychological morbidity has been noted in patients with musculoskeletal disorders. There is a bidirectional inverse relationship between pain and emotional well-being. Furthermore, it is not surprising, given the degree of pain, disability, anxiety, depression, and diminished sense of well-being experienced by patients, that many musculoskeletal disorders have social consequences.

Participation/handicap

Measures of handicap reflect the social consequence of disease. Whether an individual is handicapped can be defined either by society or by an individual. The measurement of handicap in the rheumatic diseases has attracted relatively little attention. The Disease Repercussion Profile (DRP) is a valid and reliable measure of patient-perceived handicap. Relatively few interventional studies, even recent studies, include a measure of participation/handicap.

Global assessments

Global assessments by patient and physician of the patient's overall condition are commonly used in clinical trials and in clinical practice. It is extremely important to specify in the wording of the global question which aspects of the patient's condition are being considered (e.g., overall health status, symptom severity, disease activity, or an anatomic area). The patient global assessment is particularly important because it can be phrased to assess current status or change in symptom status and can be focused on a particular anatomic area, the condition in general, or the patient as a whole. Alternatively, it can be used to assess drug tolerability and/or efficacy or other aspects of the treatment program (palatability, compliance, affordability, convenience). The time frame over which the patient should consider his or her status should be defined (e.g., 48 hours, 1 week). It is debatable whether the physician global assessment of overall health adds much to the measurement process over and above the patient's own global assessment. However, the physician (or other assessor) can consider, in addition, aspects of the condition that are not assessable by the patient (e.g., radiographic change and biochemical, hematologic, and immunologic abnormalities) and may provide insight into whether the patient tends to amplify or minimize reported symptoms. Again, the physician requires clear specification as to which aspects of the condition should be considered when making his or her assessment. The time frame for the physician global assessment usually should be specified as "today" since the assessor generally has no knowledge of the patient's interval status other than that described by the patient and captured by the patient global assessment. At the present time there is no international consensus on the exact wording of the patient global assessment question or the preferred scaling format. However, a recent study has explored clinical benchmarking issues in RA, OA (hip/knee), OA (hand), AS, and low back pain using standardized patient global assessment questions developed through group consensus of expert opinion.¹⁷

Patients and physicians may differ in their perception of the patient's global assessment of disease activity or symptom severity. The determinants and consequences of this discrepancy need careful consideration, particularly by practitioners and researchers using interviewer-administered outcome questionnaires, in which there is potential for interaction between the interviewer and patient.

MULTIDIMENSIONAL HEALTH STATUS INSTRUMENTS

A large number of disease-specific and generic multidimensional health status measures have been developed. Many are very sophisticated instruments that have undergone extensive validation procedures and have high performance characteristics with superior levels of validity, reliability, and responsiveness. They are either self-administered or occasionally interviewer administered. It is very important for users to contact the originator before initial application to obtain instructions regarding usage (e.g., presentation, scoring, analysis), to procure an authentic current version of the instrument and a copy of the user's guide, and to obtain any required permissions. Many outcome measures are protected by copyright and/or trademark. The main reason for an originator to register copyright and trademark is to secure necessary protection for the measure, and this forms the basis for maintaining its integrity, authenticity, and appropriate usage.

Some health status measures have been developed in the form of segregated multidimensional indices that contain separate, distinct subscales exploring different aspects of the condition, such as HAQ, AIMS, AIMS2, WOMAC index, and AUSCAN index. They provide subscale scores on each of several separate dimensions. Others are in the form of aggregated multidimensional indices in which scores from several different dimensions are weighted and aggregated into a single score, such as the ICS, Pooled Index, and DAS. Health-related quality of life can be assessed either using a multi-item questionnaire, such as the SF-36 (and its derivatives), Nottingham Health Profile (NHP), or EuroQol, or using a utility-based methodology, for example the Health Utilities Index (HUI). A utility is a holistic measure of

the quality of life that rates an individual along a continuum from death (0.0) to full health (1.0). Models for predicting utilities from nonutility instrument data are evolutionary. For example, a model has been developed and validated to derive a utility score from WOMAC data that, at the group level, approximates the utility score estimated from the HUI in the same group of patients.¹ This provides an opportunity to derive utility scores from previously published studies that contain WOMAC data but that did not include a utility-based measure.

ASSESSMENT OF ADVERSE REACTIONS

Adverse reactions caused by treatment can result in symptoms, clinical signs, laboratory abnormalities, or death. Problems often arise in detecting, categorizing, attributing, and grading adverse events. Adverse event rates differ significantly depending on whether the assessment is based on open-ended questioning or structured questionnaires or is determined by a standard protocol. Various systems have been developed for categorizing adverse reactions to treatment. Attribution is the process of ascribing adverse reactions to interventions or other causes. The etiologic relationship is often graded as “none,” “possible,” “probable,” or “definite.” A number of factors determine the assigned level of the relationship, including prior knowledge of the patient, the pharmacodynamic profile of the intervention, and the duration of treatment. The most difficult attribution decisions are in assigning the grades of “none” versus “possible” and “probable” versus “definite” and in grading the intensity of an adverse reaction. Often severity is rated as being “mild,” “moderate,” or “severe.” A mild adverse reaction is one that is easily tolerated by the patient, causes minimal discomfort, and does not interfere with everyday activities. A moderate adverse effect is an adverse experience that causes sufficient discomfort to interfere with normal everyday activities, whereas a severe reaction is an adverse experience that is incapacitating and prevents normal everyday activities. Finally, it is important to categorize the outcome of an adverse reaction, for example, as “resolved,” “improved,” “unchanged,” “worsened,” “hospitalization required,” “hospitalization prolonged,” or “death.”

MEASUREMENT IN CLINICAL TRIALS

There are more than 100 different rheumatic disorders, each presenting a different challenge in outcome measurement. Regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency as well as international nongovernment organizations such as the Osteoarthritis Research Society International (OARSI), OMERACT group, ACR, and Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) have pioneered the development of several evidence-based consensus-driven guidance documents. The FDA document on PROMs is particularly important in understanding the challenges of measuring patient-centered outcomes in regulatory environments.¹⁸ In addition to specifying domains and core set variables (measures) and identifying instruments, some organizations have also initiated investigations leading to the proposal of responder criteria, that is, criteria that could be used to stratify patients according to whether they have experienced a meaningful improvement with treatment. Although improvement with treatment is a very important goal, it is also important to determine the value of the final health state attained. Work in this area is, by comparison, relatively limited. However, several proposals have emerged that identify achievable, acceptable, or desirable health states. Finally, although there is a distinct paucity of general population-based normative values for PROMs, there has been some recent progress in this area.

There are a large and continually growing number of outcome measures to evaluate RA, OA, AS, reactive arthritis, systemic lupus erythematosus (SLE), low back pain, and fibromyalgia, as well as more generally applicable measures and measures of handicap, coping, helplessness, and quality of life. It is beyond the scope of this chapter to describe the development, validation, and scope of application of each of the currently available measures or the exact methods used to develop guidance documents or to develop and propose response and state-attainment criteria or normative values. Measurement preferences differ between different disorders, but pain, function, and patient global assessment are often emphasized. Where patient responses are captured and transmitted electronically, the FDA document *Guidance for Industry: Computerized Systems Used in Clinical Investigations* (2007) is relevant.¹⁹

Three areas that require special attention when considering data capture on a global scale are short-forms, alternate-language translations, and electronic data capture. Concerns regarding respondent burden in completing

PROMs has stimulated the development of shortened versions of existing measures. Although time to completion may be reduced, short-forming also reduces content validity. When short-forming is replicated in different cultures and interventional environments it is noted that the short forms differ. For example, in the case of proposed short forms of the WOMAC index, no two short forms are the same but each of the 24 items is included in at least one of the proposed short forms.²⁰ The creation of alternate-language translations of PROMs requires skill, experience, and close attention to the standard operating procedures necessary to create linguistically valid and culturally appropriate translations.²¹ The process should be conducted only in association with the originator of the measure. Users should clearly differentiate between alternate-language translations created to a commercial standard and those resulting from ad-hoc processes.²⁰ Electronic data capture is gradually replacing traditional paper-based capture of patient responses to PROMs. The development of electronic forms of existing measures may require modifications to language and format. The extent to which further linguistic and clinimetric validation are required is unclear at present. As with alternate-language creation, the development of electronic versions should be undertaken only by entities with the required special skills and experience and should adhere to standard operating procedures and be conducted only in association with the originator of the measure.²⁰

Rheumatoid arthritis

In general, RA clinical trials evaluate either fast-acting, symptom-modifying drugs, such as nonsteroidal antiinflammatory drugs and analgesics, or slow-acting disease-modifying antirheumatic drugs, which include the biologic agents. Several valid, reliable, and responsive outcome measures have been developed for the evaluation of patients with RA. In addition, ICF core sets have been specified for RA and validated from a patient perspective, and commonly used instruments have been mapped to the framework. Normative data for the HAQ have been published and minimum clinically important improvement (MCII) and patient-acceptable symptom state (PASS) estimates explored for RA (Box 2.2). The following recommendations, developed by the OMERACT group and ratified by the ACR,¹ currently

BOX 2.2 PROPOSED STATE-ATTAINMENT CRITERIA FOR ARTHRITIS AND MUSCULOSKELETAL CONDITIONS

Patient-Acceptable Symptom Severity (PASS75) (preliminary estimates based on REFLECT study¹) (all values on 0-100 scales)

Osteoarthritis (hip and knee)

WOMAC Pain = 39.3; WOMAC Stiffness = 44.8; WOMAC Function = 47.7; PGA = 47.1.

Osteoarthritis (hand)

AUSCAN Pain = 41.0; AUSCAN Stiffness = 37.8; AUSCAN Function = 44.8; PGA = 41.6.

Rheumatoid arthritis

Pain = 40.7; HAQ = 39.4; PGA = 41.6.

Ankylosing spondylitis

Pain = 40.6; PGA = 43.2; BASFI = 40.4; BASDAI = 38.9; PGA = 43.2.

Low back pain

Pain = 39.4; Roland Morris Disability Questionnaire = 30.7; PGA = 40.3.

Bellamy et al³³: Low-Intensity Symptom State-Attainment (BLISS) Index Osteoarthritis (knee)

Two components—symptom level based on the WOMAC Osteoarthritis Index (pain, stiffness, function, and total score) and time combined in a state-attainment-based analysis.

Magnitude (normalized units [nu] 0-100 scale):

≤25 nu, ≤20 nu, ≤15 nu, ≤10 nu, ≤5 nu

Time to first BLISS day:

BLISS days over 12 months

Patients in BLISS at month 12

Patients in BLISS at any time

BLISS maintained to month 12

Number of BLISS periods over 12 months

AUSCAN, Australian-Canadian Hand Osteoarthritis Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BLISS, Bellamy Low-Intensity Symptom State-Attainment Index; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; WOMAC, Western Ontario and McMaster Osteoarthritis Index.

comprise the ACR minimum core set for RA clinical trials: pain, physical function, number of swollen joints, number of tender joints, patient global assessment, investigator global assessment, erythrocyte sedimentation rate or C-reactive protein level, and imaging. Individual response criteria based on these clinical variables and referred to as the ACR20¹ have been proposed as follows: 20% or more improvement in tender and swollen joint counts and 20% or more improvement in scores on three of the five remaining ACR core set measures. These are particularly relevant for evaluating the response to symptom-modifying drugs. The sufficiency of the ACR20 criteria has been considered, and higher-level response requirements based on the ACR50 and ACR70 criteria evaluated.¹ Compared with ACR20/50/70 criteria, cut points of 50/70/85 for the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) define minor, moderate, and major responses.²²

The treat-to-target approach to management, which characterizes the ACR²³ and EULAR²⁴ recommendations for the management of RA, has stimulated further consideration of the definition of remission in RA. Definitions of remission and minimum disease activity have been proposed based on several outcome measures, including the DAS28, ACR/EULAR remission criteria, SDAI, and CDAI.²⁵⁻²⁷ Remission rates are instrument and cut-score dependent. Thus, in a comparative study in early RA, higher remission rates were observed when DAS28 criteria were used than when ACR/EULAR criteria were employed.²⁸

Osteoarthritis

Clinical trials in OA can be subdivided into those that assess symptom-modifying OA drug effects and those that assess structure-modifying drug effects. Several valid, reliable, and responsive outcome measures have been developed for the evaluation of patients with OA of the hip, knee, and hand. ICF core sets for OA have been elaborated and the WOMAC index, ICS, and Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) questionnaire mapped to the ICF core set. A unique set of age- and gender-specific general population-based normative data have been reported for the WOMAC and AUSCAN index subscales (Figs. 2.4 and 2.5)^{29,30} and MCII and PASS estimates explored for OA based on the WOMAC index for hip and knee OA and the AUSCAN index for hand OA (see Box 2.2). MCII and PASS estimates may vary across instruments, subscales, countries, and therapeutic environments.³¹ Although there are no clinical measures specific for structure-modifying drug trials in OA, it is of note that the WOMAC index detected clinical benefits associated with structural conservation in a recent double-blind, randomized, controlled clinical trial of strontium ranelate.³²

Core set measures for OA have been proposed by the OMERACT group and ratified, or in the case of hand OA, developed by the OARSI.¹ OMERACT and OARSI core set measures for future phase 3 studies in hip, knee, and hand OA are pain, function, patient global assessment, and, for studies of 1 year or longer, joint imaging using validated methods and standardized techniques. OMERACT and OARSI have jointly proposed responder criteria

for hip and knee OA, based on combinations of absolute and percentage changes in pain, function, and patient global assessment.¹ The OMERACT-OARSI responder criteria are applicable to both hip and knee OA patients and are not intervention class specific. Response criteria developed for OA and proposed by other groups include definitions of minimum perceptible clinical improvement, minimum clinically important difference, MCII, WOMAC 20-50-70, and AUSCAN 20-50-70. In addition to these definitions based on the degree of change, other definitions have been proposed based on the health state attained, the so-called state-attainment criteria. Definitions based on PASS and the Bellamy Low-Intensity Symptom State-Attainment (BLISS) Index (see Box 2.2)³³ are examples of initial attempts to establish working definitions for use in clinical practice and clinical research. Observations that statistically significant between-group differences are detectable at low or very low symptom intensity levels, so-called BLISS states, are of particular importance in the evaluation of therapeutic interventions³³ because they provide indicators of achievable health states (see Box 2.2). Although further research is necessary, observations of BLISS states have been made with the WOMAC and AUSCAN indices and in different classes of interventions and confirm that such states are achievable by some, but not all, patients. Attempts by the OARSI to develop a surrogate indicator for total joint replacement in hip and knee OA has not, to date, resulted in cut scores for pain and function capable of discriminating between patients who are and who are not considered candidates for total joint replacement by their orthopedic surgeons.^{34,35}

Ankylosing spondylitis

Several valid, reliable, and responsive outcome measures have been developed for the evaluation of symptom severity and disease status in patients with AS.³⁶ Clinical measurement in AS encompasses both the peripheral joints and extraarticular involvement, as well as axial skeletal involvement. Through the OMERACT process and the Assessment in Ankylosing Spondylitis (ASAS) Working Group, core set measures have been identified for use in different clinical research settings.¹ The ASAS group has also developed a definition of short-term improvement (ASAS20) based on four domains: physical function, pain, patient global assessment, and inflammation. ASAS20 defines improvement as 20% or more and 1 unit or more (0 to 10 scale) improvement in at least three of the four domains, with no worsening (defined as deterioration of 20% or more and 1 unit or more [0 to 10 scale]) on the fourth dimension.¹ The recent emergence from the ASAS/OMERACT initiative of the Ankylosing Spondylitis Disease Activity Score (ASDAS), based on the weighted sum of measures of back pain, morning stiffness, patient global assessment, peripheral joint pain/swelling, and either C-reactive protein level or erythrocyte sedimentation rate, provides a composite index for evaluating disease activity in AS.³⁷

The BASFI, Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), and Revised Leeds Disability Questionnaire (RLDQ) instruments have been mapped to the ICF

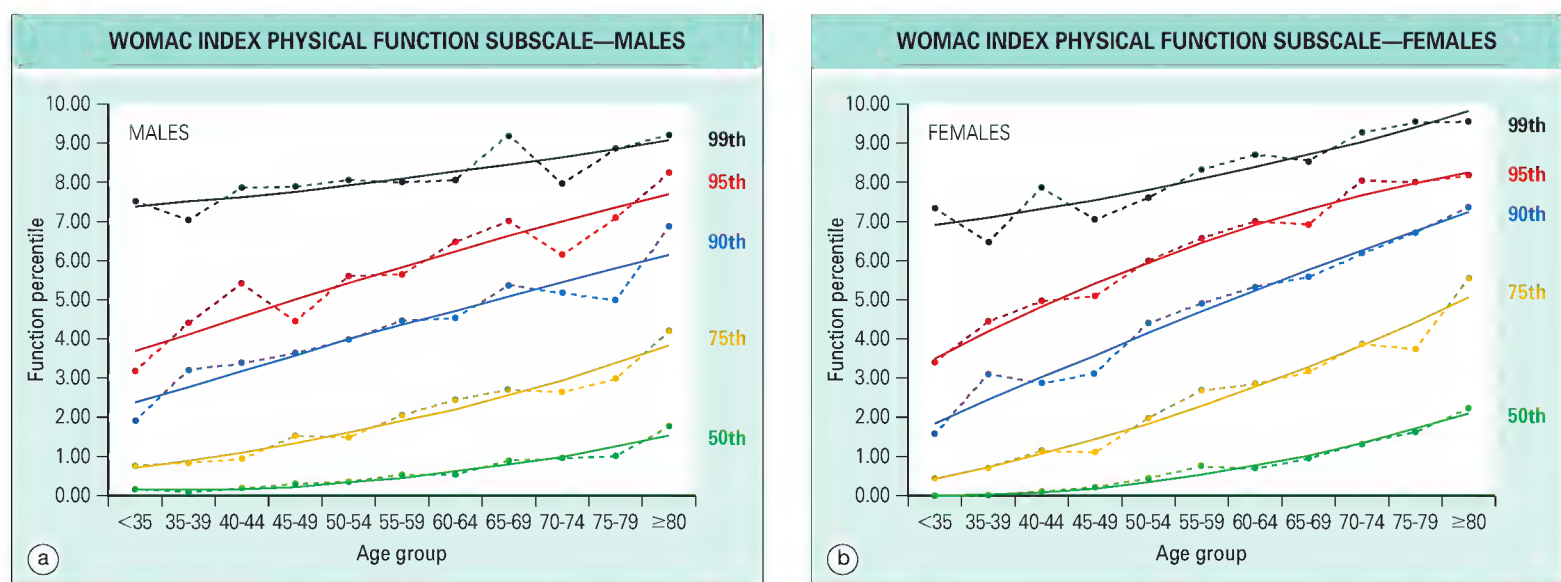


Fig. 2.4 Age- and gender-specific normative values for the Western Ontario and McMaster (WOMAC) Osteoarthritis Index Physical Function subscale based on a random sample of the general population ($n = 7336$). (From Bellamy N, Wilson C, Hendrikz J. Population-based normative values for the Western Ontario and McMaster (WOMAC) Osteoarthritis Index: part I. *Sem Arthritis Rheum* 2011;41:139-48, with permission.)

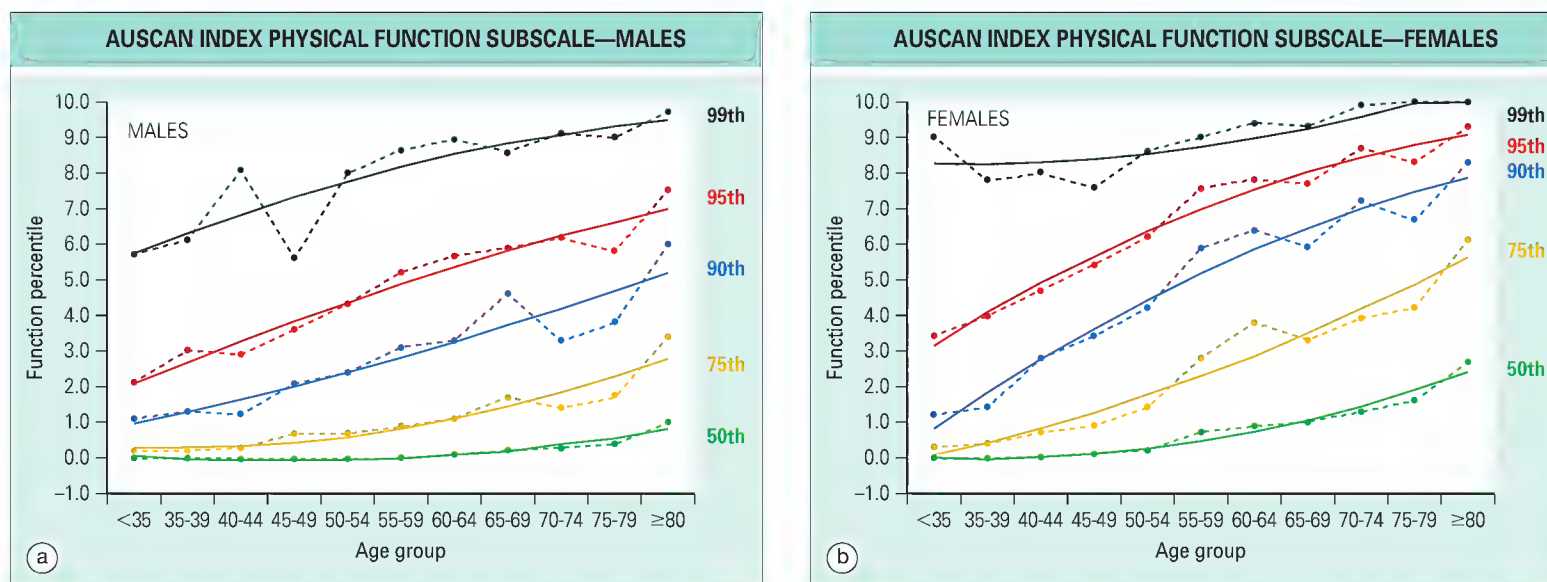


Fig. 2.5 Age- and gender-specific normative values for the Australian-Canadian (AUSCAN) Hand Osteoarthritis Index Physical Function subscale based on a random sample of the general population ($n = 7231$). (From Bellamy N, Wilson C, Hendrikz J. Population-based normative values for the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index: part 2. *Semin Arthritis Rheum* 2011;41:149-56, with permission.)

framework, and MCII and PASS estimates have been explored for AS (see Box 2.2). PASS estimates for the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and BASFI have differed for observations made on patients with AS in different countries.^{38,39}

Psoriatic arthritis

Outcome measurement in psoriatic arthritis (PsA) has undergone considerable refinement in recent years, and there are now available several instruments for evaluating different aspects of the condition.⁴⁰ Both single-domain and composite measures have been developed; the former assess only a single aspect of the condition, whereas the latter encompass more complex issues such as quality of life and disease activity.^{40,41} Consensus has been reached on core set domains for randomized controlled trials and longitudinal observational studies in PsA, namely, peripheral joint activity, skin activity, patient global assessment, pain, physical function, and health-related quality of life. In preparation for treat-to-target approaches to PsA management, a minimal disease activity definition has been proposed.⁴² Some progress has been made toward the development of response definitions for PsA-relevant outcome measures.⁴¹⁻⁴³ In mapping standard measures of functioning to the ICF framework, it has been noted that several areas of concern to patients with PsA are inadequately covered.⁴⁴

Systemic lupus erythematosus

There are several validated instruments for conducting outcome measurement in patients with SLE. Modifications of some of those measures, in particular, the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index (LAI), and Systemic Lupus Activity Measure (SLAM), have been proposed for use in SLE in pregnancy. These modifications are referred to respectively as SLEPDAI, LAI-P, and m-SLAM.

Core set domains for clinical trials and longitudinal studies have been proposed by the OMERACT group and include (1) disease activity, (2) health-related quality of life, (3) organ damage, and (4) toxicity/adverse events. The ACR has proposed response criteria for SLE clinical trials.¹ These criteria are based on absolute change, are instrument specific, and have been proposed for the British Isles Lupus Assessment Group (BILAG), SLEDAI, SLAM, European Consensus Lupus Activity Measurement (ECLAM), Safety of Estrogens in Lupus Erythematosus National Assessment Modification of SLEDAI (SELENA-SLEDAI), and Responder Index for Lupus Erythematosus (RIFLE) instruments. The criteria are in the form of threshold values for improvement and worsening. The Pediatric Rheumatology International Trials Organization and the ACR have proposed provisional response criteria for juvenile SLE based on at least 50% improvement in any two of five core set measures and with no more than one of the remaining measures worsening by more than 30%.¹ Most recently a valid and reliable responder index based on the SLEDAI-2000 has been proposed and assesses 50% or more improvement in lupus disease activity.^{45,46}

Definitions of “active disease” and minimal clinically meaningful change for the SLEDAI-2000 have also been published.⁴⁷

Systemic sclerosis

In reviewing outcome measures for clinical trials in systemic sclerosis, the OMERACT group considered that the HAQ and Scleroderma Health Assessment Questionnaire (SHAQ) were the only two patient-centered measures ready for use in clinical trials. Although the measurement of disease activity in systemic sclerosis remains challenging, the European Scleroderma Study Group has proposed preliminary activity criteria based on the summation of scores across multiple variables. In addition, estimates of minimal clinically important difference for several patient-centered outcome measures (Health Assessment Questionnaire Disability Index [HAQ-DI], fatigue, pain, sleep, patient global assessment, SF-36) have been developed based on a clinical practice setting.⁴⁸

Behçet disease

There is a paucity of measurement tools to assess disease activity and condition-specific quality of life in Behçet disease. The development and validation of the Behçet's Disease Activity Index (BDAI)¹ and the Behçet's Disease Quality of Life (BD-QoL) index¹ therefore represent important contributions to outcome measurement in Behçet disease.

Sjögren syndrome

Core set measures for Sjögren syndrome were proposed several years ago: sicca symptoms, sicca objective (oral), sicca objective (ocular), health-related quality of life, laboratory measures, and fatigue. Subsequently two indices, the Sjögren's Syndrome Disease Damage Index (SSDDI) and the Sjögren's Syndrome Disease Activity Index (SSDAI), were proposed.¹ Most recently the EULAR Sjögren's Task Force has developed two new indices, one to assess symptoms (EULAR Sjögren's Syndrome Patient Reported Index [ESSPRI]), and the other to assess disease activity (EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI]).^{49,50} Although both indices require further validation, they create novel measurement opportunities since they are based respectively on patient⁴⁹ and expert⁵⁰ opinion.

Polymyalgia rheumatica

Core set measures for polymyalgia rheumatica proposed by the European Collaborating Polymyalgia Rheumatica Group include five measures: pain, physician global assessment, morning stiffness, C-reactive protein level, and ability to elevate the upper limbs. A recent multinational collaborative evaluation of outcome measures in polymyalgia rheumatica has concluded that patient-reported global pain, hip pain, morning stiffness, physical function (Modified Health Assessment Questionnaire [MHAQ]), mental

function and an inflammatory marker are the best measures of disease activity and treatment response.⁵¹

Inflammatory myopathies

The International Myositis Assessment and Clinical Studies group has proposed three tools for the evaluation of patients with idiopathic inflammatory myopathies. These tools are the Myositis Intention to Treat Activity Index (MITAX), Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT), and Myositis Damage Index (MDI). The interrater reliability and construct validity of the MDI were confirmed in a recent evaluation.⁵² Preliminary consensus-based estimates of clinically important improvement in adult and juvenile idiopathic inflammatory myopathies have been proposed as follows: muscle strength and physical function, 15%+; physician and patient global assessment, 20%+; and serum levels of muscle-associated enzymes, 30%+. The Pediatric Rheumatology International Trials Organization and the ACR have proposed core set measures for juvenile dermatomyositis that include physician global assessment of disease activity, muscle strength, global disease activity measure, parent's global assessment of patient's well-being, functional ability, and health-related quality of life.

Vasculitis

Outcome assessment in the different pathologic entities that collectively form the vasculitides is challenging. Different conditions may require different indices and multidimensional measures to capture the impact of pathologic processes affecting different organs and structures. Attempts to develop a multisystem measure include the Combined Damage Assessment (CDA) Index for vasculitides involving small- and medium-sized vessels, Vasculitis Damage Index (VDI), and Birmingham Vasculitis Activity Score/Wegener's Granulomatosis (BVAS/WG) for evaluating patients with Wegener's granulomatosis. The reliability, construct, and discriminant validity of the BVAS/WG have been assessed and the index proposed for use in clinical investigation. In a recent comparative study, although the CDA and VDI were both reliable, the CDA was considered more complex and less practical than the VDI.⁵³ Since its inception, the BVAS has undergone revision, and version 3 has been validated for use in systemic vasculitis.^{54,55} The OMERACT group has established core set domains for clinical trials of antinuclear cytoplasmic antibody-associated vasculitis: namely, disease activity, damage assessment, PROMs, and mortality.⁵⁶

Osteoporosis

The main focus of osteoporosis studies is bone loss and fracture prevention. Core set measures for bone loss prevention studies (bone mineral density measured at two sites, biochemical markers) and fracture prevention studies (fracture; hip, knee, and spine bone mineral density; biochemical markers; change in height) in osteoporosis have been proposed by the OMERACT group. In addition, ICF core sets have been suggested for osteoporosis and the content of osteoporosis-targeted health status measures compared using the ICF framework. There are currently several condition-specific quality-of-life measures for osteoporosis, which differ in their content, format, and method of administration.⁵⁷

Low back pain

Outcomes in patients with low back pain can be assessed with various instruments as well as with quality-of-life measures. The OMERACT group has proposed preliminary response criteria (Therapeutic Responder Index [TRI]) for chronic low back pain, based on at least 30% improvements in pain and in patient global assessment and no worsening in function.¹ A further evaluation of the TRI suggests that it is particularly sensitive to the cutoff point used for improvement in the patient global assessment component.⁵⁸ MCII and PASS estimates have been explored for low back pain based on the Roland Morris Disability Questionnaire.

Fibromyalgia

The OMERACT group has developed core set domains for fibromyalgia: namely, pain, tenderness, fatigue, patient global assessment, multidimensional function, and sleep disturbance.⁵⁹ Various outcome measures have been used in fibromyalgia clinical trials.⁶⁰ An evaluation of outcome measurement performance has suggested that existing instruments adequately measure core OMERACT domains for fibromyalgia.⁶⁰ Development of a fibromyalgia responder index and disease activity score is considered both feasible and a priority.⁶⁰ Recently two responder definitions have been

proposed, both including 30% or more reduction in pain and 10% or more improvement in physical function.⁶¹ In addition, the reliability, validity, and responsiveness of the Combined Index of Severity of Fibromyalgia (ICAF) have been confirmed.⁶²

OUTCOME MEASUREMENT IN ROUTINE CLINICAL PRACTICE

For many rheumatologists in routine practice, the goal is to track efficiently the progress of individual patients, even if there is no investigational goal. In addition to the reliability, validity, and responsiveness of the measure, practitioners also value attributes such as simplicity, rapid completion, and easy scoring.⁶³

The major emphasis in musculoskeletal clinical metrology has been on the development of instruments for clinical research rather than for routine clinical purposes. The challenge now is to apply these techniques in clinical practice, in which feasibility issues become paramount (Box 2.3).

Combinations of disease-specific, generic health-related quality-of-life and global measures are particularly useful in clinical practice. Six issues of practical importance deserve special consideration:

1. Although measures of discomfort (pain), disability (function), and patient and physician global assessment are common to all rheumatic diseases, conditions with extraarticular consequences may require additional organ-specific assessments (e.g., skin scores in scleroderma).
2. Outcome measurement in children can be challenging. It is important to select scales that are valid, reliable, responsive, age-appropriate, and comprehensible in this particular group of patients.
3. In addition to defining a priori a schedule for assessing the beneficial effects of a treatment program, establishing a schedule of monitoring for adverse events, particularly for pharmacologic interventions, is equally important. Such a schedule should be capable of detecting both clinical and nonclinical (laboratory) forms of toxicity in a timely fashion.
4. Methods for handling data are important. For paper-based applications, flowcharts are particularly useful in documenting longitudinal change in clinical status as well as for charting the nonclinical (laboratory) tolerability of antirheumatic drugs. Expanding opportunities for electronic data capture are progressively solving many of the current problems with collection, storage, and analysis of quantitative data. Electronic data capture can be achieved on a variety of platforms including desktop and laptop computers, personal digital assistants, Web-based applications, and mobile telephones. Mobile telephones in particular deserve special attention because they are ubiquitous and provide opportunity for bidirectional or even multidirectional communication between patients and their health care provider(s). It should be noted that electronic data capture using mobile (cellular) phones is acceptable to patients; produces valid, reliable, and responsive data showing high levels of correlation with paper-based counterparts; can be achieved remotely, independently, and repeatedly; is able to transmit data over long distances directly into a host server

BOX 2.3 REQUIREMENTS OF AN OUTCOME MEASURE FOR CLINICAL PRACTICE APPLICATION

Clinimetric requirements

- Validity, reliability, responsiveness

Feasibility requirements

- Ease of administration, quick to complete, affordable, low burden on health care recipient and health care providers, provides information contemporaneous with patient provided interaction, aligned with other aspects of clinical record keeping

Relevance requirements

- Provides clinically relevant information that can underpin shared goal setting and decision-making

Interpretation requirements

- Provides observations that can be contemporaneously benchmarked against relevant prior assessments and can be indexed against appropriate response, state-attainment criteria, and normative benchmarks

for instant archiving; and can be conducted with a variety of commonly available mobile (cellular) phones.⁶⁴⁻⁶⁶

5. The concomitant use of disease-specific patient and physician global assessments and generic health-related quality-of-life measures provides a particularly powerful combination. In inflammatory polyarthritis these measures can readily be supplemented by an articular index in the form of a simple count of tender and swollen joints.
6. The development of responder criteria, state-attainment criteria, and normative data is an important step in the transfer of measurement procedures used in research environments into routine clinical practice. They permit clinical benchmarking and thereby facilitate data interpretation. Some of the proposed benchmarks should permit more effective monitoring of patient progress and response to treatment (Fig. 2.6).

Implementation of what might be termed *quantitative rheumatology* may require the development of new instruments or modifications to existing instruments, measurement and data-handling processes, and analysis, interpretation, and communication procedures to meet the demands of routine clinical practice. However, there is no reason to delay using some of the shorter, user-friendly, patient self-administered questionnaires and emerging technologies currently available. The ability to quantitate the clinical condition provides patients, medical practitioners, allied health professionals, third-party payers, and litigators with much important and useful information. Furthermore, proposed definitions of response and state attainment, the elaboration of general population-based normative values, and innovations in electronic data capture all contribute to an expanding capability to collect and interpret health status information in a manner capable of informing shared decision-making and goal setting in clinical practice, and the evaluation of new interventions and therapeutic strategies in clinical research.

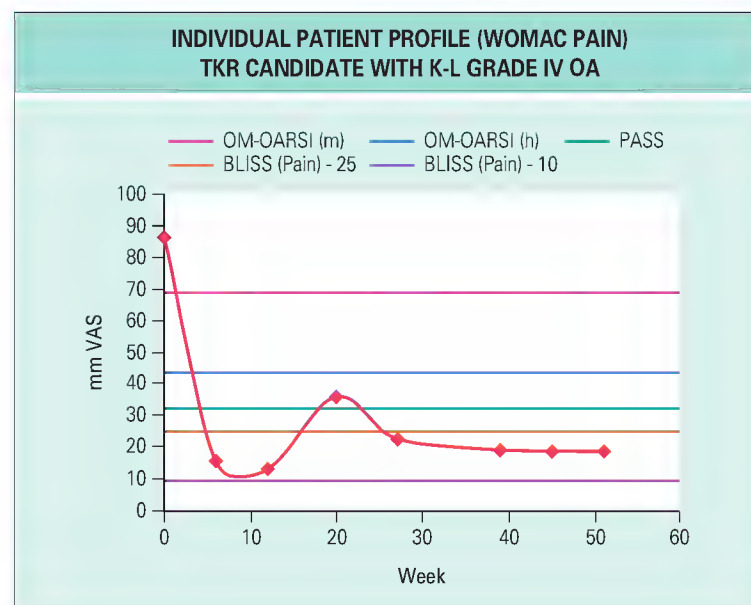


Fig. 2.6 Response to treatment in osteoarthritis (OA) can be monitored over an extended period by a combination of responder and state-attainment criteria. BLISS, Bellamy Low-Intensity Symptom State-Attainment Index; K-L, Kellgren-Lawrence; OM-OARS, Outcome Measures in Rheumatology Clinical Trials—Osteoarthritis Research Society International; PASS, Patient-Acceptable Symptom State; TKR, total knee replacement; WOMAC, Western Ontario and McMaster Osteoarthritis Index; VAS, visual analogue scale.

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3

Principles of health economics and application to rheumatic disorders

■ JOHN B. WONG

- Economic analyses in medicine include cost, cost-benefit, cost-effectiveness, and cost-utility analysis.
- The most commonly used method in health care is cost-utility analysis, often for health technology assessment to determine the most efficient use of resources.
- Beyond cost-effective use of resources, however, equity issues and budget impact analyses affect policymaker decisions.
- For physicians, these economic analyses can help inform cost-effective care, such as in the management of rheumatoid arthritis and osteoarthritis and the assessment of the risk of fragility fractures in osteoporosis.

INTRODUCTION

Excellence in the art of medicine involves making optimal decisions. Physicians make implicit or explicit choices to treat, to test, or to do neither to each patient based on that patient's unique circumstances. They also consider the safety, efficacy, adverse effects, and indications for medications, and the sensitivity, specificity, harms, and indications for diagnostic and prognostic tests. With the recent growth in novel drugs, medical devices, tests, and imaging modalities, health care costs have risen substantially worldwide, so increasingly, physicians recognize that they should incorporate economic considerations into their medical decision-making. Besides efficacy as determined by randomized controlled trials and effectiveness as determined by observational studies, physicians increasingly must also be knowledgeable about costs.

Simply considering costs, however, does not provide a measure of value or the health benefit attained; that is, does the intervention provide an efficient use of societal resources? Driven in part by advances in health care technology, such as biologic treatments for rheumatoid arthritis (RA),¹ medical care costs account for a growing proportion of each country's gross domestic product.^{2,3} Economists consider the *opportunity costs* of those expenditures; that is, would society have gained greater benefit from spending some of those health care dollars instead on education, social welfare, environment, defense, or an alternative societal investment?² The same thinking applies to societal benefits of spending on rheumatic disorders as opposed to other conditions. Thus health economics seeks to determine the optimal use of societal resources by assessing the value obtained from alternative uses for those resources.

This chapter discusses the basic concepts of economic analysis including cost-effectiveness analysis for health technology assessment followed by applications of these principles in rheumatology.

CONCEPTS OF HEALTH ECONOMIC ANALYSIS

Types of costs

Costs are usefully divided into four main types, which are described in [Box 3.1](#).

Perspectives

Economic analyses may be done from a variety of perspectives, which then affects the types of costs considered and the time frame of the analysis. These perspectives are listed in [Table 3.1](#).^{4-6,8}

Types of economic analysis

Cost analysis

Cost analysis (also called *cost minimization*, *cost identification*, or *cost consequence*) measures the economic burden incurred by a disease or treatment.^{6,9} Typical costs include direct medical and health care costs, costs associated with adverse effects, savings from prevention or alleviation of disease, and possibly costs of additional disease from prolonged life expectancy, but these costs may vary depending on the analytic perspective and time frame.³ In cost analysis, alternative strategies are demonstrated or assumed to be equivalent, so this kind of analysis provides no measure of the resulting health outcomes and simply identifies the optimal strategy by determining the "cheapest." Because alternative health interventions rarely have the same effectiveness, cost analysis is an uncommon health economic analysis.

Cost-benefit analysis

In cost-benefit analysis, all costs and health benefit outcomes are expressed in terms of a single monetary attribute, for example, dollars.^{3-6,9} Costs are determined as with cost minimization, but in addition health benefits are translated into a monetary amount. Thus cost-benefit analysis provides a measure of absolute economic cost and absolute economic benefit. Each strategy is compared with current practice, so cost-benefit analysis results may be expressed as a ratio of costs to benefits or more preferably summed to yield the *net present value*. If the net present value is positive, then savings from benefits exceed the cost of expenditures, so policymakers could simply pick those strategies with the highest net present value when choosing which programs to fund. Although many applied economists view cost-benefit analysis as the gold standard,¹⁰ it is not as well accepted in health care because of difficulties associated with placing a monetary value on health benefits, that is, human life outcomes.

Cost-effectiveness analysis

To avoid the difficulties associated with placing a monetary value on human life, cost-effectiveness analysis (or a subset called *cost-utility analysis*) has become the most prevalent form of economic analysis in health care. Costs continue to be expressed in the same unit, but benefits are expressed as a meaningful clinical outcome (e.g., satisfaction of the American College of Rheumatology 20% improvement criteria [ACR20]).^{5,6,9} In cost-effectiveness analysis, dividing the cost of the intervention by its effectiveness yields the *average cost-effectiveness ratio*.¹¹ However, for technology assessment, the average cost-effectiveness ratio can be misleading (see RA example later), so the preferred outcome measure is the *incremental cost-effectiveness ratio* (ICER; also called *marginal cost-effectiveness ratio*) comparing two alternative strategies ([Fig. 3.1](#)).^{6,9,11} It divides the additional cost of the new intervention by its additional clinically meaningful benefit, which results in one of four possible outcomes (see [Fig. 3.1](#)): (1) higher costs and lower effectiveness when the new strategy is *dominated* or *inferior*; (2) lower costs and higher effectiveness when the new strategy is *dominant* or *cost saving*; (3) lower costs and lower effectiveness (rare); and (4) higher costs and higher effectiveness. For the last two situations, an ICER can be calculated, for example, the incremental cost to obtain one more ACR20 response.

Policymakers should not adopt new strategies that are dominated but should adopt those that are cost saving. Typically, however, if something is more effective, then it usually costs more; so among these more common strategies, policymakers could then choose to fund those interventions that fall below an acceptable range called the societal *willingness to pay*; that is, those that supply sufficient value for which the benefit is judged to be worth the additional cost. For example, an ICER of \$1 to achieve an additional ACR20 may be acceptable, but \$1 million to achieve one additional ACR20 may not be.

BOX 3.1 TYPES OF HEALTH COSTS

- **Direct medical costs** include resources required to provide care such as hospitalizations, procedures, surgeries, outpatient office visits, rehabilitative and nursing home care, care by physician and allied health professionals, medications, devices, equipment, supplies, and tests.⁴⁻⁶
- **Direct nonmedical costs** reflect out-of-pocket patient costs and include the following:
 - *Patient time costs* for the time spent seeking or participating in care
 - *Marketed care giving* for out-of-pocket cost to receive family care
 - *Unmarketed care giving* for informal care giving
 - *Transportation and nonmedical services* for travel, lodging, home aids, or special food, and clothing
- **Productivity costs** are time costs frequently called *indirect costs* and refer to loss of employment due to morbidity (disability, absenteeism, reduced productivity while working) or mortality (reduction in life expectancy).^{4,6} For example, the families of children with juvenile rheumatoid arthritis spent 5% of their income on out-of-pocket medical and nonmedical costs and lost salary.⁷
- **Intangible costs** include pain, suffering, and fear for the illness or its treatment.⁵⁻⁶

TABLE 3.1**Perspectives of health costs**

Perspective	Includes
Patient	Direct nonmedical costs not covered by insurance, such as any copayments for drugs, over-the-counter medications, devices, office visits, and indirect costs
Hospital	Direct and direct nonmedical costs during a hospitalization
Payer	Excludes patient out-of-pocket costs and indirect costs
Societal	Direct medical, direct nonmedical, and indirect costs and a lifetime time frame

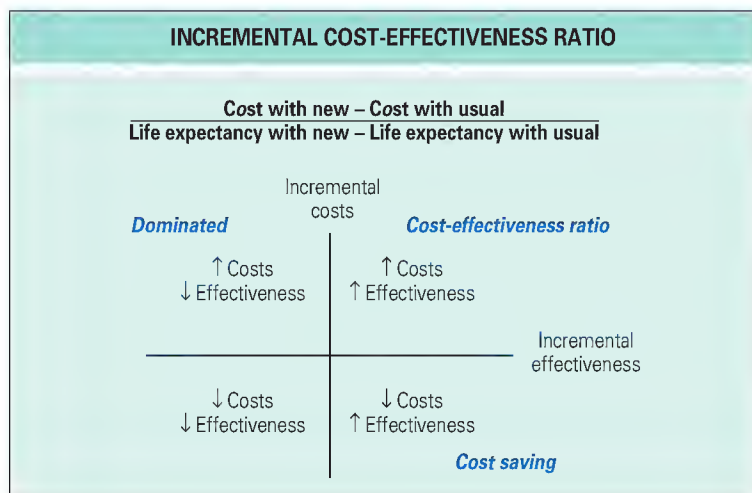


Fig. 3.1 The incremental cost-effectiveness ratio (ICER) describes the additional cost and the additional benefit obtained from a new intervention compared with standard of care. When the net cost and net benefit are considered, the new intervention may cost more or less and may yield more benefit or less, thereby yielding differences that fall into one of four quadrants. Dividing the net cost by the net benefit yields the cost to achieve one additional benefit (the ICER).

Cost-utility analysis

To avoid the difficulties associated with comparing alternative effectiveness measures in cost-effectiveness analyses—for example, cost to achieve an ACR20 response versus cost to avoid a myocardial infarction—cost-utility analysis uses a standardized effectiveness measure, namely length and quality of life, usually expressed as quality-adjusted life-years (QALYs). In

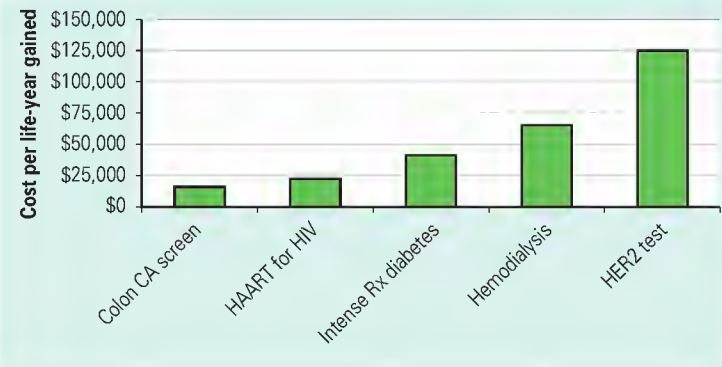
INCREMENTAL COST-EFFECTIVENESS RATIOS FOR TREATMENTS

Fig. 3.2 Published incremental cost-effectiveness ratios (ICERs). The graph displays published incremental cost-effectiveness ratios for five interventions: colon cancer (CA) screening with colonoscopy, highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) infection, intense treatment (Rx) for diabetes mellitus, hemodialysis for end-stage renal disease, and testing of metastatic breast cancer patients for tumor HER2 protein overexpression or gene amplification and treatment with trastuzumab when results are positive. Lower ICERs indicate more efficient use of resources; that is, more “bang for the buck.”

such a case, the incremental cost-effectiveness of coronary stenting for myocardial infarction could be compared with that of biologic therapy for RA because both would be expressed as cost per QALY gained (the additional cost to increase life expectancy by one QALY). Approving or funding those interventions that are cost-saving or those that have the lowest ICER would provide society with the greatest benefit for a given expenditure. A league table illustrates how a policymaker might use such information to determine value and funding priorities.¹²⁻¹⁶ For example, if a payer had \$1 million to spend, spending that amount on colon cancer screening would yield 66 QALYs (\$1 million ÷ \$15,100 per QALY gained) for the population as opposed to 8 QALYs (\$1 million ÷ \$125,000 per QALY gained) with HER2 testing and treatment with trastuzumab, a monoclonal antibody for breast cancer (Fig. 3.2).^{12,16}

Quality of life

Of particular relevance in rheumatology, patients, physicians, and policymakers increasingly recognize the importance of quality of life to account for disease morbidity, in addition to length of life. Quality of life is typically scaled from 1 for perfect health to 0 for death, so individuals with morbidity receive only partial credit for each year that they are alive.¹⁷ For example, if the quality-of-life adjustment factor is 0.4 for severe disability, patients with severe disability who live for 10 years receive credit for living 4 quality-adjusted years, so a treatment that prevents this severe disability potentially increases QALYs by 6 years. For diseases with a low quality of life, interventions that prevent or restore quality of life then have more opportunity to provide economic value by adding “life” to years instead of adding years to life. Thus, in cost-utility analysis, the outcome measure is the incremental cost to increase life expectancy by one “QALY gained,” which is equivalent to increasing life expectancy by 1 year of perfect health.

Time horizon and discounting

The time horizon for the economic analysis refers to the time period under consideration, which may range from short, for example during hospitalization, to lifelong or lifetime (or in between) depending on the perspective. When longer time horizons are examined, present costs are typically more valuable than future ones, not simply because of inflation but also because present expenditures could alternatively be invested productively to yield a larger future amount.

For example, given a choice between being given \$100 now or \$100 a year from now, most individuals would prefer to receive that money now.¹⁷ Hence, the \$100 a year from now is worth less now; it has a lower *discounted* present value. How much less depends on the annual discount rate, which varies by country. In the United Kingdom, the rate is 3.5%, and in the United States it is 3%,¹⁷ so \$100 a year from now has a present-day worth of \$97.09 in the United States and \$96.62 in the United Kingdom.

Reflecting the higher present value of money, discounting is consistent with health care policies hoping to minimize current fiscal year drug budgets and is particularly relevant for preventive treatments because treatment occurs now and disease complications occur in the future. For example, the cost of biologic therapies for patients with RA occurs now, but disability or expensive joint replacement costs occur in the future. When a 3% annual discount rate is used, spending \$10,000 this year would be comparable to spending only \$7441 in 10 years and \$5537 in 20 years.⁵ Similarly, because costs are discounted, health benefits are also discounted, so future health benefits are valued less than benefits that would accrue now (Box 3.2).

Reference case

To reduce methodologic variability in economic evaluations, the U.S. Panel on Cost-Effectiveness Analysis in Health and Medicine in 1996 established a *reference case* set of minimum standards that included the societal perspective, reasonably long time horizons, ICERs, QALYs, discounting, and sensitivity analyses to assess the robustness of the results.^{4,8} Within rheumatology, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group has proposed additional methodologic guidance.¹⁸⁻²²

Health technology assessment

Over the past 20 years, health technology assessment (Fig. 3.3) to inform health policy and clinical decision making has grown worldwide as a multidisciplinary systematic approach to assess the introduction of, access to, and diffusion of innovative health technologies, including medications, devices, diagnostics, and treatments. As one example, the United Kingdom's National Institute for Health and Care Excellence (NICE) bases national funding or reimbursement recommendations regarding new and existing medicines on a review of clinical and economic evidence. The evaluation of clinical evidence assesses how well the drug works, and the evaluation of the economic evidence determines how well the drug works relative to its costs, or, succinctly, whether the drug provides sufficient value for its cost.

BOX 3.2 KEY MESSAGE

The incremental cost per quality-adjusted life-year gained can be considered to be equivalent to the present cost (in current year or year in which the analysis was performed) to increase life expectancy by a year of perfect health in that same analysis year.

NICE recognizes an evidence hierarchy with a preference for direct head-to-head randomized controlled trial efficacy studies and indirect comparisons as a second choice. However, because NICE also appreciates the limitations of such efficacy studies—namely, selected populations, short-time spans, and limited comparators—it also acknowledges the need to supplement efficacy studies with good-quality observational or effectiveness studies. The economic evidence considers a societal perspective and a lifetime time horizon to account for future benefits and economic savings or expense. Because randomized trials have limited follow-up, achieving the lifetime time horizon involves computer simulation modeling of the relevant disease and treatments including mortality as might occur from the disease or treatment in addition to that in an age-, sex-, and race-matched general population with morbidity from the disease or treatment represented by quality-of-life adjustments, and societal costs.

Decision analysis modeling

Despite rigorous systematic reviews of efficacy and effectiveness of health care interventions, patients, providers, and policymakers may remain in doubt about what they should do because of uncertainty, tradeoffs, and values. First, residual uncertainty may remain regarding meaningful patient-relevant outcomes because of reliance on surrogate outcome measures or limited follow-up time or use of subgroups with an inadequate sample or restrictive inclusion and exclusion criteria during the randomized controlled trials. Second, treatment decisions often involve tradeoffs. Treatment benefits may occur, but harms may also ensue. Thus optimal decision-making for individuals may depend on their values (or preferences) regarding the outcomes, and those values and preferences may vary widely in a population. Decision and cost-effectiveness analyses typically invoke a prescriptive, normative approach to decision-making in the face of uncertainty by explicitly structuring decisions into (1) choices (alternative treatment strategies), (2) chances (the likelihood of outcomes resulting from the choices), and (3) consequences (valuation of the outcomes in terms of mortality, morbidity, and costs). The decision models then calculate the costs and utility of each treatment and the difference between the alternatives as an extension (or decline) in life expectancy or quality (morbidity)—adjusted life expectancy and increase or decrease in costs.

The most commonly used computer simulation model is a Markov or Monte Carlo simulation, in which a predefined and mutually exclusive set of health states represent the natural history of disease.²³ The patient cohort starts the simulation in a health state such as Well or a set of health states (e.g., some Well and others Sick). Time is divided into ticks of the clock represented by Markov cycles of a specified duration (e.g., 1 year). Over time, patients move among these health states; some may die, become sick, or maintain their same state of health. The simulation continues until all

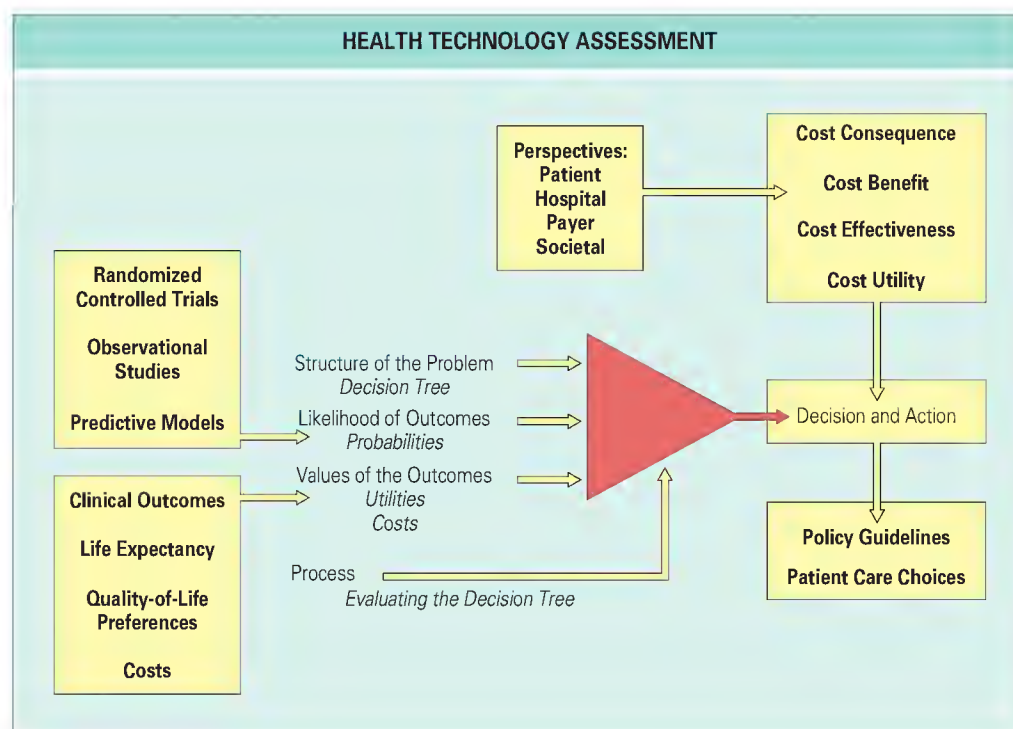


Fig. 3.3 The boxes on the left represent sources of data and information regarding health interventions natural history of a disease to assess the chances of disease incidence and progression, and testing or treatment benefit and harm coupled with health outcomes, length of life, costs, and quality of life. For each strategy, the likelihood of the resulting outcomes (probabilities) are then coupled with the value of the outcomes to determine the costs and effectiveness, which leads to a decision and action that forms health policy and patient care choices. The boxes at the top represent potential perspectives for the analysis and the four main types of economic analysis that can also inform the decision and action.

TABLE 3.2
World Health Organization cost-effectiveness thresholds based on per capita gross domestic product

Region	Subregions—patterns of child and adult mortality*	Example country within region	2005 cost-effectiveness threshold (US\$)
Afro (Africa)	D, E	South Africa	6,000
Amro (Americas)	A, B, D	United States (A)	120,000
Emro (Eastern Mediterranean)	B, D	Saudi Arabia	31,000
Euro (Europe)	A, B, C	United Kingdom (A)	90,000
Searo (Southeast Asia)	B, D	Thailand	15,000
Wpro (Western Pacific)	A, B	China	21,000

The threshold for high cost effectiveness equals the cost-effectiveness threshold divided by 3 (e.g., \$40,000 for the United States and \$30,000 for the United Kingdom).
*Each region is divided into subregions based on patterns of child and adult mortality in groups ranging from A (lowest) to E (highest).
Data from World Health Organization. Table: threshold values for intervention cost-effectiveness by region. 2005. Available at www.who.int/choice/casts/CER_levels/en/index.html. Accessed February 10, 2013.

patients in the cohort die or until a fixed time has elapsed. By tracking survival, quality of life, and costs for each cohort member, the Markov model estimates life expectancy, quality-adjusted life expectancy, and life-time costs. By accounting for the time elapsed, these disease models can discount both costs and quality-adjusted life expectancy. In such models, innovative treatments may provide value by prolonging life (e.g., decreasing the risk of dying after becoming sick), by decreasing the likelihood of becoming sick (e.g., preventing morbidity, improving quality of life), and by lowering disease costs through avoidance or delay of expensive disease complications (e.g., surgery).

Cost effectiveness

How much one is willing to pay for something depends in part on one's financial situation. Similarly, for health care policymakers, what is considered to provide value or to be "cost effective" may depend on each country's economy and its willingness to pay for that benefit. Consequently, the World Health Organization (WHO) bases cost effectiveness on the country's economic status as measured by that country's gross domestic product.²⁴ According to WHO, an intervention is considered to be cost effective if the incremental cost-utility ratio falls below three times that country's per capita gross domestic product. An intervention is highly cost effective if the ratio falls below that country's per capita gross domestic product. WHO has established cost-effectiveness thresholds for six regions based on their per capita gross domestic product (Table 3.2).²⁵

For comparison, although some recommend \$100,000 or even \$300,000 thresholds in the United States,²⁶ the frequently cited cost-effectiveness threshold is \$50,000 per QALY gained, which is similar to the WHO threshold for "high cost effectiveness." In the United Kingdom, NICE methods guidance suggests a threshold of £20,000 to £30,000²⁷ (about €25,000 to €35,000, or \$40,000 to \$56,000) per QALY, similar to the "highly cost-effective" WHO UK threshold, but as in the United States, some recommend raising it to £70,000 (\$110,000).²⁸

Raising the willingness-to-pay threshold not only expands the number of treatments that become "cost effective," but also has implications for the benefit per expenditure. For instance, spending \$100,000 on strategies with an ICER of \$100,000 per QALY gained would buy 1 year, whereas spending it on those with an ICER of \$50,000 per QALY gained would yield 2 years. In particular, policymakers should consider whether these last few dollars spent "at the margin" on health care treatments with higher ICERs would yield greater societal benefit if spent elsewhere.

Budgets

In addition, allocating resources strictly on a cost-effectiveness basis does not account for yearly budgets because these cost-effectiveness analyses consider a lifetime time horizon, including future cost savings from disease prevention or reduction in morbidity or mortality. For maximally efficient resource allocation, policymakers would establish their health care budget for the fiscal year, and then treatments would be funded going in order from cost-saving ones to those with the lowest incremental cost-effectiveness ratios up to those with the highest while accounting for their budget impact (based on next year intervention costs, disease prevalence, treatment eligibility, and available health delivery infrastructure) until the budget is entirely expended. In this case, the societal willingness-to-pay threshold would be

TABLE 3.3
Analysis on treatment sequences of disease-modifying antirheumatic drugs

Strategy	Example
Monotherapy	DMARD monotherapy (e.g., methotrexate followed by sulfasalazine)
Steroid	Glucocorticoids with DMARD monotherapy (e.g., methotrexate)
Parallel	Two or more DMARDs (e.g., TICORA2 triple therapy arm)
Step up	One or more DMARDs added to prior monotherapy (e.g., BeSt step-up arm or TICORA routine arm)
Step down	Parallel DMARDs with subsequent removal of DMARDs (e.g., COBRA, Fin-RACo trials)
Intensive	DMARD doses rapidly increased to reduce the Disease Activity Score and keep it at low levels of activity (e.g., TICORA and TICORA2 intensive arms)

COBRA, Combinatie therapie Bij Reumataide Artritis (Dutch for combination therapy for rheumatoid arthritis); DMARDs, disease-modifying antirheumatic drugs; Fin-RACo, Finnish Rheumatoid Arthritis Combination Therapy (trial); TICORA, Tight Control for Rheumatoid Arthritis (study).

the funded intervention that had the highest ICER. However, policymakers may also consider other attributes such as equity or fairness, the distribution of benefits to some and not others.¹¹

ECONOMIC APPLICATIONS IN RHEUMATIC DISEASES

Rheumatoid arthritis

As examples of applications of these economic principles, NICE has used the approach outlined earlier in health technology assessment to examine rituximab (which was recommended),²⁹ certolizumab pegol (which was not recommended),³⁰ and abatacept (which was not recommended for refractory RA).³¹ For active RA, NICE recommends adalimumab, etanercept, or infliximab but only if the Disease Activity Score (DAS28) exceeds 5.1 on at least two occasions that are at least a month apart and if patients have tried two disease-modifying antirheumatic drugs (DMARDs) including methotrexate.³²

To explore economic evaluation in more detail, the National Collaborating Centre for Chronic Conditions (NCCCC), which is an independent body funded by NICE, has developed a national clinical guideline for RA.³³ The guideline process takes into account economic considerations as recommended by the Grading of Recommendations Assessment, Development and Evaluation (or GRADE) Working Group. The clinical guideline group sought to examine the introduction and optimal sequencing of DMARDs in their translation of evidence into recommendations. Seeking to focus less on particular drugs and more on treatment sequences, their analysis considered six strategies (Table 3.3).

TABLE 3.4

Incremental cost effectiveness of six alternative rheumatoid arthritis treatment strategies from lowest to highest lifetime costs

Strategy	Lifetime cost (US\$)	Quality-adjusted life expectancy (years)	Incremental cost (US\$)	Incremental quality-adjusted life expectancy (years)	Incremental cost-effectiveness (\$ per quality-adjusted life-year gained)
Step down	78,158	15.32			
Step up	81,266	11.91	3,107	−3.41	Dominated*
Parallel	88,917	13.42	10,758	−1.90	Dominated*
Monotherapy	89,594	13.73	11,435	−1.59	Dominated*
Steroid	91,949	11.79	13,790	−3.53	Dominated*
Intensive	97,674	15.77	19,515	0.45	27,104

*Dominated by step down because it costs more yet yields lower quality-adjusted life expectancy than step down.

Trials with similar strategies were combined in a network meta-analysis of 13 randomized controlled trials to estimate the relative ACR20 and ACR50 efficacies of these alternative strategies. Treatment withdrawal rates were also based on these randomized controlled trials. Poorer Health Assessment Questionnaire (HAQ) scores were translated into lower quality of life (from 0.857 for quality of life for HAQ score of less than 0.25 to 0.034 for quality of life for HAQ score of more than 2.75 to 3) and into higher resource use (in terms of frequency of hospitalizations and office visits and the likelihood of joint replacements). Drug costs were based on the literature and national unit costs.

The computer model simulated the prognosis and costs for an individual patient (based on age, sex, and HAQ score) selected from the UK RA survey. An exact hypothetical clone of that patient was treated using each of the six treatment strategies. Over the initial 6-month period, that patient may have had a response (ACR20 or ACR50) or no response. A random number generator applied to the likelihood of each of these responses determined which path the patient took. ACR20 or ACR50 responses led to improved HAQ scores initially, but with continued therapy, HAQ scores gradually worsened until therapy was withdrawn due to loss of efficacy or an adverse event. The patient's HAQ score then worsened by the same amount by which it initially improved, and the patient then started the next therapy in that patient's particular strategy. Patients who did not respond initially moved on to the next therapy in their sequence. After two DMARD failures, a patient received biologic therapy. The simulation was continued for each patient until death. By tracking cost, quality of life, and length of life for each 6-month period for each patient over time, the computer simulation calculated quality-adjusted life expectancy and cumulative lifetime costs for each strategy for that patient. When the simulation for one patient was completed, a second hypothetical patient was then analyzed.

Table 3.4 displays the results for 100 patients run through 1000 simulations with cost converted into U.S. dollars (assuming \$1.60 = £1 here and below). To calculate the ICERs, strategies are rank-ordered from lowest to highest cost. The additional cost (incremental cost) and benefit (incremental effectiveness) compared with the next cheapest strategy is then calculated. When a strategy is more expensive but less effective (with lower quality-adjusted life expectancy), then the incremental effectiveness is negative and that strategy is “dominated” or inferior to the cheaper one and should not be considered. The next more expensive strategy is then compared with the cheaper nondominated strategy. In Table 3.4, all strategies are “dominated” by the step-down strategy except for the intensive strategy, which has an ICER of \$27,104 per QALY gained compared with the step-down strategy, falling within the WHO range considered highly cost-effective in the UK and also within the range that is likely acceptable for NICE.

Osteoarthritis

The UK NCCCC has also developed a national clinical guideline for osteoarthritis.³⁴ The guideline compared the cost effectiveness of nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors with placebo or acetaminophen for 3 months in 55-year-olds with osteoarthritis symptoms by considering the drugs' cost, gastrointestinal adverse events (dyspepsia, gastrointestinal bleeding, ulcer), cardiovascular adverse events (myocardial infarction, stroke, heart failure), and effectiveness as measured by a meta-analysis examining Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index scores, which were then translated into quality-of-life values. To mitigate gastrointestinal risk, NSAIDs in combination with proton pump inhibitor (PPI) strategies were also considered. Fig.

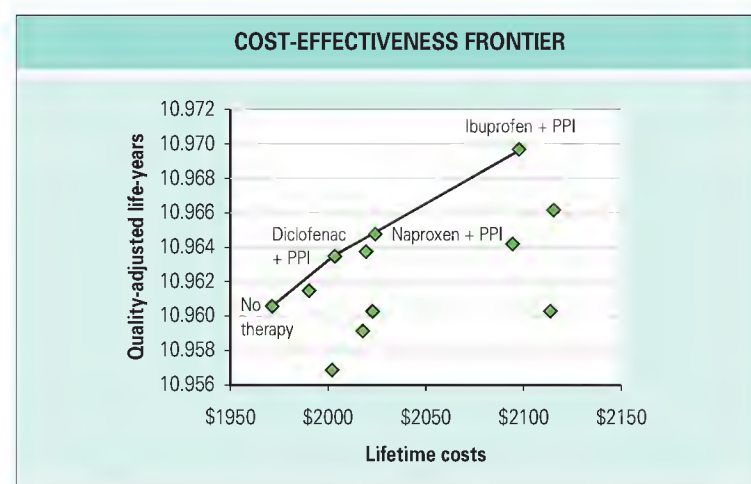


Fig. 3.4 Each diamond represents the unique combination of lifetime costs and quality-adjusted life expectancy (QALE) for each nonsteroidal antiinflammatory drug therapy with or without a proton pump inhibitor (PPI). The line represents all of the nondominated strategies at the cost-effectiveness frontier. All strategies that fall below the line (not identified for clarity) are either dominated (cost more and have lower QALE) or are weakly dominated (less efficient use of resources); for example, naproxen + PPI. Notice that moving toward the right, the cost-effectiveness frontier line flattens as the incremental cost-effectiveness ratio rises, which demonstrates that these strategies are a less efficient use of resources than those on the left side of the frontier.

3.4 displays the results as a *cost-effectiveness frontier*. All strategies falling below the frontier are inferior, either dominated (more expensive and less effective) or a less efficient use of resources, termed *extended* or *weak dominance*.

As an illustration of extended or weak dominance (Table 3.5), spending \$1 million on naproxen + PPI extends population prognosis by 6.3 QALYs (\$1 million ÷ \$160,000), but spending \$1 million on ibuprofen + PPI extends population prognosis by 18.9 QALYs (\$1 million ÷ \$52,800). Because 18.9 QALYs with ibuprofen + PPI exceeds the 6.3 QALYs with naproxen + PPI, by extended dominance naproxen + PPI should not be considered because it would be a less efficient use of resources (it would yield fewer life-years). Consequently, ibuprofen + PPI is compared with diclofenac + PPI when its ICER is calculated.

The previous analyses consider economic costs, but the numerator could also be harm. For example, in the same analysis, the guideline provides the likelihood of gastrointestinal events per 10,000 person-years. When gastrointestinal events are substituted for costs, celecoxib + PPI becomes the dominant strategy because it yields the lowest risk of gastrointestinal events (even lower than placebo or acetaminophen) and yields the highest quality-adjusted life expectancy. On the other hand, when cardiovascular events are considered, celecoxib + PPI, compared with ibuprofen + PPI, results in an additional 25,800 cardiovascular events for every QALY gained by the population. These cardiovascular and gastrointestinal analyses, however, focus

TABLE 3.5
Incremental cost-effectiveness with extended dominance (excluding a weakly dominated strategy that is a less efficient use of resources)

Strategy	Lifetime cost (US\$)	Quality-adjusted life expectancy (years)	Incremental cost (US\$)	Incremental quality-adjusted life expectancy (years)	Incremental cost effectiveness (\$ per quality-adjusted life-year gained)*
Didofenac + PPI	2003.20	10.9635			
Naproxen + PPI	2019.20	10.9638	48.00	0.0003	160,000
Ibuprofen + PPI	2024.00	10.9648	4.80	0.0010	52,800
Didofenac + PPI	2003.20	10.9635	32.00		
Naproxen + PPI	2019.20	10.9638	48.00	0.0003	Weakly dominated
Ibuprofen + PPI*	2024.00	10.9648	52.80	0.0013	16,000

**Because naproxen + PPI is weakly dominated, ibuprofen + PPI is compared with didofenac + PPI. PPI, proton pump inhibitor.*

only on harm. For comparison, the previous quality-adjusted life expectancy analysis combines the cost of these complications and their quality of life impact as well as their effect on osteoarthritis.

Osteoporosis

Finally, the NCCCC has also developed a national clinical guideline for osteoporosis: assessing the risk of fragility fracture.³⁵ The use of risk assessment tools to determine susceptibility to fracture requires physician time but may be beneficial by facilitating prevention of fragility fractures. However, if the risk assessment tool overestimates fracture risk, then treatment and its cost may be unnecessary. Alternatively, if the risk assessment tool underestimates fracture risk, beneficial preventive treatment would be omitted, which could lead to preventable hospitalization costs and morbidity.

In a cost analysis, the guideline compared the cost of bone mineral density scanning for all patients with the cost of determining a risk score followed by bone mineral density scanning only if the score is positive. The analysis considered both the FRAX and QFracture tools, with negligible cost difference between the two. For comparison, physician time to perform the risk assessment was \$58 versus \$123 for the bone density scanning. Additional consultation time for conveying results and discussion of treatment was also considered. The cost minimization analysis determined when the cost of using the risk score for screening would equal the cost of bone

density scanning for all patients. For example, in simplistic terms, if all patients have a positive screening result when risk is scored, then risk screening adds unnecessary cost (physician time) that can be avoided by directly referring all patients for bone density scanning. Conversely, if no risk-screened patients are referred for bone density scanning, then bone density screening for all will be a needless cost. The analysis found that if fewer than 68% of patients undergoing the FRAX and QFracture risk stratification process were referred for bone density scanning based on positive screening results, then risk stratification would be less costly than performing bone mineral density testing for all.

CONCLUSION

Economic analyses in medicine include cost minimization, cost-benefit, cost-effectiveness, and cost-utility analyses. The most commonly applied method in health care is cost-utility analysis, which is often used for health technology assessment to determine the most efficient use of resources. Beyond cost-effective use of resources, however, equity issues and budget impact analyses affect policymaker decisions. For physicians, these economic analyses can help inform cost-effective care, such as in determining treatment strategies in RA and osteoarthritis, and assessing the risk of fragility fractures in osteoporosis.

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4

The synovium

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- Synovium lines diarthrodial joints, tendon sheaths, and bursae.
- Specialized functions of synovium include nonadherence, control of synovial fluid volume and composition, and chondrocyte nutrition.
- The normal synovium expresses low levels of proinflammatory cytokines and some anti-inflammatory cytokines. In addition, the low levels of expression of RANKL (receptor activator of nuclear factor κ B ligand) with high levels of expression of OPG (osteoprotegerin) result in a low RANKL-OPG ratio that suppresses osteoclast formation. This balance is likely to be important in maintaining homeostasis in the normal, noninflamed synovium.
- Cadherin-11 expression by synovial fibroblasts may be critical for the development of the synovial lining by facilitating cellular organization, compaction, and matrix development.

DEFINITIONS

Synovium is the soft tissue lining the spaces of diarthrodial joints, tendon sheaths, and bursae. The term includes both the continuous surface layer of cells (intima) and the underlying tissue (subintima). The intima is composed of specialized macrophages and fibroblasts, and the subintima contains blood and lymphatic vessels, a cellular content of both resident fibroblasts and infiltrating cells in a collagenous extracellular matrix. Between the intimal surfaces is a small amount of fluid, usually rich in hyaluronan (hyaluronic acid). Together, this structure provides a nonadherent surface between tissue elements. Unlike serosal surfaces, which also have nonadherent properties, synovium is derived from ectoderm and does not contain a basal lamina.

The study of synovial tissue is of major importance in understanding the pathogenesis of inflammatory arthritis, including rheumatoid arthritis (RA) and seronegative spondyloarthritis (SpA). Despite this, our knowledge of the immunohistochemical architecture of the synovial membrane, particularly in normal subjects, is surprisingly limited.

In normal subjects, the synovium comprises an intimal layer, which is 20 to 40 μ m thick in cross section, and an areolar subintima, which can be up to 5 mm in thickness. At many sites there is no discrete membrane, especially where subintima consists of fat pad or fibrous tissue.

Synovium is often atypical. Intimal cells may be absent. Superficial bursae contain little or no hyaluronan-rich fluid.¹ Ganglia are sacs containing hyaluronan-rich fluid but do not occur at sites of shearing and do not have a typical intima and so may not be considered really to be synovial tissue. Diseased synovial tissue may lose any recognizable lining structure and only be definable by its relation to a joint. These variations probably reflect interplay of several factors in synovial histogenesis.

EMBRYOLOGY

In the early embryonic limb bud, a central core or blastema that will form the skeleton appears. Within this core, foci of cartilage appear, each destined to become a bone. Blastemal cells around cartilage foci form a perichondrial envelope showing strong CD44 expression. The area where this envelope lies between cartilage elements is known as the *interzone*, from which synovium forms. The perichondrium forming a sleeve around each cartilage element subsequently invades the cartilage to form bone marrow. Thus

synovial and bone marrow stromal cells come from the same embryonic stock.

Shortly before the joint cavity forms, CD55 expression appears on cells along the joint line,² followed later by vascular cell adhesion molecule 1 (VCAM-1) expression. After cavity formation the intimal layer also takes on a higher level of expression of CD44 and β_1 integrins compared with subintima.

The mechanism of cavity formation is not fully understood; a working hypothesis implicates interactions between interzone cells bearing CD44 (a hyaluronan receptor) and hyaluronan itself.^{3,4} Shortly before cavity formation, the cells of the potential joint line show high uridine diphosphoglucose dehydrogenase (UDPGD) activity, which suggests increased hyaluronan synthesis. At the time of cavity formation high levels of hyaluronan appear along the joint line, saturate CD44, and induce disaggregation; at low concentrations hyaluronan cross-links CD44 molecules on adjacent cells, inducing cell aggregation.

Cavity formation might be expected to require lysis of matrix fibers. However, in human joints cavity formation is not associated with high local levels of matrix metalloproteinases (MMPs) at the joint line, and matrix fibers appear to run only parallel to the joint line before cavity formation; apoptotic cells found in the interzone at this time are not localized to the joint line and are unlikely to contribute to cavity formation. It appears, therefore, that development of the joint cavity arises more from differential tissue expansion than through loss of solid elements.

An alternative explanation for the formation of the synovial lining and the synovial-lined joint space has recently been suggested by mouse model work.⁵ A study (that awaits human replication) of cadherin-11-deficient mice suggests that expression of cadherin-11 on synovial fibroblasts may be critical in the development of a recognizable synovial lining by facilitation of cellular organization, compaction, and matrix development; this raises the possibility that cadherin-11 expression by synovial fibroblasts is critical for normal synovial tissue development.

STRUCTURE

The microscopic anatomy of synovial tissue was first fully described by Key,⁶ who divided synovium into three main types on the basis of subintimal structure: fibrous, areolar, and adipose (Fig. 4.1a to c). He also noted that subintima may be periosteum, perimysium, or even hyaline or fibrocartilage.

Areolar synovium is the most specialized form (see Fig. 4.1a). It is often crimped into folds, which may disappear when stretched. Less often it carries projections or villi. A more or less continuous layer of cells lies two or three deep on the tissue surface.^{7,8} Immediately beneath these cells are capillaries. Further into the tissue there is a plexus of small arterioles and venules,^{9,10} associated with mast cells. Lymphatic vessels can be found in all types of normal synovial tissue, although they are infrequent in the fibrous type of normal synovium.¹¹ In normal synovium, most lymphatic vessels are found in the deep subintima and fibrous layers, whereas in synovium from RA patients lymphatic vessels are widespread and numerous. Nerve fibers are present, chiefly in association with blood vessels.¹² Three layers of tissue matrix may be distinguished. The intima is associated with a fine fibrillar matrix with few type I collagen fibers.¹³ Beneath this is a layer relatively rich in type I collagen, which forms the physical membrane. Deeper is a loose layer that allows the membrane to move freely. Beyond the loose layer lies ligament, tendon, or periosteum.

Adipose synovium occurs as fat pads and within villi (see Fig. 4.1b). It has a complete intimal cell layer and a superficial net of capillaries. The intima may lie directly on adipocytes, but there is usually a band of

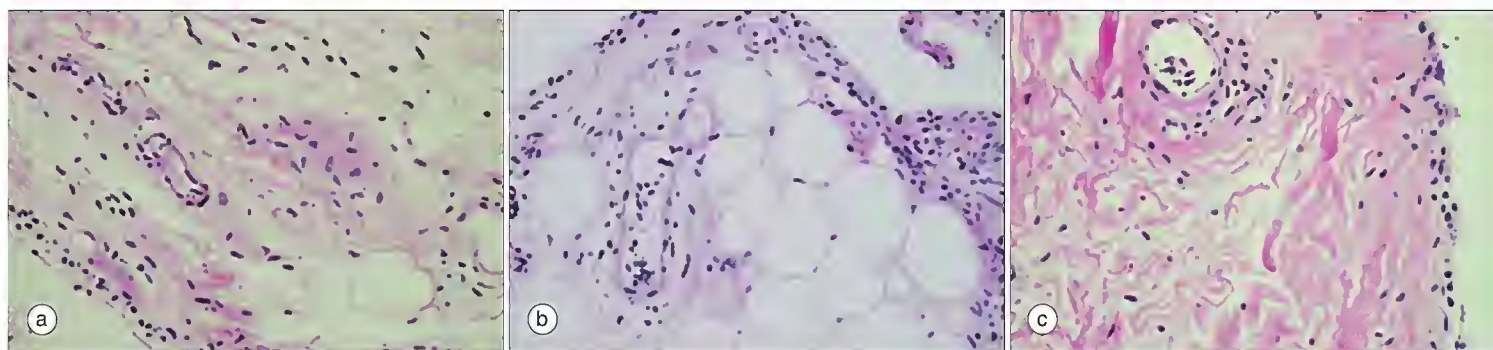


Fig. 4.1 (a) Areolar form of synovium (hematoxylin-eosin). (b) Adipose form of synovium (hematoxylin-eosin). (c) Fibrous form of synovium (hematoxylin-eosin). (Magnification $\times 200$)

collagen-rich substratum, whereas the deeper tissue is fat. Villi usually have a central arteriole and venule but can be avascular. The amount of fat in villi varies and probably decreases with age, with an increase in fibrous tissue.

Fibrous synovium is often difficult to define, consisting of fibrous tissue such as ligament or tendon on which lies an intermittent layer of cells (see Fig. 4.1c). Fibrous synovium may be indistinguishable from fibrocartilage, especially in the annular pads found in finger joints.

Intimal cells

Two types of intimal cells have been defined by electron microscopy, one consistent with a macrophage (type A) and the other with a fibroblast (type B).¹⁴ It is now generally accepted—from immunohistochemical and other lines of evidence—that intimal macrophages are true macrophages, derived from precursors in the bone marrow (although it is not certain if differentiation occurs *in situ* or before arrival), whereas the intimal fibroblasts are locally derived.¹³⁻¹⁶ In normal healthy synovium, synovial fibroblasts are the dominant cell population.¹⁷

Immunohistochemical and cytochemical methods have superseded electron microscopy as tools for cell identification.¹⁸ Intimal macrophages can be distinguished by their nonspecific esterase (NSE) activity and expression of surface markers such as CD68 and CD163. Intimal fibroblasts show intense activity of the enzyme UDPGD and prominent expression of VCAM-1 and CD55 (complement decay-accelerating factor [DAF]). In most disease states such as RA, intimal cells increase in size and number (Fig. 4.2). This is not *hyperplasia* but a complex change in cell populations, in terms of both origin and function, often dominated by macrophage influx.¹⁷

Synovial macrophages

Macrophages are present in both the intima and subintima. Intimal macrophages carry typical macrophage lineage markers. They show prominent NSE activity and are strongly positive for CD163 and CD68 but less so for CD14 (Fig. 4.3). Macrophages also express the immunoglobulin receptor Fc γ RIIIa. Strong Fc γ RIIIa expression is restricted to a subset of macrophages that correspond closely to sites of macrophage activation in rheumatoid disease: synovial, alveolar, serosal, scleral, salivary gland; lymphoid tissue and bone marrow; and Kupffer cells.¹⁹ Subintimal macrophages are Fc γ RIIIa dull or negative. Macrophages also express Z39Ig, a recently described inducible cell surface receptor linked to the classic complement pathway; Z39Ig expression can occur during macrophage differentiation and induce activation of the transcription factor nuclear factor κ B (NF- κ B) and production of matrix-degrading MMP-9.²⁰

Macrophages make up a minority of cells in normal intima (Figs. 4.3 and 4.4). In disease the proportion of macrophages may rise to 80% (see Fig. 4.2). Distribution varies, but a common pattern occurs: a superficial layer of macrophages with an intimal phenotype; beneath this a layer of intimal fibroblasts; and further beneath and beyond the limits of the intima, a zone of NSE-weak, strongly CD14+ and Fc γ RI+ macrophages, associated with venules. The deep, strongly CD14+ cells are probably freshly recruited cells and the superficial cells more mature.

In addition to true macrophages, there may be a small number of antigen-presenting interdigitating dendritic cells in normal synovial intima; these are more frequent in disease with greater overlap of markers, which confounds interpretation.^{21,22} Cells with features of osteoclasts such as expression of tartrate-resistant acid phosphatase and the vitronectin receptor also often appear in inflamed synovium. However, fully typical osteoclasts with

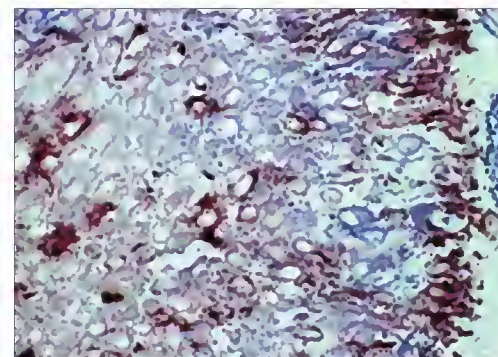


Fig. 4.2 Synovium in rheumatoid arthritis ($\times 400$) showing a thickened intimal layer containing mainly CD68+ macrophages (red) on the surface and weakly CD55+ fibroblastic cells beneath (blue).

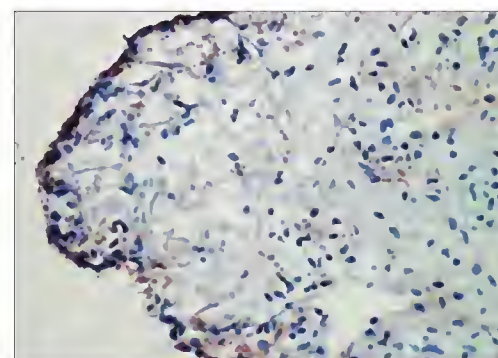


Fig. 4.3 Synovial macrophages. Normal synovium ($\times 200$) stained for CD68+ macrophages (red).

calcitonin receptors may be restricted to pigmented villonodular synovitis and giant cell tumors of tendon sheath.

Synovial fibroblasts

The synovial intima contains cells adapted to hyaluronan production. In normal synovium CD68- intimal fibroblasts alone demonstrate high activity of the enzyme UDPGD.²³ UDPGD converts UDP-glucose into UDP-glucuronate, one of the two substrates required by hyaluronan synthase for hyaluronan polymer assembly. Unlike the activity of many other enzymes, UDPGD activity in intimal fibroblasts is reduced, rather than enhanced, in diseased tissue. Synovial intimal fibroblasts express CD55 (see Fig. 4.4), a feature distinguishing them from intimal macrophages.^{24,25}

Cells disaggregated from inflamed synovium and grown in tissue culture display fibroblast characteristics and ramifying processes with production of high levels of metalloproteinases.²⁶ It is not known whether they derive from intimal or subintimal cells. In tissue sections, immunoreactivity for

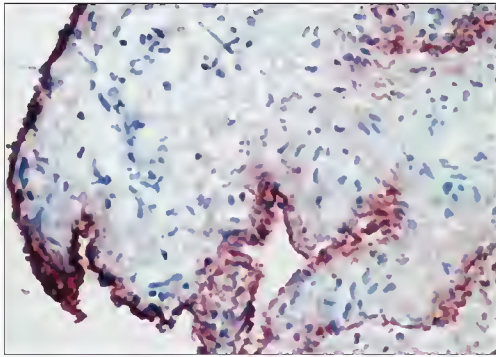


Fig. 4.4 Normal synovium (×200) stained for CD55+ fibroblasts, which are the predominant cell in the normal synovium intimal layer (contrast with Fig. 4.2).

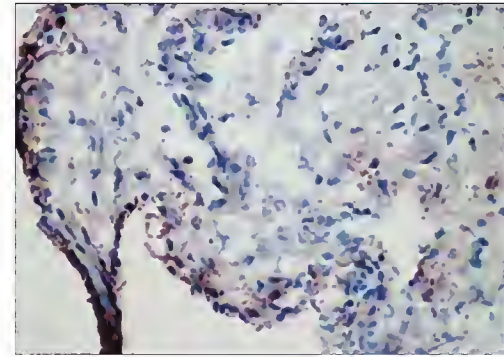


Fig. 4.5 Normal synovium (×200) stained for vascular cell adhesion molecule 1.

collagenase and gelatinase is patchy and not necessarily confined to the intima.

Synovial intimal fibroblasts also show prominent expression of several adhesion molecules,^{8,27,28} including VCAM-1, intercellular adhesion molecule 1, CD44, and β_1 and β_3 integrins. Expression of VCAM-1 (Fig. 4.5) is particularly unusual, being absent from most other normal fibroblast populations, whereas CD44 and β_1 integrins are present at lower levels. The role of VCAM-1 with respect to intimal fibroblasts is puzzling, but it may modulate cell traffic; its ligand, $\alpha_4\beta_1$ integrin, is present on mononuclear leukocytes but not granulocytes. Intimal fibroblasts may allow transmigration of polymorphs but not mononuclear cells into synovial fluid, potentially trapping inflammatory cell infiltrates within the synovial membrane in disease states such as RA.

Recently, the presence of both clusterin (a glycoprotein involved in recycling and apoptosis) and podoplanin (a membrane glycoprotein with diverse functions) has been reported in normal synovial fibroblasts; interestingly, podoplanin (which in the setting of neoplasia is associated with poor prognosis and metastatic disease) has been shown to be highly expressed in RA synovial fibroblasts with their attendant migratory and invasive potential.^{29,30}

The expression of two other surface molecules by synovial fibroblasts is noteworthy. Complement receptor 2 (CR2, CD21) is not expressed by normal intimal fibroblasts but has been induced on synovial fibroblasts in culture, in contrast to other fibroblast populations.³¹ DAF, VCAM-1, and CR2 are all involved in B-lymphocyte survival, as is a bone marrow stromal cell marker, BST-1, reported to be expressed on fibroblasts in rheumatoid, but not normal, intima.³² Other molecules associated with bone marrow stromal cells such as the chemokine stromal cell–derived factor-1 and bone morphogenetic proteins and their receptors,^{33–35} are expressed by synovial fibroblasts under various conditions. Moreover, lubricin, otherwise known as *superficial zone protein*, a glycoprotein found in synovium and the superficial zone of articular cartilage,³⁶ derives from the same gene as megakaryocyte-stimulating factor. A defect of this gene leads to CACP (camptodactyly arthropathy coxa vara pericarditis) syndrome. As indicated earlier, these patterns of gene expression may reflect a common embryologic origin for synovial and bone marrow stromal cells.

Self-renewing mesenchymal stem cells that compare favorably with bone marrow–derived mesenchymal stem cells in terms of their ability to differentiate into bone, cartilage, and adipose tissue have been isolated from the normal synovium; it is unclear which component of the synovial membrane is home to these cells.^{37,38}

Intimal matrix

Intimal matrix has an amorphous or fine fibrillar ultrastructure. It is poor in type I collagen but contains minor collagens III, IV, V, and VI^{39,40} as well as laminin, fibronectin, and chondroitin-6-sulfate–rich proteoglycan, which, with collagen IV, are components of basement membrane; however, the basement membrane is conspicuous by its absence beneath the intimal layer. The looser structure of intimal matrix may be explained by the absence of entactin, which links other components in basement membrane together. Intimal microfibrils are of two types: fibrillin-1 microfibrils form a basket-work around cells, whereas collagen VI microfibrils form a uniform mesh.

Intimal matrix contains large amounts of hyaluronan (Fig. 4.6), which tails off 20 to 50 μm deep; this possibly indicates diffusion from the surface toward clearing lymphatics.

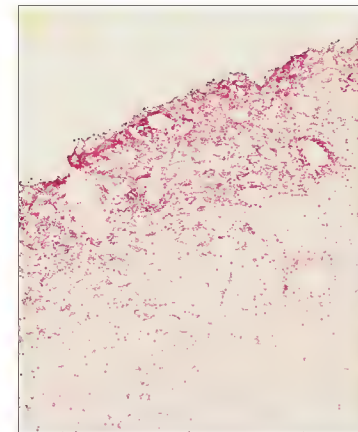


Fig. 4.6 Normal synovium stained for hyaluronan using a histochemical probe derived from proteoglycan core protein hyaluronan-binding region. Staining is most intense surrounding the lining cells and decreases further into the tissue. (Magnification ×200)

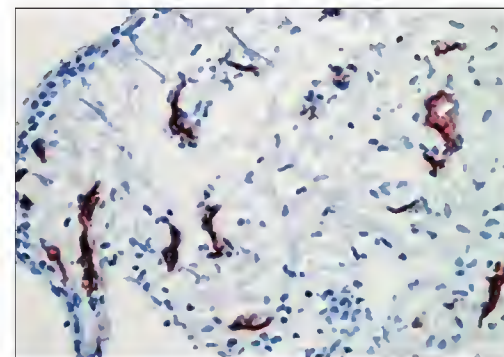


Fig. 4.7 Normal synovium (×200) stained with factor VIII to demonstrate the vascular network.

Vascular net

A rich microvascular net lies beneath the synovial surface.^{9,10} Capillaries (prominent in children and decreasing with age) occur just below or within the intima (Fig. 4.7). Some capillaries are fenestrated, and fenestrae tend to face the tissue surface⁴¹; 50 to 100 μm beneath the surface small venules are prominent. The endothelial cells lining the capillaries in normal synovium express cadherin-11 (Fig. 4.8). About 200 μm beneath the surface, larger venules, together with arterioles and lymphatics (Fig. 4.9),¹¹ form an anastomosing quadrilateral array. Vessels with lymphatic staining characteristics are prominent in RA synovium, a disease state in which increased turnover of hyaluronan and leukocyte trafficking is seen. It has been proposed that failure of lymphatic drainage of synovial fluid is a cause of villous proliferation in RA synovial tissue. If this is correct, it is likely to be due to overloading of existing lymphatic channels with hyaluronan-rich extracellular fluid and leukocytes rather than a lack of lymphatic channels.¹¹

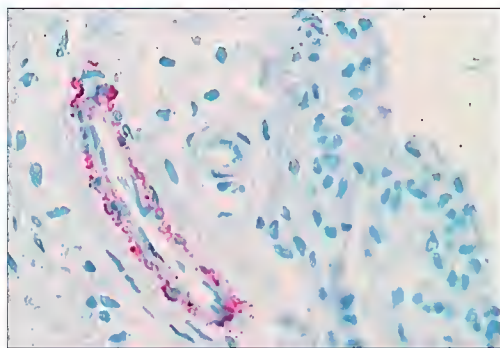


Fig. 4.8 Normal synovium ($\times 400$) stained with an antibody against cadherin-11.

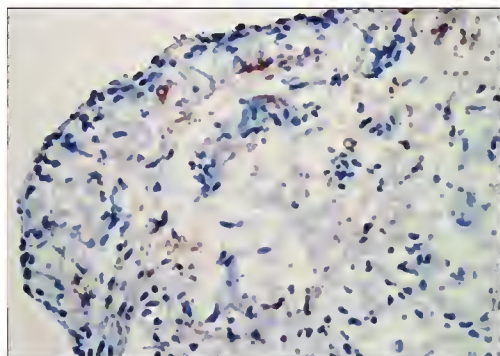


Fig. 4.9 Normal synovium ($\times 200$) stained with lymphatic vessel endothelial hyaluronan receptor-1 (LYV-1) antibody to demonstrate the lymphatic network.

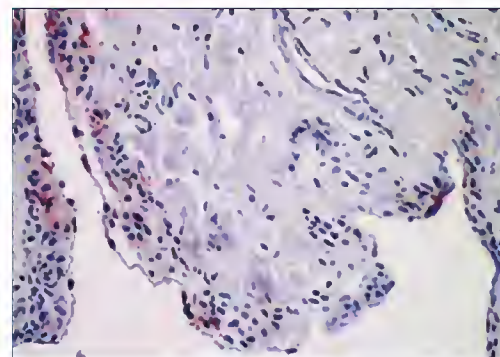


Fig. 4.10 Normal synovium ($\times 200$) stained with an antibody to detect the interleukin-1 receptor antagonist.

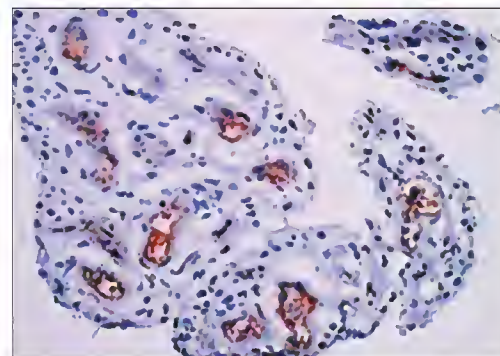


Fig. 4.11 Normal synovium ($\times 200$) stained with an antibody against osteoprotegerin, a naturally occurring inhibitor of osteoclast formation.

Apart from the fenestration of superficial capillary endothelial cells, there is little evidence of specialization in synovial endothelium. Endothelial cells enlarge in inflamed tissue and microvascular proliferation can occur, but these events are common to inflammation at many sites. Tissue-specific adhesion molecules, or *addressins*, have been sought, but nothing conclusive has been found. However, there remains the possibility that specialized lymphocyte traffic pathways apply to synovium, possibly based on chemokine-receptor interactions.

CELL ORIGINS AND RECRUITMENT

Evidence to date indicates that both intimal and subintimal macrophages derive from bone marrow via circulating monocytes, many of which probably arrive through subintimal venules and migrate to the intima.

Intimal fibroblasts are thought to arise by division within synovium, but the site remains uncertain; they might be a discrete self-replicating population, distinct from subintimal fibroblasts, but several pieces of evidence argue against this. Rates of cell division within the intima are very low, even in disease. Following arthroplasty or synovectomy, intimal cells—likely replaced from the subintima rather than arising from intimal rests—reappear and express CD55, UDPGD, and VCAM-1. Disaggregated and cultured synovial fibroblasts lose VCAM-1 and CD55 expression, but the majority, apparently including cells of subintimal origin, will readily express these markers following cytokine stimulation, in contrast to fibroblasts of dermal or subcutaneous origin. These findings suggest that synovial fibroblasts, in both the intima and subintima, belong to a specialized population with a propensity to express VCAM-1 and CD55.

Two recent studies^{7,8} have demonstrated the range of cells that can be found in the synovial subintima. CD3+ T cells, including CD4+, CD8+, and memory T cells, can be found within the normal synovial tissue; although they are likely to be simply trafficking through the normal synovium, their role, if any, in the homeostasis of synovial tissue is unknown. It is also possible to detect B cells, plasma cells, and granzyme B+ cells in normal synovium, although they are present in small numbers.

Although production of inflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α),⁸ can be detected in normal synovial tissue, it is far less than that seen in inflamed synovial tissue such as that in RA patients, and the amount of antiinflammatory cytokine production, at least in the case of IL-1 receptor antagonist (the naturally

occurring inhibitor of IL-1), is far greater than the amount of inflammatory cytokine seen (Fig. 4.10). This would achieve the desired result of suppressing an inflammatory process in the normal synovial tissue. Similarly, the amount of RANKL (receptor activator of NF- κ B ligand, an essential factor for the development of osteoclasts) seen in normal synovial tissue is low⁸ and far less than that of osteoprotegerin, its naturally occurring inhibitor (Fig. 4.11). The net result of this is to suppress the formation of osteoclasts within the normal synovium and preserve homeostasis within the normal joint.

FUNCTION

The functions of synovial tissue are often taken as evident but are remarkably difficult to define.⁴² Like other soft connective tissue, synovium provides a deformable packing that allows movement of adjacent, relatively nondeformable tissues. The difference between synovium and other soft connective tissue is that it allows most of the movement to occur between rather than within tissues. Areolar synovium may also have specialized viscoelastic properties for coping with the stretching, rolling, and folding it undergoes during joint movement.

Functions of the tissue relating to the cavity may be considered to be the following:

- Maintenance of an intact nonadherent tissue surface
- Lubrication of cartilage
- Control of synovial fluid volume and composition
- Nutrition of chondrocytes within joints

Maintenance of the tissue surface

Synovial surfaces must be nonadherent to allow continued movement. Animal models suggest that production of hyaluronan by intimal fibroblasts may be important in inhibiting adhesion.⁴³ Plasminogen activator and DAF from intimal fibroblasts may also inhibit fibrin formation and scarring. To retain synovial fluid, the intimal matrix must consist of a fibrous mat of a particular porosity that allows free exchange of crystalloids and proteins but inhibits rapid transit of the viscous hyaluronan solution that is an important component of the fluid. These functions presumably reflect the combined activities of the intimal macrophages and fibroblasts. The vasculature is

likely to be important in both intimal cell nutrition and recruitment of new cells. New macrophages are derived from blood monocytes that enter the tissue through venules, and perivascular fibroblasts may provide the main pool of intimal fibroblast precursors.

Lubrication

The ability of synovial fluid to lubricate cartilage surfaces depends on the presence of glycoprotein, especially a glycoprotein known as both *lubricin* and *superficial zone protein* because of its localization to the surface of synovium and cartilage.³⁶ Hyaluronan does not appear to contribute to the ability of synovial fluid to lubricate cartilage in *ex vivo* systems, but the glairy quality imparted by hyaluronan may be important in maintaining a film of lubricant on the cartilage surfaces *in vivo*.

Whatever the precise forces acting on fluid volume, the presence of hyaluronan is likely to be the main factor responsible for retaining a constant volume of fluid during exercise⁴⁴; this fluid is probably important as a cushion for synovial tissue and as a reservoir of lubricant for cartilage. It is likely that mechanical stimulation of intimal fibroblasts influenced by effectiveness of the synovial fluid cushion dictates the rate of synthesis and exportation of hyaluronan into the synovial fluid compartment. Thus when synovial fluid volume is high, reduced mechanical stresses on intimal fibroblasts result in reduced rate of hyaluronan production and vice versa.

Two distinct mechanisms create joint effusions. When synovium is mechanically irritated by worn bone and cartilage, the composition of the fluid remains reasonably normal. Excessive production of hyaluronan by intimal fibroblasts stimulated by frictional forces retains plasma dialysate in the synovial cavity; in synovitis the effusion is an accumulation of exudate similar to a pleural effusion (i.e., an overspill from the inflammatory edema in synovial tissue created by increased vascular permeability). Recent theories about a possible low-grade inflammatory and immune reaction contributing to the pathogenesis of osteoarthritis suggest that these two mechanisms of effusion development may not be as distinct as originally thought.⁴⁵ Additionally, recent proteomic evidence suggests that the increased vascular permeability of inflammation may be related not only to an increase in interendothelial gaps but also to glycocalyx damage and aquaporin upregulation.⁴⁶

Chondrocyte health and nutrition

The synovium provides the major route of chondrocyte nutrition. In normal joints a surprisingly large proportion of hyaline cartilage lies within 50 μm of a synovial surface. In any one position only a small proportion of cartilage is apposed to the other articular surface, and synovium packs most of the space between less congruent areas. In immature joints the incomplete subchondral plate may contribute to nutrition, but in adult joints this route is unlikely to be significant. Nutrition of areas of cartilage that do not come into close contact with synovium (concave articular surfaces in particular) must take an indirect route. Although a small proportion of nutrition may occur by smearing of a thin film of fluid over these surfaces during movement, indirect routes through cartilage matrix and the apposed articular cartilage may be more important.⁴

Diarthrodial joints (in both cartilage and synovium) have been found to have high levels of transforming growth factor- β (TGF- β), a latent complex that requires activation to induce a biological response. Recent *in vivo* experiments suggest that shearing of synovial fluid because of physiologic joint motion may play an important role in TGF- β activation, which may be essential to maintain the biochemical content and structural integrity of healthy cartilage.^{47,48}

Despite the fact that the vessels in synovium provide the most direct route for cartilage nutrition, there is no evidence that they are structurally

adapted to this function. The fenestrae seen in superficial capillaries are present in tendon sheath synovium at sites where there is no cartilage (or tendon) dependent on their supply of small molecules.

SYNOVIUM AS A TARGET FOR IMMUNOLOGIC DISEASE

Synovial joints are involved in several immunologic or inflammatory disorders, including RA, systemic lupus erythematosus, and seronegative spondyloarthritis. Except in relapsing polychondritis, patterns of inflammatory rheumatic disease indicate targeting of synovium or enthesis rather than cartilage. Perhaps the most important reason for studying the biology of synovium is to obtain insight into which immunopathologic processes are likely to be suitable therapeutic targets in inflammatory arthritides.

Autoimmune responses to synovial antigens might theoretically occur, but evidence is lacking. Moreover, none of the clinical syndromes indicates targeting of joints alone. Associated targeting of other tissues such as pericardium or uveal tract requires an explanation. Few, if any, synovium-specific antigens are known, and when rheumatic disorders are associated with autoantibodies, the antigens involved are ubiquitous. In seronegative spondyloarthritis it is doubtful whether there is a true autoimmune response.

Understanding the microarchitecture of the normal synovium, including the wide range in microscopic appearances, cellular infiltrates, and production of cytokines, enzymes, and other biologically relevant proteins, assists in understanding the relevant changes in synovial tissue architecture and immunopathology in disease states. Although the architecture of the normal synovium is not as homogeneous as previously portrayed, consistencies across the broad spectrum of normal synovial tissues can be contrasted with those seen in chronically inflamed synovial tissue. The marked increase in synovial lining layer thickness with a reversal of the normal ratio of type A to type B intimal cells, which favors type B cells in normal synovium and type A cells in RA, is an example of this. Numerous other examples can be given, including the changes in subintimal cell content and cytokine, and chemokine production; vascular and lymphatic changes; and production of metalloproteinases and stimulators of osteoclast formation. A recent study in a mouse model of arthritis has also raised the possibility of cadherin-11 expression on synovial fibroblasts as a potential therapeutic target in the treatment of RA⁴⁹; inhibition of cadherin-11 interactions in this model interfered with both synovial inflammation and cartilage invasion by pannus, without having any effect on bone erosion (predominantly osteoclast dependent). In this model inflammation could be reduced substantially by antibodies to cadherin-11 or a cadherin-Fc fusion protein. Furthermore, cadherin-11 expression (see Fig. 4.8) has been found to promote invasive behavior of fibroblasts and is increased by IL-17 and TNF- α , cytokines very relevant in RA pathophysiology.⁵⁰⁻⁵²

Only two groups of enzymes found in the joint, cysteine cathepsins and MMPs, are capable of degrading native type I and II collagen fibrils. There is some evidence that cathepsin K may play an important role in the pathogenesis of osteoarthritis and RA and may be a potential therapeutic target in treating these conditions.³³ It is important to understand the hierarchy and chronology of these synovial changes in chronic inflammatory arthritides and contrast them with those seen in the normal synovium to identify suitable therapeutic targets at various stages in the evolution of a chronic inflammatory arthritis. The identification of TNF- α , IL-1 β , and IL-6 as two likely therapeutic targets is an example of how such a strategy can lead to the introduction of useful therapeutic interventions into the management of several chronic inflammatory arthritides, including RA, psoriatic arthritis, and ankylosing spondylitis.

There is still much to be learned about the immunologic microenvironment of articular tissues, particularly the normal synovium.

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5

Articular cartilage

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- The cells in cartilage maintain function of the extracellular matrix (ECM) via controlled turnover in response to minor damage caused by fatigue and altered load by removing malfunctioning matrix constituents by breakdown and producing new ones to achieve repair.
- The cell obtains feedback on the quality of the ECM via a number of cell-surface receptors such as integrins, DDR-2 (discoidin domain receptor 2), hyaluronan receptors, and proteoglycans with specificity for different matrix molecules.
- The composition of cartilage ECM is different close to cells in the territorial matrix than in the more distant interterritorial matrix. Composition also varies between different types of cartilage and from surface to deep articular cartilage.
- The ECM of cartilage contains a specific proteoglycan—aggrecan—that provides a very high fixed charge density and therefore an osmotic environment, with water retention being essential for tissue resilience. Aggrecan is also part of a network in which globular domains interact with other molecules.
- Fibrillar networks with collagen as the major constituent provide the tensile properties essential for load distribution and dissipation. The fibers contain other matrix proteins (e.g., those bound at their surface) that mediate interactions with other tissue structures, including neighboring fibers, which enhances their mechanical qualities.
- Cartilage ECM contains growth factors and proenzymes that are sequestered by binding to matrix macromolecules, and these substances can be released upon degradation of the carrier molecules.
- As a result of degradation of cartilage matrix, the fragments formed are released into surrounding fluids and can be used as indicators of the ongoing process, the so-called molecular marker technology.
- Fragments of ECM components can activate innate immune responses such as complement.

Articular cartilage has key roles in the function of joints. A major function is to take up and distribute load such that a given point of the underlying bone can handle very high strain. Another role of cartilage is to provide low-friction movement. One key feature of joint diseases is deterioration of joint function, which results from progressive damage to articular cartilage by degradation of the structural components important for properties of the tissue. Progressive joint destruction may eventually lead to total loss of the cartilage accompanied by alterations in underlying bone in the common disease of osteoarthritis (Fig. 5.1). Mechanisms triggering this tissue destruction are not known in detail, but it is clear that excessive load may induce a remodeling process that fails to restore normal cartilage. Stimulation of chondrocytes by cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor- α (TNF- α) induces the cells to degrade their surrounding matrix and can, over an extended period, result in total dissolution of cartilage *in vitro*. The identity of the individual enzyme or enzymes responsible for specific fragmentation of a particular matrix protein is not known, although in some cases candidates have been established. A repair response often accompanies the ongoing tissue destruction. In more serious cases this response is not sufficient, and tissue failure ensues.

A prerequisite for understanding the mechanisms of tissue destruction and failed repair is to know the functions of molecules in the extracellular

matrix (ECM) and how they are assembled into larger networks. It is equally important to understand the mechanisms involved in their degradation. One important and basic clinical observation in joint diseases such as rheumatoid arthritis and osteoarthritis is that after joint replacement, the inflammation recedes and the symptoms that have been plaguing patients are ameliorated or disappear in the vast majority of cases. This brings up the question of whether the components released from cartilage actually stimulate the inflammatory reaction.

The main structural entities in cartilage include aggrecan and collagen. The proteoglycan aggrecan has a primary role in taking up load and resisting deformation. The collagen network provides tensile properties, and the type VI collagen network may have a role in protecting the cell and guiding matrix assembly. A set of molecules close to the cells have specific functions in binding to particular cell-surface receptors and thereby provide signaling of conditions in the matrix.

This chapter therefore focuses on describing the individual cartilage macromolecules and, when possible, their functional properties and how they have implications for tissue assembly. In some instances, candidate enzymes have been implicated in having roles in the degradation of specific macromolecules and will be discussed.

OVERALL TISSUE ORGANIZATION

The part of the matrix closer to cells, the territorial matrix, has a somewhat different composition and structure than the matrix at some distance, the interterritorial matrix (Fig. 5.2) (for references, see Heinegård and colleagues¹). Examples of components found in both compartments are collagen type II fibers and aggrecan; in contrast, collagen type VI is found particularly in the territorial matrix, and cartilage oligomeric matrix protein (COMP) and cartilage intermediate layer protein (CILP) are primarily found in the interterritorial matrix of normal cartilage. There is also a difference in the composition of cartilage from the superficial to deep layers. In the superficial layer, collagen fibers are thinner and arranged in parallel with the surface of the tissue, whereas in the deeper layer the fibers are thicker and arranged perpendicular to the surface, with a transition zone in between them (Fig. e5.1; also see Fig. 5.1). The superficial part of cartilage is enriched with a number of noncollagenous molecules, notably lubricin and asporin. At the same time, other molecules are much less abundant in this part of the tissue, as exemplified by aggrecan, which is particularly enriched toward the deeper parts of the tissue (Heinegård and Önnérfjord, unpublished observation). Certain molecules such as CILP are found primarily in the middle portions of articular cartilage. Although a number of cartilage components have been described in recent years, our understanding of what specific requirements and functions are met by molecules with such a restricted localization in tissue is still very limited.

Different types of cartilage have markedly different compositions. Articular cartilage has major similarities, yet multivariate analyses of proteomics data have demonstrated differences between knee and hip articular cartilage.²

AGGREGAN

The major structure of aggrecan, illustrated in Figure 5.3,¹ consists of approximately 100 chondroitin sulfate glycosaminoglycan chains, each built from a disaccharide unit that is repeated some 50 times, but with extensive variability. Each disaccharide contains uronic acid with a negatively charged carboxyl group and an *N*-acetylgalactosamine with a sulfate in either the 4



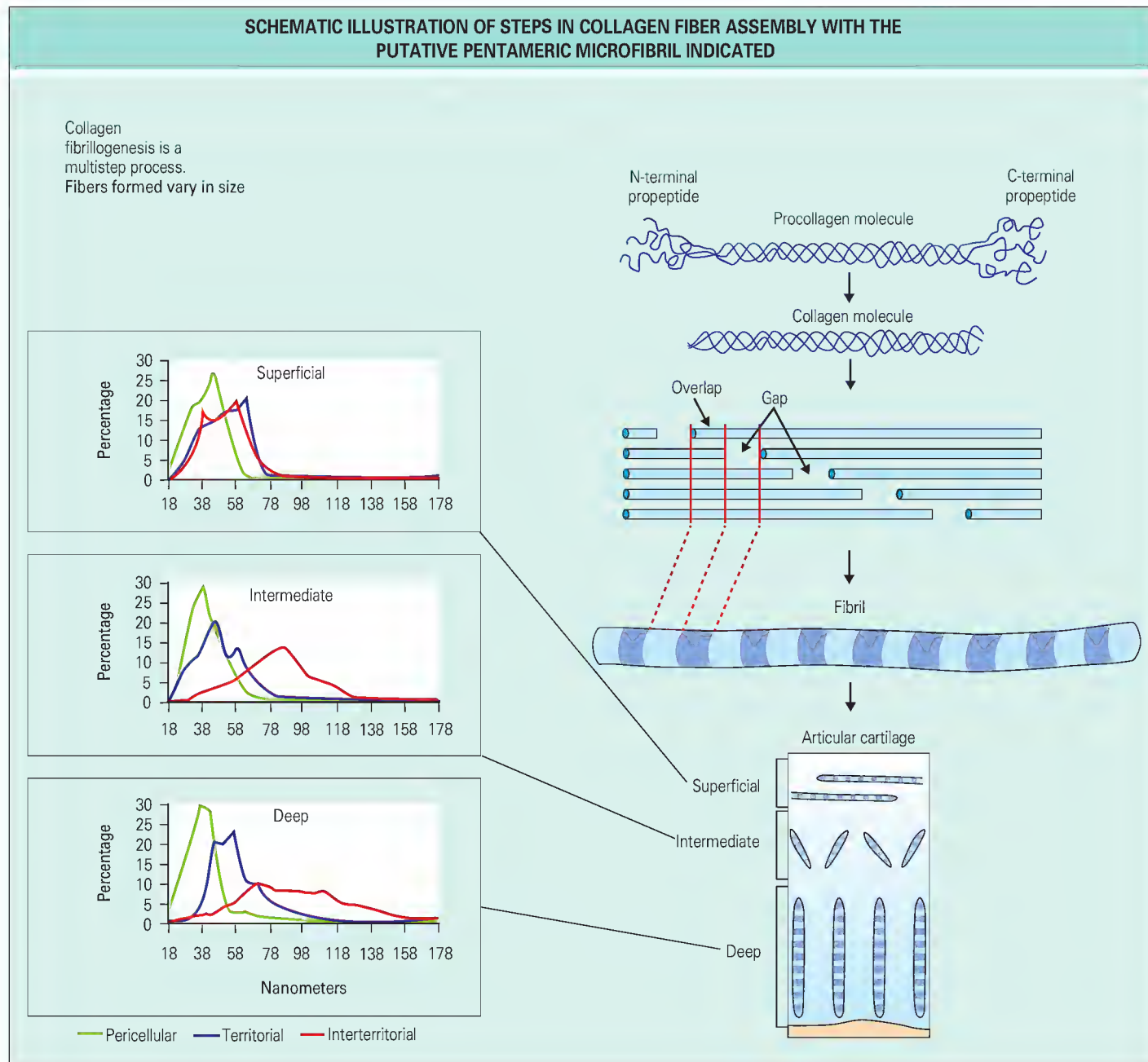


Fig. e5.1 The organization of collagen fibers at different distances from the surface of articular cartilage is shown, as well as differences in fibril diameters between the pericellular, territorial, and interterritorial compartments.

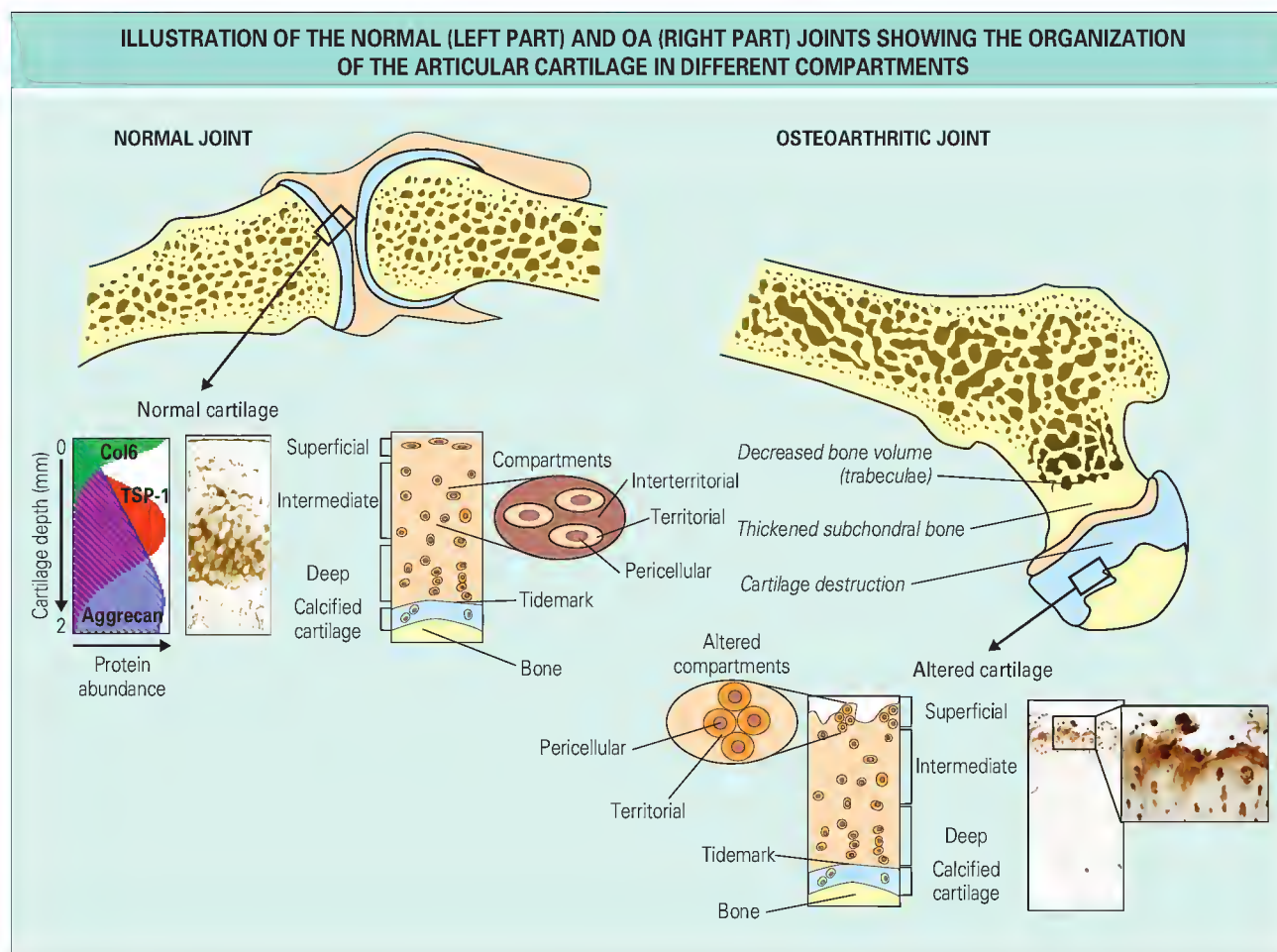


Fig. 5.1 As an example, one cartilage protein (cartilage intermediate layer protein [CILP]) shows a distinct change in localization from distribution in normal cartilage in intermediate parts of the tissue and rather selectively in the interterritorial matrix to a prominence at the superficial parts and primarily in the pericellular compartment in the diseased cartilage. The different distribution of matrix proteins with depth of the articular cartilage is illustrated by way of three examples in the left diagram. OA, osteoarthritis.

or the 6 position. Each chain will therefore contribute around 100 negatively charged groups. The glycosaminoglycans are linked to a serine residue of the protein core of the proteoglycan via their reducing terminal end. The chains are clustered, and clustering differs between the two regions referred to as CS domain 1 and CS domain 2 (see Fig. 5.3). There is an additional glycosaminoglycan, keratan sulfate, that has a disaccharide building block of galactose and an *N*-acetylglucosamine with a sulfate in the 6 position. These chains are shorter and particularly enriched closer to the N-terminal end of the protein core, in the so-called keratan sulfate-rich region. The aggrecan molecule is composed of some 30 such chains.

The proteoglycan core protein contains globular domains flanking the three domains carrying glycosaminoglycan chains. The one most N-terminal, the hyaluronan-binding domain (G1 globe), contributes specific high-affinity binding of the aggrecan molecule to hyaluronan (see below). After a short interglobular domain there is a second globular domain (G2) that has structural similarities to the G1 globe but does not bind hyaluronan and has no known function. In the very C-terminal end of the aggrecan molecule there is a G3 globe with a lectin homology domain; it contributes by binding to other proteins (e.g., fibulins and tenascins), which themselves can form molecular complexes involving several such molecules (see Fig. 5.2). Recently, mutations that abolish binding of the G3 domain to the fibulins and tenascins have been shown to lead to familial osteochondritis dissecans.³

Many aggrecan molecules will bind to a single, very long strand of hyaluronan, thereby forming large aggregates containing more than 100 glycosaminoglycan chains, each with some 100 negatively charged groups. These charges are thus fixed in the tissue, and the presence of counter ions results in an osmotic environment that retains water and has an essential role in cartilage function by resisting compression and distributing load. The interaction of aggrecan via its G1 globe with hyaluronan is stabilized by the link protein having structures similar to the hyaluronan-binding domain of aggrecan. This link protein will bind to this domain of the proteoglycan, as well as to hyaluronan.

In normal cartilage turnover, as well as in pathology, the aggrecan molecule is cleaved by enzymes called aggrecanases (i.e., ADAMTS-4 [a disintegrin and metalloproteinase with thrombospondin-4 motifs] and ADAMTS-5)^{4,5} (see Fig. 5.3). One site of this cleavage is in the interglobular domain between the hyaluronan-binding G1 globe and the G2 globe. The cleavage occurs between the amino acids EGE and ARG (for references, see elsewhere⁶). The new N- and C-terminals formed have been used to develop antibodies that recognize the fragments produced only by the cleavage. These antibodies have in turn been used to demonstrate such fragments in body fluids and tissue extracts.^{6,7} The cleavage occurring in the domain carrying the chondroitin sulfate chains results in shortening of the aggrecan with ensuing decreased number of fixed charged groups (see Fig. 5.3). With aging, shorter aggrecan molecules accumulate, the extreme being hyaluronan-binding domain with no glycosaminoglycan-binding structures remaining.⁸ Indeed, in adults a major proportion of the aggrecan molecules found in the interterritorial matrix at a distance from the cells do not contain the G3, C-terminal globular lectin homology domain (Aspberg and Heinegård, unpublished observation). On the other hand, the molecules in the territorial matrix close to the cells contain this domain, probably a result of the gradual turnover of the aggrecan molecules. At the same time there is substantial accumulation of G1 domain, apparently retained by being bound to hyaluronan.⁹ This fragment can be identified in tissue either via its new C-terminal as represented by an -EGE³⁷³-COOH sequence formed through cleavage by aggrecanase or via a further matrix metalloproteinase (MMP) cleavage that forms a C-terminal -PEN³⁴¹-COOH sequence.¹⁰

Even from early experiments by Thomas¹¹ and Fitton-Jackson and collaborators¹² it was clear that chondrocytes have a remarkable capacity to replace aggrecan molecules removed from tissue by the use of enzymes cleaving hyaluronan. It appears that a normal chondrocyte should be able to replace even large amounts of proteoglycans lost unless suppressed by cytokines such as IL-1 and TNF- α .

There is increasing evidence that the aggrecan degradation encountered in early joint disease, such as osteoarthritis, is effectively counterbalanced

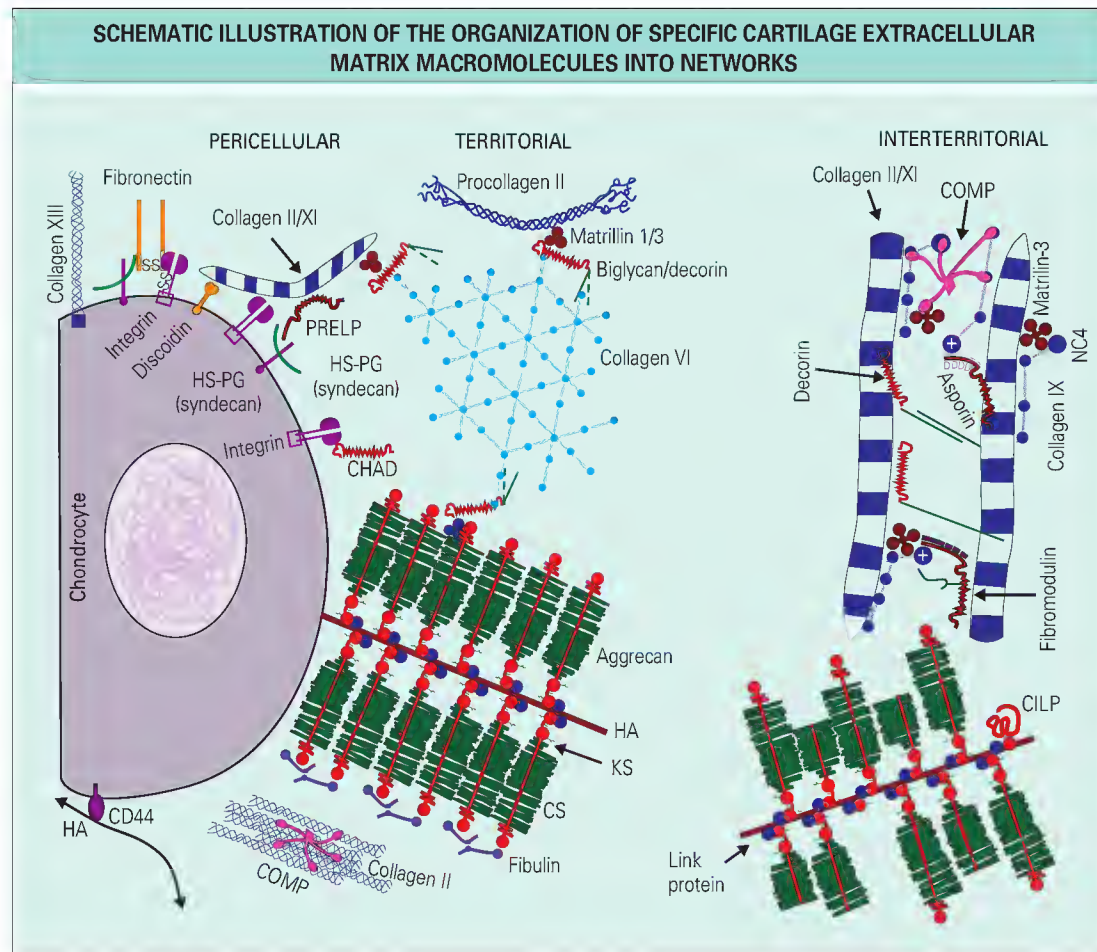


Fig. 5.2 Indicated are the interactions between extracellular matrix proteins and specific receptors at the cell surface. Note the different molecular composition of the territorial matrix closer to the cell than in the interterritorial matrix at some distance. CD44, receptor for hyaluronan; CHAD, chondroadherin; CILP, cartilage intermediate layer protein; COMP, cartilage oligomeric matrix protein; CS, chondroitin sulfate; HA, hyaluronan; HS-PG, heparan sulfate proteoglycan; KS, keratan sulfate; NC4, N-terminal globular domain of collagen 9.

by increased synthesis and deposition of the molecule such that no overall loss takes place.^{13,14}

COLLAGEN FIBRILLAR NETWORKS

A major function of the ropelike collagen fiber networks in cartilage is to provide tensile strength and distribute the load so that excessive local force is not applied to the underlying bone. One type of fiber contains a core of collagen type II with a minor constituent of collagen type XI connected via a number of molecules bound at its surface.

The other fibrillar network contains a core of collagen type VI that forms a filamentous network primarily in the territorial matrix. This network is connected by a set of linker molecules to other molecular in the matrix, including collagen type II fibers and the major proteoglycans. These networks are discussed separately.

Fibers with collagen type II as the main constituent *Collagen type II and collagen type XI*

The major fibrillar network in cartilage contains primarily collagen type II with a minor constituent of collagen type XI.¹⁵ A major feature of both these types of collagen is that the molecule forming the fibers is made up of three parallel, tightly associated polypeptide chains forming a very stable triple helix, the collagen molecule. It is extremely asymmetric—300 nm long and 1.5 nm in diameter. An amino acid quite unique for collagen is hydroxyproline, which is essential for stability of the molecule because of the hydrogen bonds formed to the hydroxyl group. Collagen type II is produced as a procollagen that does not form fibrils until the propeptides at both ends of the C- and N-termini are cleaved off (see Fig. e5.1). After this cleavage the molecules form fibers by interactions with other collagen molecules such that a large part of the surface of the molecule is engaged and the

collagen molecules are positioned so that they form a so-called quarter stagger arrangement in relation to one another.

The assembly process is regulated by a number of molecules in the matrix, including collagen type XI. It appears that the dimensions of the fiber formed depend on the relative proportion of collagens type II and XI, with the typical ratio being on the order of 50:1. This may depend on the presence of a central core of microfibrils of collagen type II and XI that direct assembly of the fiber.¹⁶

Collagen fibers in the superficial and deep layers of articular cartilage are different in dimension and direction. Thus, fibers in the superficial layer of articular cartilage are thin and run in parallel, whereas the thicker fibers in the deeper parts of cartilage run perpendicular to the surface. In the transition zone layer, fibers run at an angle (see Fig. e5.1).¹⁷ The organization can be seen as Benninghoff arcades on polarized light microscopy.

Collagen fiber formation is influenced by a number of matrix molecules, such as decorin, asporin, fibromodulin, COMP, and a special variant of an oversulfated chondroitin sulfate chain. In several of these cases the molecules are also retained bound at the surface of the collagen fiber. This is particularly evident for collagen type IX, which has part of the molecule extending out from the fiber. These molecules appear to have roles in providing sites for interaction with other matrix molecules, including fibers other than those to which the protein is bound (see Fig. 5.2).

An important feature of the collagen fiber network is that the interactions become sealed by covalent cross-link formation once the fibers are assembled outside the cell. This cross-linking depends on the oxidation of lysine and hydroxylysine residues by lysyl oxidase to provide an aldehyde function that forms a Schiff base with a neighboring lysine amino group. These are then rearranged to become stable pyridinoline groups that cross-bridge between the molecules and within the molecules of a fiber. These cross-links are important for mechanical stability of the collagen. Because they are not metabolized on degradation of the collagen, they eventually end up in urine and can be measured as indicators of collagen breakdown.¹⁸

PROTEOGLYCAN AGGREGATE STRUCTURE AND ORGANIZATION

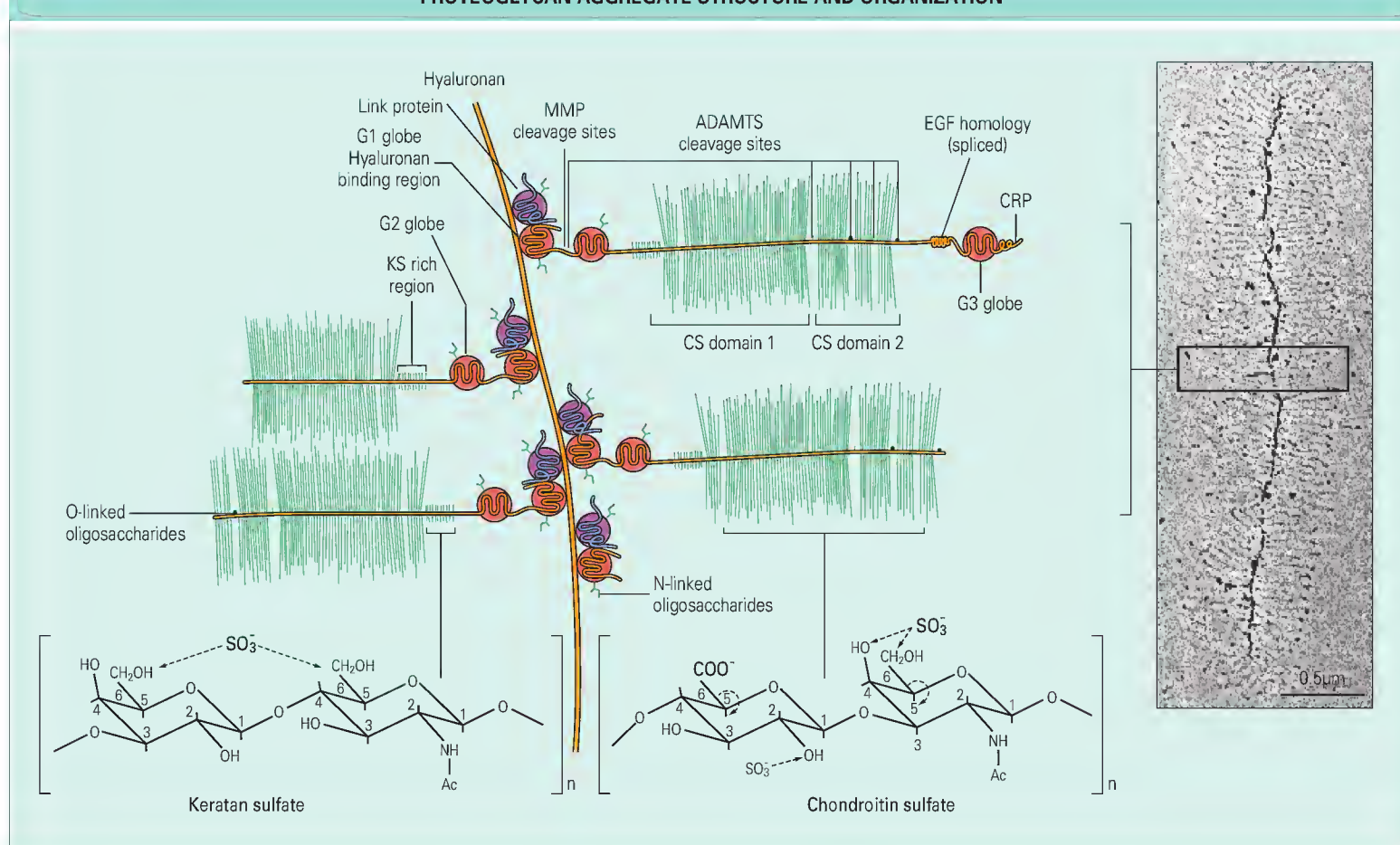


Fig. 5.3 Depiction of the structure and organization of the proteoglycan aggregate. Also shown is a rotatory shadowing electron micrograph (courtesy of Matthias Mörgelin) of an aggregate isolated from tissue. The sites for degradation by the primary active ADAMTS-4 and ADAMTS-5 are indicated, as well as one site for cleavage of matrix metalloproteinase (MMP). CRP, C-reactive protein; CS, chondroitin sulfate; EGF, epidermal growth factor.

Collagen type XI

This fibril-forming collagen is an integral component of the fibers forming the main network in cartilage. Collagen type XI consists of a major triple-helical portion, similar in size to that of collagen types I and II, but in contrast to these collagens, the N-terminal propeptides are retained with the molecule incorporated into the fiber. Some reports have indicated that the retained N-terminal parts are exposed at the surface of the fibers, with collagen type II being the major constituent and the major triple-helical portion being located more centrally in the fiber.¹⁹ Collagen type XI together with collagen type II appears to form the initial assembly of microfibrils that regulate further assembly of the cartilage collagen fiber, at least in skeletal morphogenesis.¹⁶ Interestingly, collagen type XI forms cross-links to primarily other collagen type XI molecules.²⁰ There are examples of mutations in collagen type XI chains with ensuing major growth disturbances, thus indicating a role in cartilage growth and stability.²¹

Collagen type IX

This molecule is a member of the FACIT collagens (fibril-associated collagens with interrupted triple helices) and is found in tissue bound at the surface of the fibrils, with collagen type II being the major constituent. Collagen type IX contains three different α chains with three triple-helical domains (col1, col2, and col3), each surrounded by a noncollagenous domain (NC1, NC2, NC3, and NC4). The NC4 domain with its adjacent col3 triple helix protrudes from the fibers and is available for interactions with other molecules in the ECM, as schematically illustrated in Figure 5.2.²² Examples of such ligands are COMP and the tyrosine sulfate domain of fibromodulin. Collagen type IX often contains a chondroitin sulfate side chain bound at the NC3 domain. Its role in function of the collagen is not known.

Functionally, collagen type IX has been shown to interact with matrilins, COMP, and in particular, collagen type II. The collagen is actually covalently cross-linked to collagen type II in the fibers of adult individuals.²³ When

collagen type IX is added *in vitro* to fibril-forming systems of collagen type II, assembly and fiber formation are retarded.

Mutations in collagen type IX lead to severe growth disturbances, such as pseudoachondroplasia or multiple epiphyseal dysplasia. Some of these disturbances are similar to those with a mutated COMP molecule, which is of special interest in view of the high-affinity interaction that this protein shows with all four NC domains of collagen type IX. Furthermore, early lesions of articular cartilage similar to those found in osteoarthritis develop in mice with knockout of collagen type IX.²⁴

Molecules regulating collagen fiber assembly

The dimensions and orientation of collagen fibers in tissue vary between different layers of articular cartilage. Moreover, fibers in the territorial matrix close to cells are thinner and have similar dimensions in different layers of cartilage. In contrast, fibers in the interterritorial matrix are thicker and have larger and more variable diameters in the deeper layers. This regulation of fiber diameter is achieved by a number of macromolecules that bind to collagen. The exact role of individual molecules in achieving the final dimensions and direction of the fibers is not clear, although there are a number of examples in which inactivation of individual genes of the involved proteins leads to altered dimensions of collagen fibrils. It is notable that asporin, like decorin, inhibits collagen fiber formation and that levels of these protein are selectively very high in superficial parts of the articular cartilage, where collagen fibers are thin.²⁵

The extremely long half-life of collagen type II, in excess of 100 years,^{9,26} indicates that very little collagen is eliminated over the life of an individual; however, at the same time, fibers defective as a result of fatigue have to be repaired. It is possible that the very variable dimensions of the fibers in the interterritorial matrix result from adding newly synthesized collagen molecules at the fiber surface and thus gradually increasing the diameter to provide mechanical stability.

A number of molecules bound at the surface of collagen fibers are likely to prevent further accretion of collagen. It is plausible that these molecules will need to be removed before new collagen molecules can be added to a fiber for remodeling or repair.

It appears that even though the collagen itself does not turn over, molecules on the fiber's surface are continuously removed and replenished.

Molecules with putative roles in regulating fibril formation are found among those that can bind collagen *in vitro*.

Cartilage oligomeric matrix protein

COMP is a molecule primarily found in cartilage, where it is quite abundant at a concentration of around 0.1% of the tissue's wet weight. The molecule is made up of five identical subunits, each with a molecular weight of around 87,000 Da. The five subunits are held together by a coil-coiled domain close to the N-terminal end, and disulfide bridges further stabilize the binding. The subunits are made up of several modules, including some binding calcium. At the C-terminal end there is a globular domain that is involved in interactions with other proteins in the matrix. The molecule can be viewed as a bouquet of tulips tied together at their stalks (see Fig. 5.2).²⁷

COMP, also referred to as thrombospondin-5, is a member of this family of proteins. Cartilage also contains other thrombospondins that share the same properties, with thrombospondin-1 and thrombospondin-4 being particularly abundant. These thrombospondins, however, contain an extension beyond the coiled-coil domain in the N-terminal that has a heparin-binding motif, in this manner adding additional interacting sites. Thrombospondin-4 contains five identical subunits, whereas thrombospondin-1 contains only three.¹

The three-dimensional structure of the C-terminal domain of thrombospondin-1 has been resolved, and its organization has been found to be stabilized by a large number of calcium ions.²⁸ Because the C-terminal domain of the various thrombospondins shows a great deal of conservation, it is likely that its structure is similar in all five members of the family.

COMP has been shown to bind to collagens type I and II,¹ where each individual C-terminal globular domain provides high affinity in the nanomolar range. Four binding sites are evenly distributed along the collagen molecule. There is one at each end and two positioned along the filament such that the distance is similar between the four binding sites. Even though each COMP molecule has five identical binding sites, an individual molecule can engage only one binding site on each collagen molecule and not span the distance between two such sites. Therefore, each COMP molecule has the potential to bind to five different collagen molecules. The quarter stagger arrangement of collagen in the fiber and the fact that a pentameric microfibril unit appears to exist²⁹ may relate to the four similarly spaced collagen binding sites in the molecule. COMP will accelerate and provide faster collagen fibril formation *in vitro*. It appears that this effect is mediated by the COMP molecule bringing together several collagen molecules to facilitate their interactions in the forming fiber. The COMP molecule does not remain bound directly to the surface of the forming fiber. The molecule thus appears to function as a catalyst to enhance fibril formation.

In the cartilage of growing individuals and notably in the growth plate, COMP is primarily localized close to the cells in the territorial matrix, where it may have a role in stimulating collagen fibril formation.³⁰

COMP has the ability to interact with all four NC domains of collagen type IX with similar high affinity in the nanomolar range. The interaction is mediated via the C-terminal globular domains (see Fig. 5.2).

In adults, COMP is localized primarily in the interterritorial matrix and may be bound to collagen type IX or one of the matrilins, which in turn bind to the surface of the collagen fiber (see Fig. 5.2). The role of COMP in adult cartilage appears to be stabilization of the collagen fiber network.

Mutations in the calcium-binding domain of COMP, as well as in the C-terminal domain, have been shown to lead to severe growth disturbances in the form of pseudoachondroplasia or multiple epiphyseal dysplasia. A feature of these conditions is that material retained in the endoplasmic reticulum of chondrocytes contains both COMP and collagen type IX.³¹

On the other hand, the COMP-null mouse shows no detectable alteration in phenotype.³² It is possible that other molecules compensate for the lack of COMP function in such mice.

COMP is significantly upregulated in early stages of osteoarthritis, even long before diagnosis, in an apparent attempt at repair. At the same time the protein already deposited is cleaved and released from the tissue. Indeed, assay for such fragments released into body fluids has been used to measure altered cartilage metabolism as a biomarker for arthritic disease.³³

Decorin

Decorin was the first molecule in the leucine-rich repeat (LRR) protein family to be cloned and sequenced. This family of molecules in the ECM

contains four subclasses with a total of 12 members, all of which appear to share the function of binding to collagen (Fig. e5.2).¹

One functional domain of these molecules is a central LRR region, where residues, particularly leucine, are found at conserved locations in each repeat of some 25 amino acids, albeit somewhat variably long. Most of these molecules have 10 to 11 such repeats, and the entire domain contains a disulfide loop structure at each end. One subgroup contains molecules with only six repeats.

For further details on decorin, see ExpertConsult.com.

Decorin binds tightly to the fibril-forming collagens with a K_D in the nanomolar range. Binding is close to the C-terminus of the collagen as shown for collagen type I. Binding occurs via the LRR region and particularly involves repeats 4 and 5.¹ The critical sequence has been identified as SYRIADTNIT.³⁶

Via its binding to collagen, decorin inhibits the formation of collagen fibers *in vitro* in a dose-dependent manner. Accordingly, mice lacking decorin as a result of knockout technology have irregular collagen fibers with increased diameter, particularly prominent in skin.³⁷ They do not show increased early joint pathology, thus indicating that other molecules may compensate for the lack of decorin in articular cartilage.

Decorin is bound to collagen fibers in tissue, with the glycosaminoglycan chains being free to interact with other molecules. Thus, decorin can cross-bridge to neighboring collagen fibers, as well as to other molecules in the local environment (see Fig. 5.2).

Fibromodulin and lumican

Fibromodulin and lumican belong to the same subclass of LRR proteins but with a gene arrangement distinct from that of decorin. Other members of this subgroup are keratocan, osteoadherin, and PRELP. All these molecules except PRELP contain tyrosine sulfate residues in the N-terminal extension. Notably, the number of such sulfate residues is variable both with regard to the relative proportion of candidate tyrosine residues that are sulfated within a given molecule and with regard to the number of such tyrosine residues that may carry a sulfate. One extreme is represented by fibromodulin, which contains up to nine sulfate residues; osteoadherin contains up to eight, lumican up to four, and keratocan only one.³⁸ PRELP, in contrast, contains a cluster of basic residues that contribute heparin-binding activity for this molecule.³⁹

Collagen binding of fibromodulin has been studied extensively. It has been shown that the molecule inhibits fibril formation *in vitro*. The fibromodulin-null mouse shows altered collagen fibril dimensions, particularly apparent in the tail tendon. Unexpectedly in view of the inhibitory effects observed *in vitro*, the tendon contains a much larger number of thin fibrils. An explanation appears to be a higher abundance of the related lumican molecule, which could be shown to bind to the same site on the collagen, albeit with somewhat lower affinity. It thus appears that lumican may guide early events in fibril formation. The molecule may then be completed away by fibromodulin to introduce a different function. Because the mRNA levels and therefore synthesis of lumican were lower in the null mouse, it appears that the higher levels of this protein were caused by retarded elimination apparently secondary to lack of competition by fibromodulin.¹

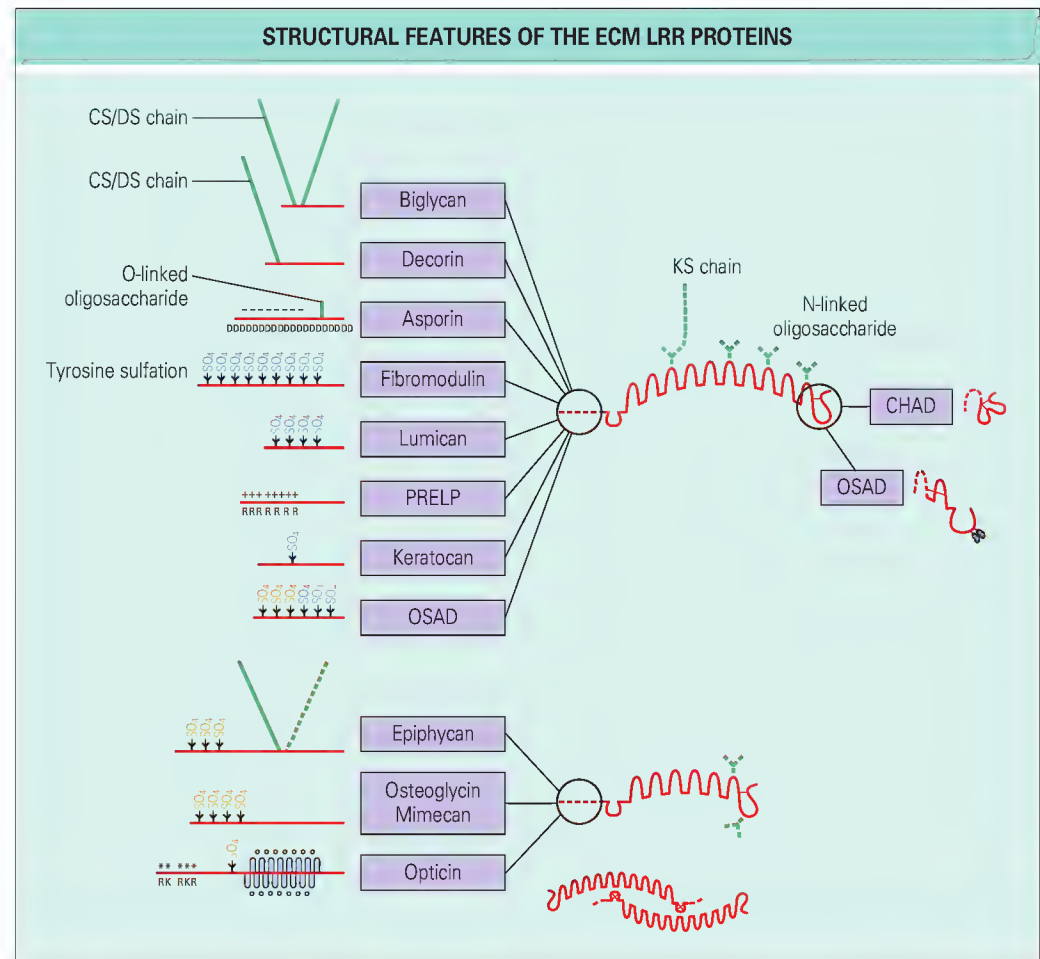
These findings illustrate that fibril formation takes place in many steps involving a set of different molecules with different roles.

Fibromodulin is also present on collagen fiber in tissue, where it is bound in the gap region.¹ It appears to be bound via its protein core with exposure of a keratan sulfate chain, as well as the tyrosine sulfate domain, which then become available to interact with PRELP and the NC4 domain of collagen type IX located on neighboring fibers. Such interactions are important for the stability and properties of the collagen network.

Fibromodulin is a target in joint disease. In a model of articular cartilage destruction caused by stimulation with IL-1 in explant culture, we have been able to show that fibromodulin is degraded after aggrecan and that the molecule is initially cleaved by MMP-13 to release almost the entire N-terminal tyrosine sulfate domain while the remainder of the molecule is initially retained in the tissue, probably bound to the collagen.⁴¹ This loss of the anionic domain is likely to alter the properties and interactions of fibromodulin. At the same time, MMP-13 can release the entire NC4 domain of collagen type IX from cartilage.⁴² This results in loss of function, with impaired noncovalent associations between collagen fibers most likely leading to impaired maintenance of structure and function of the cartilage. This may represent a central mechanism in the swelling and surface fibrillation observed in early osteoarthritis.

It is of interest to note that the particular fragment retained in the tissue is found only in pathologic and not in normal tissue, although there is continuous turnover of matrix constituents in response to altered load,

Fig. e5.2 Note the variability in the N-terminal domain between molecules, which shows negatively charged groups of different character (glycosaminoglycan, tyrosine sulfate, polyaspartate, or a cluster of basic amino acids). The C-terminal extensions of two members have distinct features. The dimeric form found for decorin and biglycan on x-ray crystallography is illustrated schematically. CHAD, chondroadherin; ECM, extracellular matrix; LRR, leucine-rich repeat; OSAD, osteoadherin.



Decorin—additional information

One variable of almost all the molecules in the family is an N-terminal extension of generally less than 20 amino acids, which may contain a variety of substituents (see Fig. e5.2). Some of the molecules also have a C-terminal extension. There is also variation in glycosylation of the repeat domain, which usually contains a few N-linked oligosaccharides. In some of the small LRR proteins, such as fibromodulin and lumican, some of the oligosaccharides may contain a variably long array of 6-O-sulfated lactosamine repeat disaccharides (see Fig. 5.3) extended to form the glycosaminoglycan keratan sulfate.

The three-dimensional structures of decorin³⁴ and biglycan³⁵ have been resolved by x-ray crystallography. These molecules contain one (decorin) or two (biglycan) glycosaminoglycan chains bound at the N-terminal extension. These chains are chondroitin sulfate or dermatan sulfate, depending on the tissue, though very similar between the molecules in a given tissue. In articular cartilage the chain is a low-epimerized dermatan sulfate in which a few of the glucuronic acid residues have been epimerized to iduronic acid, thereby increasing its structural variability. This glycosaminoglycan has the capability of specific interactions with other molecules in the matrix, including binding other dermatan sulfate chains.¹

Based on the x-ray crystallographic data presented, the LRR family of molecules forms a curved structure in which two molecules form a dimer in the crystals that overlap in opposite directions in about 50% of their length such that the N-terminus of one molecule is located in the middle of the curved domain of the other. Support for such a dimeric structure was obtained by other techniques such as gel filtration with on line dynamic light scattering.³⁴ Electron microscopy indicates that decorin and biglycan, as well as chondroadherin, may also exist in a monomeric form at very low concentrations (Mörgelin and Heinegård, unpublished work).

The presence of the proteoglycan as a monomer or a dimer has specific relevance for interactions and functions. Thus, a monomeric molecule has only one of each interacting site, whereas a dimer may exhibit two of each binding site.

Fibromodulin and lumican—additional information

The function of this domain with clustered tyrosine sulfate residues is becoming clearer. The domains in fibromodulin and osteoadherin mimic heparin in many interactions and bind growth factors (e.g., fibroblast growth factor-2 [FGF-2]), cytokines (e.g., oncostatin M and IL-10), MMPs (e.g., MMP-13 for fibromodulin), and a number of matrix proteins via their heparin-binding domains (e.g., PRELP and chondroadherin).⁴⁰ Thus, the fibromodulin on a collagen fiber appears to extend its tyrosine sulfate domain, which can bind to molecules with cationic domains. One such charged structure is the NC4 domain of collagen type IX, which has been shown to interact with the anionic N-terminal extension of fibromodulin,⁴⁰ as schematically outlined in Figure 5.2.

All the molecules in this family appear to bind to collagen via their LRR domain with dissociation constants ranging from 1 to 10 nM.¹ Only in a few cases has it been established exactly where along the collagen that the LRR protein binds.

including removal of damaged components. This normal turnover appears to involve different mechanisms of cleavage.

Other leucine-rich repeat proteins

PRELP is distinguished by having a basic, heparin-binding N-terminal domain.⁴³ This mediates binding to molecules with heparan sulfate side chains, including perlecan and cell-surface syndecan and glypican. Simultaneously, the protein binds via its LRR domain to two sites on fibril-forming collagen types I and II. Thus, the molecule has the potential to bridge from the collagen network back to the cell surface. It consequently has the potential to provide feedback to cells on the condition of the matrix. Little is known of alterations in PRELP in joint disease. An interesting observation is that the isolated heparin-binding domain of PRELP binds to osteoclast precursors via cell-surface proteoglycans. The peptide becomes internalized and translocates to the nucleus, where it inhibits nuclear factor- κ B (NF- κ B), the target of receptor activator of NF- κ B ligand (RANKL), an important stimulator of osteoclast development. The effect of the peptide is thus to inhibit osteoclast formation. Indeed, PRELP has been used to prevent the development of osteoporosis in ovariectomized mice.⁴⁴

Chondroadherin is a cell-binding protein that forms its own subclass. The protein is further discussed below.

Asporin is a close relative of decorin but differs in having a variably long polyaspartate sequence in the N-terminal end. The number of aspartate residues varies between individuals.⁴⁵ It has been demonstrated in studies of several cohorts of individuals in Asia that osteoarthritis is overrepresented in individuals with 14 such residues versus those with 13 residues in the asporin N-terminal structure.⁴⁶ In a different study from the United Kingdom, no such pronounced relationship could be discerned, thus indicating that other factors are also involved.⁴⁷ One function of the polyaspartate sequence appears to be calcium binding, for which there may be a difference between the 13 and 14 aspartate variants.⁴⁸ At the same time, asporin binds to collagen at the same sites that decorin does,⁴⁸ which can facilitate its fixation to collagen fibers in the tissue. The molecule may thus have roles in regulating mineralization, which is relevant to the development of osteoarthritis. Asporin, like decorin, biglycan, and fibromodulin, appears to bind transforming growth factor- β (TGF- β).

There is a set of LRR proteins with only six repeats.¹

Heparin/heparan sulfate

A glycosaminoglycan not prominent in cartilage is heparan sulfate, which has structural features overlapping those of heparin. Heparan sulfate is found as side chains of extracellular perlecan (discussed below), which has a very large protein core with several domains interacting with a number of other proteins in the ECM. The proteoglycan contains an N-terminal domain with some three glycosaminoglycan chains and a C-terminal domain with up to two chains. These chains may be heparan sulfate or chondroitin sulfate (discussed later).

Heparan sulfate contains two types of disaccharide repeats consisting of either a glucuronic acid and an N-acetylglucosamine or an iduronic acid and an N-acetylglucosamine. The hexosamine carries an O-sulfate group, and some of the residues have an additional N-sulfate instead of the N-acetyl group. Also, the uronic acid may be sulfated, usually in its 2 position. Thus, there is extensive variability in the building blocks, which are then assembled in variably long stretches with different repeat stretches of low- and high-sulfated residues.

Other heparan sulfate-containing proteoglycans are found at the cell surface of the chondrocyte. These include four different syndecans,⁴⁹ which contain a domain intercalated in the cell membrane, and some six glypicans, which are joined via a glycosylphosphoinositide linkage.⁵⁰ The syndecans contain an intracellular signaling domain, and as discussed below, they are involved in a number of cell reactions, and bound molecules can induce signal transduction.

Fibers/networks with collagen type VI as the main constituent

There is a different fibrillar network in cartilage with a more restricted distribution in tissue. It has collagen type VI as a major constituent and is primarily present in the territorial matrix surrounding the cells (see Fig. 5.1).

Collagen type VI

Collagen type VI has a distinctive network of beaded filaments. This molecule contains three different α chains with a central triple-helical domain flanked by globular domains. The N-terminal portion, particularly the α_3 (VI) chain, contains nine von Willebrand factor A (vWFA)-like repeats. In addition, the

C-terminal portions of all three chains contain two vWFA repeats, as well as other motifs with less clear functions. The vWFA domain is found in many proteins, where it is involved in protein-protein interactions.⁵¹

While still within the cell, two collagen type VI molecules associate in an antiparallel fashion such that the dimer is flanked by the N-terminal domains and the two C-terminal domains are placed so that they form two interior globular structures along the filament formed by the two triple helices. Two such dimers associate laterally to form a tetramer, with the globular domains at each end representing a pair of the vWFA-rich globules. Internally in the triple-helical central filament are found the two globular structures representing the C-terminals.⁵¹ The tetramer is secreted from the cell, and its N-terminal structures lay the ground for further associations with fibrils involving both end-to-end and side-to-side interactions. This assembly process appears to be governed by other molecules, particularly members of the LRR protein family.

Biglycan and decorin

Biglycan and decorin both bind with high affinity to the collagen type VI N-terminal domain, independently of their glycosaminoglycan side chains. This binding is a prerequisite for formation of the collagen type VI beaded filament network *in vitro*. Regulation of collagen type VI assembly also depends on the presence of the chondroitin/dermatan sulfate side chains, where the two present in biglycan provide more efficient filament formation than the single chain in decorin does. The two closely related proteoglycans appear to bind to the same site, which interestingly does not seem to involve the triple-helical domain in this collagen.⁵²⁻⁵⁴

Matrilins

Cartilage matrix protein (CMP; matrilin-1) was the first of the four matrilins identified. These proteins (for references, see Klatt and colleagues³⁹) contain vWFA domains. Matrilin-1 has two such domains in each of the three identical subunits with a molecular mass of around 50,000 Da; matrilin-3, with four subunits, has only one such domain.

Matrilin-1 and matrilin-3 are quite restricted to cartilage and show similar distribution between different tissues, whereas the others have a more general distribution. Interestingly, matrilin-1 is even further restricted and not found in articular cartilage and intervertebral disks, but it is particularly prominent in tracheal cartilage. The protein is present in the more immature cartilage of the femoral head during earlier phases of development and can be seen in the early bone anlagen. Its role in cartilage is becoming clearer, and data indicate roles in collagen network function and integrin binding (for references, see Klatt and colleagues³⁹). Its two vWFA homology domains (only one in matrilin-3) may mediate the ability of the protein to bind to collagen. Matrilin-1 was initially isolated because of its apparent ability to bind to aggrecan.

Mutations in matrilin-3 can induce multiple epiphyseal dysplasia or pseudoachondroplasia with skeletal malformations, similar to those caused by mutations in the interacting partners of the proteins, such as collagen IX.⁵⁶

Matrilin-1 can be isolated from cartilage as a mixed polymer that contains subunits of matrilin-1, as well as matrilin-3. The functional significance of this heterocomplex is not understood.⁵⁷

A module cross-linking to other matrix constituents

Decorin and biglycan appear to also have roles in the completed network. Collagen type VI isolated from chondrosarcoma cartilage-like tissue contains biglycan or decorin bound at the N-terminal globules. The proteoglycan in turn has a bound member of matrilin-1, matrilin-2, or matrilin-3. This interaction is tight with a dissociation constant on the order of nanomolar. The matrilin, in turn, binds to a procollagen type II molecule or a completed collagen fiber. Alternatively, matrilin can bind to an aggrecan molecule (see Fig. 5.2).⁵⁴ Thus, collagen type VI seems to be a center in a scaffold that binds to the other major networks in the matrix. Collagen type VI is found only in the territorial matrix closer to cells and is absent from the interterritorial matrix at some distance from the cells. Information on alterations in collagen type VI in joint disease is limited, but it is important to note that the protein is found to be particularly enriched in tissue subjected to load.

MOLECULES INTERACTING AT THE CELL SURFACE AND MODULATING CHONDROCYTE BEHAVIOR

It is important to realize that chondrocytes have the ability to both degrade the matrix and replenish lost molecules with new constituents in a process

Other leucine-rich repeat proteins—additional information

Such proteins include epiphykan, mimecan, and opticin. In addition, these molecules appear to have the ability to bind collagen. They all contain N-terminal extensions carrying glycosaminoglycan chains (epiphykan), tyrosine sulfate residues (mimecan), or *O*-glycosidically linked oligosaccharides (opticin) (see Fig. e5.2). Mimecan has also been named osteoglycin. There is limited knowledge on alterations of these proteins in joint disease. They do show interesting differences between different types of cartilage. Mimecan is present in articular cartilage, menisci, and intervertebral disks but virtually absent in nasal and tracheal cartilage, whereas epiphykan is prominent in the latter cartilage and absent from the others. Opticin is particularly prominent in connective tissues other than those of joints.

of remodeling the tissue in response to material fatigue or to altered load. The cells are guided in this endeavor by receptors at their surface that recognize specific molecules in the matrix (see Fig. 5.2). Binding elicits specific signals that will either induce cellular spreading and migration by engaging the cytoskeleton or lead to alterations in transcription and protein synthesis. Other stimuli that will affect cells include mechanical forces, which provide signals that crosstalk with those from other interactions at the cell surface. Indeed, some data indicate that some of the signals elicited by mechanical load involve integrins.⁵⁸

Integrin binding proteins

The integrins contain an α chain noncovalently bound to a β chain. The cells in connective tissues contain either a β_1 or a β_3 chain in conjunction with one of many α chains. The various integrins have different preferred ECM ligand proteins.⁵⁹ As an example of the organization of integrins, members of one such family with four members bind to collagens. They contain a β_1 chain in combination with either an α_1 , α_2 , α_{10} , or α_{11} chain. These various integrins have different tissue distributions such that the one with α_{10} appear to be unique to cartilage whereas the others have more ubiquitous distributions. Their binding to collagen may elicit different responses and result primarily in either altered production of enzymes degrading the matrix or production of building blocks such as collagen molecules.

A number of factors limit our ability to discern which integrins are present on chondrocytes in tissue. One factor is limited accessibility by the antibodies used and another is changes in the presence of integrin during the long procedure for cell isolation. Thus, the current information on the presence of integrins at the cell surface is variable. It is likely that a number of integrins change their expression on chondrocytes in normal and in pathologic tissue in response to environmental factors.

Many of the molecules binding to integrins are not unique for cartilage. The collagen-binding integrins do not appear to be specific for a particular fibril-forming molecule. One exception is chondroadherin. This protein appears to be restricted to cartilage and can bind $\alpha_2\beta_1$ integrin, though not other integrins containing the same β chain.

Chondroadherin

Chondroadherin is a member of the LRR protein family that is in its own subclass. This protein differs from other LRR family members in that the C-terminal cysteine loop is double and the protein has a short C-terminal extension of basic amino acids. The protein has no N-terminal extension. Chondroadherin specifically binds to cell-surface $\alpha_2\beta_1$ integrin^{1,60} via a sequence in one of its C-terminal disulfide loops. Interestingly, integrin binding elicits signals that do not induce cell spreading. The very C-terminal short extension peptide of chondroadherin contains a different cell-binding sequence that engages the heparan sulfate chains of cell-surface proteoglycans, notably syndecans.⁶¹ Binding leads to cell spreading, as well as enhanced integrin activity. The combined engagement of integrins and heparan sulfate leads to cells forming focal adhesion complexes.

Chondroadherin is present in articular cartilage but virtually absent from menisci. The protein is particularly enriched during growth in the prehypertrophic zone of the growth plate where cell multiplication is slowed, in line with its *in vitro* effects on cell behavior. Interestingly, the protein appears to be lost early in the process of joint damage in osteoarthritis (unpublished observations).

Fibronectin

Fibronectin⁶² is present in most tissues and can actually form its own fibrils, which appear to have roles in guiding matrix assembly and cell migration. The protein contains two identical subunits held together by disulfide bonds close to their C-terminal end.

Fibronectin contains a collagen-binding domain with preference for denatured collagen (gelatin). There are integrin-binding domains in which the RGD (arginine-glycine-aspartic acid) sequence represents the classic motif of integrin binding. This motif in fibronectin preferentially binds $\alpha_5\beta_1$ integrin, although $\alpha_v\beta_3$ integrin can also interact. Fibronectin also has other integrin-binding domains.⁶³

Another motif is represented by the two heparin-binding domains on each subunit, each some 20 kDa. These domains can interact with heparan sulfate proteoglycans at the cell surface, including syndecan, which also represent signaling molecules.⁶⁴

Although the details are not known, fragments of fibronectin (e.g., those containing either of the heparin-binding domains), when added to cartilage in explant culture, as well as injected into the joint, will stimulate chondrocytes to produce proteases and induce cartilage breakdown.^{65,66} In contrast,

the intact fibronectin molecule will not have such effects on cells. It is possible that fragmentation of fibronectin is one mechanism for propagating joint destruction in disease. The active fragments have not yet been identified in body fluids.

Fibronectin is already upregulated in articular cartilage at very early stages of osteoarthritis in many species, including humans.¹³ The functional consequences of this upregulation are not known but may represent part of an attempt at repair. A result is further availability of fibronectin, which may be fragmented to further increase tissue degradation.

Collagen and the discoidin domain 2-containing receptor

Collagen has an additional cell receptor for discoidin domain receptor 2 (DDR-2). This receptor has been shown to be upregulated in mice in which osteoarthritis is developing. DDR-2 will bind collagen type II, thereby inducing upregulation of MMP-13 production.⁶⁷ Exposure of collagen type II may be enhanced by removal of proteins bound at the fibrillar surface, thus making the molecule available for interactions.

Hyaluronan

Hyaluronan is an extremely long glycosaminoglycan chain that is distinct from all the others in that it is not bound to a protein core. It does not contain any sulfate groups. The backbone is made up of one to several thousand repeating disaccharides of glucuronic acid and *N*-acetylglucosamine. As discussed earlier, hyaluronan specifically binds to a domain in aggrecan that is essential for the formation of aggregates.

Hyaluronan also interacts with specific cell-surface receptors. These receptors are CD44 molecules⁶⁸ that interact with a minimally long hexasaccharide sequence of the polymer. The interactions with hyaluronan are important for organizing the pericellular environment and providing signals to the cell. CD44 occurs in many different splice forms with variable presence on different cells, but a role for such variability in joint disease is unclear. Another receptor for hyaluronan is RHAMM,⁶⁹ also a signaling receptor and, like CD44, present on a variety of cells.

Ligands for heparan sulfate/syndecans

In addition to the heparin-binding domains present in fibronectin, various other matrix proteins contain such domains. Examples are most members of the thrombospondin family, with the exception of COMP, many MMPs, CILP, and PRELP.¹ As discussed above, isolated heparin-binding domain fragments can have variable effects on, for example, cells, depending on their fine structure. Effects range from inducing cartilage breakdown *in vitro* and *in vivo* to decreasing bone breakdown by targeting osteoclast precursors.

Interestingly, as discussed earlier, the N-terminal tyrosine sulfate domain of fibromodulin can mimic heparin in many interactions and bind other proteins to crossbridge networks, as well as sequester growth factors.

OTHER MOLECULAR FUNCTIONS

In joint disease, inflammation is a frequent component causing pain and limiting function. The inflammation is usually chronic, and one issue is whether components from cartilage can propagate the inflammatory activity. It is a long-standing observation that when cartilage is removed in joint arthroplasty, the inflammation recedes, thus indicating that factors released from the tissue have a role in propagating inflammation.

It has been shown that some patients with rheumatoid arthritis have circulating antibodies to collagen type II. Furthermore, an arthritis condition can be elicited by injecting mice and rats with collagen type II (collagen-induced arthritis). The disease can be transferred by antibodies to specific collagen type II epitopes.⁷⁰ It is hence possible that antibody binding activates complement and inflammation.

More recent findings indicate that matrix proteins may activate innate immunity. Fibromodulin has been shown to be as active as immune complexes⁷¹ in activating the classical pathway of complement, although it does not bind to the same site. Fibromodulin binds to the head domains of C1q rather than to the triple-helical stalk region with ensuing deposition and activation of C4 and C3.

Interestingly, fibromodulin can also recruit factor H by binding to a different site than that for C1q and thereby inhibit further activation of the complement cascade. Whether different fragments released in disease will have different roles in complement activation remains to be shown.

In other experiments it has been demonstrated that biglycan can also bind the triple-helical stalk of the complement factor C1q and in so doing inhibit activation of the classical pathway of complement. It appears that other LRR proteins such as biglycan and decorin can also bind factors involved in regulating the complement cascade. One example is a tight interaction with C4BP having a role in regulating complement activity.⁷²

COMP is a potent activator of the alternative pathway via its C-terminal globular domain. Interestingly, this activity can be observed in synovial fluid from subjects with both osteoarthritis and rheumatoid arthritis, as well as in blood in the form of COMP-C3b complexes created between the activator COMP and the C3b fragment formed.⁷³

Binding and sequestering growth factors in the extracellular matrix

The ECM of cartilage contains a number of factors that are sequestered and thereby bind to specific interaction partners. On degradation of the matrix one can envisage that these factors are released and affect cellular activities. In particular, a number of growth factors have been found to have the capacity to bind to matrix proteins.

Transforming growth factor- β

TGF- β has been shown to bind to a number of matrix proteins, and binding to some members of the LRR protein family has been investigated in particular. All three TGF- β variants bind to bacterially expressed decorin, biglycan, and fibromodulin, as well as to these proteins with the full range of posttranslational modifications. More recently, there are indications that asporin can also bind TGF- β . It has been demonstrated that active TGF- β is released from decorin on treatment with MMP-3. Indeed, cartilage contains substantial amounts of TGF- β , which has been extracted and purified from the tissue.

Fibroblast growth factor

Some matrix proteins contain heparan sulfate side chains, which are likely to bind growth factors within the FGF family. In the case of syndecan at the cell surface, these side chains appear to be involved in presenting the growth factor to its receptor.⁷⁴

Other molecules in the extracellular matrix

Perlecan was found to have a central role in cartilage development when a mouse with the gene inactivated was developed. Most of these mice die during early development as a result of problems with the heart and major blood vessels, but those that survive until birth show major growth disturbances with an extensively altered growth plate lacking a large proportion of the collagen fibers.⁷⁵ Further studies have revealed that chondroitin sulfate side chains specific for perlecan can actually accelerate and catalyze collagen fiber formation.⁷⁶

FRAGMENTS OF MATRIX PROTEINS RELEASED DURING CARTILAGE BREAKDOWN AS MOLECULAR INDICATORS OF DISEASE

In processes resulting in destruction of cartilage tissue, proteolytic enzymes degrade ECM proteins. Some of the fragments formed will no longer be retained in the tissue but are released to surrounding body fluids. By using sensitive immunoassays such fragments can be quantified in synovial fluid or serum. This so-called molecular marker technology (biomarkers) is intended to provide new means of assaying ongoing active processes in articular cartilage. With further development such techniques may be used in diagnosis, for estimation of the activity of the tissue-destroying process, to document effects of therapeutic intervention, and most importantly, to discover processes during the early stage before clinical symptoms become apparent. One example is the demonstration that COMP can be used to identify patients who will have the most extensive joint destruction in both osteoarthritis and rheumatoid arthritis.^{33,79} Also, a number of collagen fragments created by cleavage with collagenases, as well as by subsequent gelatinase activity, have been used to monitor disease.^{80,81} With further development of the technology we hope to be able to identify indicators specific to a particular pathologic process in a given tissue. Thus, it should be possible to identify the activity of a process in the meniscus on the one hand and activity in cartilage on the other.

As discussed earlier, some of the fragments released will activate immune responses with the potential to further enhance disease activity.

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Other molecules in the extracellular matrix—additional material

GP-39 is a protein upregulated in osteoarthritis. It shares homology with a chitinase, but the true activity of the protein is not known.⁷⁷ GP-39 is additionally expressed in a number of other tissues, particularly in disease.

Cartilage matrix also contains a number of proteins that are made elsewhere and are normally found primarily in the circulation. There is a preference for certain proteins, and low-molecular-weight basic proteins (e.g., lysozyme) in particular appear to bind to the matrix.⁷⁸ Whether these molecules contribute specific functions is not known.

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6

Bone structure and function

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- Bone is organized differently and for different functions at the organ, tissue, and molecular levels.
- Noncollagenous proteins function as structural support in the bone matrix and regulate mineral deposition, crystal growth, and cell attachment.
- Bone mineralization is effected through hormonal action (fibroblast growth factor 23 [FGF-23]) as well as through the bioactivity of intracellular and secreted matrix proteins with emerging roles (dentin matrix protein-1, FAM20c, and matrix extracellular phosphoglycoprotein).
- Growth factors including insulin-like growth factor 1, the autocrine/paracrine FGFs, and transforming growth factor- β play key roles in bone growth and structure.
- Osteoclasts are the primary bone-resorptive cells and originate from precursors of the hematopoietic lineage upon stimulation with receptor activator of nuclear factor- κ B ligand (RANKL) and macrophage colony-stimulating factor.
- The rate of osteoclast generation determines the extension of the bone-remodeling unit, whereas the life span of osteoclasts determines the depth of resorption.
- Osteoblasts are responsible for bone formation and originate from mesenchymal progenitors that also give rise to chondrocytes, muscle cells, and adipocytes.
- Osteocytes form a network that senses mechanical and hormonal environmental cues and orchestrates the function of osteoblasts and osteoclasts.
- Osteocytes produce and secrete factors (sclerostin/Sost, RANKL, osteoprotegerin) that affect other bone cells by paracrine/autocrine mechanisms and also secrete hormones (FGF-23) that affect other tissues by endocrine mechanisms.
- Four dynamic processes—growth, modeling, remodeling, and repair—control skeletal development and adaptation, defined by the relationship of bone resorption and bone formation to each other.

INTRODUCTION

Bone is a complex natural composite material that undergoes millions of loading cycles during a lifetime without failure. Its structure is hierarchical, being organized differently at the organ (whole bone), tissue (material), and molecular (collagen-mineral) levels.

The mechanical functions of bone are the most widely recognized and are often described in terms of strength and stiffness. Although strength and stiffness are important, bone is particularly effective at dissipating energy that could cause a fracture over repeated cycles of loading. Beyond its mechanical function, the marrow cavity and the porous trabecular bone in the ends of long bones and in the vertebrae and iliac crest are regions in which red blood cells are formed and stored. Bone is in fact a primary blood-storing organ. Additionally, bone is the body's primary storehouse of calcium and phosphorus; 99% of the body's calcium is stored in bone. These minerals are necessary for the proper function of a variety of systems in the body and are essential for enzyme reactions, blood clotting, the proper function of contractile proteins in muscles, and the transmission of nerve impulses.

ORGANIZATION OF BONE

Macroscopic (organ) level

Bone at the organ level consists of the diaphysis (shaft), the metaphysis and the epiphysis (Fig. 6.1). In the long bones of growing children, the growth plate separates the epiphysis from the metaphysis. The primary component of the diaphysis is cortical or compact bone. The haversian canals in cortical bone create a porosity of about 3% to 5%, although this increases in older age and with osteoporotic changes to the skeleton. Compact bone is also found surrounding the spongy bone of the vertebral body and in the skull. It is very strong and provides both support and protection.

Cancellous (trabecular or spongy) bone is found in the metaphyses of the long bones and in the vertebrae, surrounded by cortical bone. During growth, the primary spongiosa is composed mostly of disorganized woven bone, or primary lamellar bone surrounding a core of calcified cartilage. It is separated from the remodeled, more highly oriented secondary spongiosa by an arbitrary boundary. The secondary spongiosa reflects patterns of stress and functions largely to funnel stresses to the stronger and more massive cortical bone. In regions beneath joint surfaces it also attenuates forces generated by mechanical loading and may protect the joint surface from loading-related trauma. The cancellous bone itself is composed of plates and rods of bone, each about 200 μ m thick, with a porosity of about 75% to 85%. The marrow in the spaces between the trabecular struts are regions in which red blood cells are formed (red marrow). In osteoporosis, the differentiation of cells in the bone lineage can be partly diverted to adipocytes, and the marrow becomes more fatty (yellow marrow). Because cancellous bone has a large surface area in contact with vascular marrow, it is ideal for the long-term exchange of calcium ions. In osteopenia, regions of cancellous bone are affected first. This is why the vertebral column, which is mainly composed of cancellous bone, is affected earlier and more severely in osteoporosis than even the femoral neck and hip.

Microscopic (tissue) level

At the microstructural level, bone is organized differently for different functions (Fig. 6.2). In humans bone tissue can be divided into three broad categories based partly on the arrangement of the collagen fibers and partly on whether it has replaced preexisting bone: (1) woven bone, (2) primary bone, and (3) secondary bone.

Woven bone is characterized by randomly oriented collagen fibers, which tend to be smaller in diameter than those in more highly organized primary or secondary bone. Woven bone is not lamellar, is very porous, and may become highly mineralized. Woven bone can be deposited *de novo* without any bony or cartilaginous substrate or anlage, but it can also be formed as part of the process of endochondral ossification, either at the growth plate during development or during fracture repair. Woven bone proliferates rapidly because it has a large cell-volume ratio, which makes its role in fracture repair ideal. It is often found associated with osteosarcoma, probably because of proliferation especially of the cellular periosteum. The function of woven bone is primarily mechanical, rapidly providing both temporary strength and scaffolding upon which lamellar bone may be deposited. However, it can also be associated with pathologic processes that involve inflammatory cytokines.

Primary bone must be deposited on a preexisting substrate and is organized into lamellar layers. Because of this, trabecular plates, which are composed mainly of primary lamellae, cannot be replaced once they are perforated. This accounts for the loss of trabeculae with age and is part of



Fig. 6.1 At the organ level, bone consists of compact (cortical) bone, which forms a shell around the more porous, cancellous (trabecular) bone, or spongiosa. In the cancellous regions of the long bones, such as the proximal tibia shown here, the primary spongiosa is separated from the secondary spongiosa by an arbitrary boundary. Primary spongiosa is composed of primary bone, often laid down during growth on a calcified cartilage core that is subsequently remodeled. Secondary spongiosa is remodeled, reflects patterns of stress, and directs these stresses to the cortical shell.

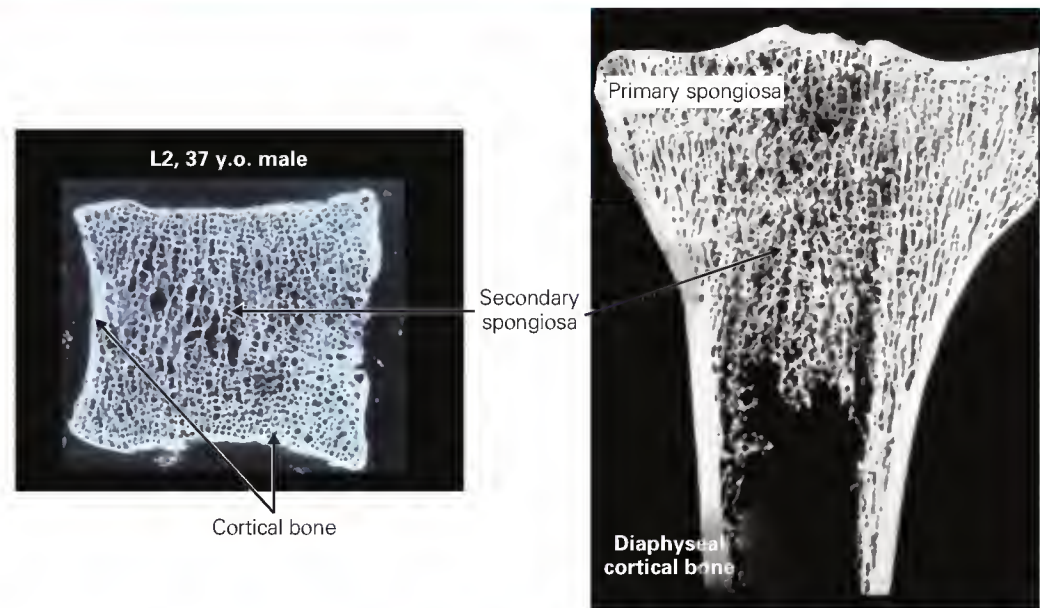
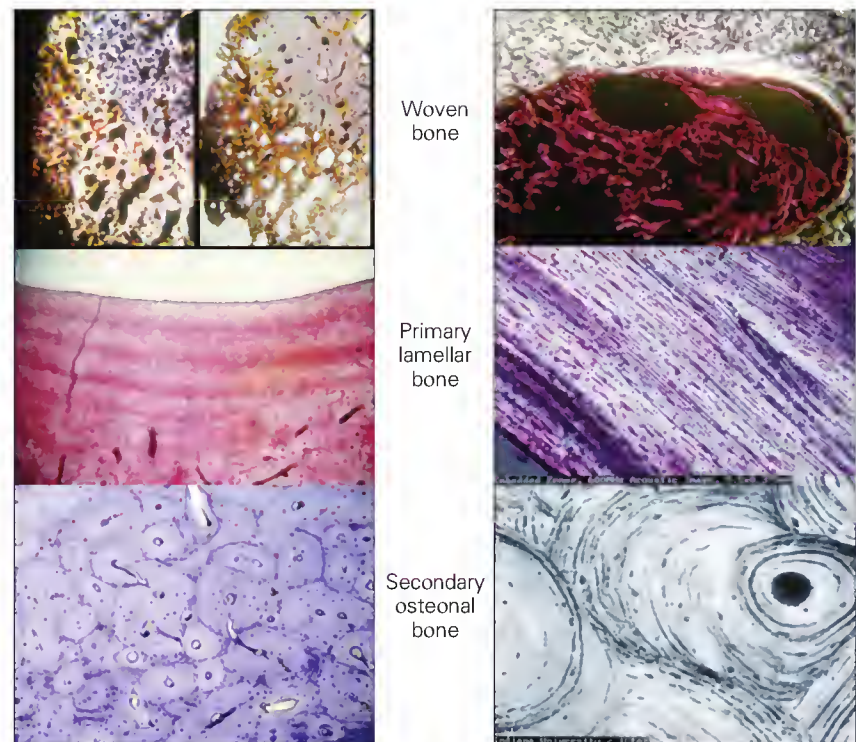


Fig. 6.2 These photomicrographs show the three general microscopic types of bone, defined morphologically. Woven bone is composed of disorganized, randomly oriented collagen fibers. It is found at sites of fracture or inflammation. Lamellar bone can be divided into primary and secondary. Primary bone is deposited in layers by direct apposition on a substrate. It is found circling the endocortical and periosteal circumferences of a long bone, and within trabeculae. Secondary bone is formed by replacement of primary bone through the process of resorption and subsequent new bone formation. (Woven bone: polarized light. Primary lamellar bone: *left*, basic fuchsin; *right*, polarized light. Secondary osteonal bone: *Left*, toluidine blue; *right*, scanning electron microscopic image.)



the reason that it is difficult to reverse osteoporotic changes once trabecular connectivity has been lost. Primary lamellar bone also forms in rings around the endocortical and periosteal surfaces of whole bone (circumferential lamellae). Primary lamellar bone itself is not very vascular and can become very dense. Primary bone can also be arranged in concentric rings around a central canal—much like a secondary haversian system, except without a definable cement line. These primary osteons tend to be small with few concentric lamellae. In reality, primary osteons are modified vascular channels that have “filled in” by the addition of lamellae to the surface of the vascular space.

Secondary bone is the product of the resorption of preexisting bone and its replacement with new bone. This can occur within dense cortical bone (resulting in a secondary osteon, or haversian system) or begin on the surfaces of trabeculae (sometimes called a *hemi-osteon*). The distinction between primary and secondary bone is important because it is likely that control of primary bone apposition is different from replacement of preexisting bone by secondary bone. A secondary haversian system has a central vascular canal 50 to 90 μm in diameter. The blood vessels in the canal have the characteristics of capillaries and are generally paired within the canal. Venous sinusoids and lymphatic vessels are not found in haversian canals,

although it has been suggested that prelymphatic vessels may exist.¹ The vessel walls contain no smooth muscle but are fenestrated capillaries lined by an incomplete layer of endothelial cells, similar to vessels in other blood-forming organs like the spleen and bone marrow.² The vessel is accompanied about 60% of the time by two to seven unmyelinated or poorly myelinated nerve fibers.³ Because the capillaries have no smooth muscle, these nerves do not serve a vasomotor function but are primary sensory nerves or autonomic nerves from the sympathetic nervous system. Both primary afferents and sympathetic nerve fibers express neuropeptides that may play some role in regulating bone remodeling. Afferent nerve fibers also express GAP43, which is associated with axonal growth, and may reflect the need for vessel growth and reinnervation during bone remodeling.

Lining cells (resting osteoblasts) cover the haversian canal, which is surrounded by a series of concentric lamellae containing bone cells—osteocytes. The relationship between the size of the osteon and the size of its canal is a measure of the balance between bone resorption (osteon diameter) and bone formation (canal diameter). The secondary osteon is bounded by a cement line, probably composed largely of sulfated glycosaminoglycans.⁴ The cement line forms an effective boundary that can arrest cracks in bone and stop them from growing to a critical size.

COMPOSITION OF BONE

Bone is composed of organic and mineralized components, mainly consisting of a matrix of cross-linked type I collagen mineralized with nanocrystalline, carbonated apatite. Bone matrix incorporates a small fraction of noncollagenous proteins that serve to control collagen assembly and size as well as the process of mineralization and cell attachment. The mineral comprises about 65% to 67% of the bone by weight, the organic component about 22% to 25%, and water the remaining fraction (approximately 10%). Within the organic fraction, collagen makes up about 90%, with the remainder accounted for by several minor collagens (types III and V) and a variety of noncollagenous proteins, most of them extracellular, with cell protein accounting for about 15% of the noncollagenous proteins in bone.

Type I collagen in bone is formed by a triple helix composed of two $\alpha 1$ chains and a single $\alpha 2$ chain. At either end of the collagen molecule are an N-telopeptide and a C-telopeptide, which can be cleaved when bone is resorbed and which are used to measure bone resorption biochemically. These individual triple helical collagen molecules self-associate into a periodic arrangement of parallel molecules spaced in quarter-staggered array at distances of 67 nm between their ends to form collagen fibrils (Fig. e6.1). The spaces between the ends of the collagen molecules are known as *hole zones*, and the 35-nm gap zones that run longitudinally parallel between the molecules are known as *pores*. Poorly crystalline hydroxyapatite [$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$] nucleates within these spaces. The initial deposition of mineral—or primary mineralization—occurs rapidly after new bone is deposited, with about two thirds of the eventual mineral content achieved within about 3 weeks.⁵ As the bone tissue matures, the mineral crystals grow, become more platelike, and orient themselves parallel to one another and to the collagen fibrils. This process of crystal growth is sometimes called *secondary mineralization* and occurs over the next year or so until full mineralization is achieved. In cancellous bone, the c-axis or long axis of the mineral crystal aligns with the longitudinal axis of the trabeculae, whereas in cortical bone the mineral orients to the long axis of the osteon. Other elements can easily substitute into the hydroxyapatite crystal, changing its character and its ability to withstand mechanical loads. Collagen fibers can become cross-linked through the action of enzymes, which results in either immature or reducible (divalent) cross-links or mature and irreducible (trivalent) cross-links such as pyridinoline and deoxypyridinoline, which are formed from divalent forms through the action of lysyl oxidase. Divalent cross-links are rapidly converted into mature trivalent cross-links under normal circumstances, and so the quantity of divalent cross-links in bone is an indirect measure of remodeling rate. Divalent and trivalent cross-links are associated with the N- and C-terminals of the collagen molecule. Cross-links can also be formed between the fibers without the action of enzymes. These cross-links are formed by the condensation of arginine, lysine, and free sugars, or through various oxidation reactions, which results in the formation of advanced glycation end products. Accumulation of advanced glycation end products occurs in diabetes, making the bone more brittle and increasing the risk of fracture.

The skeletal noncollagenous proteins comprise 10% to 15% of total bone protein. These molecules constitute a wide range of polypeptide species and have roles in multiple skeletal processes in addition to functioning as structural scaffolding within the bone matrix.

Proteoglycans

Proteoglycans (PGs) are a ubiquitous family of molecules composed of a core protein and one or several covalently attached sulfated glycosaminoglycan chains. The glycosaminoglycans are linear polymers of repeated disaccharide units of hexosamine and hexuronic acid, except for keratan sulfate, in which hexuronic acid is replaced by galactose. The core proteins attached to the glycosaminoglycans are a diverse protein group and range in size from 10 to 500 kDa. The wide variety of protein structure may aid in directing the unique functional roles of each PG family.

The bone matrix contains PG families of several primary structures, including the following:

1. *Hyaluronan/CD44, chondroitin sulfate-containing* PGs are expressed in several regions of bone. Hyaluronan is expressed in focal regions within periosteum and endosteum, and surrounding most of the major bone cell types including osteoblasts, osteoprogenitor cells, osteoclasts, and osteocyte lacunae. CD44 is a cell-surface hyaluronan receptor that may play roles in guiding bone development and has been localized to osteoclasts, osteocytes, and bone marrow cells.⁶ Versican, a chondroitin sulfate-containing PG, may be enriched

during early osteoid formation and may provide a temporary framework in newly formed cartilage matrix during bone development.⁷ Results from studies of a mouse model carrying a disrupted versican gene (the hdf transgenic mouse) also suggest that mature versican PG may be essential for precartilaginous aggregation.⁸

2. *Heparan sulfate PGs (HSPGs)* are produced by osteoblast and osteoclast lineage cells. These molecules play important roles in cell-cell interactions during bone formation by trapping autocrine and paracrine heparin-binding fibroblast growth factor (FGF) family members, as well as acting as coreceptors with the FGF receptors. Also, other secreted molecules bind HSPGs, such as transforming growth factor- β (TGF- β , betaglycan) and osteoprotegerin (syndecans). The bioactivity of these factors is modulated by HSPGs, potentially through focusing of concentrations of these potent molecules near differentiating cells.
3. *Small leucine-rich PGs* are the most abundant of the PGs in bone matrix and include decorin, biglycan, fibromodulin, lumican, and osteoadherin. These molecules help to provide the structural organization of the bone matrix and interact with specific growth factors and collagen to increase factor concentration and bioactivity in the matrix (Fig. 6.3). The localization of these proteins in mature bone varies; decorin may localize with specific matrix areas, whereas biglycan is evenly distributed throughout the matrix. Decorin-null animals have alterations in collagen fibril size and bone shape,⁹ whereas biglycan-null animals demonstrate reduced bone mass due to lower osteoblast numbers and also show reduced numbers of osteoclasts.¹⁰ Small leucine-rich PGs play an essential role in the regulation of growth factor activity. In this regard, decorin, biglycan, and fibromodulin all possess the ability to bind to TGF- β ; however, decorin is the best-characterized of these proteins for the ability to bind this factor. Decorin enhances TGF- β binding with its cognate receptors and enhances its bioactivity, and, in concert, may act to sequester TGF- β in the collagen fibrils, thus reducing its activity. TGF- β activity is associated with increased apoptosis of osteoprogenitors; therefore biglycan and decorin appear to be essential for maintaining mature osteoblast numbers through regulation of the proliferation and survival of bone marrow progenitor cells.

Osteocalcin

Osteocalcin (OC) is a polypeptide posttranslationally modified to carry dicarboxylic glutamyl (Gla) residues, which relies on vitamin K for proper production (another identifier for OC is bone γ -carboxyglutamic acid [Gla] protein [BGLAP or BGP]). In humans, vitamin K is primarily a cofactor in the enzymatic reaction that converts glutamate residues into γ -carboxyglutamate residues in these vitamin K-dependent proteins including OC but also in proteins involved in blood clotting such as factor IX. These Gla-containing motifs are thought to enhance calcium binding, which may function to control mineral deposition and bone remodeling. A nine-residue domain proximal to the N-terminal of secreted OC shares high homology with the corresponding regions in known propeptides of the γ -carboxyglutamic acid-containing blood coagulation factors. This common structural feature may be involved in the posttranslational targeting of these proteins for γ -carboxylation.

OC may also act as a hormone to regulate the activity of osteoclasts and their precursors. In support of this, the skeleton of the OC-null animal manifests osteopetrosis compared with wild-type litter mates. In humans, OC is expressed largely by osteoblasts and osteocytes, and the measurement of this protein in serum has been used as a marker of bone turnover. OC messenger RNA (mRNA) is upregulated by vitamin D through interactions with *trans*-acting factors in vitamin D response elements in the OC promoter.¹¹ Due to its cell-specific expression, the OC promoter has proven to be invaluable as an active, functional DNA to drive foreign complementary DNAs in osteoblasts in transgenic animals.

Osteopontin

Osteopontin (OPN), also referred to as *secreted phosphoprotein-1*, is a member of the SIBLING (small integrin-binding ligand N-linked glycoprotein) family, which is a group of noncollagenous extracellular matrix proteins involved in bone mineralization. The genes coding for these proteins are localized to human chromosome band 4q21-25, have similar exon arrangements, and also include those coding for dentin matrix protein-1, dentin sialoprotein, dentin phosphoprotein, integrin-binding sialoprotein, and matrix extracellular phosphoglycoprotein (MEPE). The SIBLING proteins share common structural features, such as multiple phosphorylation sites, a highly acidic nature, the presence of an arginine-glycine-aspartic

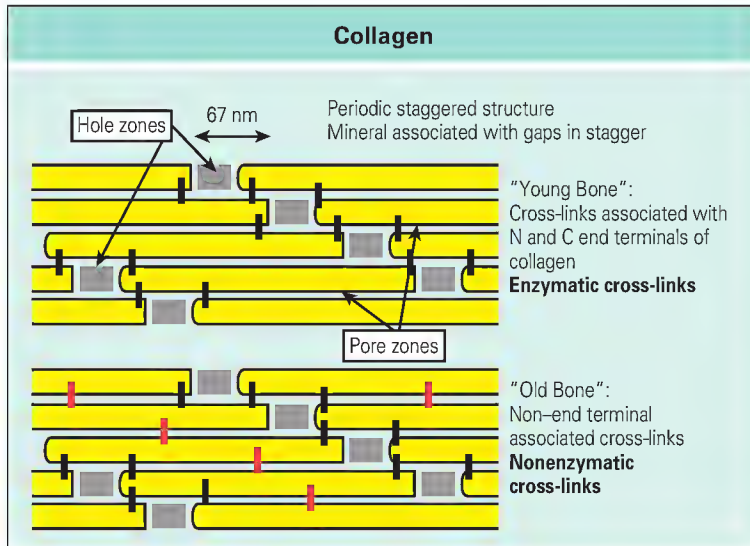
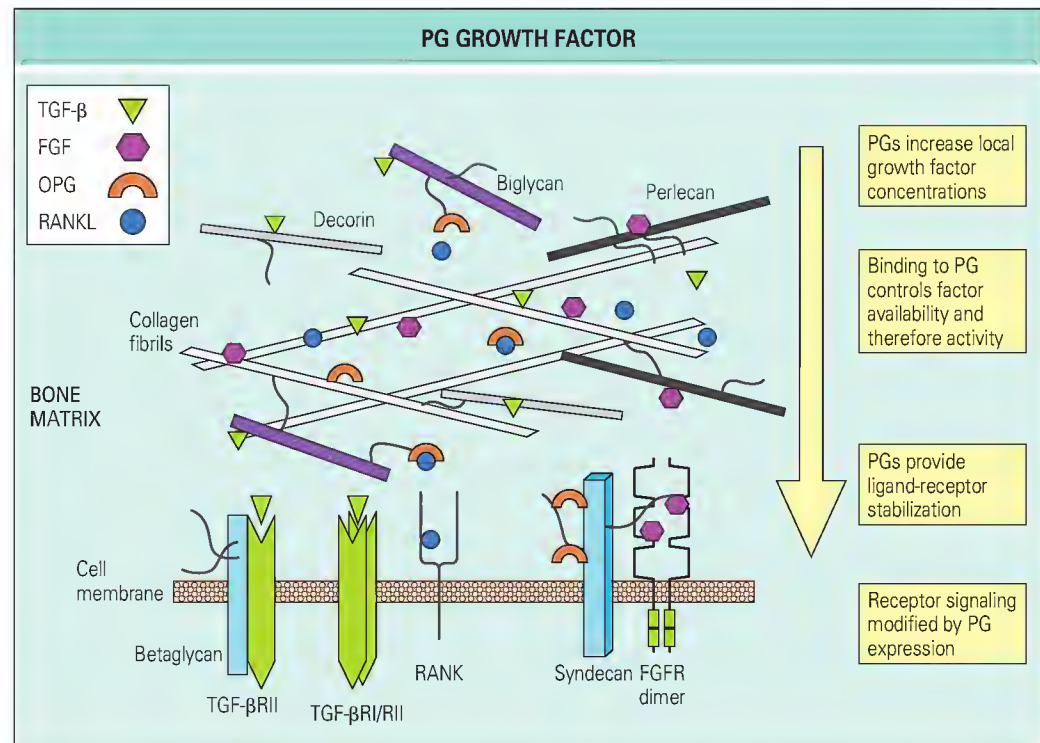


Fig. e6.1 In the collagen fibril, molecules are organized in a quarter-staggered array, with hole and pore zones between them where mineral can deposit. The hole zones give the collagen fibril its banded appearance when viewed by electron microscopy. Cross-links are formed either through the action of enzymes (divalent and trivalent cross-links) or through nonenzymatic processes, the latter forming advanced glycation end products that can make bone behave in brittle fashion.

Fig. 6.3 Proteoglycans (PGs) regulate growth factors at several levels in the bone matrix and in bone cells. These polypeptides trap and locally concentrate endocrine and paracrine growth factors within the matrix. Soluble PGs such as decorin, biglycan, and perlecan also modulate activity through binding, thus controlling the concentrations of bioavailable factor. Membrane-bound PGs such as betaglycan and syndecan modulate ligand-receptor interactions and thus play roles in regulating intracellular signaling. FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor- κ B; RANKL, receptor activator of nuclear factor- κ B ligand; TGF- β , transforming growth factor- β ; TGF- β RI/RII, transforming growth factor- β receptor types I and II. (Adapted from Lamoureaux F, Baud'huin M, Duplomb L, et al. Proteoglycans: key partners in bone cell biology. *Bioessays* 2007;29:758-771.)



acid cell attachment domain, and proteolysis-resistant acidic serine aspartate-rich MEPE-associated motif.

OPN has a high sialic acid content and is produced by osteoblasts under stimulation by calcitriol. OPN is expressed within cement lines and may thus act as a promoter of adhesion and allow the arrangement of dissimilar tissues together in biologic composites such as teeth and bone.¹² OPN binds tightly to hydroxyapatite and may be involved in the anchoring of osteoclasts to the mineral of bone matrix. The vitronectin receptor, which has specificity for OPN, is focused within the osteoclast plasma membrane in the regions involved in the binding process. Long bones from OPN-null mice are indistinguishable from those from wild-type litter mates by radiography, but the relative amount of mineral in the more mature areas of the bone (central cortical bone) of the OPN-null mice is significantly increased, as is the mineral maturity (mineral crystal size and perfection) throughout all regions of the bone.¹³ *In vitro*, exogenous OPN inhibits inorganic pyrophosphate (PP_i)-dependent mineralization of a cultured osteoblast cell line.¹⁴ These findings indicate that OPN is a potent inhibitor of mineral formation as well as crystal growth and proliferation.

Osteonectin

Osteonectin, also referred to as *secreted protein acidic and rich in cysteine*, or SPARC, is a phosphoprotein that is the most abundant noncollagenous polypeptide expressed in bone. The mature protein binds selectively to hydroxyapatite, collagen fibrils, and vitronectin at distinct sites and may allow proper organization of the bone matrix through contacts with the cellular surface. Osteonectin also inhibits cellular proliferation through arrest of cells in the G1 phase of the cell cycle. It may regulate the activity of platelet-derived growth factor, vascular endothelial growth factor, and FGF-2. The osteonectin crystal structure has revealed a novel follistatin-like component and an extracellular calcium-binding region containing two EF-hand motifs. The osteonectin-null mouse develops severe osteopenia, which indicates that this gene may have roles in osteoblast proliferation and in mineralization.

Alkaline phosphatases and ectonucleotide pyrophosphatase/phosphodiesterases

Alkaline phosphatases are widely distributed and are membrane-bound glycoproteins that hydrolyze monophosphate esters.¹⁵ The liver-bone-kidney alkaline phosphatase, referred to as *tissue-nonspecific alkaline phosphatase* (encoded by the *ALPL* gene), acts as a lipid-anchored phosphoethanolamine and pyridoxal 5'-phosphate ectophosphatase. Loss-of-function mutations in the *ALPL* gene lead to hypophosphatasia, which is characterized by marked

defects in bone mineralization and is lethal in the infantile form. The PP_i produced by cells inhibits mineralization by binding to crystals, and the presence of PP_i may thus prevent the soft tissues from undergoing mineralization. The degradation of PP_i to inorganic phosphate by ALPL in bones and teeth may facilitate crystal growth; therefore it is thought that loss of function of the *ALPL* gene in hypophosphatasia results in accumulation of PP_i and reduced skeletal mineralization. Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) is a type II transmembrane glycoprotein and a member of the ENPP family. ENPP1 has broad specificity and cleaves phosphodiester bonds of nucleotides and nucleotide sugars as well as pyrophosphate bonds of nucleotides and nucleotide sugars. This protein may function to hydrolyze nucleoside 5'-triphosphates to their corresponding monophosphates and may also hydrolyze diadenosine polyphosphates. Loss-of-function mutations in ENPP1 result in autosomal recessive hypophosphatemic rickets type 2, characterized by a rickets phenotype and elevation of FGF-23¹⁶ (see below).

Thrombospondin 1 and 2

The thrombospondins (TSPs) are a family of secreted glycoproteins of high molecular mass. TSP1 and TSP2 share high homology and form 450-kDa homotrimers. Both TSP1 and TSP2 are expressed by mesenchymal cells and chondrocytes during cartilage formation. As osteoblasts replace the mineralizing cartilage, TSP2 expression decreases in chondrocytes and increases in the matrix within areas undergoing ossification. TSP1 and TSP2 are strong angiogenic factors and therefore may also play a role in controlling blood vessel organization in forming bone.

In the developing animal, TSP1 and TSP2 are expressed in temporal and spatial patterns distinct for each gene. TSP1 (mouse gene, *Thbs1*) and TSP2 (*Thbs2*) have both been disrupted in mice and have unique phenotypes associated with each gene. *Thbs1* is a regulator of TGF- β *in vivo*, and these null animals have lower viability and prolonged wound healing. For skeletal phenotypes, this model has spine curvature and craniofacial alterations. *Thbs2* mice have increased cortical bone density, higher numbers of mesenchymal stem cells, and a resistance to bone loss due to ovariectomy. The fact that the *Thbs2*-null mice demonstrate less bone resorption than wild-type controls following ovariectomy may suggest a role for this molecule in estrogen-dependent reductions in bone mass and in the control of osteoclast function.

Proteins involved in mineralization Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF-23) is a phosphaturic hormone produced in bone (Fig. 6.4), and the encoding gene was identified as the mutated gene

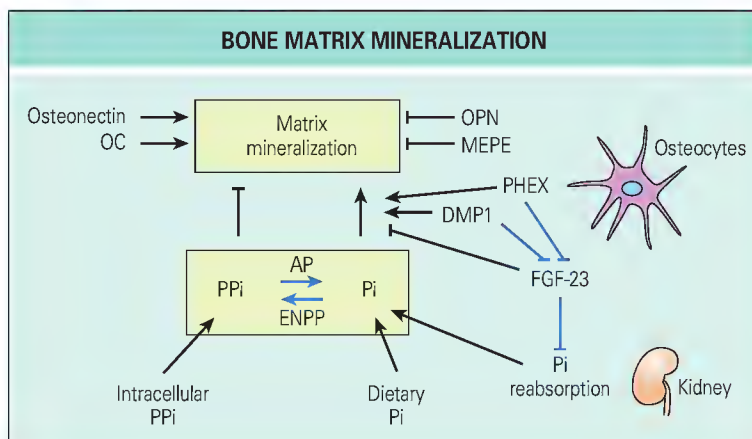


Fig. 6.4 Bone matrix mineralization involves an interplay of factors and is controlled by the balance between inorganic phosphate (P_i) and inorganic pyrophosphate (PP_i) and the expression of key local and systemic factors. An excess in P_i induces mineralization, whereas PP_i inhibits it. Proteins expressed in osteocytes and osteoblasts regulate mineralization. Specifically, PHEX and dentin matrix protein-1 (DMP1) induce mineralization, whereas fibroblast growth factor 23 (FGF-23) inhibits mineralization. Inhibition of mineralization by FGF-23 is believed to be due to inhibition of P_i reabsorption in the kidney, which would reduce blood and bone P_i levels. Induction of mineralization by PHEX and DMP1 may be secondary to inhibition of FGF-23 and thus increases in circulating P_i . The P_i levels in the extracellular matrix depend on dietary intake and on its rate of synthesis from PP_i catalyzed by alkaline phosphatase (AP). Conversely, the levels of PP_i depend on its conversion from P_i by ectonucleotide pyrophosphatase/phosphodiesterase enzymes (ENPP). Other bone-derived proteins such as matrix extracellular phosphoglycoprotein (MEPE), osteopontin (OPN), osteocalcin (OC), and osteonectin coordinately regulate mineralization, likely through direct interactions with the mineralized matrix. (Adapted from Bellido T, Plotkin LJ, Bruzzaniti A. Bone cells. In: Burr DB, Allen MR, editors. *Basic and applied bone biology*. San Diego: Academic Press; 2014, p. 27-46, Figure 14.)

in autosomal dominant hypophosphatemic rickets (ADHR), a metabolic bone disorder of isolated renal phosphate wasting.¹⁷ Full-length FGF-23 (32 kDa) is the biologically active form of the protein and is inactivated upon cleavage into 20- and 12-kDa protein fragments. Intracellular cleavage of FGF-23 occurs at a subtilisin-like proprotein convertase site (R₁₇₆XXR₁₇₉/S), which inactivates the protein. The human FGF-23 ADHR mutations R176Q, R179Q, and R179W destroy this site and stabilize the full-length active form of the protein. FGF-23 acts in the kidney to inhibit phosphate reabsorption by reducing expression of the proximal tubule type I sodium-phosphate cotransporters Npt2a¹⁸ and Npt2c. The subsequent low serum phosphate level results in marked osteomalacia and rickets, fracture, and dental anomalies. Application of *in-situ* hybridization to adult trabecular bone revealed the presence of FGF-23 mRNA in osteocytes and flattened bone-lining cells. In regions of active bone formation, newly formed osteocytes and osteoprogenitor cells also express FGF-23.¹⁹ FGF-23 levels are elevated *in vivo* by increased serum phosphate and 1,25-dihydroxyvitamin D concentrations, and FGF-23 then completes the feedback loop by reducing phosphate reabsorption and 1,25-dihydroxyvitamin D production in the kidney. Evidence also indicates that FGF-23 is directly regulated by parathyroid hormone (PTH) in osteocytes.²⁰

Whether FGF-23 has direct effects on the skeleton is uncertain, because the FGF-23 coreceptor α -Klotho is predominantly expressed in the kidney and parathyroid glands. However, because FGF-23 is produced in bone, FGF-23 expression and its actions on serum phosphate concentrations may be coordinated with intraskeletal signals to allow proper bone formation and mineralization.

PHEX

X-linked hypophosphatemia, a disorder of rickets and osteomalacia, is caused by inactivating mutations in *PHEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome).²¹ *PHEX* encodes a protein that is similar to the M13 family of membrane-bound metalloproteases such as neutral endopeptidase and endothelin-converting enzymes 1 and 2 (see Fig. 6.4). These proteases are known to cleave small peptide hormones. Mutations in *PHEX* lead to dramatic over expression of FGF-23;

however, the *PHEX* substrate and molecular mechanisms underlying this increase are currently unknown.

Dentin matrix protein-1

Dentin matrix protein-1 (DMP1), like OPN, is a member of the SIBLING gene family. DMP1 is highly expressed in osteocytes and is comprised of 513 residues but is secreted in bone and dentin as 37-kDa N-terminal (residues 17 to 253) and 57-kDa C-terminal (residues 254 to 513) fragments from a 94-kDa full-length precursor (see Fig. 6.4). Recombinant DMP1 binds calcium-phosphate ions and the N-telopeptide region of type I collagen with high affinities, so *in vivo* DMP1 may regulate local mineralization processes in bone and teeth. The C-terminal portion of DMP1 has been implicated in DNA binding, in gene regulation, and as an integrin-binding protein. Inactivating mutations in DMP1 result in the metabolic bone disease autosomal recessive hypophosphatemic rickets, which is associated with elevated FGF-23 levels in these patients. As shown in the *Dmp1*-null mouse (and in the Hyp mouse model of X-linked hypophosphatemia), the primary cellular defect caused by loss of *Dmp1* may be an alteration in osteoblast to osteocyte maturation, leading to inappropriate expression of typically “osteoblastic” or “early osteocyte” genes such as type I collagen, alkaline phosphatase, and FGF-23 in mature embedded osteocytes. The relationship of DMP1 to cell differentiation is currently unknown. Interestingly, FAM20c, a novel secreted kinase,²² has been shown to phosphorylate the SIBLING proteins DMP1 and MEPE (see next section). Loss of FAM20c in mice results in a DMP1-null phenotype,²³ which indicates a complex relationship between the phosphorylation of extracellular matrix proteins and their normal functions.

Matrix extracellular phosphoglycoprotein

Another member of the SIBLING family found in the mineralizing matrix is matrix extracellular phosphoglycoprotein, or MEPE (see Fig. 6.4). MEPE is predominantly expressed in odontoblasts and osteocytes embedded in the mineralized matrix. *In-vitro* studies of human osteoblast cell cultures indicate that MEPE expression is the highest during the mineralization phase.²⁴ *Mepe*-null mice display increased trabecular and cortical bone mass, due to increases in both osteoblast number and activity, and these mice are also resistant to age-dependent trabecular bone loss.²⁵ Taken together, these findings indicate that MEPE likely has a role as an important gene for the negative regulation of skeletal mineralization.

Growth factors

Multiple growth factors, either produced within bone or circulating to bone, are critical for skeletal development and function. These factors may be sequestered within bone matrix via the bloodstream or may be produced by the major bone cell types and act as paracrine and autocrine factors.

Insulin-like growth factors

The insulin-like growth factors IGF-1 (somatomedin C) and IGF-2 (somatomedin A) are produced primarily in the liver but are also produced in bone. These factors predominantly circulate complexed with IGF binding proteins (IGFBPs) to facilitate their transport to tissues. IGFBPs can either enhance or inhibit IGF activity. IGF-1 and -2 act through the IGF-1 receptors (IGFR1 and IGFR2) and possess bioactivity that promotes cell proliferation and differentiation.

The IGF-1-null mouse has reduced cortical bone and femur length; however, trabecular density is increased. *In-vitro* findings suggest that IGF-1 also increases osteoclastogenesis, and IGF-1-null mice have reduced levels of receptor activator of nuclear factor- κ B ligand (RANKL) in osteoblasts isolated from bone marrow. Therefore IGF-1 may regulate osteoclastogenesis through direct and indirect actions. Overexpression of IGF-1 specifically in osteoblasts leads to increased bone mineral density and increased trabecular volume, although osteoblast numbers are not increased.²⁶ These studies suggest that IGF-1 acts directly on osteoblasts to enhance their function. Specific removal of IGFR1 from osteoblasts results in decreased trabecular number and volume and a dramatic decrease in bone mineralization, which further supports the role of the IGFs with regard to osteoblasts. Less is known regarding the functions of IGF-2 in bone. However, it has been suggested that IGF-2 may be a local regulator of bone cell metabolism.

Bone morphogenetic protein family

Bone morphogenetic proteins (BMPs) are members of the TGF- β superfamily. There are now more than 20 BMP-related proteins, which are classified into subgroups based on structure and function. These factors play important roles in skeletal development by directing the fate of mesenchymal cells, through differentiation of these precursor cells into cells of the osteoblastic

lineage, and by inhibiting their differentiation into myoblastic lineage cells. BMPs also increase osteoclastogenesis, which is tightly coordinated with osteoblastogenesis. BMPs activate specific receptors and induce cell signaling by phosphorylating cytoplasmic receptor-regulated Smads, which enter the nucleus to recruit transcription factors and enhance gene expression. The human disorder fibrodysplasia ossificans progressiva is a disease of dramatic ectopic bone formation, which can be accelerated following blunt trauma. A recurrent mutation in activin receptor 1A/activin-like kinase 2, a BMP type I receptor, was reported as the molecular cause of fibrodysplasia ossificans progressiva.²⁷ These findings underscore the potent effects of BMP signaling on bone formation.

Fibroblast growth factors

Members of the FGF family of proteins primarily act as paracrine and autocrine factors and bind to one or several of four FGF receptors (FGFRs). FGFRs normally exist as an inactivated monomer. With FGF binding in the presence of heparin/heparan sulfate, the FGFRs dimerize, which leads to the autophosphorylation of tyrosine residues. The FGF family has potent effects on bone development. This is clearly evident by the fact that activating mutations in FGFR1 and FGFR2 are responsible for disorders of cranio-synostosis and limb patterning, and FGFR1 and FGFR3 mutations result in disorders of hypochondroplasia and achondroplasia. The FGFs interact with HSPGs and are sequestered within the mineralizing matrix. In addition, the HSPG syndecan may stabilize FGF-FGFR interactions and promote FGF signaling and bioactivity.

The FGF family members play important roles in bone development and formation. Expression of several FGF ligands including FGF-2, FGF-5, FGF-6, FGF-7, and FGF-9 has been observed in mesenchyme surrounding initial condensation. In limb bud, FGFR1 and FGFR2 are expressed in condensing mesenchyme. In rat growth plates, mRNAs encoding all four FGFRs and FGF-2 can be detected, and FGF-2 is also present in osteoblasts. FGF-2 treatment of osteoblasts enhances the binding of Runx2 to the Cbfa1 consensus sequence in the OC promoter and may therefore have a role in differentiation.

Transforming growth factor- β

Transforming growth factor- β (TGF- β) controls proliferation, differentiation, and other functions in many cell types. TGF- β 1, TGF- β 2, and TGF- β 3 all function through the type I and type II TGF receptors. The type I TGF- β receptor forms a heterodimer with the type II TGF- β receptor. TGF- β stimulation leads to activation of SMAD2 and SMAD3, which form complexes with SMAD4 that accumulate in the nucleus and regulate the transcription of target genes.

TGF- β 1 is the most abundant growth factor in human bone; it is localized within the bone matrix and has functions both during embryonic development and in mature bone. During embryonic development, TGF- β 1 plays a role in cell migration, controlling epithelial-mesenchymal interactions, and the formation of cellular condensations, which influence bone shape. This factor also plays a key role in inducing mesenchymal cell differentiation to either chondrocytes or osteoblasts. In adult bone, TGF- β 1 controls osteoblast differentiation, which affects matrix formation and mineralization. TGF- β 1 inhibits the expression of the differentiation markers Runx2 and OC in osteoblast cell lines, and its functions interplay with those of other systems in bone such as the PTH and the Wnt/ β -catenin systems.

The skeletal disorder Camurati-Engelmann disease (CED) highlights the importance of TGF- β 1 in skeletal formation. CED is a progressive diaphyseal dysplasia characterized by hyperostosis and sclerosis of the diaphyses of the long bones. The *TGFB1* gene was screened and three different heterozygous missense mutations were found in exon 4 in the nine families examined. All of the mutations in the CED patients were located either at C225 or near R218, which suggests the importance of this region in activating TGF- β 1 in the bone matrix.

Platelet-derived growth factor and vascular endothelial growth factor

All platelet-derived growth factors (PDGFs) and vascular endothelial growth factors (VEGFs) are dimers of disulfide-linked polypeptide chains, encoded by nine different genes that direct production of four different PDGF chains (PDGF-A, PDGF-B, PDGF-C, and PDGF-D) and five different VEGF chains (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor). All members of these families carry a growth factor core domain that is necessary for receptor activation. PDGFs mediate their bioactivity through two receptors, PDGFR- α and PDGFR- β . These receptors both have five extracellular immunoglobulin loops for ligand binding and an intracellular tyrosine kinase domain. The VEGFs act through a homologous family of receptors,

VEGFR1, VEGFR2, and VEGFR3. PDGFs act primarily as paracrine growth factors.

PDGF is chemotactic and mitogenic for osteoblasts and osteoprogenitor cells, and it upregulates cytokines that are crucial to bone healing. This factor also destabilizes blood vessels during healing to allow sprouting of new vessels. VEGF is produced by many cell types including fibroblasts, hypertrophic chondrocytes, and osteoblasts. VEGF may act not only in bone angiogenesis and vascular differentiation but also in aspects of development, such as chondrocyte and osteoblast differentiation, as well as osteoclast recruitment.

BONE CELLS

Bone development and the adaptation of the adult skeleton to mechanical needs and hormonal changes depend on the ability of bone cells to resorb and form bone in the right places and at the right time. Bone growth, modeling, and remodeling are defined by the spatial and temporal relationship between bone resorption and bone formation. Osteoclasts resorb bone, osteoblasts form bone, and osteocytes detect the need for bone augmentation or reduction and coordinate the activity of osteoclasts and osteoblasts.

Osteoclasts

Osteoclasts are the primary bone-resorptive cells. They are needed for bone modeling, which leads to changes in the shape of bones, and for bone remodeling, which maintains the integrity of the adult skeleton. Osteoclasts originate from precursors of the monocyte/macrophage family of the hematopoietic lineage that differentiate to multinucleated cells upon stimulation with RANKL and macrophage colony-stimulating factor (M-CSF) (Fig. 6.5). Upon completing bone resorption, all osteoclasts undergo programmed cell death or apoptosis and disappear from the bone surface.

Osteoclast morphology and function

Osteoclasts adhere firmly to bone through the interactions established between integrins expressed in the osteoclast membranes with collagen, fibronectin, and other bone matrix proteins. Expression of α_v and α_3 integrin is induced during osteoclast differentiation, and the integrin binds to the amino acid sequence Arg-Gly-Asp present in OPN and bone sialoprotein. The importance of these events for osteoclast activity is underscored by the inhibition of resorption with competitive Arg-Gly-Asp ligands²⁸ and a progressive increase in bone mass due to osteoclast dysfunction in mice null for β_3 integrin.

The intimate contact between the osteoclast and the bone matrix creates a space called the *sealing zone*. There is also polarization of the osteoclast fibrillar actin into a circular structure called the *actin ring*, containing podosomes composed of an actin core surrounded by $\alpha_v\beta_3$ integrins and associated cytoskeletal and signaling proteins. Thus the area in which the osteoclast apposes the bone is isolated from the general extracellular space and becomes acidified by the activity of a proton pump and a chloride channel.²⁸ The low pH in this area dissolves the mineral and exposes the organic matrix, which is subsequently degraded by the activity of lysosomal cathepsin K and matrix metalloproteases. These degrading enzymes are transported into acidified vesicles that fuse with the osteoclast plasmalemma forming a villous structure referred to as the *ruffled border*. This structure and the actin ring are essential features of a resorbing osteoclast, and abnormalities of either structure lead to arrested bone resorption.

The cytoplasmic domains of integrins serve as platforms for signaling proteins involved in osteoclast function, such as the kinase Src, which is crucial for osteoclast attachment and resorption. Src regulates podosome disassembly and ruffled membrane formation by its ability to interact with the focal adhesion-related kinase Pyk2 and the proto-oncogene c-Cbl. Rho, Rac, and the guanine nucleotide exchange factor Vav3, which activates guanosine diphosphatases into guanosine triphosphatases, also play a central role in modifying the resorptive capacity of osteoclasts by modulating the actin cytoskeleton. Osteoclast resorption products are transported in vesicles through the cytosol to the basolateral surface and discharged to the extracellular milieu or directly released to the surrounding fluid after osteoclast retraction from the resorption pits.

Osteoclast formation and differentiation

Mature, multinucleated osteoclasts are formed by fusion of mononuclear precursors of the monocyte/macrophage lineage (see Fig. 6.5). The earliest recognized osteoclast precursor is the granulocyte-macrophage colony-forming unit, which also gives rise to granulocytes and monocytes.

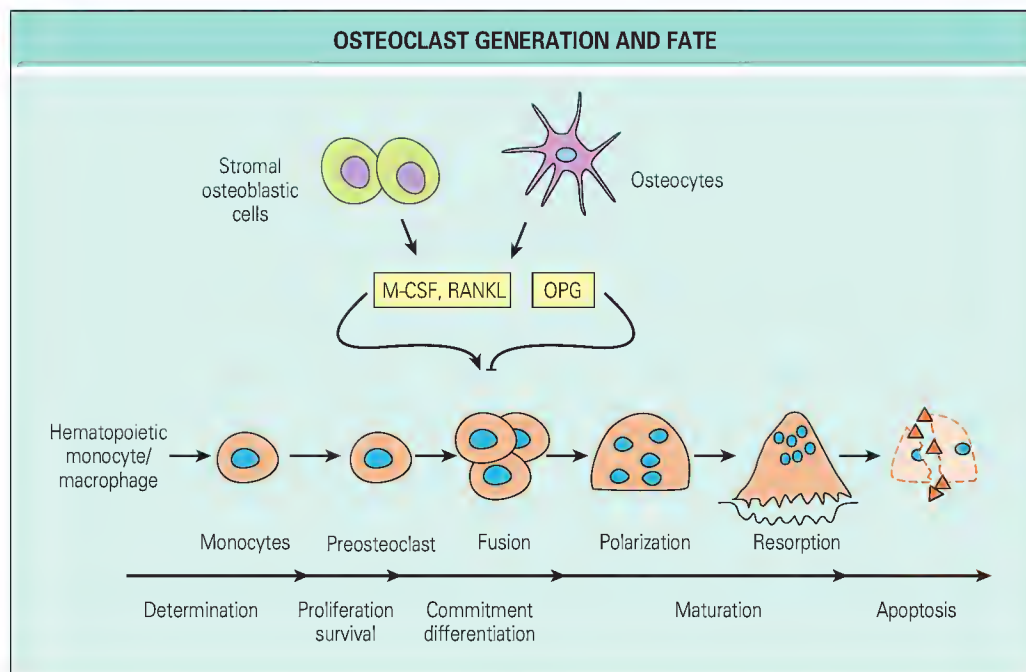


Fig. 6.5 Osteoclast differentiation is governed by receptor activator of nuclear factor- κ B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) secreted by osteoblasts and osteocytes, which control various steps of the osteoclast differentiation process, including precursor proliferation, commitment, differentiation, and maturation. Osteoprotegerin (OPG), which is also secreted by osteoblasts and osteocytes, acts as a decoy receptor for RANKL and reduces osteoclast differentiation. (From Bellido T, Plotkin LJ, Bruzzaniti A. Bone cells. In: Burr DB, Allen MR, editors. *Basic and applied bone biology*. San Diego: Academic Press; 2014, p. 27-46, Figure 5.)

Osteoclast precursors proliferate in response to growth factors such as interleukin-3 (IL-3) and colony-stimulating factors like granulocyte-macrophage colony-stimulating factor (GM-CSF) and M-CSF to form postmitotic, committed mononucleated osteoclast precursors, which differentiate and fuse to form multinucleated osteoclasts under the influence of RANKL, a member of the tumor necrosis factor (TNF) family of ligands.

M-CSF and RANKL are critical for osteoclastogenesis, and deletion of M-CSF, RANKL, or RANK, the receptor for RANKL expressed by osteoclasts and their precursors, inhibits osteoclast differentiation, leading to osteopetrosis in mice. Both M-CSF and RANKL are expressed by bone marrow stromal cells and osteoblastic cells, as well as T lymphocytes. Importantly, osteocytes have now been found to be a major source of M-CSF and RANKL, as well as osteoprotegerin (OPG), the RANKL decoy receptor,^{29,30} which suggests a central role of these cells in osteoclastogenesis (see Fig. 6.5). M-CSF contributes to osteoclast differentiation, migration, and survival by binding to its receptor c-Fms on osteoclast precursors, whereas RANKL facilitates osteoclast formation via direct binding to the receptor RANK. RANKL is expressed on the cell surface and is also secreted as a soluble form. Although the soluble form of RANKL is found in the circulation and its presence is sufficient to induce differentiation of osteoclast precursors *in vitro*, its actual role in osteoclast formation *in vivo* remains unproven.

RANKL expression is upregulated by hormones and cytokines known to induce osteoclast generation. This explains the long-observed property of primary osteoblastic cells or osteoblastic cell lines that, upon treatment with vitamin D, PTH, or IL-11, IL-6, TNF, and IL-1, support osteoclast development when co-cultured with osteoclast precursors derived from spleen or bone marrow. RANKL mediates several aspects of osteoclast differentiation, including fusion of mononucleated precursors into multinucleated cells, acquisition of osteoclast-specific markers, attachment of osteoclasts to the bone surfaces, stimulation of resorption, and promotion of osteoclast survival. Although M-CSF contributes to RANKL effects, RANKL appears to play a dominant role in bone resorption. Thus, whereas M-CSF-null mice recover with time from the decreased osteoclast number and activity, RANKL knockout mice do not. Furthermore, RANKL appears to stimulate osteoclast formation and resorption in mice even in the absence of functional M-CSF.³¹

RANKL activates several signal transduction pathways involving the recruitment of the adapter protein TRAF6 (TNF receptor-associated factor 6) to the intracellular domain of the receptor RANK. TRAF6 in turn activates kinase-dependent signaling as well as transcription factors. Among them, NF- κ B has been shown to undergo nuclear translocation leading to upregulation of c-Fos. Fos, in turn, binds to nuclear factor of activated T cells, cytoplasmic 1 (NFATc1) and upregulates genes crucial for osteoclast differentiation and function. Although other signaling pathways are activated by RANKL in osteoclasts, the evidence that deletion of NF- κ B, c-fos/AP1, and NFATc1 leads to osteoclast dysfunction demonstrates the crucial role of these genes in osteoclasts.³¹

OPG is an inhibitor of RANK activation and osteoclastogenesis that also belongs to the TNF family of receptors. OPG is a secreted protein with no transmembrane domain, and therefore it has no direct signaling capabilities. OPG suppresses osteoclast formation and resorption by binding to RANKL, thereby impeding RANKL interaction with RANK.

Osteoclast apoptosis

All osteoclasts undergo apoptosis and disappear from the bone surface after completing bone resorption. High concentrations of extracellular calcium, like the ones present in resorption cavities, induce osteoclast apoptosis *in vitro* and may be the triggering event. Fas ligand stimulates osteoclast apoptosis, and Fas-deficient mice exhibit more osteoclasts and decreased bone mass, which suggests that this pathway controls osteoclast life span *in vivo*. Osteoclast apoptosis might also result from loss of survival signals provided by integrin interactions with the matrix or by changes in the production of cytokines or growth factors that preserve osteoclast viability. Potential antiapoptotic factors are M-CSF and RANKL, the same cytokines that induce osteoclast differentiation. TNF- α and IL-1 also delay osteoclast apoptosis. All these cytokines activate the extracellular signal-regulated kinases (ERKs), which is required for osteoclast survival. Phosphatidylinositol 3'-kinase (PI3-K) and its target the kinase Akt are required for osteoclast differentiation but not for survival. Instead, mammalian target of rapamycin (mTOR), another PI3-K target, is required for the antiapoptotic actions of M-CSF, RANKL, and TNF- α in osteoclasts. Since mTOR is also activated by ERKs, it appears to be a point of convergence in the action of prosurvival kinases in osteoclasts.

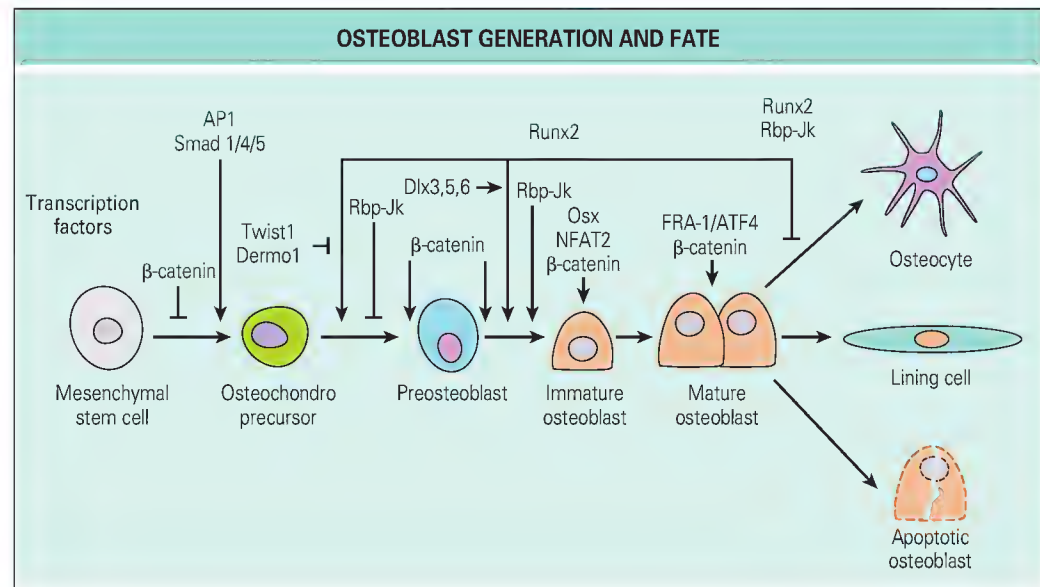
RANKL, TNF- α , and IL-1 also activate NF- κ B, a transcription factor shown to inhibit apoptosis in various cell types. Downregulation of NF- κ B mRNA inhibits IL-1-dependent survival, and blockade of NF- κ B binding to DNA with specific oligonucleotides induces apoptosis. However, osteoclast precursors lacking NF- κ B subunits have normal survival rates, and inhibition of NF- κ B activation via a dominant-negative IKK2 does not affect the ability of IL-1 to promote osteoclast survival. Therefore the relevance of NF- κ B signaling for osteoclast survival is still controversial.

Regulation of osteoclast generation and survival

In the bone-remodeling unit, the rate of osteoclast generation determines the extension of the bone-remodeling unit, whereas the life span of osteoclasts determines the depth of resorption. Although both genesis and apoptosis of osteoclasts lead to changes in osteoclast number and bone resorption, alteration of osteoclast life span might represent a more effective mechanism to accomplish rapid changes in bone resorption rate.

Sex steroids have profound effects on osteoclasts. Both estrogens and androgens inhibit osteoclast generation by regulating the production of pro-osteoclastogenic cytokines (such as IL-6 and IL-1) by cells of the stromal/osteoblastic lineage. Estrogens also induce apoptosis of mature osteoclasts. This, together with an inhibitory effect of the hormones

Fig. 6.6 Osteoblastogenesis is controlled by transcription factors that affect the proliferation and differentiation of osteoblast precursors. Mature osteoblasts can surround themselves by bone matrix and differentiate further to become osteocytes, flatten to cover the quiescent bone surface as lining cells, or die by apoptosis. (From Bellido T, Plotkin LI, Bruzzaniti A. *Bone cells*. In: Burr DB, Allen MR, editors. *Basic and applied bone biology*. San Diego: Academic Press; 2014, p. 27-46, Figure 7.)



on osteoblast generation, leads to attenuation of the rate of bone remodeling.

Mice receiving excess glucocorticoids exhibit reduced osteoclast progenitors, but cancellous osteoclast number does not decrease in the early phases of the disease, because glucocorticoids prolong the life span of preexisting osteoclasts. This effect may account for the early transient increase in bone resorption in patients with hyperglucocorticoidism. In contrast to the rapid pro-survival effect of glucocorticoids on mature osteoclasts, glucocorticoids induce a decrease in osteoclast formation caused by a reduction in the pool of osteoblastic cells that support osteoclastogenesis. This effect leads to the typical low remodeling rate observed in chronic glucocorticoid-induced osteoporosis.

Osteoblasts

Osteoblasts are the cells responsible for bone formation. They originate from mesenchymal progenitors, which also give rise to chondrocytes, muscle cells, and adipocytes (Fig. 6.6). Commitment of mesenchymal cells to the osteoblastic lineage depends on the specific activation of transcription factors induced by morphogenetic and developmental proteins that carry out the functions of bone matrix protein secretion and bone mineralization. Upon completion of bone matrix formation, some mature osteoblasts remain entrapped in bone as osteocytes, some flatten to cover quiescent bone surfaces as bone-lining cells, and most die by apoptosis.

Osteoblast function

The main function of osteoblasts is to synthesize collagen type I and other specialized matrix proteins that serve as a template for the subsequent mineral deposition in the form of hydroxyapatite. Mature osteoblasts actively engaged in this process are recognized by their location on the bone surface and by their morphologic features typical of cells secreting high levels of proteins: cuboidal shape with large nucleus, enlarged Golgi apparatus, and extensive endoplasmic reticulum. Osteoblasts express high levels of alkaline phosphatase and OC, and the level of these proteins in blood reflects the rate of bone formation.

Interaction of osteoblasts among themselves, with lining cells, and with bone marrow cells is established by adhesion junctions, tight junctions, and gap junctions. Adhesion junctions mainly mediated by cadherins and tight junctions serve to join cells and facilitate their anchorage to the extracellular matrix. Changes in the expression level of the major cadherins expressed in osteoblasts, N-cadherin and cadherin 11, influence osteoblast differentiation and survival. Intercellular communication among osteoblasts and neighboring cells is maintained by cell coupling via gap junctions. Opening of gap junction channels contributes to coupling and the coordination of responses within a cell population. The major gap junction protein expressed in bone cells is connexin 43. Its absence or dysfunction leads to impaired osteoblast differentiation, premature apoptosis of osteoblasts and osteocytes, and deficient response to hormones and pharmacotherapeutic agents.³² Furthermore, gap junction communication is fundamental for the maintenance of a continuum from bone, where osteocytes reside, through bone surface

cells, osteoblasts and osteoclasts, bone marrow cells, and endothelial cells of the blood vessels.³³ This functional syncytium might be responsible for the coordinated response of the bone tissue to changes in physical and chemical stimuli, as it will be discussed later. Interactions between osteoblasts and the bone matrix via integrins also modulate osteoblast differentiation, function, and survival. In particular, loss of antiapoptotic signals provided by the extracellular matrix causes apoptosis, a phenomenon referred to as *anoikis*.

Osteoblast formation and differentiation

The process of osteoblastogenesis can be divided into steps comprising proliferation, extracellular matrix development and maturation, mineralization, and apoptosis. Each stage is characterized by activation of specific transcription factors and genes leading to a succession of osteoblast phenotypic markers (see Fig. 6.6). Transcription factors of the helix-loop-helix family (Id, Twist, and Dermo) are expressed in proliferating osteoblast progenitors and are responsible for maintaining the osteoprogenitor population by inhibiting the expression of genes that characterize the osteoblast mature phenotype. Transcription factors of the activating protein family such as c-fos, c-jun, and junD, are expressed during proliferation as well as later in the differentiation pathway and may activate or repress transcription. Runx2 and osterix are essential for establishing the osteoblast phenotype. Their absence from the mouse genome results in lack of skeletal mineralization and perinatal lethality. Runx2 and osterix regulate the expression of other genes that control bone formation and remodeling including OC and RANKL. Runx2 regulates differentiation, survival, and function of osteoblasts by affecting several signaling pathways, including those activated by Wnts, BMPs, integrins, and the PTH receptor.

Osteoblast apoptosis

Upon completing the process of bone formation, 60% to 70% of osteoblasts die by apoptosis; the remainder becomes lining cells or osteocytes. Apoptosis occurs throughout all stages of osteoblast life.³⁴ The prevalence of osteoblast apoptosis in bone sections can be quantified by measuring fragmented DNA. Apoptosis of cultured osteoblasts has been extensively studied using several methods,³⁵ including increased activity of initiator or effector caspases, presence of cleaved genomic DNA by TUNEL or ISEL assay, and nuclear fragmentation and chromatin condensation using fluorescent dyes that bind to DNA. Examination of the nuclear morphology of cells transfected with fluorescent proteins containing a nuclear localization sequence has proven a particularly useful tool for studying apoptosis in cells cotransfected with genes of interest. Cell detachment from the substrate, changes in the composition of the plasma membrane, and changes revealing cell shrinkage are also features that have been used to detect and quantify apoptotic cells.

Regulation of osteoblast generation and apoptosis

Most major regulators of skeletal homeostasis influence both generation and survival of osteoblasts. The BMP and Wnt signaling pathways promote osteoblast differentiation, but whereas BMPs induce osteoblast apoptosis,

Wnts inhibit it. BMPs induce apoptosis of mature osteoblasts as well as of mesenchymal osteoblast progenitors in interdigital tissues during the development of the hands and feet. Wnt signaling has a profound effect on bone as shown by the high-bone-mass phenotype of mice and humans with activating mutations of low-density lipoprotein receptor–related protein 5 (LRP5), which together with Frizzled proteins are receptors for Wnt ligands. Wnts stimulate differentiation of undifferentiated mesenchymal cells toward the osteoblastic lineage and stimulate differentiation of pre-osteoblasts. Canonical Wnt signaling in osteoblasts also affects osteoclasts by enhancing the expression of the RANKL decoy receptor OPG, which leads to inhibition of osteoclast development. In addition, Wnt signaling inhibits apoptosis of mature osteoblasts and osteocytes.³⁶ The increased bone formation exhibited by mice lacking the Wnt antagonist known as *secreted frizzled related protein-1* (sFRP-1) is associated with decreased osteoblast and osteocyte apoptosis. The prevalence of osteoblast and osteocyte apoptosis is also decreased in mice expressing the high bone mass–activating mutation of LRP5 (G171V), which exhibit reduced ability to bind the Wnt antagonist sclerostin secreted by osteocytes. Consistent with this, sclerostin induces osteoblast apoptosis *in vitro*. Moreover, reduction of sclerostin levels by PTH and mechanical loading increases osteoblast number and activity as a result of stimulation of osteoblast differentiation and increased survival.^{37,38} Activation of Wnt signaling *in vitro* by ligands known to activate the so-called canonical as well as noncanonical pathways also prevents apoptosis of osteoblast progenitors and differentiated osteoblasts through a mechanism that involves the Src/ERK and PI3/AKT pro-survival kinases.³⁹

Glucocorticoids induce rapid bone loss resulting from a transient increase in resorption due to delayed osteoclast apoptosis. This initial phase is followed by a sustained and profound reduction in bone formation and turnover due to decreased osteoblast and osteoclast generation and increased osteoblast apoptosis.

Both persistent excess of PTH, as in hyperparathyroidism, and intermittent elevation of PTH (by daily injections) increase the number of osteoblasts. Sustained PTH elevation inhibits the expression of sclerostin, with a consequent increase in Wnt signaling and in differentiation of osteoblast precursors. A major effect of intermittent elevation of PTH is inhibition of apoptosis of osteoblasts, which thereby prolongs their life span and ability to form bone.

Osteocytes

Osteocytes are former osteoblasts that become entombed during the process of bone deposition and are regularly distributed throughout the mineralized bone matrix. Osteocyte bodies are individually encased in lacunae and exhibit cytoplasmic dendritic processes that run along narrow canaliculi excavated in the mineralized matrix. Osteocytes communicate with each other, with cells on the bone surface, and with cells of the bone marrow through gap junctions established between cytoplasmic processes of neighboring cells. Today it is accepted that osteocytes are the mechanosensory cells. Osteoblasts and osteoclasts are present on bone only transiently, in low number, and in variable locations. On the other hand, osteocytes are the most abundant resident cells and are present in the entire bone volume. Osteocytes are also the core of a functional syncytium that extends from the mineralized bone matrix to the bone surface and the bone marrow, and all the way to the blood vessels. This strategic location permits the detection of variations in mechanical signals as well as in levels of circulating factors, and allows amplification of the signals leading to adaptive responses.

Osteocyte apoptosis: consequences and regulation

Osteocytes are long-lived cells. However, like osteoblasts and osteoclasts, osteocytes die by apoptosis, and decreased osteocyte viability accompanies the bone fragility syndromes that characterize glucocorticoid excess, estrogen withdrawal, and mechanical disuse.³⁴ Conversely, preservation of osteocyte viability might explain at least part of the antifracture effects of bisphosphonates, which cannot be completely accounted for by changes in bone mineral density.⁴⁰

Preservation of osteocyte viability by mechanical stimuli

Osteocytes interact with the extracellular matrix in the pericellular space through discrete sites in their membranes, which are enriched in integrins and vinculin, as well as through transverse elements that tether osteocytes to the canalicular wall. Loading of the bones induces extracellular matrix deformation and fluid flow through the canaliculi, producing tension in the tethering elements and strain on osteocyte membranes. The consequent integrin engagement leads to intracellular signaling. Physiologic levels of

mechanical strain imparted by stretching or pulsatile fluid flow prevent apoptosis of cultured osteocytes. Mechanotransduction is accomplished by molecular complexes assembled at caveolin-rich domains of the plasma membrane and composed of integrins, cytoskeletal proteins, and kinases, including the focal adhesion kinase FAK and Src, which results in activation of the ERK pathway and osteocyte survival. Intriguingly, a ligand-independent function of the estrogen receptor is indispensable for mechanically induced ERK activation in both osteoblasts and osteocytes. This observation is consistent with reports that mice lacking estrogen receptor- α and estrogen receptor- β exhibit a poor osteogenic response to loading.

In vivo mechanical forces also regulate osteocyte life span. Apoptotic osteocytes are found in unloaded bones or in bones exposed to high levels of mechanical strain. In both cases, increased osteocyte apoptosis is observed before any evidence of increased osteoclast resorption. Apoptotic osteocytes accumulate in areas subsequently removed by osteoclasts. Targeted ablation of osteocytes in transgenic mice is sufficient to induce osteoclast recruitment and resorption leading to bone loss. These findings led to the notion that dying osteocytes become the beacons for osteoclast recruitment to the vicinity and the resulting increase in bone resorption.⁴¹ Whether living osteocytes continually produce molecules that restrain osteoclast recruitment or whether in the process of undergoing apoptosis osteocytes produce pro-osteoclastogenic signals remains to be determined. Taken together with the evidence that osteocyte apoptosis is inhibited by estrogens and bisphosphonates,^{40,42} these findings raise the possibility that preservation of osteocyte viability contributes to the antiremodeling properties of these agents.

Osteocyte apoptosis and aging

One of the purported functions of the osteocyte network is to detect microdamage and trigger its repair. During aging, there is an accumulation of microdamage and a decline in osteocyte density accompanied by decreased prevalence of osteocyte-occupied lacunae, an index of premature osteocyte death. Age-related loss of osteocytes due to apoptosis could be partially responsible for the disparity between bone quantity and quality that occurs with aging. The decline in physical activity and thus reduced skeletal loading with old age is a potential mechanism for the increased prevalence of osteocyte (and osteoblast) apoptosis, as is the loss of estrogen in women during and after menopause.

Hormonal regulation of osteocyte life span

Estrogen and androgen deficiency both lead to increased prevalence of osteocyte apoptosis. Conversely, estrogens and androgens inhibit apoptosis of osteocytes as well as osteoblasts.⁴² This antiapoptotic effect is due to rapid activation of the Src/Shc/ERK signaling pathway through nongenotropic actions of the classical receptors for sex steroids. This effect requires only the ligand-binding domain of the receptor, and unlike the classical genotropic action of the receptor protein, it is eliminated by nuclear targeting.

Excess of glucocorticoid activity in bone may also contribute to induction of osteocyte (and osteoblast) apoptosis, because aged mice exhibit higher serum levels of corticosterone, elevated adrenal weight, and increased expression in bone of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), the enzyme that amplifies glucocorticoid action. The apoptotic effect of glucocorticoids is reproduced in cultured osteocytes and osteoblasts in a manner strictly dependent on the glucocorticoid receptor.³⁴ Induction of osteocyte and osteoblast apoptosis by glucocorticoids can result from the direct action of the steroids, because overexpression of the enzyme that inactivates glucocorticoids, 11 β -HSD2, specifically in these cells abolishes the increase in apoptosis. Strikingly, in osteocytic MLO-Y4 cells the proapoptotic effect of glucocorticoids is preceded by cell detachment due to interference with FAK-mediated survival signaling generated by integrins. In this mechanism, Pyk2 (a member of the FAK family) becomes phosphorylated and subsequently activates proapoptotic JNK signaling. The proapoptotic actions of glucocorticoids may involve suppression of the synthesis of locally produced antiapoptotic factors including IGF-1- and IL-6-type cytokines, as well as MMPs, and stimulation of the proapoptotic Wnt antagonist SFRP-1.

Regulation of bone formation by osteocytes: sclerostin

Osteocytes express sclerostin, the product of the *Sost* gene, which antagonizes several members of the BMP family of proteins and also binds to LRP5/LRP6, preventing canonical Wnt signaling. Loss of *Sost* in humans causes the high-bone-mass disorders van Buchem syndrome and sclerosteosis. In addition, administration of an antisclerostin antibody increases bone formation and restores the bone lost after ovariectomy. Conversely, transgenic

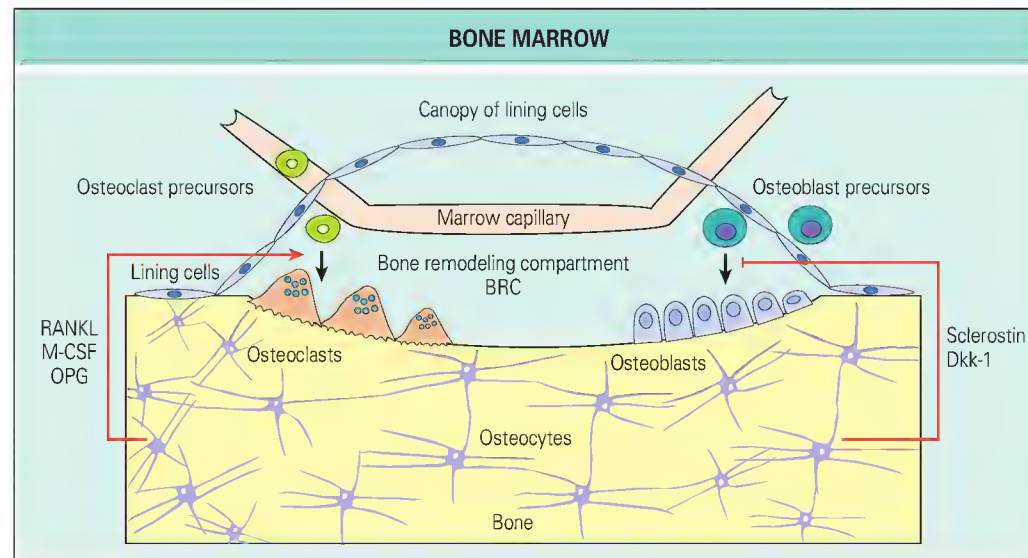


Fig. 6.7 Osteocytes sense the need for bone resorption and send signals to lining cells, which retract from the bone surface and form a canopy under which remodeling occurs, called the *bone-remodeling compartment* (BRC). Osteoclast precursors are transported to the BRC by marrow capillaries, differentiate to mature osteoclasts under the influence of pro-osteoclastogenic and antiosteoclastogenic cytokines (receptor activator of nuclear factor- κ B ligand [RANKL], macrophage colony-stimulating factor [M-CSF], and osteoprotegerin [OPG]) derived from osteocytes, and initiate bone remodeling. Osteoblast precursors from the bone marrow or the circulation differentiate into mature, bone-synthesizing cells in response to factors released from the bone matrix by resorption. Differentiation and function of osteoblasts is controlled by molecules derived from osteocytes, including sclerostin and Dkk-1. (From Bellido T, Plotkin LJ, Bruzzaniti A. *Bone cells*. In: Burr DB, Allen MR, editors. *Basic and applied bone biology*. San Diego: Academic Press; 2014, p. 27-46, Figure 10.)

mice overexpressing Sost exhibit low bone mass.⁴³ These lines of evidence demonstrate that sclerostin derived from osteocytes exerts a negative feedback control at the earliest step of mesenchymal stem cell differentiation toward the osteoblast lineage. Moreover, PTH and mechanical loading downregulate the expression of sclerostin in osteocytes, which reveals a novel mechanism of bone anabolism triggered by osteocytes.

Regulation of bone resorption by osteocytes: RANKL and osteoprotegerin

The cues that signal bone resorption are not completely understood. Apoptotic osteocytes could regulate the recruitment of osteoclast precursors and their differentiation in two ways. Osteocyte apoptosis may indirectly stimulate osteoclastogenesis by inducing stromal/osteoblastic cells to secrete RANKL. In addition, osteocytes can directly secrete RANKL. Indeed, *in vitro*, purified osteocytes express higher levels of RANKL than osteoblasts and bone marrow stromal cells. The severe osteopetrotic phenotype observed in mice lacking RANKL in osteocytes and their resistance to bone loss induced by tail suspension strongly suggests that osteocytes are a major source of RANKL *in vivo*. Osteocytes also secrete OPG, which, as in osteoblasts, is regulated by the Wnt/ β -catenin pathway. Mice lacking β -catenin in osteocytes are osteoporotic due to increased osteoclast numbers, whereas osteoblast function is normal. Emerging evidence also points to osteocytes as an additional source of secreted M-CSF in bone. Together, these new findings suggest that osteocytes control the bone-remodeling process by regulating osteoclast and osteoblast differentiation and function.

Osteocytes and the bone-remodeling compartment

Lining cells play an important function in initiating bone remodeling by retracting from quiescent bone surfaces and creating a canopy over osteoclasts and osteoblasts in the bone multicellular unit.⁴⁴ On the endocortical surface, this canopy presumably encases bone marrow osteoblast precursors and is penetrated by blood vessels that provide hematopoietic osteoclast progenitors. The lining cell canopy, associated capillaries, osteocytes, osteoclasts, and osteoblasts form a compartment, the bone-remodeling compartment (BRC), which is separated from the rest of the marrow and which can sequester molecules that regulate the cells that remodel bone (Fig. 6.7). The signals that trigger lining cell detachment to form the BRC in a particular bone area are unknown. Premature apoptosis of osteocytes has been shown to precede osteoclast accumulation and resorption,⁴¹ which raises the possibility that osteocytes release molecules that induce lining cell retraction facilitating access of osteoclast precursors to bone surfaces. However, the molecular entities responsible for this purported osteocytic function remain unknown. As discussed earlier, osteocytes express M-CSF⁴⁵ which stimulates proliferation of preosteoclasts, and RANKL,^{46,47} the master cytokine

TABLE 6.1

Dynamic processes of skeletal development and adaptation

Process	Mechanism	Morphology	Function
Growth	F	Woven, lamellar	Increased mass
Modeling	A-F	Primary lamellar	Net increased mass or Adaption of architecture
	A-R	Control of drift and curvature	
Remodeling	A-R-F	Secondary lamellar (osteons, hemi-osteons)	Bone maintenance Repair of microdamage Prevention of bone loss
Repair	F	Woven Rapid mechanical adaptation	Repair of fractures

A, activation; F, formation; R, resorption.

inducer of osteoclast differentiation, both of which could reach the BRC. Factors released from the bone matrix upon resorption, in turn, stimulate osteoblastogenesis. It is also likely that osteocyte-derived sclerostin reaching the BRC through the canalicular system, and secretion of the other Wnt antagonist Dkk-1 by osteocytes as well as osteoblasts, influence the rate of bone formation, providing an additional level of control of osteoblast activity. Based on these lines of evidence, the BRC might provide a supportive environment for differentiation of osteoclast and osteoblast progenitors. Thus, regulation of the bone-remodeling rate by hormonal and mechanical stimuli could be accomplished by controlling the balance between resorption and formation within the BRC through the regulation of osteocytic molecules, including sclerostin, RANKL, and OPG.

GROWTH, MODELING, REMODELING, AND REPAIR

Four dynamic processes are involved in skeletal development and adaptation. These are defined by the relationship of bone resorption and bone formation to each other (Table 6.1). These mechanisms include a

coordinated system that first involves the activation (A) of cell populations, followed by the resorption (R) of preexisting tissue and/or the formation (F) of new or replacement tissue. Bone growth serves to increase bone mass through bone formation. Resorption of bone is not part of the growth process, and the function of growth is only to increase mass, not to adapt the developing structure to its mechanical needs. Growth can occur on a substrate but may involve ossification directly from fibrous tissue (intramembranous bone formation) or by formation of a model with cartilage first and then replacement of the cartilage with bone (endochondral ossification). Modeling uses the tissue formed during the growth process to further increase bone mass and to shape its geometry to mechanical needs. Modeling occurs through the activation of cells followed by either formation or resorption. Formation and resorption are coordinated processes in modeling, but do not occur sequentially on the same surface of bone. Remodeling, on the other hand, is defined by the sequential processes on the same bone surface of activation-resorption-formation (the A-R-F sequence). The function of remodeling is bone maintenance, not increase in bone mass. Bone remodeling is also involved in skeletal repair of microdamage. Bone's repair function, which restores its mechanical properties following a complete fracture or trabecular microfracture, usually occurs through the process of endochondral ossification, which forms a cartilage callus that also includes woven bone to bridge the fracture gap. This is eventually replaced through remodeling with replacement by lamellar bone.

Growth, modeling, and remodeling are present concurrently in all growing children. When skeletal maturity is reached, growth naturally stops. Modeling slows down or stops but may still be present at a reduced rate on trabecular surfaces and on the periosteal surface of the bone. However, at maturity, the predominant process is bone remodeling, which serves to maintain the bone that has been formed and to repair microscopic damage that may be sustained in bone during normal daily activities. Dysfunction in the remodeling process is associated with the loss of bone found in osteoporosis.

Growth

Growth of bone can occur through two different skeletal processes, one involving formation of bone from fibrous membranes and the other involving the formation of a skeletal anlage, or model. Intramembranous bone formation occurs at centers of ossification via direct mineralization in highly vascular fibrous tissues through the action of mesenchymal cells. The calvaria of the skull is the best example of intramembranous bone formation, with the individual bones of the skull acting as centers that eventually grow together at the sutures. Apposition of bone on the periosteal surface of long bones can also occur through intramembranous ossification and has been demonstrated especially in the region of the femoral neck.⁴⁸

In the long bones development generally occurs by the initial condensation of mesenchyme or hyaline cartilage in the form of the eventual skeletal structure. This cartilage model mineralizes over time and becomes detectable as a primary center of ossification. Some bones are formed from a single ossification center, although most of the long bones form secondary centers of ossification at the ends (epiphyses), which eventually fuse to the bone that developed from the primary ossification center (diaphysis) (Fig. e6.2). The secondary centers allow growth to occur at a cartilaginous growth plate until skeletal maturity in the late teens or (for the vertebral bodies) in the early part of the third decade. The growth plate slowly converts into primary spongiosa that become remodeled into lamellar trabecular plates in the metaphysis of the bone.

Modeling

Long bones must grow both in length and in diameter (Fig. 6.8). At the ends of the long bones—near the epiphyses—growth of bone demands that the wider joint surface continually be reshaped and narrowed as it moves down into the metaphysis and diaphysis. Modeling is a continuous and prolonged process—unlike remodeling, which is episodic—and involves a coordinated process of bone resorption on some surfaces, while other surfaces undergo bone formation. Bone modeling occurs on both periosteal and endocortical envelopes, and sculpts bone shape while allowing for expansion of the marrow cavity and periosteal diameter of the diaphysis. At the metaphysis, this occurs by osteoclastic resorption on the periosteal surfaces. As growth continues, however, bone is added to the periosteal surface by osteoblasts and simultaneously removed from the endocortical surface by osteoclasts. This increases whole-bone diameter and expands the marrow cavity, necessary for the formation of blood. It serves a second purpose: to increase the mechanical strength of the bone, while at the same time not increasing its mass or weight at the same rate. Bone curvature is also

THE METAPHYSEAL CUTBACK THAT OCCURS THROUGH MODELING PROCESSES DURING GROWTH TO SHAPE THE BONE

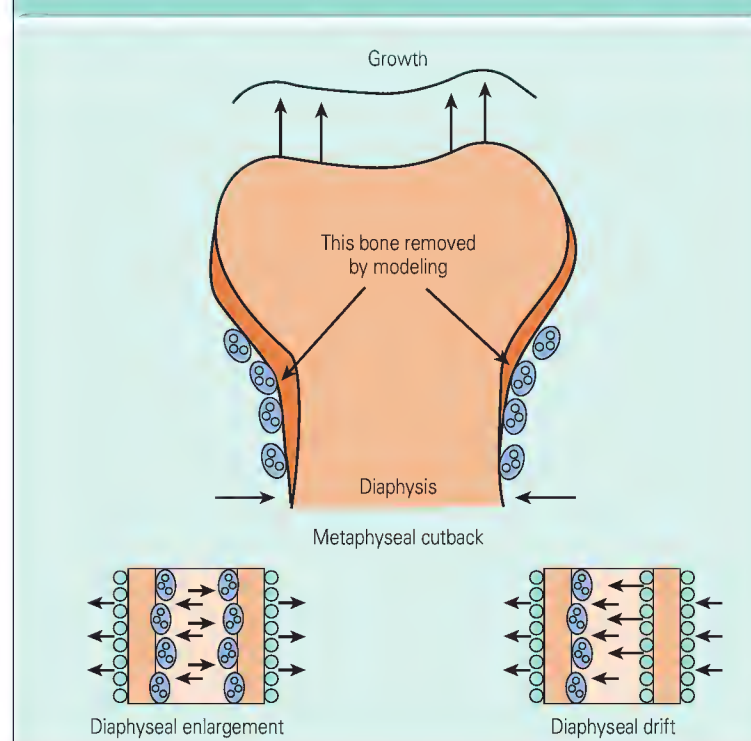


Fig. 6.8 During growth, metaphyseal bone is removed by modeling processes to shape the bone. Subsequent enlargement of the diaphysis occurs through direct periosteal apposition, which is often accompanied by resorption on the endocortical surface to enlarge the marrow cavity. Bone can also change its location and curvature through “drift.” Arrows indicate direction of drift, with smaller circular cells representing osteoblasts and bone formation, and larger ellipsoidal cells representing osteoclasts and bone resorption. (From Martin RB, Burr DB, Sharkey NA. *Skeletal tissue mechanics*. New York: Springer; 1998, p. 62, Figure 19, with permission.)

adjusted during growth through a process known as *drift*, in which the periosteal surface on one side of the bone is undergoing apposition while the other is undergoing resorption. Likewise, different portions of the endocortical surface are undergoing formation or resorption in coordination to maintain the cortical thickness of the diaphysis.

Remodeling

The quantum concept of bone-remodeling states that bone is replaced in packets through the coupled activity of osteoclasts and osteoblasts. The coupling between osteoclasts and osteoblasts is the reason that it was difficult for so many years to control the processes involved in bone loss. When bone resorption is suppressed, formation is also suppressed because these activities are linked by intercellular signaling mechanisms that are still little understood. In remodeling, bone resorption and bone formation are coupled, but in fact may not be balanced. Coupling and balance are not the same; *balance* refers to the relationship between the amount of bone resorbed and the amount formed, whereas *coupling* denotes only that the processes are linked in some way. Bone resorption and bone formation are in balance in the healthy skeleton, but when these are out of balance the amount of bone that is resorbed can be either greater or less than the amount that is subsequently formed. Thus, even though cells are coupled, bone can be lost or added in several different ways based on the altered balance of resorption and formation. In actuality, one almost never finds a balance in favor of bone formation in a remodeling system, although this has been shown to occur with anabolic treatments for osteoporosis, such as the intermittent administration of recombinant human PTH(1-34) (Forteo).⁴⁹ More often, the balance is in favor of resorption. This is the case in osteoporosis, in which global resorption is increased but formation at each of the erosion sites is normal or reduced, which leads to a deficit in bone mass.

This coupled system is termed a *bone multicellular unit* (BMU) because different cell populations are involved. A BMU typically consists of about

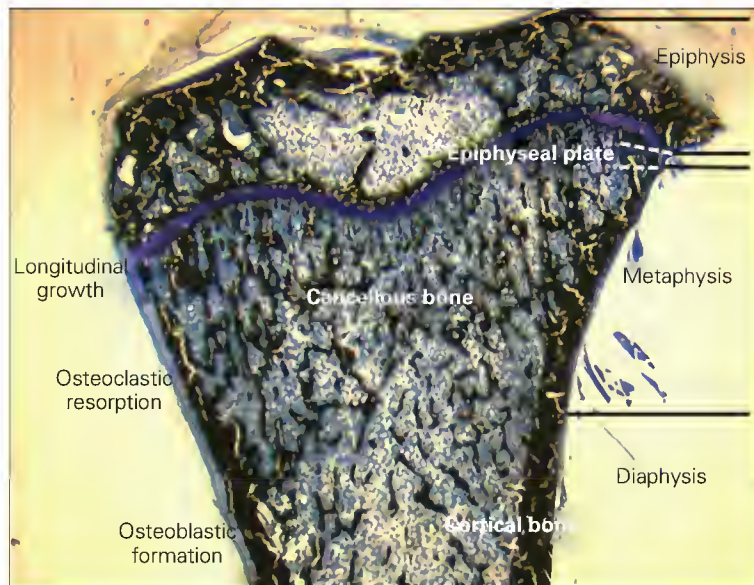


Fig. e6.2 Bone consists of the diaphysis (shaft), the metaphysis, and the epiphysis. In growing children, the growth (epiphyseal) plate separates the epiphysis from the metaphysis. During growth, the periosteal surface of the metaphysis must be constantly resorbed, while concurrent bone formation occurs on the endocortical surface, to convert the thin-walled but flared metaphysis into the narrower but thicker-walled diaphysis (McNeal tetrachrome stain).

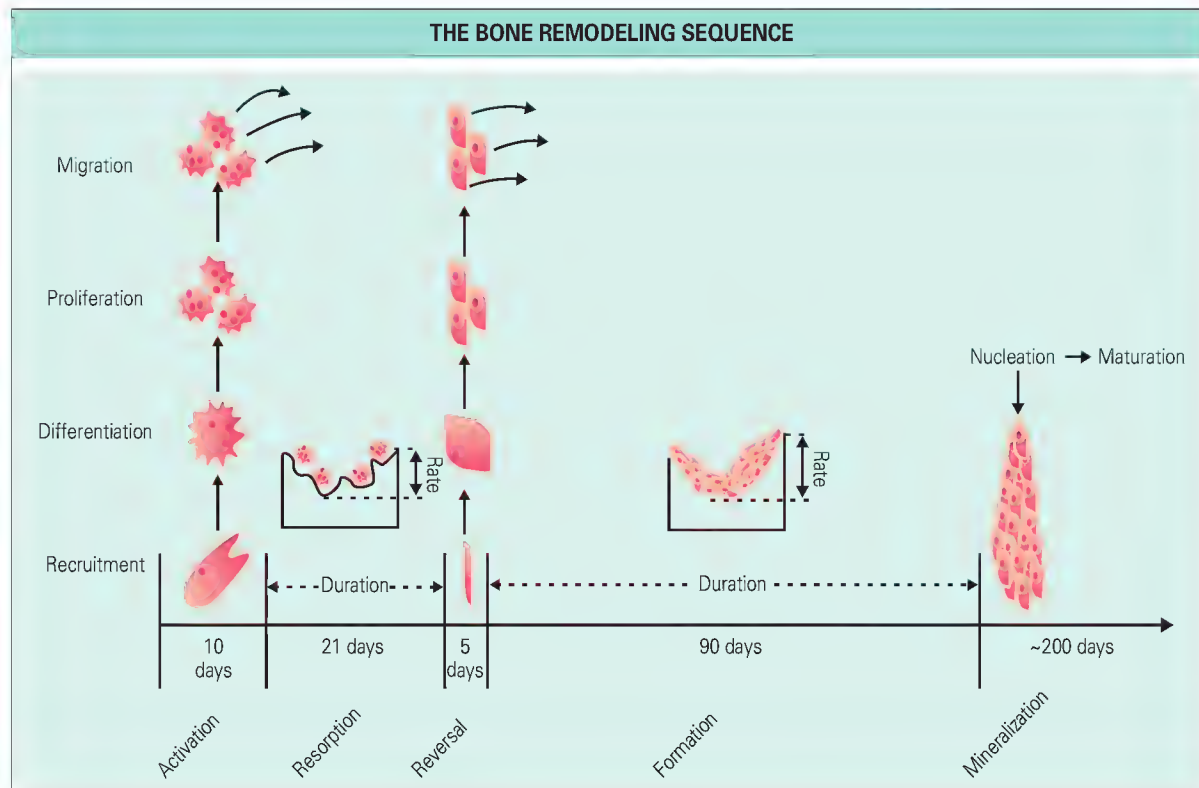


Fig. 6.9 The entire bone-remodeling sequence, not including mineralization, takes about 4 months in people. There are many cellular processes that occur during each part of the activation-resorption-formation (A-R-F) sequence of events. The amount of resorption and formation are determined both by the individual activity of the cells and by the duration of the cells' lifetime. In cross section, formation requires about four times longer than the resorption of the same amount of bone, and consequently there are many more osteoblasts in bone than osteoclasts. (From Burr DB. *Orthopedic principles of skeletal growth and remodeling*. In: Carlson DS, Goldstein SA, editors. *Bone biodynamics in orthodontic and orthopedic treatment*. Craniofacial Growth Series, vol. 27. Ann Arbor, Mich.: Center for Human Growth and Development of the University of Michigan; 1992, p. 15-50.)

10 osteoclasts and several hundred osteoblasts. When cut in longitudinal section, the BMU shows the sequential aspects of the A-R-F system and the various cell populations that are involved (Fig. e6.3). Each of the phases in this sequence is location, magnitude, and rate specific, so that alterations in the magnitude or timing of one can produce morphologic features characteristic of specific skeletal abnormalities (Fig. 6.9). Activation is initiated by chemical or mechanical signals but actually involves a series of events that include recruitment of precursor cells, differentiation and proliferation of cells, and migration to the site of activity. In humans, these processes take about 5 to 10 days. Bone resorption by mature osteoclasts takes about 3 weeks at a given site, although osteoclasts moving longitudinally through bone at a rate of about 40 $\mu\text{m}/\text{day}$ may live much longer than this. There is a period of reversal during which there is neither bone resorption nor formation; this may represent a period like the activation period during which osteoblasts are undergoing differentiation and proliferation from their precursors. This is followed by a period of bone formation that lasts about 3 months. As unmineralized bone—or osteoid—is laid down, it subsequently begins to mineralize, quickly at first, and then more slowly over the following year. This sequence of events occurs on all four skeletal envelopes (periosteal, endocortical, trabecular, and intracortical).

Changes in bone mass can occur simply through changes in activation frequency. Changes in activation frequency may lead only to transient changes in bone mass if resorption and formation are in balance. Early losses of bone mass due solely to increased activation frequency may resolve after several months as the newly resorbed sites are refilled. Likewise, bone mass may change because some aspect of the recruitment, proliferation, migration, or differentiation of either osteoclasts or osteoblasts is interrupted. These changes may be manifest as alterations of resorption-formation balance but may be caused by activation defects during cell maturation.

Repair

Fracture healing involves several stages in the repair (or regeneration) process (Fig. 6.10). The injury is typically followed by the development of a hematoma with associated inflammatory responses. This phase is followed within a week or so by a regenerative phase characterized by the formation of a cartilage callus. Also, there is direct woven bone apposition on periosteal surfaces through a process typical of intramembranous ossification. This unites the two ends of the bone to stabilize the fracture, but the bone is still not mechanically adapted to normal loads and may be quite weak. The callus subsequently matures to primary bone over a period of months via processes like those involved in endochondral ossification.

Over time, the cartilage callus remodels via the A-R-F sequence of events to become lamellar bone, and eventually the bone is reshaped through modeling processes to achieve something close to its original dimensions. When this process is complete the bone will be geometrically and mechanically similar to its prefracture state.

The rate and extent of healing is dependent on the fracture and also on the mechanical environment. Large amounts of motion increase the size of the cartilage callus and interrupt its remodeling to bone. Small amounts of motion and juxtaposition of the fractured ends of the bone can allow healing without the development of much, or any, callus. Small loads also facilitate healing. There are a variety of local factors that can influence healing. Non-unions can occur if early signals for repair (e.g., from TGF- β and other growth factors and cytokines) are not received, if there is compromise to the local blood supply, or if there are complicating factors due to infection or bone death caused by radiation or thermal injuries. Comorbid conditions (e.g., poor diet, smoking, calcium or vitamin D deficiencies, and excessive alcohol intake) can prolong the time required to heal a fracture.

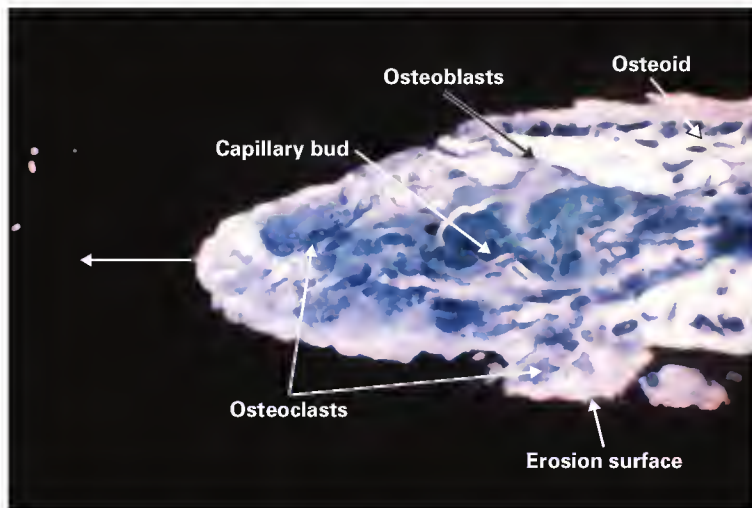


Fig. e6.3 A bone multicellular unit, or BMU, is shown. This system shows the sequential aspects of the activation-resorption-formation (A-R-F) system, and the various cells that are involved. At the head of the resorption front (also called the *cutting cone*), there is a capillary bud, which supplies nutrients to the multicellular osteoclasts that are decalcifying and resorbing bone matrix. Behind the resorption front, teams of osteoblasts are lined up along the wall of the BMU, laying down new bone, or osteoid, that will subsequently become mineralized. Some of these osteoblasts will eventually embed themselves and become terminally differentiated osteocytes (McNeal tetrachrome stain).

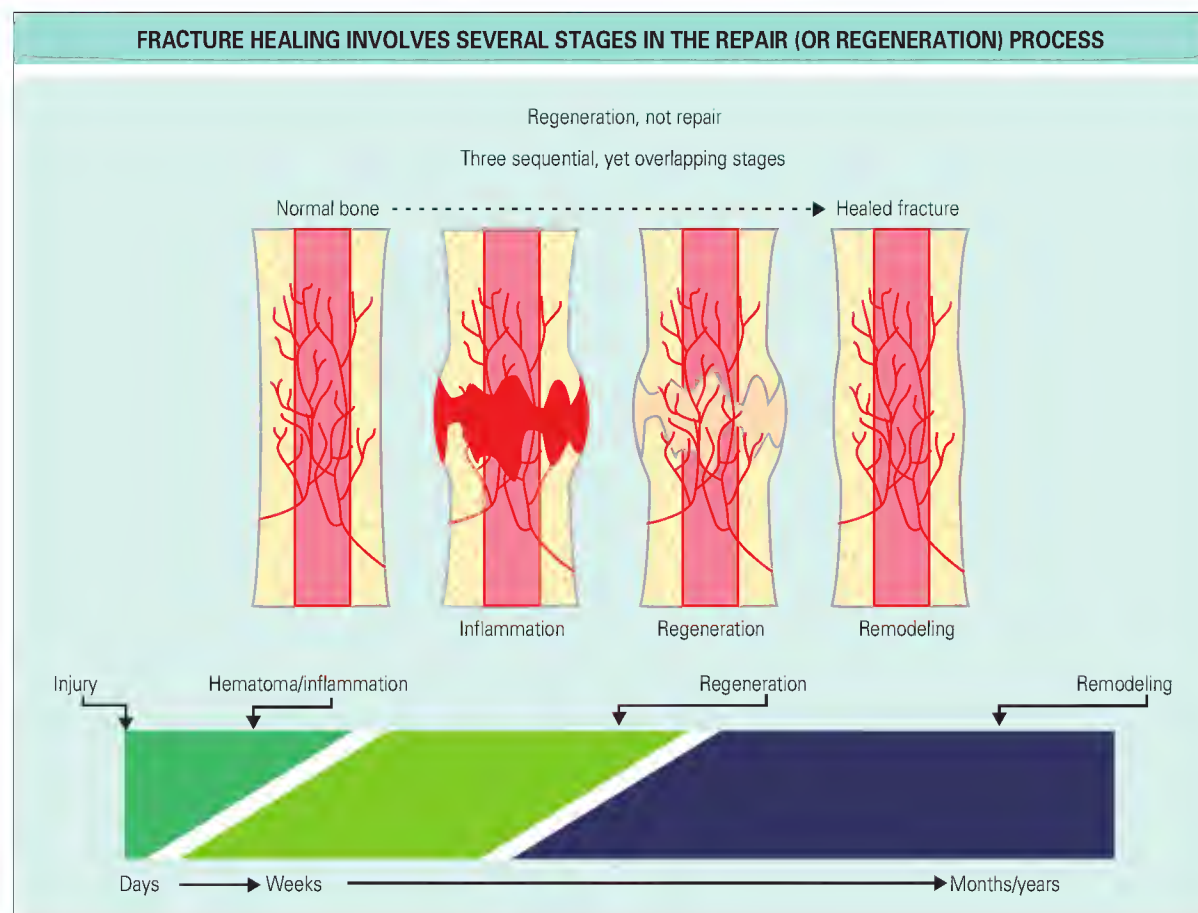


Fig. 6.10 An injury to bone is typically followed by the development of a hematoma with associated inflammatory responses. This phase is followed by the development of a periosteal bridging callus (at least in separated and unstable fractures) that is composed of calcified cartilage. Over time, this cartilage callus remodels to become bone, and eventually the bone is reshaped through modeling processes to achieve something close to its original dimensions. (*With permission from Dr. Stuart Warden.*)

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7

Tendons and ligaments

■ GRAHAM RILEY

- Although tendons and ligaments generally respond similarly to injury, there are anatomic and regional differences in the speed and quality of repair.
- Chronic painful conditions are more common in tendons, but some ligaments may also be affected.
- Most chronic conditions are degenerative and associated with “overuse.”
- Although inflammatory cells are not usually found in chronic lesions, various inflammatory mediators are present both in and around the affected tissue.
- Many current therapies for chronic conditions are not supported by good clinical trials.
- Future therapies in development include the use of mesenchymal stem cells to promote better-quality repair and regeneration of the extracellular matrix.

INTRODUCTION

Tendons and ligaments are dense fibrous connective tissues that are essential for joint movement and stabilization. They have a similar composition and structure and are composed primarily of a hierarchic arrangement of collagen fiber bundles primarily aligned with the long axis of the tendon. They are metabolically active and capable of responding to extrinsic factors such as mechanical load, exercise, and immobilization. However, there are differences in structure, composition, and function between tendons and ligaments that make it unwise to extrapolate directly from one tissue to another.¹

Both tendons and ligaments are frequently subjected to acute injury as a result of trauma, overload, or direct mechanical insult resulting from crushing blows or penetrating objects. The repair response follows the same general pattern, with the important proviso that some ligaments and tendons are apparently able to mount a more effective repair response than others.² This has been linked to a number of factors, such as whether tendons are intrasynovial or extrasynovial or whether ligaments are intraarticular or extraarticular, and the ability to repair may be dependent on the quantity and quality of the vascular network at different sites. Tendons are more prone than ligaments to chronic, insidious forms of injury. These conditions, best described as “tendinopathies,” are often associated with repeated strain and repetitive microtrauma (“overuse”) rather than a single traumatic episode.^{3,4}

ACUTE TENDON AND LIGAMENT INJURIES

The cellular events occurring after traumatic injury to a tendon or ligament are similar and common to all soft connective tissues.¹ The response is usually divided into three phases, more for convenience because the phases merge imperceptibly into each other and represent a continuum rather than discrete stages. The initial phase, which occurs in the first week after disruption of the tendon fibers, is characterized by inflammation, edema, and infiltration of a variety of cell types attracted to the region by inflammatory mediators. Platelets and mast cells release histamine, a potent agent that promotes vasodilation and increases blood vessel permeability. Serotonin, bradykinin, leukotrienes, and prostaglandins act together to recruit polymorphonuclear leukocytes and lymphocytes from the circulation. Growth

factors released by platelets include platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), and epidermal growth factor (EGF). Macrophages, which are present within 24 hours, phagocytose tissue debris and release numerous inflammatory mediators and growth factors, including basic fibroblast growth factor (bFGF), TGF- α , TGF- β , and PDGF. These growth factors are chemotactic for fibroblasts and other cells and generally act to stimulate matrix synthesis. Angiogenic factors such as bFGF and vascular endothelial growth factor stimulate capillary ingrowth into the fibrous clot. Toward the end of the inflammatory phase, which may last several days, fibroblasts become the predominant cell type. The second phase, generally lasting up to 6 weeks after injury, is characterized by cell proliferation and synthesis of new matrix by fibroblasts. This new matrix is different in both quality and quantity from the normal matrix. Described as granulation tissue, it consists of a disorganized matrix with an elevated cell density that fills the tissue defect. The third phase, which occurs from 3 to 6 weeks after injury and lasts for at least a year, is a prolonged period of remodeling and maturation in which the matrix components and tissue cellularity gradually revert toward normal. During this stage many cells in the scar are contractile myofibroblasts, which are specialized cells important for organization of the wound tissue.

LIGAMENT INJURY AND REPAIR

Although ligaments are generally similar to tendons, the quality of repair in ligaments from different anatomic locations is known to have substantial differences.² Most ligaments, such as the collateral ligaments of the knee, are extraarticular and in close relationship with the joint capsule and adjacent vascular structures. This environment is apparently more conducive to repair than that surrounding the intraarticular cruciate ligaments. Injury to the cruciate ligaments, for example, provokes a profuse vascular response, but healing by second intention (i.e., contraction and filling of the defect by the formation of granulation tissue) does not occur. The medial collateral ligament, in contrast, heals spontaneously without the need for surgical repair. A variety of explanations have been proposed, such as the presence of synovial fluid preventing fibrin clot formation and the more dynamic mechanical environment of the cruciate ligament inhibiting repair. There are also thought to be intrinsic differences in cell types from different ligaments, with differences in morphology as well as in mitogenic, chemotactic, and synthetic responses. Medial collateral ligament fibroblasts, for example, are more proliferative and produce more type III collagen than do cells from the anterior cruciate ligament, and they show a greater response to growth factors such as EGF, TGF- β , and bFGF.⁵

CHRONIC TENDON PATHOLOGY

A variety of different terminologies are used for the chronic pathology that is more commonly seen in tendons, although some ligaments (e.g., the patellar) may also be affected. This confusion is partly due to incomplete understanding of the pathology, as well as difficulty making the diagnosis, because biopsy specimens are rarely obtained at early stages of the disease. Terms such as *tendinitis* imply that inflammation is present, although little evidence of any inflammatory process has been found in histologic studies.⁶ Conditions are consequently best considered as either acute or chronic, whether caused by trauma or repeated microtrauma (often attributed to “overuse”) or the result of an insidious process of clinically silent (i.e., “pain-free”) degeneration. Unless the presence of inflammation or degeneration has been unequivocally demonstrated, most tendon pain and dysfunction are best described as a “tendinopathy.”

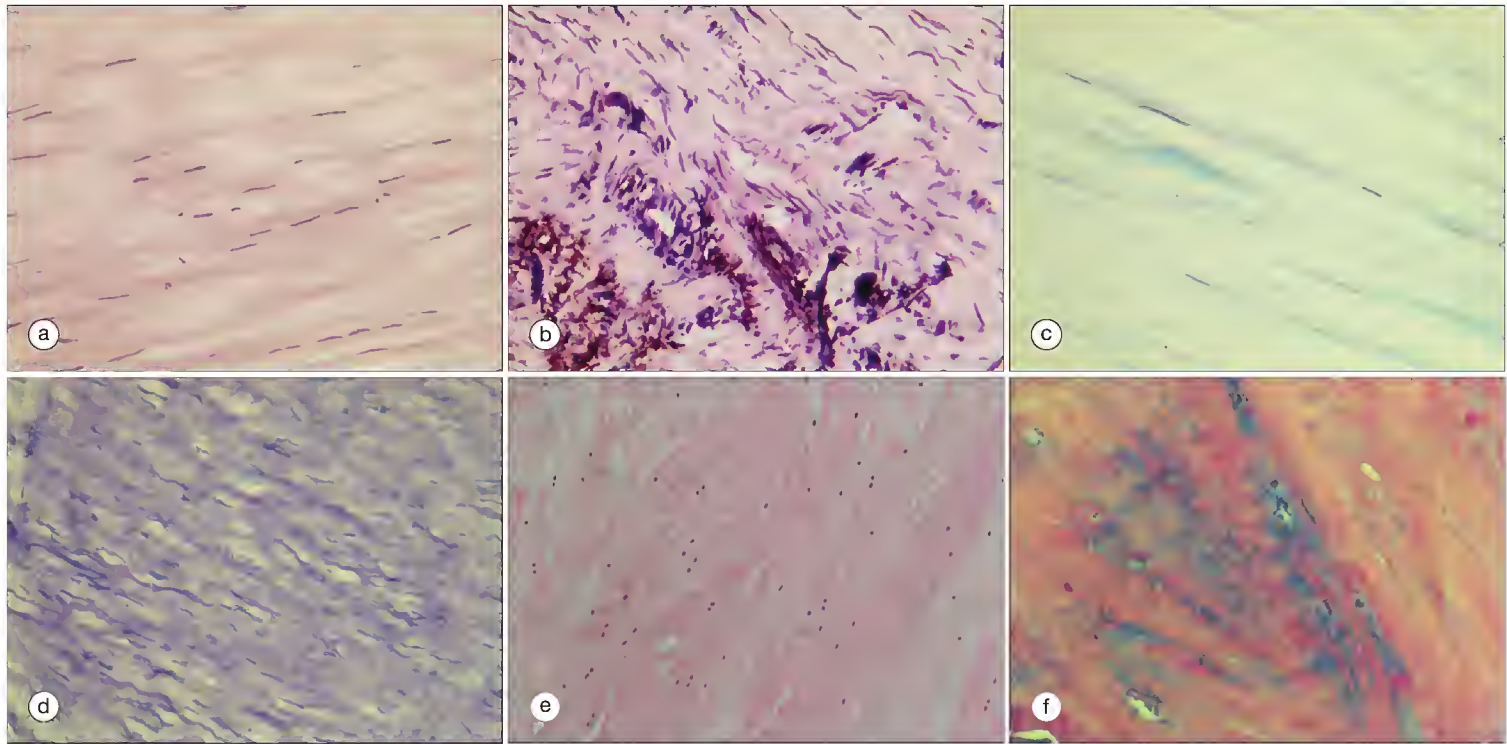


Fig. 7.1 Histologic features of tendinopathy. (a) Normal Achilles tendon showing dense bundles of highly organized collagen fiber bundles and relatively few tenocytes arranged in columns (hematoxylin-eosin [H&E]). (b) Specimen from a patient with painful tendinopathy showing increased cellularity and vascularity at the site of the lesion (H&E). (c) Normal Achilles tendon showing a low abundance of proteoglycan (toluidine blue). (d) Specimen from a patient with Achilles tendinopathy showing a much increased abundance of proteoglycan throughout the tendon matrix (toluidine blue). (e) Degenerative supraspinatus tendon specimen from a patient with rotator cuff pathology showing loss of matrix organization, disruptions in fibrillar structure, and reduced cellularity (H&E). (f) Specimen of the supraspinatus tendon from a patient with rotator cuff pathology showing increased proteoglycan associated with rounded cells in a "fibrocartilaginous" matrix (H&E/Alcian blue).

Sites commonly affected by tendinopathy include the supraspinatus and long head of the biceps in the shoulder, the medial and lateral extensors of the elbow, the patellar ligament, the posterior tibialis, and the Achilles tendon. In most cases, with the notable exception of the Achilles tendon, the site affected is at or near the bone insertion. These sites have several common features: they are more highly stressed, are often exposed to repeated strain, including shear or compressive force, and are relatively less vascularized than the tendon midsubstance. The insertion also has a different structure and composition than the midsubstance; it is fibrocartilaginous and contains matrix components that are more commonly associated with articular cartilage, such as type II collagen and aggrecan.⁷ The highly specialized structure is thought to help dissipate the stress and compressive force acting on the insertion site.

ETIOLOGY OF CHRONIC TENDINOPATHY

The cause of chronic tendinopathy is not fully understood, and many different factors have been implicated. Many lesions are associated with a reduction in vascular perfusion, particularly at specific sites in the supraspinatus and the Achilles. Because most tendon ruptures occur in the fifth decade, age-related changes are also implicated; however, rupture of the Achilles tendon is most common in a younger, physically active population. More tendon ruptures tend to occur in males than in females, although it is thought unlikely that this is directly associated with gender because the age and activity level of male and female patients are frequently very different.⁸ The combination of a more sedentary existence with increased leisure time, recreational sports, and a propensity to obesity may account for the greater incidence of tendinopathy in the developed world. A strong association has been found with particular sports and activities that result in high levels of stress being applied to specific sites. Leg-length discrepancies and other anatomic variants, such as the shape and slope of the acromion in the shoulder, are implicated in some individuals. Joint laxity may predispose to some conditions such as rotator cuff lesions. Genetic factors have also been identified, with an increased risk for tendon injury in individuals with specific variants of genes encoding for structural proteins such as collagen type V and tenascin-C.^{9,10}

HISTOPATHOLOGIC FINDINGS

Many histopathologic investigations of tendinopathy have been conducted, usually on specimens taken from either ruptured tendons or chronic painful tendons. Ruptures are frequently described as "spontaneous," which means that the rupture occurred without any preceding clinical symptoms, although underlying degeneration of the extracellular matrix is almost always present.⁶ Painful tendons frequently do not progress to frank rupture, and specimens are generally obtained from patients who have failed prolonged conservative treatment before surgery, at which time a specimen was removed for analysis. Painful tendons generally show increased cellularity, cell rounding, increased glycosaminoglycan (GAG) content ("mucoid degeneration"), decreased matrix organization, and increased blood vessel infiltration (Fig. 7.1). Ruptured tendons show similar degenerative features of the extracellular matrix, although cellularity is generally reduced and there is often little evidence of neovascularization. The cell changes in ruptured tendons are consistent with hypoxia, and calcific deposits and lipid droplets are frequently found in the matrix.⁶ The calcification seen in many ruptured tendons is thought to be a degenerative phenomenon that occurs as a result of precipitation of calcium salts nucleated by cell debris or matrix constituents,¹¹ although a cell-mediated process similar to endochondral ossification has been identified in some pathologic tendons.¹² Apoptosis (programmed cell death) is increased significantly in both patellar tendinopathy and ruptured supraspinatus tendons.^{13,14} Most cells in painful tendinopathy specimens are fibroblast-like, albeit generally more rounded or ovoid, and there is an absence of inflammatory cells, at least in the tendon substance. Overall, the histopathologic findings in most cases of tendinopathy are consistent with matrix degeneration, and in painful tendons the cellular and vascular response suggests at least some attempt at repair. Some evidence suggests that the cellular changes, such as the rounder appearance and increased number, occur before any clinical symptoms become apparent.¹⁵

Extracellular matrix changes in tendinopathy

The extracellular matrix of tendons consists mainly of the structural protein collagen, which accounts for approximately 65% of the dry weight.¹ Around

TABLE 7.1
Changes in the extracellular matrix in painful tendinopathy

Molecule	Potential significance
Collagen type I (mRNA) ↑	Attempted repair/adaptation ^{16,17}
Total collagen (protein) →	No significant tendon growth or adaptation ^{18,19}
Collagen type III (mRNA/protein) ↑	Fibrosis/scar formation ¹⁸ Smaller-diameter fibrils ¹⁶ Decreased fibril strength ²⁰
Fibronectin (mRNA) ↑	Repair response? ¹⁶ Altered cell-matrix interactions ²¹
Tenascin-C (mRNA/protein) ↑	Repair response? ²² Altered cell-matrix interactions ¹⁶
Glycosaminoglycan (sugar moiety) ↑	Fibrocartilaginous change ²³ Resistance to compression ¹⁹
Aggrecan (mRNA/protein) ↑	Fibrocartilaginous change ²⁴ Resistance to compression ¹⁹
Biglycan (mRNA/protein) ↑	Fibrocartilaginous change ²⁴ Resistance to compression ¹⁹
Fibromodulin (protein) ↑	Modulation of collagen fibril formation and fibril diameter ¹⁹
Versican (mRNA/protein) ↑ →	Increased or no change ¹⁶ Significance not known ¹⁷
HP/LP collagen cross-links ↑	Fibrosis/scar formation ¹⁹ Adaptation to increased load? ²⁵
Pentosidine (AGE) ↓	Replacement of mature collagen and increased matrix remodeling ²⁵

Arrows indicate the direction of change (→ indicates no change).

AGE, age-related glycation end product; HP, hydroxyprolydinaline; LP, lysylpyridinaline.

95% is type I collagen, with lesser amounts of collagen types II, III, IV, V, VI, IX, XII, and XIV. In tendinopathy, numerous molecular changes have been identified, consistent with the hypothesis that dynamic changes in the regulation of matrix turnover by the resident tenocytes are responsible for the altered tendon function (Table 7.1). The level of expression of some collagen genes changes, and increased amounts of collagen type III are found throughout the tendon matrix, not just restricted to the endotenon as in normal tendons.¹⁷⁻²⁰ Similar changes are found in scar tissue or pathologic fibrosis and have implications on the strength of the tendon because type III collagen tends to form heterotypic fibrils with type I collagen, which has a smaller average diameter and forms a meshwork rather than closely aligned fibril bundles. There are also increases in type V collagen, an increase in denatured collagen, and substantial changes in the cross-links that stabilize the collagen matrix.²⁰⁻²⁴ Strong evidence has shown increased turnover of the collagen matrix in tendinopathy because the collagen carries less of the glycation product pentosidine, which accumulates on long-lived matrix proteins with age.²⁵⁻²⁷ There are also differences between tendons, with evidence of higher rates of collagen turnover in the supraspinatus tendon than in the biceps brachii tendon in the forearm in association with the increased prevalence of tendon injury and pathology in the shoulder, although whether this is cause or effect remains to be established.

Though less abundant than collagen, proteoglycans are important constituents of the tendon matrix and have a range of important functions, including water retention, sequestration of growth factors, and mediation of cell-matrix interactions.¹ A diverse family of molecules, they all contain at least one chain of a repeating disaccharide GAG. Small leucine-rich proteoglycans (SLRPs) such as decorin, fibromodulin, biglycan, and lumican are present in normal tendons, and they function to modulate fibril growth, diameter, and organization, as well as bind growth factors such as TGF- β . The large proteoglycans versican and aggrecan are also present, although aggrecan is more abundant at the insertion or at sites where the tendon is subject to compression.⁷ The large proteoglycans, aggrecan in particular, carry more GAG chains than the SLRP, and the high negative charge density of the sulfated GAG holds water in the tissue, which is important for its viscoelastic properties and resistance to shear or compressive load. In tendinopathy, one of the most frequent observations is increased GAG in the matrix, often associated with rounded cells.²⁸ The identity and processing

of the particular proteoglycan associated with the GAG have not been fully characterized at the protein level, although molecular analysis has shown increased expression of genes encoding for aggrecan and biglycan, even in the midsubstance of the Achilles tendon, where fibrocartilage is not normally found.²⁴ These changes are consistent with an adaptive response to shear or compression, thus suggesting that at least some of the molecular alterations are the result of changes in the level and direction of mechanical forces acting on the resident tendon cells (tenocytes). Although most tendinopathies are reported to have similar molecular changes, some differences can be noted. For example, levels of gene expression for the large proteoglycan versican were reported to be unchanged in painful Achilles tendons,¹⁷ even though increased versican has been reported in patellar tendons.²⁹

Other constituents of the tendon matrix have received relatively little attention in studies of tendinopathy. Fibronectin, a large multidomain glycoprotein that can form many different interactions with cells and other matrix molecules, is of very low abundance in normal tendon.³⁰ The large increase reported in ruptured Achilles and supraspinatus tendons is consistent with a role in the repair response, where fibronectin is involved in cell adhesion and migration at the wound site. Tenascin-C, a multimeric glycoprotein that may function to help organize the matrix, is abundant in normal tendon but is increased in tendinopathy.²² There are changes in splice variant expression and a strong association of tenascin-C with the rounded cells in the pathologic tendon. In addition, there is evidence of enzyme-mediated degradation of tenascin-C in rotator cuff disease, consistent with the increased matrix remodeling associated with the condition.

Matrix turnover and remodeling

Matrix degradation, both in health and disease, is to a large extent mediated by a family of enzymes known as matrix metalloproteinases (MMPs). Humans have 23 MMPs and a family of four naturally occurring inhibitors known as tissue inhibitors of matrix metalloproteinases (TIMPs). These enzymes have a variety of different substrate specificities, with activity against all the different structural matrix components, although they are also involved in the processing and activation of growth factors and their receptors and implicated in the control of cell activity, as well as in matrix degradation. In tendinopathy, the expression and activity of various MMPs and TIMPs exhibit changes consistent with increased proteolytic activity and turnover of the matrix. For example, ruptured rotator cuff tendons showed greatly increased collagenase (MMP-1) activity and reduced gelatinase (MMP-2) and stromelysin (MMP-3) activity in comparison to normal tendons, and these changes have been correlated with high levels of collagen turnover.²⁵ A study of gene expression in Achilles tendons showed that painful and ruptured tendons have distinct patterns of expression consistent with quantitative and qualitative differences in catabolic activity in the different clinical entities.³¹ Ruptured tendons showed higher levels of expression of MMP-1, MMP-9, MMP-19, MMP-25, and TIMP-1 and lower levels of MMP-3, MMP-7, TIMP-2, TIMP-3, and TIMP-4. Painful tendons displayed reduced expression of MMP-3, MMP-10, and TIMP-3 and increased expression of A disintegrin and metalloproteinase-12 (ADAM-12) and MMP-23. Very little is known about the role and function of ADAM-12 and MMP-23 in tendons, although both have been associated with changes in cell phenotype: ADAM-12 with myogenesis and lipidogenesis and MMP-23 with endochondral ossification.^{32,33} In summary, the changes in tendon matrix composition are consistent with the changes in cell-mediated matrix remodeling that precede the onset of clinical symptoms, and these changes are mediated at least in part by metalloproteinases.

Mechanical strain and regulation of cell activity

The cellular and molecular processes driving the changes in tendon matrix remodeling in tendinopathy have yet to be determined. It is uncertain to what extent remodeling of the tendon matrix represents a limited (or potentially failed) repair response to microscopic fiber damage or an adaptive (or potentially maladaptive) response to changes in cell loading. Cyclic tensile loading of tenocytes *in vitro*, simulating overuse, has been shown to elicit the expression of several inflammatory mediators and growth factors, as well as metalloproteinase enzymes, and it has been suggested that this may trigger neovascularization, inflammation, and increased proteolytic activity in the tendon.³⁴ However, the levels of strain required to elicit this response are high, potentially much higher than the strain experienced by cells in

TABLE 7.2
Changes in cytokines and signaling molecules in painful tendinopathy

Molecule	Potential role/significance
TGF- β $\uparrow$	Repair/growth/fibrosis ³⁶ Matrix synthesis ³⁷
VEGF $\uparrow$	Associated with angiogenesis and neovascularization ^{38,39}
IL-1 $\uparrow$	Inflammation in surrounding tissues (bursa, synovium) ^{40,41}
IL-6 $\uparrow$	Inflammation within tendon ⁴²
IL-15 $\uparrow$	Inflammation within tendon ⁴²
IL-18 $\uparrow$	Inflammation within tendon ⁴²
COX-2 $\uparrow$	Production of prostaglandin within and around tendon ³⁷
Glutamate $\uparrow$	Neurotransmitter—associated with pain and/or apoptosis ^{43,44}
Substance P $\uparrow$	Neurotransmitter—associated with pain perception and edema ⁴⁵
PGE ₂ $\rightarrow$	Mediator of pain and inflammation ^{43,44}
PDGFR $\uparrow$	Mediates cell response to PDGF—cell proliferation ⁴⁶
NMDAR $\uparrow$	Glutamate receptor—effect on tendon cell not known ⁴³
TGF β R1 $\downarrow$	Mediates cell response to TGF- β —possible reduced response and poor repair ³⁶

*Arrows indicate the direction of change ($\rightarrow$ indicates no change).
 COX-2, cyclooxygenase-2; IGF-1, insulin-like growth factor 1; IL-1, interleukin-1; NMDAR, N-methyl-D-aspartate receptor; PGE₂, prostaglandin E₂; PDGFR, platelet-derived growth factor receptor; TGF- β , transforming growth factor- β ; TGF β R1, transforming growth factor- β type 1 receptor; VEGF, vascular endothelial growth factor.*

vivo. More recently, it has been shown that when released from tension, tenocytes will upregulate their expression of the collagenase MMP-13 and that this typically occurs after failure of one or more of the tendon fiber bundles in the stretched tendon.³⁵ Thus, it appears that MMP output is attenuated by normal loading conditions and that damage to tendon fibers releases the cells from this strain regulation, which results in increased collagenase expression and the potential for matrix degradation.

Inflammation and inflammatory mediators in tendinopathy

Although inflammatory cells are absent, this does not mean that inflammatory mediators are not implicated in tendinopathy, at least at some stage in the disease, and changes in a number of cytokines, growth factors, and signaling molecules have been detected in tendinopathy (Table 7.2). Increased levels of interleukin-1 (IL-1) have been detected in tissues surrounding painful tendons, such as the bursa in the shoulder.^{40,41,47} Prostaglandin E₂ and other inflammatory mediators such as thromboxane, bradykinin, and IL-6 are increased in peritendinous tissue after prolonged periods of intense exercise.⁴⁸ Levels of growth factors such TGF- β and insulin-like growth factor 1 (IGF-1) are also increased, and these factors have been shown to have a stimulatory effect on collagen synthesis.^{48,49} However, some or all of these changes may be part of the adaptive response or be involved in tissue repair, and their precise contribution to the pathology is uncertain.

Pain and neuropeptides

Pain in tendinopathy has been associated with the ingrowth of nerve endings and release of neurotransmitters such as substance P, calcitonin gene-related peptide, and glutamate.⁴³⁻⁴⁵ Levels of substance P were increased in the subacromial bursa fluid of patients with rotator cuff tendinopathy and correlated with the degree of pain during motion.⁴⁵ Apart from modulation of pain, substance P and other neuropeptides regulate the local circulation and may also directly affect tenocyte activity, as well as mediate neurogenic inflammation, thereby potentially accounting for the bilateral occurrence of tendinopathy in many patients. Consequently, antagonists of neuropeptides and neurotransmitters such as glutamate have been proposed for the treatment of tendinopathy.⁵⁰ However, nerve ingrowth and increased expression

of neuropeptides are part of the normal tendon repair response, and injection of substance P has been used for the treatment of tendon injuries because it increases the organization of collagen fibrils and the strength of the repair.⁵¹

TREATMENT OF TENDON AND LIGAMENT PATHOLOGY

A great variety of treatments have been used for acute and chronic tendon and ligament injuries, although relatively few have shown clinical benefit in properly controlled clinical trials.⁴ Injection of a sclerosant to target the neovascularization seen in tendinopathy is advocated by some practitioners,⁵² although there is some concern that the vascular response is part of the repair process and may have negative consequences in the long term.

Nonsteroidal antiinflammatory drugs (NSAIDs) are often used for ligament and tendon injuries and may be of some benefit in managing pain in chronic tendinopathies. Their pharmacologic target is cyclooxygenase (prostaglandin synthase), a key enzyme in the formation of prostaglandins, which are mediators of pain and inflammation. Studies of their effects on tendon healing have been inconclusive, with both positive and negative effects being reported. However, because cyclooxygenase-2 was shown to be increased in patellar tendinopathy⁵³ and prostaglandin injected around a tendon can induce a form of degenerative tendinopathy,⁵⁴ a rational basis may exist for the use of NSAIDs, at least in some patients.

Corticosteroid injection is a common treatment of chronic tendon lesions despite limited evidence to strongly support its use, and any benefit achieved is usually short term. Many case reports have described rupture, often bilateral, of the Achilles and other tendons after long-term oral corticosteroid treatment and also after local injections. Ruptures are associated with reduced collagen content and decreased mechanical strength, presumably as a result of the suppression of collagen synthesis and turnover.

Controlled-motion therapy for acute tendon and ligament injuries is now generally accepted and also used for the treatment of chronic tendinopathies, particularly in the form of high-loading eccentric exercises.⁵⁵ It is well known that prolonged immobilization has deleterious effects on the quality of repair, in addition to other complications such as muscle atrophy, joint stiffness, cartilage deterioration, adhesions, and thrombosis. Tension, applied cyclically or as a constant load, has a positive influence on the intrinsic fibroblast response and the strength of repair. It promotes cell proliferation and migration, facilitates the alignment of fibroblasts, and increases collagen synthesis, presumably mediated by the stimulation of growth factors such as IGF-1, TGF- β , and connective tissue growth factor in and around the tendon.⁴⁸ More experimental work and controlled studies are required to define the optimum exercise/loading regimen for promoting reorganization and remodeling of the damaged tissue so that higher strength and better function can be achieved.

CONCLUSION

Ligaments and tendons are similar but not identical; they respond similarly to acute injury, but chronic pain and degeneration are more common in tendons. These tissues are metabolically active and respond to changes in their mechanical and chemical environment, with matrix changes mediated by altered cell synthetic activity and the local production of a variety of matrix-degrading proteases. Injury results in substantial and permanent changes in the quantity and quality of the extracellular matrix. Regional differences in the response to injury are related to tissue cellularity, vascularity, matrix composition, and organization. The repair tissue can be affected and modulated by both physical and chemical factors, although the precise conditions required to optimize repair have not been rigorously defined. In tendons, most pathology is degenerative and results in either a “spontaneous” tendon rupture or a chronic painful tendinopathy, sometimes associated with calcification. Degeneration in tendinopathy has been shown to be an active, cell-mediated process involving increased levels of matrix remodeling, with the increased synthesis and degradation of matrix components mediated by a variety of enzymes. The source of pain in chronic tendinopathy is uncertain because inflammatory mediators may not be present in the tendon, although mediators of pain and inflammation may be increased in the surrounding peritendinous tissue or fluid. Current forms of treatment are based largely on empirical observations, and their effectiveness is in most cases questionable. More clinical and experimental work remains to be done to develop an evidence-based approach to therapy.

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8

Connective tissue responses to mechanical stress

■ DONALD M. SALTER

- Bone, cartilage, tendon, skeletal muscle, and other connective tissue require exposure to physiologic levels of mechanical stress to remain healthy.
- Moderate exercise improves the strength and function of connective tissue.
- Withdrawal of mechanical stimuli or prolonged exposure to excessive mechanical load results in tissue degeneration and the development of diseases such as osteoarthritis.
- Mechanotransduction is the mechanism by which a mechanical signal is recognized by connective tissue cells and translated into biochemical and molecular responses.
- Connective tissue cells express mechanoreceptors that allow recognition of the physiochemical changes that occur within connective tissue during mechanical loading.
- Activation of mechanoreceptors results in the generation of secondary messenger molecules and activation of signaling events that regulate gene expression and control cell function.

Exposure to physiologic mechanical forces is important for the maintenance of most, if not all connective tissues, including bone,^{1,2} cartilage,³ tendon,⁴ and skeletal muscle. Movement and mechanical stimulation are essential for normal embryonic development and morphogenesis of the skeleton and joints. Wolff's law states that bone in a healthy person will adapt to the loads under which it is placed. When loading increases, bone remodels to become stronger to resist that sort of loading, whereas when loading decreases, bone will atrophy because there is no stimulus for continued remodeling, which is required to maintain bone mass. This ability to alter structure in response to mechanical loading is shared with all connective tissue and is referred to as *tissue mechanical adaptation*.

In general, mechanical loading of connective tissue within a physiologic range such as is encountered during normal, everyday activity is sufficient to keep connective tissue healthy. Clinical observations and *in vivo* studies show that moderate exercise increases connective tissue performance. Changes in skeletal muscle bulk and strength are obvious, but other connective tissues are similarly affected. Differences in bone mass in the dominant and nondominant arms of tennis players who start training before puberty are a result of the differences in applied mechanical load.⁵ The mechanical strength and collagen content of tendons are increased by physical exercise,⁶ and exercise promotes proteoglycan synthesis and increases the thickness of articular cartilage.⁷ In contrast, withdrawal of mechanical stimuli results in connective tissue atrophy, as evident in paraplegics, patients undergoing prolonged bed rest, and astronauts. The bones in paralyzed and underused limbs are architecturally and mechanically inferior to those subjected to normal mechanical loading. Similarly, immobilization results in major loss of the mechanical properties of tendons,⁸ and significantly, both overloading and underloading of articular cartilage are associated with loss of cartilage matrix and the development of osteoarthritis.⁹

MECHANOSENSITIVE CONNECTIVE TISSUE CELLS

For tissue adaptation to occur in response to applied mechanical forces, cells within connective tissue need to receive information from their environment

and modify the environment appropriately to the mechanical stress to which it is exposed. This process can be divided into four main phases (Fig. 8.1)¹⁰: (1) macroscopic forces are translated into local action at the surface of the mechanosensitive cell—mechanocoupling; (2) forces are transduced from the exterior of the mechanosensitive cell into biochemical signals within the cell—mechanotransduction; (3) signal transmission from the mechanosensitive cell to effector cells; and (4) extracellular matrix (ECM) modeling/remodeling. Most connective tissue cells are mechanosensitive. In cartilage, chondrocytes both sense mechanical stimuli and act as effector cells that produce the matrix macromolecules and proteases required for tissue turnover and homeostasis. Tenocytes have a similar role in mechanical tissue adaptation in tendons.¹¹ In bone the situation is more complex in that multiple cell types are present, including progenitor cells, endothelial cells, and bone-forming and bone-resorbing cells. Nevertheless, there is growing consensus that osteocytes are likely to be the most important mechanosensitive cells in bone remodeling through paracrine effects on cells of the osteoprogenitor and osteoclast lineage.^{1,2}

MECHANOCOUPLING

The mechanical loads applied to connective tissue have been extensively measured *in vivo* and vary in different tissues. In adult bone, peak strain magnitudes of 2000 to 3500 microstrain are encountered during vigorous exercise, whereas in normal activity, magnitudes of less than 10 microstrain occur thousands of times per day. Cartilage and tendon are exposed to much greater loads.¹² Normal walking generates forces three to four times body weight in the hip and knee, which rises to seven times body weight with rapid walking. During standing or climbing stairs, forces up to 20 megapascals are produced in the hip within milliseconds. The Achilles tendon is thought to encounter forces 4 to 12 times body weight during walking and running as the forces generated in muscles are transmitted to bone.¹³ Cells are not directly exposed to mechanical forces because they are surrounded by ECM, which acts to absorb, transmit, and dissipate these forces. Cartilage, for example, contains a type II collagen network that imparts tensile strength, as well as proteoglycan to resist compression, which allows the tissue to withstand high compressive and shearing loads. The forces encountered by cells in most connective tissue are not precisely known.

Dynamic compression of cartilage causes a range of physiochemical changes, including hydrostatic pressure gradients, fluid flow, streaming potentials, and alterations in matrix water content, fixed charge density, mobile ion concentrations, and pH and osmotic pressure, as well as chondrocyte deformation.¹⁴ All these changes may influence cell behavior. Loading of bone induces shear, strain, and compression, with up to 5000 microstrain generated at the osteocyte cell surface¹⁵ and the development of pressure gradients that stimulate flow of interstitial fluid through the osteocytic lacunar network.¹⁶ Osteocytes may encounter much higher levels of strain as flow of interstitial fluid through the canalicular network is resisted by the nonmineralized pericellular matrix and drag forces are induced.¹⁶ In tendon, the complex three-dimensional structure¹⁷ results in a tensile load at the macroscopic level being converted into tensile, shear, and compressive strains encountered by the tenocyte.

MECHANOTRANSDUCTION

Connective tissue cells express mechanoreceptors that recognize the physiochemical changes that occur within connective tissue during mechanical loading. Activation of these receptors results in stimulation of the intracellular signaling cascades that regulate gene expression, changes in

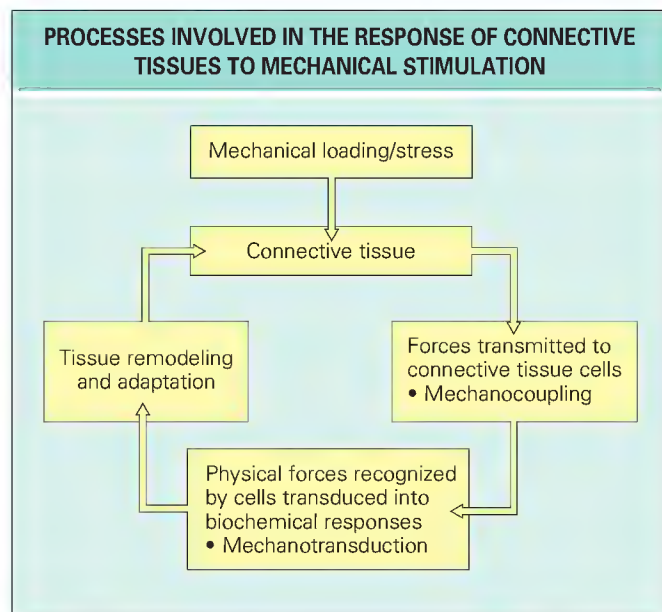


Fig. 8.1 Processes involved in the response of connective tissues to mechanical stimulation.

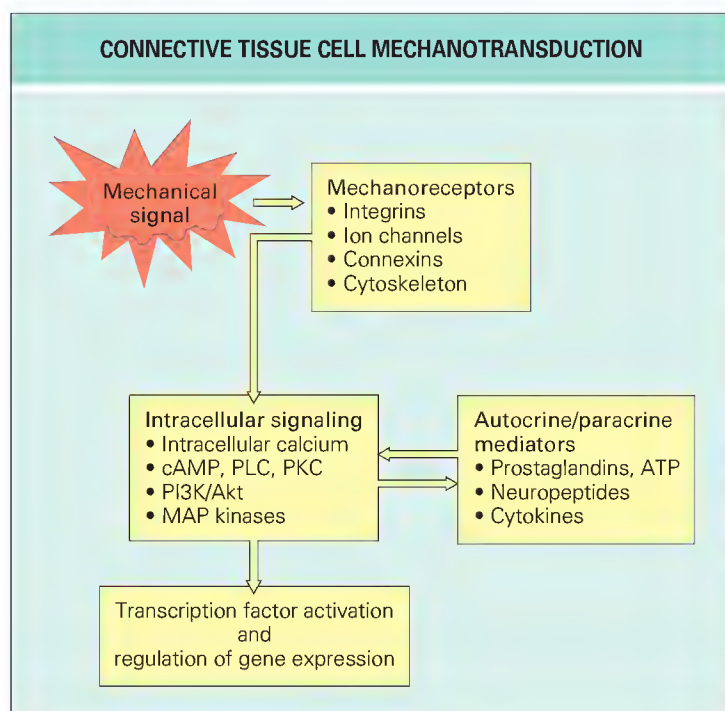


Fig. 8.2 Mechanical stimuli are recognized by mechanoreceptors that activate a range of intracellular signal pathways, either directly or through autocrine/paracrine signaling. This leads to changes in gene expression and tissue remodeling. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; MAP, mitogen-activated protein; PI3K, phosphatidylinositol-3'-kinase; PKC, protein kinase C; PLC, phospholipase C.

protein expression, and tissue remodeling (Fig. 8.2). A number of molecules and molecular complexes that recognize physicochemical changes, including alterations in cell shape, cell membrane deformation, local ion concentration, and fluid flow, have been identified as candidate mechanoreceptors and include integrins,¹⁸ mechanosensitive ion channels,¹⁹ and connexins.²⁰

Integrins

Integrins are heterodimeric transmembrane glycoproteins that contain α and β subunits. Each α and β subunit consists of an extracellular domain, a single transmembrane region, and a cytoplasmic tail. The extracellular domain provides the binding site for ligands, including fibronectin and

collagen. The cytoplasmic tail is coupled to the cytoskeletal network by focal adhesions, or specialized large macromolecular assemblies that include actin-associated proteins and signaling molecules such as focal adhesion kinase. This enables the integrin receptor to transduce mechanical signals transmitted through the matrix into biochemical responses within the cell. Integrins have been demonstrated to be involved in cellular responses to stretch, elevated hydrostatic pressure, fluid shear stress, and osmotic forces.²¹ Stretch activates integrins and recruits focal adhesion components, which leads to activation of a subset of unoccupied integrins and induces their binding to ECM proteins and stimulation of intracellular signaling. Other mechanical forces may act in a similar way and increase the activation of integrins to stimulate cell adhesiveness and signaling.²² The cytoskeleton also responds to forces channeled through integrins by rearranging its inter-linked actin microfilaments, microtubules, and intermediate filaments. Chondrocytes and bone cells express a variety of integrins, many of which may function as mechanoreceptors. Roles for $\alpha_5\beta_1$, $\alpha_v\beta_5$, and $\alpha_v\beta_3$ have been demonstrated *in vitro*, but $\alpha_5\beta_1$ integrin, the classic fibronectin receptor, appears to be the major integrin mechanoreceptor in connective tissue. The anabolic response of human articular chondrocytes to mechanical stimulation is dependent on $\alpha_5\beta_1$ and involves phosphorylation of focal adhesion proteins.²³ Integrins may be part of larger mechanoreceptor complexes, including accessory molecules such as CD47, that control integrin activation²⁴ and regulate intracellular signaling and gene expression. Conditional knockout of β_1 integrin in cortical osteocytes limits the response of bone to disuse, thus indicating that the β_1 integrins on osteocytes are active in responses of these cells to mechanical loading.²⁵

Stretch-activated ion channels

Stretch-activated or stretch-sensitive ion channels (SACs) open on mechanical deformation of the cell membrane.²¹ Potassium-selective channels (TREK-1 family of 2P domain channels and adenosine triphosphate [ATP]-sensitive potassium channels), the Shaker-IR K^+ channel, the N-type Ca^{2+} channel, ionotropic N-methyl-D-aspartate receptors (NMDARs), and Ca^{2+} -dependent BK channels have all been shown to act as SACs. SACs are directly activated by mechanical forces applied along the plane of the cell membrane. These forces induce membrane tension and distortion of the cell membrane lipid bilayer, which results in conformational changes that alter opening or closing rates and allow ion flux.²⁶ Hydrostatic pressure, in which mechanical forces are applied perpendicular to the cell membrane, appears to be less effective in activating SACs.¹⁹ Opening of calcium-permeable SACs increases intracellular calcium levels and stimulation of downstream calcium-dependent intracellular signal cascades. SACs sensitive to gadolinium are necessary for load-related increases in prostaglandin and nitric oxide (NO) production, cytoskeletal reorganization, and changes in gene expression in response to fluid flow of bone cells and responses of chondrocytes to both strain and compression. The effects of different forms of mechanical stress may be regulated by the activity of voltage-gated or ligand-gated ion channels. L-type calcium channels have roles in bone cell responses to fluid flow rather than to strain, whereas K^+ channels of the TREK family but not gadolinium- or nifedipine-sensitive ion channels are important for stretch-induced elevation of parathyroid hormone-related protein gene expression in bone cells. NMDARs are ligand-gated ion channels that may be involved in chondrocyte mechanotransduction.²⁷

Connexins and primary cilia

Connexins form gap junctions and hemichannels that allow continuity between cells and permit diffusion of ions, metabolites, and small signaling molecules such as cyclic nucleotides and inositol derivatives. They also associate directly with intracellular signaling molecules and regulate cell function through activation of intracellular signal cascades. Connexins are widely expressed in connective tissue, where networks of cells are seen such as in bone,²⁸ tendon,²⁹ and meniscus,³⁰ and probably act to allow propagation of a mechanical stimulus through a tissue. Cx43 is the most abundant connexin family member present in skeletal tissue and is thought to be involved in responses to mechanical loading. Junctional communication between osteocytes modulates shear stress-induced bone remodeling.³¹ In view of the limited cell-cell communication evident in mature articular cartilage, the role of connexins in the mechanical responses of chondrocytes may be to provide communication between intracellular and extracellular compartments and, by release of small molecules such as glutamate and ATP, mediate signal propagation. In tenocytes, Cx32 junctions form a communication network that stimulates collagen production in response to strain, whereas a Cx43 network links tenocytes in all directions and is inhibitory for collagen production.³²

Primary cilia are solitary, immotile cilia present in most cells, including chondrocytes and bone cells, grow from the centrosome, and extend from the cell surface. They contain a variety of cell membrane receptors such as integrins and function as chemosensors or mechanosensors (or as both).^{33,34} Matrix or cell deformation induces bending of the cilium and activation of integrins, SACs, and connexin hemichannels,³⁵ thereby leading to downstream signaling and changes in gene expression.

MECHANICAL STIMULATION-ACTIVATED SIGNALING

Following recognition of the mechanical stimulus, secondary messenger molecules are generated and a cascade of downstream signaling events take place that regulate gene expression and cell function. A wide range of intracellular signaling molecules have been shown to be activated following mechanical stimulation of connective tissue cells. Such molecules include G proteins, protein kinases, and transcription factors that regulate the expression of matrix molecules and proteases involved in tissue remodeling. They may be activated directly as a consequence of mechanoreceptor signaling or indirectly following the production of autocrine/paracrine-acting molecules through rapid production and release of soluble mediators that provide crosstalk between different components of a mechanotransduction cascade and integrate the cellular and tissue response to mechanical stimuli.

G protein-coupled and phosphatidylinositol-3'-kinase-Akt/protein kinase B pathways

Heterotrimeric guanine nucleotide binding proteins (G proteins) are associated with a variety of cell-surface (G protein-coupled) receptors and, depending on the subclass, activate different intracellular signal cascades. G_s induces the formation of cyclic adenosine monophosphate and activation of protein kinase A, whereas G_q and G_o activate phospholipase C, which leads to the production of inositol-triphosphate and diacylglycerol with subsequent release of calcium from intracellular storage sites and activation of protein kinase C (PKC). There is extensive evidence for the roles for these G protein-associated signaling molecules in mechanotransduction but limited evidence for G proteins as mechanoreceptors.

Protein kinase B (PKB)/Akt is a serine/threonine kinase activated by phosphatidylinositol-3'-kinase (PI3K). Mechanical forces activate PI3K via integrin stimulation and, via this route, can inhibit cell death. Inactivation of the PI3K/PKB pathway may be important in the deleterious effects of mechanical overloading of cartilage and bone or tissue atrophy in response to withdrawal of loading.³⁶

Mitogen-activated protein kinases and nuclear factor- κ B

Mitogen-activated protein kinases regulate cellular activities such as gene expression, mitosis, differentiation, and cell survival/apoptosis. ERK1/2, JNK, and p38 have each been shown to be activated in chondrocytes, bone cells, and fibroblasts^{2,37,38} following mechanical stimulation and are of critical importance in the regulation of matrix protein and protease gene expression. Nuclear factor- κ B (NF- κ B) is a protein complex that acts as a transcription factor. In bone cells NF- κ B is directly stimulated by mechanical stimulation through a pathway involving intracellular release of calcium.³⁹

Dynamic biomechanical signals of low physiologic magnitude and mechanical stimulation within the physiologic range block NF- κ B activity and the signaling that promotes chondrocyte responses to proinflammatory cytokines and matrix fragments⁴⁰ and regulation of the proapoptotic or antiapoptotic pathways. Conversely, high-amplitude dynamic stimulation, a catabolic stimulus, induces rapid nuclear translocation of NF- κ B subunits p65 and p50 in a similar manner to interleukin-1 β (IL-1 β).

Prostaglandins, nitric oxide, and adenosine triphosphate

Prostaglandins, predominantly prostaglandin E_2 (PGE $_2$), and NO are rapidly produced when bone cells are mechanically stimulated and are required for the anabolic response of bone to mechanical loading *in vivo*. Prostaglandin production is dependent on integrin; follows the activation of SACs, PKC, and phospholipase A_2 ; and may regulate gap junction activity and expression of receptor activator of NF- κ B ligand (RANKL). In contrast, in cartilage PGE $_2$ is catabolic. Physiologic mechanical loading of chondrocytes inhibits the production of PGE $_2$ and NO, whereas pathologic loading results in release of PGE $_2$.⁴¹ Mechanical loading-induced release of ATP by bone cells and chondrocytes acts through the metabotropic P2Y receptors and P2X receptors expressed by the cells to further regulate the cellular response.

Cytokines and growth factors

IL-4 and IL-1 β autocrine/paracrine activity is seen in the integrin-dependent mechanotransduction cascade of chondrocytes (IL-4 and IL-1 β) and bone cells (IL-1 β) following mechanical stimulation.⁴² In chondrocytes, release of IL-4 relies on secretion of the neuropeptide substance P, which binds to its NK1 receptor. Both IL-4 and substance P are necessary but not sufficient for the increased expression of aggrecan mRNA and decrease in matrix metalloproteinase-3 mRNA induced by the mechanical stimulus, thus suggesting crosstalk with other mechanosensitive signaling pathways. IL-1 β is involved in the early mechanotransduction pathway of both osteoarthritic chondrocytes and human trabecular bone-derived cells. Mechanical loading may also induce the release or activation of sequestered growth factors in the ECM, which will then act on nearby resident connective tissue cells. Basic fibroblast growth factor-2 is a possible mediator of mechanical signaling in cartilage through such a mechanism.

CONCLUSION

Individuals are exposed to a wide range of mechanical stress during daily activity, which is required to maintain connective tissue, including bone, cartilage, and tendons, in a healthy state. Moderate exercise can improve the strength and function of connective tissue, but withdrawal of mechanical stimuli or prolonged exposure to excessive mechanical loads results in tissue degeneration and the development of diseases such as osteoarthritis. The mechanisms by which mechanical stress regulates connective tissue cell function are beginning to be understood. It is likely that identification of mechanoreceptors and mechanotransduction pathways will increase our knowledge of how adverse mechanical environments have detrimental effects on connective tissue and allow the development of novel therapeutic interventions such as mechanomimetics to preserve or reconstitute connective tissue in aging and disease.

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9

Biomechanics of peripheral joints

■ MATTHEW F. KOFF

- Diarthrodial joints in the body act as levers with poor mechanical advantage.
- Joint lubrication is a combination of boundary lubrication, hydrodynamic lubrication, and boundary film lubrication.
- The characteristic stress-strain curve of collagenous tissues, such as tendon and ligament, is an initial toe region followed by a steep linear region before eventual failure.
- Many tissues in the body are viscoelastic and exhibit anisotropic behavior.
- The response of a tissue to an applied load or deformation depends on the tissue's structural composition and fluid content.

INTRODUCTION

Biomechanics is the application of mechanical engineering principles to living organisms. Biomechanics of organisms can be examined at different levels: cellular level (e.g., response of cells to an externally applied force or deformation), tissue level (e.g., strain of the anterior cruciate ligament during normal gait), and whole-joint level (e.g., joint contact forces during activities of daily living).

Engineering principles may be used to understand the cause and progression of many rheumatic diseases. A basic understanding of these principles is beneficial for clinicians and medical professionals. This chapter presents a rudimentary background of engineering mechanics pertaining to whole-joint and tissue mechanics in the human body.

BIOMECHANICS OF WHOLE JOINTS

The effects of a rheumatic disease are often seen at the microscopic level, but the symptoms of the disease are commonly found at the whole-joint level. For example, not only does osteoarthritis cause the formation of clefts and fissures in articular cartilage, but it also produces symptoms including joint pain, stiffness, and reduced range of motion. Examining the transmission of forces through a diarthrodial joint is one way of determining the changing functional capabilities of the joint during the onset and progression of a rheumatic disease.

Statics and dynamics

Whole-joint force analyses are commonly performed to determine the forces that a diarthrodial joint may experience during activities of daily living. A static analysis examines the forces and moments (torques) acting on a body at rest. An example is the evaluation of forces in the knee during standing. In vector notation, this is written as $\Sigma \vec{F} = 0$, $\Sigma \vec{M} = 0$, where $\vec{F}$ are the forces acting on the body and $\vec{M}$ are the moments (torques) acting on the body. A dynamic analysis examines the forces and moments acting on a body in motion. A dynamic analysis includes descriptions of the inertial properties of the body being analyzed. In vector notation, this is written as $\Sigma \vec{F} = m\vec{a}$ and $\Sigma \vec{M} = I\alpha$, where $\vec{a}$ and α are the linear and angular accelerations, respectively, of the body; m is the mass of the body; and I represents the inertial properties (mass distribution) of the body.

An example of a static force analysis is that performed for the shoulder joint. Although this analysis is performed in two dimensions for ease of

analysis, important generalized biomechanical characteristics of whole joints are evident from the results. The goal of this analysis is to calculate the static *in vivo* muscular forces and contact force between the proximal humerus and the glenoid fossa of the shoulder joint. We examine a shoulder at 90 degrees of abduction with a ball held in the hand (Fig. 9.1a).

To perform a force analysis (static or dynamic), it is necessary to construct a free-body diagram, which displays all forces and moments acting on a body or body segment of interest. A free-body diagram of a simplified shoulder joint is shown in Fig. 9.1b. For ease of analysis, the radius, ulna, and humerus have been combined into a single bone segment to represent the arm, forearm, and hand. All forces and moments acting on the selected body segment must be included in the free-body diagram. Forces included in the free-body diagram may be separated into four classes:

1. *Contact force* from the humerus acting on the glenoid fossa.
2. *Muscle forces* from muscle groups that flex, extend, and rotate the shoulder joint; only the deltoid muscle is modeled in this analysis.
3. *Intrinsic weight* of the arm.
4. *External forces* such as the weight of the ball in the hand.

It is also important to record the lines of action of the forces and moments in the free-body diagram. The point of application, direction (orientation), and magnitude of each force are included in the free-body diagram. The contact force is placed at the proximal end of the humerus; however, its direction (θ_j) and magnitude (F_j) are unknown.

The muscle force of the deltoid muscle is placed at its point of attachment to the humerus at a distance “a” from the glenohumeral joint center. The magnitude of the muscle force (F_M) is unknown. Lines of action of muscle forces (θ_M) are assumed on the basis of detailed anatomic dissections of joints. The force representing the weight of the arm (W_A) is assumed to be known and is placed at the center of mass of the arm at a distance “b” from the joint center. The force representing the arm weight is in the direction of gravity. The same is true for the ball of known weight held in the hand (W_B and distance “c”). The unknown variables are the magnitude of the contact force (F_j), the direction of the contact force (θ_j), and the magnitude of the muscle force (F_M). These variables are calculated using static force analysis.

A body is considered to be in static equilibrium when all forces and all moments acting on the body sum to zero. The summation of forces and moments may be performed around any point on the free-body diagram. For this two-dimensional model, the static equilibrium vector equations may be written in terms of their individual x, y, and z components:

$$\Sigma F_x = 0, \Sigma F_y = 0$$

and

$$\Sigma M_z = 0$$

When the force equilibrium equations are applied to the free-body diagram in Fig. 9.1b, the result is the following:

$$\Sigma F_x = 0 \rightarrow F_j \cdot \cos(\theta_j) = F_M \cdot \cos(\theta_M)$$

$$\Sigma F_y = 0 \rightarrow F_j \cdot \sin(\theta_j) = F_M \cdot \sin(\theta_M) - W_A - W_B$$

In a static analysis, the sum of moments (ΣM_z) may be taken at any coordinate location. In the current analysis, the sum of moments was taken about the point of application of the contact force on the humerus. The sum of moments was taken at this point to preclude the presence of the articulating surface contact force in the moment equation, yielding:

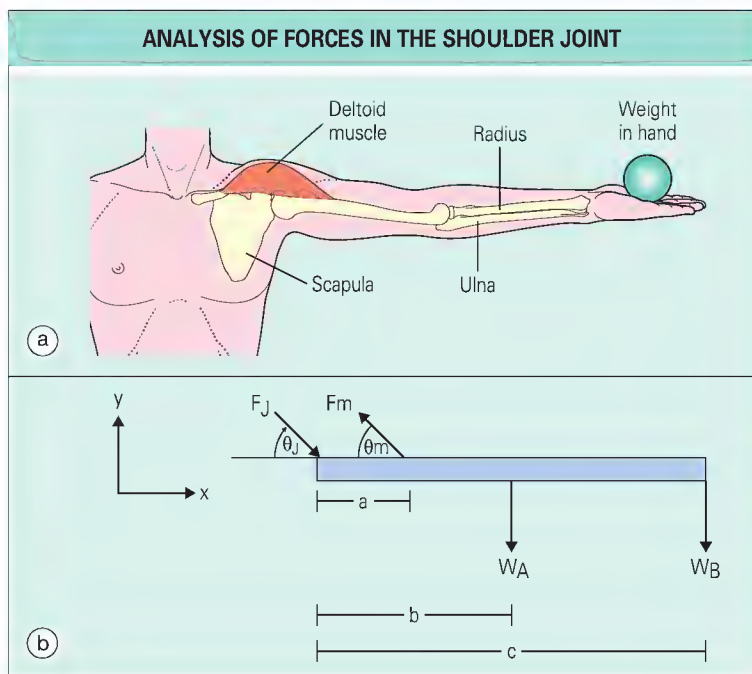


Fig. 9.1 (a) Person holding a ball in the hand at 90 degrees of shoulder abduction. Relative positions of bones in arm are indicated. (b) Free-body diagram of arm in 90 degrees of shoulder abduction (humerus, radius, and ulna are grouped together for simplification of analysis). a , b , c , distances from the glenohumeral joint center to forces acting on the limb; F_J , joint contact force; F_M , deltoid muscle force; θ_J , angle of joint contact force; θ_M , angle of deltoid muscle force; W_A , weight of arm; W_B , weight of ball.

$$\sum M_z = 0 \rightarrow F_M \cdot \sin(\theta_M) \cdot a = W_A \cdot b + W_B \cdot c = 0$$

The preceding equations are then solved to obtain the following:

$$F_M = (W_A \cdot b + W_B \cdot c) / (\sin(\theta_M) \cdot a)$$

$$\theta_J = \tan^{-1}((F_M \cdot \sin(\theta_M) - W_A - W_B) / F_M \cdot \cos(\theta_M))$$

$$F_J = \sqrt{(F_M \cdot \cos(\theta_M))^2 + (F_M \cdot \sin(\theta_M) - W_A - W_B)^2}$$

We now substitute values for the known variables $a = 15$ cm, $b = 30$ cm, $c = 60$ cm, $\theta_M = 15$ degrees, $W_A = 40$ N, and $W_B = 60$ N to solve for the unknown variables F_M , θ_J , and F_J . The calculated values are $F_M = 1236.4$ N, $F_J = 1214.3$ N, and $\theta_J = 10.4$ degrees.

This simple analysis shows a characteristic common to diarthrodial joints throughout the human body: poor mechanical advantage. The poor mechanical advantage of the shoulder is shown when the weight of the ball in the hand is compared with the muscle force required to maintain the ball position. The calculated muscle force is more than 20 times the weight of the ball! Altering two factors of the analysis may increase the mechanical advantage of the system by decreasing the muscle force required to hold the ball. First, an increase of θ_M would increase the component of F_M that resists the downward force of the weight of the arm and the weight of the ball. Another alternative would be to increase the moment arm of F_M , distance “ a ,” but this is often not practical. Second, we can flex the elbow and bring the weight of the arm and the weight of the ball closer to the center of rotation of the shoulder. This would change the resulting value from our moment equation and reduce our effective muscle force and resulting contact force.

A number of limitations to the static analysis exist due to the number of unknown variables. The number of static equilibrium equations available for use prevented the inclusion of additional muscle or ligamentous forces. That is, for a two-dimensional problem we could only use two force equations ($\sum F_x = 0$, $\sum F_y = 0$) and one moment equation ($\sum M_z = 0$) to solve the unknown variables. Stated differently, only three unknown variables may be determined in a two-dimensional analysis. If the analysis were performed in three dimensions, it would be possible to solve nine unknown variables. Owing to complex human anatomy and numerous muscle forces, we often have a greater number of unknown variables to solve than we have equations to use in the analysis. This results in an indeterminate problem.

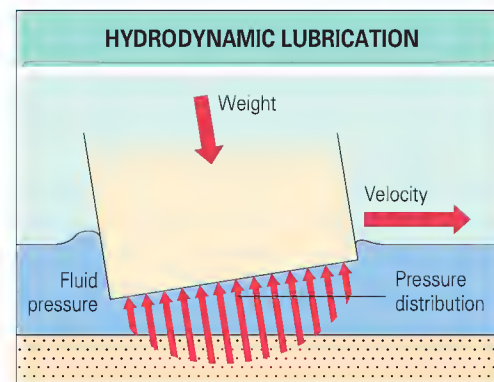


Fig. 9.2 Fluid film lubrication. During motion at sufficiently high velocities, the weight tilts and forms a wedge shape. Because of the viscous properties of the fluid, a pressure will be created within the fluid to support the weight.

Several computational methods have been developed to increase the number of variables that may be solved. One is the exclusion of selected forces. For example, in the previous analysis, the teres minor muscle, an adducting muscle of the shoulder, was excluded because the shoulder was in pure abduction. A second is to reduce the number of unknown forces by assuming a force relationship between the different muscle units. For example, the supraspinatus muscle is also active during shoulder abduction, but it was excluded to limit the number of unknown variables. We may have assumed a relationship between the deltoid and supraspinatus, such as $F_2 = A \cdot F_1$, where F_2 is the muscle force of the supraspinatus, F_1 is the muscle force of the deltoid, and A is a constant. The relationship between different muscular units not included in the analysis may be formatted in a linear or nonlinear manner.

A third method to decrease the number of unknown variables would be to incorporate direct muscle electromyographic measurements into the analysis. A fourth method to increase the number of unknown variables is to use numerical optimization. Optimization is performed by minimizing a mathematical function that is defined as the “cost” of performing an activity of daily living. Various cost functions that have been used include minimization of muscular forces, muscle stress, and muscle energy. These cost functions have been successful in evaluating muscle forces during various activities of daily living. More advanced methods of optimization have incorporated muscle architecture to predict muscular forces accurately during activities of daily living.

Joint lubrication

The human joints are exposed to great variation in loading conditions. There can be high-impact, short-duration loads such as in running; moderately low loads with a prolonged loading time such as in standing; and low loads with rapid motion in the swing phase of walking. Over a lifetime there is relatively little wear in the joints, which indicates a highly effective lubricating system.

Two types of lubrication exist: boundary lubrication and fluid film lubrication. Boundary lubrication is due to a single layer (monolayer) of lubricant adsorbed on each bearing surface. In the case of a joint, boundary lubrication is achieved by a macromolecular monolayer attached to each articular surface. These layers carry loads and are effective in reducing friction. Fluid film lubrication is due to a thin film of lubricant and produces a greater bearing-surface separation. The pressure developed in the lubricating fluid carries the loads applied to the joint (Fig. 9.2).

The lubricating characteristics depend on the lubricant properties, such as viscosity, and on the shape of the gap between the two bearing surfaces and the relative velocity of the surfaces. In a human joint, the bearing materials, such as the articular cartilage, are not rigid and stiff. This results in what is known as *elastohydrodynamic lubrication*. As the joint surfaces move and pressure is developed, the fluid pressure deforms the surfaces (Fig. 9.3). This changes the film geometry by increasing the surface area, reducing escape of the lubricant from between the bearing surfaces and generating a longer-lasting film. These factors produce a lower stress within the joint.

In diarthrodial joints, a mixed mode of lubrication occurs, with the joint surface loads being sustained by fluid film pressures in areas of noncontact and by boundary lubrication in areas of contact (Fig. 9.4). In addition, cartilaginous joint surfaces differ from typical engineering bearings in that the cartilage is filled with fluid and is porous and permeable so that the surfaces can exude a lubricating fluid. As the joint moves and the surfaces

slide, fluid is exuded in front of and beneath the leading half of the load. Once the peak stresses decrease, fluid is reabsorbed back into the cartilage, and it returns to its original dimensions.

The viscosity of a lubricating fluid is important. Synovial fluid undergoes large changes in viscosity with changes in both temperature and velocity gradient. For very low velocities, a thinner lubricating film is desirable. Because synovial fluid is thixotropic, which means it can become fluid when agitated and then settle when left at rest, it can meet these requirements.

If a joint effusion is present, the velocity-dependent properties of the synovial fluid may be lost, which results in reduced lubrication and subsequent wear of the joint surfaces.

BIOMECHANICS OF TISSUES

Understanding how tissues respond to applied loads and deformation often provides insight into the progression of various rheumatic diseases. When

a force is applied to a tissue, the tissue will deform in response to the applied load. If a displacement is applied to the tissue, the tissue will produce a resistive force as a reaction to the applied displacement. Different loading modes exist throughout joints and tissues in the body (Fig. 9.5), often in combination. The amount of resulting deformation or reaction force produced by the tissue is directly related to the material composition, size, and shape of the tissue.

Structural properties versus material properties

Tissues can be tested as isolated individual samples (mechanical testing) or in an entire structural complex (structural testing). The structural properties of a tissue incorporate not only the material composition of the tissue but also its geometric configuration and mechanical environment.¹ Output from structural testing is shown as a force–displacement curve (Fig. 9.6). The units of force are newtons (N) or pounds force (lbf) and the units of displacement are typically millimeters (mm). Stiffness is a structural property of a body and is calculated as the slope of the elastic region of the force–displacement curve.

On the other hand, material properties of a tissue encompass the inherent material (chemical and physical) composition of the tissue itself (e.g., contribution of collagen fibrils in a tendon).¹ Output from mechanical testing is shown as a stress–strain curve. The units of stress are typically pascals (Pa, N/m²), whereas strain has no assigned units. The mechanical property of modulus is calculated from the stress–strain curve. Stress and strain are considered normalized values of load and displacement, respectively, on the

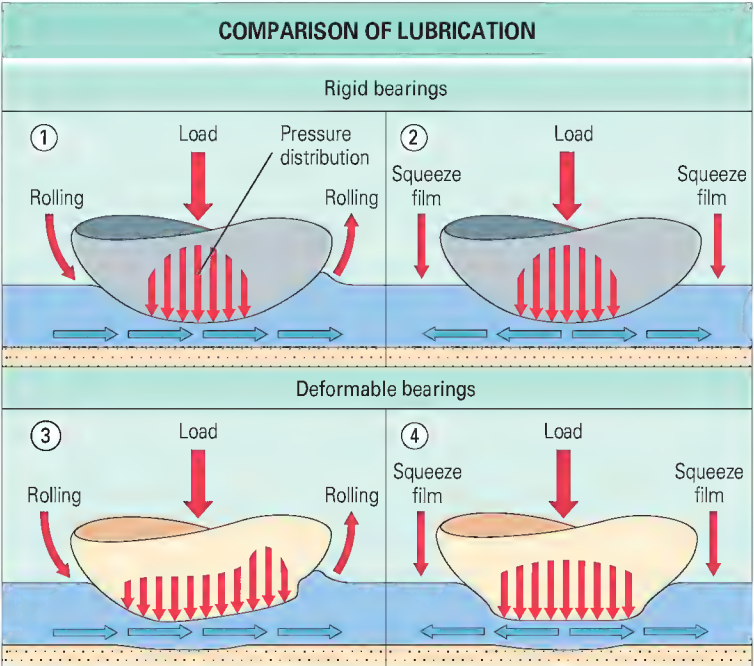


Fig. 9.3 Load carrying by lubricated bearings. A comparison of hydrodynamic lubrication (1) and squeeze film lubrication (2) of rigid surfaces, and elastohydrodynamic lubrication of deformable bearing surfaces under a hydrodynamic (sliding) action (3) and a squeeze film action (4). Surface deformation of elastohydrodynamically lubricated bearings increases the contact area, thus increasing the load-carrying capacity of these bearings.

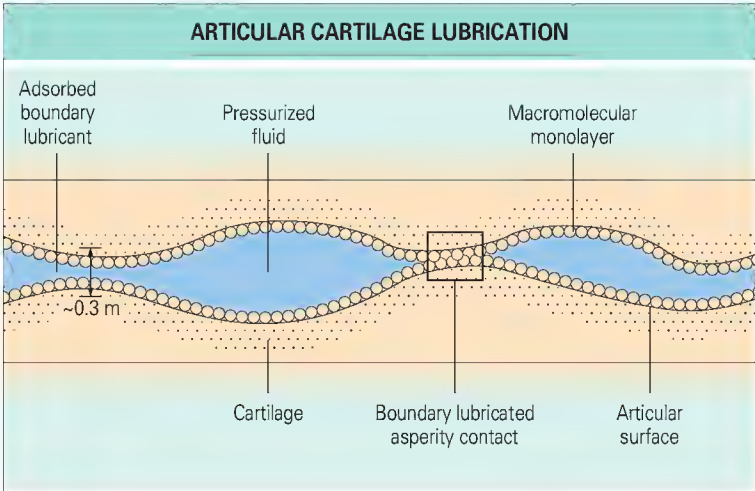


Fig. 9.4 Mixed lubrication operates in articular cartilage: boundary lubrication in which the fluid film is as thick as the roughness of the bearing surfaces, and fluid film lubrication in which surfaces are more widely separated.

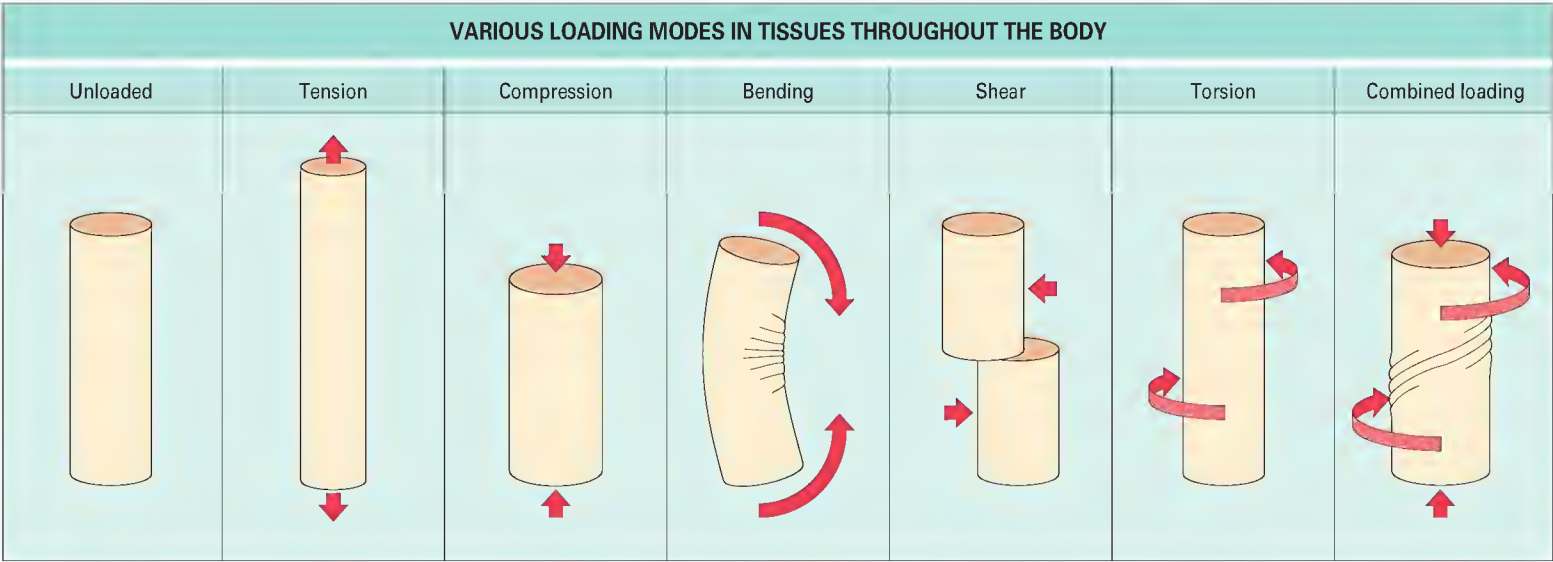


Fig. 9.5 Schematic representation of various loading modes.

basis of the geometry of the sample being tested (Fig. 9.7). Stress (σ) is calculated as the applied force divided by the initial cross-sectional area of the tissue sample: $\sigma = F/A_0$. Strain (ϵ) is calculated as change of length of the tissue sample divided by the initial length of the sample: $\epsilon = \Delta L/L_0$. Stress and strain and force and displacement may be positive or negative values. Additional information about the tissue may be extracted from the stress-strain curve (Fig. 9.8). For example, ductility is a measure of the amount of plastic deformation of a sample when it reaches failure, and resilience is the ability of a material to absorb energy when deformed elastically and to release the energy when unloaded.

Stress and strain

The stress distribution in a body is a quantitative description of the distribution of external forces acting through the body (Fig. 9.9). In three

dimensions, six independent stress components are required to describe the state of stress at each point in a body. Three of the stress components are normal stresses (tension-compression), and three stress components are shear stresses.

When an external force acts on the body, the body deforms to resist the applied load; this deformation is called *strain* (Fig. 9.10). In three dimensions, six independent strain components are required to describe the state of strain at each point in a body. Three of the strain components represent longitudinal elongation or compression of the body along the x, y, and z axes of the local coordinate system. The remaining three strain components represent the change of angles between the x-y axes, y-z axes, and z-x axes of the local coordinate system of the body.

We must assume a stress-strain relationship to calculate the stress within a tissue on the basis of experimental strain measurements. The stress in a body is related to the strain by the modulus of the body's material. This

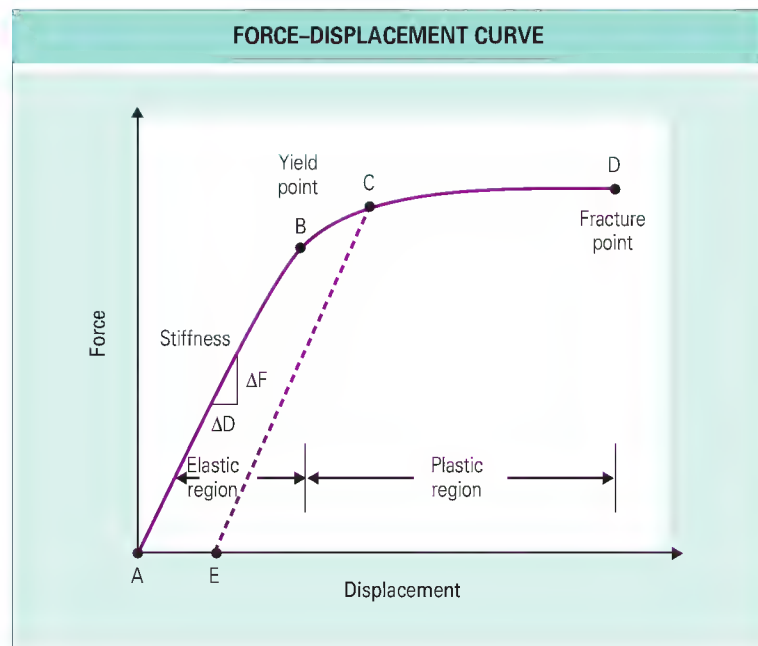


Fig. 9.6 Force-displacement curve for a structure composed of a pliable material. If a load is applied within the elastic region (A-B) and removed, no permanent deformation occurs. If loading continues past the yield point (B) and into the plastic region (B-D) and is then released, permanent deformation results. The amount of permanent deformation that occurs if the structure is loaded to point C in the plastic region and then unloaded is represented by the distance between A and E. Structural stiffness is calculated as the slope of the linear portion of the elastic region.

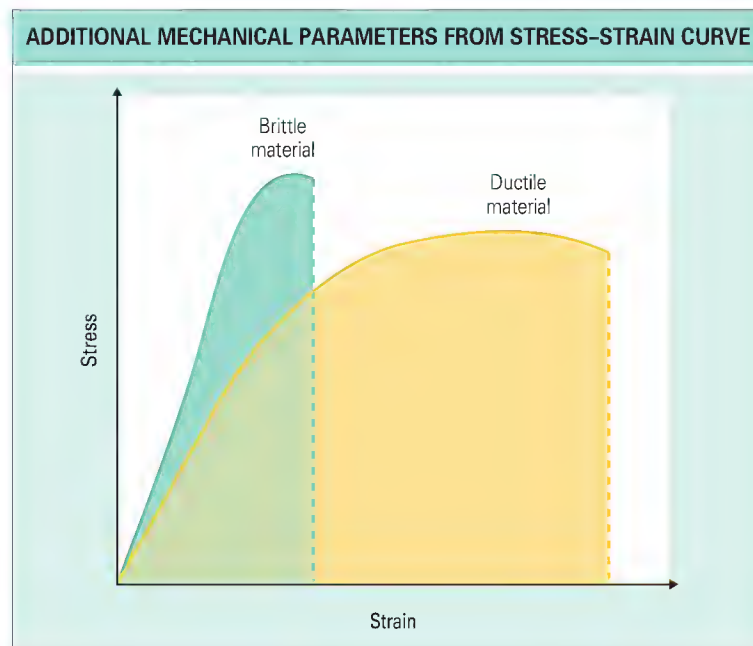


Fig. 9.8 Ductility is a measure of the amount of plastic deformation at failure and is shown in this figure. Resilience is the ability of a material to absorb energy when deformed elastically and to release the energy when unloaded. Resilience is calculated as the area under the stress-strain curve line. The presence of shear strain in a structure loaded in tension and in compression is indicated by angular deformation.

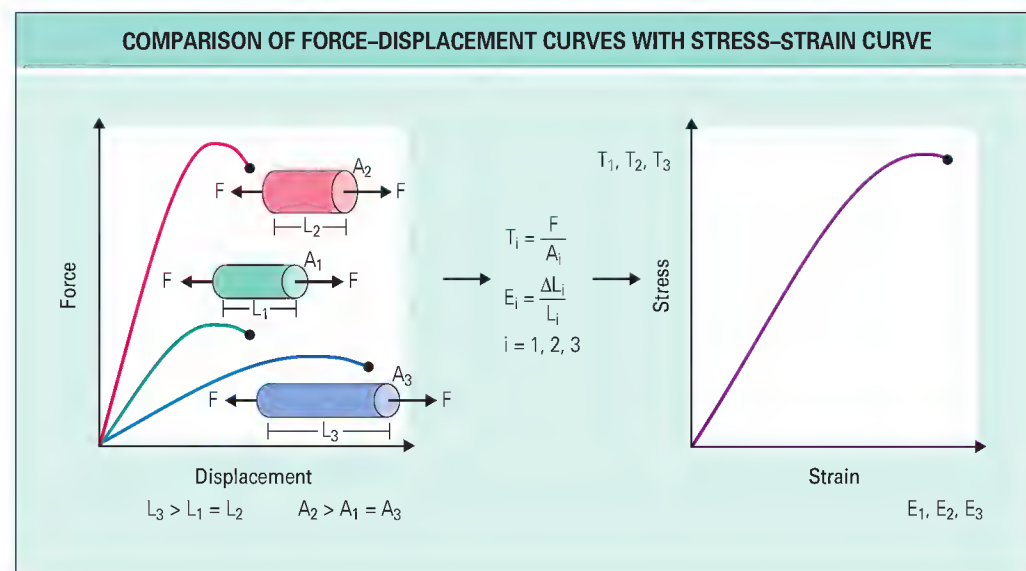


Fig. 9.7 Different continuous structures composed of the same pliable material but with different geometries are tested. When individual forces are converted to stress and displacements are converted to strains, all loading curves are superimposed onto one another.

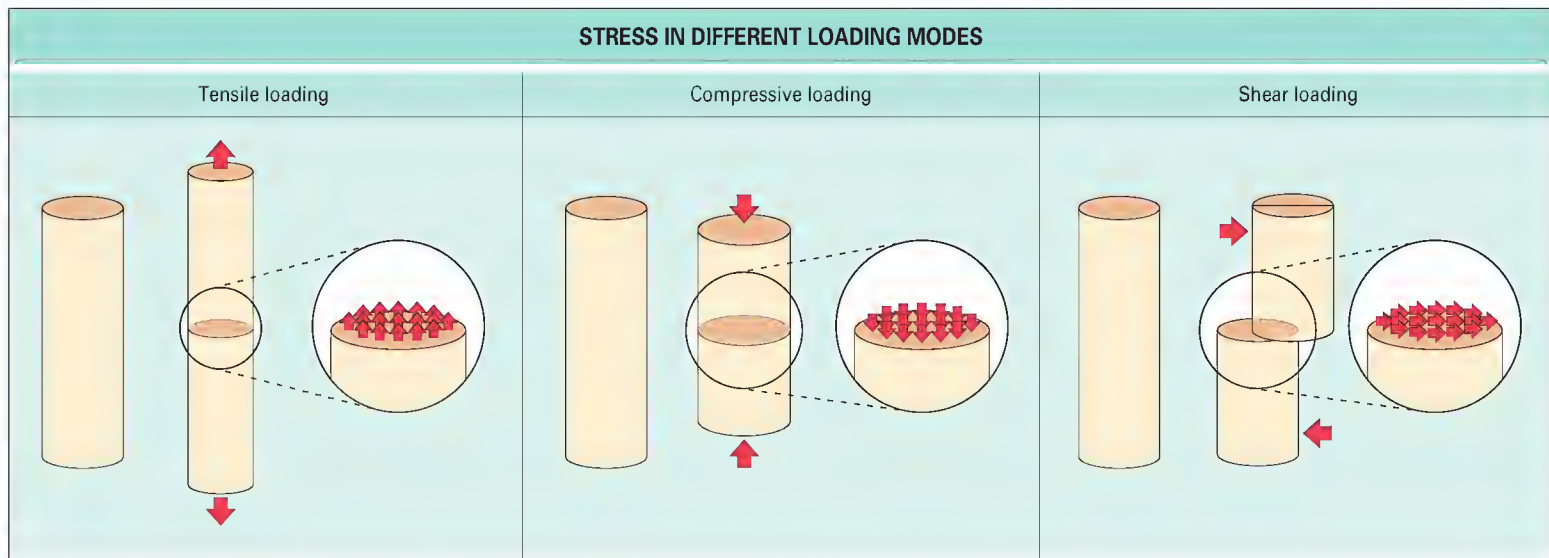


Fig. 9.9 Stress distribution within a material with tensile loading, compressive loading, and shear loading.

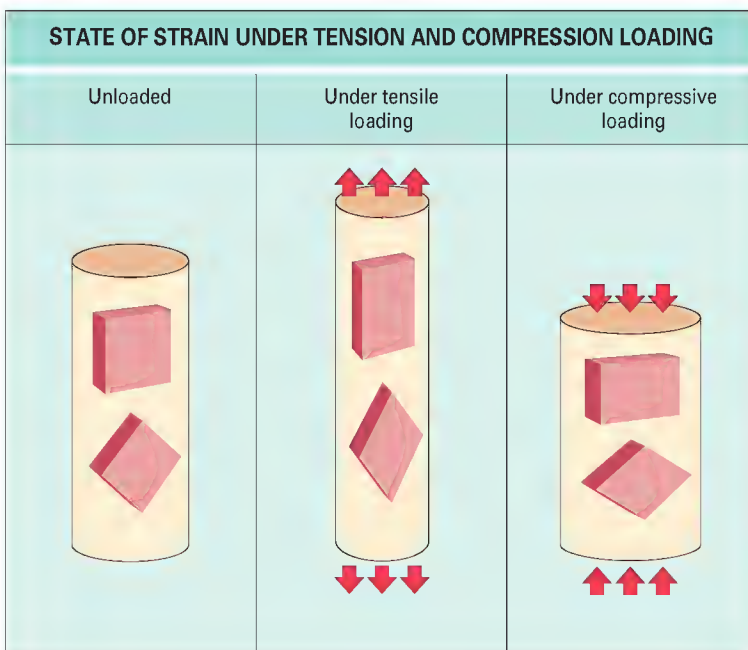


Fig. 9.10 Tension and compression strain are indicated by longitudinal elongation or compression of the body of the local coordinate system. The presence of shear strain in a structure loaded in tension and in compression is indicated by angular deformation of the local coordinate system.

relationship may be complex and may consist of numerous modulus values. The exact number of modulus values depends on the homogeneity and isotropy of the test sample.² If a tissue is homogeneous, the mechanical properties of the tissue do not differ depending on the source location of the tested tissue sample. If a tissue is isotropic, the mechanical properties of the tissue do not change as the orientation of the tissue sample is changed. Most tissues in the body are inhomogeneous and anisotropic. Stress-strain plots of tissue samples from an inhomogeneous and anisotropic tissue (cartilage) are shown in Fig. 9.11.

The orientation and source location of the tissue sample significantly influence the stiffness of the tissue. Cartilage samples that are aligned with the preferred direction of collagen fibrils are stiffer than samples that are oriented perpendicular to the preferred direction. In addition, tissue samples from the articular surface are stiffer than tissue samples from deep within the tissue. Researchers often assume a tissue to be homogeneous and isotropic. This results in a requirement for only two variables to fully describe the force-displacement response of a tissue to mechanical loading: Young's modulus (E_y) and Poisson's ratio (ν). In one dimension, Young's modulus is calculated as the slope of the linear portion of the stress-strain curve. Poisson's ratio relates the longitudinal elongation (ϵ_y) of the material to the

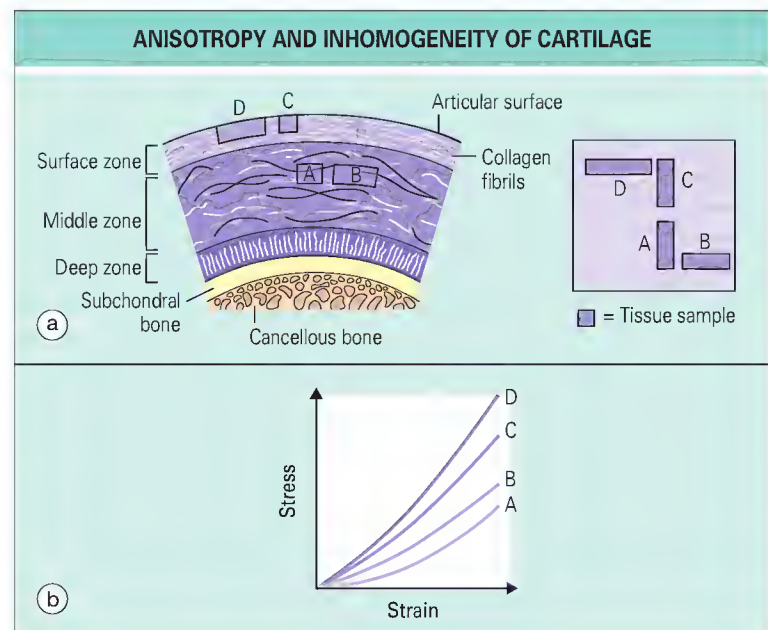


Fig. 9.11 (a) Schematic diagram of collagen fiber orientation through the depth of articular cartilage. Superficial fibers are tangent to the articular surface. Fibers in the middle zone have no preferred orientation. Fibers in the deep zone are oriented radially to the subchondral surface. (b) Stress-strain diagram of cartilage testing in tension. Tissue sample A is from the same region as tissue sample B but is oriented 90 degrees to tissue sample B. Tissue sample C is from the same region as tissue sample D but is oriented 90 degrees to tissue sample D. Differences in stress-strain response indicate the anisotropic and inhomogeneous material nature of cartilage.

lateral contraction (ϵ_x) of the material (Fig. 9.12). Furthermore, soft tissues in the body have an evident viscoelastic component.

Viscoelasticity

For a viscoelastic tissue, the stress-strain response depends not only on the magnitude of the applied stress or strain, but also on the rate of the applied stress or strain. Viscoelastic tissues have three characteristic stress-strain responses: creep, stress-relaxation, and hysteresis. Creep is the deformational response of a tissue sample under a constant load (Fig. 9.13). Stress-relaxation is the stress response of a tissue sample under a constant displacement (Fig. 9.14). Hysteresis is the difference in path between loading and unloading of the tissue sample on a stress-strain diagram (Fig. 9.15). These responses can be shown diagrammatically on a ligament sample. We assume a ligament has been removed from a joint as a

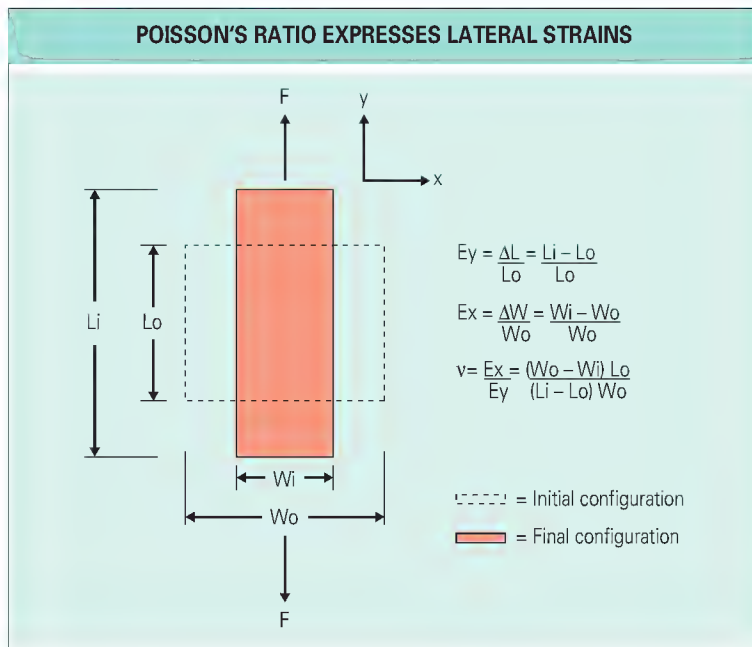


Fig. 9.12 Poisson's ratio relates the longitudinal elongation of the material to the lateral contraction of the material. In an ideal incompressible material $v = 0.5$.

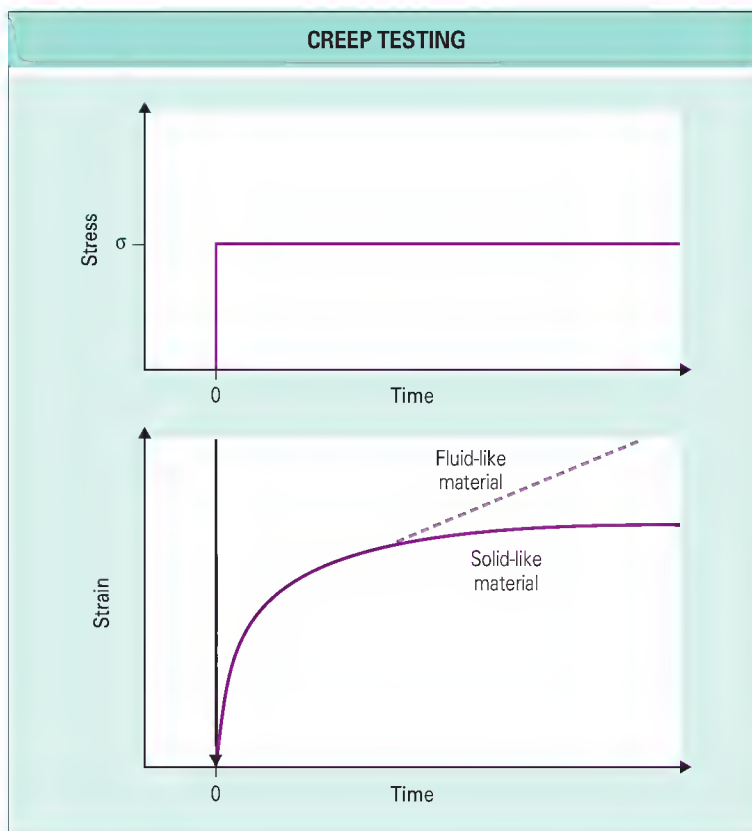


Fig. 9.13 In creep testing, an instantaneous stress (ϵ_o) is applied to a tissue sample at time t_o and maintained while the resulting tissue strain is recorded. Solid-like materials will exhibit an equilibrium deformation in response to the applied load, whereas fluid-like materials will elongate continuously.

bone-ligament-bone (BLB) segment. One end of the BLB has been anchored to the testing system through a load cell to measure applied force, and the other end of the BLB has been attached to the moveable cross-head of the testing system.

In a creep test, an instantaneous step or ramp load is applied to the tissue sample and held constant for an extended period of time (see Fig. 9.13). This is considered a load control test, and the resulting tissue displacement is measured. The displacement shows an initial elastic response of the tissue

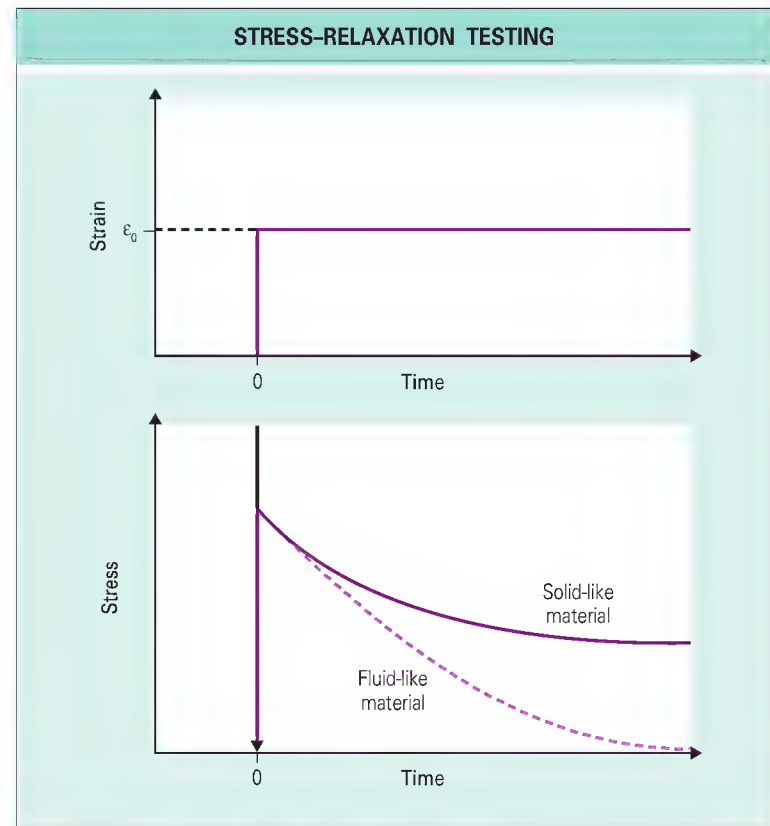


Fig. 9.14 In stress-relaxation testing, an instantaneous deformation (σ_o) is applied to a tissue sample at time t_o and maintained while the resulting tissue stress is recorded. Tissues in the body have a solid component that will resist the applied deformation after interstitial fluid has been exuded from the tissue.

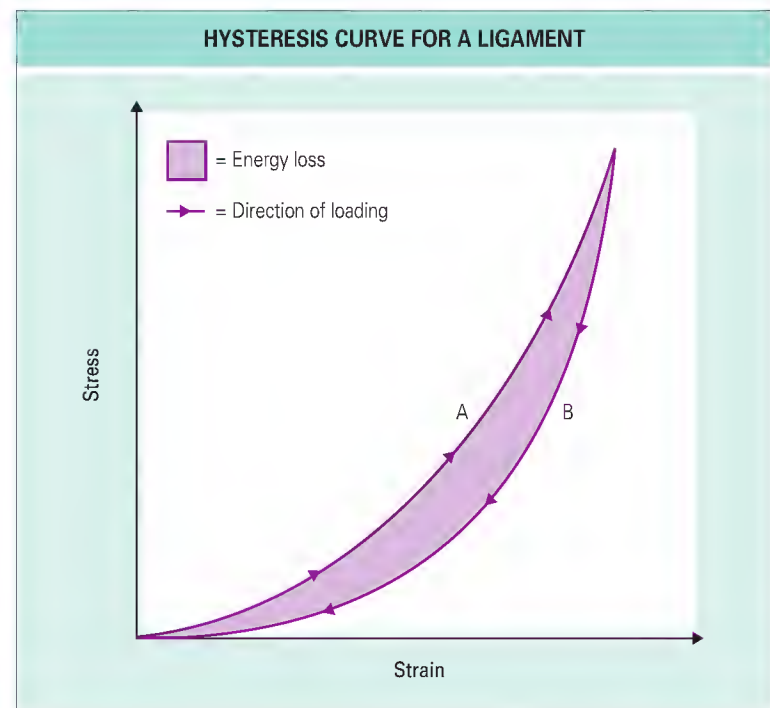


Fig. 9.15 The loading portion of the hysteresis curve (A) is always above the unloading portion of the curve (B). The area between the loading and unloading portions of the curve indicates relaxation of the collagen fibers within the ligament and the exuding of fluid from the ligament.

followed by a gradual increase of lengthening of the tissue. As the test proceeds, fluid is exuded from the tissue, and the solid components of the tissue are supporting the applied load. A "solid-like" material will be distracted to a point at which the solid components of the tissue will balance the applied load and will not elongate further. The modulus of the tissue is calculated as the stress of the tissue divided by the end displacement of the tissue. A

“fluid-like” material will not be able to balance the applied load and will continue to elongate.

In a stress–relaxation test, an instantaneous step or ramp displacement is applied to the tissue sample and held constant for an extended period of time (see Fig. 9.14). This is considered a displacement control test; the resulting tissue force is measured. An initial increase in force measured by the load cell is followed by a gradual reduction in force. The force eventually approaches an equilibrium value. The magnitude of the equilibrium value depends on the solid or fluid nature of the tissue. A solid-like material will have a final stress that is not zero. A fluid-like material will have a final stress that is close to or equal to zero.

Finally, hysteresis of a soft tissue is displayed while the tissue is cycled to a known force or displacement and back to its initial position (see Fig. 9.15). As shown in the figure, the loading portion of the force–displacement curve is always higher than the unloading portion of the curve. The area

between the loading and unloading curves represents nonrecoverable energy that is lost during testing.

The viscoelastic responses of the ligament are due to the interaction of fluid and solid components of the ligament: water and collagen, respectively. In a relaxed state before loading, the ligament is approximately 60% to 80% water and contains collagen bundles that have a wavy appearance. When a force or displacement is applied to the ligament, the fluid is exuded through pores in the tissue and the collagen fibers begin to straighten. In a creep test, a majority of the fluid is exuded from the tissue and the applied load is balanced by the straightened collagen bundles. In a stress–relaxation test, the collagen bundles are straightened by the imposed displacement and fluid is initially exuded in response to the rapid increase in interstitial fluid pressure. As time passes, the interstitial fluid pressure comes to equilibrium and fluid is no longer exuded. A combination of the fluid-solid effects is seen in a hysteresis loop.

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10

Biomechanics of the spine

■ MICHAEL A. ADAMS ■ PATRICIA DOLAN

- Genes and the environment contribute approximately equally to the strength of spinal tissues.
- Moderate mechanical loading strengthens vertebrae and (eventually) intervertebral disks.
- Muscle forces on the spine usually exceed gravitational forces, and inertial forces arising during accelerations and falls are often the greatest of all.
- Intervertebral disks and vertebral bodies resist spinal compression, with the fluid properties of the disk nucleus spreading compressive load evenly on the vertebral bodies in all postures.
- Neural arches protect the intervertebral disks (and spinal cord) from shear, torsion, and bending.
- The intervertebral ligaments limit spinal bending, but most are slack in upright postures so that the spine can move freely within its “neutral zone.”
- Compressive overload damages the vertebral body, decompresses the adjacent disk, and can lead to internal disk disruption.
- Combined loading in bending and compression can create radial fissures in the disk anulus and cause disk prolapse, even in macroscopically normal disks.
- Injury to the disk anulus or endplate alters the mechanical environment of disk cells and thereby creates a vicious circle of matrix weakening, reinjury, and frustrated healing.
- Loss of anulus height can initiate a “degenerative cascade” involving segmental instability, vertebral osteophytosis, and apophyseal joint osteoarthritis.
- In elderly people, vertebral strength decreases with decreases in activity and hormone levels, and patterns of vertebral deformity also depend on disk degeneration.

INTRODUCTION

Relevance of biomechanics

Spinal pain and deformity often arise from degenerative conditions that depend on age and genetic inheritance, and all aspects of human behavior (including responses to pain and to treatment) are strongly influenced by psychosocial factors. Consequently, the old *injury model* of back pain has been replaced by the *biopsychosocial model*,¹ which recognizes all these diverse influences. This does not mean, however, that biomechanics can be disregarded. Mechanical loading can make spinal tissues stronger or initiate degenerative changes within them, and genes influence mechanical characteristics as much as biologic ones.

Genes versus environment

Studies on human twins can reveal the “heritability” of a specific disease, expressed as the percentage of the disease variance that is associated with genetic inheritance. Early studies of intervertebral disk degeneration, vertebral fracture, back pain, and neck pain reported heritability values in excess

of 70%, but most current estimates are closer to 50%.²⁻⁴ The finding that heritability of disk degeneration falls to 30% in the lower lumbar spine, where mechanical loading is most severe, highlights the complementary role of environmental influences.⁴ It appears that genes and the environment contribute in approximately equal measure to the most common manifestations of spinal pathology and pain, and of the environmental influences, mechanical loading is the best documented and most easily modified. Also, of course, the genetic component includes inherited influences on mechanical factors, such as body weight and muscle strength.

Adaptation versus injury

The old “injury model” supposed that all mechanical loading is harmful to the spine, even though repetitive mechanical loading is known to strengthen muscles and bones according to the principles of adaptive remodeling.⁵ Articular cartilage and intervertebral disks can also become mechanically conditioned given enough time.^{6,7} Evidently, it is not mechanical loading that should be avoided but mechanical *overload*, which physically disrupts tissues. Epidemiologic studies that fail to make this distinction underestimate the influence of mechanical overload on spinal health. So too do cross-sectional surveys that ignore the “healthy worker effect” whereby those with back pain move to less arduous occupations.⁸ From a biomechanics standpoint, moderate spinal loading should be encouraged, although the risk for injury should be minimized. In the words of Nietzsche, “What does not kill him makes him stronger!”

The purpose of this chapter is not to revive the “injury model” but to take a fresh look at biomechanical influences in spinal disorders, including intervertebral disk degeneration, osteoarthritis, osteoporosis, and whiplash.

FORCES ACTING ON THE SPINE

Compression, shear, bending, and torsion

Compressive forces on the spine act down its long axis, at right angles to the midplane of the intervertebral disks (Fig. 10.1). The curvature of the spine ensures that the direction of the compressive force varies between spinal levels, and this is consistent with the origins of this force, which is primarily tension in the paraspinal muscles. *Shear* acts at right angles to the compressive force and causes vertebrae to slide forward, backward, or sideways relative to adjacent vertebrae. *Bending* moments (measured as a force multiplied by a lever arm in units of Newton meters [Nm]) cause the spine to bend, usually relative to the center of rotation within each intervertebral disk. *Torsional* moments, or torques, have the same units as bending moment and cause the spine to twist about its long axis (axial rotation).

Gravitational forces

Gravity exerts a vertical force on each body segment: its weight. Superincumbent body weight ranges from 55% of whole-body weight at the fifth lumbar vertebral level to 7% at the first cervical level. These forces are generally only a small proportion of the total force acting on the spine during vigorous activity.

Inertial or dynamic forces

When a body segment is accelerated, the force acting on it is amplified according to Newton’s second law of motion: Force = mass × acceleration.

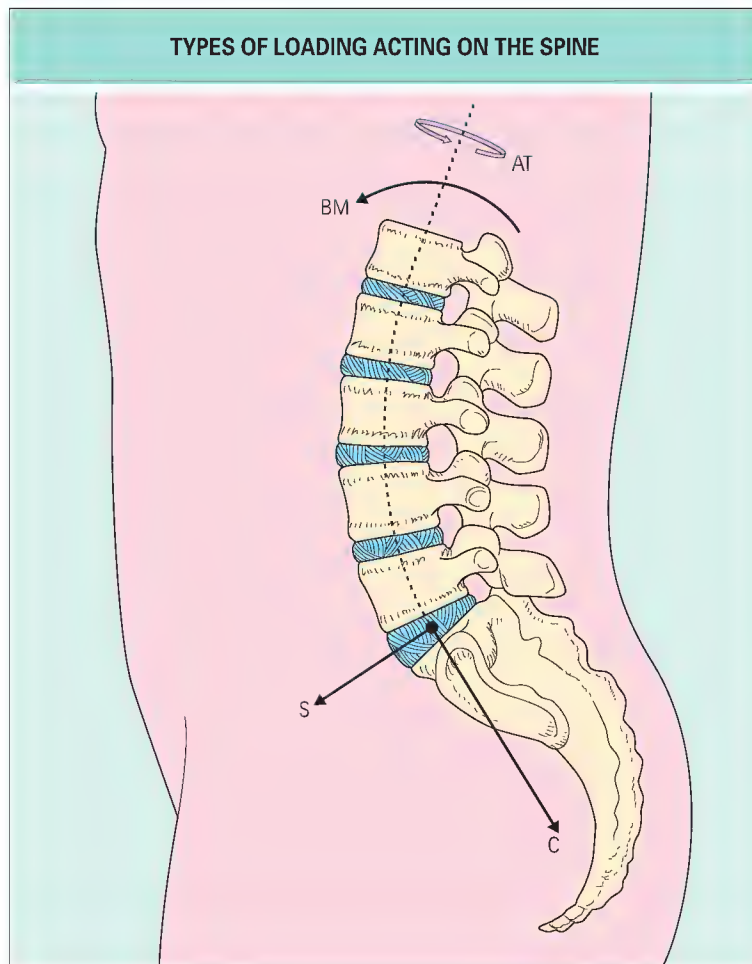


Fig. 10.1 The lumbar spine showing the directions of compressive (C) and shear (S) forces acting on the lumbosacral disk. Spinal compression acts perpendicular to the midplane of the disk, and thus its direction varies with the spinal level. A bending moment (BM) causes the spine to bend in flexion, extension, or lateral bending. Axial torque (AT) causes axial rotation about the long axis of the spine. (Reproduced with permission from Adams MA, Bogduk N, Burton K, Dolan P. *The biomechanics of back pain*. 3rd ed. Edinburgh: Churchill Livingstone; 2013.)

Exceptionally high acceleration occurs when the human body is ejected from an aircraft, and the compressive force on the lumbar spine can then be enough to cause vertebral fracture. More typically, the human spine is subjected to high deceleration during falls, especially when the impact velocity is high and the surface is so hard that velocity is brought to zero in a very short time.

Muscle forces

Tension in a contracting muscle compresses the bones that lie between the muscle's tendinous insertions. Muscle forces are hidden in the sense that they are internal to the body, but they often reach high levels for the reason illustrated in Figure 10.2. Essentially, muscles act on short internal lever arms and consequently must exert forces that are several times greater than the external loads that often act on much greater lever arms. Frequently, the external load is dominated by the weight of the upper part of the body, which is why lifting an object as small as a pen from the floor can generate a peak tensile force in the back muscles of greater than 200 kg.⁹ (Approximately 1 kg = 2.2 lb = 9.81 N.) The highest forces tend to arise when muscles accelerate or decelerate body segments, especially during eccentric (lengthening) contractions when the collagenous tissue within muscle is severely stretched. The need to stabilize the body in a moving environment often requires high levels of cocontraction of the paraspinal and abdominal muscles.

High muscle forces have a number of practical implications. In the medicolegal arena, many clinicians underestimate muscle forces by supposing (quite wrongly) that forces on the spine or neck must be low when the external loads are light. The potential danger of muscle contractions is

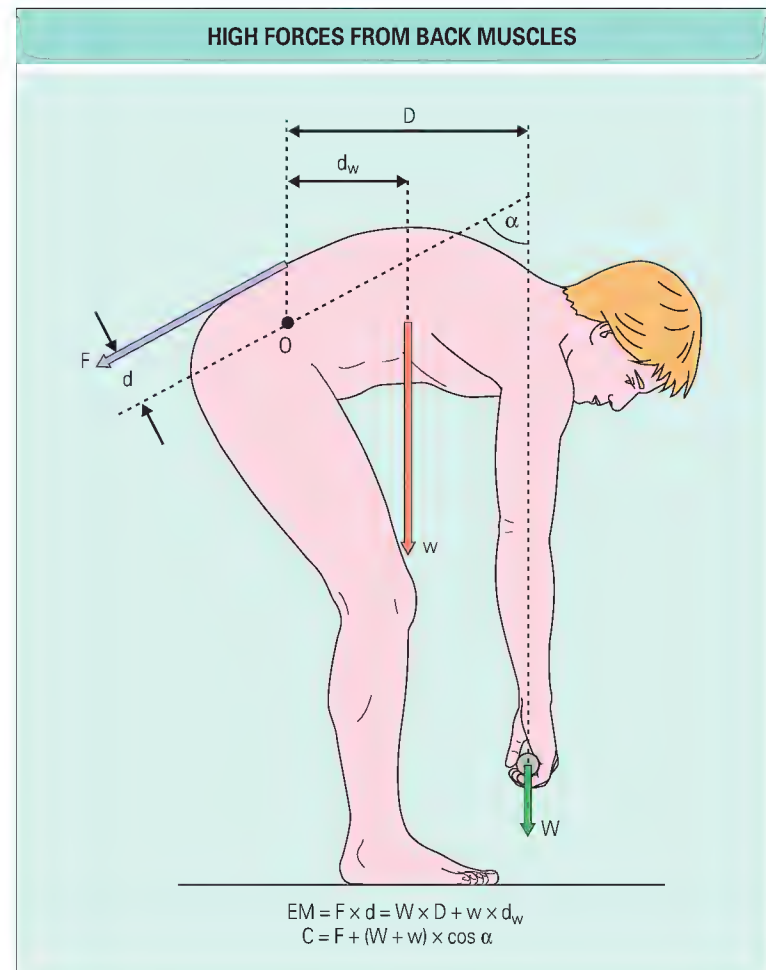


Fig. 10.2 During manual handling, high tensile force (F) must be created by the back muscles to generate an extensor moment (EM) large enough to lift up an external weight (W) and the weight of the upper part of the body (w). The back muscles act on a short internal lever arm (d) as opposed to the long lever arms (D, d_w) of the objects being lifted. In practice, muscle force F is often much greater than the weight being lifted, so the compressive force acting on the spine (C) rises to approximately 500 kg when a weight of 20 kg is lifted. (Reproduced with permission from Adams MA, Bogduk N, Burton K, Dolan P. *The biomechanics of back pain*. 3rd ed. Edinburgh: Churchill Livingstone; 2013.)

illustrated by the finding that epileptic fits can cause the back muscles to crush vertebrae, even when no falls are involved.¹⁰

Intraabdominal pressure

People struggling to lift a heavy weight usually hold their breath and go red in the face, thus indicating a common if unwitting strategy to stabilize the spine and protect it from high force. Contracting trunk muscles generate high pressure in the abdominal cavity, which can then transmit a compressive force directly from the thoracic spine and ribs to the pelvis and bypass the lumbar spine. The mechanism is difficult to quantify because tension in some abdominal muscles acts to compress the spine further. However, raising intraabdominal pressure would be most beneficial when the spine is flexed, when a thick belt is worn to provide lateral support to the abdomen, or when the pressure is raised primarily by contraction of the transversus abdominis, which does not compress the spine.¹¹

Diurnal variation

In the early morning, disks are swollen with water, so the anulus and intervertebral ligaments resist bending strongly and are most vulnerable to injury.¹¹ As the day progresses, disks lose 20% of their water and height, so the spine becomes more supple, but the neural arches then resist more of the compressive force on the spine. These diurnal changes explain why backache often increases after several hours of standing and why recurrent

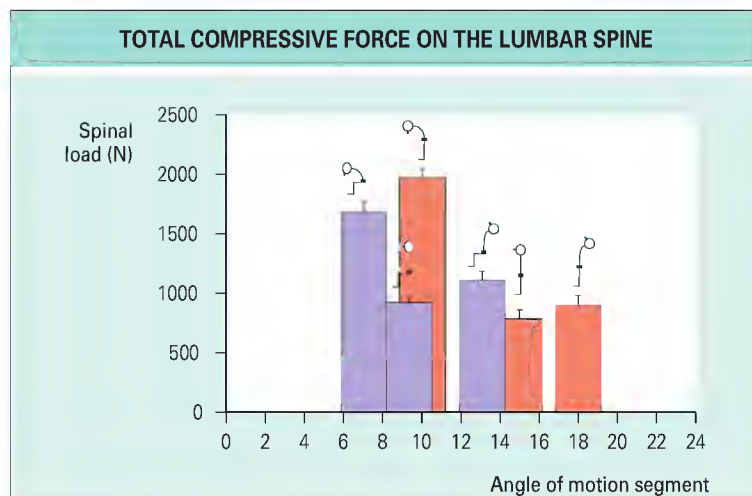


Fig. 10.3 The compressive force acting on the lumbar spine increases to 2000 N (approximately 200 kg) with stooped, standing postures. Forces were calculated from pressure in the L4-5 intervertebral disk nucleus measured *in vivo* by a miniature pressure transducer. "Angle of motion segment" refers to the relative orientation of the upper and lower endplates of the L4-5 disk. (Reproduced with permission from Sato K, Kikuchi S, Yonezawa T. *In vivo* intradiscal pressure measurement in healthy individuals and in patients with ongoing back problems. *Spine* 1999;24:2468-74.)

back pain can be reduced by avoiding flexion movements during the early morning.¹²

Measurement of spinal loading *in vivo*

The total compressive force acting on the spine of a living volunteer can be measured by inserting a pressure-sensitive needle into an intervertebral disk. Hydrostatic pressure measured in the disk nucleus can then be converted to compressive force by calibrating the transducer in cadaveric spines. The compressive force on the L4-5 disk of healthy subjects (average body weight, 73 kg) ranges from 14 kg when lying prone to more than 200 kg in the stooped, standing position,¹³ as shown in Figure 10.3. Relaxed sitting increases disk compression more than standing does because sitting flexes the lower lumbar spine and generates additional tension in the posterior ligaments whereas a lordotic standing posture causes some of the compressive force to be resisted by the neural arch.¹⁴

Measurement of spinal loading *in vivo* can be difficult when the spine is moved forcefully because inserted pressure transducers cannot be used safely. During manual handling, spinal compression can be quantified from the electromyographic signal recorded from the skin surface of the back. The electromyogram can be calibrated against the moments and forces generated during isometric exertions and then used to calculate muscle forces on the spine during vigorous movements.⁹ Peak compressive forces on the lumbar spine vary between 250 and 500 kg when lifting objects weighing up to 30 kg from the floor. Rapid lifting increases peak loading by more than 60% when compared with slow lifting, and forces of this magnitude can cause fatigue ("wear-and-tear") damage to accumulate in some spines. Similar peak forces are reported when mathematic models are used to calculate spinal loading from optical measurements of the movement and acceleration of various body parts.¹⁵

Shear forces and torques have not been measured reliably *in vivo*, but mathematic models show that peak anterior shear forces reach 150 to 200 kg in the lower lumbar spine when heavy weights are lifted.¹⁵ Much of this force can be resisted by the back muscles.¹¹

The peak bending moments acting on the spine of a living person can be estimated by measuring the moment required to bend a cadaveric spine to the same angle. The technique has been used to show that bending moments on the lumbar spine rise to 10 to 25 Nm during heavy lifting.⁹ Cadaveric spines can be flexed more than this before they are damaged, so in life, back muscles must normally protect the spine from excessive flexion. However, protective muscle reflexes can be impaired if the spine is flexed repeatedly or for periods of an hour or more.¹⁶ This could explain why activities such as gardening and long-distance driving are often associated with back pain.

MECHANICAL FUNCTION OF THE SPINE

Spinal curvature

Cervical lordosis appears when infants first lift their heads up, and lumbar lordosis develops when walking begins. Thoracic kyphosis appears to be a compensatory mechanism to maintain a level line of sight and to increase the volume of the thoracic cavity. Spinal curves probably play a shock-absorbing role during locomotion because the natural tendency for the curves to flatten and accentuate as the body rises and falls is resisted by the muscles of the trunk. The tendons of these muscles have a great capacity to store strain energy (which is proportional to tendon tension multiplied by stretch) such that the tendons of paraspinal muscles are able to act as shock absorbers and minimize vertical accelerations of the head.¹¹ A similar mechanism allows the quadriceps tendons to absorb energy when the knees are flexed to soften the landing from a jump.

Spinal movements

Intervertebral movements in living people combine angular rotations with small gliding movements (*translations*) in the plane of the disk. Angular rotations involve stretching and compressing the disk anulus in such a manner that the center of rotation (the theoretical pivot point) moves around within the disk nucleus.¹¹ The oblique surfaces of the apophyseal and uncovertebral joints ensure that certain movements are mechanically "coupled"; for example, attempted lateral bending normally creates a small axial rotation as well. The cervical spine is the most mobile region because the cervical intervertebral disks are relatively thick in comparison to the height of adjacent vertebral bodies. Conversely, the thoracic spine is the least mobile because its disks are narrow and movements are inhibited by the ribs and dipping spinous processes. Mobility of the lumbar spine declines by approximately 50% between the ages of 16 and 85 years.¹¹ This is partly due to disk narrowing, which brings the neural arches of adjacent vertebrae closer together and causes the center of rotation for flexion and extension to migrate posteriorly toward the apophyseal joints.¹⁷

Intervertebral disk mechanics

The central nucleus pulposus of an intervertebral disk normally has such a high water content that it behaves like a pressurized fluid, with compressive load being spread evenly on the adjacent vertebral bodies¹³ even when the vertebrae are angled in flexion or extension. The layers (lamellae) of the anulus fibrosus act in tension to retain this pressurized nucleus, but the adult human anulus is sufficiently fibrous to resist direct compressive loading as well. The internal mechanical functioning of loaded cadaveric lumbar disks has been investigated by pulling a needle-mounted pressure transducer along their midsagittal diameter. The resulting "pressure profiles" (see later) show the extent of the fluid-like region and the pressure within it. Both decrease with age, whereas the compressive stress (force per unit area) resisted by the anulus increases.¹⁸ Cervical disks behave in essentially the same way.¹⁹

Spinal resistance to noninjurious loading

Compression

Compressive loading of the spine is resisted mostly by the disks and vertebral bodies. As the compression increases, the disk anulus bulges radially outward and the vertebral endplates bulge vertically into the vertebral bodies.²⁰ The relatively high stiffness of the intervertebral disks and vertebral endplates (in comparison to tendons, for example) ensures that they are not good shock absorbers. A small proportion of the compressive force is normally resisted by the neural arch; this rises to 20% after sustained loading of the disk and when the spine is bent backward slightly to simulate the upright standing posture.¹⁴

Shear

The apophyseal joints resist the forward shearing movements of adjacent vertebrae (see Fig. 10.1), with the more frontal plane orientation of the lower lumbar joints making them particularly well suited to prevent any forward slip of the overlying vertebra.

Torsion

Similarly, the articular surfaces of the apophyseal joints are well orientated to resist axial rotation. In the lumbar spine, only 1 to 2 degrees of rotation is permitted before the articular surfaces make firm contact, but considerably more movement is allowed in the thoracic and cervical spine.¹¹

Stretching of the apophyseal joint capsule and ligaments on the tension side and deformation of the disk annulus also contribute substantially to the spine's resistance to torsion. Loss of apophyseal joint articular cartilage after osteoarthritis can allow more free play in these joints and increased range of axial rotation. The unique shape of the first two cervical vertebrae allows a much greater range of axial rotation.

Bending

Ligaments of the neural arch initially reorient when the spine is flexed. They then resist the movement strongly, with the interspinous and supraspinous ligaments being the first structures to be damaged during hyperflexion. The strong capsular ligaments of the apophyseal joints resist flexion the most, followed by the disk.¹¹ The ligamentum flavum has such a high content of elastin that it can be stretched by up to 100% in full flexion, even though it is the only intervertebral ligament to be prestressed in the upright “neutral” position. The posterior longitudinal ligament is weaker than the annulus to which it adheres and therefore does not protect it effectively from hyperflexion. A plexus of the mixed (autonomic/sympathetic) sinuvertebral nerve lies in the posterior longitudinal ligament, thus suggesting that its primary function may be to serve as a “nerve net” for detection of abnormalities in the underlying disk.¹¹ Backward bending (spinal extension) is resisted by the bony surfaces of the neural arch, with most resistance coming from either the facet joints or the spinous processes, depending on individual variations in anatomy. The shape of most disks (wider from side to side than from front to back) suggests that they resist lateral bending strongly, together with the apophyseal joint on the side that is being compressed. In life, lateral bending is often combined with flexion when individuals bend awkwardly to pick something up that is not directly in front of them. Such bending movements permit extra stretching of one posterolateral corner of the disk (the most usual site of herniation) because the additional component of lateral bending is not resisted by the interspinous and supraspinous ligaments, which lie on the axis of lateral bending.

INJURY

Fracture of the vertebral body

Compressive overload invariably damages the vertebral body before the intervertebral disk, even if the inner annulus of the disk is artificially weakened.¹¹ In a young or middle-aged person, the vertebral endplate is the most common site of injury since it is fractured by high pressure in the nucleus of the adjacent disk. Cranial endplates (relative to the vertebra) are injured more often than caudal endplates because they are thinner and supported by less dense trabecular bone.²¹ If nuclear tissue is expressed into the vertebral body (Fig. 10.4a), it eventually becomes surrounded by a calcified layer known as a Schmorl node (Fig. 10.4b). Endplate lesions in general are associated with mechanical loading, disk degeneration, and back pain.²²

Spondylolysis and spondylolisthesis

Spondylolysis represents a fracture of the pars interarticularis and occurs either unilaterally or bilaterally in the lower lumbar spine. It can be reproduced in cadaveric spines by bending the neural arch backward relative to the rest of the vertebra or by simulating spinal flexion movements that cause the tension in ligaments and muscles to pull the neural arch forward and downward.¹¹ Alternating movements in extension and flexion therefore have the potential to bend the neural arch backward and then forward²³ and create stress reversals, which are problematic for bone metabolism. This could explain why spondylolysis is associated with sports such as cricket and gymnastics, which involve extreme flexion and extension. Adolescents are affected the most because the reduced mineralization in their vertebrae allows much greater angular movements at the pars.²³ The L5 disk is affected most because it joins the mobile spine to the relatively immobile sacrum and it often lies at a steep angle to the horizontal (see Fig. 10.1) such that gravity contributes to the forward shearing force.

Spondylolisthesis is forward slip of a vertebra. It often follows bilateral spondylolysis in adolescents, but not invariably, thus suggesting that strong back muscles can keep the vertebrae in place.

Apophyseal joint injury

These small synovial joints are most likely to be injured by excessive shear or torsional loading. They are particularly vulnerable to torsion, which concentrates compressive loading on only one of the two joints, and damage occurs at a torque of 10 to 30 Nm.¹¹ The inferior and superior margins of

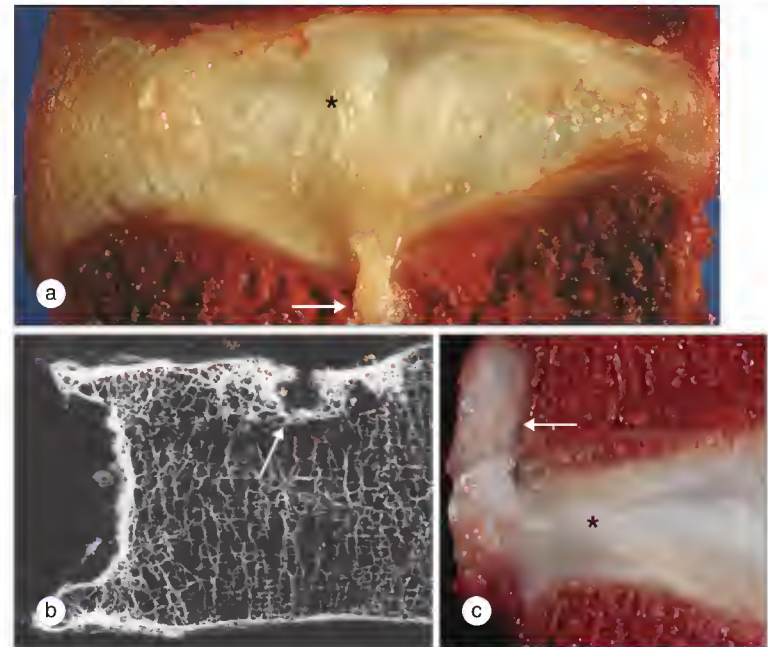


Fig. 10.4 (a) Midsagittal section through a lumbar disk and vertebrae showing vertical herniation of the nucleus pulposus (arrow) as a result of compressive overload *in vitro*. In life, calcification around the herniation would create a Schmorl node. Note the inward collapse of the inner annulus (*). (b) Radiograph of a midsagittal section of a lumbar vertebra (anterior on the left). Note the large Schmorl node extending from the center of the upper endplate (arrow) and the large osteophytes on the anterior vertebral margins. (c) Compressive and bending overload *in vitro* can cause some nucleus pulposus (arrow) to herniate through a radial fissure in the posterior annulus (*). (Adapted from Adams MA, Bogduk N, Burton K, Dolan P. *The biomechanics of back pain*, 3rd ed. Edinburgh: Churchill Livingstone, 2013.)

the articular surfaces are most frequently affected by cartilage loss and by osteophytes,²⁴ which suggests that damage also occurs when the spine is heavily loaded in flexion or extension and when disk height is reduced. Hyperextension of the spine can cause the inferior articular processes to stretch and probably damage the apophyseal joint capsules.²³

Disk herniation

Cadaveric experiments have shown that apparently normal disks can be made to herniate (i.e., prolapse) posteriorly by loading them simultaneously in bending and compression.²⁵ A single application of severe loading can cause extrusion of the nucleus pulposus (see Fig. 10.4c), and the disks most readily affected are the lower lumbar disks in those aged 30 to 50 years. In these experiments, either the bending or the compression had to exceed normal limits, but not both. More moderate but repetitive loading of disks in those aged 20 to 40 years can create radial fissures that allow nuclear material to migrate posteriorly but without permitting bulk extrusion of the nucleus from the disk space.¹¹ The underlying mechanism, which is explained by mathematic models,²⁶ is that spinal bending stretches and thins the opposite wall of the annulus so that the annulus rather than the vertebral endplate fails first when compressive loading increases nuclear pressure. If a radiopaque gel is forcibly injected into the nucleus, it can insinuate itself into and between the lamellae of the annulus,²⁷ thus suggesting that compressive loading alone might create a radial fissure in a human disk over a time scale of weeks or years rather than hours.

Herniated nuclear material swells by 200% to 300% in just a few hours before shrinking again over a period of several days as it loses proteoglycans.¹¹ This transient phenomenon could explain why sciatica sometimes develops gradually after a back injury.

Internal disk disruption

Internal disruption of the lamellar structure of the annulus is more common than disk prolapse. Circumferential or radial fissures may develop in the annulus (see Fig. 10.4c), or it may collapse into the nuclear cavity (see Fig. 10.4a). Internal disruption can be caused *in vitro* by traumatic or repetitive

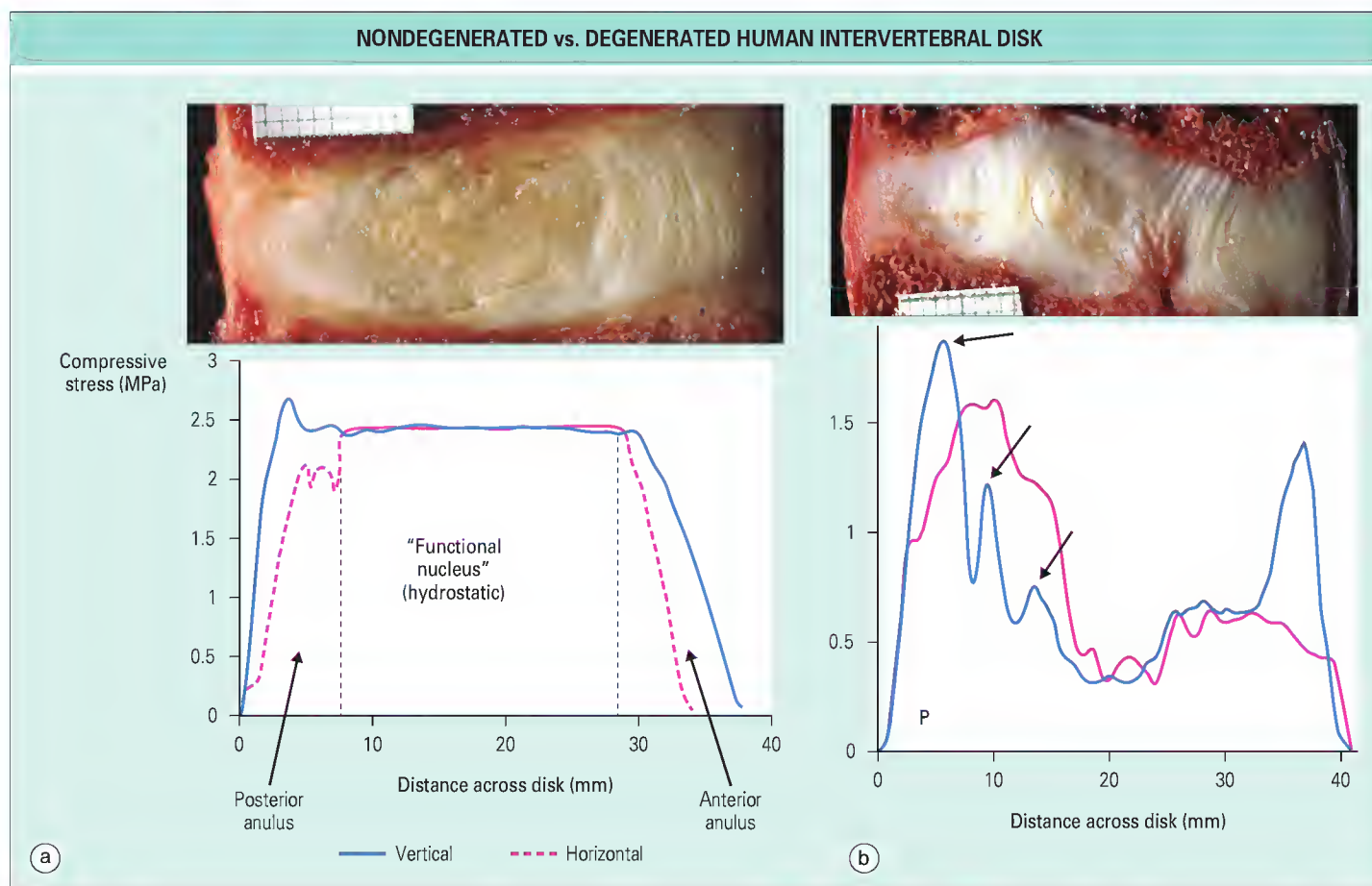


Fig. 10.5 (a) Photograph showing a mature nondegenerated human intervertebral disk cut through in the midsagittal plane. The graph below it shows how the horizontal and vertical components of compressive stress vary within such a disk. There is a central region of hydrostatic pressure (the “functional nucleus”) and a small concentration of compressive stress in the posterior annulus. (b) Internal disruption of the annulus lamellae and the damaged endplate indicate that this young adult disk is degenerated. Stress distributions in such a disk show a decompressed nucleus and high stress concentrations (arrows) in the annulus. The generally low disk stress suggests that some compression has been transferred to the neural arch. Approximately 1 MPa = 10 kg/cm². (Adapted from Adams MA, Bogduk N, Burton K, Dolan P. *The biomechanics of back pain*. 3rd ed. Edinburgh: Churchill Livingstone; 2013.)

loading involving bending and compression.²⁵ The simplest method is to damage the weak vertebral body endplate, which allows the pressurized nucleus to expand vertically, thereby reducing the pressure within it (Fig. 10.5) and allowing inward collapse of the inner annulus (see Figs. 10.4a and 10.5b). This mechanism has been demonstrated in cadavers²⁵ and confirmed in live animals.²⁸

Ligament injuries

Excessive flexion tears the interspinous and supraspinous ligaments, followed by the capsular ligaments of the apophyseal joints. Extreme hyperflexion is required to tear the posterior wall of the disk or the ligamentum flavum, typically at a bending moment of 60 Nm.¹¹ In extension, injury may occur at 35 Nm. Equivalent values for the cervical spine are 7 and 8 Nm, respectively. The elastic limit probably marks the end of the physiologic range of motion, at which point a clinically relevant injury would be sustained in life. Little is known about injuries to the iliolumbar ligaments or their role in back pain.

Whiplash

The essential feature of whiplash is a painful bending injury to the neck that is caused by a low-velocity insult, such as a car “shunt.” Low velocity does not mean that low force is involved. Laboratory simulations on cadavers²⁹ and live volunteers³⁰ show that a rear impact thrusts the shoulders forward relative to the head such that the neck is initially distorted into an “S” shape, involving hyperextension of the lower cervical levels and variable flexion and extension of the upper cervical levels (Fig. 10.6). This initial distortion is followed by general hyperextension. Finally, depending on the nature of the impact and the position of the headrest, the neck can be thrown into hyperflexion. The key feature of whiplash is that significant movements occur in less than 50 msec, before the neck muscles can resist them. Consequently, the head is thrown around relative to the slender neck

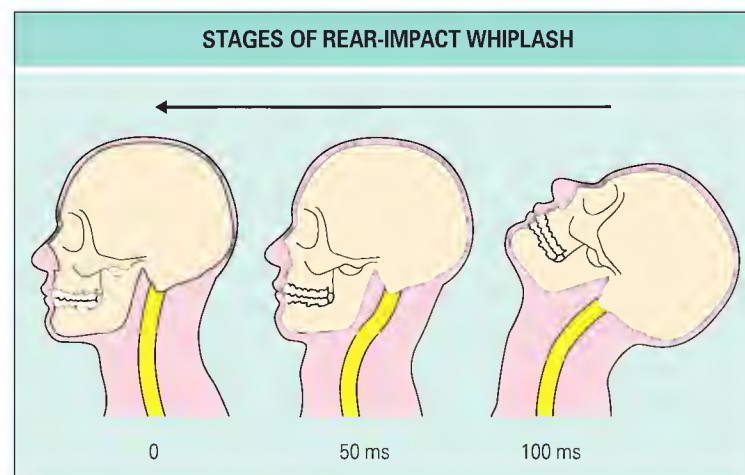


Fig. 10.6 During a rear-impact whiplash injury the neck adopts an S-shaped deformity after only 50 msec, before it can be protected by muscle action. Subsequently, the neck is thrown into hyperextension and possibly also into hyperflexion. (Reproduced with permission from Adams MA, Bogduk N, Burton K, Dolan P. *The biomechanics of back pain*. 3rd ed. Edinburgh: Churchill Livingstone; 2013.)

like a “balloon on a stick.” The cervical spine has approximately 45% of the compressive strength of the lumbar spine but only 20% of its strength in bending,³¹ which suggests that the neck is particularly vulnerable to bending injury.

The frequent involvement of both flexion and extension ensures that practically any structure in or around the cervical spine can be injured

during whiplash.³² The site of injury would move away from the sagittal midline (perhaps to an apophyseal joint) if the victim was turning his head around at the time of impact. Any previous warning would allow the victim to contract the neck muscles in alarm, thereby causing a higher proportion of compression to bending to act on the cervical spine and possibly increasing the risk for injury to muscles and intervertebral disks. As with any other human behavior, reports of symptoms persisting after whiplash are subject to a variety of psychosocial influences.³²

BIOMECHANICS OF DISK DEGENERATION

Middle-aged disks are vulnerable to injury

Loss of proteoglycans and water from aging intervertebral disks is confined mostly to the nucleus, where it leads to a smaller hydrostatic region exhibiting lower pressure. Consequently, high concentrations of compressive stress (force per unit area) develop within the annulus, particularly posterior to the nucleus.¹⁸ Aging annulus tissue is stiffened by increased collagen cross-linking, especially the nonenzymatic glycation reactions that are known to stiffen articular cartilage and render it more vulnerable to injury.³³ The accumulation of small defects in the annulus ensures that its strength does not increase with stiffness; in fact, strength can fall slightly.⁷ The vertebral endplates and their supporting trabeculae also weaken with age, in common with most bone structures, and endplates develop increasing concavity on the disk side. This further reduces nucleus pressure and concentrates stress in the annulus. Hence, increasing stress concentrations, increasing stiffness, and accumulating structural defects make middle-aged disks vulnerable to injury. The risk for injury appears to decrease in old age, possibly because older people are less active and because sarcopenia reduces the peak forces that can be generated by aging back muscles.³⁴

Injury alters matrix stress

As described earlier, severe loading in bending and compression can create radial fissures in the annulus and allow disk herniation, whereas excessive compressive loading can damage the endplate and lead to internal disruption. Either way, the annulus loses height and bulges radially like a “flat tire.”²⁰ Within the disk, the distribution of compressive stress often becomes highly irregular, as shown in Figure 10.5b.

Injury, degeneration, and “frustrated healing”

Disk cells respond to moderate fluctuating hydrostatic pressure by synthesizing more proteoglycans, and they respond to extreme or static pressure by synthesizing less.³⁵ The altered stress distributions in injured disks should therefore inhibit proteoglycan synthesis and lead to reduced nuclear hydration and pressure, which is the reverse of what would be required to reinflate the injured disk. This then provides a mechanism for progressive disk degeneration: injury affects the mechanical environment of disk cells in such a manner that their metabolism becomes aberrant, thereby leading to further weakening of the matrix and reinjury.³⁶ The mechanism is supported by evidence from animal experiments²⁸ and organ culture.³⁷ Attempts by the disk to heal itself are frustrated by metabolite transport problems, which limit disk cell density³⁸ and hence tissue turnover. However, metabolite transport through the endplate increases with age and degeneration,³⁹ so it is unlikely to be a primary cause of disk degeneration.

Discogenic pain

Intervertebral disks become avascular at about the time that a child learns to stand upright, presumably because the high hydrostatic pressure within the tissue collapses any blood vessels. Conversely, any loss of pressure in an injured or decompressed disk would allow blood vessels and nerves to grow back in again, as reported in severely degenerated and painful disks.⁴⁰ Ingrowth will be facilitated by focal loss of proteoglycans and reduced mechanical pressure within annulus fissures,⁴¹ and by structural damage to the endplate. There is no longer any doubt that disk degeneration is associated with an increased risk for back pain,⁴² and mechanical factors contribute directly to that pain, as well as to the underlying degeneration.

Disk prolapse

As degeneration progresses, internal disruption and radial fissures typically reduce disk height by 3% per year⁴³ and allow the nucleus pulposus to

approach the disk periphery. Excessive loading can precipitate herniation at any stage, and the fact that prior degeneration is not essential for prolapse to occur (see Fig. 10.4c) is an important medicolegal consideration.¹¹

SPINAL DEGENERATIVE CASCADE

Intervertebral disks play such an important role in spinal mechanics that disk failure initiates a whole cascade of adverse changes in adjacent tissues.

Segmental instability

Loss of nuclear pressure and volume removes tension from the surrounding annulus, and loss of disk height creates slack in the intervertebral ligaments. These mechanical changes are sufficient to create “segmental instability” in the motion segment, as manifested by reduced resistance to bending and an increase in horizontal shearing movements.¹⁷ In effect, the segment “wobbles” and has an increased region of free play (or “neutral zone”). The situation is more serious if the endplate becomes damaged because this causes immediate and gross decompression of the nucleus, as shown in Figure 10.5a. Segmental instability is associated with back pain, although the supporting evidence is slight. Pain could arise from the stress concentrations in the annulus (and apophyseal joints) that accompany nuclear decompression rather than from the small movements themselves. Instability should not be confused with hypermobility, which is a systemic condition involving increased ranges of movement.

Vertebral body osteophytes

Segmental instability is probably a transient phenomenon because it can be corrected by the growth of osteophytes on the margins of the vertebral bodies (see Fig. 10.4b) adjacent to the “wobbling” disk. Osteophytes can be created by an injury to the annulus⁴⁴ and grow in parallel with disk narrowing,⁴³ presumably because increased bulging of the annulus pulls on the periosteum. The primary mechanical effect of vertebral body osteophytes is to increase the disk’s resistance to bending,⁴⁵ hence reversing the initial destabilizing influence of disk degeneration. In this light, osteophytes can be viewed as adaptive rather than degenerative.

Apophyseal joint osteoarthritis

Loss of height because of a degenerated annulus brings the adjacent neural arches closer together so that they resist up to 90% of the compressive force acting on the lumbar spine rather than the normal 0% to 20%.¹⁴ Abnormal load-bearing creates high concentrations of compressive stress in the inferior margins of the joint, especially in habitual upright postures.⁴⁶ In addition, direct bone-on-bone contact between the inferior articular processes and the laminae below can lead to gross bone remodeling, including osteophytes. A close relationship between high load-bearing and osteoarthritic changes, including cartilage loss, bone eburnation, and sclerosis, has been noted in cadaveric apophyseal joints.⁴⁷ Imaging studies *in vivo* have long suggested such a relationship.

Spinal stenosis

The height of the intervertebral foramen is decreased by narrowing of the annulus fibrosus. Its anteroposterior diameter is also decreased as a result of radial bulging of the disk and by osteophytosis of the apophyseal joint. These changes can combine to cause a severe reduction in the cross-sectional area of the foramen and subsequent trapping of the exiting nerve. The consequences of spinal stenosis are usually most severe at L5-S1, which has a particularly small foramen.

Degenerative scoliosis

The two apophyseal joints at each spinal level often show pronounced left-right asymmetry, a condition known as *tropism*. If the affected joints become heavily load bearing as a result of disk narrowing (see earlier), their oblique articular surfaces will create an unbalanced torque about the long axis of the spine that leads to axial rotation. Axial rotation is mechanically “coupled” to lateral bending and can also be coupled to flexion and extension, so a “triplanar” spinal deformity develops that involves permanent twisting, lateral bending, and flexion of the thoracolumbar spine. This is a plausible explanation for degenerative scoliosis, but the mechanism has not been proved.

OSTEOPOROTIC VERTEBRAL DEFORMITY

Reduced loading weakens old vertebrae

When a vertebral body is loaded naturally by adjacent intervertebral disks, its compressive strength depends primarily on its size and bone mineral density (BMD).⁴⁸ Old vertebrae lose BMD and strength, partly as a result of hormonal changes and partly because muscle strength decreases with age³⁴ and thus provides a reduced mechanical stimulus to maintain bone mass.⁴⁹ Hormone levels and muscle strength are themselves influenced by genetic inheritance, as well as by environmental factors.

Mechanisms of deformity

The nucleus and inner annulus of a nondegenerated disk press evenly on adjacent vertebral bodies (see Fig. 10.5a), even when the spine is flexed or extended. If BMD falls, nuclear pressure can drive the central region of the adjacent vertebral endplates outward and create “biconcave” deformities in the vertebrae. Degenerated disks, on the other hand, concentrate compressive stress on the anterior and posterior vertebral body margins (see Fig. 10.5b) in flexion and extension, respectively. If the disk is also grossly narrowed, the neural arch resists much of the compressive load on its own, especially in upright postures.¹⁴ In many elderly spines, these factors combine to “stress-shield” the anterior vertebral body in upright postures, which causes it to lose BMD (Fig. 10.7). Unfortunately, flexion movements can then disengage the neural arches and transfer high compressive stress onto the weakened anterior vertebral body,⁵⁰ thereby creating anterior wedge deformities and senile kyphosis. (It is sometimes assumed that kyphotic posture is a cause of anterior wedge deformity rather than a consequence, but this is mistaken; if increased habitual loading of the anterior vertebral body was threatening it with collapse, this region of bone would have an elevated BMD rather than the reduced BMD commonly seen.) The third type of vertebral deformity, a “crush fracture,” probably results from high compressive impacts when the disks are degenerated.

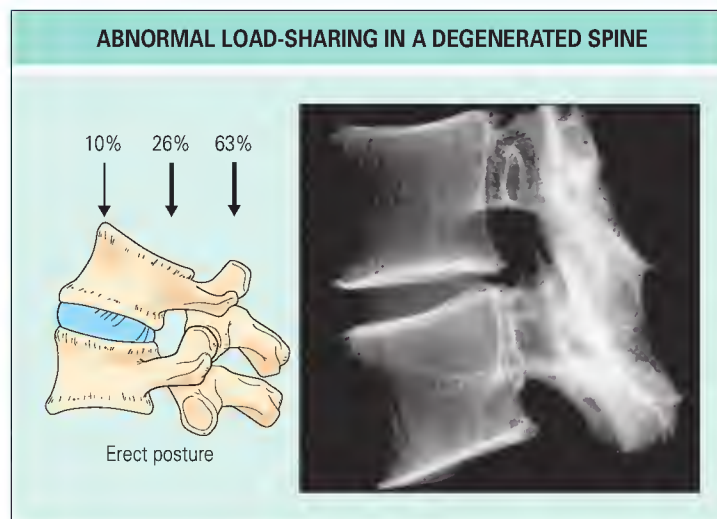


Fig. 10.7 (Left) The three percentages show how an applied compressive force is distributed between the anterior half of the vertebral body and disk, the posterior half of the vertebral body and disk, and the neural arch (average data for cadaveric specimens with severely degenerated disks tested in the simulated erect standing posture). (Right) Plain radiograph of such a specimen showing how image intensity (which reflects bone mineral density) is very low anteriorly and very high in the apophyseal joints. (Image and data adapted from Adams MA, Pollintine P, Tobias JH, et al. Intervertebral disc degeneration can predispose to anterior vertebral fractures in the thoracolumbar spine. *J Bone Miner Res* 2006;21:1409-16.)

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11

Principles of genetic epidemiology

■ JANE WORTHINGTON ■ STEVE EYRE

- The majority of rheumatic conditions have a complex etiology in which multiple genetic and environmental effects interact to cause disease.
- Many rheumatic diseases are associated with HLA class II or class I locus alleles, thus suggesting an immune-mediated component in these conditions.
- Genome-wide association studies using hundreds of thousands of single nucleotide polymorphisms genotyped in large samples of cases and controls have successfully identified large numbers of susceptibility loci for the rheumatic diseases.
- Identification of genetic factors for rheumatic disease etiopathogenesis is likely to assist in prediction of risk, early diagnosis and intervention, differential diagnosis and resolution of clinical heterogeneity, determination of variation in response to treatment, and discovery of novel drug targets.

INTRODUCTION

A genetic basis for the majority of rheumatic conditions is now established, and for a small number of these diseases the genetic contribution is clear and can be attributed to a disease-causing mutation in a single gene. Examples of such monogenic disorders include some cases of multiple epiphyseal dysplasia and periodic fever. For single-gene disorders, penetrance of the disease-causing allele may not always be complete (i.e., the presence of a mutation may not result in the full disease phenotype), although the conditions are inherited in a strict mendelian fashion in either a dominant or a recessive manner.

In contrast, the more common rheumatic diseases are not inherited as a simple mendelian trait but are the cumulative result of multiple genetic and environmental effects. The challenge of identifying risk factors for these complex diseases is significantly greater; however, in the past few years, significant advances in the characterization of variations across the genome and the development of high-throughput, accurate, and affordable technologies for single nucleotide polymorphism (SNP) genotyping have resulted in major advances in the identification of genetic loci for complex diseases. The focus of this chapter is to describe the current approaches used to identify susceptibility loci for complex diseases and, in particular, to illustrate how, since the introduction of SNP-based whole-genome association studies in 2007, knowledge of complex disease risk loci, using rheumatoid arthritis (RA) as an example, has increased exponentially. The genetics of a number of monogenic musculoskeletal disorders and the complex diseases of RA, ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and osteoarthritis (OA) are described in separate chapters.

COMPLEX RHEUMATIC DISEASES

A large number of rheumatic conditions are now considered to represent complex disease phenotypes, including RA, juvenile idiopathic arthritis, SLE, OA, osteoporosis, and AS. Twin studies have proved useful in confirming the existence of a genetic component to susceptibility and also in estimating the relative contributions of both genetic and environmental effects. Monozygotic twins are genetically identical and thus share 100% of their DNA. If a disease is caused solely by genetic factors, it would be expected

that when the condition develops in one twin, the other twin should also be affected. The proportion of monozygotic twins in which both are affected is referred to as the level of disease concordance. Crude monozygotic twin disease concordance figures reflect approximately the relative contribution of genetic factors and environmental/stochastic events. These estimates can be further refined by comparing concordance rates in monozygotic twins with those observed in dizygotic (nonidentical) twins, who have, on average, only 50% of their genes in common. Because both monozygotic and dizygotic twins usually share early environmental exposure, monozygotic and dizygotic disease concordance figures can be modeled to more accurately measure disease heritability. Monozygotic and dizygotic twin concordance figures for a number of rheumatic conditions are summarized in [Table 11.1](#).¹⁻¹⁰

Many twin studies have been based on relatively small data sets or have suffered from sampling bias and should be interpreted with caution. For RA, estimates of monozygotic twin disease concordance rates range from 12% to 34%. Analysis of the heritability of RA suggests that up to 60% of disease etiology is likely to be explained by genetic factors.¹¹

An alternative strategy for assessing increased familial risk is to compare the levels of disease risk in close blood relatives of probands (affected cases) with those seen in the open population. One measure used is familial disease recurrence risk, and for RA this has been calculated as being between 2 and 10.¹² Thus, the disease is 2 to 10 times more likely to develop in first-degree relatives of patients with RA than in individuals without an RA-affected relative. This approach has been further modified to take account of how rare or common a disease is in the population. The coefficient of familial clustering (λ_s) was defined by Risch¹³ as a measure of how much genetic or shared environment component is involved in the etiology of a disease. It is calculated by dividing the sibling recurrence risk by the population prevalence. Depending on which published figures for RA sibling risk and prevalence are used, λ_s for RA has been estimated to be between 2 and 10.¹⁴ λ_s values for a range of rheumatologic and autoimmune conditions are summarized in [Table 11.2](#).¹⁴⁻²⁰

RATIONALE FOR INVESTIGATING THE GENETIC BASIS OF RHEUMATIC DISEASES

An understanding of the risk factors for disease has the potential to have an impact on medicine and patient care at a number of points. Knowledge of genetic susceptibility factors could be used to identify individuals in whom modification of lifestyle might be advised to minimize exposure to environmental triggers of disease. Recognizing potential cases before the onset of symptoms or at the very earliest stages of the disease process may identify a window of opportunity in which therapeutic interventions might be used to prevent the development of full-blown disease. These possibilities may be futuristic, however, and more immediately achievable targets include identification of novel targets for therapy. This has already been illustrated in inflammatory bowel disease, in which identification of an association with polymorphisms in the genes involved in autophagy highlighted this pathway for the first time in the pathogenesis of this disorder.²¹ Sirolimus, which is licensed for use in human organ transplantation, is known to have autophagy-promoting as well as immunosuppressant and antifibrotic activities. In psoriasis and type 2 diabetes, recently identified genetic associations have been identified in genes encoding proteins that are already the target of successful therapeutics²²; for example, ustekinumab, a drug that targets interleukin-12 and interleukin-23 receptor, has been used to treat psoriasis.²³

RA is an example of a disease showing considerable heterogeneity in terms of clinical features and disease course, thus making it challenging for

TABLE 11.1
Twin concordance rates

Condition	Monozygotic concordance (%)	Dizygotic concordance (%)	Reference
Rheumatoid arthritis	34	4.9	Harvard and Hauge, 1965 ¹
	32	6.0	Lawrence, 1970 ²
	12.3	3.5	Aho et al., 1986 ³
	21	0	Bellamy et al., 1992 ⁴
	15.4	3.6	Silman et al., 1993 ⁵
Systemic lupus erythematosus	57	0	Block et al., 1975 ⁶
	24	3	Deapen et al., 1992 ⁷
	25	0	Grennan et al., 1997 ⁸
Ankylosing spondylitis	50	15	Jarvinen, 1995 ⁹
	75	13	Brown et al., 1997 ¹⁰

TABLE 11.2
Sibling recurrence risks

Condition	λ_s	Reference
Rheumatoid arthritis	5-10	Oilier and Worthington, 1997 ¹⁴
Systemic lupus erythematosus	20	Vyse et al., 1996 ¹⁵
Ankylosing spondylitis	46	Brown et al., 1998 ¹⁶
Behçet disease	11.4-52.5	Gul et al., 2001 ¹⁷
Juvenile idiopathic arthritis	15	Glass and Giannini, 1999 ¹⁸
Systemic sclerosis	11-158	Englert et al., 1999 ¹⁹
Paget disease	14	Ralston, 2002 ²⁰

clinicians to identify patients who should be targeted for the most aggressive therapies and those in whom the condition may resolve with little or no intervention. It seems likely that this heterogeneity is genetically determined, and thus identification of genetic markers to predict outcome would have significant clinical utility. Response to therapies is also likely to be genetically determined, and identification of markers to predict the probable response to treatment or identify those at risk for adverse events would have major advantages in improving targeting of expensive therapies. Being able to achieve any or all of the aforementioned will have a significant impact on the diagnosis and treatment of patients and will lead to a more personalized approach to disease.

APPROACHES FOR IDENTIFYING DISEASE GENES

Historically, two different scientific strategies have been used to search for genetic variants that determine susceptibility to disease: linkage and association studies. Traditional parametric linkage analysis, used with great success to identify loci determining monogenic diseases, relies on the use of multi-case extended pedigrees, of the type rarely available for complex rheumatic diseases. In contrast, nonparametric linkage analysis carried out on smaller “affected sibling pair” pedigrees has been used widely to search for complex disease genes. These studies depend on analysis of hundreds of highly informative genetic markers (usually microsatellites) in large numbers of affected sibling pair families. The markers are used to identify regions of the genome shared “identical by descent” by the affected sibling pairs more frequently than expected by chance and therefore likely to contain disease genes. Before the advent of genome-wide association studies (GWASs), linkage studies offered the only method for screening the whole genome in a hypothesis-free approach.²⁴ The success of linkage studies in identifying risk loci for complex diseases was limited because the majority were underpowered based on current understanding of typical effect sizes.

In contrast, association studies are based on comparison of polymorphic markers in cohorts of cases and controls, with a difference in allele or genotype frequency providing evidence that the polymorphism, or one in linkage disequilibrium with it, is associated with disease. The vast majority of

association studies before GWASs were candidate gene investigations based on a limited number of polymorphisms. Sequencing of the human genome and the subsequent exponential increase in the identification and characterization of millions of polymorphic markers were vital to the development of association studies that screen the whole genome. Also critical was the development of technologies for rapid and accurate genotyping of SNP markers in large numbers of samples.

In the past few years, GWASs and targeted association studies have superseded whole-genome linkage for the study of complex disease genetics, so discussion here is limited to these approaches.

Association studies

The principle of association studies is simple and based on the assumption that the marker under investigation is either causally related to disease or strongly correlated with the causal variant (i.e., in linkage disequilibrium). A difference in allele or genotype frequency between groups of cases and controls provides evidence of disease association of the variant under investigation. Before 2007, disease association studies targeted candidate genes or were the approach used to fine-map linkage peaks. The advent of technologies facilitating accurate, high-throughput genotyping of hundreds of thousands of SNPs has heralded the era of GWASs in which association studies screening the genome in a hypothesis-free manner are carried out by using 0.5 to 1 million SNPs and large numbers of cases and controls.

Provided that basic epidemiologic principles, discussed below, are followed, both candidate gene studies and GWASs are robust approaches and the key methods by which new susceptibility loci will be identified and characterized.

Selection of cases and controls

Perhaps the most common reason given for false-positive associations is population stratification. This problem arises when the population studied contains subpopulations that differ both in allele frequency and in the prevalence of the disease under study. Differences in allele frequency between ethnic groups are well documented, and most studies endeavor to take cases and controls from the same ethnic group. Methods to test and correct for population stratification have been available for some time,²⁵ and it is envisaged that panels of markers sensitive to population structure, so-called ancestry markers, will be developed and incorporated into future studies to overcome problems arising from population stratification. GWASs have a built-in opportunity to adjust for population-based differences in cases and controls, and the utility of three different approaches for these large data sets—(1) structured association tests, (2) principal components analyses, and (3) multidimensional scaling—has been demonstrated. The availability of such methods brings an additional advantage to GWASs in that it becomes possible to use large common population controls for studies involving different diseases and different populations, thereby resulting in significant cost savings.²⁶

A further consideration when sampling subjects for association studies is whether the cases are truly representative of the disease group as a whole. This issue is well illustrated by studies of HLA associations in patients with RA. Numerous studies over many years have characterized the HLA-DRB1 associations with RA and have shown quite variable effect sizes.²⁷ What now emerges is that most of the earlier studies and those showing the highest effect sizes tended to be based on hospital-derived cohorts of patients, which typically consisted of those with more severe disease. It was only by the establishment of prospective primary care-based cohorts with longitudinal follow-up, such as the U.K. Norfolk Arthritis Registry, that it was demonstrated that the HLA shared-epitope alleles much less strongly associated with inflammatory arthritis (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.4 to 2.4). The risk increases for patients satisfying the American College of Rheumatology criteria (OR, 2.3; 95% CI, 1.7 to 3.1) but is strongest for hospital-based studies (average fivefold increased risk), thus suggesting that shared-epitope alleles may be more important in influencing disease severity than susceptibility.²⁸

Power/effect sizes

The power of a study to detect a genetic effect size depends on the sample size of the study and the frequency of the alleles that predispose to disease. Most association studies use similar numbers of cases and controls, although more power is gained by increasing the ratio of controls to cases (a ratio of four times more controls than cases is considered the most efficient). It is now clear that the effect size for the majority of complex disease loci is very small, with the majority identified so far having ORs below 1.5, thus emphasizing the importance of using adequately powered studies, which for GWASs of most diseases means sample sizes of many thousands.

Selection of genetic markers

Candidate genes for association studies have tended to be selected on the basis of knowledge of pathological and biologic processes. SNPs have been the markers most commonly used, largely because they are most easily genotyped. Three major initiatives have focused on the identification and characterization of SNPs, and as a result it is now possible to select markers in a systematic and efficient manner to ensure coverage of common variation (minor allele frequency >1%) for a given locus or gene. First, sequencing of the human genome provided a template against which genetic variation could be studied and mapped; second, the availability of markers was dramatically increased by characterization of millions of polymorphic markers (www.ncbi.nih.gov/SNP); and third, patterns of linkage disequilibrium between markers (www.hapmap.org) have been defined with data generated from four populations (Yoruba, Nigeria, $n = 90$; North American whites living in Utah, $n = 90$; Han Chinese, $n = 45$; and Japanese, $n = 44$). More recently, the 1000 Genomes Initiative (www.1000genomes.org), which involves complete resequencing of the genome in samples from three populations, has revealed further detail of genetic variation between individuals and populations.

The presence and knowledge of linkage disequilibrium between markers mean that it is usually unnecessary to type every known variant at a locus of interest. Data for untyped polymorphisms can be imputed with programs such as IMPUTE.^{29,30}

Analysis and interpretation of results

Applying a significance threshold of $P = .05$ means that 1 in 20 observed associations will have occurred by chance. Performing multiple tests, such as following a GWAS, without adjustment of the threshold is certain to generate false-positive findings.³¹ Applying a Bonferroni correction is thought to be overly conservative, particularly if SNPs are in linkage disequilibrium with each other. An alternative is to perform permutation testing to empirically test the probability of having observed an association by chance.³² The issue of multiple testing is key to the interpretation of GWASs based on a comparison of many hundreds of thousands of markers. A generally accepted threshold for the current generation of GWASs (500,000 to 1 million SNPs) is $P < 5 \times 10^{-8}$.

Replication of the findings in an independent cohort provides compelling evidence that the original result was real and not a false-positive finding.

An interesting phenomenon in this context is the “winner’s curse” whereby there is an upward bias in effect sizes reported in the first published study.³³ This has been shown in a study of 55 meta-analyses, which demonstrated that subsequent studies showed weaker or no association when compared with the original studies.³⁴ Hence, follow-up studies should at least be powered to detect effects at the lower limit of the confidence interval around the OR of the first study.

SUCCESSFUL EXAMPLES OF CANDIDATE ASSOCIATION STUDIES

The first genetic associations in rheumatic diseases were identified some 30 years ago and involved alleles of genes located in the HLA region.³⁵⁻³⁷ Since then, many other associations between HLA antigens and a wide range of rheumatic diseases have been reported, a considerable number of which have been replicated. A summary of these associations is reported in Table 11.3.^{3,27,37-53} A detailed discussion of how HLA may contribute to the etiology of RA is presented elsewhere (see Chapter 89).

Protein tyrosine phosphatase N22

PTPN22 is one of a number of protein tyrosine phosphatase genes involved in regulating the immune response. A functional polymorphism of the PTPN22 gene, 1858C>T, was initially found to be associated with type 1 diabetes.⁵⁴ Subsequently, researchers performed a large-scale case-control association study of candidate genes for RA (16,000 SNPs) and found that the most significant association was with the same nonsynonymous SNP identified in the type 1 diabetes study.⁵⁵ The initial association with RA has since been replicated in all the studies that have followed.⁵⁶⁻⁶³ Association with the same SNP has been found in juvenile idiopathic arthritis,⁵⁶ SLE,^{58,64-66} autoimmune thyroid disease,⁶⁷⁻⁷¹ and a number of other autoimmune diseases.⁷² Interestingly, the 1858C>T variant is found only extremely rarely in the Asian population, and there is no evidence that PTPN22 has a role in susceptibility to RA in Asians. Despite the fact that the disease-associated variant in PTPN22 resulted in an amino acid change, elucidation of the functional impact of this variant has proved surprisingly difficult and has served to demonstrate the importance of considering cell specificity for functional biology experiments.^{73,74}

TABLE 11.3
HLA classic associations

Condition	HLA association	Reference
Rheumatoid arthritis	DR4, DR1, DR10, DR14 (Native American)	Ollier and Thomson, 1992 ²⁷
Systemic lupus erythematosus	DR3/DQB1*0201; DR2/DQB1*0201	Schur, 1995 ³⁸
Ankylosing spondylitis	B27, B60, DR1	Brewerton et al., 1973 ³⁷ Wordsworth, 1998 ³⁹
Juvenile arthritis	A2, DR8, DR11, DR13, DPB1*0201	Donn and Ollier, 1996 ⁴⁰
Giant cell arteritis	DR4	Dababneh et al., 1998 ⁴¹
Polymyalgia rheumatica	DR4, DR13	Dababneh et al., 1998 ⁴¹
Reactive arthritis	B27	Aho et al., 1986 ³
Scleroderma	DR11, DR3, DR2 (Japanese)	Tan and Arnett, 2000 ⁴²
Polymyositis/dermatomyositis	DR3, DQB1*0201, DR13 (black)	Shamim et al., 2000 ⁴³
Primary Sjögren syndrome	DR3	Kay et al., 1991 ⁴⁴
Psoriatic arthritis	B27, B38, B17, B13, DR7, CW6	Silman, 2001 ⁴⁵
Paget disease	DR2	Singer et al., 1985 ⁴⁶
Lyme disease	DR7, DR4	Wang and Hilton., 2001 ⁴⁷ Steere et al., 2001 ⁴⁸
Behçet disease	B51	Ohno et al., 1982 ⁴⁹
Erythema nodosum	DR1	Amoli et al., 2001 ⁵⁰
Kawasaki disease	B51	Krensky et al., 1983 ⁵¹
Takayasu’s arteritis	B52 (Japanese)	Kimura et al., 1996 ⁵²
ANCA-associated granulomatous vasculitis	B8	Katz et al., 1979 ⁵³

ANCA, antineutrophil cytoplasmic antibody.

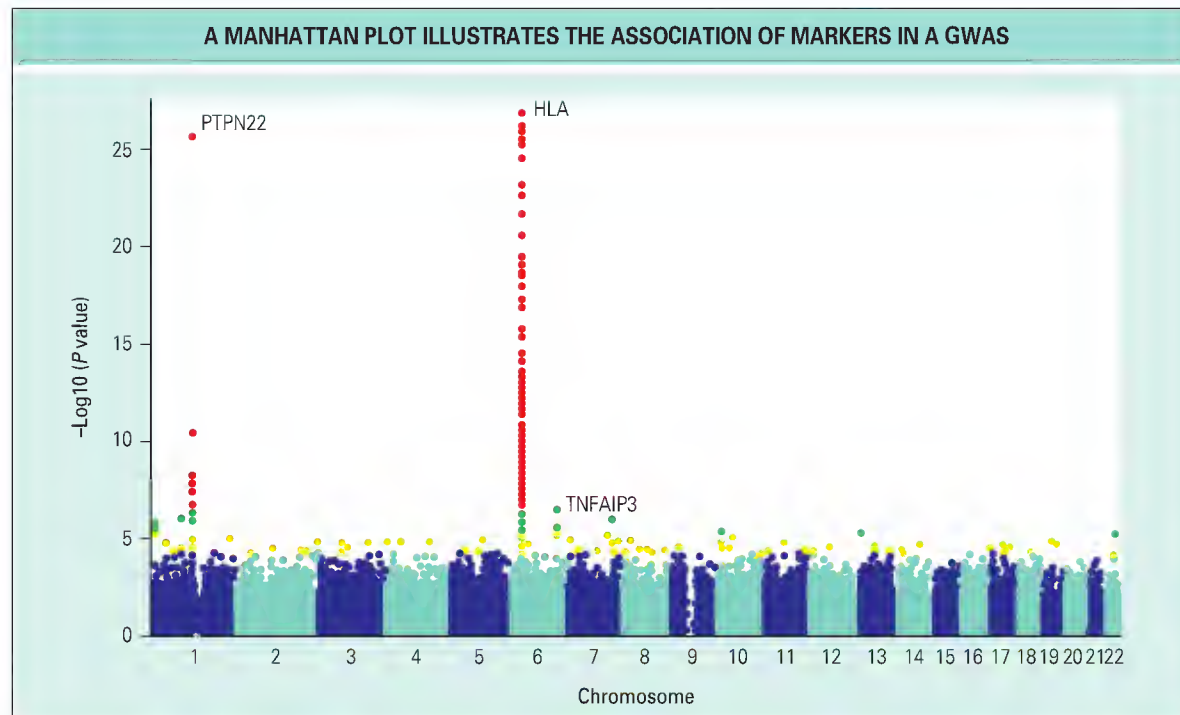


Fig. 11.1 Each dot represents the P value for comparison of genotype frequencies for each marker when comparing cases ($n = 2000$) and controls ($n = 3000$). Shades of blue are used to represent alternate chromosomes. Levels of significance of association are indicated. Red spots: $P < 5 \times 10^{-7}$; green spots: $P < 10^{-5}$ to 5×10^{-7} ; yellow spots: $P < 10^{-4}$.⁵⁹ GWAS, genome-wide association study.

WHOLE-GENOME ASSOCIATION STUDIES OF RHEUMATOLOGIC CONDITIONS

The proof-of-principle investigation that demonstrated the practicality and utility of GWASs came in 2007 from the Wellcome Trust Case Control Consortium (WTCCC), which undertook a genome-wide analysis of seven common diseases, including RA. The Affymetrix Gene Chip 500k Mapping Array Set was used to genotype 500,000 SNPs in 2000 cases with each of seven diseases and in a set of 3000 common controls, all samples from white U.K. residents.⁷⁵ For RA, markers in the *HLA-DRB1* and *PTPN22* gene regions were highly significantly associated with disease ($P < 5 \times 10^{-7}$). Strong but not incontrovertible evidence of association was detected to more than 50 additional loci ($P < 10^{-4}$ to 5×10^{-7}) (Fig. 11.1). Analysis of markers from these loci in large independent sample sets has since confirmed RA loci at 6q23,⁷⁶ 10p15, 12q13, and 22q13,⁷⁷ thus implicating the genes *TNFAIP3*, *PRKCQ*, *KIF5A*, and *IL2RB*. Further GWASs in different populations and meta-analyses of GWASs providing ever greater power have led to the identification of more than 60 RA loci in all populations (Fig. 11.2).⁷⁸⁻⁸⁰

Successful GWASs have now been carried out for all the major rheumatologic conditions, including SLE,^{81,82} AS,⁸³ OA,⁸⁴ psoriatic arthritis,⁸⁵ juvenile idiopathic arthritis,⁸⁶ and systemic sclerosis.⁸⁷ In all cases the studies have both confirmed some of the established associations and identified new susceptibility loci.

GWASs can now be carried out as a matter of routine. The challenge remains to distinguish all true-positive associations from among a considerable number of highly significant results arising as false positives. Increasing sample sizes and meta-analyses offer one solution, but bioinformatics has great potential to assist in this challenge. A computational method (GRAIL) that applies statistical text mining to PubMed abstracts has been used with success across a number of diseases. It was used to prioritize association signals with a functional connection to established RA loci from signals with relatively weak evidence of association in the GWAS data ($P < .001$) for investigation,⁸⁸ and as a result, further RA loci were identified.

Genes for a number of RA-confirmed loci are known to function in T- and B-cell signaling pathways, and it is likely that additional genes involving the same or related pathways may harbor risk alleles. The considerable overlap between loci identified for RA and those identified for other autoimmune diseases, including type 1 diabetes and celiac disease (Fig. 11.3), is quite amazing and implicates common dysregulated immune pathways. It appears that the vast majority of susceptibility loci identified for arthritic diseases are not unique to one disease.⁸⁹

TIMELINE OF THE DISCOVERY OF RA SUSCEPTIBILITY LOCI, ILLUSTRATING THE IMPACT OF GWASs

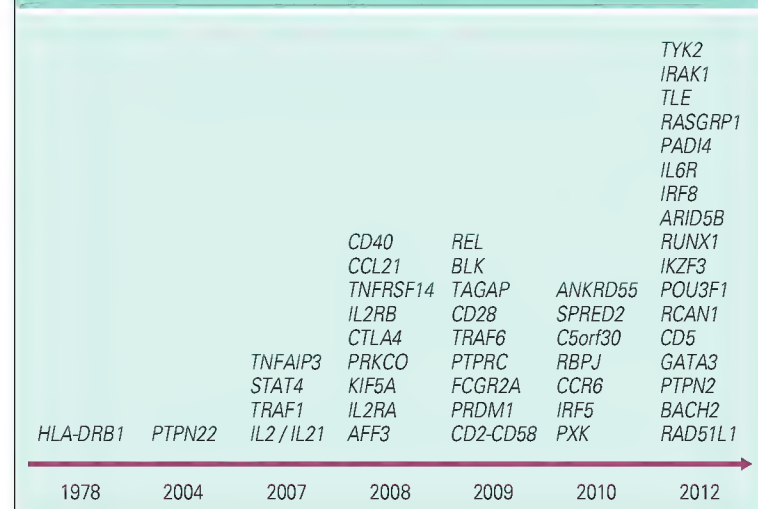


Fig. 11.2 GWASs, genome-wide association studies; RA, rheumatoid arthritis.

Although rapid progress has been achieved in the identification of disease susceptibility markers implicating genetic loci, for the most part our understanding of these loci and how associated alleles cause disease is very limited. The next key step will involve in-depth characterization of the genetic architecture at each locus. Subsequently, understanding how associated variants affect function will require an array of approaches but is likely to benefit considerably from the ENCODE initiative,⁹⁰ a program aimed at annotating all protein coding sequences in the genome.

NEW HORIZONS

Progress in complex disease genetics has been driven largely by staggering advances in technology and computer-based informatics. Although it took a major international consortium with teams of scientists and many DNA-sequencing machines 10 years to complete the sequencing of the human

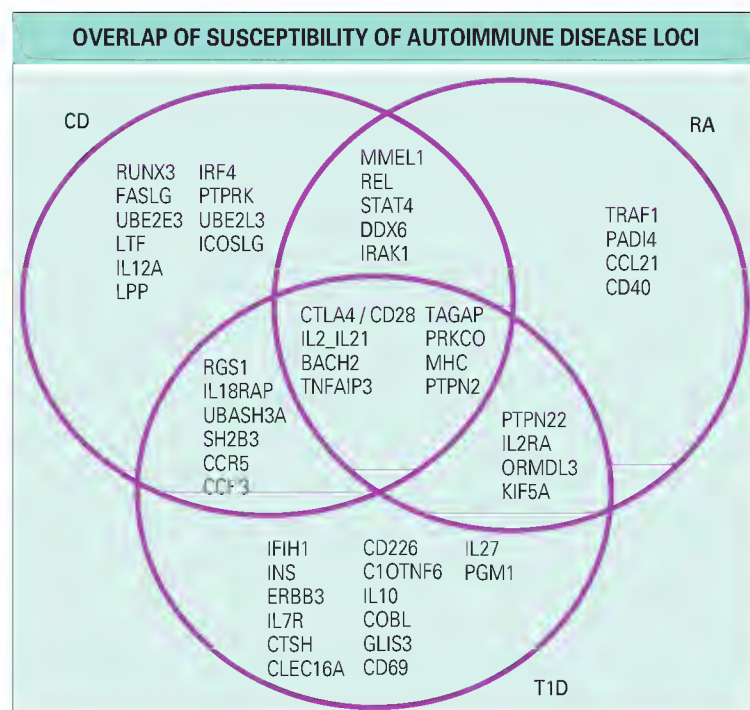


Fig. 11.3 Illustrated here are some of the loci identified for type 1 diabetes (T1D), celiac disease (CD), and rheumatoid arthritis (RA). The specific markers associated with each disease may differ.

genome, we are now entering an era when resequencing the genome of an individual is possible in hours at affordable prices. The impact that such information could have on medicine in general and rheumatology in particular is hard to imagine.

Furthermore, the postgenome era has led to a greater realization that disease etiology and processes should not just be viewed one-dimensionally from the level of gene sequences but, rather, how these sequences are transcribed differently by differentiated cells and how such transcripts are translated into proteins. The great expansion in complexity that increases from approximately 20,000 genes in the human genome to an estimated 300,000 different proteins, largely through alternative gene splicing and posttranslational protein modification, including epigenetic modifications, is becoming better appreciated. The way that such proteins interact and the metabolic processes and products that result are now providing important insight into unraveling disease processes and pathways. Scientists are now increasingly realizing that a holistic approach has to be taken to fully understand disease etiopathogenesis. The development of genomic technologies such as transcriptomics, proteomics, and metabolomics is being powerfully combined with genomics into an approach called "systems biology." This is increasingly driving translational medicine and is anticipated to have a major impact on rheumatology.

Full translation of the information that resides in our genome and how it relates to complex diseases will come only through understanding how it interacts with environmental factors. These factors could be gene-nutrient, gene-microbiome, gene-lifestyle (e.g., alcohol/smoking), or gene-drug (pharmacogenetics) interactions. Such studies are difficult, and many can be appropriately addressed only through large longitudinal population-based cohorts in which premorbid environmental exposure data and biological samples can be collected.

There is increasing realization that response to drug treatment, in terms of both efficacy and adverse reactions, is largely encoded within our genes, and this is poised to have great impact in the field of rheumatology. Pharmacogenetic studies are already beginning to explain why some patients are resistant to some second-line drugs or have reactions to drugs such as azathioprine. The next 5 years in the genetic study of rheumatic disease will undoubtedly be very interesting.

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12

Principles and techniques
in molecular biology

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- Restriction enzymes, DNA and RNA polymerases, DNA ligases, reverse transcriptases, phosphatases, kinases, and thermostable DNA polymerases are enzymes used to clone, modify, and amplify DNA in the laboratory.
- Incorporation of exogenous DNA fragments into vectors that can replicate in bacteria, yeast, or insect cells permits large-scale production of the cloned gene or encoded protein.
- Massively parallel high-throughput sequencing, which allows for the simultaneous analysis of nucleic acid sequence at billions of positions, is an extremely powerful tool that facilitates genomewide or transcriptome-wide investigations of both mendelian and complex genetic traits.
- Northern blot and real-time polymerase chain reaction are methods that quantitatively measure the expression of specific genes, whereas microarray expression profiling and RNA sequencing simultaneously evaluate the expression of thousands of genes.
- Electrophoretic mobility shift assays and chromatin immunoprecipitation assays detect DNA interactions with proteins, such as transcription factors and modified histones that are regulators of gene expression.
- Transfection methods are biochemical, physical, or viral techniques for transferring exogenous DNA into cultured cells for expression. In a variant of the method, the expression vector directs transcription of short inhibitory RNAs that block the endogenous gene's expression.
- Transgenic mice are genetically modified animals into which an exogenous DNA construct has been transferred, whereas in knockout mice the endogenous gene has been disrupted, which thereby prevents its expression.
- Protein-protein interactions can be analyzed by coimmunoprecipitation and yeast two-hybrid screening. Fluorescence resonance energy transfer can be used to evaluate protein-protein interactions in living cells.

INTRODUCTION

The past decade has witnessed rapid advancement in genomic medicine, driven initially by the Human Genome Project and subsequently by the 1000 Genomes Project and other large-scale, population-based genomic sequencing efforts. Together, these projects continue to reveal the scope and complexity of genetic and genomic variation in human beings, and they continue to afford scientists and physicians extraordinary opportunities to advance our understanding of physiology and pathology.¹ Until just a few years ago these possibilities were more science fiction than science. However, a number of critical technologic breakthroughs have truly revolutionized biomedical research. The opportunities for improving our understanding of rheumatic and autoimmune diseases are now astounding. Moreover, it is likely that recent advances will accelerate the pace at which disease susceptibility genes are identified and their functions analyzed. It is likely that this information will also improve treatment and propel the discovery of new therapeutic modalities.

It is therefore intended in this chapter to review the basic tools that rheumatologists now see being employed when they read the literature.

Given the space constraints, the chapter does not review basic concepts in DNA replication, transcriptional control, and signal transduction. There are several excellent textbooks that cover these topics.^{2,3} Rather, the focus is on the methods used to study these processes, but the intent is not for this to be a laboratory manual or “how to” guide; again there are ample sources that provide detailed protocols of this sort.^{4,5} Instead, the goal is to present the principles underlying important techniques with which the average rheumatologist should be familiar to comprehend studies that are pertinent to clinical work. Skimming through the rheumatologic literature one sees references to a variety of techniques such as next-generation sequencing, RNA sequencing, chromatin immunoprecipitation sequencing, electrophoretic mobility shift assays, microarrays and gene expression profiling, and tissue-specific knockouts using the cre/lox system. This chapter will therefore discuss some of the major techniques and their modifications to facilitate comprehension of the literature.

THE HUMAN GENOME SEQUENCE AND
BIOMEDICAL RESEARCH

The human genome consists of about 3 billion adenine (A), guanine (G), cytosine (C), and thymine (T) bases (Fig. 12.1) arranged in 23 pairs of chromosomes. A great surprise was that the immense amount of potential genetic information encodes a relatively small number of genes, fewer than 30,000,^{6,7} which makes humans about twice as complex as model organisms such as yeast and *Drosophila* but less complex than rice. It is important to emphasize, however, that alternative splicing and protein modifications greatly increase the complexity of the polypeptides encoded by the human genome.

The onslaught of information brought about by the Human Genome Project, the 1000 Genomes Project, and other similar large-scale sequencing projects have provided both new opportunities and new challenges to investigators. DNA and protein sequences, sequence variation, expression data, and structural data are among the information being deposited into a growing number of public and private databases. Savvy investigators can mine these databases to obtain useful information with a variety of search and computational tools. Many publicly accessible databases and tools are available at the National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov/). Tools such as BLAST (Basic Local Alignment Search Tool), which facilitates sequence comparisons, can be used, for example, to find additional members of gene families that may have functions similar to one another. Comparisons of homologous genes of several species can identify regions that are conserved among species. These elements may be expressed parts of genes or unexpressed regions that may be conserved because they contain important regulatory elements. Managing and analyzing the data derived from genomewide approaches to expression profiling and disease-gene linkage and association studies can also require sophisticated computational and organizational approaches. The computational power, statistical sophistication, and computer programming skills required for development and implementation of tools applicable to biologic problems have resulted in rapid explosion of the field of bioinformatics, surely an area that will continue to grow for the foreseeable future.^{8,9}

The molecular biology revolution, of course, began long before the Human Genome Project. Major steps in the revolution were the development of techniques that permitted the *in-vitro* manipulation of DNA and advances in large-scale DNA sequencing. These advances permitted the identification, sequencing, isolation, and expression of genes, which allowed their functions to be discerned.

BASIC MANIPULATION OF DNA: CLONING VECTORS AND CUTTING AND PASTING DNA USING ENZYMES

Vectors are engineered DNA molecules used to replicate, isolate, and express foreign DNA. There are several general types of commonly used vectors, which were derived from bacteria and bacteriophage.

Plasmids are extrachromosomal, double-stranded circular DNA molecules. Often they are relatively small (3 to 5 kb), and they have three important features: a drug selection marker, convenient cloning sites, and a replicator that permits autonomous replication in cells (Fig. 12.2). Some plasmids also have mammalian promoters that permit expression of the protein in mammalian cells, whereas others are designed for expression in bacteria, yeast, or insect cells, the last being a very efficient means of generating large quantities of protein for crystallography studies. Sometimes, plasmids are constructed to permit the production of fusion proteins.

A commonly used vector permits cloning of a given gene in frame with glutathione *S*-transferase (GST). Glutathione-coupled agarose beads bind GST with high affinity and allow one to do “pull-down” experiments (see later). Another commonly used technique is to fuse the protein of interest to green fluorescent protein (GFP), a protein made by jellyfish, which can be easily visualized within cells (Fig. 12.3).¹⁰ Remarkably, most fusions to

GFP retain the localization properties of the original protein molecule, provided that expression levels are not extremely high. As discussed later, this permits one to visualize trafficking of molecules in cells by live cell imaging. This is aided by the fact that fusion fluorescent proteins can now be engineered in a wide variety of colors from blue to far red, which permits simultaneous detection of multiple proteins and studies of protein-protein interaction by fluorescence resonance energy transfer.¹¹

The bacteriophage λ has been a heavily used tool in molecular biology for many years. Its genome is about 50 kb, but the central portion of the viral genome is not essential for lytic growth and can be replaced by 10- to 20-kb inserts; for this reason, it is a commonly used vector to create libraries of genes. Cosmid vectors are hybrids between λ and plasmid vectors that can accommodate larger inserts of foreign DNA (35 to 50 kb). P1 vectors are derived from bacteriophage P1 and are large, circular DNA molecules that can contain 70 to 100 kb of eukaryotic DNA. P1-derived artificial chromosomes can accommodate even larger DNA inserts (up to 150 kb), whereas bacterial artificial chromosomes have a still larger insert capacity (up to 200 kb) and have become the preferred vector for sequencing large DNA fragments and are used for multiple purposes, including generation of transgenic mice. Although yeast artificial chromosomes can accommodate even larger DNA inserts (about 1 Mb), these vectors are used less frequently because of problems with instability and chimerism. Finally, vectors derived from the M13 filamentous bacteriophage can accommodate small inserts

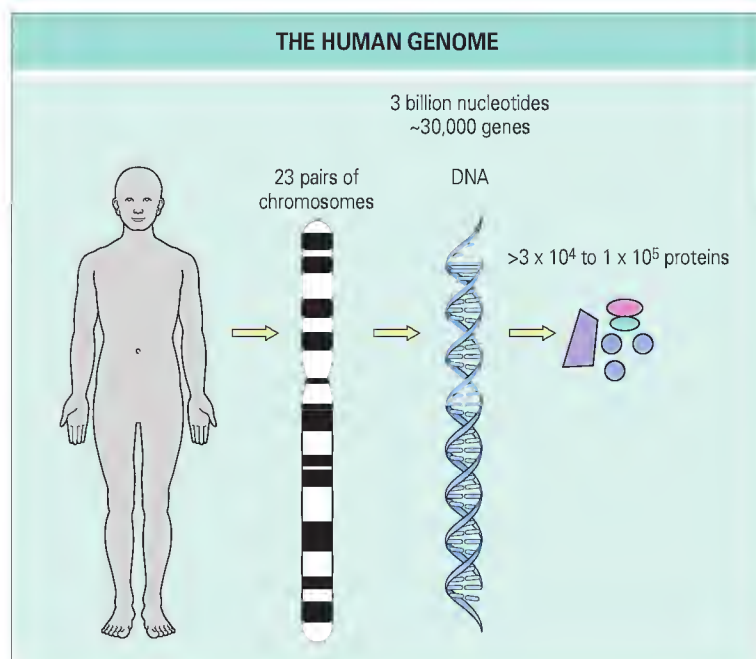


Fig. 12.1 Although the human genome is less complex than initially thought in terms of the actual number of human genes, regulatory phenomena such as alternative splicing may considerably increase the diversity of proteins produced.

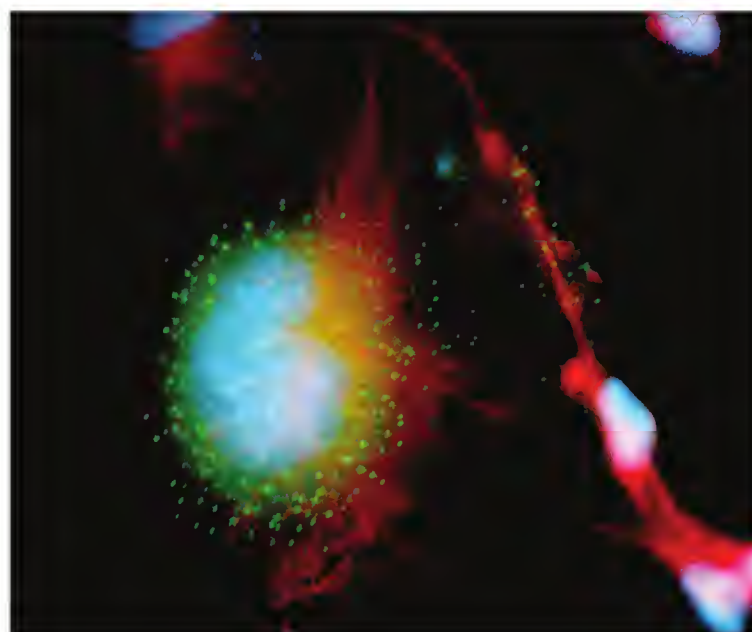


Fig. 12.3 The ability to visualize the trafficking of cell proteins by tagging them with green fluorescent protein (GFP) has revolutionized cell biology and cell signaling. In this case, the *Cybr* gene is fused to GFP (green). Actin is visualized by binding of rhodamine-labeled phalloidin (red), and nuclei are stained with 4',6-diamidino-2-phenylindole (blue). (Courtesy Dr. Massimo Gadina, National Institute of Arthritis, Musculoskeletal and Skin Disease, National Institutes of Health.)

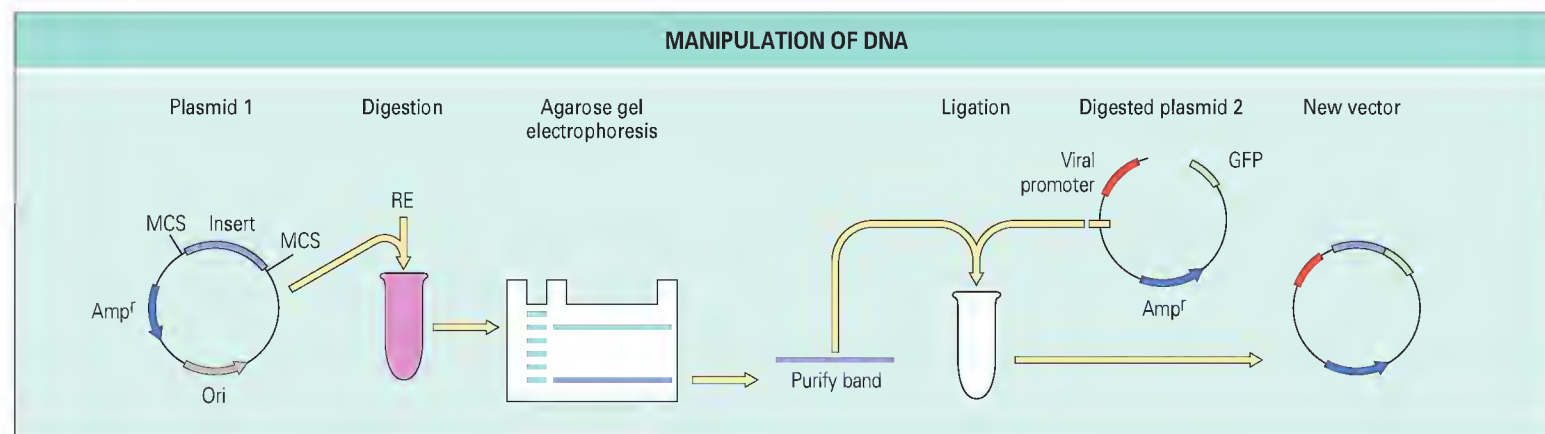


Fig. 12.2 Abundant commercially available enzymes (ligases, polymerases, and restriction enzymes) and vectors make the *in-vitro* manipulation of nucleic acids feasible. Amp^r, ampicillin resistance gene; GFP, green fluorescent protein; MCS, multiple cloning site; Ori, origin of replication; RE, restriction enzyme.

(up to 1 kb) and can be used to produce single-stranded or double-stranded DNA.

Libraries containing many different inserts representing different genes can be made using most of the aforementioned vectors. Libraries are made using genomic or complementary DNA (cDNA) and in some cases can permit expression of the gene encompassed by the insert.

Many different enzymes are commercially available that permit replication and joining of DNA; such enzymes are termed *DNA polymerases* and *ligases*. Modifying enzymes such as phosphatases and kinases are also important in DNA ligation reactions. Exonucleases and endonucleases cut DNA, whereas restriction enzymes are bacterially derived enzymes that cut DNA at specific sites. These are among the most important tools in molecular biology. Hundreds of restriction enzymes are commercially available that allow one to cut DNA in a predictable manner.

With the use of the enzymes just listed, pieces of DNA can be copied and spliced into vectors, which allows large-scale production of the gene or the encoded protein. An example of how these different enzymes can be used to move a piece of DNA from one vector to another is provided in Figure 12.2. RNA also can be synthesized from DNA by DNA-dependent RNA polymerase, and the RNA, in turn, can be translated *in vitro* into protein. Conversely, reverse transcriptase, derived from retroviruses, synthesizes DNA from RNA. This enzyme is used to make cDNA and to make libraries from messenger RNA (mRNA) and can be the starting point in the polymerase chain reaction.

POLYMERASE CHAIN REACTION

The polymerase chain reaction (PCR) is a rapid procedure for *in-vitro* amplification of DNA; the development of this procedure was another landmark in molecular biology. There are a large number of applications of PCR, including the following:

- Cloning of genomic DNA or cDNA
- Mutagenesis or modification of DNA
- Assays for the presence of pathogens
- Detection of mutations
- Analysis of allelic sequence variations
- Genetic fingerprinting of forensic samples
- Nucleotide sequencing

A schematic of PCR is shown in Figure 12.4. The reaction includes the following components: a segment of double-stranded DNA to be amplified (template); two single-stranded oligonucleotide primers, each complementary to one of the two template strands; and deoxyribonucleoside triphosphates. Another critical component is a heat-stable DNA polymerase such as *Taq* polymerase. Its heat stability is an essential feature because the enzyme must withstand repeated cycles of heating and cooling to denature and replicate the target sequence many times. PCR takes place in a device termed a *thermocycler*, which can rapidly change the reaction temperature.

First, the double-stranded DNA template is heated to generate single-stranded DNA. The primers, added in vast excess compared with the template DNA, anneal or hybridize to opposite strands of single-stranded DNA. The DNA polymerase then synthesizes new strands of DNA complementary to the template. After the first round of synthesis the reaction mix is again heated, with subsequent denaturation of the double-stranded DNA, annealing of primers, and synthesis of DNA. These cycles permit a millionfold amplification of DNA. By designing particular primers, one can mutagenize DNA or add cloning sites.

An important application of PCR is to detect RNA transcripts or to amplify their sequences to permit cloning and/or sequencing. This requires first converting RNA templates to cDNA using reverse transcriptase (RT-PCR).

DNA SEQUENCING

Manual techniques to sequence DNA were devised in the 1970s; however, sequencing the human genome was made possible by the development of automated sequencing technology. This technology continues to play an important role in the rheumatology research laboratory and is beginning to be applied as a diagnostic tool. In the research setting, DNA sequencing is being used to refine the human genome sequence and to provide information regarding normal and disease-associated variation in the human genome. Sequencing cDNAs constructed by reverse transcription of mRNA can provide information regarding the structure of gene products. The DNA sequence is also obtained to confirm the structure of cloned DNA and

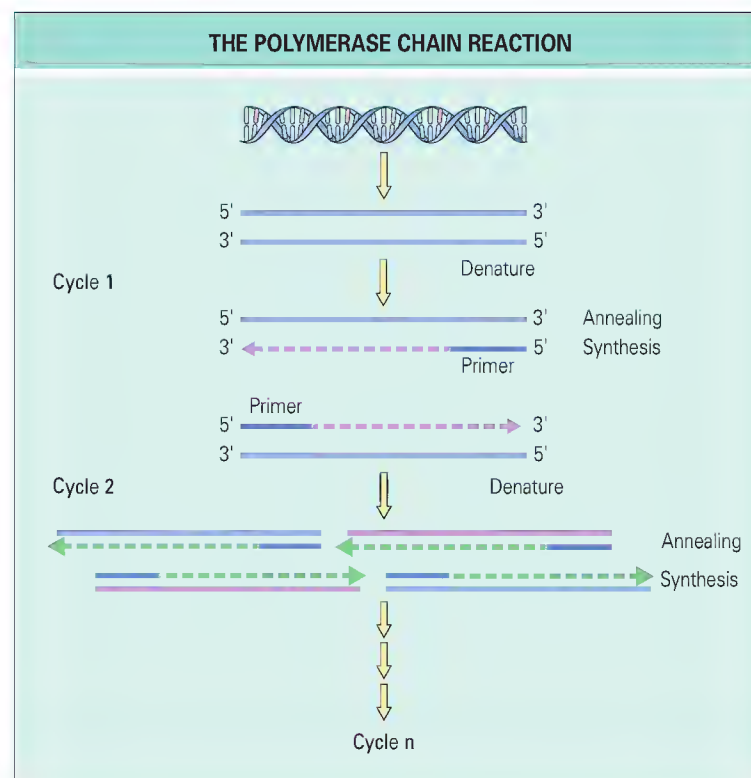


Fig. 12.4 The use of thermostable DNA polymerases and automated thermocyclers permits vast amplification of DNA and RNA templates through the polymerase chain reaction (PCR) method. Double-stranded DNA (template, light blue) is denatured by heat and, when cooled, primers (dark blue) anneal, which allows synthesis of new DNA (broken line, lavender). These cycles of denaturing, annealing, and synthesis are repeated with continued amplification of DNA (green). One can start with double-stranded DNA or with messenger RNA and use reverse transcriptase to generate the first complementary DNA strand, which is further amplified as earlier. PCR has many applications, ranging from diagnostics to mutagenesis, and has become an indispensable laboratory tool.

manipulated DNA constructs used for expression, gene transfer, or gene-targeting experiments.

In the clinical setting, several rheumatic diseases are now known to be genetic disorders for which mutations have been identified. These include several of the periodic fever syndromes, as well as some musculoskeletal disorders such as Marfan syndrome and familial osteochondral dysplasias causing early-onset osteoarthritis. For such disorders, sequencing can be used as a diagnostic tool, for example, to confirm the diagnosis of familial Mediterranean fever, which might be confused with a number of different inflammatory disorders. A definitive diagnosis permits the clinician to apply the most effective therapy as a treatment instead of using response to the therapy as a diagnostic tool.

Sequencing by the Sanger method¹² requires isolated DNA fragments specifically amplified by cloning or PCR. Complementary strands are synthesized by complementary base pairing on denatured DNA templates using enzymes (DNA polymerases) that normally perform this job in replicating cells. There are several variations on the strategy to obtain the sequence of the DNA fragment automatically. In the most common variant, four different fluorescent dye-labeled "terminator" analogues of the four deoxyribonucleotides, which incorporate into the growing strand but then terminate the reaction, are included in the replication mix (Fig. 12.5). The dye-labeled fragments are then separated by size through gel or capillary electrophoresis. The dye associated with each fragment identifies the last nucleotide analogue incorporated. The sequence can then be automatically read by detecting the succession of dyes detected as the fragments move through the separation medium. The initial sequencing of the human and mouse genomes was accomplished using these automated sequencing instruments.

A landmark event in the evolution of nucleic acid sequencing was the emergence of massively parallel high-throughput sequencing methods, referred to in aggregate as next-generation sequencing (NGS). NGS approaches simultaneously generate sequence information at tens to hundreds of billions of base pair positions. Because of the substantial time and cost savings

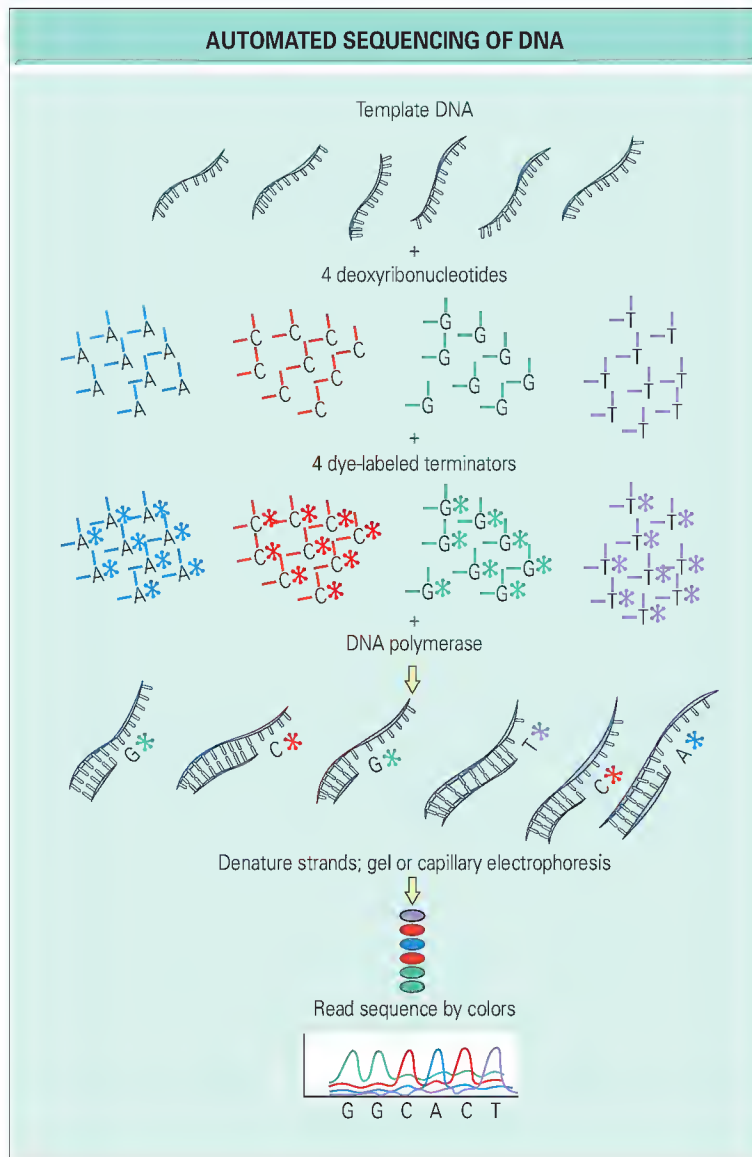


Fig. 12.5 Sequencing of DNA is performed by extending oligonucleotide-primed DNA templates with a thermostable DNA polymerase in the presence of dye-tagged dideoxy terminators that block further extension of the newly synthesized DNA strand and label the strand with one of four different fluorescent dyes identifying the last base incorporated. Automated methods for size fractionating the fragments, detecting the fluors, and reading the DNA sequence have made possible the large-scale sequencing required for sequencing the human genome.

of NGS, compared with traditional sequencing methods, NGS has ushered in an era of genome-level sequencing projects that were previously unimaginable. Although there exists an ever-growing number of NGS platforms and techniques,¹³ they each share a central schema which includes preparation of a library of DNA templates, sequencing and imaging of the template library, and finally analysis of the data. A general example of this process is depicted in Figure 12.6.

Creation of a library of DNA templates is the starting point for NGS, and a range of strategies may be employed in library creation. Whole-genome sequencing uses DNA libraries created from whole genomic DNA, in contrast to target-enrichment strategies, which extract from the whole genomic DNA only those regions of interest. Target enrichment may be accomplished by a variety of methods, each of which effectively captures and separates the DNA segments of interest for library preparation. Exome sequencing, the most widely adopted target-enrichment strategy, seeks to capture and sequence the coding regions of the genome. In general, the DNA template library is generated by first breaking the genomic DNA into homogeneously sized fragments that are then ligated to adapter molecules on both ends. These adapter molecules facilitate the immobilization of DNA templates onto glass slides or beads, which produces a spatial distribution of DNA templates that allows for each of them to be imaged independently. In some

cases, the immobilized DNA templates are amplified with universal primer sequences contained within the adapters, which transforms each DNA template into a cluster of identical DNA molecules. In other cases, the signal intensity generated by a single DNA template molecule is adequate for detection, and no DNA template amplification is required.

Upon generation of a library of DNA templates, most NGS approaches use dye-labeled nucleotides that are specifically incorporated during cycle sequencing and are subsequently imaged. After the imaging step of each cycle, the labeled nucleotides are modified to remove the dye molecules and to allow progression of the next cycle of incorporation and imaging. Although the chemistry and experimental design vary among platforms, every NGS platform requires the sequential imaging of fluorescent signals at fixed locations to facilitate and assemble sequence reads from the DNA templates or clusters.

The raw data generated by NGS consist of a very large number of sequence reads, the lengths and configuration of which are dictated by the platform and experimental design used for the sequencing. These sequence reads must be aligned to a known reference sequence to allow for identification of variant alleles. In some cases it may be beneficial to first assemble the sequence reads with one another in the absence of the reference sequence, referred to as *de novo* assembly. In the case of structural variants, gene families with a high degree of homology, or regions rich in repetitive elements, sequence reads may align with multiple genomic locations in the reference sequence and as a result may be excluded from subsequent analysis. With *de novo* assembly, one attempts to harness the power of the overlapping sequence reads to place these otherwise multiply-mapping reads into their correct genomic position. Once the sequences have been assembled and aligned, one may generate a list of positions at which the experimental sample differs from the reference, and rapidly evolving bioinformatic tools can annotate sequence variants based upon characteristics such as the type of variant, the depth of coverage or quality scores of a variant, the degree of conservation of that reference position across other organisms, and the predicted effect of the variant on its protein product.

Even when sequencing is performed by the most experienced sequencing centers and bioinformaticians, errors are inescapably introduced at multiple steps of the NGS workflow, leading to an errant base call rate as high as 1%.¹⁴ Potential sources of error are widespread and may include the limited fidelity of polymerase enzymes during the whole-genome amplification or cluster amplification processes, the incorporation of degraded dye-labeled nucleotides or the misincorporation of dye-labeled nucleotides during cycle sequencing, the presence of optical interference that precludes proper identification of bases, and the false-positive and false-negative variant identification that may result from erroneously mapped sequence reads. In response to this problem, there is a rapid emergence of both experimental and bioinformatic approaches that promise to better identify erroneously called variants. At this point, validation of NGS findings by Sanger sequencing remains the gold standard.

GENE TRANSCRIPTION

Insights into the physiologic and pathologic functions of a given gene may be gained by analyzing the expression of its mRNA in tissue and cells and delineating when, where, and how the gene is regulated. Northern blotting and quantitative real-time PCR are useful to measure the level of gene expression of one or a few genes, and *in-situ* hybridization can be used to show the gene expression in tissue.

RNA is often isolated using acid guanidinium-phenol-chloroform-based methods and in some cases is further purified by oligo-dT columns with immobilized short sequences of deoxythymine nucleotides, which bind the poly A tail of mRNA. In Northern blotting, RNA is separated by size in an agarose gel, transferred to a membrane, and detected by a labeled probe using RNA-DNA hybridization. The amount of mRNA corresponds to the binding of the radioactive probe, which can be visualized by autoradiography.

In real-time PCR, a quantitative method for measuring mRNA, mRNA is transcribed into cDNA by reverse transcriptase (Fig. 12.7). A probe with a fluorescent dye at its 5' end and a quencher dye at the 3' end is added to the reaction tube. During the PCR reaction, the reporter dye is separated from the quencher dye; DNA polymerase has 5' nuclease activity, which degrades the hybridized probe as a new DNA strand is synthesized in its place. When the reporter dye is separated from the associated quencher dye, its fluorescence is detected and accumulates with each successive round of PCR. Generation of the fluorescence is quantitatively dependent on the number of transcript copies in the cDNA sample. A reference probe for a housekeeping gene is also included, which allows this to be a quantitative assay. Because of the use of PCR, this technique is very sensitive, and

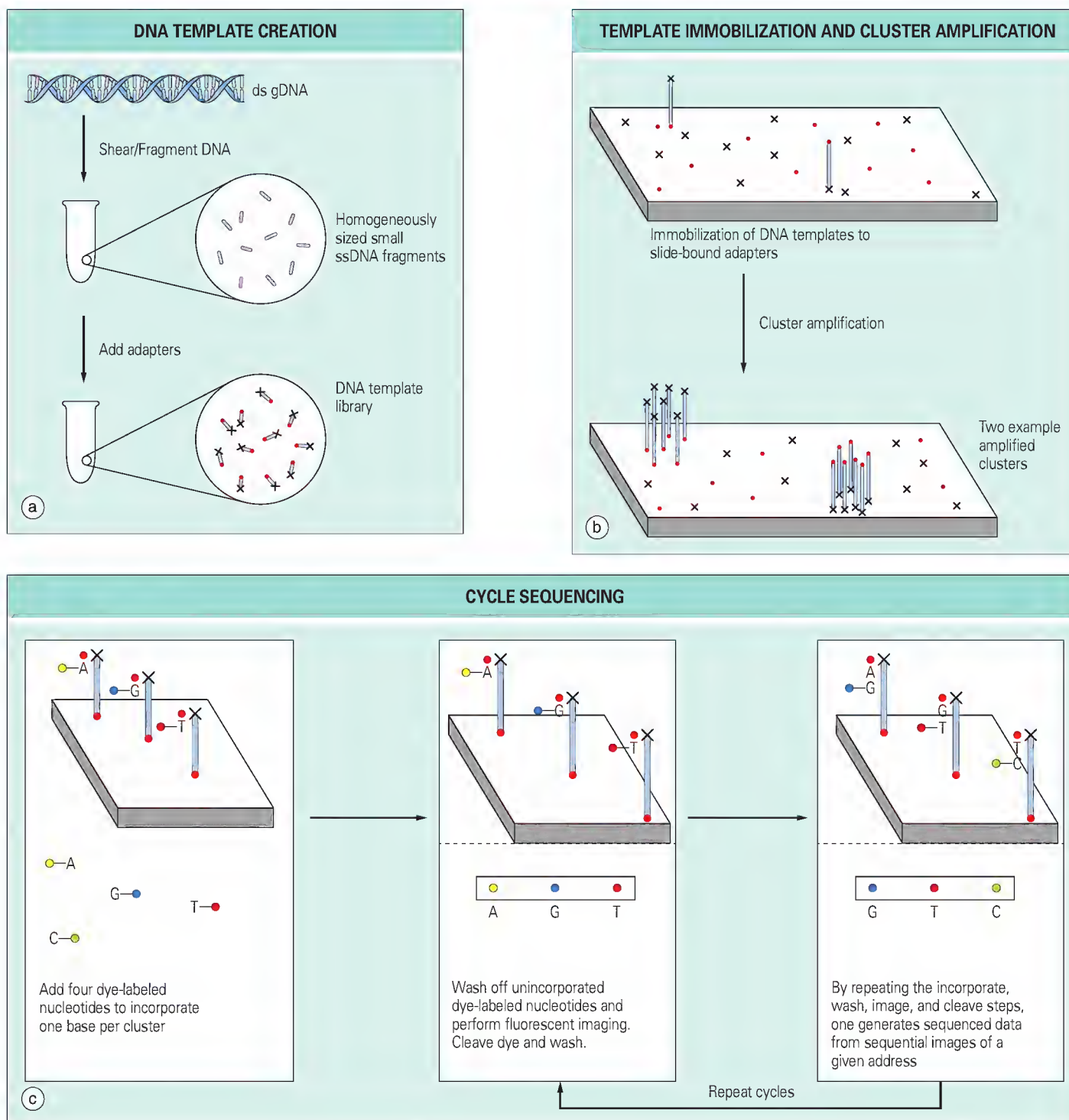


Fig. 12.6 Next-generation sequencing permits simultaneous generation of sequence information at tens to hundreds of billions of base pair positions. (a) A library of DNA templates is created by fragmenting double-stranded genomic DNA (ds gDNA) into small, single-stranded pieces (ssDNA) to which adapter molecules are attached. (b) The DNA templates are immobilized to slide-bound adapter molecules, and through the use of oligonucleotides that recognize primer sites within the adapter molecules, cluster amplification transforms each immobilized DNA template molecule into a cluster of identical DNA templates. (c) Cycle sequencing begins with single-base-pair incorporation of dye-labeled nucleotides onto each DNA template molecule. The unbound dye-labeled nucleotides are thoroughly washed and removed, after which fluorescent images are captured for each cluster of DNA templates. The dyes are then cleaved from the incorporated nucleotides, and the subsequent cycle of sequencing begins again with the incorporation dye-labeled nucleotides at the next position of each DNA template.

methods have been developed to quantitate gene expression from single cells with a commercial platform using microfluidics, which allows profiling of a set of genes from single cells. These studies can highlight the heterogeneity in gene expression among cells in an apparently identical population that may have impact on their function or developmental potential.¹⁵ Ribonuclease (RNase) protection is another means of measuring mRNA and has the advantage that multiple genes can be analyzed simultaneously. In this method, labeled antisense riboprobes are hybridized to RNA in solution and then digested with RNase, which digests single-stranded but not double-stranded RNA. The amount of riboprobe protected by the mRNA is therefore

a measure of the gene expression. Another method to quantify multiple different mRNA molecules has recently been developed and is commercially available (NanoString Technologies Inc., Seattle). This method uses a two-probe barcoded detection system¹⁶ that can make direct measurements of the abundance of up to 800 RNA species in RNA from as few as 10,000 cells without enzymatic reactions or bias.

In-situ hybridization identifies which type of cell in a tissue expresses a particular gene. In this method, one hybridizes a specifically labeled nucleic acid probe to the cellular RNA in individual cells or tissue sections. In principle, this employs the same strategy as Northern blotting

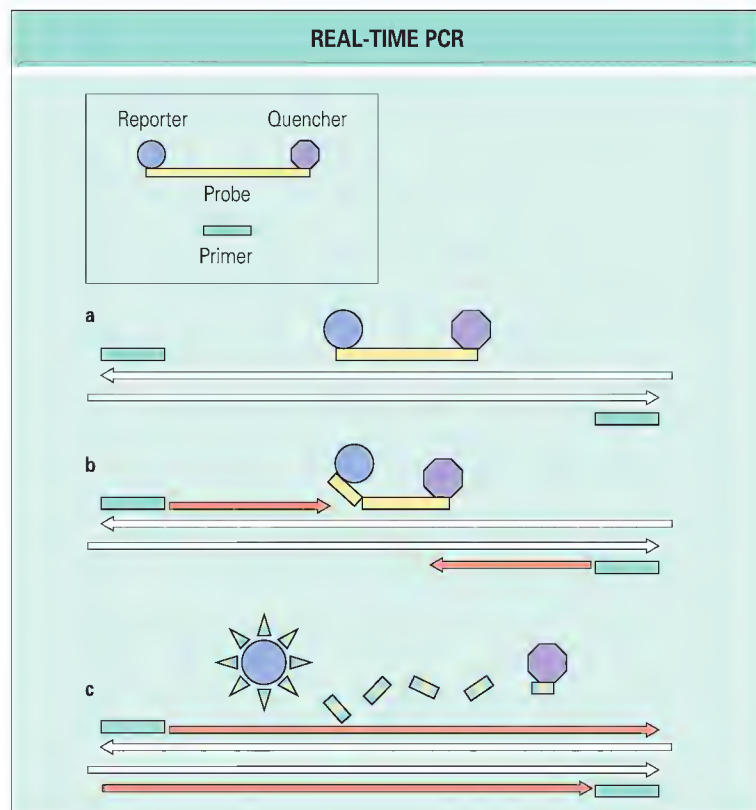


Fig. 12.7 In quantitative real-time polymerase chain reaction (PCR), oligonucleotide probes coupled to a reporter dye are synthesized along with ordinary primer pairs and used in the reaction. The intact probe does not fluoresce because a quencher is also coupled to the probe. However, the probe is cleaved by DNA polymerase during amplification, which separates reporter dye from quencher dye and results in increased fluorescence. The amount of PCR products generated can therefore be measured by monitoring the intensity of fluorescence with each cycle, because the amount of probe cleaved parallels the amount of PCR products produced. This is a reflection of the initial amount of complementary DNA (cDNA) generated from messenger RNA. This test can be further standardized by including probes and primers for housekeeping genes and can be made more quantitative by generating a standard curve using known amounts of cDNA encoding the gene of interest.

(hybridization of RNA with labeled cDNA), but in this case the hybridization is visualized within cells using microscopy. The gene's protein product or other proteins can also be visualized by immunohistochemistry, which may be quite informative in the analysis of clinical samples or in assessing the role of the gene in development.

The steady-state levels of mRNA are influenced by several factors, including the rate of its transcription as well as its stability, transport, and translation. The nuclear run-on assay measures the levels of primary transcript production without influence of other factors and thus can be used to distinguish whether a change in mRNA level is due to a difference in the rate of transcription per se or to other reasons such as altered mRNA stability.

EXPRESSION PROFILING

Although expression of genes can be evaluated by *in-situ* hybridization, RNase protection assay, Northern blotting, or quantitative real-time PCR (see earlier), the selection of genes for study is limited by the extent of our prior knowledge. New technologies building on the identification of most expressed genes by the Human Genome Project and more recently using high-throughput sequencing permit expression profiling; that is, analysis of the expression of thousands of genes, including those with unknown function, in a tissue or cell population. Indeed, these newer methods permit evaluation of the expression of not just a few genes but potentially *all* genes.

Several techniques have been developed for expression profiling. In serial analysis of gene expression, a small tag (short DNA fragment) is generated from each transcript. The tags are concatenated, and these larger DNA fragments are sequenced to identify the transcripts as well as their frequency in the transcript pool derived from a tissue or cell population.¹⁷ Array-based

methods of expression profiling use specific nucleic acid probes immobilized in an ordered array on a solid surface. Hybridization techniques in which labeled cDNA or cRNA fragments bind to the immobilized probes are then used to estimate the relative number of copies of each gene transcript in RNA extracted from a tissue or cell sample by the amount of label that binds to the immobilized probe. To achieve probe density sufficient to assay expression of tens of thousands of genes from relatively small tissue or cell samples, microarray technology was developed. There are two commonly used expression-profiling microarray techniques: DNA chip microarrays and spotted DNA arrays. In the DNA chip microarray technique the probes are oligonucleotides synthesized on the surface of a DNA chip or attached to the surface of beads that are affixed to the surface of a slidelike bead array; in the second technique they are fragments of cDNA clones or synthetic oligonucleotides that are spotted onto the surface of glass microscope slides.^{18,19} The newest methods for expression profiling use NGS technologies to comprehensively characterize and quantify the transcriptome.

DNA chip microarrays

DNA chip microarrays (Fig. 12.8) are manufactured by Affymetrix, Inc. (Santa Clara, Calif.) using a proprietary photolithographic process to synthesize 25-base oligonucleotides tethered to the chip surface; each is confined to a space 11- × 11-μm square. Each gene is represented by 22 squares with oligonucleotide probes covering various parts of the gene. Half the probes are perfect-match and half are hybridization controls, that is, copies of the perfect-match oligonucleotides, each with a single nucleotide mismatch. Probes for up to 47,000 transcripts can be synthesized on a single chip that is less than 1 cm². RNA is extracted from tissue or cells, and cDNA is synthesized. The cDNA is used to produce biotin-labeled complementary RNA (cRNA), which is fragmented and hybridized to the probes on the chip surface. The chips are washed and stained with a streptavidin-conjugated fluorescent dye, which binds to the hybridized biotinylated cRNA. The chips are scanned and the fluorescent signals are processed to determine the expression level of each gene. Normalized expression levels determined from different tissue or cell samples on different chips can then be compared (see Fig. 12.8).

A variant of the DNA chip microarray is the BeadChip microarray (Illumina, Inc., San Diego, Calif.). In this technique beads are coated with oligonucleotide probes (50-mers) attached to an address tag oligonucleotide (30-mers). The beads are randomly affixed to the surface of a slidelike solid support. About 30 beads of each type (representing a single transcript) are affixed to each BeadChip microarray, and their locations are determined by the address tags. Labeled cRNA is produced and hybridized to the BeadChip. The chips are scanned, and the signal intensity for each probe type is measured.

An advantage of DNA chip or bead microarrays is that, because the microarrays are mass-produced under highly controlled conditions, reproducibility of the expression data obtained from them can be very high. A disadvantage is that production of the microarrays is inflexible (custom arrays are expensive). Furthermore, only genes with sufficient sequence data to generate the probes can be represented on a DNA chip microarray.

Spotted DNA microarrays

A somewhat different technique is used for spotted DNA microarrays (Fig. 12.9). The arrays are produced by robotically spotting cDNA fragments or synthetic oligonucleotides onto glass microscope slides. The cDNA fragments are produced by PCR amplification of collections of cloned cDNA plasmids to obtain the cDNA inserts. Up to 40,000 elements can be printed on a single glass microscope slide. Unlike the DNA chip microarrays, in which transcripts from a single sample are hybridized to the array, cDNA transcripts from two samples the investigator wishes to compare are simultaneously hybridized to the spotted DNA microarray. RNA is extracted from the two samples and converted to cDNA in the presence of nucleotides labeled with either Cy3 or Cy5 (fluorescent dyes). The labeled transcripts are then cohybridized to the DNA probes on the microarray. Hybridization signals from the two dyes are used to determine expression ratios for all the genes on the microarray (see Fig. 12.9).

A variant of the cDNA spotted array technique is to spot long oligonucleotides (60-mers) in the place of the cDNA fragments. This change permits selection of a region or multiple regions of a transcript to be used as probes, which allows exclusion of regions that may be involved in nonspecific hybridization as well as separate evaluation of differentially spliced forms of genes.

An advantage of spotted DNA microarrays is that, because the arrays are produced on a small scale, they can be customized, for example to include

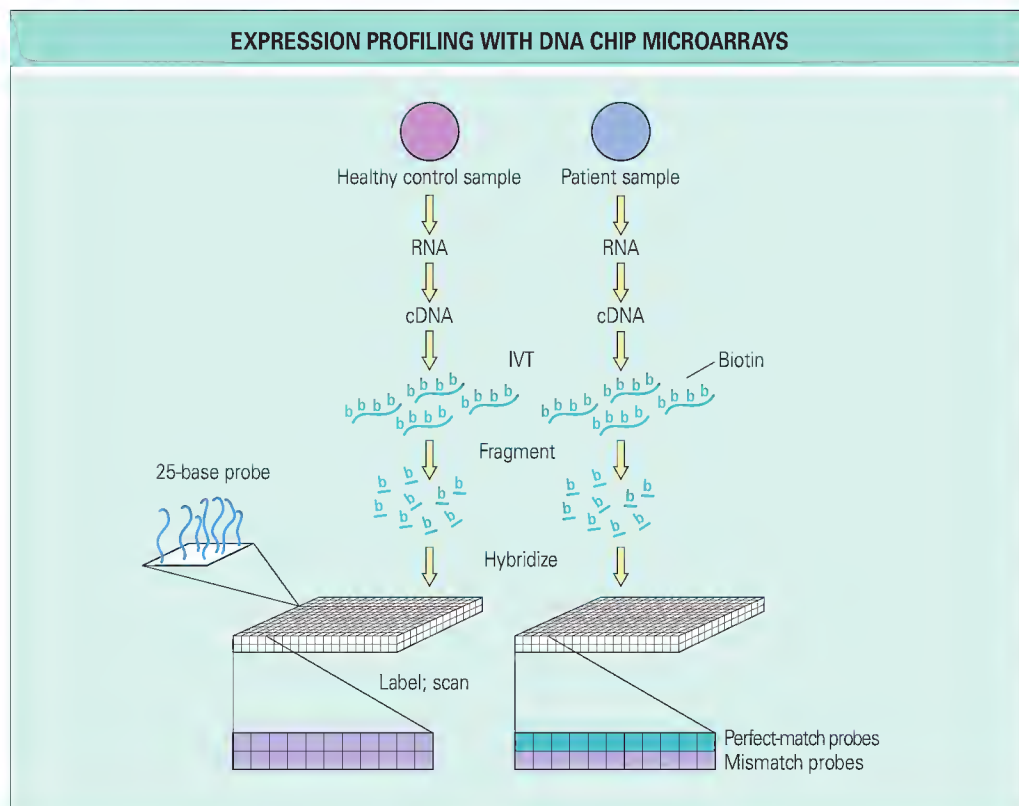


Fig. 12.8 With the use of DNA chip microarrays, the expression of tens of thousands of genes can be determined simultaneously using messenger RNA (mRNA) extracted from samples. The mRNA is reverse transcribed to complementary DNA (cDNA), which is *in vitro* transcribed (IVT), producing biotin-labeled complementary RNA (cRNA). The cRNA is fragmented and hybridized to oligonucleotide probes that have been synthesized on the surface of a silica chip. The hybridized cRNA is labeled with a streptavidin-conjugated fluor and scanned for detection. Specific hybridization is gauged by comparison of hybridization to pairs of perfect-matched and single-base-mismatched oligonucleotides, represented in the figure by the blocks directly above and below one another. Approximately 11 pairs of oligonucleotides on the chip represent each gene. The intensity of the specific hybridization signal is a measure of the gene expression in the sample.

newly discovered genes. A disadvantage is that the cDNA clone or oligonucleotide libraries must be acquired for production of the arrays. Furthermore, cDNA microarrays are technically difficult to produce and can be subject to reproducibility problems.

Massively parallel sequencing of RNA

Massively parallel sequencing of RNA (RNA-Seq), which employs NGS to interrogate RNA sequence and abundance, is perhaps the most powerful tool for unbiased investigation of RNA species. RNA-Seq has been most widely used in the investigation of mRNA, in which case the polyadenylated RNA species are captured from a sample. The captured RNA is fragmented to a size of several hundred bases, either before or after producing cDNA by reverse transcription, and the cDNA fragments are concurrently sequenced using NGS technology. Each sequencing read is then assembled and aligned to the human genome, and the prevalence of each RNA species may be determined. In addition to accurately quantifying genomewide expression, RNA-Seq may also identify the presence of variant alleles, alternatively spliced transcripts, posttranscriptional mutations or RNA editing, and gene fusions. Furthermore, using a variety of different RNA capture conditions, RNA-Seq may be modified to interrogate noncoding RNA, micro-RNA, or any other population of RNA. Because of the inherently error-prone nature of reverse transcriptase enzymes, the process of creating a cDNA library may introduce errors and bias to an RNA-Seq study. As a result, efforts are under way to develop protocols to perform RNA-Seq on RNA molecules themselves.

REGULATION OF GENE EXPRESSION AND PROTEIN-DNA INTERACTIONS

Understanding what controls the expression of a given gene is of considerable interest in the pathogenesis of rheumatic diseases. Typically, the first step in the process involves the identification of the promoter and enhancers of the gene of interest. Generally, this is accomplished by identifying the transcriptional start site and the 5' untranslated regulatory portion of the gene. These regions of the gene are then subcloned into reporter systems, which are used as surrogates to measure transcriptional regulation and the interactions of *cis*- and *trans*-acting elements with promoters and enhancers. Typically, regulatory sequences are ligated to reporter genes, such as firefly luciferase, and these plasmids are transfected into cells of interest that are stimulated in various ways. In this manner, the luciferase gene is transcribed in the place of the native gene, and the level of transcription can be detected

by light produced by the translated luciferase protein, which is regulated by stimuli that act on the heterologous promoter (Fig. 12.10). The fine structure of promoter/enhancer regions can be analyzed by introducing a series of mutations and examining the effects on reporter gene expression. The effect of patient-derived mutations or polymorphisms in promoters may also be examined to assess their influence on gene expression.

Identifying transcription factors that bind promoter/enhancer sequences is another important aspect of understanding gene regulation. The electrophoretic mobility shift assay is a commonly used technique to detect specific DNA-protein interactions (Fig. 12.11). Nuclear proteins are incubated with radioactively labeled oligonucleotides, are subjected to electrophoresis on polyacrylamide gels, and are visualized by autoradiography. DNA bound to protein “shifts,” that is, it migrates more slowly than the unbound radioactive oligonucleotide probe. Bound proteins can be identified by the use of specific antibodies that cause the protein-DNA complex to migrate even more slowly, a so-called supershift. The deoxyribonuclease (DNase) footprinting assay is another assay used to look for transcription factors bound to DNA and to determine precisely which nucleotides are bound by transcription factors that protect them from degradation by DNase treatment.

The chromatin immunoprecipitation (ChIP) assay is a technique that detects protein-DNA interaction in cells (Fig. 12.12).²⁰ In this procedure, nuclear proteins are cross-linked to DNA by formaldehyde. The DNA is sheared and the protein-DNA complexes are immunoprecipitated with antibodies against the proteins that putatively interact with the DNA of interest, so that the DNA bound to these proteins is coprecipitated or captured. The cross-links are reversed, and PCR is used to amplify the regions of genes of interest. These products are then run out on agarose gels. Alternatively, real-time PCR can be employed to detect the DNA that was bound by the immunoprecipitated protein. An extension of these principles allows the identification of virtually all the targets of the investigated DNA-binding protein in different cells under different circumstances. This can be accomplished by labeling the immunoprecipitated DNA fragments and hybridizing them to DNA sequences on a microarray slide (ChIP-on-chip) or by sequencing all of the immunoprecipitated DNA fragments using efficient NGS technologies (ChIP-Seq). When used in combination with other gene expression data, these techniques provide a powerful genomewide screening method to identify target genes of transcription factors.

Recent evidence shows that modification of the histone tail (e.g., acetylation, methylation, phosphorylation) is of considerable importance in regulating chromatin structure and the accessibility of genetic loci to transcription factors.²¹ Alterations of histone modification are very important in explaining transcriptional on-off states. These changes can be assessed using ChIP

Fig. 12.9 With the use of complementary DNA (cDNA) microarrays, the relative expression of tens of thousands of genes can be compared in pairs of samples by extracting RNA from each sample and producing cDNA labeled with one of two different fluorescent dyes (Cy3 or Cy5). The labeled cDNAs are combined and cohybridized to cDNA library probes (polymerase chain reaction [PCR] products) that have been spotted onto the surface of glass microscope slides. The relative intensity of the hybridization signal from the two dyes is a measure of relative gene expression in the two samples.

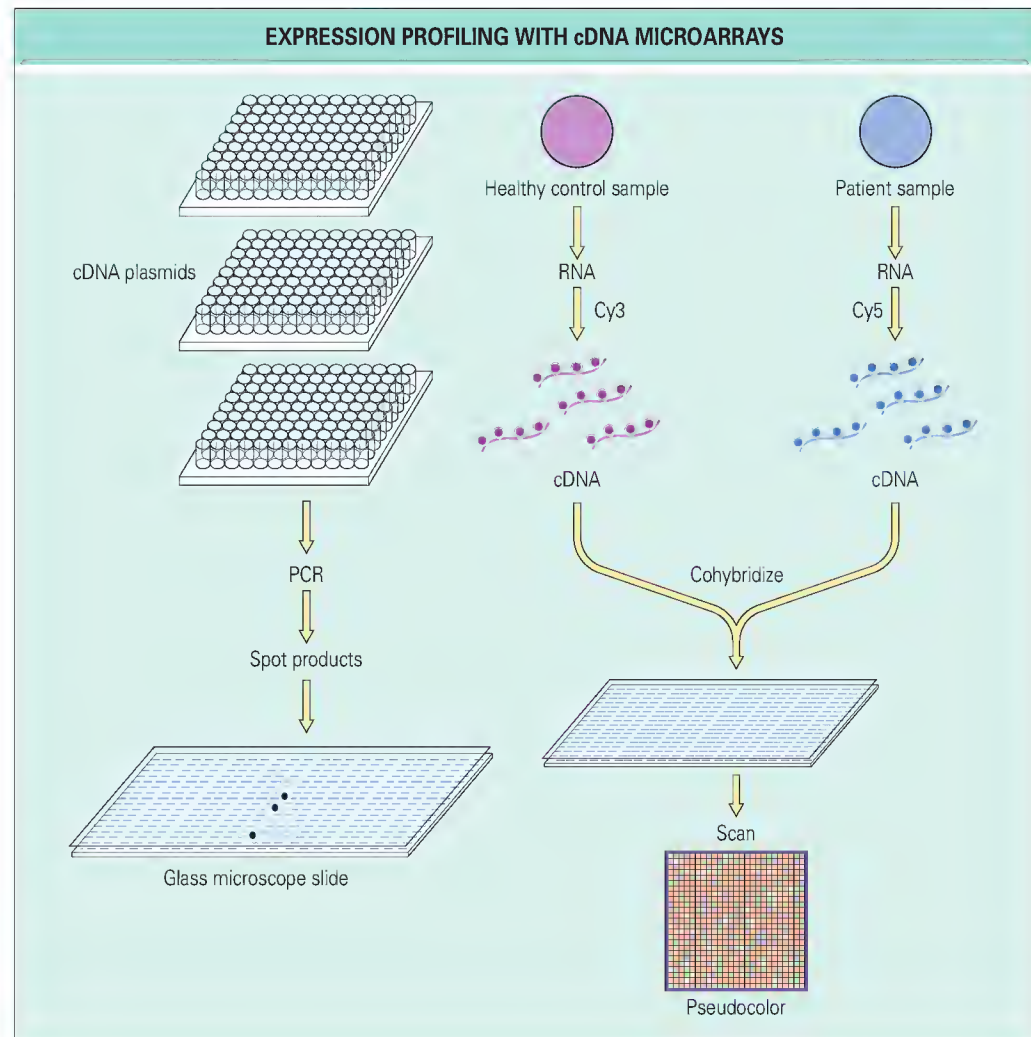
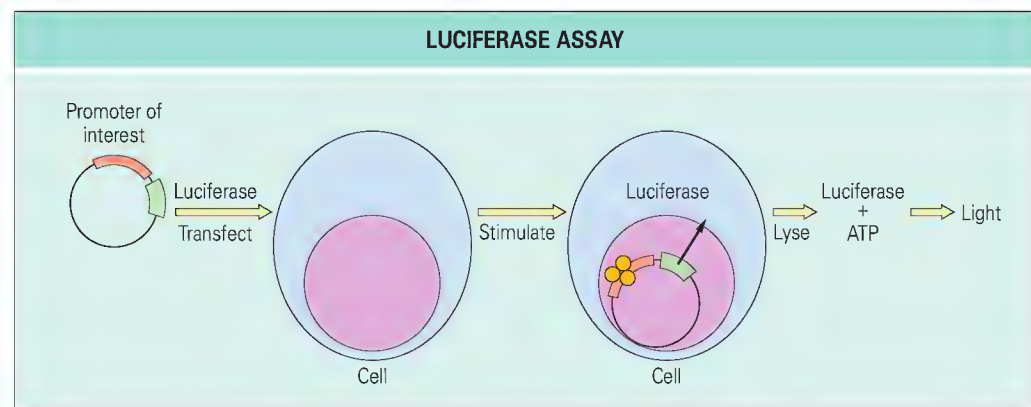


Fig. 12.10 To determine if a segment of DNA has enhancer/promoter activity, it is cloned upstream of a reporter gene that, when transcribed, will produce the protein encoded by the reporter—such as the luciferase enzyme. The transcription of this gene and hence the production of the protein is measured by an *in-vitro* assay that produces light, with the amount of light produced being proportional to the activation of the promoter. ATP, adenosine 5'-triphosphate.



with antibodies that specifically detect these modifications. The interaction of other transcription factors with promoters and enhancers can also be determined using ChIP in regions with altered histone modifications. Histone modifications are thought to affect the accessibility of genes, and therefore their ability to be acted on by *cis*-acting transcription factors. Accessibility of genes can also be assessed by their ability to be digested with DNase; DNase hypersensitivity is another means of assessing the transcriptional potential of a locus.

Recent work has illustrated that transcriptional regulation can also take place in the context of interactions between disparate genomic loci. Chromosome conformation capture assay (3C assay) is designed to detect these interactions of genomic loci *in vivo*.²² In living cells, two loci that are seemingly far apart on the genome can move into close proximity by “looping out” of the chromosome and sharing DNA-binding proteins. A chemical cross-linker is used to stabilize these interactions. Subsequently, the

captured DNA is digested and ligated to generate a novel junction between the two interacting DNA loci. PCR is then used to detect these novel ligation products, which are indicative of intrachromosomal interactions between a gene locus and a distant enhancer element and even interactions between two loci on different chromosomes. The 3C assay has the potential to uncover coordinated regulation of genes that are not located close together on the genome yet become physically close together during regulatory remodeling of the chromatin.

Many assays of gene regulatory elements are now being performed on a genomewide scale on a myriad of different cell types and the results are being deposited into searchable databases such as the *Encyclopedia of DNA Elements* (ENCODE) (www.nature.com/encode/#/threads)²³ that allow investigators to query the locations of regulatory elements and to design experiments to evaluate their contributions to processes involved in normal as well as diseased states.

ELECTROPHORETIC MOBILITY SHIFT ASSAY

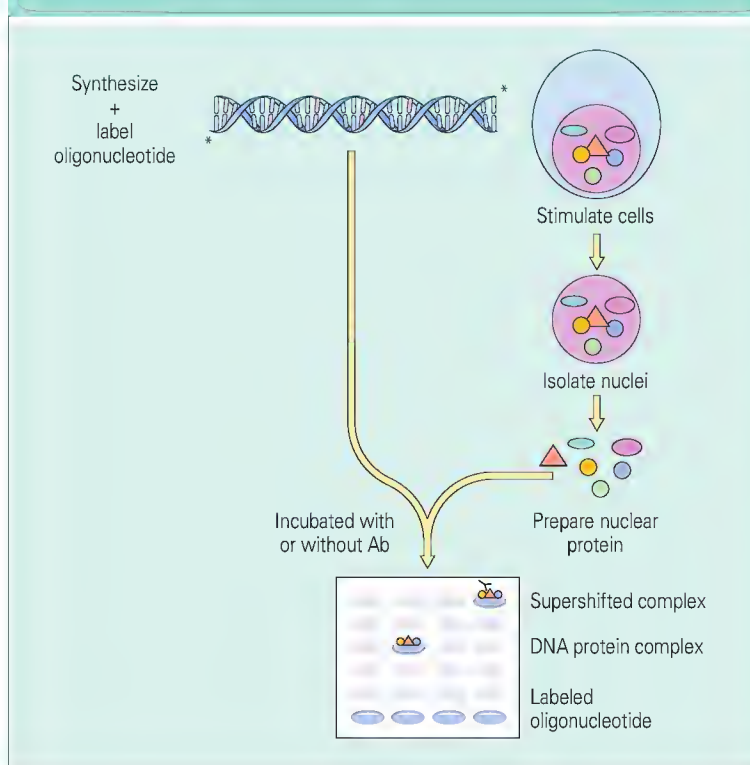


Fig. 12.11 When radiolabeled oligonucleotides are bound by nuclear proteins, their migration in acrylamide gels is retarded or slowed because of their larger molecular weight. This is also referred to as a *shift* in their mobility in the gel. If antibodies (Ab) against the putative DNA-binding proteins are also included, the complex is said to be *supershifted*, and this provides evidence that a particular transcription factor is bound to the oligonucleotide. Chemiluminescent methods can be used to detect biotinylated oligonucleotides to avoid the use of radionuclides.

ANALYSIS OF GENE FUNCTION

The transfer of genes into mammalian cells has been an essential tool to study gene function. These techniques allow examination of the consequence of expression of a new or altered gene and provide us with a great deal of our knowledge about the action of the encoded protein. The cDNAs corresponding to the genes of interest are cloned into expression vectors and are coupled to a strong promoter enabling high expression in cells. For instance, viral promoters are often used to allow high expression in various cell lines. Many different methods are used to transfect these constructs into mammalian cells. These include biochemical methods such as calcium phosphate, diethylaminoethyl-dextran, and liposome-based techniques. Alternatively, for cells that are difficult to transfect by these methods, physical methods such as electroporation and microinjection are used. A third way to transduce genes is by using viral vectors. Developed as tools for gene therapy, these are now widely used in many experiments. The vectors can infect various types of mammalian cells, including cells that are hard to transfect by the other two methods. Adenovirus and retroviruses are representative viruses used for gene transfer. Adenovirus can infect most types of cells and allows transient but high protein expression, whereas retroviruses infect only dividing cells and are characterized by moderate but long-term protein expression.

These methods allow transient expression of genes, which are translated into protein; the effect on cell function can be determined over hours to days. Over time, the cells lose the introduced plasmid construct because of degradation and dilution, but in a few cells the gene is integrated stably into the genome and maintained in offspring cells. These rare cells can be selected by using drug-selection reagents to establish stable transfectants. They typically show lower expression of the gene than with transient expression but are of great use for various experiments.

Recently, new methods have been devised for “knocking down” gene expression. This approach is based on RNA interference (RNAi) and is being heavily employed both in cells in tissue culture and more recently in animal models. For determining the nonredundant function of a particular gene, reducing gene expression has clear advantages over introducing the gene exogenously with plasmid or viral vectors. It is also important for determining whether the functional effects of a treatment depend on a particular gene. RNAi has largely supplanted earlier techniques such as those using

CHROMATIN IMMUNOPRECIPITATION ASSAY

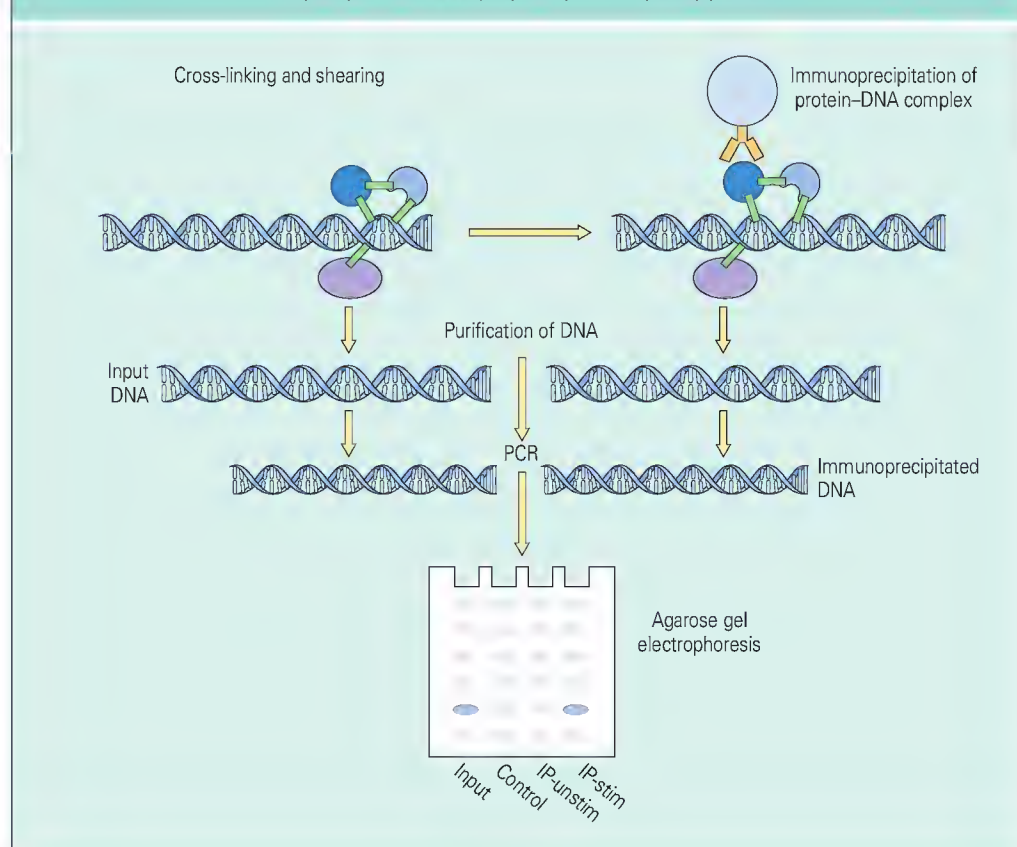


Fig. 12.12 Transcription factors, coactivators, and other DNA-binding proteins can be analyzed by cross-linking these proteins to DNA, followed by DNA shearing and immunoprecipitation with antibodies directed against the proteins of interest. Then protein is digested and the DNA is amplified by polymerase chain reaction with primer pairs for the DNA region of interest. A positive band indicates interaction of the protein with the DNA region (IP-stim) compared with what is seen in the absence of stimulation (IP-unstim). This is normalized to the amount of DNA present initially (input). PCR, polymerase chain reaction.

ribozymes or antisense oligonucleotides for reducing expression of specific genes. RNAi takes advantage of a recently discovered RNA silencing mechanism that is conserved from worms to mammals.²⁴ Double-stranded RNA containing sequences complementary to the targeted gene are cut into 21- to 23-base-pair small interfering RNA (siRNA) fragments using a specialized RNase III enzyme called *Dicer*. These fragments are then incorporated into the RNA-induced silencing complex (RISC), a multiprotein assembly that unwinds the double-stranded siRNA fragments, which bind to complementary sequences in an mRNA molecule. The RISC cleaves the target RNA at a single site in the middle of the complementary sequence, effectively inactivating further translation of the target mRNA. Because a single siRNA in the RISC can inactivate multiple target mRNAs, knockdown of gene expression through this mechanism can be potent (more than 90%) and long lasting (up to 5 days from a single transfection of siRNA duplexes).

The promise of this technique for basic research and therapeutic intervention is beginning to be realized.²⁵ In most higher organisms, including humans and mice, transfection of long double-stranded RNA and even some shorter sequences can activate an antiviral gene response program that induces type I interferon induction and nonspecific RNA degradation by RNase L, so siRNA oligonucleotides shorter than 23 base pairs are used. Synthetic siRNA can be delivered to a variety of cultured cells through conventional transfection methods. More recently, injection of siRNA with a fluid bolus was found to silence gene expression efficiently in mice, and coupling protamine-bound siRNA to a Fab antibody fragment specific for a cell surface molecule was able to target siRNA to specific cell subsets.^{26,27} For long-term silencing of target genes, expression of a “short-hairpin” RNA (shRNA) sequence containing the target siRNA connected by a loop region under the control of an RNA polymerase III promoter is preferred. *Dicer* cleaves the expressed shRNA into siRNA, which is incorporated into the RISC. Viral vectors have been engineered that can drive stable expression of shRNA and silence target RNA molecules in primary cells.^{28,29}

GENETIC MANIPULATION OF MICE

Another way investigators can learn about the function of a gene is to study its *in-vivo* function in a genetic model organism in which its expression and structure can be experimentally manipulated. The mouse is particularly amenable to such studies. Because it is a mammal, its genes and gene functions are very similar to those of humans, but it is possible to manipulate its genome by introducing or overexpressing genes in transgenic mice or by using targeted disruption to destroy a gene in knockout mice.³⁰ Investigators can then study the effects of these genetic alterations in the animals, their tissues, or cells.

Transgenic mice

Transgenic animals are genetically modified animals in which foreign DNA has been experimentally inserted into the transgenic genome. This is accomplished by injecting a DNA construct into the pronucleus of a fertilized oocyte. Blastocysts that develop from these injected oocytes are transferred to pseudopregnant females, in which they develop, to produce potentially transgenic pups (Fig. 12.13). The pups are screened for the presence of the transgene and bred. If the transgene was integrated into the genome of its germline, the animal will then transmit the transgene to the next generation.

The investigator can target expression of the transgene to specific tissues by using tissue-specific promoters or enhancers. The investigator can also control expression of a transgene by using an inducible promoter system such as a tetracycline-regulated system, in which a construct encoding a tetracycline-induced factor under the control of a tissue-specific promoter is introduced in one mouse line and the gene of interest, under the control of a promoter that is controlled by the factor, is introduced into a second line. The tetracycline-induced factor can be either an expression activator or an expression repressor. The lines are then crossbred to generate animals with both genetic alterations, in which expression of the transgene can be controlled in the target tissue by administering or withdrawing tetracycline. Transgenes typically integrate as a tandemly repeated unit within the recipient genome. It is not possible to control the integration site or the number of copies integrated.

Knockout mice

Another way to study the function of a gene is to determine in animals the effect of disrupting the gene so that its product is not produced. Spontaneous mutations that have this effect on genes have provided investigators

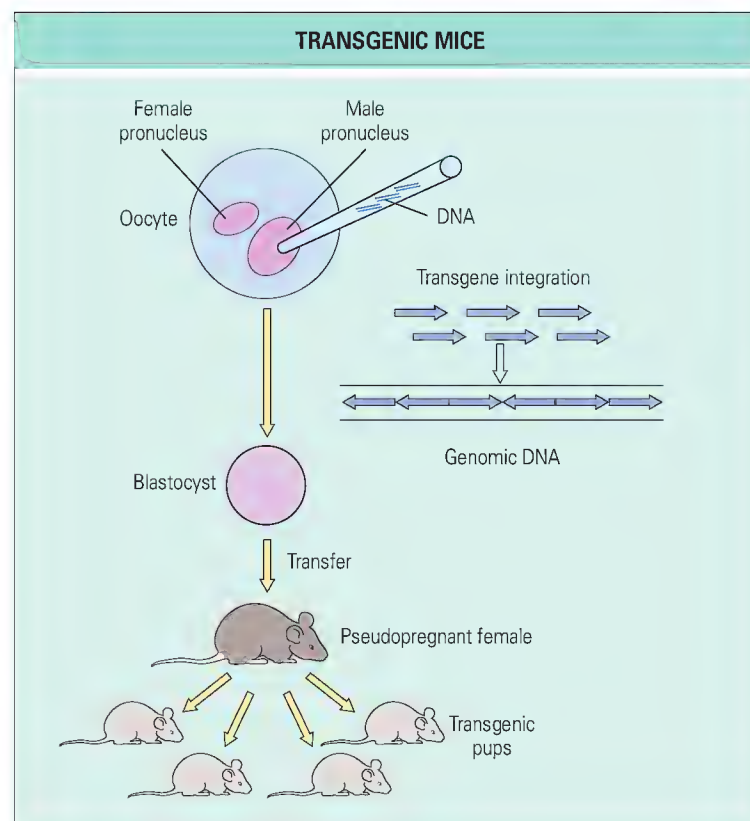


Fig. 12.13 Overexpression of DNA constructs in transgenic animals is achieved by injecting a DNA construct (containing the transgene) into the male pronucleus of a fertilized oocyte. The transgene may integrate as a tandem repeat within the recipient genome. Blastocysts are allowed to develop *in vitro* and are then transferred to pseudopregnant female mice. If the transgene has integrated into the genome of the germline, the transgenic offspring (founders) will transmit the transgene to their offspring.

with a great deal of information regarding the function of the affected genes. It is now possible for investigators to experimentally manipulate the genomes of mice by disrupting a gene in pluripotent embryonic stem cells and incorporating those cells into a developing blastocyst (Fig. 12.14).

The technique used to disrupt a gene is to transfect the embryonic stem cells *in vitro* with a DNA construct in which a fragment of the gene sequence has been disrupted by incorporating a selectable marker gene, such as the neomycin resistance marker, that can also be used for positive selection of cells that have integrated the construct. Disruption of the endogenous gene occurs by the process of homologous recombination, whereby homologous sequences flanking the disruption facilitate the exchange of the disrupted gene fragment with the intact fragment of the endogenous gene. The construct may include a coding sequence deletion and/or a premature termination and polyadenylation signal, which, when incorporated within the endogenous gene, blocks its expression. The construct also contains, outside of the gene disruption cassette, a second marker, such as the thymidine kinase marker, that can be used for negative selection to eliminate transfectants in which nonhomologous recombination occurred.

Cells in which homologous recombination occurred are injected into blastocysts and the blastocysts are transferred to foster mothers. Some of the pups produced may be chimeras, in which the genetically altered embryonic stem cells have expanded and contributed to the developing embryo. Through the use of blastocysts and stem cells from strains with different-colored coats, the chimeric pups can be recognized by the contribution of the stem cells to the coat color.

As with transgenic mice, the chimeric offspring are then bred to determine whether the embryonic stem cells contributed to the development of germ cells and will therefore be transmitted to the next generation. Carriers of the chromosome with the disrupted gene can be interbred to produce knockout or gene-targeted mice in which both copies of the gene are disrupted.

A variant of the knockout mouse, the knockin mouse, can be used to trace the temporal and spatial expression patterns of a gene and to study regulation of its expression. In this technique the targeting construct includes a reporter gene, such as the β -galactosidase gene, as well as the

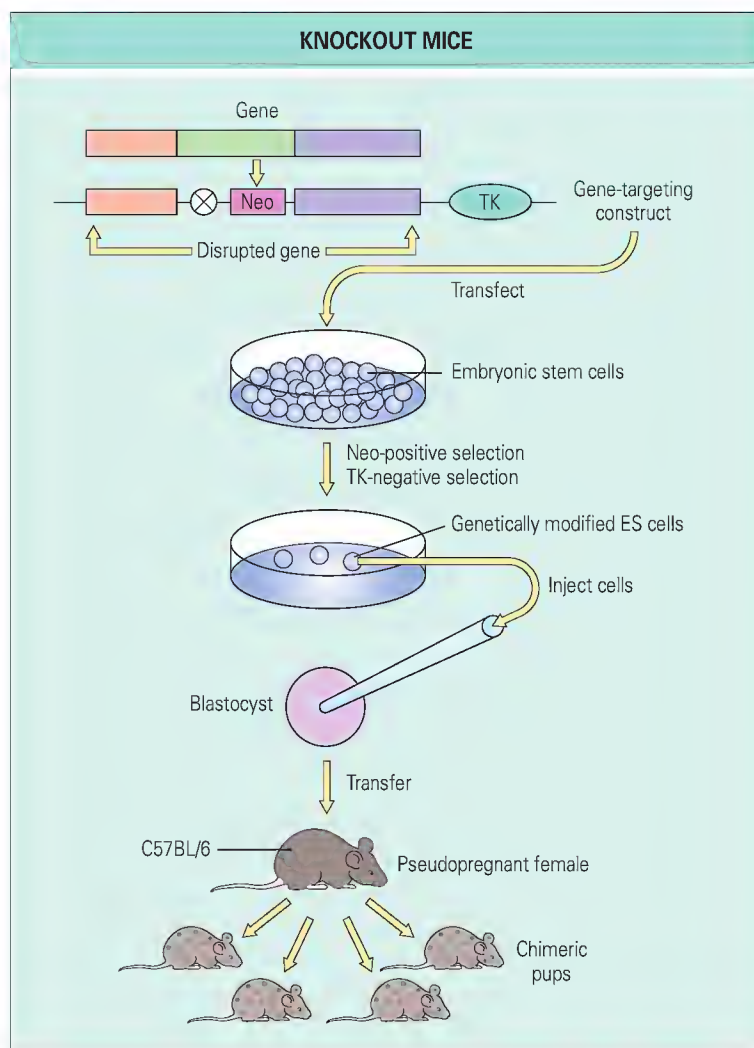


Fig. 12.14 A gene can be effectively deleted from (knocked out of) an animal's genome by disrupting it or deleting an essential domain in embryonic stem cells that can then be transferred to blastocysts, in which they may be incorporated into the germline tissue of the developing embryo. A gene-targeting construct is transfected into embryonic stem (ES) cells, and a disruption cassette replaces a part of the cell's gene by the process of homologous recombination. Because this process is inefficient, a positive selection gene (Neo) is incorporated within the disruption cassette and a negative selection gene (TK) is incorporated outside the cassette to eliminate untransfected cells and transfectants with integration of the targeting construct elsewhere in the genome. Rare cells that have undergone homologous recombination are expanded in culture and injected into blastocysts. Chimeric offspring, into which the targeted embryonic stem cells have been incorporated, can be recognized by the contribution of agouti (brown) targeted (L129) stem cells to the nonagouti (black) coat of the recipient (B6) blastocyst. If the stem cells have contributed to the offspring germline, the offspring will transmit the disrupted gene to its offspring.

selectable marker. The targeted animals produce a chimeric protein in which the reporter gene is fused to a portion of the gene under study. The chimeric gene is expected to be expressed in the same manner as the gene under study. Expression of the chimeric gene can be evaluated by analyzing expression of the reporter gene. This knockin technology can also be used to introduce a disease-associated or other mutation into the gene of interest.

Cre/lox-directed targeted disruption

If disruption of a gene interferes with embryonic development or is lethal, it is difficult to discern its function in knockout mice. Investigators may, however, examine the effect of eliminating the gene's expression from specific tissues or at specific times. These experiments are made possible by the cre/lox recombination system in which lox sites, recognized by the cre recombinase, are inserted in intron sequences flanking an essential portion of the targeted gene. This genetic alteration does not interfere with the gene's

expression. In the presence of the cre recombinase, however, the targeted region is excised from the gene, which leaves a nonfunctional remnant. The cre recombinase can be inserted into the genome as a transgene and an inducible or tissue-specific promoter can direct its expression. In this way, a gene can be disrupted in a specific tissue or at a specific developmental stage by regulating the location and timing of cre expression in the animal.

ANALYSIS OF PROTEINS

The regulation of expression of proteins in cells pertinent to rheumatologic disease is often analyzed. Flow cytometry allows detection of cell surface and intracellular proteins recognized by specific antibodies on a single-cell basis and, with multicolor staining, permits the simultaneous analysis of the expression of several molecules in specific cell populations. Because of the ease of this technique it is commonly employed. To identify the location of a protein of interest within tissues, immunohistochemistry is often used; again, the detection of the protein is dependent on its recognition by specific antibodies. For localization within a cell, electron microscopy or confocal microscopy and immunofluorescence are often employed. Transfection of cells with proteins fused to GFP to be detected under video imaging is a modern technology used to track localization and movement of the molecule in a living cell (see Fig. 12.3).

Immunoblotting or Western blotting is still the most widely used technique to identify protein expression, modification, and interactions with other proteins. In brief, proteins are separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis, transferred to a membrane, and detected by specific antibodies bound to enzymes such as horseradish peroxidase. These antibody-protein complexes are detected by chemiluminescence, autoradiography, or similar methods (Fig. 12.15).

Protein function is regulated by various posttranslational modifications and through dynamic protein-protein interactions; indeed, a paradigm shift in cell signaling has been the understanding of the importance of these interactions. For instance, tyrosine phosphorylation and serine/threonine phosphorylation are major modifications that regulate protein function and assembly of protein complexes. Increasingly, antibodies against phosphorylated forms of various proteins are being made available for the dissection of signal transduction pathways. These antibodies can be used in immunoblotting (see Fig. 12.15) and even in flow cytometry.

Protein-protein interactions can be analyzed by various techniques. Coimmunoprecipitation of one protein with another is a standard technique, but the interactions can be influenced by the detergents used to lyse the cells. Immunoprecipitation reactions require a specific antibody to the protein of interest. Alternatively, using a GST–fusion protein pull-down assay provides good evidence for protein-protein interactions without the need to produce a specific immunoprecipitating antibody. The GST-tagged protein binds with high affinity to glutathione attached to agarose beads. Noninteracting proteins are removed by washing. Proteins that remain bound to the GST-tagged protein can then be assayed by two-dimensional gel electrophoresis or other analytic techniques. A third method for assessing protein-protein interactions is far-Western blotting, in which a labeled recombinant protein is used to “blot” a membrane in which cell lysates have been separated. If the recombinant protein interacts with a cellular protein, the interaction is visualized as a “band.”

Fluorescence resonance energy transfer (FRET) can be used to study protein-protein interactions in living cells as an important complement to strictly biochemical methods. Energy emitted by a fluorophore can be transferred to an acceptor fluorophore causing sensitized emission at a longer wavelength only if the two molecules are in extremely close proximity (<10 nm). Antibodies conjugated to appropriate fluorochromes originally were used to measure protein-protein interactions in this way. More recently, fusion of proteins to fluorescent protein pairs with properties suitable for FRET such as cyan fluorescent protein and yellow fluorescent protein have been used to assess interactions of proteins by microscopy and flow cytometry.³¹ In cell-free systems, protein-protein interactions can be quantitatively measured using surface plasmon resonance.³²

Yeast two-hybrid screening is another method that not only provides a means of detecting interactions between known proteins but also permits the identification of new partners. Most proteins consist of multiple domains with independent functions. Two-hybrid technology takes advantage of these modular functions of a transcription factor protein. Typically, a fusion protein is created in which the DNA-binding domain of the transcription factor is linked to the protein for which interacting partners are sought. This fusion protein, referred to as the “bait,” is expressed in yeast cells. A “prey” library of proteins fused to the transcriptional activation domain of the transcription factor is also expressed in the yeast cells. Cells in which an

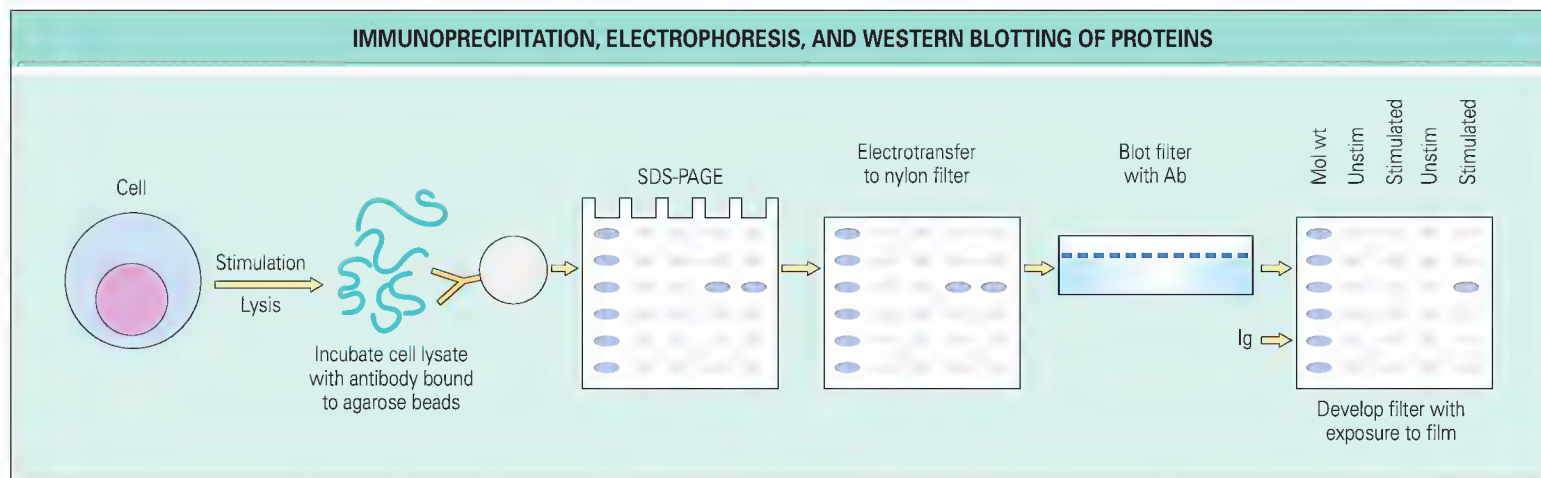
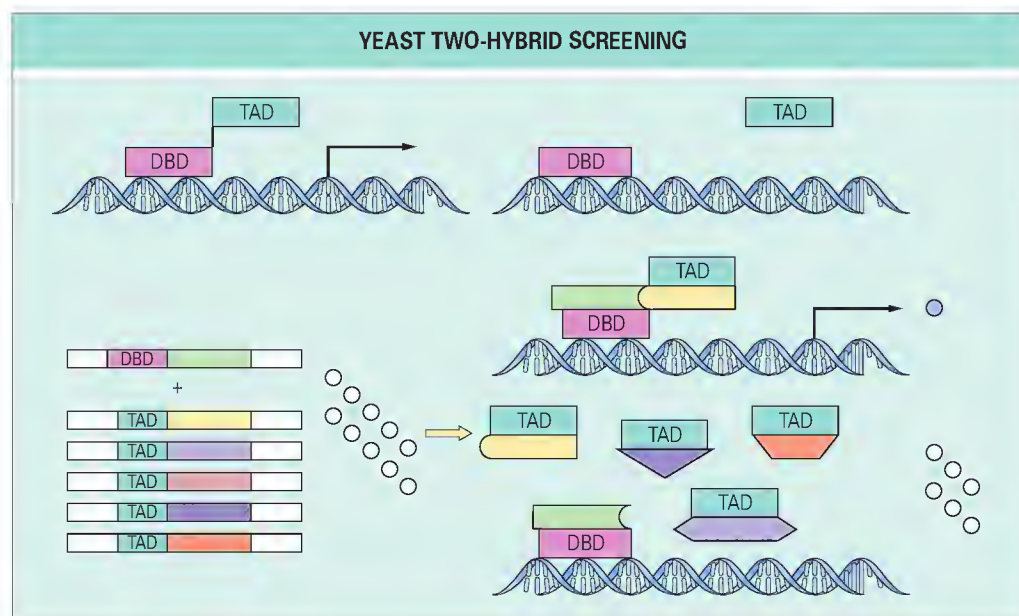


Fig. 12.15 In immunoprecipitation, electrophoresis, and Western blotting, cells are typically activated in some way and lysed with detergent-containing buffers. The insoluble material is removed by centrifugation. Staphylococcal protein A bound to agarose beads is incubated with a desired antibody, and this complex is then incubated with cell lysates. The protein or protein complex recognized by the antibody is isolated in this way and then subjected to electrophoresis on polyacrylamide gels, which separates proteins by molecular weight. The proteins can then be electrotransferred to membranes. Modifications of these proteins (e.g., phosphorylation), proteins that coassociate, or the proteins themselves can be detected by incubating the membranes with antibodies (immunoblotting). Ab, antibodies; Mol wt, molecular weight; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; Unstim, unstimulated.

Fig. 12.16 The yeast two-hybrid system is a powerful technique for discovering proteins that interact with a protein of interest. In most transcription factors DNA-binding domains (DBDs) and transcriptional activation domains (TADs) are present in a single protein, which regulates gene transcription through the proximity of the two domains. In the yeast two-hybrid system, these two domains are separated and one fused to the "bait" polypeptide and the other to a library of "prey" polypeptides, which are both expressed in yeast cells. In cells expressing interacting polypeptides, a physical interaction between "bait" and "prey" brings together the transcription factor DBD and TAD domains, facilitating transcription of a reporter gene, in this case β -galactosidase, which turns yeast colonies blue.



interaction of the bait and the prey occurs transcribe the reporter gene. Often the reporter gene encodes β -galactosidase, so that protein-protein interaction is visualized by the blue color of the yeast colonies. If the DNA-binding domain and activation domain are not in proximity, no activation of the reporter occurs (Fig. 12.16).

PROTEOMICS

Proteomics is a term that connotes some of the same issues as genomics. It is defined as the study of the expressed protein complement of the genome and seeks to gain a global and integrated view of changes in protein expression in cells or tissues.^{33,34} Whereas the human genome comprises about 30,000 genes, alternate splicing and different types of modification probably result in at least 100,000 different proteins. Furthermore, proteomics also includes protein-protein interactions and localization, which makes this field far more complex than genomics. It is worth emphasizing in this regard that proteins, and not genes, are the regulators of cell function.

Two-dimensional gel electrophoresis is a multistep procedure that can be used to separate hundreds to thousands of proteins with extremely high resolution. It works by separating proteins by their isoelectric points in the first dimension (isoelectric focusing) and then by their molecular weights in the second dimension (polyacrylamide gel electrophoresis). Using

sophisticated image analysis methods, the proteins from different samples can be compared to identify differences among the samples. Proteins of interest can then be extracted, identified, and further analyzed.

Sequencing of proteins by Edman degradation has been performed since the 1940s, but automation of this technique and microsequencing of proteins transferred to membranes after electrophoresis has greatly improved the ability to identify polypeptides. Mass spectroscopy was devised more than a century ago, but biomolecules are large and polar and are not easily transferred to the gas phase and ionized. However, the development and automation of two methods, electron spray ionization and matrix-assisted laser desorption ionization, has facilitated the application of mass spectroscopy to biology. The identification of polypeptides is also greatly enhanced by the availability of amino acid sequence and peptide mass fingerprinting databases; in this respect, advances in genomics facilitate advances in proteomics.

Like genomics, the field of proteomics has been driven by advances in technology. A variety of new techniques involving microarrays of proteins and tissues are permitting large-scale analysis of protein interactions and localization. Spotting of cell lysates on microarrays is allowing efficient evaluation of pathways; for example, the kinetics of signal transduction pathways has been probed with phosphorylation-specific antibodies.³⁵ Of particular interest to rheumatologists, autoantigen microarrays have been used to profile serum autoantibodies in patients with autoimmune diseases.³⁶

MOLECULAR BIOLOGY: THE NEW PATHOLOGY FOR THE PRACTICING RHEUMATOLOGIST?

Aside from helping the clinician to understand the research papers that appear in the medical literature, what is the utility of the material presented in this chapter? Or to put it another way, what is the likely impact of the molecular biology revolution on the clinical practice of rheumatology?

Rheumatology in the 21st century specializes in a number of disorders that have defied understanding by application of current cellular, biochemical, and immunologic techniques. Whereas systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis are often viewed as single disease entities, there is great clinical heterogeneity among patients, and it is likely that these conditions are actually syndromes that subsume multiple disorders, each with a distinct pathogenesis, prognosis, and treatment.

Although it is unlikely that molecular biology will be the prism that resolves all of the rheumatic syndromes into their etiologic subsets, the genome revolution and molecular biology techniques provide us with new tools that are already beginning to have an impact. DNA diagnostics for mendelian rheumatic disorders, and gene expression profiling and proteomic analyses for complex rheumatic disorders, are among the molecular techniques that make up what might be regarded as the “new pathology,” and in many cases these approaches promise to redefine the clinical practice of rheumatology. For certain conditions it is already common practice to obtain blood specimens for DNA or RNA extraction for clinically indicated tests. For other conditions, particularly complex rheumatic diseases, molecular studies are still at the level of bench research. However, the practitioner can help to catalyze the potential molecular transformation of rheumatology by participating in studies that often require samples from hundreds or even thousands of patients. The ultimate payoff will be a deeper understanding of and better therapeutic options for rheumatic diseases.

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13 Cytokines

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- Cytokines are critical factors in host defense and immunoregulation and key players in autoimmunity and inflammation.
- Cytokines belong to different families and bind structurally distinct receptors.
- Mutations and polymorphisms of cytokines, cytokine receptors, and their signaling pathways are associated with a number of human diseases.
- Targeting cytokines themselves or their signal transduction pathways provides many new opportunities for therapy.

INTRODUCTION

Given the extraordinary success of biologic therapies that target cytokines and cytokine receptor signaling, it is hardly necessary to convince readers of the pivotal roles that cytokines play in the pathogenesis of rheumatologic diseases. On the contrary, because of all these exciting developments, rheumatologists are well aware of the criticality of cytokines. Indeed, rheumatologists are increasingly functioning as “applied immunologists,” and other practitioners are looking to rheumatologists for their expertise in the use of these biologic drugs. However, “new” cytokines continue to be identified and new anticytokine therapies continue to be developed. It is also clear that anticytokine therapies are not effective in all patients with a given disease. Furthermore, agents that are efficacious for a given autoimmune disorder are ineffective in others. This suggests differential roles of cytokines in various disorders and perhaps subgroups of patients. For all these reasons it is incumbent on rheumatologists to be experts in the area of cytokine biology. However, this is a daunting task given the sheer number of cytokines and the complexity of their actions. In this chapter our goal is to be reasonably complete but also to provide the reader a conceptual framework for considering the different classes of cytokines. To facilitate the understanding of cytokine action, we provide a few details regarding the signal transduction pathways used by cytokines; however, in an attempt to make the chapter accessible we do not provide an exhaustive discussion of all cytokines and their mechanisms of action.

An additional challenge is that the term *cytokine* does not denote a specific class of structurally or functionally related molecules; on the contrary, many different types of factors produced by immune and nonimmune cells can be included in this category of secreted factors. Terms such as *cytokine*, *lymphokine*, *interleukin*, and *interferon* have been in use for more than 30 years; however, it is probably most reasonable to simply accept the imprecision of the terms and understand that a wide variety of secreted polypeptides can modulate immune and inflammatory responses. Because the problem of intercellular communication is a fundamental one for homeostasis in all multicellular organisms, the boundary between what we think of as cytokines, growth factors, and hormones is also indistinct. For instance, hormones such as growth hormone (GH), prolactin (PRL), erythropoietin (EPO), and leptin are clearly cytokines based on their receptor usage and signaling mechanisms (see below). For this reason it is probably easiest to simply accept that the term “cytokine” is necessarily broad and refers to a subset of factors involved in cell-cell communication. Their actions primarily relate to host defense and regulation of immune and inflammatory cells, but evolutionarily, these factors are homologous to molecules that influence development and coordinate communication between other tissues and organs.

For this reason, in this chapter we classify cytokines not by their function but rather by the type of receptor that they bind. This classification is also useful because it reflects the evolutionary relatedness of cytokines, growth factors, and hormones and emphasizes similarities in modes of signal transduction. Thus, we will broadly discuss the following cytokine categories: interleukin-1 (IL-1), tumor necrosis factor (TNF), type I (hematopoietin) and type II (interferon) proteins, IL-17, receptor tyrosine kinase, transforming growth factor- β (TGF- β), and chemokine receptor families. In the interest of brevity, cytokines that have important immunologic and inflammatory functions will be stressed; only cursory discussion of other cytokines will be provided.

INTERLEUKIN-1 RECEPTOR FAMILY

Ligand and receptor structure

IL-1, a highly pleiotropic factor produced by leukocytes, induces fever, inflammation, and catabolism.¹⁻³ Cytokines of the IL-1 family are evolutionarily ancient and present in echinoderms, tunicates, and annelids, in addition to all species of vertebrates. IL-1 family members form a β -trefoil structure consisting of 12 strands folded into three sheets. These cytokines bind to receptors whose extracellular portions are formed by immunoglobulin domains (typically three) and whose cytoplasmic domains contain a conserved fold known as the TIR domain. TIR domains are also shared with another important class of molecules in host defense known as Toll-like receptors (TLRs). Indeed, TIR is an acronym derived from “Toll, IL-1R, plant Resistance genes,” all of which contain this ancient fold. The known functional receptor complexes are heterodimeric such that the cytokine binds its primary receptor subunit (e.g., the IL-1 receptor [IL-1R]), which then allows recruitment of a second subunit; in the case of IL-1 itself, an “accessory protein” (AcP) is required for initiation of signal transduction.

Family members and their action

The IL-1 family consists of 11 members, whereas the IL-1R family has 10 identified members (Figs. 13.1 and 13.2). Most IL-1 family members lack a signal peptide, the exception being IL-1 receptor antagonist (IL-1Ra, encoded by *IL1RN*—see below). Other than IL-1 α , most IL-1 family members have prodomains, which need to be removed for the cytokine to be biologically active. The prodomains of IL-1 β and IL-18 are removed by caspase-1 cleavage within a protein assembly called the inflammasome (Fig. 13.3). Secretion of active cytokines occurs in concert with their cleavage, although the mechanism of how these cytoplasmic molecules are secreted is not well understood.

The term *inflammasome* refers to a multiprotein assembly whose formation results in the activation of caspase-1 and maturation and secretion of IL-1 β and IL-18.⁴ It has two key components: caspase-1 itself and a recognition/assembly component that is a so-called NOD-like receptor (NLR). Frequently, another protein called ASC (a simple adapter protein containing both pyrin and CARD domains) is required to facilitate assembly. NLR proteins are intracellular pattern recognition receptors that contain three domains: a segment with multiple leucine-rich repeats whose role is to recognize the trigger for activation (whether directly or indirectly remains unclear); a portion called a NACHT domain that leads to adenosine triphosphate (ATP)-dependent dimerization of the NLR after recognition of the trigger; and a protein-protein interaction domain, most commonly either a pyrin or a CARD domain, that recruits caspase-1. The best-studied inflammasome is the so-called NLRP3 inflammasome (see Fig. 13.3). Recognition



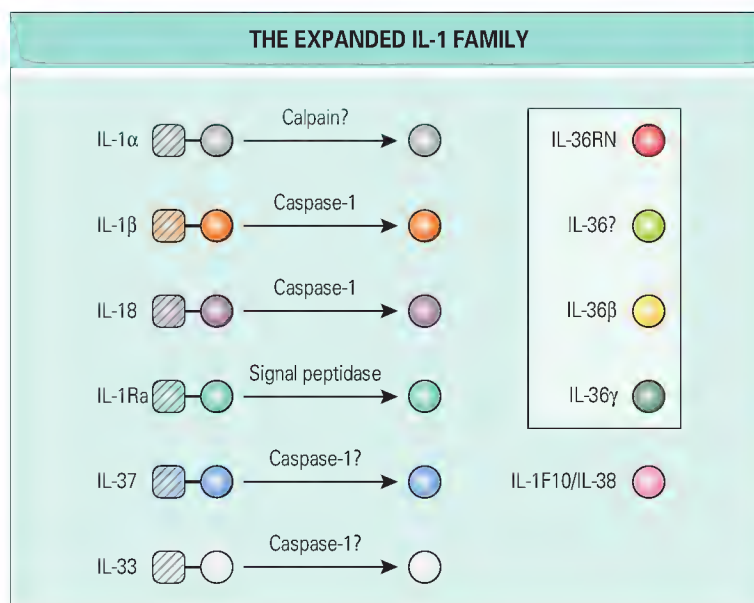


Fig. 13.1 The interleukin-1 (IL-1) cytokine family has 11 members that are encoded by a cluster of genes on chromosome 2q. These cytokines are shown schematically, with the prodomains of each cytokines depicted in hatched colors. The putative proteases that process the proforms of these cytokines to mature forms are indicated. Although IL-1 α and, probably, IL-33 have prodomains, removal of the prodomains is not necessary for these cytokines to become active. IL-1 receptor antagonist (IL-1Ra) has a signal peptide.

of the trigger by NLRP3 causes its dimerization, recruitment of ASC via interaction of the pyrin domains of NLRP3 and ASC, and subsequent recruitment of caspase-1 via the CARD domains present in both ASC and caspase-1. Dimerization of caspase-1 on assembly of the inflammasome allows it to become autoactivated by cleavage of the proform to generate active enzyme. The NLRP3 inflammasome is activated by ATP; components of gram-positive bacterial cell walls such as muramyl dipeptide; intracytoplasmic DNA, such as occurs during viral infection; molecules resulting from tissue damage, such as hyaluronin fragments; crystals, including those of uric acid (released from necrotic cells), alum (a commonly used adjuvant), silica and asbestos (environmental contaminants that lead to lung disease), and amyloid- β , a key protein in Alzheimer disease. Cigarette smoke also leads to activation of caspase-1 in mice, but the mechanism is poorly understood. Mutations in NLRP3 result in several hereditary periodic fever syndromes, including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multiorgan inflammatory disease (NOMID; in Europe called chronic infantile neurologic, cutaneous, articular syndrome [CINCA]). NLRP3 is also called cryopyrin, and these disorders have been collectively referred to as cryopyrinopathies.^{5,6} The consequence of disease-causing mutations is excessive release of IL-1 β . Other NLR proteins, including NLRP1, IPAF, NAIP, and AIM2, assemble into their own inflammasomes, which are triggered by other types of stimuli such as gram-negative bacteria and viruses. Mutations in NLRP1 are associated with vitiligo, and several single nucleotide polymorphisms (SNPs) in this gene have been linked to systemic lupus erythematosus (SLE).⁷ Although IL-1 β and IL-18 require cleavage by active caspase-1 to generate their active forms, evidence suggests that secretion of IL-1 α also requires active caspase-1, even though it is not a direct caspase substrate. It is worth noting that although the inflammasome controls the production of IL-1 in monocytes and macrophages, the IL-1 β made by other cells (e.g., neutrophils) is released in its precursor form on cell death and cleaved extracellularly by proteases such as the neutrophil protease PR3.

IL-1 α and IL-1 β

IL-1 α and IL-1 β are the family members with the most widespread influence. Their biologic activities are identical, although they are made by different cells under different influences. The most abundant sources of IL-1 β are monocytes and macrophages. In contrast, IL-1 α is made by many types of cells, but keratinocytes and endothelial cells are particularly rich sources. IL-1 α often remains associated with the plasma membrane of the cell that produces it, whereas IL-1 β is released from cells and diffuses into the surrounding tissue and systemic circulation. The prodomain of IL-1 α also has a nuclear localization signal and is thought to influence the transcription of

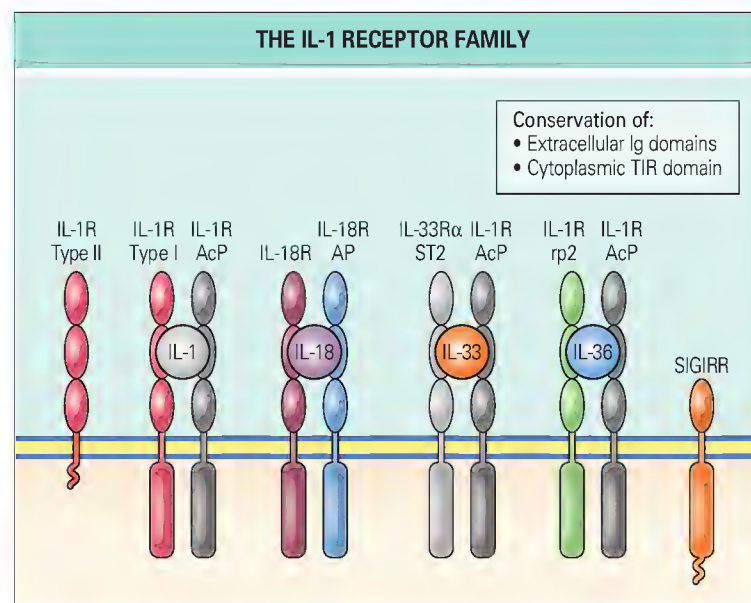


Fig. 13.2 The eight members of the interleukin-1 receptor (IL-1R) family, which bind IL-1 family cytokines, are depicted schematically to illustrate the composition of the heterodimeric receptor bound to its cognate ligand. All but the nonsignaling decoy receptor have cytoplasmic TIR (Toll, IL-1R, plant resistance) domains in addition to extracellular immunoglobulin domains. SIGIRR also has an additional 100 to 150 amino acids C-terminal to the TIR domain. IL-1R accessory protein (AcP) is shared by the receptors IL-1R type I, IL-1Rrp2, and IL-33R.

certain genes.⁸ In general, most of the biology of IL-1 can be rationalized by thinking of it as a coordinator of the early host response to infection or tissue injury. Some of the specific effects of IL-1 on different cell types and organs are listed below.

IL-1 is strongly induced by pathogens via stimulation of TLRs on macrophages and other cell types, and it is strongly induced by tissue damage.^{4,9} IL-1 also induces other inflammatory cytokines such as TNF and IL-6, which themselves coordinate aspects of the host response, as well as small-molecule mediators, including nitric oxide and prostaglandins. In addition, IL-1 induces the synthesis of multiple chemokines (see below), particularly those that attract neutrophils to sites of infection or injury. It also induces adhesion molecules on leukocytes and endothelial cells for the same purpose. Simultaneously, IL-1 promotes the release of neutrophils from bone marrow and enhancement of granulopoiesis. Moreover, IL-1 enhances adaptive immune responses by increasing the potency with which antigen is presented by monocyte/macrophages and dendritic cells (DCs). IL-1 is also a key driver of type 17 helper T (Th17) cell differentiation^{10,11} and can also induce Th2 responses. An *IL1B* polymorphism has a large effect on the severity of periodontitis. It is noteworthy that most poxviruses have a homologue of the inhibitory IL-1R type II (see below), thus suggesting that IL-1 plays a role in control of poxvirus infection. Deletion of the IL-1R2 homologue from vaccinia virus leads to greater pathology in mice.

IL-1 is a strong inducer of acute-phase proteins, either directly or via induction of IL-6. IL-1 also promotes cartilage destruction by inducing the production of aggrecanases and collagenases by chondrocytes and by suppressing the synthesis of new collagen and proteoglycan. In addition, it enhances bone resorption, primarily via induction of receptor activator of nuclear factor- κ B ligand (RANKL).

IL-1 is a key mediator of the injury associated with ischemia and reperfusion, and mouse models demonstrate a significant contribution of IL-1 to atherosclerotic lesion formation.

IL-1 is a potent inducer of fever through stimulation of central nervous system (CNS) prostaglandin synthesis. It also causes loss of appetite, enhancement of slow-wave sleep, decrease in energy expenditure, and social withdrawal, a constellation known as "sickness behavior."¹² Inhibition of IL-1 relieves inflammatory and neuropathic pain in rodent models and reverses morphine tolerance. Some of the effects of IL-1 on pain seem to be mediated via induction of matrix metalloproteinases. Finally, IL-1 also seems to play a role in spatial memory in the hippocampus.

There is evidence linking IL-1 to Alzheimer disease and stroke. In many animal models, IL-1 inhibition reduces infarct size, probably by preventing recruitment of neutrophils and thus decreasing bystander tissue damage.¹³ IL-1 is elevated in brains with Alzheimer disease and induces amyloid

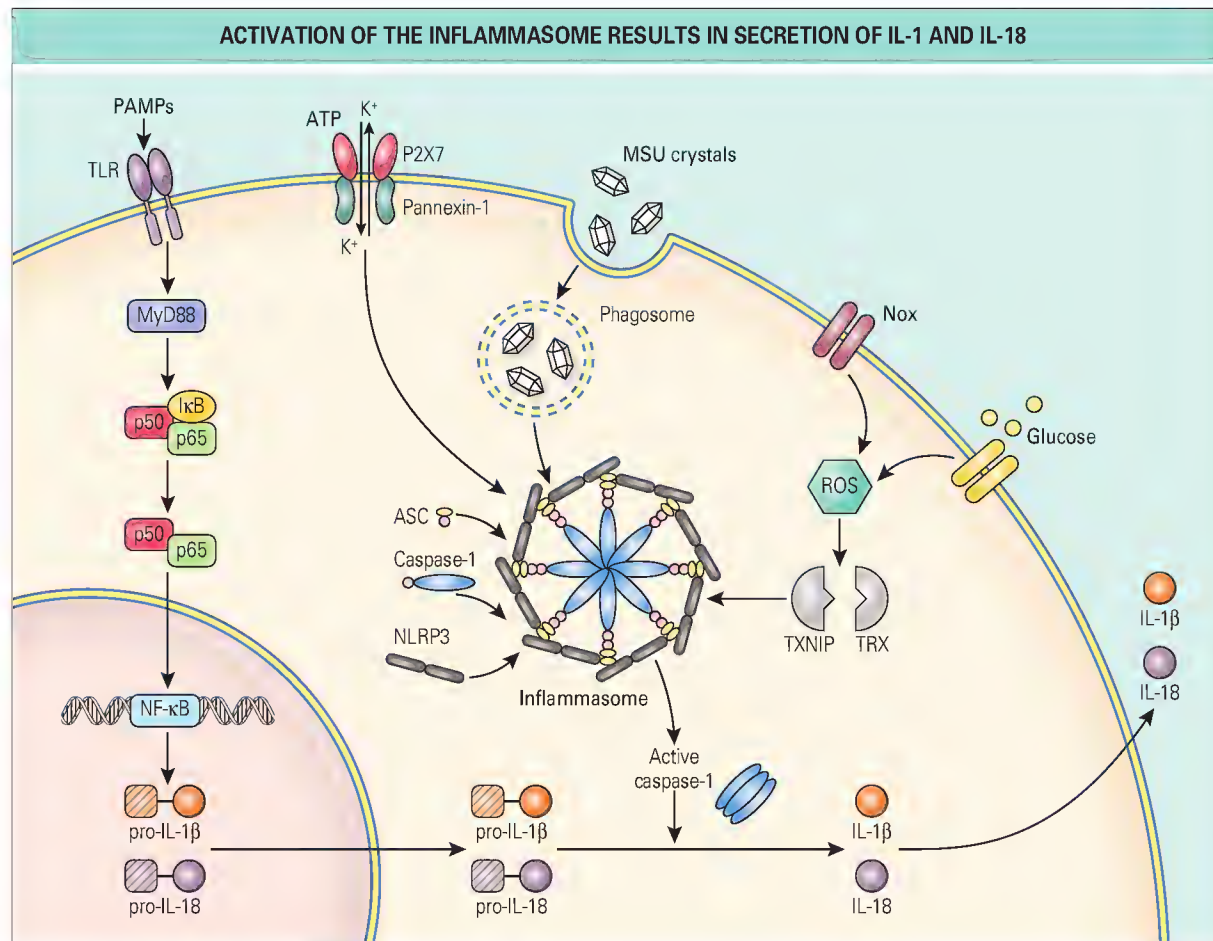


Fig. 13.3 Toll-like receptor stimulation by bacterial products induces the production of pro-interleukin-1 β (pro-IL-1 β) and other cytokines. Diverse endogenous and exogenous products ranging from bacterial, viral, and fungal products to adenosine triphosphate, monosodium urate (MSU) crystals, and elevated glucose concentrations lead to activation of a multiprotein complex known as the inflammasome. The inflammasome, in turn, activates caspase-1, which cleaves pro-IL-1 β to form active IL-1 β and IL-18. Patients carrying mutations in *NLRP3* exhibit augmented active caspase-1 and increased IL-1 secretion. ATP, adenosine triphosphate; I κ B, inhibitor of NF- κ B; IL-1 β , interleukin-1 β ; PAMP, pathogen-associated molecular pattern; RANK, receptor activator of nuclear factor- κ B; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAF, TNF receptor-associated factor; TRX, thioredoxin; TXNIP, thioredoxin-interacting protein.

precursor protein. In addition, amyloid- β is a trigger for the inflammasome and can induce IL-1.¹⁴ Furthermore, polymorphisms in *IL1A* and *IL1B* alter the risk for development of Alzheimer disease.

Several hematologic malignancies (multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia) constitutively secrete IL-1 β , and for early-stage multiple myeloma there is suggestive evidence that IL-1 blockade may reduce the frequency of transition to aggressive disease.

Genetic evidence indicates that polymorphisms in *IL1B* and *IL1RN* affect the risk for and prognosis of gastric, cervical, pancreatic, and breast cancer. The polymorphisms are thought to increase IL-1 β or lower IL-1Ra levels (or both), thereby contributing to cancer risk by promoting inflammation and progression of cancer. These cytokines also induce secretion of IL-8 and vascular endothelial growth factor, which in turn promote angiogenesis.

Negative regulation of IL-1 α and IL-1 β

The actions of IL-1 are tempered by the actions of a critical natural cytokine antagonist, IL-1Ra encoded by the *IL1RN* gene. Mutations in *IL1RN* cause a systemic autoinflammatory disease called deficiency of IL-1Ra (DIRA).¹⁵ A polymorphism in *IL1RN* is also associated with coronary artery disease and restenosis.¹⁶

A recombinant version of IL-1Ra, anakinra, is approved for the treatment of rheumatoid arthritis (RA); however, in most patients the outcome is inferior to that when treated with other biologics such as TNF inhibitors. By contrast, the systemic-onset form of juvenile idiopathic arthritis and its adult counterpart Still's disease respond well to IL-1 inhibition. IL-1 inhibition is highly effective in the treatment of cryopyrinopathies, including NOMID, and has been approved by the Food and Drug Administration (FDA) for these diseases. IL-1 inhibition has also been reported to be effective in treating other autoinflammatory disorders, including Schnitzler syndrome, Behçet disease, hyper-IgD syndrome, PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome, and TNF receptor-associated

periodic syndrome (TRAPS). IL-1 inhibition has likewise shown efficacy in the treatment of gout flares.

IL-1 β has recently been found to play a role in more common diseases not formerly considered inflammatory. IL-1 β is made by the pancreas and at low concentration enhances islet beta-cell survival and proliferation and insulin synthesis. At higher concentrations, which can be induced by elevated glucose, IL-1 β has cytotoxic effects on islet beta cells. Amyloid polypeptide accumulates in the islets in diabetes and is also a potent activator of the NLRP3 inflammasome, which may feed back to accelerate diabetogenesis.¹⁷ Early clinical trials also suggest that IL-1 inhibition may be useful in lowering blood glucose and enhancing pancreatic function in type 2 diabetes.¹⁸ Antagonizing IL-1 is also protective against neointima formation following arterial injury in animal models, and IL-1Ra is being studied for the treatment of stroke as well.

Riloncept is a fusion protein containing the extracellular portions of the two IL-1 receptor components IL-1R and AcP, and it has been approved by the FDA for the treatment of cryopyrinopathies. The fully human monoclonal antibody canakinumab is now also used for treatment of the same set of pathologies, and other antibodies are in various stages of clinical development. In addition, canakinumab is being studied as therapy for atherosclerosis.¹⁹

IL-1R type II is a protein homologous to IL-1R type I that binds IL-1 but does not signal. IL-1R type II serves as a decoy receptor to lure IL-1 away from the signaling-competent IL-1R type I. A splice variant of the IL-1 AcP, termed AcPb, negatively regulates IL-1 responses in the CNS.²⁰ Soluble versions of IL-1R type II and AcP also exist and contributes to negative regulation (in the case of soluble AcP, most likely by competition with full-length AcP for binding to surface IL-1/IL-1R complexes). Mice lacking AcPb suffer greater neurodegeneration following the application of a direct inflammatory stimulus to the brain.

Another negative regulator of IL-1 signaling is a cell-surface receptor called SIGIRR. SIGIRR-deficient mice have increased susceptibility to

infection, asthma, and inflammatory bowel disease (IBD) and enhanced signaling by all IL-1 family members that are known agonists (IL-1 α and IL-1 β , IL-18, IL-33, and IL-1F6, IL-1F8, and IL-1F9).²¹ The ST2 receptor may have similar functions.

IL-18

IL-18 is made primarily by DCs and macrophages. Unlike IL-1 β , there is a constitutive pool of pro-IL-18 in producer cells, so regulation of secretion is determined largely by inflammasome activation rather than by transcription. IL-18 acts to promote Th1 cell activation and enhance the cytotoxic activity of CD8⁺ T cells and natural killer (NK) cells by upregulation of FasL.¹ IL-18 is a strong inducer of inflammatory cytokines, especially IFN- γ (its original name was “interferon- γ -inducing factor”). Typically, IL-18 activity is dramatically enhanced by other cytokines, including IL-2, IL-12, IL-15, IL-21, and IL-23. The main reason for the synergy is that IL-18 and the complementing cytokines mutually induce the other's receptors, which are normally expressed at very low levels. In certain circumstances, IL-18 can also lead to induction of Th2 or Th17 cytokines.

IL-18 is elevated in synovium from RA patients and can have a catabolic effect on cartilage. It both induces and is induced by TNF and IL-1. IL-18 is also elevated in IBD (both Crohn's disease and ulcerative colitis). There is likewise a connection with vascular disease. After either stroke or myocardial infarction, IL-18 levels are elevated and correlate with greater extent of atherosclerotic plaque and worse outcome. Individuals carrying an allele in the *IL18* promoter that leads to less IL-18 production have a lower rate of sudden cardiac death. On the other hand, a condition similar to human metabolic syndrome (insulin resistance, hyperglycemia, altered lipid metabolism, obesity, and atherosclerosis) develops in IL-18 or IL-18R knockout mice (or in IL-18bp transgenic animals). Whether this reflects differences between the biology of IL-18 in mice versus humans or simply a level of complexity greater than we currently understand is not yet clear. IL-18R is necessary in mice for the development of inflammation and emphysema following exposure to cigarette smoke, and levels of IL-18 in the lung are elevated in humans with chronic obstructive pulmonary disease (COPD).

The IL-18 receptor (IL-18R α) and its AcP (IL-18R β) are both members of the IL-1R family. An entirely separate gene product, IL-18 binding protein (IL-18bp), acts as a decoy receptor that attenuates the actions of IL-18. It circulates at serum levels typically 20 to 30 times greater than those of IL-18, which is in sufficient excess to block any IL-18 activity. Analogous to IL-1R type II, poxviruses contain a homologue of IL-18bp, thus suggesting a role of IL-18 in controlling viral infection. IL-18bp has been tested in the clinic for psoriasis and RA with limited success. Whether this is due to its relatively short half-life or to IL-18 not playing a key role in these diseases is not clear. Antibodies to both IL-18 and IL-18R are in development for several indications, including IBD (see Table 13.3).

Recent evidence suggests the possibility of other ligands in the IL-18 system. IL-18R-deficient mice are reportedly resistant to experimental autoimmune encephalomyelitis, a model of multiple sclerosis, whereas IL-18 knockout animals are susceptible. On the other hand, IL-18R knockouts have accelerated rejection of transplants and enhanced cytokine production, whereas IL-18 knockouts have the opposite phenotype. Such data suggest the existence of an additional ligand or ligands that act through IL-18R; more work will be required to clarify this picture.

IL-33

IL-33 (previously known as IL-1F11) is abundant in tissues rather than hematopoietic cells.^{1,22} IL-33 promotes Th2 cell activation and cytokine secretion via a receptor formed by the IL-1R family member IL-33R α (previously called ST2 or IL-1RL1) and the same AcP used by IL-1R. In addition, IL-33 promotes survival, maturation, and activation of various cells, including eosinophils, basophils, and mast cells, in which it promotes degranulation, as well as Th2, NK, and NK T cells. IL-13-producing innate lymphoid tissue in the gut is another important target of IL-33. Notably, IL-33-treated basophils have been shown to suppress arthritic inflammation. IL-33 also acts on endothelial and epithelial cells, in which it induces angiogenesis and the production of other cytokines and chemokines. Interestingly, the prodomain of IL-33 can bind DNA. Pro-IL-33 is localized to the cell nucleus and may serve to affect transcription in endothelial and other cells. It is unclear at present whether processing of full-length IL-33 is required for biologic activity. IL-33 does not possess a signal peptide for secretion, and unlike other IL-1 family members, cleavage by caspase-1 can inactivate IL-33.²³ It is thought that IL-33 acts more like an alarmin because necrotic and damaged cells release it.

A soluble form of IL-33R α is generated by alternative splicing and is capable of inhibiting responses to IL-33. Soluble IL-33R α levels are elevated

in acute asthma attacks as opposed to stable asthma and are higher in individuals with stable asthma than in those without asthma. Polymorphisms of IL33RA are associated with the development and severity of asthma and with eosinophilia. Soluble IL-33R α levels are also elevated following myocardial infarction or during destabilized heart failure and correlate with a poor prognosis. Elevated levels of soluble IL-33R α suggest an attempt by the body, usually unsuccessful, to counteract excessive IL-33 signaling in that disease. In addition to strongly inducing typical Th2 cytokines such as IL-4, IL-5, and IL-13, IL-33 can promote typical Th1 responses such as TNF and IFN- γ production. Accordingly, inhibition of the IL-33/IL-33R pathway is beneficial in mouse models of arthritis.

IL-36 members and IL-36 receptor antagonist

IL-36 has three family members: IL-36 α , IL-36 β , and IL-36 γ (formerly designated IL-1F6, IL-1F8, and IL-1F9, respectively). All these cytokines signal via IL-1Rrp2 (HUGO nomenclature, IL-1RL2) and IL-1RAcP.²⁴ Like IL-1, a receptor antagonist exists and is encoded by the gene *IL36RN* (formerly identified as *IL1F5*). These cytokines are highly expressed in the skin and airways and are involved in diseases such as psoriasis. Homozygous loss of *IL36RN* results in pustular psoriasis, whereas inhibition of IL-36 in human psoriatic skin reduces inflammation.

IL-37 and IL-1F10

IL-37 (also known as IL-1F7) exists in several splice variants, of which IL-1F7 β seems to be the most prominent. IL-37 binds to IL-18R α , albeit with lower affinity than IL-18 does. Despite binding to the same receptor and its capacity to complex with IL-18RAcP, IL-37 does not act as a receptor antagonist for IL-18. IL-37 also translocates to the nucleus and binds SMAD3, thereby regulating gene transcription. The biologic function of IL-37 is to negatively regulate excessive inflammatory response and IL-37 transgenic mice are resistant to lipopolysaccharide (LPS)-induced shock.²⁵ IL-1F10 has been claimed to bind to IL-1R. The structure of IL-1F10 suggests that it may be an antagonist as well, but no functional studies have been conducted. IL-37 is the only family member that does not have a murine ortholog.

Signal transduction

IL-1 signaling is initiated by recruitment of the adapter protein MyD88 to the IL-1R/AcP complex via TIR-TIR domain interactions. MyD88 in turn recruits the kinase IRAK-4, which leads to a chain of protein interactions and complexes that include the molecules IRAK-1 or IRAK-2, TRAF6, TAK1, TAB1, and TAB2. This results in activation of the mitogen-activated protein (MAP) kinases extracellular signal-related kinase (ERK), Jun N-terminal kinase (JNK), and p38 and the transcription factors nuclear factor- κ B (NF- κ B), activator protein 1 (AP-1), and related family members. This results in gene induction and mRNA stabilization.²⁶ Phosphatidylinositol-3'-kinase is also activated and contributes via a complementary pathway to the activation of these same MAP kinases and transcription factors. IL-33 and IL-36 likewise activate NF- κ B and MAP kinases.

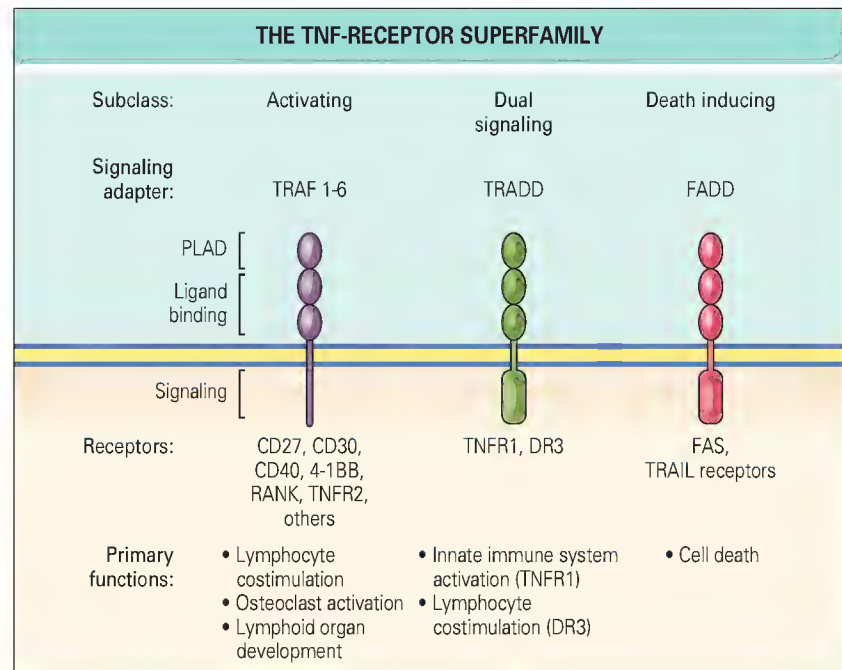
TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY

Ligand and receptor structure

The TNF family of cytokines and their receptors is a structurally related group of molecules that control diverse aspects of cellular function, with a central role in the regulation of both adaptive and innate immune responses (Fig. 13.4; Table 13.1). The seminal observation that antibodies to TNF block endotoxic shock in mice paved the way for investigation of TNF blockade in treating a wide variety of inflammatory conditions, which culminated in the widely successful use of TNF-blocking agents for RA and other rheumatic diseases. These successes validated TNF family cytokines and receptors as therapeutic targets and led to current studies of blocking the action of other members of the TNF superfamily, which are now coming to fruition with a number of agents in late-stage clinical trials (see Table 13.3). With such a large number of cytokines and receptors in this family, translation of knowledge about TNF family cytokines into clinical benefit is only beginning.

All cytokines in the TNF family are synthesized as type II transmembrane proteins. Despite low primary sequence homology, the structures of all TNF family molecules examined to date share a common “ β -jellyroll” structure composed of stacks of β -sheets with variable loops projecting from the core structure that allow specificity of interactions between each TNF family

Fig. 13.4 Receptors that bind cytokines of the tumor necrosis factor (TNF) superfamily are schematically depicted according to their function and the adapter proteins that they bind. Activating receptors induce biologic responses principally through activation of the nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase signaling pathways initiated by the TNF receptor-associated factor (TRAF) family of adapter proteins. Death-inducing receptors exert their effect via activation of caspase-8 through the adapter protein FADD. Dual signaling receptors can activate either cell death or activation through the adapter protein TRADD, which initially interacts with TRAF family proteins. Under certain circumstances, these receptors can interact with FADD in a delayed manner and induce cell death.



molecule and distinct receptors. The basic structure of TNF family cytokines, whether membrane bound or secreted, is a homotrimer stabilized by noncovalent interactions between residues found in the central core of the TNF homology domain. Lymphotoxin is unique in that it can exist as a heterotrimer composed of one lymphotoxin- α (LT- α) and two LT- β subunits. Cleavage by proteases, typically in the metalloproteinase family, produces soluble versions of most TNF family cytokines that can circulate systemically, although serum levels of TNF family cytokines are often relatively low and not good biomarkers of their activity.

TNF receptors also share basic structural similarities. The extracellular domains of all receptors in the TNF family are composed of variable numbers of cysteine repeat domains (CRDs) forming a rodlike structure stabilized by intrachain disulfide bonds. Receptors can have between one and four CRDs, thus allowing a large degree of diversity. The relationship between ligands and receptors in the TNF superfamily is not always 1:1. Rather, many TNF family cytokines bind more than one receptor, such as TNF interacting with TNFR1 and TNFR2, and a few receptors, such as TACI, bind more than one ligand (APRIL and BAFF). In all ligand-receptor crystal structures examined to date, the TNF cytokine homotrimer is interdigitated within the receptor chains such that each chain of the ligand makes contact with two chains of the receptor at points within the second and third CRDs of the receptor. This hexameric structure allows the relatively low affinity of each ligand chain for receptors to be multiplied by the high valency of interactions to result in nanomolar affinities for most TNF family ligands for their receptors. Interestingly, the N-terminal CRD of receptors contains more than one CRD not bound by ligand, which allows this domain to participate in homotypic receptor-receptor interactions or interactions between TNF receptors and both pathogen-derived and mammalian molecules outside the TNF family. These interactions can serve as mediators for entry of pathogens and also modulate TNFR function.²⁷

TNF family receptor signaling

Unlike some cytokine receptors, TNFRs possess no intrinsic kinase activity, nor do they stably recruit kinases to their cytoplasmic tails. Instead, TNFRs signal through the ordered recruitment of a series of signaling complexes that determine the outcome of engagement by their cognate TNF family cytokine ligands.²⁸ Oligomerization of receptors and downstream signaling proteins is critical for efficient signaling by TNF family receptors, and a number of mechanisms regulate oligomerization of TNF family members.

The majority of TNF family receptors signal through the recruitment of multifunctional adapter proteins termed “TNF receptor-associated factors” [TRAFs]. TRAF proteins bind to short consensus sequences in the intracellular tails of the receptors, with the sequence PXQXT (in which X is any amino acid) preferentially recruiting TRAF proteins 1, 2, 3, and 5 and the sequence QXPXEX preferentially recruiting TRAF6. TRAF proteins are mushroom-shaped homotrimers held together by a coiled-coil “stalk”

domain. Each lobe of the TRAF trimer binds one TRAF interaction motif in the receptor, which results in a hexameric structure that mirrors the TNF-TNFR complex on the outside of the cell. TRAF6 also interacts with TLRs and IL-1R family members, thus explaining the more severe phenotype in individuals with TRAF6 deficiency. A ring finger domain in the N-termini of TRAF2 to TRAF6 allows these proteins to nucleate the assembly of a complex containing the molecules cIAP-1 and cIAP-2, which also contain ring finger domains.²⁹ These ring domains act as E3 ubiquitin ligases and catalyze the addition of K63-linked ubiquitin to many of the components in this signaling complex, including the kinase RIP1 (receptor-interacting protein kinase 1). RIP1 has multiple functions in TNFR1 signaling, such as mediating activation of the NF- κ B and p38 MAP kinase signaling pathways, as well as nonapoptotic cell death. Small molecules have been developed that potently alter signal transduction by inactivating some of these molecules. SMAC mimetics, which mimic a short peptide motif that can bind IAP proteins, induce ubiquitin-dependent degradation of IAPs, a process that potentiates the cell death induced by TNF through TNFR1.^{30,31} Small molecules termed necrostatins bind to RIP1 and inhibit its kinase activity, thereby blocking the ability of RIP1 to induce cell death.³²

Six TNF family receptors (Fas, TNFR1, TRAIL receptors 1 and 2, DR3, and EDAR) are termed “death receptors” because of their ability to trigger programmed cell death. The death domain in the cytoplasmic tail of these receptors confers this ability, although the efficiency of the cell death induced by these receptors depends on the particular adapter proteins recruited to this domain. The death domain forms a globular structure made up of a knot of six α -helices with multiple protein-protein interaction surfaces. Fas and TRAIL receptors recruit the adapter protein FADD through interactions between the death domains present in both proteins. FADD also contains a structurally related domain termed a “death effector domain” (DED) that mediates the recruitment of two proteases, caspase-8 and caspase-10, through tandem DEDs at their N-termini. Caspases are cysteinyl proteases defined by their ability to cleave proteins after aspartate residues based on specific tetrapeptide motifs. Caspases can cleave substrates that initiate inflammation or cell death, and when activated in the signaling complex of TNFRs, caspase-8 and caspase-10 act as initiator caspases in a cascade of protease activation that amplifies the receptor signal and thereby results in efficient death of cells within a few hours after receptor ligation by TNF ligands or agonistic antibodies.³³

Two TNF family receptors, TNFR1 and DR3, contain a death domain but combine both apoptotic and nonapoptotic signaling through recruitment of the adapter protein TRADD. TRADD contains a death domain that mediates recruitment to the death domains of these receptors. However, rather than a DED, TRADD contains a TRAF recruitment sequence in its N-terminus that allows it to recruit TRAF1 and TRAF2 and secondarily cIAP-1, cIAP-2, and RIP to the primary receptor signaling complex. This signaling complex functions similar to that recruited by the non-death domain-containing members of the TNF receptor family. However, after receptor internalization, TRADD dissociates from the receptor and nucleates a second signaling

TABLE 13.1

Selected human tumor necrosis factor family receptors

Common name(s)	Gene symbol	Chromosomal location	Ligands, TNFSF (number)*	Primary adapter protein	Key functions	Disease and therapeutic associations
Lymph node development						
Lymphotoxin- β receptor (LT β R)	TNFRSF3	12p13	LIGHT (14), LT β (3)	TRAF	Lymphoid organ formation	Blocking antibodies have been used in clinical trials for RA
Receptor activator of nuclear factor- κ B (RANK)	TNFRSF11A	18q22.1	RANKL (11)	TRAF	Lymphoid organ formation, dendritic cell costimulation, osteoclast maturation and activation	Blocking anti-RANKL (denosumab) in trial for cancer-associated bone lesions and osteoporosis. Familial osteolytic lesions associated with activating mutations in RANK
Inflammation						
Tumor necrosis factor receptor 1 (TNFR1), p55, CD120A	TNFRSF1A	12p13.2	TNF- α (2), LT β (1)	TRADD	Mediates TNF-induced inflammation by acting on myeloid cells and nonhematopoietic cells such as hepatocytes (and apoptosis in some cells)	Periodic fever syndrome (TRAPS) associated with heterozygous extracellular mutations. Multiple biologics (anti-TNF, TNFR2Fc) effective for RA, spondyloarthritis, inflammatory bowel disease
Lymphocyte costimulation						
Tumor necrosis factor receptor 2 (TNFR2), p75, CD120b	TNFRSF1B	1p36.3-p36.2	TNF- α (2), LT α (1)	TRADD	CD8+ T-cell costimulation	
OX40, CD134	TNFRSF4	1p36	OX40L (4)	TRAF	T-cell costimulation	Anti-OX40L in trials for asthma and other diseases
CD27	TNFRSF7	12p13	CD27L (7)	TRAF	T-cell costimulation	Blocking anti-CD70 in development for autoimmune and inflammatory diseases
CD30	TNFRSF8	1p36	CD30L (8)	TRAF	? Inhibition of CD8+ T-cell effector function	Agonistic anti-CD30 in trials for cancer immunotherapy
4-1BB, CD137	TNFRSF9	1p36	4-1BBL (9)	TRAF	T-cell costimulation	
Herpes virus entry mediator (HVEM)	TNFRSF14	1p36.3-p36.2	LIGHT (14), herpesviruses	TRAF	T-cell costimulation	
Glucocorticoid-induced TNF receptor (GITR)	TNFRSF18	1p36.3	GITRL (18)	TRAF	T-cell costimulation, marker for CD4+CD25+ Tregs, modulates Treg function	
Death receptor 3 (DR3)	TNFRSF25	1p36.2	TL1A (15)	TRADD	T-cell costimulation, secondary T-cell responses	Blocking antibodies effective in mouse models of autoimmune and allergic diseases
CD40	TNFRSF5	20q12-q13.2	CD40L (5)	TRAF	Costimulation and differentiation of B cells and APCs	Hyper-IgM syndrome associated with CD40L or CD40 mutations. Blocking anti-CD40L used for SLE in trials but associated with thrombosis
TACI	TNFRSF13B	17p11.2	APRIL (13), BAFF (13B)	TRAF	May inhibit some of the prosurvival effects of BAFF-R	Mutations in TACI found in $\approx$ 10% of common variable immunodeficiency
BAFF receptor (BAFF-R)	TNFRSF13C	22q13.1-q13.31	BAFF/BlyS (13B)	TRAF		Anti-BAFF/BlyS monoclonal antibody approved for treatment of SLE
Apoptosis						
Fas, CD95	TNFRSF6	10q24.1	FasL (6)	FADD	Apoptosis (chronically stimulated T cells, B cells, dendritic cells, and others)	Autoimmune lymphoproliferative syndrome associated with heterozygous dominant-interfering mutations
Decoy receptor 3	TNFRSF6B	20q13.3	FasL (6), TL1A (15), LIGHT (14)	NA	Soluble decoy receptor for FasL, LIGHT, and TL1A. May have a role in tumor immune evasion	
Death receptor 4 (DR4), TRAIL receptor 1	TNFRSF10A	8p21	TRAIL (10)	FADD	Mediator of dendritic cell and tumor cell apoptosis	TRAIL and agonistic anti-TRAIL-R antibodies in trials for cancer
Death receptor 5 (DR5)	TNFRSF10B	8p22-p21	TRAIL (10)	FADD	Mediator of dendritic cell and tumor cell apoptosis	TRAIL and agonistic anti-TRAIL-R antibodies in trials for cancer
Decoy receptor 1, TRAIL-R3	TNFRSF10C	8p22-p21	TRAIL (10)	NA	GPI-linked decoy receptor, interferes with TRAIL function	
Decoy receptor 2, TRAIL-R4	TNFRSF10D	8p21	TRAIL (10)	NA	Transmembrane decoy receptor, interferes with TRAIL function	

*The number in parentheses refers to the gene symbol number for the TNF family cytokine ligand; for instance, (6) is for TNFSF6.

APCs, antigen-presenting cells; BlyS, B-lymphocyte stimulator; GPI, glycosylphosphatidylinositol; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TRAF, TNF receptor-associated factor; TRAIL, TNF-related apoptosis-inducing ligand; TRAPS, TNF receptor-associated periodic syndrome; Treg, regulatory T cell.

complex containing FADD and caspase-8. Normally, NF- κ B upregulates antiapoptotic molecules such as c-FLIP, which blocks activation of caspase-8 in “complex 2,” but if NF- κ B is blocked, caspase-8 becomes activated and initiates apoptosis.³⁴

TNF can also kill certain cell types even if caspases are inhibited, and it has recently been discovered that an additional pathway of caspase-independent cell death triggered by TNFR1, termed “necroptosis,” exists and is mediated by the kinase activity of RIP1 and RIP3 proteins, which are normally inactivated by caspase-8.³⁵

This was dramatically confirmed in mice in which RIP3 deficiency completely reversed the developmental and lymphocyte activation defects seen with caspase-8 deficiency.³⁶ Small-molecule agents termed necrostatins block RIP kinase activity and are useful for probing the function of this pathway in human cells.³² When cell death occurs after triggering by TNF in the intact animal is still a subject of active investigation.

Although these signaling pathways are common to the receptor superfamily, a large number of regulatory mechanisms allow each TNF family ligand to perform distinct functions that can be quite specialized. Expression of TNF family ligands and receptors is under tight control to produce highly divergent patterns of expression in and outside cells of the immune system. The subcellular localization and cleavage of TNF family ligands are also regulated, and both TNF family ligands and receptors can be cleaved by proteases to produce soluble forms. Genetically related “decoy receptors” can block signaling by binding to a number of ligands and receptors and may themselves initiate “reverse signaling” on engagement with their receptors. Signaling pathways triggered by other cytokines, environmental factors, or genetic programs allow many TNF family receptors to perform more than one function even in the same cell type, for example, switching from inducing cell death to inducing protection from cell death. Not surprisingly, a number of pathogens have evolved proteins that modulate signaling through TNF receptors in a number of interesting ways. Studies of knockout mice and blocking of agonistic agents that affect the function of specific TNF-TNFR interactions, as well as genetic diseases stemming from mutations in genes coding for TNF cytokines and their receptors, have provided a wealth of knowledge about the functions of TNF family cytokines in the intact immune system.

TNF receptor family members and their actions

TNF cytokines can be categorized into subgroups according to their function. The LT- β receptor (LT β R) and RANK share the property of being important for the development of lymphoid structures in the spleen and lymph nodes. Secondary lymphoid structures such as lymph nodes, the white pulp of the spleen, and Peyer patches are induced by the seeding of tissue with specialized bone marrow-derived cells termed lymphoid tissue inducer (LTi) cells. The LT α 1 β 2 heterotrimer produced by LTi cells acts through LT β R on surrounding nonhematopoietic stromal cells to begin this process. In response to lymphotoxin, stromal cells upregulate chemokines and integrins essential for attracting and binding lymphocytes and also secrete RANKL, a TNF family member that in turn can act on LTi cells to enhance expression of lymphotoxin and thereby perpetuate this cycle. This regulatory circuit for lymphoid tissue was discovered through mouse knockout studies, which showed that mice lacking LT- α , LT- β , or LT β R have no lymph nodes, spleen germinal centers, or Peyer patches. Mice lacking RANK or RANKL still have lymph nodes but no spleen DCs or Peyer patches. Lymphotoxin may have distinct functions in the peripheral immune system. LT-LT β R interactions are essential for the ability of DCs to migrate to and proliferate in lymph nodes.^{37,38} Ectopic expression of LT- β promotes “tertiary” lymphoid tissue at sites of inflammation in animal models and a number of disease states.³⁹

TNF acting through TNFR1 is a key amplifier of innate inflammatory responses and septic shock. Local injection of TNF produces acute inflammation, and mice deficient in TNF or TNFR1 are defective in innate immune responses to bacteria but resistant to endotoxic shock. In transgenic mice overexpressing TNF, multiorgan inflammatory pathology develops. However, this pathology of TNF in transgenic mice is independent of T and B cells, thus suggesting that once TNF is produced, its actions are primarily on cells of the innate immune system.⁴⁰ In RA, myeloid cells are the probable source of TNF production, but signals from activated T cells are likely to be important in inducing TNF production within the inflamed joint. Abundant evidence from both mouse and human studies has shown that TNF is a key “master cytokine” in the inflammatory cascade. Patients with RA have elevated levels of TNF- α in their synovial fluid,⁴¹ and TNF levels in synovial fluid correlate with bone erosions.⁴² The efficacy of TNF blockade in reducing the inflammatory activity and erosions in RA has borne out these correlations.

A third group of TNF family members mediates costimulation of lymphocytes and other cells of the immune system. Costimulatory signals synergize with T-cell and B-cell receptor signals on lymphocytes and TLR signals on innate immune cells to enhance the functions of these primary stimuli. Germinal center formation and subsequent B-cell class switching are dependent on interactions between CD40L (CD154) on T cells and CD40 on B cells. CD40L costimulation is also important for DC maturation. CD40L-deficient mice or humans lack germinal centers and have severe defects in B-cell responses (hyper-IgM syndrome). BAFF (also known as B-lymphocyte stimulator [BlyS]) derived from DCs is an additional survival and differentiation factor for germinal center B cells expressing the BAFF receptor. BlyS also binds TACI, which provides additional costimulatory signals for B-cell class switching. About 10% of cases of common variable immunodeficiency have been linked to loss-of-function mutations in TACI.^{43,44} Overexpression of BAFF can induce systemic autoimmunity, and BAFF blockade can inhibit disease in animal autoimmune models. Interestingly, unlike most autoimmune disease models, the autoantibody production mediated by BAFF overexpression is independent of T-cell help.⁴⁵ Another group of TNFRs mediates costimulation for T cells. This large group of receptors includes DR3, 4-1 BB, HVEM, GITR, TNFR2, CD30, OX40, CD27, and their cognate ligands. Mice deficient in these receptors are defective in specific aspects of T-cell responses, and GITR and TNFR2 may play a role in counteracting the suppression mediated by regulatory T (Treg) cells. Mice lacking DR3, OX40, and CD27 are resistant to a number of T cell-dependent autoimmune diseases, and preclinical and clinical development is under way for blocking agents aimed at these targets (see Table 13.3).^{46,47}

TNFRs containing death domains that recruit FADD are particularly efficient in triggering programmed cell death. Fas (also known as CD95) triggers programmed cell death in a number of cell types. For T cells, this occurs when activated cells are restimulated through the antigen receptor, which triggers both FasL gene synthesis and increased sensitivity to the apoptotic effect of Fas ligation, a process known as restimulation-induced cell death. *In vivo*, this cellular suicide mechanism acts to limit the expansion of chronically restimulated T cells, such as those that recognize ubiquitous self-antigens. This pathway can also be experimentally triggered through repetitive doses of antigen, which has been shown to eliminate autoreactive T cells in mouse models of multiple sclerosis. The importance of Fas-FasL interactions in maintaining immunologic self-tolerance is illustrated by the development of systemic autoimmune disease in Fas-deficient mice and humans harboring dominant-negative mutations in Fas associated with autoimmune lymphoproliferative syndrome.⁴⁸ The exquisite sensitivity of chronically activated lymphocytes to Fas-mediated apoptosis may allow strategies to specifically eliminate autoreactive lymphocytes through Fas, although systemic administration of anti-Fas antibodies induces hepatocyte apoptosis and significant liver toxicity in animal models. Receptors for the TNF family cytokine TRAIL mediate efficient cell death in tumor cells, but the role of TRAIL in nontransformed cells seems to be much more restricted. CD8+ cells may express TRAIL and undergo TRAIL-mediated autocrine cell death when CD4+ T-cell help is lacking. However, a nonredundant role for TRAIL in the human immune system has not been clearly identified.

Finally, a group of TNF family receptors mediates the development and function of nonimmune cells. The TNFR RANK is expressed on osteoclasts and is essential for osteoclast function, as shown by the osteopetrosis seen in RANK or RANK ligand deficiency in both mice and humans. In experimental arthritis models, RANKL is expressed by activated CD4+ T cells and is important in causing bone erosions. The TNF family receptor EDAR mediates the formation of teeth and sweat glands, and ectodermal dysplasias characterized by impaired formation of these structures result from loss-of-function mutations in EDAR.

TYPE I AND II CYTOKINE RECEPTORS—HEMATOPOIETIN AND INTERFERON RECEPTORS

Cytokines that bind the class of receptors termed the *type I* or *hematopoietic cytokine receptor superfamily* include hormones such as GH and EPO, colony-stimulating factors (CSFs), and many interleukins. Closely related are the IFNs IFN-related cytokines and IL-10 family cytokines, which bind *type II* receptors. The ligands that bind this receptor superfamily are structurally similar and referred to as the α -helical bundle cytokine family. Structurally, type I family receptors have a conserved Trp-Ser-X-Trp-Ser motif (where X indicates any amino acid) in their extracellular domains, a single transmembrane domain, and divergent cytoplasmic domains; nonetheless, they use the same mode of signal transduction⁴⁹ (Fig. 13.5). Some cytokine receptors, such as the EPO and GH receptors, exist as homodimers. However,

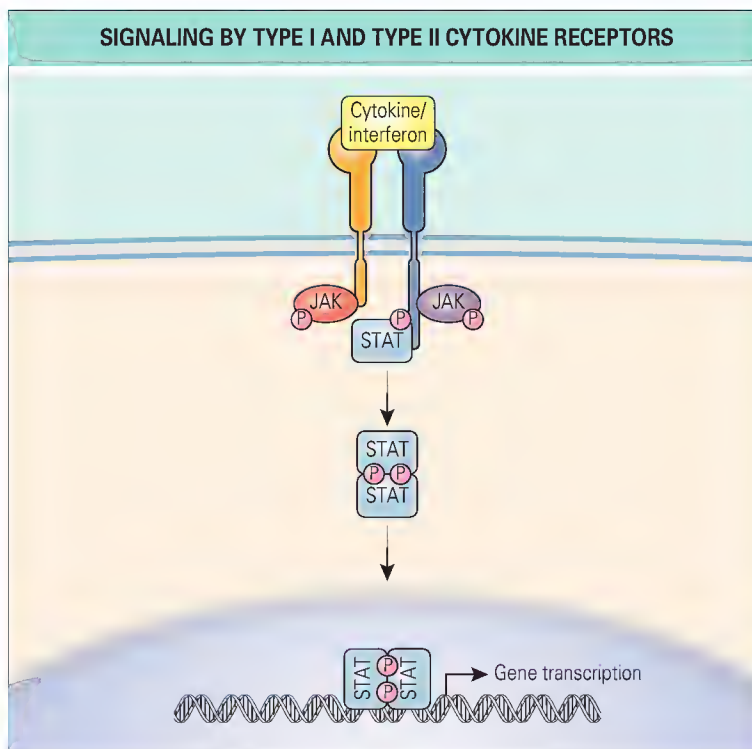


Fig. 13.5 Many cytokines, interleukins, interferons, colony-stimulating factors, and certain hormones bind to type I and II cytokine receptors. These receptors associate with a small family of protein tyrosine kinases known as Janus kinases or JAKs (JAK1, JAK2, JAK3, and TYK2). Cytokine binding activates JAKs, which in turn phosphorylate cytokine receptors so that STAT (signal transducer and activator of transcription) family DNA binding proteins can dock to cytokine receptors and become phosphorylated. Activated STATs dimerize, translocate to the nucleus, and regulate gene expression. A typical heterodimeric receptor is depicted, although some cytokine receptors are homodimers. Mutations in *JAK3* underlie autosomal severe combined immunodeficiency. Mutations in *TYK2* are associated with autosomal recessive hyperimmunoglobulin E syndrome (HIES), whereas mutations in *STAT3* result in autosomal dominant HIES or Job's syndrome. Mutations in *STAT1* are associated atypical mycobacterial infections, and polymorphisms of *STAT4* are linked with susceptibility to systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome.

many cytokines bind receptors that contain two distinct subunits, one of which is often shared by other cytokines. The shared use of receptor subunits is how we will categorize the type I family of receptors (Table 13.2).

Cytokines that use gp130: IL-6 as a prototype

The shared receptor subunit designated glycoprotein 130 (gp130) is a receptor component for a variety of cytokines, including IL-6, IL-11, IL-27, IL-31, leukemia inhibitor factor (LIF), oncostatin M, ciliary neurotrophic factor, and cardiotropin-1. From a rheumatologist's perspective, IL-6 is the most important cytokine in this subfamily.

IL-6R consists of an 80-kDa IL-6 binding protein (α chain) (CD126) and gp130 (CD130). IL-6 is a major proinflammatory cytokine. It induces febrile and acute-phase responses and stimulates the production of fibrinogen, serum amyloid A, haptoglobin, C-reactive protein, and complement proteins. IL-6 decreases the synthesis of albumin and transferrin and induces the production of hepcidin and thereby contributes to pathogenesis of the anemia of chronic disease.⁵⁰ In T cells, IL-6 is an inducer of IL-17 production and Th17 differentiation.⁴⁹ IL-6 is a growth and differentiation factor for B cells and induces immunoglobulin production, including IgA. IL-6 also promotes catabolism, induces insulin resistance, and plays a role in osteoporosis by enhancing osteoclast function.

IL-6 is produced by a wide range of cell types, including T cells, macrophages, adipocytes, and muscle cells. It is induced by other cytokines, including IL-1, TNF, and microbial products. Produced in response to infection, inflammation, and trauma, circulating levels of IL-6 are detectable in serum. Patients with RA, cardiac myxoma, Castleman disease, and other autoimmune diseases have high levels of IL-6 in their sera. Targeting IL-6

with a monoclonal antibody directed against IL-6R (tocilizumab) is efficacious in the treatment of RA, systemic juvenile idiopathic arthritis, and Takayasu arteritis.⁵¹ Other IL-6–blocking antibodies such as siltuximab (a chimeric anti-IL-6) and sirukumab are currently in various phases of clinical experimentation for diseases ranging from cancer to RA to SLE (see Table 13.3). LIF is important for blastocyst implantation and maintenance of stem cell pluripotency in culture. IL-31 is produced by Th2 cells, and overexpression of it results in atopic dermatitis. IL-27 also signals through gp130 but is a heterodimeric cytokine (see below).

Cytokine receptors using the β chain: IL-3, IL-5, and GM-CSF

The cytokines IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) all bind to receptors that share a common β -chain (β_c) receptor subunit (CD131) and also have a ligand-specific α subunit. IL-3 synergizes with other cytokines to stimulate the growth of immature hematopoietic progenitors. In addition, it promotes the survival of macrophages, mast cells, and megakaryocytes. IL-5 promotes the differentiation of eosinophils and thereby contributes to the pathogenesis of allergic disease. GM-CSF promotes myelomonocytic differentiation but also increases the microbicidal activity of myeloid cells. GM-CSF is important for the pathogenesis of Th17 cells in animal models.^{52,53}

Biologics targeting IL-5R (reslizumab) and IL-5 (mepolizumab) itself are being developed for the treatment of asthma, as well as skin and gastrointestinal inflammation (see Table 13.3).

Cytokine receptors using the γ chain: IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21

IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 all bind to receptors that share the common γ_c (CD132) in association with a ligand-specific subunit. Mutation of the gene encoding γ_c causes X-linked severe combined immunodeficiency (X-SCID), which is characterized by lack of T cells and NK cells and poorly functioning B cells.⁵⁴

IL-2R consists of three subunits: α (CD25), β (CD122), and γ . T cells, B cells, and other immune cells have inducible expression of the IL-2R α subunit, which creates a high-affinity receptor for IL-2. IL-2 is produced principally by activated T cells and is a prototypic autocrine T-cell growth factor. It augments the cytolytic activity of T and NK cells and induces IFN- γ secretion. IL-2 is also important for CD8+ memory cells. Interestingly, mutation in the genes encoding IL-2 or IL-2R results in autoimmune and lymphoproliferative disease.⁵⁵ This is thought to be due to impaired expression of the transcription factor FoxP3 and impaired development and function of Treg cells. IL-2 also inhibits IL-17 production. IL-2 contributes to class switching in B cells and activates macrophages. IL-2 is approved for the treatment of renal cell carcinoma and has been used to boost CD4+ T-cell counts in patients infected with human immunodeficiency virus (HIV), but its clinical utility is limited by toxicity, including hepatic dysfunction and vascular leak syndrome. Blocking IL-2 with anti-IL-2R α monoclonal antibodies such as daclizumab and basiliximab is approved for use in patients with allograft rejection, but these antibodies are also being considered for the treatment of multiple sclerosis, uveitis, and ulcerative colitis. Polymorphisms of *IL2* and *IL2RA* are associated with a range of autoimmune diseases.^{56,57}

The β_c and γ_c subunits of IL-2R can bind another cytokine, IL-15. IL-15 is critical for NK-cell development and in the generation of memory T cells. IL-15 is produced by hematopoietic and nonhematopoietic cells, and high levels of IL-15 are associated with several autoimmune diseases. Monoclonal anti-IL-15 antibody was studied for RA, but no studies are ongoing at present.

There are two types of IL-4R: one consisting of IL-4R α and γ_c and a second comprising IL-4R α and IL-13R. The former is predominantly expressed on hematopoietic cells. IL-4 promotes an allergic response and differentiation of naive CD4+ T cells into a subset that produces IL-4 and IL-5.⁵⁸ These cells are denoted as Th2 cells. IL-4 also promotes B-cell proliferation and class switching, particularly to IgG1 and IgE. With GM-CSF, IL-4 is also a growth factor for mast cells and basophils. IL-4 inhibits macrophages and the production of proinflammatory cytokines. IL-4 is made by the Th2 subset of CD4+ T cells, NK1.1 CD4+ T cells, basophils, and mast cells. The second receptor is more broadly expressed; consequently, IL-13 has actions on many different types of cells and can promote fibrosis. A fully human antibody to IL-4R (lebrikizumab) is being tested for the treatment of atopic eczema and asthma.⁵⁹

IL-7R consists of IL-7R α (CD127) in association with γ_c . It is expressed on both immature and mature thymocytes. Humans with mutations in

TABLE 13.2
Characteristics of major cytokine families

Receptor subfamily	Cytokine and receptor	Source	Target	Action
Homodimeric	GH	Pituitary, placental	Diverse tissues	Growth, adipocyte differentiation
	PRL	Pituitary, uterus	Mammary epithelium	Growth, differentiation
	EPO	Kidney, liver	Erythroid precursors	Erythroid differentiation
	TPO	Liver, kidney	Committed stem cells and megakaryocytes	Platelet
	Leptin	Adipocytes	Hypothalamus, thyroid	Satiety, controls metabolic rate
	G-CSF	Many tissues, macrophages, endothelium, fibroblasts	Committed progenitors	Differentiation, activates mature granulocytes
gp130-using cytokines	IL-6	Macrophages, fibroblasts, endothelium, epithelium, T cells, other	Liver, B cells, T cells, thymocytes, myeloid cells, osteoclasts	Acute-phase reactants, proliferation, differentiation costimulation
	IL-11	Stromal cells	Hematopoietic stem cells	Proliferation
	CNTF	Schwann cells	Neuronal	Survival
	LIF	Uterus, macrophage, fibroblasts, endothelium, epithelium, T cells	Embryonic stem cells, neurons, hematopoietic cells	Survival
	OSM	Macrophages, fibroblasts, endothelium, epithelium	Myeloid cells, liver, embryonic stem cells	Differentiation, acute-phase induction
β _c -using cytokines	CT-1	T cells, others, myocardium	Myocardium	Growth
	GM-CSF	T cells, macrophages, endothelium, fibroblasts	Immature and committed myelomonocytic progenitors, macrophages, granulocytes, DCs	Growth, differentiation, survival, activation
	IL-3	T cell	Immature hematopoietic progenitors of multiple lineages	Growth, differentiation, survival
γ _c -using cytokines	IL-5	Th2 cells	Eosinophils, B cells	Proliferation, activation
	IL-2	T cells	T, B, NK cells; macrophages	Proliferation, cytotoxicity, IFN-γ secretion, antibody production
	IL-4	Th2 cells, mast cells	T cells, B cells, macrophages	Proliferation, Th2 differentiation, IgG1 and IgE production, inhibition of cell-mediated immunity
	IL-7	Bone marrow, thymic stromal cells, spleen	Thymocytes, T cells, B cells	Growth, differentiation, survival
	IL-9	Th2 cells	T cells, mast cell precursors	Proliferation
	IL-15, IL-21	Many cells	T cells, especially memory cells, NK cells	Proliferation, survival
Heterodimeric	IL-12, IL-23, IL-27, IL-35	Macrophages, B cells	T cells, NK cells	Th differentiation, proliferation, cytotoxicity
Interferons	IFN-α/β	Macrophages, fibroblasts, other	All NK cells	Antiviral, antiproliferative, increased MHC class I activation
	IFN-γ	Th1 cells, NK cells	Macrophages, endothelium, NK cells	Activation, increased MHC class II expression, increased antigen presentation
IL-10 family	IL-10, IL-22	Th2 cells, other cells	Macrophages	Decreased MHC class II expression, decreased antigen presentation

CNTF, ciliary neurotrophic factor; CT-1, cordiotropin-1; DCs, dendritic cells; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp130, glycoprotein 130; IFN, interferon; IL-6, interleukin-6; LIF, leukemia inhibitor factor; MHC, major histocompatibility complex; NK, natural killer; OSM, oncostatin M; PRL, prolactin; Th2, type 2 helper T cell; TPO, thrombopoietin.

IL-7Rα have SCID characterized by the absence of T (T-B+ SCID).⁶⁰ IL-7 is also important for memory T cells. It is produced by a wide variety of cells, including marrow and thymic stromal cells. TSLP is an IL-7–like cytokine expressed by epithelial cells and keratinocytes. Its receptor is composed of TSLPR and IL-7Rα, which is expressed primarily on monocytes and DCs, as well as on B cells. TSLP seems to promote Th2 differentiation through its effects on DCs. Polymorphisms of *IL7R* are associated with multiple sclerosis.⁶¹

IL-9 synergizes with stem cell factor (SCF) to promote the growth and differentiation of mast cells, potentiates the IgE production induced by IL-4, and promotes mucus production. IL-9 is also secreted by eosinophils and activated Th2 cells. A new subset of helper T cells designated Th9 cells has been identified that selectively produces this cytokine.⁶² These cells also secrete IL-10 but augment inflammatory responses. Conversely, IL-9 inhibits Th1 cytokine production. Anti-IL-9 monoclonal antibody (enokizumab) is being tested for the treatment of asthma.

IL-21 binds to a receptor composed of the IL-21 α and γ chains. IL-21 is produced by Th17 cells and by follicular helper T (T_{fh}) cells. IL-21, along with IL-6 and other cytokines, promotes T_{fh} differentiation. T_{fh} cells are localized to B-cell follicles and promote immunoglobulin class switching and B-cell differentiation into memory cells and plasma cells. IL-21 can also

promote Th17 differentiation. It is highly expressed in SLE and models of autoimmunity.⁶³

Homodimeric receptors

A large number of cytokines that use homodimeric receptors are classic hormones, including the factors GH, PRL, leptin, and granulocyte colony-stimulating factor (G-CSF). EPO is included in this subfamily and is required for erythrocyte growth and development. Similarly, thrombopoietin is required for megakaryocytic development. These recombinant cytokines are commonly used drugs.

Heterodimeric cytokines

A small number of cytokines are structural distinct in that they are heterodimers; this family includes IL-12, IL-23, IL-27, and IL-35. These heterodimers consist of one subunit that is homologous to other cytokines and another that is homologous to cytokine receptors. For instance, IL-12 has two subunits, p35 and p40. IL-12 p35 shares homology with cytokines, whereas p40 resembles IL-6R. Thus, these cytokines can be thought of as a preformed ligand/receptor complex. IL-12R consists of two subunits, IL-12Rβ1 and

IL-12R β 2, which are present on T and NK cells. A major action of IL-12 is to promote the differentiation of naive helper T cells to the Th1 subset, which makes IFN- γ . Humans with IL-12R mutations have blunted immune responses and are susceptible to infections by intracellular pathogens. In contrast, IL-23 is composed of p19 and IL-12 p40, and its receptor consists of IL-12R β 1 paired with IL-23R.⁶⁴ This receptor is expressed on activated T and NK T cells, and IL-23 promotes the production of IL-17. As a result, IL-23 is very important for host defense against extracellular bacteria and in the pathogenesis of autoimmune and autoinflammatory disorders.⁶⁵ DCs and macrophages produce IL-12 and IL-23 in response to occupancy of pattern recognition receptors. Polymorphisms of the gene encoding IL-23R are associated with IBD, spondyloarthritis, and multiple sclerosis.⁶⁶ The human monoclonal antibody ustekinumab targets the p40 subunit shared by IL-12 and IL-23. In the clinic this drug has proved to be very effective for the treatment of psoriasis and psoriatic arthritis. It is also efficacious in the treatment of IBD but, interestingly, not multiple sclerosis.⁶⁷⁻⁶⁹

IL-27 is composed of two subunits designated EB13 and p28. It signals through a receptor composed of gp130 and WSX-1/TCCR (T-cell cytokine receptor), which is expressed on naive CD4+ T cells. IL-27 can promote Th1 differentiation and induce IL-21 production, but it also has critical antiinflammatory properties. An important effect of IL-27 is to induce production of the antiinflammatory cytokine IL-10.⁷⁰ IL-35 is another dimeric cytokine consisting of IL-12 p35 and EB13.⁷¹ It is produced by Treg cells, and Treg cells are also a target of IL-35 activity because it induces the proliferation and production of IL-10 by such cells. The receptors for IL-35 are homodimers and heterodimers of gp130 and IL-12R β 2.⁷² Administration of recombinant IL-35 reduces the incidence of arthritis in mouse models.

Interferons

The type I IFNs include IFN- β , IFN- ω , and IFN- β ; however, there are at least 14 separate IFN- α genes. All these ligands bind to a heterodimeric receptor composed of two subunit, IFNAR1 and IFNAR2, and therefore have similar actions. Discovered more than 50 years ago, the major effect of type I IFNs is their antiviral action: inhibition of viral replication, protein translation, and cellular proliferation.⁷³ They also upregulate major histocompatibility complex (MHC) class I expression, downregulate MHC class II expression, and increase the cytolytic activity of NK cells.

Type I IFNs are produced ubiquitously and induced by viral and bacterial infections. A subset of DCs, plasmacytoid DCs, produce especially high levels of IFNs. Type I IFN is used clinically for the treatment of viral hepatitis and leukemia. IFN- β has also been used as an immunosuppressant in the treatment of multiple sclerosis. The IFN signature of changes in gene expression is now a well-recognized characteristic of SLE, and therapeutic use of type I IFNs has additionally been associated with the appearance of antinuclear antibodies and the development or exacerbation of autoimmune disease. Therapeutic blockade of type I IFNs (e.g., rontalizumab and sifalimumab) is currently being tested in patients with SLE, dermatomyositis, and polymyositis (see Table 13.3). Curiously, though, in other settings such as multiple sclerosis, administration of IFN- β is immunosuppressive. Exactly how IFNs can promote and inhibit autoimmunity is far from clear.

IFN- γ , also known as type II IFN, binds to a dimeric receptor composed of IFN γ R α and IFN γ R β subunits. IFN- γ is a major activator of macrophages, and it enhances their ability to kill microorganisms. It induces nitric oxide and upregulates MHC class II expression. IFN- γ acts on CD4+ T cells to promote Th1 differentiation and inhibit Th2 differentiation. It augments NK and CD8+ T-cell cytolytic activity. In B cells, it promotes switching to IgG2a and IgG3 and inhibits switching to IgG1 and IgE.

IFN- γ is produced primarily by Th1 and NK cells. Humans with mutations in IFN γ R subunits are also susceptible to *Mycobacterium* and *Salmonella* infections.⁷³ Conversely, IFN- γ has been used to treat patients with immunodeficiencies (e.g., chronic granulomatous disease) and disseminated mycobacterial infections. Clinical use of IFN- γ can be associated with the production of autoantibodies and a lupuslike syndrome. A monoclonal anti-IFN- γ antibody, fontolizumab, was tested for RA, but the trial was terminated. Other IFN-like cytokines, including IL-28A, IL-28B, and IL-29 (also designated IFN λ 1, IFN λ 2, and IFN λ 3), have been identified. These molecules appear to be involved in antiviral responses, but their exact functions are less well understood than those of other IFNs.

IL-10 family

IL-10 is a critical immunosuppressive cytokine; mice lacking this cytokine have autoimmunity and IBD. Its receptor consists of two chains, IL-10R1 and IL-10R2, and IL-10 inhibits the production of inflammatory cytokines

and decreases the expression of MHC class II, adhesion molecules, and costimulatory molecules. IL-10 is produced by a wide variety of immune cells and is induced by IL-6, LPS, and TNF. Levels of IL-10 are present in the blood of patients with septic shock and other inflammatory and immune disorders.

IL-22 binds to IL-10R2, but it also uses another receptor, termed IL-22R. It is produced by Th17 cells but is likewise made by nonconventional NK cells (NKp44/46+). It is important for epithelial barrier function and host defense in the gut but also has critical antiinflammatory effects. Moreover, it is involved in the pathogenesis of psoriasis. Other IL-10–related cytokines include IL-19, IL-20, IL-24, and IL-26, but their biologic actions are less well understood and they exhibit considerable sharing of receptors.⁷⁴

Signaling by type I/II cytokine receptors

Type I and II receptors have no intrinsic enzymatic activity but instead are associated with Janus kinases (JAKs), which play a pivotal role in signaling via this family of cytokine receptors (see Chapter 14).⁴⁹ There are four JAKs, JAK1, JAK2, JAK3, and TYK2, and they bind to different cytokine receptor chains. Ligand binding activates the JAKs, and they in turn phosphorylate cytokine receptor subunits on tyrosine residues, thereby allowing the recruitment of signaling molecules. Deficiency of JAK3 results in autosomal recessive SCID with failure to signal by γ_c cytokines, whereas mutation of TYK2 is associated with an autosomal recessive form of hyperimmunoglobulin E syndrome (HIES). JAK2 is important for many cytokines, including EPO, and mutation of JAK2 underlies most cases of polycythemia vera. Polymorphisms of TYK2 and JAK2 are also associated with autoimmune disease. JAK inhibitors, or jakinibs, represent a new class of immunomodulatory drugs.⁷⁵ One JAK inhibitor, tofacitinib, is approved for the treatment of RA in patients with inadequate responses to methotrexate. Tofacitinib is also being studied for IBD and psoriasis. Other jakinibs are in various levels of development and testing (see Table 13.3).⁷⁶

An important class of molecules activated by JAKs is the signal transducer and activator of transcription (STAT) family of DNA binding proteins. Seven mammalian STATs are recognized: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Mutations in STAT1, which is activated by IFNs, results in increased susceptibility to *Salmonella* and *Mycobacterium* infections, as well as autosomal dominant chronic mucocutaneous candidiasis.^{73,77} STAT3 is activated by a variety of cytokines, and mutations in this gene result in an autosomal dominant primary immunodeficiency syndrome referred to as AD-HIES or Job syndrome.⁷⁸ An important aspect of the susceptibility of these patients to infection is the failure to generate Th17 cells. Conversely, polymorphisms of STAT3 are associated with IBD. STAT4 is activated by IL-12, and type I interferons have critical functions in Th1 differentiation; polymorphisms of STAT4 are associated with RA, SLE, and Sjögren syndrome.⁷⁹ STAT6 is activated by IL-4 and IL-13 and is important in Th2-mediated responses. STAT5a and STAT5b are homologous and have overlapping functions. STAT5 is important for the expression of FoxP3, and mice lacking these transcription factors have impaired Treg cell development and autoimmunity. Mutations in STAT5B are associated with impaired responses to GH, immunodeficiency, and autoimmunity.⁷⁶

INTERLEUKIN-17 RECEPTORS

The IL-17R family comprises five receptors, IL-17RA through IL-17RE, which are ubiquitously broadly expressed.⁶⁵ IL-17 family ligands include IL-17A to IL-17F; IL-17E is also called IL-25.

IL-17 (IL-17A) and IL-17F are produced by a subset of CD4+ T cells referred to as Th17 cells.⁸⁰ These cells can be differentiated in different ways by using cocktails of cytokines that include IL-1 β , IL-6, IL-21, and TGF- β . IL-23 appears to have a critical role in regulating the biologic activity of these cells. IL-17 cytokines are also produced by $\gamma\delta$ T cells, CD8+ T cells, invariant NK cells, and LT α cells.⁸¹ IL-17A is important for host defense against gram-negative extracellular bacteria such as *Klebsiella pneumoniae*.⁶⁵ Additionally, though, abundant data point to pathogenic roles of IL-17A in models of immune-mediated disease and in human autoimmune disorders. IL-17A and IL-17F evoke inflammation by inducing the production of G-CSF, GM-CSF, and chemokines. Accordingly, they are important regulators of stress granulopoiesis and recruitment of myeloid cells to sites of inflammation. Given the importance of IL-17 in immune-mediated disease, targeting of IL-17 has attracted a great deal of attention. Ixekizumab and secukinumab, which bind IL-17A, as well as brodalumab, an antagonist of IL-17RA, appear to be effective in psoriasis and are being considered for other disorders, including uveitis, Crohn disease, RA, psoriatic arthritis, and

ankylosing spondylitis (see Table 13.3). Autoantibodies can be produced against IL-17 and other cytokines critical for host defense⁸² and result in increased susceptibility to infection.

IL-17E (IL-25) is produced by Th2 cells and mast cells and evokes an inflammatory response characterized by overproduction of Th2 cytokines, mucus production, epithelial cell hyperplasia, and eosinophilia. IL-25 is essential for elimination of helminthic parasites. IL-17B, IL-17C, and IL-17D are less well studied.

The IL-17 family receptors include a group of five subunits, IL-17RA to IL-17RE. All have single transmembrane domains with large cytoplasmic tails that contain a motif similar to the TIR domain of TLRs. This is referred to as a SEFIR domain. The adapter molecule Act-1 also has a SEFIR domain and binds to IL-17R through a homotypic interaction. In addition, IL-17RA contains a C/EBP β activation domain. Another adapter molecule used by TNF family cytokines, TRAF6, also contributes to IL-17 signaling. Engagement of IL-17R activates MAP kinases and NF- κ B, as well as the generation of C/EBP β and C/EBP δ dimers via the activation of GSK3 β . IL-17 acts synergistically with TNF.

TRANSFORMING GROWTH FACTOR- β RECEPTOR FAMILY CYTOKINES

The TGF- β family consists of more than 40 cytokines, including TGF- β 1, TGF- β 2, and TGF- β 3, bone morphogenic proteins, activins, inhibins, and müllerian inhibiting substance; only TGF- β 1 is discussed here. The receptor for TGF- β 1 is a dimer consisting of two receptor serine-threonine kinases, TGF β R1 and TGF β R2. Functionally, TGF- β inhibits many aspects of lymphocyte function, including T-cell proliferation and cytokine production. TGF- β 1 also induces FoxP3 and promotes differentiation of Treg cells. Accordingly, mice lacking this cytokine or its receptor have overwhelming autoimmune disease. The TGF- β cytokines are expressed as biologically inactive disulfide-linked dimers that require processing to be active. The enzyme furin cleaves TGF- β , and deficiency of furin is associated with systemic autoimmunity. Paradoxically, TGF- β 1 acting with IL-6 induces the proinflammatory cytokine IL-17.⁸¹ Thus, TGF- β 1 has both proinflammatory and antiinflammatory activity. TGF- β cytokines also induce fibrosis and may participate in the pathogenesis of diseases such as systemic sclerosis.

Signaling

On ligand binding, the type II receptor phosphorylates the type I receptor, which allows recruitment of the SMAD family transcription factors SMAD2 and SMAD3. Activated SMADs associate with SMAD4, and the complex translocates to the nucleus to bind promoters of TGF- β -responsive genes. SMADs interact with a variety of other transcription factors, transcriptional coactivators, and transcriptional corepressors. TGF- β also signals via TAK1 (TGF- β -associated kinase-1), which associates with TAB1 (TAK1-associated binding protein), and activates members of the MAP kinase family.

RECEPTOR TYROSINE KINASES

Classic growth factors such as the epidermal growth factor and insulin signal through receptor that are themselves tyrosine kinases and hence are designated receptor tyrosine kinases. Most of the ligands that use these receptors are not classified as cytokines, but some are, including CSF-1 (macrophage colony-stimulating factor [M-CSF]), SCF (c-kit ligand or steel factor), FMS-like tyrosine kinase 3 ligand (FLT3L), and platelet-derived growth factor (PDGF). Structurally, SCF and CSF-1 are similar to the four α -helical cytokines, thus suggesting a common evolutionary ancestor for both groups of cytokines. SCF is widely expressed during embryogenesis and makes stem cells responsive to other CSFs. It is also important for the differentiation of mast cells. FLT3L acts with SCF to induce proliferation of hematopoietic precursors. It is likewise important for the generation of DCs. Gain-of-function mutations in c-kit cause systemic mastocytosis, and mutations resulting in fusion of the *PDGFRA* and *FIP1L1* genes underlie hypereosinophilic syndrome. CSF-1 supports the survival and differentiation of monocytic cells. IL-32 is distinct from CSF-1 but binds the same receptor.

CHEMOKINES

As a collection of functionally integrated but anatomically dispersed populations of hematopoietic cells dedicated to defense of the host, the immune system, like any army, depends absolutely on communication and mobility.

Within the immune system, cell migration is necessary during development, homeostasis, and response to pathogen challenge. Several classes of molecules regulate this migration, among them chemoattractants and their receptors. The largest gene family of chemoattractants is the chemokines (chemotactic cytokines), and it contains more than 40 members.⁸³

Ligand and receptor structure

All the chemokines are small, secreted proteins (molecular weight of approximately 10 kDa), with the exceptions of CX₃CL1 and CXCL16, which are membrane anchored through transmembrane domains, in addition to having soluble forms generated through proteolytic cleavage. Although chemokines are secreted, they become immobilized by binding to glycosaminoglycans on cell surfaces and extracellular matrix, and it is generally thought that the immobilized chemokines are the active forms, sometimes forming fixed gradients for chemotaxis.

Chemokines can be divided on the basis of the arrangement of conserved cysteine residues near the N-termini into CXC, CC, CX₃C, and XC subfamilies, where X is a variable amino acid. The CX₃C and XC subfamilies contain only one and two members, respectively, with all the rest being CXC or CC chemokines. The systematic names for chemokines consist of the subfamily, followed by “L” for ligand and a number, which generally reflects the order of discovery.

Chemokines signal through seven-transmembrane domain G protein-coupled receptors (GPCRs), 19 of which have been identified in humans. The superfamily of GPCRs contains almost 1000 members in humans, including the subfamilies of odorant and taste receptors and receptors for light, neurotransmitters, and catecholamines. Because GPCRs have been successfully targeted by a large number of small-molecule drugs, studies of the chemokine system have always maintained a view to potential therapeutic applications. For further details on chemokines, including discussion of CXCL12, CXCR4, CCR7 and CCR5, see the online supplement.



Signaling

GPCRs are defined by the central feature of their signaling pathway, namely, activation of heterotrimeric G proteins through conformational changes in their cytoplasmic domains that are induced by binding of ligands to their extracellular domains. Heterotrimeric G proteins contain 1 each of 23 different α , 5 β , and 10 γ subunits. Receptor-mediated G-protein activation leads to replacement of G α subunit-bound guanosine diphosphate (GDP) with guanosine triphosphate (GTP) and dissociation of the trimer into G α -GTP and a $\beta\gamma$ dimer. For chemokine receptor-mediated processes (e.g., chemotaxis), the $\beta\gamma$ dimer is the critical activator of downstream signaling proteins, such as phosphatidylinositol-3'-kinase, which ultimately leads to actin polymerization and the formation of lamellipodia at the leading edge and actin-myosin-mediated retraction of the uropod at the trailing edge.¹⁰⁶ The 23 G α subunits fall within four subfamilies, and heterotrimers are grouped similarly, based on their G α components, into the G_i, G_s, G_q, and G_{12/13} subfamilies. All chemokine receptors signal through G_i proteins, which by using pertussis toxin—the specific inhibitor of G_{i/o} subunits—can be shown to be essential for chemotaxis. G_{12/13} proteins have also been implicated in chemotaxis, with activated G_i and G_{12/13} proteins being responsible for creating, respectively, the front-specific and back-specific components of migrating cells.¹⁰⁷

Control of chemokine receptor function also requires limiting the duration of the activating signals, which is achieved through a number of mechanisms. G α subunits have intrinsic GTPase activity, and once GTP is hydrolyzed to GDP, the G α -GDP reassociates with a $\beta\gamma$ dimer to form the “resting” heterotrimer. G α -GTPase activity can be accelerated by GTPase-activating proteins (GAPs), which for the G α subunits are members of the RGS family of proteins.¹⁰⁶ The chemokine receptors themselves are typically desensitized after chemokine binding through the activity of G protein-coupled receptor kinases (GRKs), which phosphorylate serine/threonine residues in the receptors' C-terminal tails. Receptor phosphorylation leads to the recruitment of arrestin proteins, which is typically followed by receptor internalization leading to degradation or recycling of receptors to the cell surface. At the same time that they serve to limit receptor-mediated activation of G proteins, arrestins can also activate additional, G protein-independent signaling pathways.¹⁰⁸

Sphingosine-1-phosphate

Another key pair of proteins that are not within the chemokine system but have an important related function in lymphocyte trafficking through lymphoid organs are sphingosine-1-phosphate and one of its receptors, the

An important aspect of receptor-ligand relationships in the chemokine system is promiscuity. One ligand can often bind to more than a single receptor, and receptors generally bind to more than a single ligand. Nonetheless, a given receptor will bind chemokines only within a single subfamily, a feature that underlies the receptor nomenclature: CXCR1 to CXCR7 and CCR1 to CCR10 are receptors for CXC and the CC chemokines, respectively, whereas CX₃CR1 and XCR1 are the receptors for CX₃CL1 and XCL1, respectively. In addition to receptor-ligand promiscuity, an additional level of complexity is seen in the patterns of expression of receptors on leukocytes. Although some receptors are dominant in controlling migration of a given cell type, such as CXCR1 and CXCR2 on neutrophils and CCR3 on eosinophils, all leukocytes express multiple chemokine receptors, so within a given context, blocking a single receptor may not prevent recruitment of the cells. Finally, a number of chemokine receptor–like proteins, although they bind chemokines, do not produce intracellular signals. These so-called atypical chemokine receptors seems to function as chemokine scavengers and can have critical roles in establishing the spatial distribution of chemokines in tissue.⁸⁴

As discussed below, a number of clinical trials of antagonists of individual chemokine receptors as antiinflammatory drugs have not been encouraging and led to the proposal that “promiscuous” drugs that target multiple receptors need to be developed so that the system’s redundancy can be overcome.⁸⁵ On the other hand, clinical investigations focused on the chemokine system are still in their early stages, particularly given the complexity of the system and the limited understanding of how the system is functioning in disease. It may therefore be premature to abandon the goal of using single-receptor antagonists to treat inflammatory disorders.

It is important to note that chemokines/chemokine receptors are only one component of the molecular system important for leukocyte trafficking, a critical step of which is movement of cells out of postcapillary venules into tissue. Such transendothelial migration has been described in studies using a multistep model of selectin-mediated rolling, followed by activation of a chemoattractant GPCR, integrin-mediated firm arrest, and diapedesis.⁸⁶ Selectins and their ligands are expressed on both leukocytes and endothelial cells, whereas the relevant chemoattractant GPCRs and integrins are expressed on leukocytes with their ligands on endothelial cells—in the case of chemokines, immobilized on the endothelial cell surface. It is generally thought that chemokines also form gradients within tissues up which cells move, and there is some direct evidence for such gradients.⁸⁷

CXCL12 and CXCR4 and immune cell development

A role for chemokines in leukocyte development has best been shown in studies of CXCL12 and its receptor CXCR4, which are unusual in the chemokine system in being highly conserved during evolution.⁸⁸ Cxcl12^{−/−} mice show defective B lymphopoiesis and bone marrow myeloopoiesis.⁸⁹ This presumably reflects the role of CXCL12/CXCR4 in homing and retention of hematopoietic stem cells to appropriate niches within bone marrow.⁹⁰ A CXCR4 antagonist, plerixafor (AMD3100/Mozobil), is now being used clinically to enhance stem cell mobilization for subsequent autologous transplantation in individuals with non-Hodgkin lymphoma or multiple myeloma.

CCR7 and CCR5 and immune anatomy

Roles for chemokines in immune system anatomy and homeostasis are evident in the functions of CCL19 and CCL21 and their receptor CCR7 and in the function of CXCL13 and its receptor CXCR5. CCL19 and CCL21 are expressed on high endothelial venules and in the T-cell zones in lymph nodes and other secondary lymphoid organs, and these chemokines are required for trafficking and positioning of T cells and DCs within secondary lymphoid organs.^{91–93} The counterparts for B cells are CXCL13, which is expressed in B-cell follicles,⁹³ and CXCR5, which is expressed on B cells and on effector/memory T cells that traffic to B-cell follicles, so-called T_{fh}, or follicular helper cells.⁶² Because B cells are critical for the formation of lymphoid organs during development, lymph nodes and Peyer patches in mice lacking CXCR5 are absent or rudimentary.⁹⁴

Other family members

The majority of chemokines and their receptors function in recruiting leukocytes, including myeloid cells, NK cells, and activated/memory lymphocytes, into inflamed tissue sites. Most of these chemokines/receptors do not have roles restricted to specific organs or tissues, but there are exceptions. The chemokine best documented as being specific for a peripheral tissue is CCL25, the ligand for CCR9A/B, which (in addition to a role on thymocytes) has a role in recruiting lymphocytes specifically to the gut and preferentially to the small intestine. Together with the gut-associated integrin $\alpha_4\beta_7$, CCR9 is induced on T cells specifically by DCs from Peyer patches, thereby imprinting activated/memory T cells to home to the bowel.⁹⁵ As a result of these

and related findings, a CCR9 antagonist is currently being investigated in phase 3 trials for the treatment of Crohn disease (ClinicalTrials.gov identifiers NCT01318993 and NCT01316939) following preliminary reports of the drug’s effectiveness in treating this disorder in a phase 2 study.

The major chemokine receptors for recruitment of the principal populations of myeloid “effector” cells are CXCR1 and CXCR2 on neutrophils and CCR2 on monocytes/macrophages. A number of agents have been developed to block CXCR1 or CXCR2 and have been evaluated in clinical trials for diseases with neutrophil-mediated tissue damage, such as COPD, cystic fibrosis, ulcerative colitis, and graft dysfunction following transplantation. Although results from most of these trials have not been published, recent data suggest a beneficial effect of combined CXCR1/CXCR2 blockade following islet cell transplantation.⁹⁶ In another approach, antibody against CXCL8 (IL-8), a ligand for CXCR1 and CXCR2, has been evaluated as a topical therapy for psoriasis (ABCream) and is being marketed in China for that indication.

Based on mouse models, CCR2 and its ligands, particularly CCL2, have been suggested to play important roles in recruiting macrophages and thereby contributing to the pathogenesis of disorders such as multiple sclerosis, atherosclerosis, RA, systemic sclerosis, and lupus nephritis. Both small-molecule antagonists and antibodies to CCR2, as well as agents that block CCL2, have been undergoing clinical evaluation for treating some of these diseases. Although the beneficial effects of these drug candidates are not yet clear, many of the clinical investigations of CCR2/CCL2 blockade are in their early stages.⁹⁷ A recent trial using an anti-CCR2 antibody has shown efficacy in reducing serum C-reactive protein, which suggests a potential beneficial effect on inflammation related to risk for cardiovascular disease.⁹⁸

Effector/memory T cells can express at least 15 different types of chemokine receptors to produce complex, combinatorial patterns. Although the factors and mechanisms regulating chemokine receptor expression during T-cell activation and differentiation have not been studied extensively, it is clear that some receptors are induced as part of defined pathways for commitment to the T-cell lineage. Cells of the three principal effector/memory lineages of human CD4⁺ T cells, Th1, Th2, and Th17, are each wholly contained within the subsets expressing CXCR3, CCR4, or CCR6, respectively. Not surprisingly, then, the CXCR3, CCR4, and CCR6 genes are inducible, respectively, by the transcription factors T-bet, GATA-3, and ROR γ t, which are critical, respectively, for Th1, Th2, and Th17 differentiation. Given the expression of these receptors on subsets of effector/memory helper T cells implicated in a broad range of diseases, they might be considered good drug targets. Although antagonists have been developed for CXCR3 and CCR4, these inhibitors have undergone limited clinical testing for inflammatory disease, with as yet no encouraging results.^{99,100} However, one significant bright spot has been successful trials using an anti-CCR4 antibody to treat CCR4-expressing adult T-cell leukemia-lymphoma.¹⁰¹

The recent description of Th17 cells as a separate lineage has engendered tremendous interest because of the finding that these cells are important mediators of tissue injury in models of autoimmune disease.⁴⁹ Recognition of the relationship between Th17 differentiation and CCR6 have led to studies that demonstrated an essential pathogenic role for CCR6 in mouse models of arthritis, multiple sclerosis, and psoriasis. These data are likely to spur the development and testing of CCR6 antagonists for autoimmune disorders.

One of the most significant clinical outcomes from studies of the chemokine system is related to the use of CCR5 and CXCR4 by HIV-1 as coreceptors, together with CD4, for entry into cells.¹⁰² All clinical isolates of HIV-1 use CCR5 or CXCR4 (or both) as obligate coreceptors. CCR5 is the coreceptor of primary importance because viruses found in an individual early after infection use CCR5 (and not CXCR4), and individuals who are homozygous for an allele encoding a truncated and inactive CCR5 are highly resistant to HIV-1 infection. The latter observations, together with the apparent absence of deleterious consequences in CCR5-null individuals, has led to the development of CCR5 antagonists for use therapeutically to block viral entry in individuals infected with HIV-1. The first of these agents to reach clinical practice has been maraviroc, which has been shown to be effective in reducing viral loads in treatment-experienced individuals with CCR5-using HIV-1.¹⁰³ The availability of maraviroc will probably lead to its evaluation as an antiinflammatory drug; however, its utility for RA has not been demonstrated.¹⁰⁴

Despite the good general health of CCR5-null individuals, it has recently been reported that CCR5 deficiency is a strong risk factor for symptomatic disease in individuals infected with West Nile virus.¹⁰⁵ These data provide the first good evidence in humans supporting the presumption that CCR5 and other inflammation-associated chemokine receptors have roles in host defense, as well as a cautionary note on the use of chemokine receptor antagonists.

■ **TABLE 13.3**
Selected biologics currently in clinical use or clinical development

Name	Target	Type	Phase	Indications
Anakinra	IL-1	Human recombinant IL-1Ra	In clinic	Autoinflammatory syndromes, RA
IL-1 Trap/rilonacept	IL-1	Human IL-1R–Fc (IgG1) fusion protein	In clinic	Autoinflammatory syndromes, RA, gout, JIA
Canakinumab	IL-1β	Human MAb	In clinic	Autoinflammatory syndromes, RA
MABp1	IL-1α	Human Mab	1/2	Cancer, atherosclerosis, RA
Gevokizumab	IL-1β	Humanized MAb	2	RA, types 1 and 2 diabetes, Behçet disease, uveitis, acne, osteoarthritis
LY-2189102	IL-1β	Human MAb	1	Atherosclerosis, RA
Basiliximab	IL-2Rα	Chimeric (mouse/human) MAb	In clinic	Transplantation, uveitis, ulcerative colitis
Reslizumab	IL-5R	Humanized MAb (from rat)	2/3	Asthma, inflammation of skin and gastrointestinal tract
Tocilizumab	IL-6R	Humanized Mab	In clinic	RA, JIA, Castleman disease, ankylosing spondylitis
Clazakizumab	IL-6	Humanized MAb	2	RA, cancer, psoriatic arthritis
Sarilumab	IL-6R	Human MAb	3	RA, ankylosing spondylitis
Sirukumab	IL-6	Human MAb	2	Lupus erythematosus, lupus nephritis, RA
Ustekinumab	IL-12/23 p40	Human Mab	In clinic	Psoriasis, psoriatic arthritis, Crohn disease, sarcoidosis, palmoplantar pustulosis
Anrukinzumab	IL-13	Humanized MAb	2	Ulcerative colitis
Ixekizumab	IL-17	Humanized Mab	3	RA, psoriasis, psoriatic arthritis
Secukinumab	IL-17	Human MAb	3	Psoriasis, psoriatic arthritis, ankylosing spondylitis, RA, Crohn disease, multiple sclerosis, xerophthalmia
GSK-1070806	IL-18	Humanized MAb	1	Inflammatory bowel disease, diabetes mellitus
NNC-114-0005	IL-21	Human MAb	1	RA
SCH-900222	IL-23		2	Plaque psoriasis
Belimumab	BAFF/BlyS	Human MAb	In clinic	Lupus erythematosus
Sifalimumab	IFN-α	Human MAb	2	Lupus, dermatomyositis, polymyositis
Rontalizumab	IFN-α	Humanized MAb	2	Lupus
Denosumab	RANKL	Human MAb	In clinic	Osteoporosis, RA, hypercalcemia of malignancy, cancer
Fresolimumab	TFG-β 1, 2, and 3	Human MAb	2	Systemic sclerosis, renal sclerosis, pulmonary fibrosis, cancer, renal fibrosis, liver fibrosis
Etanercept	TNF-α	TNFR2-Fc (IgG1) fusion protein	In clinic	RA, JRA, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis
Infliximab	TNF-α	Chimeric MAb	In clinic	RA, psoriasis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis
Adalimumab	TNF-α	Human MAb	In clinic	RA, plaque psoriasis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, JIA
Golimumab	TNF-α	Human MAb	In clinic	RA, ankylosing spondylitis, psoriatic arthritis
Pegsunercept	TNF-α	PEGylated TNFR2-Fc (IgG1) fusion protein	2	RA, JRA, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis
Certolizumab	TNF-α	PEGylated Fab' fragment of humanized MAb	3	RA, JRA, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis

BlyS, B-lymphocyte stimulator; IFN-α, interferon-α; IL-1, interleukin-1, IL-1Ra, IL-1 receptor antagonist; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-κB; TGF-β, transforming growth factor-β.

GPCR S1P₁. Sphingosine-1-phosphate and S1P₁ mediate egress of lymphocytes from the thymus and lymph nodes.¹⁰⁹ This is of particular interest given the discovery that an immunosuppressive drug, fingolimod (FTY720), acts as a functional antagonist of S1P₁ *in vivo*.¹⁰⁹ Fingolimod has shown promise in the treatment of relapsing multiple sclerosis.¹¹⁰ Although the beneficial effects may be related to fingolimod's activity in blocking the egress of activated cells from lymph nodes, the drug has also been reported to increase numbers of suppressive Treg cells¹¹¹ and to inhibit Th17 cell differentiation¹¹² in mouse models.

OTHER CYTOKINES

IL-32 is another structurally distinct cytokine. Induced by IL-12 and IL-18, IL-32 activates NF-κB and p38 and enhances production of the other inflammatory cytokines. It is found in rheumatoid synovium. The function of IL-16 and IL-14 are uncertain.

Table 13.3 lists selected biologic agents currently in clinical use or clinical development.

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14

Signal transduction in immune cells

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- Response to environmental changes requires a variety of signaling pathways within the cell.
- The majority of these pathways start at cell surface receptors.
- Signals are commonly passed on via phosphorylation (kinases) or dephosphorylation (phosphatases).
- Several enzymes can be successfully targeted, and drugs blocking enzymes close to the surface are candidates for therapies for rheumatic diseases.

INTRODUCTION

Immune cells constantly survey their milieu and respond to intrinsic and extrinsic stimuli. This surveillance and response occur by a chain reaction of enzyme-mediated signaling events that are initiated when ligands bind specific receptors. The chemical modifications that take place are varied but often consist of the addition or removal of phosphate groups, small proteins (ubiquitin or sumo), or the generation of second messengers (cyclic adenosine monophosphate [cAMP], phospholipids). These intracellular signaling messengers eventually trigger key events such as activation of transcription factors, cytoskeletal changes, or release of preformed granules. This impacts cell shape and motility, metabolism, gene transcription, differentiation, proliferation, and cell death.

Conceptually, understanding signal transduction starts with considering the nature of the ligands and their receptors. Gases, for instance, directly traverse the plasma membrane, exerting their effects in the cytosol and nucleus. Cell-permeant ligands also traverse lipid bilayers and can bind cytosolic or nuclear receptors that function as transcription factors. Many other ligands, however, require interaction with some kind of membrane receptor, because they cannot cross the plasma membrane. For rheumatologists, most relevant ligands fall into this last category; for example, antigens and immune complexes, cytokines, chemokines, and bacterial, viral, and fungal components. To exert their effects, these ligands interact with a cell surface receptor that has a cytosolic component and initiate signal transduction cascades via modification of the cytosolic portion of the receptor.

Some cell-surface receptors have intrinsic catalytic activity, but others that lack enzymatic activity of their own associate with enzymes instead. Adapter molecules bring signaling molecules together, which act in concert to produce diverse responses. In some cases, the response to the engagement of receptors almost immediately changes cell shape or motility. Other receptors can induce cell death programs or the release of preformed mediators, which act in an autocrine or paracrine manner. In still other cases, ligand binding has delayed effects, altering gene expression and inducing cell growth and differentiation. In the latter cases, activation of DNA-binding transcription factors is often critical. All of these events contribute immune responses, and a few examples of each are provided here.

MEMBRANE-PERMEABLE LIGANDS THAT BIND INTRACELLULAR RECEPTORS

Factors that readily cross the plasma membrane represent the simplest conceptual means of modulating cell function. One of the simplest ligands is nitric oxide (NO), a key signaling molecule that regulates vascular tone.

Activated macrophages produce NO through an enzyme called *inducible nitric oxide synthase* (iNOS), a deficiency of which leads to defective cytokine signaling and impaired innate immune cell activation.¹ NO diffuses across cell membranes and activates soluble guanylate cyclase (sGC),² which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). As a soluble second messenger within the cell, cGMP regulates protein kinases, ion channels, and phosphodiesterases, the latter of which serve to inactivate sGC in a negative feedback loop. Phosphodiesterases PDE5, a phosphodiesterase, interrupts this inhibitory feedback loop by converting cGMP back to GTP. Phosphodiesterase inhibitors, therefore, can be used to raise levels of cGMP, which act on cGMP-dependent protein kinase, leading to smooth muscle relaxation and vasodilatation. This provides the rationale for the use of PDE inhibitors in the treatment of pulmonary hypertension. Alternatively, drugs like riociguat activate sGC, and this agent is currently in phase 3 trials for the treatment of persistent or recurrent pulmonary hypertension.

Steroid hormone receptors with ligand-binding, DNA-binding, and transactivation domains

Almost as simple as gases are lipid-soluble ligands which bind to receptors that reside in the cytosol or nucleus. Arguably, for rheumatologists, the most important group of ligands in this category is the class of glucocorticoid hormones that bind nuclear hormone receptors. In addition, the nuclear hormone receptor superfamily includes the peroxisome proliferator-activated receptor (PPAR) and the receptors for vitamin A, vitamin D, estrogen, and thyroid hormone. Retinoid-related orphan receptor γ (ROR γ) is important for differentiation of type 17 helper T cells, but its natural ligands are poorly understood; nonetheless, ROR γ antagonists are being developed for use in autoimmune disease.³ Vitamin A, which binds to other retinoid receptors, inhibits interleukin-17 (IL-17) and upregulates Foxp3, thereby promoting the function of regulatory T cells.⁴ Similarly, the immunomodulatory effects of vitamin D are increasingly recognized, and drugs that target this family of receptors could emerge as important immunomodulatory agents. PPARs display isoform-specific effects on metabolism, cell differentiation and proliferation, and immune responses. These intracellular receptors have ligand-binding, DNA-binding, and transactivation domains and are often associated with coactivators or corepressors. PPAR agonists are widely used in the treatment of hyperglycemia and hyperlipidemia.^{5,6}

The aryl hydrocarbon receptor (AHR) binds a diverse array of exogenous compounds, including endogenous products of tryptophan that are generated by ultraviolet light exposure. AHR can regulate IL-17, IL-22, and Foxp3 expression and thus provides a means by which environmental toxins and ultraviolet light can have immunoregulatory actions^{7,8} and sustain mucosal innate lymphoid cells.

RECEPTORS WITH INTRINSIC ENZYMATIC ACTIVITY

Because most ligands are water soluble and cannot cross the plasma membrane, they must interact with some kind of receptor on the cell surface. Conceptually, the simplest architecture encompasses receptors that themselves are enzymes. These receptors include those that have intrinsic phosphotransferase (kinase), phosphatase, and guanylate cyclase activity.

An intensively studied class of such receptors is the receptor tyrosine kinase (RTK) family. These receptors have a ligand-binding domain outside the cell with a short transmembrane domain followed by a kinase domain on the intracellular portion of the receptor. Examples include receptors

for insulin, epidermal growth factor, vascular endothelial growth factor, platelet-derived growth factor, colony-stimulating factor-1, and stem cell factor (c-KIT).

Ligand binding to RTKs activates their enzymatic activity, and the receptors themselves become phosphorylated at specific sites. These sites are then bound by proteins that specifically recognize phosphotyrosine residues surrounded by specific sequences of amino acids via modules termed *src-homology 2* (SH2) domains. Of the many molecules that have SH2 domains, some are kinases or phosphatases, but others are molecules that lack enzymatic activity and instead serve as adaptor molecules. These adaptor molecules work in concert with enzymes to create platforms for the transmission of signals. For instance, the SH2-containing adaptor Grb2 brings the guanine-nucleotide exchange factor Sos into proximity with membrane-bound Ras, which activates downstream kinases including Raf1 and mitogen-activated protein kinase (MAPK). Inhibitors of p38 MAPK have been studied for the treatment of rheumatoid arthritis but exhibit unacceptable toxicity. In addition, there are data indicating that p38 isoforms can be protective.⁹ RTKs also activate phosphatidylinositol 3'-kinase (PI3-K) and phospholipase C γ (PLC γ); the consequences of activation of these pathways are discussed later.

Transforming growth factor- β (TGF- β) is a critical antiinflammatory cytokine that also promotes fibrosis and has been implicated in the pathogenesis of systemic sclerosis. The architecture of its receptor is similar to that of the RTKs in that it also contains an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular kinase domain. In this case, though, the enzyme has serine/threonine kinase activity.¹⁰ There are many types of bone morphogenetic proteins that also bind receptors of this class. For instance, mutations of activin receptor 1A that activate its kinase activity underlie the disorder fibrodysplasia ossificans progressiva. Critical substrates for the TGF- β /activin receptors are receptor-activated Smads (R-Smads). Upon phosphorylation these cytosolic DNA-binding proteins translocate to the nucleus and activate gene transcription. In addition, two inhibitory Smads (I-Smads) function to negatively regulate TGF- β signaling.

Rather than possessing kinase activity, some receptors have phosphatase activity; that is, they remove phosphate groups from proteins. A large group of receptors include the receptor protein tyrosine phosphatases, which in certain cases remove phosphates that serve an autoinhibitory role. Thus these phosphatases are "activating."¹¹ For instance, CD45, an abundant receptor on the surface of immune cells, is a protein tyrosine phosphatase required for normal signaling in T and B cells; mutations of CD45 result in severe combined immunodeficiency.¹²

RECEPTORS THAT ASSOCIATE WITH ENZYMES

Some receptors without intrinsic enzymatic activity do the next best thing—they associate with enzymes. A large receptor family that associates with a small family of dedicated kinases is discussed first.

Type I/II cytokine receptors

More than 60 cytokines, interleukins, colony-stimulating factors, and hormones bind type I/II cytokine receptors (see Chapter 13). These receptors have extracellular ligand-binding domains and a single transmembrane domain. Their intracellular domain lacks enzymatic activity but instead binds Janus kinases (Jaks)—Jak1, Jak2, Jak3, or Tyk2—which selectively bind different cytokine receptor subunits¹³ (Fig. 14.1).

Upon ligand binding, the Jaks activate each other and phosphorylate the receptor. This provides docking sites for signaling molecules that have SH2 domains, especially signal transducers and activators of transcription (STATs), DNA-binding proteins that are phosphorylated by Jaks. Activated STATs translocate into the nucleus and regulate gene expression. There are seven members of the STAT family that have distinct functions, and genetic variants in STAT genes are associated with immune-mediated disease. The criticality of the Jaks in transmitting cytokine signals is vividly illustrated by genetic evidence; JAK3 mutations cause severe combined immunodeficiency and TYK2 mutations cause a primary immunodeficiency associated with atopic disease. The importance of the Jaks is also evidenced by the clinical utility of Jak inhibitors (jakinibs).¹³ Tofacitinib blocks Jak1, Jak3, and to a lesser extent Jak2. It is approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis in patients with inadequate responses to methotrexate, and European Medicines Agency approval is expected shortly. Other jakinibs are in development and clinical testing and have been approved for other indications. Many adverse effects of

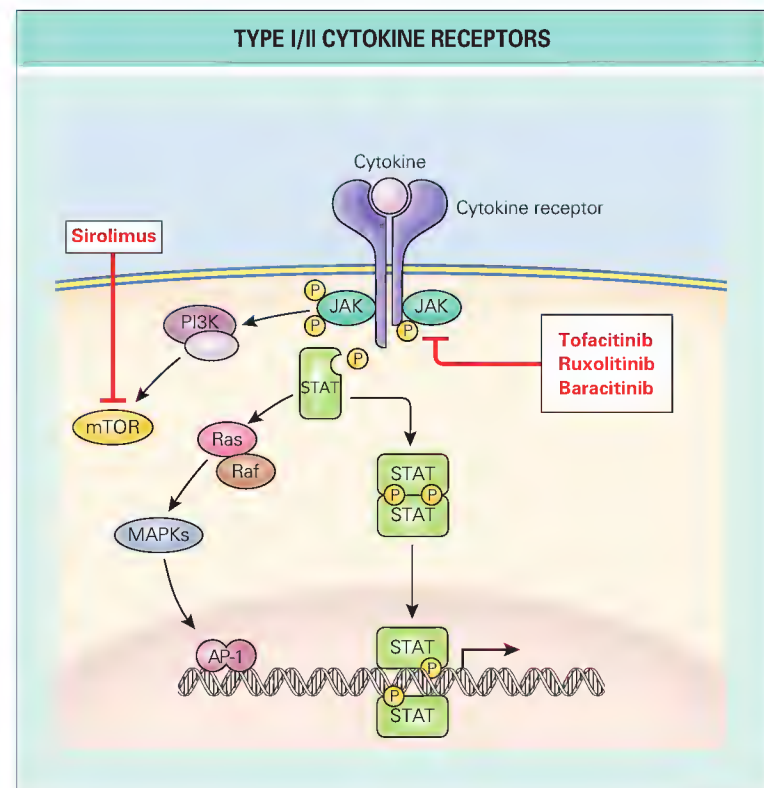


Fig. 14.1 Type I/II Cytokine Receptors. The majority of cytokines bind this class of receptors. Unlike receptor tyrosine kinases, this class of receptor has no enzymatic activity. Instead, the different receptor chains specifically associate with one of four Janus kinases, JAK1, JAK2, JAK3 or TYK2. Upon ligand binding JAKs are activated and phosphorylate the cytokine receptors. This allows binding of various signaling molecules, one important family being the signal transducer and activator of transcription (STAT) family, which comprise STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Activated STATs translocate to the nucleus, bind DNA and regulate gene expression. A new class of immunomodulatory drugs is the Jak inhibitor or jakinib family.

jakinibs, including infection, anemia, leukopenia, and elevation of lipid levels, are directly related to their mechanism of action. Erythropoietin and other colony-stimulating factors signal via Jak2, which helps explain the adverse effects of anemia and leukopenia in patients receiving jakinibs. The elevation of lipid levels is similar to that seen with the IL-6 receptor blocker tocilizumab, which is consistent with the ability of jakinibs to inhibit IL-6 signaling.

As with the RTKs, engagement of cytokine receptors also leads to receptor phosphorylation and recruitment of SH2-containing proteins and activation of the Ras, Raf, and downstream MAPKs, which ultimately lead to activation of AP-1 family transcription factors. Cytokines can also activate PI3-K and mTOR. The mammalian target of rapamycin (mTOR), as its name suggests, is inhibited by the macrolide rapamycin, now licensed for the treatment of graft rejection as the drug sirolimus. Sirolimus and other mTor inhibitors are being tested in autoimmune diseases. Sirolimus does not directly bind mTOR but acts indirectly by associating with FK506-binding protein 12.

Antigen receptors and Fc receptors: the multichain immune recognition receptor family

The antigen receptors for T cells and B cells and the Fc receptor are multimeric receptor complexes. They belong to a family of more than 80 receptors, including killer inhibitor receptors, killer-activating receptors, dectin-1, and costimulatory receptors (CD28, CTLA-4).¹⁴ These receptors do not have intrinsic enzymatic activity, but instead associate with Src family protein tyrosine kinases—a family of at least 10 members that phosphorylate receptor chains and associated proteins. In T cells, the CD4 or CD8 coreceptor binds the major histocompatibility class II or class I molecule, respectively, and associates with the Src kinase Lck.^{15,16} In B cells and myeloid cells, other Src family kinases function as the first-tier activators (Fig. 14.2).

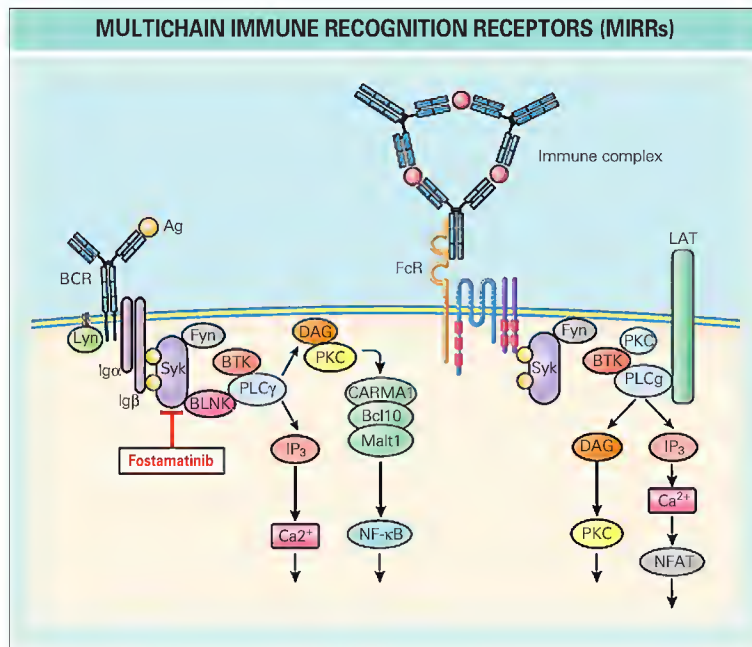


Fig. 14.2 Like the T-cell antigen receptor, the B-cell antigen receptor (BCR) and Fc receptor (FcR) depicted are multichain receptor complexes. Upon engagement by ligands, these receptors are phosphorylated by Src family tyrosine kinases (Lyn and Fyn in the case of BCR and FcR signaling). The phosphorylated receptor is bound by another kinase, Syk. This leads to phosphorylation of adapter molecules, including LAT and SLP-76. This allows the recruitment of a third family of tyrosine kinases, which includes Itk and Btk. Phospholipase Cγ (PLCγ) is activated by these signals, which generates diacylglycerol (DAG) and inositol triphosphate (IP₃). DAG activates protein kinase C (PKC) and IP₃ induces release of intracellular calcium (Ca²⁺) from the endoplasmic reticulum. Release of intracellular Ca²⁺ also induces entry of extracellular Ca²⁺ through calcium channels (CRAC), Orai1, and Stim1. Entry of magnesium ions is also important. Elevated levels of intracellular calcium activate the phosphatase calcineurin, which causes the translocation of nuclear factor of activated T cells (NFAT) to the nucleus. Multichain immune recognition receptors (MIRRs) also activate the phosphatidylinositol 3′ kinase (PI3-K), nuclear factor-κB (NF-κB), and mitogen-activated protein kinase (MAPK) pathways. Sirolimus inhibits mTor (mammalian target of rapamycin), which is downstream of PI3-K, whereas cyclosporine and tacrolimus inhibit calcineurin. Mutations of *ZAP70*, *Orai1*, and *BTK* result in primary immunodeficiency.

The phosphorylated receptor subunits recruit two important kinases, spleen tyrosine kinase (Syk) and Zap70, via SH2 domains. Mutation of *ZAP70* causes severe combined immunodeficiency with characteristic loss of CD8 T cells. Syk is used by the B-cell receptor and Fc receptors (see Fig. 14.2). Fostamatinib inhibits Syk and other kinases and has efficacy in rheumatoid arthritis.^{17,18} Adverse effects of fostamatinib include diarrhea, hypertension, and neutropenia. The basis of hypertension may not be related to effects on Syk, but has been speculated to be an off-target effect due to inhibition of vascular endothelial growth factor receptor, an RTK expressed by endothelial cells.

Receptor-associated tyrosine kinases also phosphorylate adapter molecules termed LAT and SLP-76, which in turn lead to the activation of a number of key downstream pathways. LAT binds multiple GAB2 family members and associated molecules that recruit SOS, the guanine nucleotide exchange factor. When localized to the plasma membrane, SOS is brought in proximity to its substrate RAS, which then triggers the serine threonine kinase Raf1 and MEK. A major pathway activated via LAT and SLP-76 is initiated by activation of PLCγ. This enzyme generates two important products, the transmembrane lipid diacylglycerol (DAG), and inositol triphosphate (IP₃). Production of second-messenger lipids activates yet another family of kinases that contain plextrin-homology domains, structures shared by many signaling and cytoskeletal proteins. In B cells, the key member of this kinase family is Bruton tyrosine kinase (BTK), which is mutated in X-linked agammaglobulinemia. Ibrutinib is a BTK inhibitor that has shown promise in the treatment of B-cell malignancies¹⁹; such inhibitors may also be useful in the treatment of autoimmune diseases.²⁰

Through the generation of DAG, antigen receptor signaling leads to activation of the RAS-RAF/MAPK pathway. DAG also activates serine-threonine kinases of the protein kinase C (PKC) family, of which at least 11 different isozymes exist. In T cells and B cells, activation of PKCθ and PKCγ leads to the phosphorylation and activation of the CARMA1-Bcl10-Malt1 complex.²¹ Together with activated TRAF6 and TAK1, these factors recruit and activate a complex composed of IκB kinase-α (IKKα), IKKβ, and IKKγ (NEMO), which activates nuclear factor-κB (NF-κB), a transcription factor involved in immunity and inflammatory disease.^{22,23} The complex does so by phosphorylating inhibitory proteins (IκBs) that hold NF-κB family members in the cytoplasm. Phosphorylation degrades IκBs, releasing NF-κB members for nuclear translocation. NEMO and IκBα mutations that impair NF-κB activation lead to a spectrum of developmental defects and immunodeficiency.^{24,25}

By activating PLCγ, antigen receptors generate IP₃, which releases calcium from the endoplasmic reticulum. This, in turn, causes plasma membrane channels to allow calcium to enter from outside the cell. Mutations in the PLCγ2 isoform lead to defective antibody production, cold-induced urticaria due to spontaneous mast cell degranulation, and autoinflammation.^{26,27} Calcium release-activated calcium (CRAC) channels are regulated by the products of two genes, *Orai1* and *STIM1*, mutation of which cause primary immunodeficiency and autoimmunity.^{28,29} Elevation of intracellular calcium concentration activates the phosphatase calcineurin, which dephosphorylates the transcription factor nuclear factor of activated T cells (NFAT). Calcineurin inhibition is the mechanism by which cyclosporine A and tacrolimus exert their immunosuppressive effects.

The early events in cell signaling and elevation of intracellular calcium levels lead to actin polymerization, alteration in cell shape, and changes in cell motility. The Wiskott-Aldrich syndrome protein carries out diverse functions involving actin polymerization, and mutations cause immunodeficiency, thrombocytopenia, eczema, and autoimmunity.³⁰ In addition to the role of calcium, the importance of magnesium flux in T-cell activation has recently been recognized: mutations of the magnesium channel *MAGT1* result in CD4 lymphopenia and immunodeficiency.³¹

For T cells, antigen signaling alone is not sufficient to fully activate the cells. CD28 is a critical costimulatory molecule that is activated by its ligands, CD80 and CD86. Such binding induces phosphorylation of CD28 by Lck, leading to activation of PI3-K, protein kinase B, and PLCγ. The immunomodulatory drug abatacept works by blocking CD28-dependent costimulatory signals. Related to CD28 is the molecule CTLA-4, which inhibits T-cell activation. Blockade of the inhibitory signal of CTLA-4 with the drug ipilimumab is used to treat cancers.³² Another important inhibitory receptor is PD-1 (programmed death 1). It is induced in T cells from patients with chronic viral infections, and blockade of PD-1 is useful in the treatment of cancer.³³

PTPN22 is a nonreceptor phosphatase linked to increased risk of various autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes. The risk allele encodes a single amino acid change in the proline-rich SH3-binding domain (R620W), a site that binds the kinase CSK. Details on how this leads to autoimmunity are still under investigation; the mutant allele seems to affect T-cell and B-cell antigen receptor signaling, possibly by regulating Src family kinases. Expression of the risk allele is associated with ineffective negative selection of autoreactive lymphocytes.^{11,34-36}

Tumor necrosis factor receptor superfamily

Tumor necrosis factor (TNF) and related cytokines bind to a family of almost 30 different trimeric receptors (TNFRs), many of which have significance for rheumatologists. Members of this family include TNFR1, FAS, CD40, TNFRSF13C (BAFFR), TNFRSF13B (TACI), osteoprotegerin, and RANK. In the era of biologics, the importance of this family does not have to be emphasized.³⁷ TNFRs do not have enzymatic activity; instead, TNFR family members associate with adapters termed *TNFR-associated factors* (TRAFs) (Fig. 14.3).

These adapters and some TNFRs have a domain called the *TRAF domain*, which allows for homotypic interactions. TNFR1 does not contain a TRAF domain, but, via interaction with TRADD through their mutual death domains, couples to TRAF2 and the serine kinase RIP. Activation of TNFR1 leads to activation of the kinases TAK1 and MEKK3, which activate a second level of kinases. This activates MAPKs and IKK, and subsequently AP-1 and NF-κB.

All TRAFs except TRAF1 also contain a RING domain, which enables them to induce ubiquitination of themselves and of signaling molecules such as TAK1, RIP1, and NEMO. Different forms of ubiquitin direct proteins

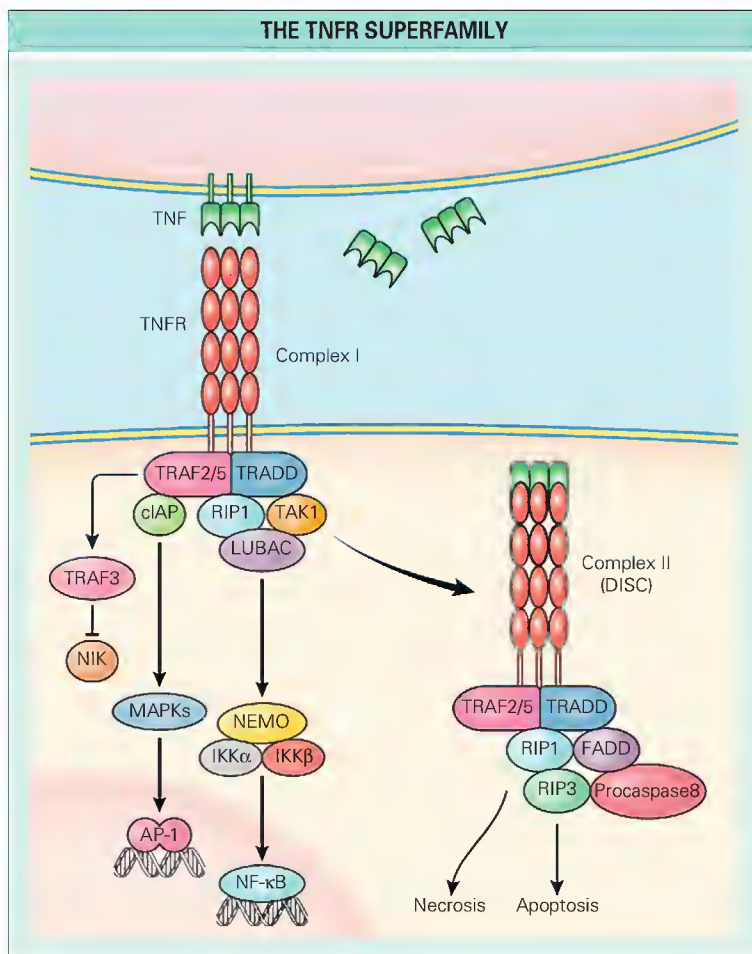


Fig. 14.3 Soluble or membrane-bound ligands cause oligomerization of these tumor necrosis factor receptors (TNFRs), which are associated with adaptor proteins such as TRAFs (TNFR-associated factors) or TRADD (TNFR-associated death domain protein). Association with different adaptors leads to the activation of cell death, developmental, or activating pathways. Various TNFR members signal through the linear ubiquitin assembly chain complex (LUBAC), which leads to linear polyubiquitination of NEMO and RIP1. Activation of TNFR1 leads to recruitment of the kinases TAK1 and MEKK3, which trigger a second level of kinases, mitogen-activated protein kinase (MAPKs) and inhibitor of nuclear factor- κ B kinase (IKKs); this induces the transcriptional activity of AP-1 and nuclear factor- κ B (NF- κ B), respectively. FADD also has a death effector domain (DED) that binds DEDs in cysteine proteases (caspases). Activation of complex II leads to either apoptotic cell death or necrosis. Mutations in *TNFR1*, *HOIP-1* (a LUBAC component), and *IKBK*, which codes for NEMO (or IKK γ), lead to primary immunodeficiency and autoinflammatory disease. cIAP1, cellular inhibitor of apoptosis protein-1.

to various compartments in the cell, such as to the receptor signaling complex following cell stimulation or to the proteasome for degradation. Just as protein ubiquitination is an important aspect of signaling by immune receptors, so is deubiquitination, a process carried out by enzymes known as *deubiquitinases*, which are discussed later.

Another class of adaptors associated with the TNFR family is the inhibitor of apoptosis proteins (cIAP-1, cIAP-2 and XIAP). The cIAPs are E3 ligases that ubiquitinate signaling molecules, including themselves, which leads to the activation of MAPK and NF- κ B. Mutations in the closely related XIAP cause a disorder that mimics Crohn disease, but with additional signs of immunodeficiency.³⁸

Some TNFR family members (TNFR1, FAS, DR3-6) can also recruit a specialized series of proteases to induce cell death.³⁹ Receptors that can induce this death pathway associate with an adaptor called *Fas-associated protein with death domain* (FADD) through a motif termed the *death domain*. FADD also has a death effector domain that binds death effector domains in cysteine proteases (caspases). Activation of the caspase cascade culminates in apoptotic cell death. Mutations of FAS, FASL, and caspase-10 cause autoimmune lymphoproliferative syndrome, which results in the accumulation of B and T cells in lymph nodes due to failure of apoptosis. In addition,

somatic mutations in these proteins have been identified that lead to autoimmune disease.⁴⁰ Release of cytochrome C from mitochondria in response to different forms of cell stress can trigger caspase activation and the intrinsic cell death pathway through the formation of a macromolecular structure called the *apoptosome*.⁴¹

INNATE RECOGNITION OF PATHOGENS

The principal receptors that recognize products of microbial pathogens (pattern recognition receptors) are Toll-like receptors (TLRs), the nucleotide-binding oligomerization domain (NOD)-like family of receptors (NLRs), the RIG-I-like family receptors (RLRs), and C-type lectin receptors (CLRs).⁴²

TLRs are located either on the plasma membrane or intracellular organelles and recognize lipopolysaccharide (TLR4), peptidoglycans and glycolipids (TLR1, TLR2, TLR6), flagellin (TLR5), single-stranded RNA and bacterial DNA (TLR7, TLR9), and double-stranded RNA (TLR3).⁴³ Sensing of these molecular structures occurs via the leucine-rich repeat motif, which is found in a wide variety of signaling molecules including other classes of pattern recognition receptors. Closely related to TLRs is the IL-1 family of receptors, which share a conserved motif known as the *TIR* (Toll/IL-1 receptor) domain. TLRs have no enzymatic activity, but bind adapters including Myd88, TRIF, and Mal, which link the receptors to IL-1 receptor-associated kinases IRAK-1, IRAK-2, and IRAK-4.⁴⁴ By a series of phosphorylation and ubiquitination events similar to those occurring in TNFR signaling, NF- κ B, ERK, JNK, and p38 MAPK are activated. TLR3 and TLR4 can also induce type I interferons via activation of the TBK1 kinase through the activity of TRAF3, which has other important roles in the regulation of signaling.^{45,46}

In humans, the NLR family is composed of 22 members that respond to diverse products, including bacterial and viral products. Other stimuli are damage-associated molecular patterns such as K efflux, adenosine triphosphate, crystals of monosodium urate, cholesterol, and asbestos.⁴⁷ Gain-of-function mutations of NOD2 underlie the granulomatous inflammatory disease Blau syndrome, whereas polymorphisms of this gene are associated with Crohn disease.^{48,49} These receptors contain protein-protein interaction domains such as the caspase recruitment (CARD), pyrin (PYD), NOD,⁵⁰ and leucine-rich repeat domains. NLRs activate the adaptor protein RIP2 (also known as *RICK*), which leads to activation of NF- κ B and the MAPKs. Activation of other NLRs leads to formation of a large heptameric structure called the *inflammasome* (Fig. 14.4).

NLRs that contain a PYD domain interact with ASC (adaptor protein apoptosis speck protein with caspase recruitment), which then links to procaspase-1 through mutual CARD domain interactions. Active caspase-1 converts pro-IL-1 β and pro-IL-18 into their active forms. Mutations in NLRP3 lead to a spectrum of diseases called the *cryopyrin-associated periodic fever syndromes*. Use of anakinra and related IL-1 β -targeting therapies has been extremely useful in controlling symptoms in a majority of patients.⁵¹ Mutations in another pyrin family gene, *MEFV*, underlie the prototypical autoinflammatory disease familial Mediterranean fever.

Intracellular viral RNA is sensed by RLRs, which have CARD domains, central RNA-binding domains, and a C-terminal autoregulatory repressor domain.⁵² Viral RNA induces activation of RLRs and association with the adaptor protein MAVS/IPS-1. Via recruitment of the kinases IKK and TBK1, RLRs activate the transcription factors NF- κ B and IRF3⁵³ and trigger type I interferon production. The proinflammatory response following RLR signaling also involves activation of the caspase-1-dependent inflammasome pathways (described later).^{53,54}

CLRs recognize polysaccharide products of *Mycobacterium tuberculosis*, viruses, and fungi.⁵⁵ Members include Dectin-1, Dectin-2, the dendritic cell-specific ICAM3-grabbing nonintegrin (DC-SIGN), the macrophage mannose receptor, and the circulating mannose-binding lectin (MBL).⁵⁶ Following ligand binding, dendritic cell-bound CLRs induce phagocytosis and antigen presentation. Signaling is triggered either through association with adaptor molecules containing immunoreceptor tyrosine-based activation motif, such as Fc receptor γ chain (FcR γ), or associated kinases (Src, Syk, or Raf1) and phosphatases. Syk induces formation of the CARD9-Bcl10-Malt1 complex, which activates ROS, NF- κ B, and the NLRP3 inflammasome. Mutations of Dectin-1 or MBL cause primary immunodeficiency.⁵⁷

G PROTEIN-COUPLED RECEPTORS

The G protein-coupled receptors (GPCRs) constitute the largest class of receptors in the genome and comprise roughly 350 members divided

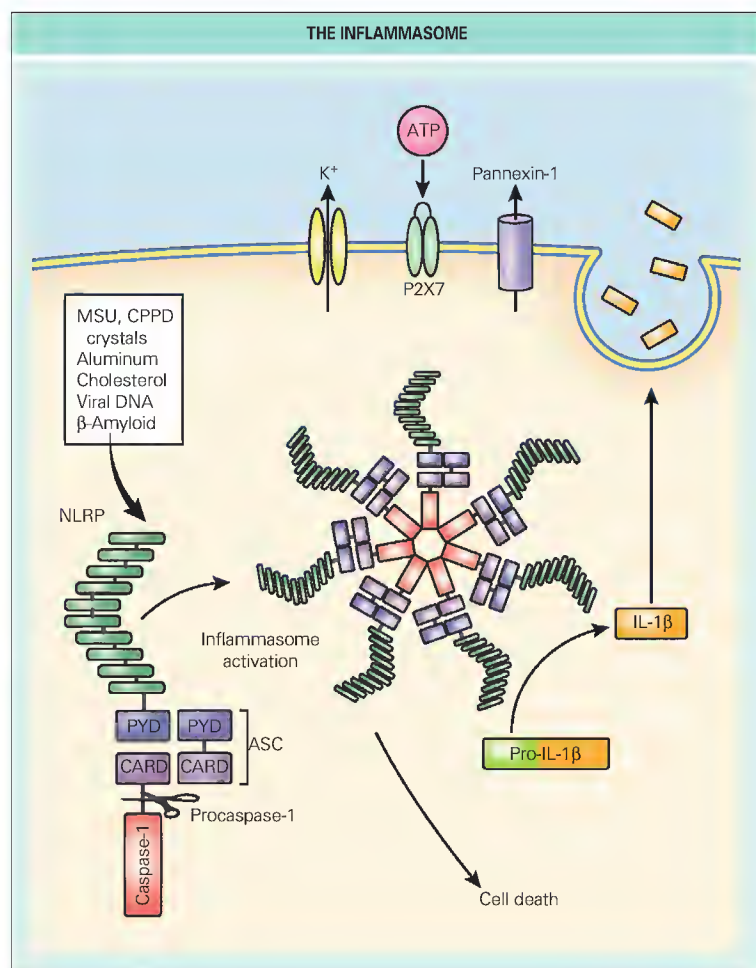


Fig. 14.4 Upon stimulation, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that contain a pyrin domain (PYD) elicit formation of the inflammasome, a large multimolecular complex that serves to process the proinflammatory caspase-1 to its mature form. Triggers of the inflammasome such as extracellular adenosine triphosphate (ATP), released at sites of cellular injury or necrosis, stimulate rapid K^+ efflux from the purinergic P2X7 receptor, triggering recruitment and pore formation by Pannexin-1. Other known triggers are phagocytosed crystals of monosodium urate, cholesterol, and microbial products. Activation of the NLRP leads to homotypic PYD interactions between the NLRP and a bridging protein, ASC. ASC associates with procaspase-1 via mutual CARD domains; this leads to a conformational change and converts procaspase-1 to active caspase-1, which processes immature forms of interleukin-1 β (IL-1 β) and IL-18, leading to their release. Mutations in *NALP3* are associated with susceptibility to the cryopyrin-associated periodic syndromes, which are effectively treated by blockade of IL-1 β . CPPD, calcium pyrophosphate dihydrate; MSU, monosodium urate.

into 19 groups. GPCRs include receptors that sense a variety of signals: light, odor, or taste; neurotransmitters (serotonin, dopamine, glutamate, epinephrine, norepinephrine, and acetylcholine); hormones; lipids (sphingolipids, leukotrienes, prostanoids); and chemokines and related factors.

GPCRs are seven-transmembrane-domain receptors and bind guanine nucleotide-binding proteins, complexes comprising α , β , and γ subunits. Upon activation, the α subunit exchanges guanosine diphosphate for guanosine triphosphate and dissociates from the β and γ subunits, which remain as heterodimers.⁵⁸ Some $G\alpha$ family members produce cAMP through the activation of adenylate cyclase, a 12-transmembrane-domain protein. In turn, cAMP activates protein kinase A (or cAMP-dependent protein kinase), which regulates a variety of enzymes. Recently, a link was made between cAMP generation and the NLRP3 inflammasome.⁵⁹ cAMP binds to NLRP3 directly to inhibit inflammasome assembly, and *in vitro*, downregulation of cAMP using phosphodiesterase inhibitors relieves this inhibition.

Some GPCR subunits activate PLC γ , which cleaves the membrane lipid phosphatidylinositol 4,5-bisphosphate into DAG and IP $_3$. DAG activates PKC and the Ras-Raf-MAPK pathway. In addition to inducing calcium mobilization and lipid phosphorylation, G $\beta\gamma$ dimers activate Rho family G proteins, which regulate actin filament assembly.⁶⁰ Actin filaments play a key role in the trafficking of immune cells and are crucial components of the cytoskeleton. Changes within the cytoskeleton, such as those induced by chemokine receptors, C5a anaphylotoxin, FMLP receptor, or histamine, are critical and are among the most rapid events induced by cell-surface receptors. The receptor for sphingosine-1-phosphate, a signaling lipid molecule present in blood and lymph, is highly expressed on endothelial cells and is important for the egress of lymphocytes from the thymus and lymph nodes.⁶¹ Fingolimod, a drug approved for multiple sclerosis, downmodulates this receptor and thereby interferes with lymphocyte trafficking.⁶²

SUMMARY

The molecular biology revolution and completion of the human genome permitted the development of the biologic therapies, which have revolutionized the practice of rheumatology. These same advances have allowed the discovery of key immunologic receptors and their signaling pathways. The first oral small-molecule inhibitors targeting key nodes in signal transduction such as the jakinibs, Syk inhibitors, and other agents have entered the rheumatologist's armamentarium. These drugs already have considerable impact on the practice of rheumatology. In addition, the discovery of these pathways has provided insight into the immunopathogenesis of autoimmune, autoinflammatory, and immunodeficiency disorders. As we learn more and more about signaling in immune cells, new therapeutic opportunities will emerge along with opportunities for assessment of disease risk, diagnosis, and better disease monitoring. Ideally, these insights will ultimately facilitate long-term remissions and possibly the cure of rheumatic diseases.

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15

Principles of adaptive immunity

■ SERGEI P. ATAMAS

- Cells of the adaptive immune system, T and B lymphocytes, produce large repertoires of T-cell receptors and immunoglobulins using somatic gene recombination.
- In contrast to the innate immune system, the adaptive repertoire of lymphocytes can recognize and eliminate a broad variety of new antigens not previously encountered by the host or the host's species. Clonal selection preserves and expands those lymphocytes whose products prove useful in protecting the host.
- The adaptive immune system has an inherent potential for self-reactivity, or autoimmunity. The potential to induce autoimmunity is usually controlled by a combination of deletional and regulatory mechanisms jointly referred to as *immune self-tolerance*.
- Immune receptor triggering involves the movement of receptors and costimulatory molecules into specialized complexes followed by the assembly of enzymatic cascades within the cells' interior.
- Helper T cells of diverse phenotypes control the functioning of the adaptive immune system.
- All these processes provide targets for therapeutic manipulation in autoimmune diseases.

INTRODUCTION

Most rheumatic diseases are autoimmune in nature or have an autoimmune component. Although the innate immune mechanisms often deliver the immediate damage in rheumatic diseases, the primary defect leading to autoimmunity—failure to maintain tolerance to the body's own tissues—affects the adaptive immune system. The purpose of the immune system is to provide protection against microscopic invaders and their toxic products. As a result of coevolution with pathogens, species acquired innate ability to recognize the pathogen-associated molecular patterns and to fight off the microscopic intruders. Such innate immunity is not strict in specifically identifying the foreign molecules: anything that resembles commonly occurring infections is considered as a sign of a potential problem. Therefore general molecular patterns rather than specific molecules are recognized through the innate pattern recognition receptors (PRRs) (see Chapter 16). Although the innate immune system is very effective at its job, its limitation is that the spectrum of PRRs is shaped solely by the history of host-pathogen interactions. As a result, innate immunity fails in situations in which a new infectious agent appears that has not been previously encountered in the history of the host species. By constantly mutating, pathogens (viruses, bacteria, fungi, and protozoa) generate new molecular patterns that may avoid recognition by the preexisting PRRs. There is a need for a kind of immunity that is able to adapt to whatever unforeseen pathogens attack the host. The adaptive (to the novelty of the future) immune system developed later evolutionarily than the innate immune system, yet they are tightly integrated into a very sophisticated cellular and molecular protective system. The cells of adaptive and innate immunity use a complex spectrum of cell-surface molecules and soluble factors to orchestrate a precisely timed and highly effective protection at the microscopic level.

Both innate and adaptive parts of the immune system must first recognize their targets; this process is commonly referred to as the *cognitive phase*. It is followed by the *effector phase*, during which the immune cells respond to the threat. The cognitive phase defines the central difference between innate

and adaptive immunity. In the innate immune system, the PRRs are rather ubiquitously expressed and are ready to bind pathogen-associated molecular patterns immediately, which leads to instant activation of the effector phase. In contrast, the adaptive recognition system is constructed to identify and respond effectively to myriads of unpredictable new foreign molecules (antigens) without confusing them with the body's own molecules. This process is more complex and less efficient than the functioning of innate immunity, and therefore it is slower. To save time during the subsequent encounters with the newly “learned” antigens, adaptive immunity is capable of retaining specific memory of previous experiences and responds much faster and more effectively the next time a previously encountered antigen threatens the host.

THE ADAPTIVE IMMUNE SYSTEM

Numerous subpopulations of B and T lymphocytes, or B and T cells, compose the adaptive immune system. When precursors (progenitors) of immune cells differentiate and mature into numerous subsets of functional cell types, they differentially express various functional molecules—“clusters of differentiation” (CDs)—on their cell surface. These molecules are often used as markers of immune cell subtypes. For example, CD19 and CD20 are expressed on B cells, whereas CD3 and CD28 are expressed on T cells. Despite phenotypic diversity and functional specialization of lymphocytes, each of them is ultimately defined by its antigen receptor, whereas adaptive immunity as a whole is defined by the vast repertoires of lymphocytes bearing their unique receptors for antigens.

The B cells terminally differentiate into plasma cells, which are the sole source of specialized protective molecules synonymically called *immunoglobulins*, or *antibodies*, or *γ-globulins*. The secreted antibodies mediate the so-called humoral (or fluid-based) immunity. Their goal is to circulate through the body in fluids, or humors, and bind to and neutralize extracellular microbes or any other targets that can be present outside cells. However, some pathogens can evade humoral immunity by hiding in the host's cells as intracellular parasites and thus becoming inaccessible to antibodies. In such cases, cytotoxic T cells will recognize and kill the infected host cells, and thus prevent further spreading of the infection. The innate immune cells (e.g., macrophages that phagocytize and digest microbes) and adaptive immune cells work together to provide molecular protection to the body. Even at this superficial level of analysis, there appears to be a need to integrate and orchestrate the activities of various cell populations in the humoral and cell-mediated branches of immunity. A major population of T cells acts as such a central regulator of immunity. They are CD4+ helper T cells, the principal regulator of the entire immune response, which produce cytokines regulating activities of other types of immune cells.

Clonal selection and expansion of lymphocytes

The adaptive immune system can respond to previously unencountered antigens. A preprogrammed system such as the innate immune system, by definition, cannot be instructed in dealing with the unknown. The adaptive immune system uses the only successful strategy in the face of the unknown—diversification with subsequent selection of useful elements. The more broadly a system is diversified, the more likely the possibility that at least one of the diverse elements will, by random chance, be adaptive in a new, changed environment. Such an adaptive element, no matter how small initially, can be expanded to ensure adaptation of the whole system to the new environment.

Each individual lymphocyte is functionally defined by its antigen-specific receptor, either B-cell receptor (BCR) or T-cell receptor (TCR). On its cell

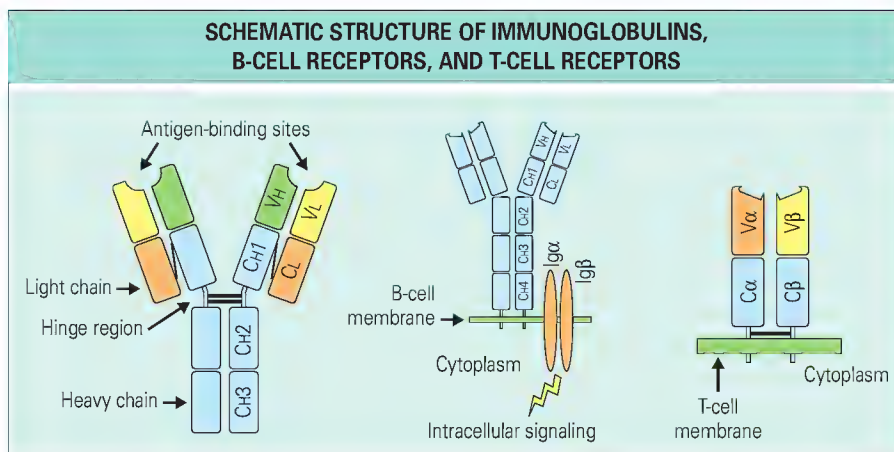


Fig. 15.1 A model of immunoglobulin G (IgG) is shown on the left, a model of surface IgM B-cell receptor is shown in the middle, and a model of T-cell receptor $\alpha\beta$ is shown on the right. Constant (C) and variable (V) domains are indicated, as well as heavy (H) and light (L) chains of immunoglobulins.

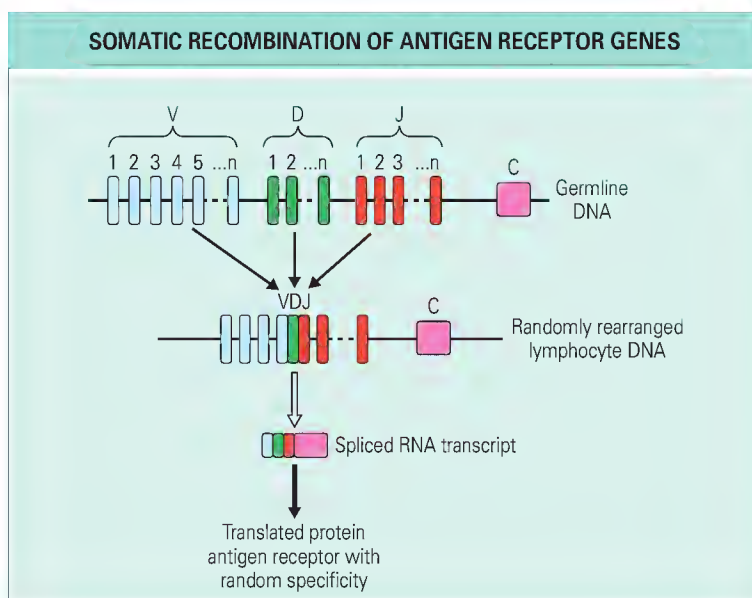


Fig. 15.2 This diagrammatic representation shows features common to B-cell receptor and T-cell receptor genes. Gene recombination randomly joins one of each variable (V), diversity (D), and joining (J) gene segments together to form a variable domain-encoding V-D-J region. Following transcription of this region, as well as the constant (C) gene segments, into pre-messenger RNA, the final messenger RNA transcript is formed by RNA splicing.

surface, each lymphocyte expresses multiple (tens to hundreds of thousands) copies (molecules) of antigen-binding receptor of only one specificity. Slight variations in the structure of antigen receptors among individual lymphocytes lead to a tremendous variability of antigen-binding specificities. It has been estimated that about 10^{11} diverse BCRs can be generated in the bone marrow and 10^{18} diverse TCRs can be produced in the thymus, with about 10^7 BCR and 10^7 TCR specificities present in a human at any given time. Each of the receptors is stochastically generated and has a binding specificity for a random, unpredictable antigen. As a result of the presence of such a broad repertoire of lymphocytes, chances are that no matter what new antigen is encountered by the organism, at least one (or likely more than one) lymphocyte will happen to be responsive to that antigen. In a simplified scenario, binding of an antigen molecule to an antigen receptor stimulates proliferation of the lymphocyte that expresses the receptor. When a lymphocyte proliferates, its offspring inherit the antigen-receptor specificity and thus form an expanding clone (i.e., multiple copies of a lymphocyte with exactly the same specificity). The proliferating lymphocytes also undergo functional activation and eliminate the antigen in the effector phase of the immune response. Thus antigens select their own killers—lymphocytes that are the “fittest” for dealing with these specific antigens—from a vast variety of the preexisting randomly generated repertoire of lymphocytes. Such clonal selection of lymphocyte repertoires by antigens—a kind of cellular Darwinism—is the basis of functioning of the adaptive immune system.

Antigen receptors of lymphocytes

Immunoglobulins can be either membrane bound (acting as the BCRs) or soluble effector molecules (Fig. 15.1). The Y-shaped immunoglobulin molecule consists of four chains: two identical heavy chains and two identical light chains (see Fig. 15.1). There are nine heavy-chain isotypes (α 1, α 2, δ , ϵ , γ 1 to γ 4, and μ) that determine immunoglobulin class and subclass (IgA1, IgA2, IgD, IgE, IgG1 to IgG4, and IgM, respectively) as well as the effector mechanisms that a particular antibody can elicit. Two light-chain isotypes (κ and λ) can associate with any heavy chain. The light chains are folded into a variable and a constant domain, whereas the heavy chains are folded into a variable domain in addition to three (α , γ , and δ) or four (ϵ and μ) constant domains. Mature naive B cells express IgM and IgD with identical variable domains. These cell-surface immunoglobulins are coexpressed with Ig α and Ig β chains, forming together a functional BCR capable of antigen recognition and binding (see Fig. 15.1), which leads to initiation of intracellular signaling and subsequent clonal selection of the antigen-specific B cells.

The TCR is a cell-surface heterodimer composed of α and β chains or, in about 5% of T cells, of γ and δ chains. Each of these chains is folded into two domains, one of which is the variable domain that determines antigen specificity, and the other of which is the constant domain that includes hydrophobic sequences that anchor the receptor to the surface of the T cell (see Fig. 15.1). The TCR associates with four other invariant chains at the cell surface: the CD3 proteins γ , δ , ϵ , and ζ chain. Collectively they are known as the TCR complex. Unlike immunoglobulins, the TCRs cannot bind antigens directly. Instead, the TCR-chain variable domains bind antigen-major histocompatibility complex complexes, as discussed later.

A functionally important structural similarity between BCRs and TCRs is that they have variable domains that function to bind antigens. Within these variable domains are hypervariable regions, also called *complementarity-determining regions*, that define the complementarity of the antigen receptors to antigens in terms of geometric shape and spatial distribution of electric charges and/or hydrophobic patches. Variations of amino acid sequences in these hypervariable regions are the basis for the spectrum of antigen-binding specificities within an adaptive immune repertoire.

Generation of diversity of antigen receptors

A newly generated B cell expresses BCRs and a newly generated T cell expresses TCRs of a unique, randomly generated specificity. These immune repertoires develop in a unique process of somatic chromosomal recombination of gene segments in the antigen receptor loci of DNA. This permanent change to DNA, more specifically referred to as *V(D)J recombination*, occurs only in lymphocytes.¹ The variable regions of antibodies and TCR chains are encoded in DNA by multiple different variable (V), diversity (D), and joining (J) gene segments. During somatic recombination of DNA, select V, D, and J segments are brought together (Fig. 15.2). Depending on the gene (Ig heavy chain, Ig light chain, TCR α , TCR β , TCR γ , TCR δ), the number of V segments can vary from dozens to hundreds, the number of D segments from none to a few, and the number of J segments from a few to dozens. The random V(D)J recombination leads to combinatorial diversity of antigen receptors. This process is subject to complex regulation by numerous factors, including TdT, RAG1, RAG2, Ku70, Ku80, XRCC4, DNA ligase 4, DNA-PKcs, Artemis, and other factors that continue to be vigorously investigated. In addition to the variability produced by combinatorial diversity, even more variability is added by junctional diversity resulting

from imprecise joining of the V, D, and J segments; that is, insertions and deletions that occur during V(D)J gene segment recombination. These mechanisms are operative during lymphocyte maturation. In addition, mature naive B cells, but not T cells, undergo receptor editing, somatic hypermutagenesis, and isotype switching processes that are discussed briefly in the section devoted to B cells.

B CELLS AND HUMORAL IMMUNITY

B-cell development

Maturation of B cells in the bone marrow (Fig. 15.3) occurs under the control of cell-surface molecules and soluble growth factors produced by bone marrow stromal cells,^{2,3} as well as several key transcription factors.^{4,5} Pro-B cells begin rearrangement of the Ig heavy-chain (H) genes and express the pro-BCR. DJ rearrangements begin first, and V to DJ rearrangements follow. Productively rearranged μ chains are expressed on the cell surface with a surrogate light chain and Ig α and Ig β . This pre-BCR induces cell division and the generation of nondividing small pre-B cells. It also suppresses further Ig heavy-chain (H) gene recombination (allelic exclusion) by decreasing RAG expression and appears to make further VH genes less accessible to the recombination machinery. The subsequent rearrangement of the light chain leads to expression of the mature BCR, in which the surrogate light chain in the pre-BCR is replaced by a mature κ or λ chain. Expression of the BCR leads to suppression of further light-chain recombination; however, allelic exclusion at the light chain locus is “leaky,” and about 10% of B cells express two separate light chains. At this stage the lymphocyte becomes an immature B cell expressing surface IgM (BCR), and it is at this stage that induction of immune tolerance occurs. Because the mechanism of generating BCR specificity is intrinsically stochastic, the likelihood is high that many (up to 60%) of the newly generated BCRs will, by a random chance, be reactive against own-body molecules. If the BCR on an immature B cell reacts with own-body molecules (self-antigens), then it should be removed to avoid the development of a self-reactive, autoimmune clone of B cells. Such clonal deletion occurs by apoptosis, but not instantly. First, autoreactive immature B cells become anergic (not able to proliferate in response to stimulation). Then, a unique process called *receptor editing* occurs, in which immunoglobulin rearrangements continue even after assembly of a functional BCR.^{6,7} This mechanism, in contrast to anergy or deletion, spares many autoreactive B cells by replacing their receptor with a new one, possibly one that is not

self-reactive. However, if the new receptor is also self-reactive, such self-reactive B cell becomes apoptotically deleted. Censoring of potentially autoreactive B cells may also take place before the BCR is fully matured, at the level of pre-BCR,⁸ or in the mature naive B cell, to maintain peripheral tolerance.⁹ The process of receptor editing may be either inhibited or accelerated in patients with rheumatic autoimmune diseases. Such impairments contribute to the pathogenesis of autoimmune disorders by promoting the uncontrolled emergence and/or persistence of autoreactive B-cell clones.^{10,11}

Immature B cells that emigrate from the bone marrow are known as *transitional B cells*. The transitional cell pool is homeostatically controlled to maintain mature B-cell numbers. Mature naive B cells express membrane-bound monomeric IgM (as opposed to soluble IgM pentamer) and IgD with identical variable domains. This is accomplished by alternative RNA splicing. These IgM and IgD-coexpressing B cells will survive between 3 and 8 weeks if they successfully enter primary follicles in secondary lymphoid tissues. This is where they will encounter specific antigen. If that happens, the B cell will interact with helper T cells and become activated. Some B cells will proliferate and differentiate directly into immunoglobulin-secreting plasma cells, whereas others will enter into nearby primary follicles. These primary follicles become secondary follicles with germinal centers where large proliferating B cells (centroblasts) undergo somatic hypermutation and class switching before becoming nonproliferating centrocytes. Affinity maturation, in which affinity of antibodies to antigens increases over time, is a phenomenon unique to B cells. The mechanism by which this is achieved is somatic hypermutation, in which additional sequence variation is introduced into the recombined V(D)J sequence. Some activated B cells that have survived the affinity maturation process will home to other secondary lymphoid tissues or bone marrow and differentiate into plasma cells secreting IgG, IgA, or IgE high-affinity antibodies; others will become quiescent, long-lived memory B cells. The immunoglobulin class switching, or isotype switching, upon B-cell stimulation involves recombination of so-called switch regions of DNA that are located upstream of each constant heavy-chain gene segment. This process moves the rearranged VDJ segment closer to the intended constant heavy-chain gene segment by excising the intervening sequence.^{12,13} An enzyme activation-induced deaminase is critical for both somatic hypermutation and isotype switching.^{14,15}

The survival of peripheral B cells depends critically on B-cell activation factor of the tumor necrosis factor family (BAFF), also called BlyS, and a proliferation-inducing ligand (APRIL). Elevated levels of BAFF and APRIL have been associated with autoimmunity. Inhibitors of BAFF and/or APRIL are promising agents for treatment of rheumatic diseases.¹⁶

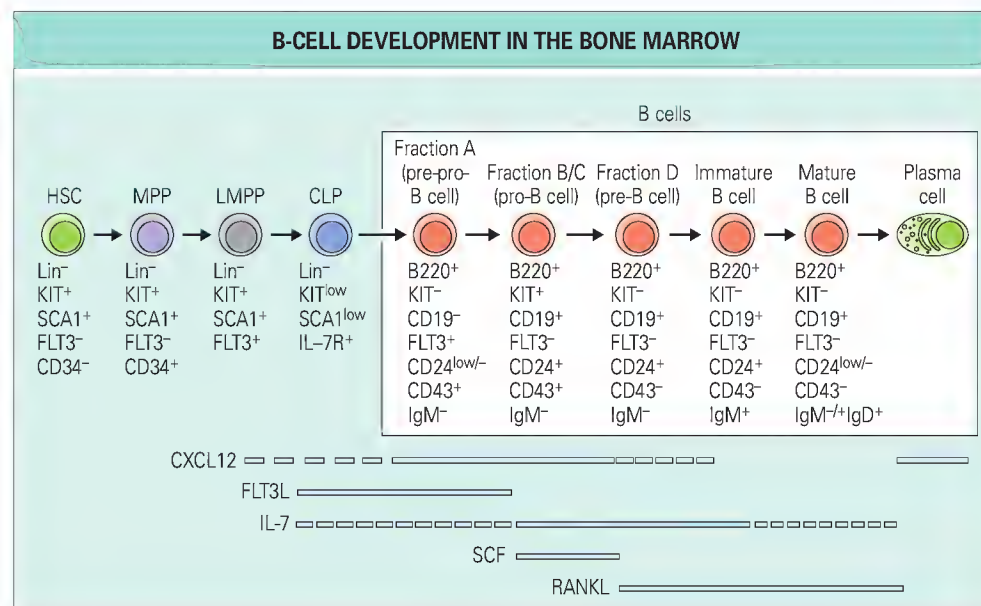


Fig. 15.3 Hematopoietic stem cells (HSCs) differentiate into non-self-renewing hematopoietic multipotential progenitors (MPPs), then into lymphoid-primed multipotential progenitors (LMPPs), and then into common lymphoid progenitors (CLPs). Expression of various markers is shown for each differentiation stage. Immature B cells, which are generated from fraction D cells, exit the bone marrow and reach the spleen, where they mature into peripheral mature B cells and plasma cells. Factors that regulate B-cell development at the indicated stages are shown at the bottom. CD20 is a target for therapeutic monoclonal antibodies (rituximab), which deplete B cells in patients with autoimmune disorders, including rheumatic diseases. This cell-surface molecule is expressed on B cells during the indicated stages of development, as well as on activated and memory B cells, but it is lost during terminal plasma cell differentiation. Ig, immunoglobulin; IL, interleukin. (Adapted by permission from Macmillan Publishers Ltd: Nagasawa T. Microenvironmental niches in the bone marrow required for B-cell development. *Nat Rev Immunol* 2006;6:107-16, copyright 2006.)

B-cell activation and functions

The BCR as well as soluble immunoglobulin can bind both linear and conformational (three-dimensional) epitopes on a wide variety of molecules, including protein, polysaccharide, and lipid antigens. They recognize such antigens directly, without the need for antigens to be presented to them. Certain antigens (thymus-independent antigen) can activate B cells without the need for helper T cells, but many require T-cell help and are thymus dependent.

Upon BCR ligation with antigen, numerous intracellular signaling molecules become activated, such as kinases of the Src family, Syk, and Btk; also, Ca^{2+} mobilization and Ras activation, as well as phosphorylation of $\text{Ig}\alpha$ and $\text{Ig}\beta$ chains, takes place. Activation of a downstream signaling cascade ensues (see Chapter 14), with final activation of a series of transcription factors, resulting in dramatic changes in the pattern of gene expression and in overall B-cell activation.^{17,18} Engagement of the BCR by an antigen is not sufficient by itself to activate a B cell. Instead, the BCR relies on costimulatory receptors to bring about B-cell activation.¹⁹ The costimulatory receptors CD19 and CD21 form a noncovalent complex that is co-ligated with the BCR to promote B-cell activation. Upon phosphorylation, CD19 recruits phosphatidylinositol 3'-kinase, Src family kinases, and Vav to facilitate activation of the mitogen-activated protein kinase pathways and Ca^{2+} mobilization. Negatively regulating coreceptors such as CD22, CD72, and $\text{Fc}\gamma\text{RIIB1}$ inhibit B-cell proliferation and Ca^{2+} mobilization. Thus the activation state of B cells is determined by the integration of stimulatory and inhibitory signaling events. This signaling system is very finely tuned, and disturbances in the signaling/cosignaling may lead to autoimmune activation of B cells that start producing antibodies against the body's own tissue, particularly in rheumatic diseases.

The principal function of B cells is to differentiate into plasma cells and secrete antibodies. When secreted as soluble molecules, antibodies perform various protective effector functions following their binding to pathogens, such as direct neutralization, activation of the complement system or of antibody-dependent cellular cytotoxicity, or opsonization of pathogens for phagocytosis. These are innate immune mechanisms that are discussed in detail in Chapter 16 of this book. In addition, B cells, along with dendritic cells and macrophages, can serve as antigen-presenting cells (APCs) for T lymphocytes (see later). In their capacity as APCs, B cells express cell-surface molecules B7.1 (CD80) and B7.2 (CD86) that bind to CD28 or cytotoxic T-lymphocyte antigen 4 (CTLA-4 or CD152) expressed on T lymphocytes and provide either activating (CD28) or inhibitory (CTLA-4) costimulatory signals (see section on **T-cell activation** later). Resting B cells express low levels of CD86. Their activation leads to expression of CD80 and enhanced expression of CD86. Dysregulated expression of these molecules on B cells has been associated with autoimmune and rheumatic diseases.

T CELLS AND CELL-MEDIATED IMMUNITY

Recognition of antigens by T cells

Unlike immunoglobulins, TCRs cannot bind antigens directly. Instead, antigens for TCRs have to be processed and presented to T cells by a specialized class of molecules called *human leukocyte antigen* (HLA) proteins that are encoded in the major histocompatibility complex (MHC) of genes (Fig. 15.4a). In other words, T cells recognize antigens presented in the context of MHC molecules. The terms *HLA* and *MHC* are often used interchangeably to denote the same genomic region and corresponding protein products in humans. There are two classes of these cell-surface heterodimeric glycoproteins: class I (e.g., HLA-A, HLA-B, and HLA-C) and class II (e.g., HLA-DP, HLA-DQ, and HLA-DR). The class I proteins consist of a three-domain α chain noncovalently complexed with β_2 -microglobulin. They are expressed on the surface of most nucleated cells and bind the CD8 molecule expressed on T cells. The class II molecules consist of an α and a β chain. Each of these two class II chains has a two-domain structure. Class II molecules are constitutively expressed on so-called professional APCs, such as dendritic cells, macrophages, and B cells, but can be induced on other cell types. They bind a T-cell coreceptor, CD4. All the HLA molecules therefore have a four-domain structure with a peptide-binding site formed between the two domains most distal from the cell surface ($\alpha 1$ and $\alpha 2$ for class I and $\alpha 1$ and $\beta 1$ for class II molecules). The peptide-binding groove, lying between two α helices and floored by a β -pleated sheet, shows degenerate binding specificity. Class I molecules bind peptides limited to about 8 to 10 amino acids in length because of the pockets that anchor the peptide at the ends of the binding site. Class II molecules, which are free of this constraint, bind peptides between 13 and 25 amino acids long.

In each individual, each class of MHC is represented by multiple different genes (HLA-A, HLA-B, and HLA-C; HLA-DP, HLA-DQ, and HLA-DR), and each gene is highly polymorphic (having dozens to hundreds of genetic variants in a population). MHC haplotypes (sets of genes inherited from each parent) are codominantly (equally) expressed. As a result of the polygenic and polymorphic nature of the MHC genes, each individual in an outbred population expresses a unique set of MHC proteins. This genetic diversity of the MHC loci defines each individual's unique spectrum of peptides that can be presented to the TCRs.

In contrast to presentation of peptides by MHC molecules, lipid and glycolipid antigens are presented by CD1 molecules. These transmembrane proteins expressed on APCs are homologous to MHC class I molecules and noncovalently paired with β_2 -microglobulin.^{20,21} Five CD1 molecules have been identified in humans (CD1a to CD1e). They present self or foreign lipid antigens such as microbial lipids derived from the cell walls of mycobacteria to $\alpha\beta$ and $\gamma\delta$ T cells (CD1a, CD1b, CD1c) or to natural killer T cells (CD1d).

Processing of antigens for presentation to T cells

The purpose of the MHC class I pathway is to survey for possible intracellular problems such as viral or bacterial infections or malignant transformation and report such problems to CD8+ T cells. In contrast, the purpose of the MHC class II pathway is to survey the overall extracellular environment and to present antigens in it to the central regulating and integrating immune cell type, CD4+ T cells. The mechanisms of these antigen processing pathways differ substantially (Fig. 15.4b and c).

In the class I pathway, a significant proportion of newly synthesized intracellular proteins is degraded by proteasomes, which are multisubunit protein complexes with a number of different proteolytic activities. It is likely that rapid synthesis of viral proteins in the host cells' ribosomes occurs with numerous errors, which leads to accumulation of defective ribosomal products. Such proteins are the major supplier of peptides for the class I pathway.²² Peptides generated by proteasomes are transported by TAP (transporter associated with antigen processing) across the membrane of the endoplasmic reticulum, whereas class I MHC molecules translated by ribosomes at the endoplasmic reticulum membrane are chaperoned by calnexin until they associate with β_2 -microglobulin. Additional chaperones, including calreticulin and tapasin, facilitate peptide loading. The completed MHC-peptide complex is transported through the endoplasmic reticulum and the Golgi apparatus to the cell surface.

Class II MHC molecules present antigens internalized by professional APCs. Protein antigens taken up by phagocytosis, macropinocytosis, endocytosis, and receptor-mediated endocytosis are delivered to an endosomal compartment that contains class II MHC molecules. Peptides are generated from these proteins by proteases that are active in this acidic environment. MHC class II heterodimers, stabilized by their association with the invariant chain (Ii), are targeted to this endocytic compartment through a signal in the cytoplasmic tail of the invariant chain. Once there, the Ii is sequentially digested, so that only a fragment (class II-associated Ii peptide [CLIP]) is left in the peptide-binding site. HLA-DM and HLA-DO (also encoded in the MHC class II region) then catalyze the exchange of CLIP for antigenic peptides, after which the antigen-loaded MHC class II molecules are transferred to the cell surface.

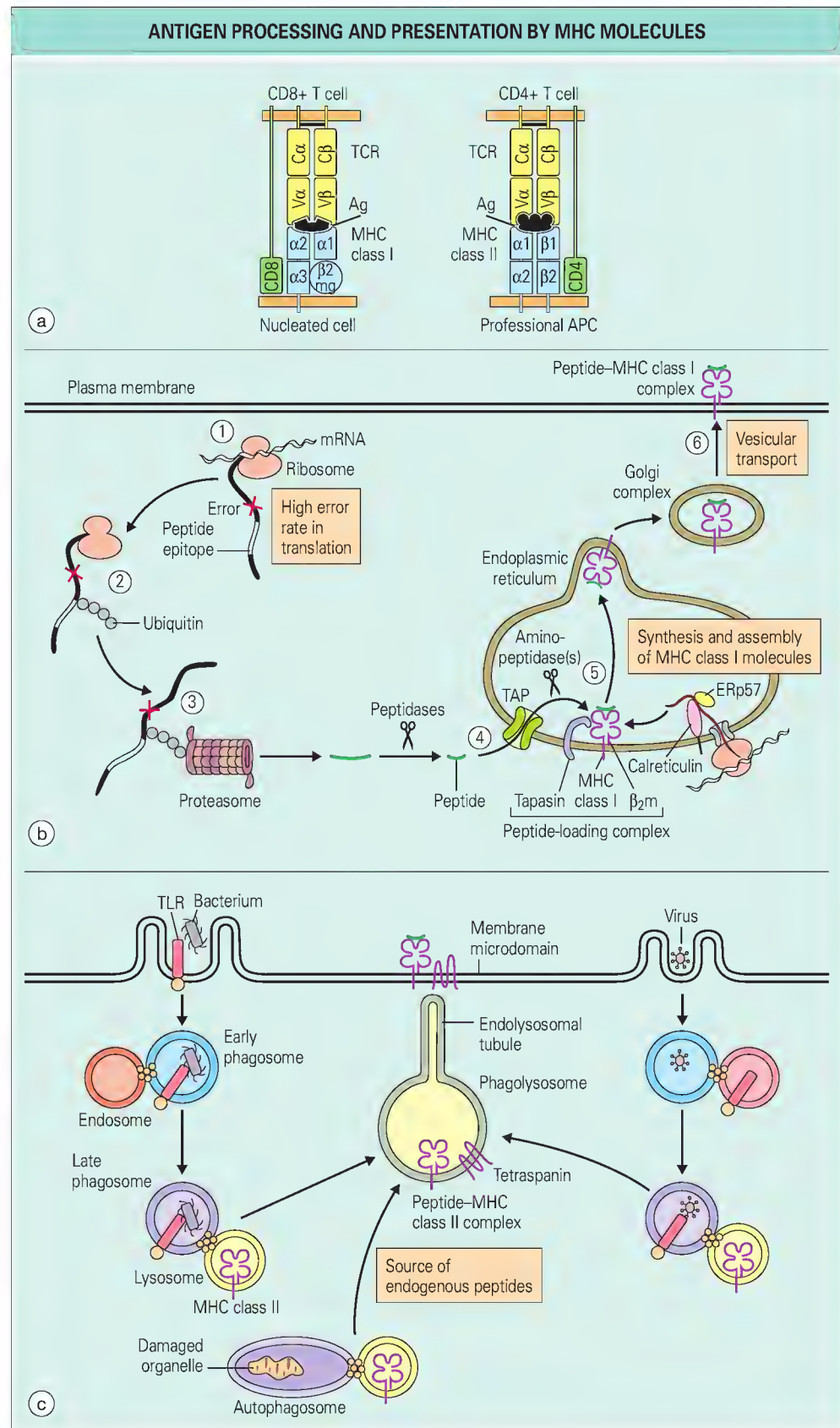
Recent studies emphasized the role of a process called *autophagy* in modulating MHC class I and class II presentation of cytoplasmic and nuclear antigens.^{23,24} Autophagy is only one of numerous mechanisms of a process called *cross-presentation*, in which MHC class I molecules present extracellular proteins to CD8+ T cells.^{25,26}

In the CD1 pathway, foreign lipid antigens are taken up through internalization of clathrin-dependent apolipoprotein E-lipid complexes bound to the low-density lipoprotein (LDL) receptor; phagocytosis of particulate material or whole pathogens; C-type lectins, which can bind mannose residues on glycolipids; and scavenger receptors, which can bind modified forms of LDL and apoptotic cells. Loading of self-lipids onto CD1 occurs through a poorly characterized mechanism that involves microsomal triglyceride transfer protein.^{20,21}

T-cell development

T-cell development occurs in the thymus (Fig. 15.5), controlled by complex regulatory mechanisms.^{27,28} The most immature thymic T cell, the early T-lineage progenitor, develops from a bone marrow-derived hematopoietic cell precursor. These progenitors lack the cell-surface proteins CD4 and CD8 (double-negative cells). They are also negative for the interleukin-2 receptor α chain, CD25, but positive for the adhesion molecule CD44. As

Fig. 15.4 Presentation of antigen peptides by major histocompatibility complex (MHC) molecules (a), as well as class I (b) and class II (c) antigen-processing pathways, are shown. In the class I pathway, proteins with errors are tagged with ubiquitin for degradation and degraded by proteasomes into peptides, which are delivered into endoplasmic reticulum, loaded into nascent MHC class I molecules, and transported via the Golgi complex to the cell surface. In the class II pathway, the internalized pathogens activate Toll-like receptors (TLRs), which leads to maturation of phagosomes, formation of phagolysosomes, loading of MHC class II molecules with peptide fragments of the bacteria or viruses that are formed by lysosomal proteases, and transport in endolysosomal tubules to the cell surface. Autophagosomes also fuse with lysosomes and serve as an additional source of peptides, including endogenous peptides, for MHC class II presentation. Ag, antigen; APC, antigen-presenting cell; β_2m , β_2 -microglobulin; mRNA, messenger RNA; TAP, transporter associated with antigen processing; TCR, T-cell receptor. (b and c, Adapted by permission from Macmillan Publishers Ltd: Vyas JM, Van der Veen AG, Ploegh HL, et al. The known unknowns of antigen processing and presentation. *Nat Rev Immunol* 2008;8:607-18, copyright 2008.)



the progenitors undergo differentiation, they acquire CD25, lose CD44, and complete somatic rearrangement of the gene loci encoding the TCR β , γ , and δ chains. If both TCR γ and δ chains undergo productive rearrangement, then the T cell expresses this heterodimer and becomes committed to the $\gamma\delta$ lineage. If, however, the β chain undergoes productive rearrangement first, then the TCR β chain is expressed on the cell surface along with an invariant chain called pre-T α , forming the pre-TCR complex. Expression of the pre-TCR stimulates proliferation of these T cells, suppresses VDJ recombination in the second TCR β locus on the allelic chromosome, and

stimulates recombination in the TCR α locus. Failure to successfully undergo any of these steps causes apoptotic death of the maturing T cell. After acquiring the CD4 and CD8 coreceptors (double-positive cells), the thymocytes undergo the selection process. Positive selection allows the small percentage of the thymocyte population capable of recognizing MHC-peptide complexes to mature further, leaving the remainder to die by apoptosis. Similar to newly emerging B cells in the bone marrow, many of the TCRs generated through the stochastic mechanisms in the emerging thymic T cells are autoreactive. Negative selection deletes T cells that bind

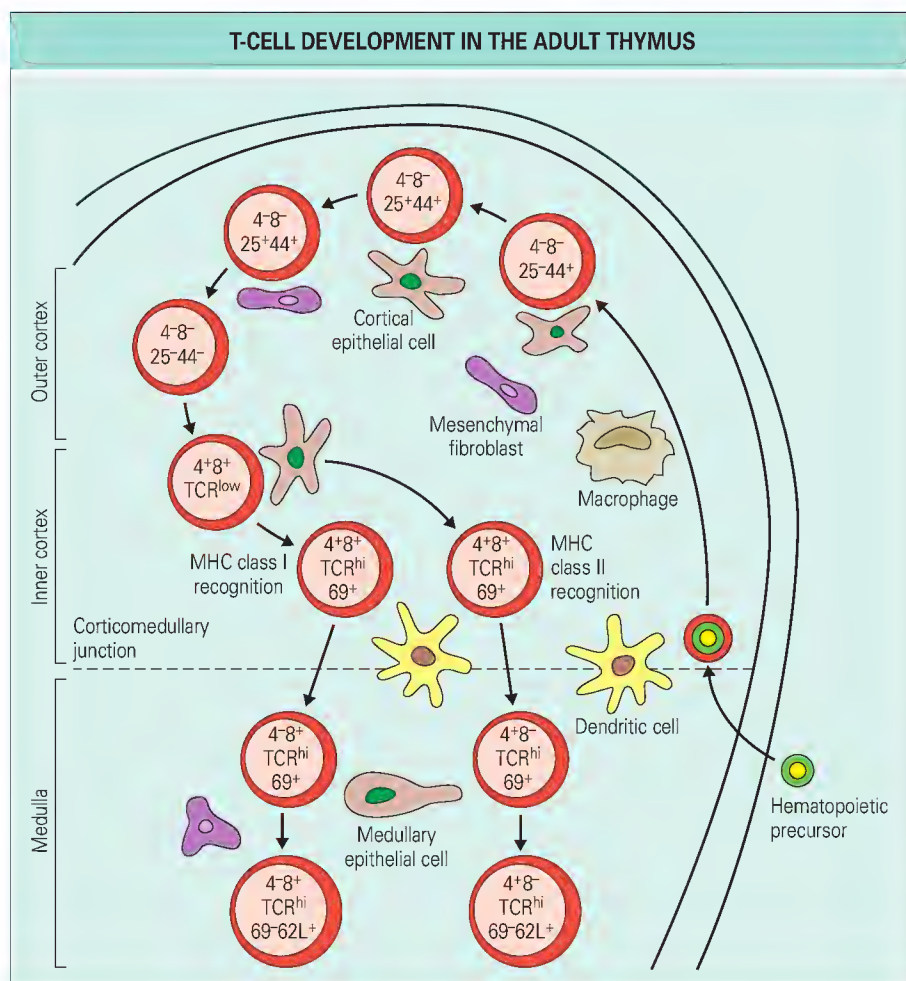


Fig. 15.5 Thymic lobes are organized into discrete cortical and medullary areas, each of which is characterized by the presence of particular stromal cell types as well as thymocyte precursors at defined maturational stages. Thymocyte differentiation can be followed phenotypically by the expression of cell-surface markers, including CD4, CD8, CD44, CD25, CD69, and CD62L, as well as the status of the T-cell receptor (TCR). Interactions between thymocytes and thymic stromal cells drive T-cell maturation, resulting in the generation of self-tolerant CD4+ helper and CD8+ cytotoxic T cells, which emigrate from the thymus to establish the peripheral T-cell pool. MHC, major histocompatibility complex. (Adapted by permission from Macmillan Publishers Ltd: Anderson G, Jenkinson EJ. Lymphostromal interactions in thymic development and function. *Nat Rev Immunol* 2001;1:31-40, copyright 2001.)

self-peptide-MHC complexes so strongly as to be potentially autoimmune. During the final stage of development, CD4+CD8+ T cells suppress the expression of either their CD4 or CD8 coreceptors to give rise to single-positive CD8+ or CD4+ mature thymocytes, respectively. T cells that express MHC class I-restricted TCRs become CD8+ and lymphocytes that express MHC class II-restricted TCRs become positive for the CD4 coreceptor alone. Therefore, along with acting as an environment for T-cell development, the thymus also acts as the principal site of deletion of autoreactive T cells and, as such, shapes the immune repertoire. However, the central thymic elimination of autoreactive T cells is not perfect. Some such cells leak into the periphery, normally becoming subject to complex regulation by peripheral tolerance mechanisms.

T-cell activation

To be activated successfully, T cells require two signals.^{29,30} The first is recognition of antigen by the TCR. On its own, this event can trigger anergy, a nonresponsive state in which T cells are resistant to subsequent activation. T-cell activation requires a second signal delivered by costimulatory molecules expressed on the surface of T cells. The most potent costimulatory signals are delivered when CD28, CD154, or both are ligated on the surface of T cells. Blockade of costimulatory signals by monoclonal antibodies or recombinant receptor antagonists confers potent immunosuppression and allows the acceptance of tissue allografts. Simultaneous blockade of both the CD28 and CD154 pathways is significantly more immunosuppressive than blockade of a single costimulatory pathway. The ligand for CD154 is CD40, a protein expressed on the surface of activated B cells, dendritic cells, and macrophages. The ligands for CD28 (CD80, CD86) are expressed on the surface of APCs such as dendritic cells, monocytes, and B cells. Their expression is induced when APCs are activated in the course of microbial infection. This property heightens the immune response in the setting of perceived danger (e.g., microbial infection). CD80 and CD86 have overlapping immunostimulatory roles; mice lacking either protein are only partially deficient in generating an immune response to foreign antigen.

Following TCR cross-linking, a series of complex intracellular signaling events takes place (see Chapter 14). The early events following TCR cross-linking include activation of Src family kinases Fyn and the CD4/CD8-associated Lck, as well as recruitment of a Syk family kinase, ZAP-70. Activated ZAP-70 phosphorylates LAT, which allows for activation of a set of adapter molecules such as PLC- γ 1, Grb2, and GADS. Numerous downstream molecules then become activated, which leads to cytoskeletal rearrangements; formation of the immune synapse; activation of transcription factors such as ATF-2, NF-AT, NF- κ B, and AP-1; changes in gene expression and expression of numerous cell-surface and secreted proteins; and cell cycle entry.

In unstimulated T cells, TCRs and coreceptors are distributed homogeneously over the T-cell surface. At the synapse between T cells and APCs, however, a large number of receptor-ligand pairs, adhesion molecules, and signaling complexes come together in an organized manner to promote cellular activation.^{31,32} This immunologic synapse is organized so that the TCR, MHC-peptide complexes, and θ -type protein kinase C are enriched in a central circle, surrounded by integrins and intercellular adhesion molecule 1.

The activation signals triggered by TCR ligation are balanced by inhibitory signals that dampen T-cell activation. For example, TCR ligation without CD28 costimulation induces induction of an anergic T-cell state rather than stimulation. Moreover, the inhibitory receptor CTLA-4 competes for the same ligands as CD28 (B7 expressed on APCs) and antagonizes TCR signaling via recruitment of PP2A or SHP-2 phosphatase.³³ The integration of activation and inhibitory signals determines the state of T-cell activation.

T-cell function

Functionally and phenotypically, T lymphocytes are likely the most diverse known population of cells in the human body. A vast amount of data indicates that disturbances in the specific subsets of T cells are directly involved in pathophysiologic mechanisms of autoimmunity and rheumatic diseases.

Cytotoxic T cells

The main function of CD8+ cytotoxic T cells is to induce elimination of “altered-self” cells such as infected or mutated cells. They can also secrete cytokines and participate in regulation (or dysregulation) of immune responses, including in rheumatic diseases. The cytotoxic function is carried out by releasing cytotoxins from lytic granules secreted at the site of target cell contact. These cytotoxins include a family of serine proteases, granzymes A, B, and H, that are capable of inducing caspase-dependent and caspase-independent cell death.³⁴ The role of another secreted cytotoxin, perforin, is to form pores in the target cell membrane and deliver granzymes into the target cell cytosol.^{35,36} Cytotoxic T cells can also trigger cell death through the Fas–Fas ligand pathway. When stimulated through their TCRs, CD8+ T cells transiently upregulate FasL. Subsequent contact with target cells expressing Fas induces apoptotic cell death.

Helper and regulatory T cells

There are several CD4+ helper T-cell (Th) types, based on the cytokines that they produce and the functions that they perform. New T-cell subsets are continually being discovered and characterized.³⁷ Some of the better characterized subsets are shown in Fig. 15.6. Their functions vary broadly: Th1 cells control protection against infection with intracellular microbes, Th2 cells promote humoral immune response necessary to clear parasitic infections, and Th17 cells contribute to autoimmunity and inflammation. Following activation of the immune response and elimination of pathogen, there is a need to downregulate, or suppress, the activity of lymphocytes.^{38,39} Regulatory T cells comprise a subset of peripheral blood CD4+ T cells that express CD25 (a subunit of the interleukin-2 receptor), and transcription factors FOXP3^{40,41} and Helios.^{42,43} They suppress the activity of effector T cells (CD4+CD25–) and inhibit autoimmune processes, ensuring immune tolerance to the body’s own tissues.^{38,39} Numerous subsets of regulatory T cells have already been described, and more subsets are likely to be found in the future.⁴⁴

AUTOIMMUNITY AND TOLERANCE

The advantage of having adaptive immunity is the ability to fend off new, unpredictable pathogens. The prerequisite for such functioning of the adaptive immune system is formation of stochastic repertoires of B- and T-cell specificities, as discussed earlier. However, because newly generated antigen specificities of lymphocytes are random, the numerous emerging lymphocytes are able to react with the own-body molecules as if they were foreign pathogens. In other words, the first target for the adaptive immune system should be the body’s own tissues—the concept of so-called horror autotoxicus. In most cases, this central problem is successfully avoided through a series of regulatory mechanisms that collectively are called *tolerance*. If these mechanisms do not function properly, autoimmunity ensues—a process that is very common in rheumatic diseases. Mechanisms that prevent B cell- or T cell-mediated autoimmune damage are complex but can be separated into central and peripheral mechanisms. Central tolerance is achieved by deletion of high-avidity autoreactive B cells in the bone marrow and autoreactive T cells in the thymus during their maturation, as discussed earlier. The mechanisms that control central tolerance are being vigorously investigated.^{45,46}

Peripheral tolerance is even more complex and diverse. Its mechanisms can be grouped into apoptotic deletion of lymphocytes that are repeatedly stimulated by persistent antigens; anergy of lymphocytes (without deletion) through lack of costimulation, inhibitory signals (such as CTLA-4), or regulatory action of regulatory T cells; immune indifference, or ignorance, due to low avidity of the antigen receptors, low lymphocyte precursor frequency, or low concentration of the antigen; and homeostatic interactions, including immune deviation (switching of cytokine profiles leading to suppression), interclonal competition of lymphocytes for antigen, and idiotype network interactions (antibodies developing against other own-body antibodies). In autoimmune—including rheumatic—diseases, immune tolerance is broken through diverse mechanisms. Such mechanisms may include molecular or

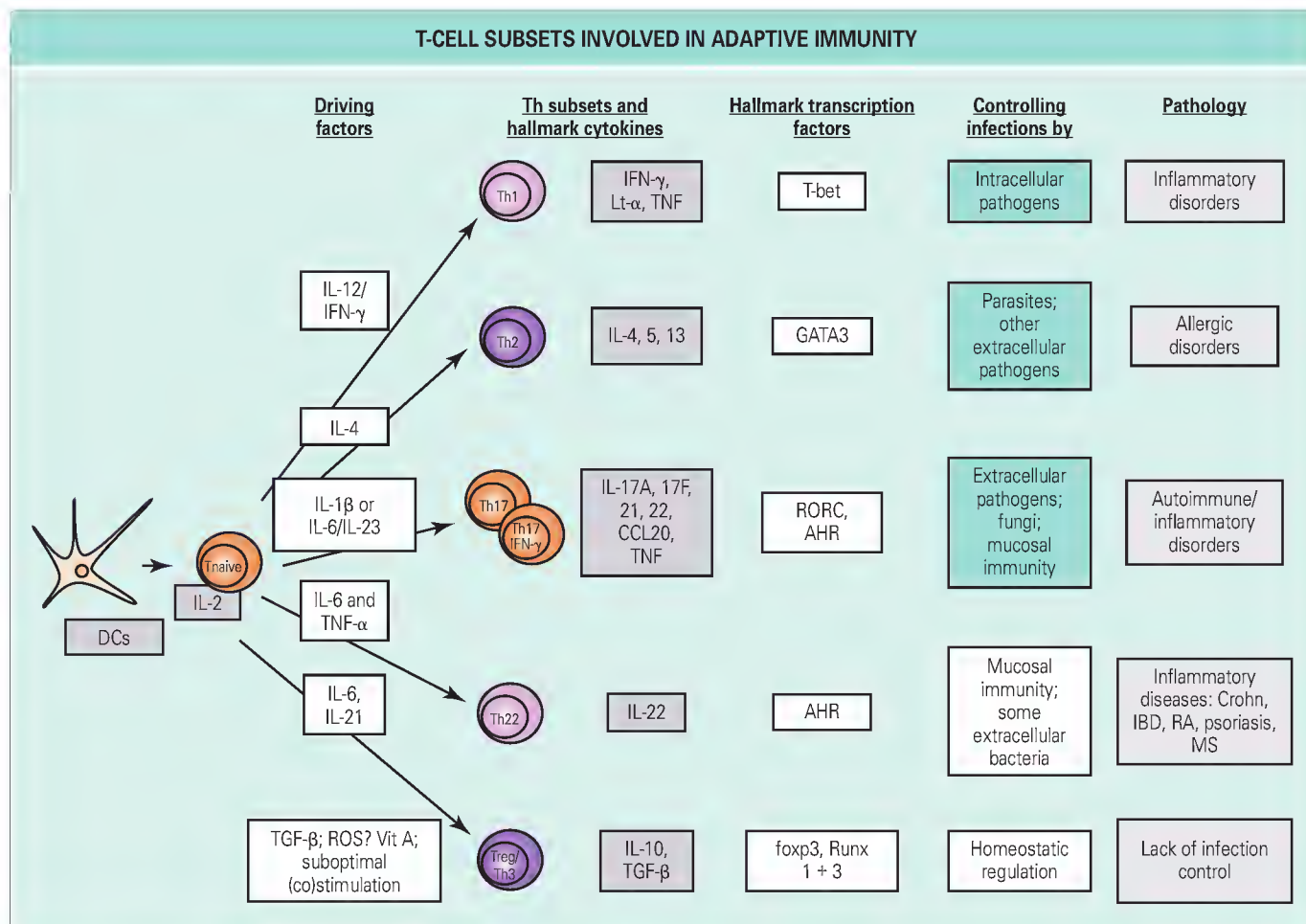


Fig. 15.6 Some of the CD4+ T-cell subsets, with their signature cytokines, hallmark transcription factors driving their differentiation, functions, and related pathologic conditions are shown. DCs, dendritic cells; IFN-γ, interferon-γ; IBD, inflammatory bowel disease; IL, interleukin; Lt-α, lymphotxin-α; MS, multiple sclerosis; RA, rheumatoid arthritis; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor; Th, helper T cell; Tnaive, naive T cell; Treg, regulatory T cell; Vit A, vitamin. (Adapted by permission from Elsevier: Ottenhoff THM. New pathways of protective and pathological host defense to mycobacteria. *Trends Microbiol* 2012;20[9]:419-28.)

cellular defects weakening central and peripheral tolerance; molecular mimicry (confusion of the adaptive immune system regarding non-self-antigens versus self-antigens); exposure of normally sequestered antigens from immunologically privileged sites; peculiarities of antigen presentation by particular MHC haplotypes; female sex hormones; and various environmental influences. Once the immune tolerance is broken, autoreactive antibodies, T lymphocytes, and circulating immune complexes cause damage to the tissues. The damage may be tissue or organ specific, or systemic, depending on the specifics of a particular disease. In all cases, however, the main cause of autoimmunity is a dysregulation of the adaptive immune system.

CONCLUSION

T and B lymphocytes are the cells of the adaptive immune system. They produce a large repertoire of immunoglobulins and TCRs using somatic

gene recombination. Clonal selection preserves those cells whose products prove useful in fighting off pathogens. Specialized helper T cells such as Th1, Th2, or Th17 produce characteristic cytokines that divide immune responses into several distinct types. There is an intrinsic risk of autoimmunity built into the adaptive immune system that is the cost of generating virtually unlimited repertoires of immune specificities. The potential of the adaptive immune system to induce autoimmunity is usually controlled by a combination of deletional and regulatory tolerance mechanisms. Regulatory T cells play a central role in maintaining immune tolerance. Failure of tolerance leads to autoimmunity, in which the immune system attacks its own tissues. Autoimmunity commonly occurs in and contributes to mechanisms of rheumatic diseases. By its nature, the adaptive immune system potentially represents the most specific target for therapy in autoimmune diseases. As our understanding of immune function at the cellular and molecular levels increases, we may soon be in a position to modulate the immune response for the benefit of patients with autoimmune rheumatic disease.

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16

Principles of innate immunity

■ TSUNEYASU KAISHO ■ SHIZUO AKIRA

- Innate immunity senses and responds to a variety of microorganism- or host-derived molecules.
- Innate immune sensors are functionally categorized into three classes: signaling, internalizing, and soluble sensors.
- Signaling sensors, such as Toll-like receptors, trigger signaling pathways for activating immune response genes.
- Internalizing sensors incorporate microorganisms and degrade or process them for presentation to T cells.
- Soluble sensors opsonize microorganisms, thus marking them for internalization, and activate protease cascades.
- Innate immunity induces inflammation, triggers adaptive immune responses, and provokes antiviral immunity.
- Innate immune sensors are involved in the pathogenesis of not only infectious and autoimmune diseases but also various inflammatory conditions in metabolic diseases.

INTRODUCTION

Host defense consists of two types of immunity: innate and adaptive immunity (Table 16.1). Adaptive immunity is found only in jawed vertebrates and is mediated by B and T lymphocytes. These cells possess the RAG genes that mediate a somatic recombination system and thereby create a large repertoire of antigen receptors. Antigen receptors with certain specificity are clonally expressed, and, owing to allelic exclusion, each lymphocyte bears only one antigen receptor. Thus groups of lymphocytes are highly heterogeneous in terms of antigen specificity. During the immune response, receptors with high affinity for an invading antigen are clonally selected, and lymphocytes bearing such receptors later stay on as memory cells.

Although this defense system is highly beneficial for the host, to establish adaptive immunity and to mount an adaptive immune response takes time. Especially early in the course of an infection, an immediate response is required for efficient host defense. This immediate response is mediated by innate immunity. Innate immunity is an evolutionarily ancient system that is found in all multicellular organisms, including plants and insects. In mammals, innate immunity depends on macrophages or dendritic cells (DCs), which do not possess rearranged receptors. Insects can develop resistance to infection, which indicates that innate immunity is sufficient to eradicate pathogens effectively. In contrast to adaptive immunity, innate immunity is mediated by a group of germline-encoded receptors with a fairly limited repertoire of antigen receptors. Those innate immune sensors can recognize various molecular structures derived from microorganisms, which can be referred as *pathogen- or microorganism-associated molecular patterns*.¹ They are called *microorganism-associated molecular patterns* (MAMPs) hereafter because such structures are found irrespective of pathogenicity. Unlike rearranged antigen receptors in the adaptive immune system, any given innate immune sensor is expressed on a variety of innate immune cells, and each cell possesses a combination of several sensors. Therefore innate immune cells are simultaneously or sequentially activated through a variety of sensors. Importantly, innate immune sensors also recognize host-derived endogenous molecules, called *danger/damage-associated molecular patterns* (DAMPs), and are involved in a variety of noninfectious inflammatory conditions. This chapter discusses the innate immune system as a sensor system for activating immune or inflammation responses.

SENSING BY INNATE IMMUNITY

Innate immune sensors can be functionally divided into three categories: signaling, internalizing, and soluble sensors (Fig. 16.1).

Signaling sensors

Signaling sensors are expressed on the cell surface, in the endosome, or in the cytosol, where they recognize their corresponding ligands. On recognition, these sensors can stimulate signaling pathways leading to activation of various signaling molecules, such as nuclear factor κ B (NF- κ B) or mitogen-activated protein kinases (MAPKs). This then leads to expression of a variety of immune response genes, including inflammatory cytokines or costimulatory molecules such as CD40 and CD86.

Toll-like receptors

The Toll-like receptor (TLR) family is a group of typical signaling sensors.^{2,3} TLRs are expressed on the plasma membrane or in the endosome and play major roles in activating antigen-presenting cells (APCs). TLRs are type I transmembrane proteins. Their extracellular domain includes a repetitive structure rich in leucine residues, called *leucine-rich repeat* (LRR), that is involved in the recognition of a variety of TLR ligands. The intracellular region contains a common structure in TLR and interleukin-1 receptor (IL-1R) family members called *Toll/IL-1R homologous* (TIR) domain that is essential for signal transduction through TLRs.

TLRs can recognize a variety of MAMPs. TLR ligands can be categorized as lipid, protein, and nucleic acid components (Fig. 16.2). Phylogenetically related TLRs can recognize similar types of ligands. All TLR ligands are potent immune adjuvants that can trigger a vigorous immune response. The most widely investigated TLR ligand is lipopolysaccharide (LPS).⁴ LPS is found in the outer cell walls of gram-negative bacteria and is recognized by TLR4. LPS is first bound to a soluble factor, LPS-binding protein, in the serum and transferred to target cells such as macrophages. Macrophages express a phosphatidylinositol-anchored cell surface molecule, CD14, which can capture and retain LPS. LPS then activates TLR4. A small secreted molecule, myeloid differentiation factor 2 (MD-2), is associated with TLR4 and critically involved in forming an LPS-recognizing complex.⁵

Other lipid-containing components of cell walls of a variety of microorganisms are recognized by TLR2 and related TLRs, such as TLR1 and TLR6. Heterodimerization is critical for TLR2-mediated recognition. For example, TLR2 can recognize mycoplasma macrophage-activating lipopeptide 2 (MALP-2) when associated with TLR6. Meanwhile, a TLR2-TLR1 heterodimer is involved in recognizing bacterial lipopeptides. MALP-2 and bacterial lipopeptides carry a diacylated and triacylated cysteine residue at their N-terminals, respectively, and this subtle difference is discriminated by TLR2-containing heterodimers.

TLR5 is involved in recognizing a protein, flagellin, that is a component of the bacterial flagella used for propulsion in a liquid medium. Flagellin can elicit mucosal immune responses by acting on epithelial cells or macrophages. Although flagellin is a protein, its amino acid structure is highly conserved, which suggests that it is a target for innate immune recognition.

Nucleic acids are equally important MAMPs recognized by TLRs. Bacterial DNA has long been known to be a strong immune adjuvant.⁶⁻⁸ This adjuvant activity depends on an unmethylated CpG (cytosine phosphate guanine) motif. The CpG motif is more abundant in bacterial DNA than in mammalian DNA. Furthermore, mammalian CpG DNA is often methylated. Therefore unmethylated CpG DNA can be regarded as nonself and is recognized by TLR9. Viral DNA is also rich in the CpG motif, and DNA virus infection does indeed trigger TLR9 signaling.

TABLE 16.1

Innate and adaptive immunity

	Innate immunity	Adaptive immunity
Evolution	Ancient	Jawed vertebrates or higher
Cells	Macrophages Dendritic cells (Antigen-presenting cells)	T and B lymphocytes
Receptors	Encoded in germline Limited repertoire Nonclonal	Created by rearrangement Large repertoire Clonal expression
Memory	No	Yes
Ligands	Molecular structures conserved in a group of microorganisms (MAMPs; e.g., LPS, CpG DNA), host-derived damaged molecules (DAMPs)	Fine structures (peptides)
Responses	Immediate	Slow

CpG, cytosine phosphate guanine; DAMPs, danger/damage-associated molecular patterns; LPS, lipopolysaccharide; MAMPs, microorganism-associated molecular patterns.

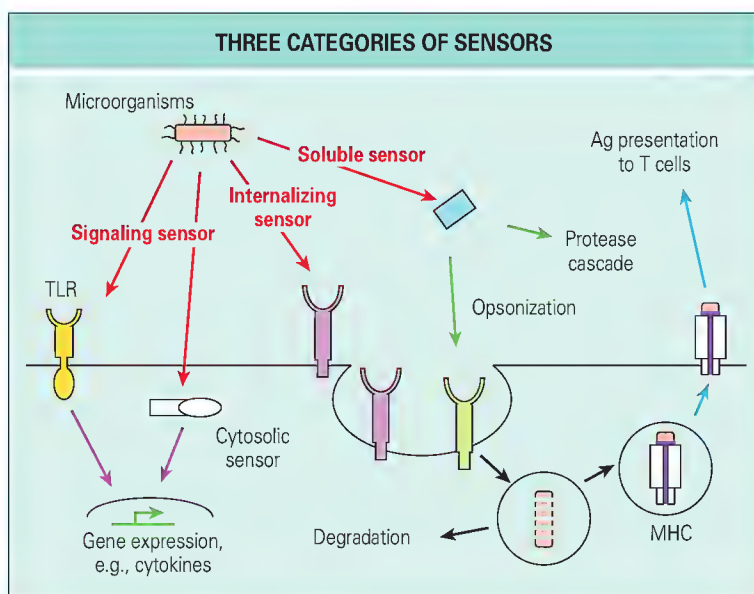


Fig. 16.1 Signaling sensors trigger signal transduction pathways upon recognition. Internalizing sensors directly incorporate microbes into the cell. Soluble sensors attach to the microbes and support the function of internalizing sensors. Soluble sensors also activate protease cascades. Ag, antigen; MHC, major histocompatibility complex; TLR, Toll-like receptor.

Several small synthetic molecules, including imidazoquinoline derivatives and several anticancer drugs, have long been known for their antiviral activity. This activity depends on TLR7. Single-stranded RNA (ssRNA) from influenza or human immunodeficiency virus is also a ligand for TLR7 and its close relative, TLR8. This interaction is critical for sensing RNA virus infection. RNA virus infection also induces the production of double-stranded RNA (dsRNA) in infected cells, and these dsRNAs can act as immune adjuvants and are recognized by TLR3.

TLRs can also recognize DAMPs. DAMPs are host-derived endogenous molecules, hidden within cells and ignored by the immune system in the steady state. After tissue damage or cell death, they are released and detected by the innate immune sensors. Nucleic acids are typical DAMPs and are recognized by TLR3, TLR7, TLR8 and TLR9. These TLRs fail to distinguish between microorganism- and host-derived nucleic acids (see later). RNAs damaged by ultraviolet radiation or mitochondrial DNA are sensed by TLR3 and TLR9, respectively. TLR4 also recognizes a variety of DAMPs. These include not only lipids such as saturated fatty acids or oxidized low-density lipoprotein cholesterol but also proteins such as heat shock proteins or S100 family proteins.

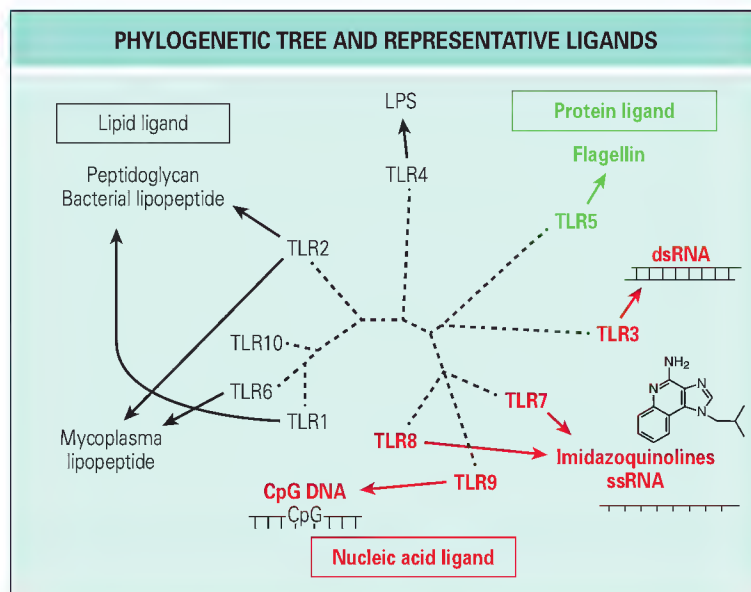


Fig. 16.2 The phylogenetic relationships of the human Toll-like receptors (TLRs) are shown by the dotted lines based on an analysis of their amino acid structures. Branch lengths are proportional to evolutionary distances. CpG, cytosine phosphate guanine; dsRNA, double-stranded RNA; LPS, lipopolysaccharide; ssRNA, single-stranded RNA.

Importantly, TLR2 and TLR4 are expressed mainly on the plasma membrane, whereas nucleic acid-recognizing TLRs are expressed in the endoplasmic reticulum. Upon activation, chaperone molecules such as UNC93B1 escort nucleic acid-recognizing TLRs to the endosome, where nucleic acids are released from virus or virally infected cells. Thus lipid and nucleic acid TLR ligands are recognized in distinct cellular compartments.

Cytosolic signaling sensors

Signaling sensors also exist in the cytosol. DExD/H-box helicase family members, which are characterized by motifs that include the DExD/H amino acid sequence (D, E, x, and H represent aspartic acid, glutamic acid, any amino acid and histidine, respectively) and are highly conserved throughout species, function as cytosolic sensors for a variety of nucleic acids, mainly from microorganisms including viruses. The representative members are retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) such as RIG-I and melanoma differentiation-associated gene 5 (MDA5).^{9,10} RIG-I and MDA5 carry tandem caspase recruitment domains (CARDs) and an RNA helicase domain at the N-terminal and C-terminal, respectively, and the RNA helicase domain is involved in recognizing the ligands. Both RIG-I and MDA5 can recognize virally derived RNAs, but they sense distinct molecular structures and play differential roles in viral infection.¹⁰ For example, RIG-I is essential for recognizing various ssRNA viruses, including paramyxoviruses, influenza virus A, and Japanese encephalitis virus, whereas MDA5 is critical for sensing picornaviruses. RIG-I can recognize 5'-triphosphate ssRNA, which is a typical structure found in viral, nonself RNA. Host-derived self-RNA, on the other hand, has a cap structure to mask 5'-triphosphate RNA. Thus RIG-I can distinguish viral RNA from self-RNA.

Several other DExD/H-box helicases are also involved in sensing nucleic acids.¹¹ DDX3 and DDX60 bind to viral RNA. DDX1, DDX21, and DHX36 also recognize viral dsRNA. Furthermore, DDX41 recognizes double-stranded DNA (dsDNA). These sensors play their specific roles in diverse cell types.

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) also are cytosolic sensors (Fig. 16.3).¹² NLRs consist of more than 20 members in humans and mice. They carry a CARD, a pyrin domain, or a baculoviral inhibitor of apoptosis repeat (BIR) domain as a protein interaction domain at the N-terminal, which is followed by a NACHT nucleotide-binding domain (NBD) and an LRR domain. NOD1 and NOD2 are representative NLR members involved in recognizing bacterial peptidoglycan-derived molecules.¹³ NLR family apoptosis inhibitory protein 5 (NAIP5) can sense flagellin derived from intracellular bacteria such as *Salmonella* or *Legionella*. An NAIP5-related molecule, NAIP2, can detect conserved rod proteins of the type III secretion system from *Salmonella* or *Burkholderia*. Notably, NLR family pyrin domain-containing 3 (NLRP3) is required for responses against a variety of MAMPs and DAMPs. These include bacterial

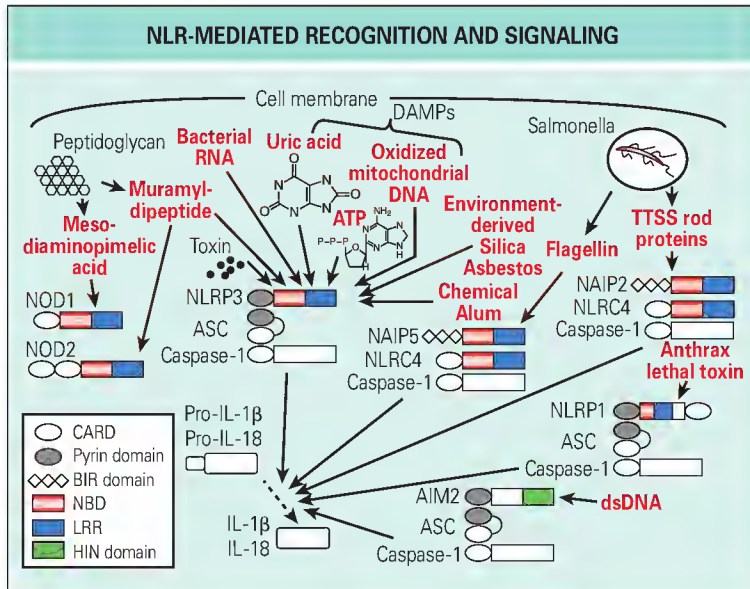


Fig. 16.3 Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are cytosolic signaling sensors and recognize a variety of microorganism-associated and danger/damage-associated molecular patterns. Importantly, NLRs can activate inflammasome and induce production of active interleukin- β 1 (IL-1 β) and IL-18. ATP, adenosine 5'-triphosphate; DAMPs, danger/damage-associated molecular patterns; dsDNA, double-stranded DNA; IL, interleukin; TTSS, type III secretion system.

products such as RNA or toxin, host-derived nucleic acid metabolites such as adenosine 5'-triphosphate, uric acids, and oxidized mitochondrial DNA. Furthermore, environmental substances such as silica crystals or asbestos and a widely used chemical immune adjuvant, alum, can also activate NLRP3-mediated signaling.

Members of the pyrin and hematopoietic interferon-inducible nuclear (HIN) domain-containing protein (PYHIN) family also function as cytosolic sensors. This family carries an N-terminal pyrin domain and two DNA-binding HIN domains. Both absent in melanoma 2 (AIM2) and interferon- γ -inducible protein 16 (IFI16) belong to this family and are involved in detecting dsDNA.

Internalizing sensors

Internalizing sensors are expressed on the surface of neutrophils, macrophages, or DCs. They bind to and internalize MAMPs or microorganisms, which are subsequently transported to lysosomal compartments (see Fig. 16.1). This process is termed *phagocytosis*, and the group of sensors involved can thus also be referred to as *phagocytic sensors*.¹⁴ After phagocytosis, organism-derived proteins are degraded or processed for presentation to T cells. Internalizing sensors mainly function to incorporate the organisms or their components, but some internalizing sensors can also transduce the activation signals.

Lectin

Lectins generically represent carbohydrate-recognizing proteins, and some lectins function as internalizing sensors. The mannose receptor is a type I transmembrane protein that can bind terminal mannose and fucose residues of glycoproteins or glycolipids, which are found on microbial cell walls. The macrophage scavenger receptor SR-A is a type II transmembrane protein. Although originally defined by its ability to bind and mediate endocytosis of oxidized or acetylated low-density lipoprotein, it can also bind a variety of microorganisms. Macrophage receptor with collagenous structure (MARCO) is structurally and functionally similar to SR-A and can bind to gram-positive and gram-negative bacteria.

Dectin-1 is a C-type lectin and is involved in recognizing β -1,3-linked or β -1,6-linked glucans found in fungal or other microbial cell walls. Dectin-1 carries an immunoreceptor tyrosine-based activation motif (ITAM) in the intracytoplasmic region and also functions as a signaling sensor. Dectin-1 is colocalized with TLR2 in the phagosome and activates macrophages in synergy with TLR2. Macrophage-inducible C-type lectin (Mincle) also carries an ITAM and can induce macrophage activation by sensing a mycobacterial glycolipid, trehalose-6,6'-dimycolate, also called *cord factor*. Mincle also detects a nuclear ribonucleoprotein that belongs to the DAMP

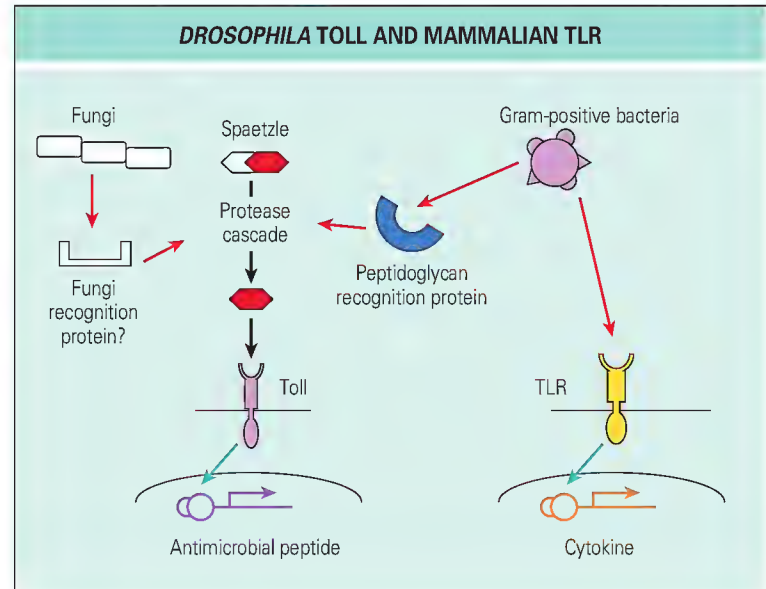


Fig. 16.4 Mammalian Toll-like receptors (TLRs) directly recognize microbial components, whereas *Drosophila* Toll detects a host-derived molecule. In *Drosophila*, microbes are discriminated by soluble factors in the hemolymph, which leads to the activation of protease cascades.

group. Another ITAM-carrying C-type lectin, CLEC9A, also known as *DNGR-1*, senses exposed actin filaments, which also are DAMPs.

Soluble sensors

Soluble sensors are produced by macrophages or hepatocytes and bind to the cell wall of microorganisms, thus designating them as targets for phagocytosis (see Fig. 16.1). This coating process is termed *opsonization*, and the coating substances are called *opsonins*. The serum levels of certain soluble sensors, such as C-reactive protein and serum amyloid P component, increase in response to inflammatory cytokines; therefore, these sensors are also referred to as *acute-phase proteins*.¹⁵ Soluble sensors are linked to the complement system and can activate protein cascades that are capable of eradicating pathogenic microbes.

Complement system

The complement system consists of more than 35 soluble or membrane proteins (see Chapter 20).¹⁶ Microbial infection activates three distinct pathways—the classical, alternative, and lectin pathways—for complement activation. All pathways activate a common pathway that involves cleavage of C3 into C3a and C3b. C3b attaches to the microbial surface, and microbes opsonized by C3b are then eliminated by phagocytosis or killed by membrane attack complex.

PHYLOGENETIC COMPARISON OF THE RECOGNITION SYSTEM

Toll-like receptors have been so named because their molecular structure is similar to that of *Drosophila* Toll.^{17,18} Toll is a type I transmembrane protein carrying an LRR repeat and a TIR domain. Toll-deficient flies display increased susceptibility to fungal infection, which indicates that Toll is essential for antifungal immunity in insects. Furthermore, both Toll and TLRs can activate signaling pathways leading to the release of antimicrobial substances.

The *Drosophila* Toll system, however, is distinct from the mammalian TLR system (Fig. 16.4). Toll does not directly recognize fungi-derived products. The pathogens are recognized by certain still-unidentified soluble factors. In fungal infection, protease cascades are activated to induce cleavage of a secreted protein, Spätzle. Processed Spätzle then binds to Toll. Thus Toll recognizes a host-derived product.

Toll is also involved in immunity against gram-positive bacteria.¹⁹ A soluble molecule, peptidoglycan recognition protein SA (PGRP-SA), recognizes peptidoglycans from bacteria, which leads to activation of protease cascades that also cleave Spätzle. PGRP-SA-deficient flies are susceptible to infection with gram-positive bacteria but retain immune responses against

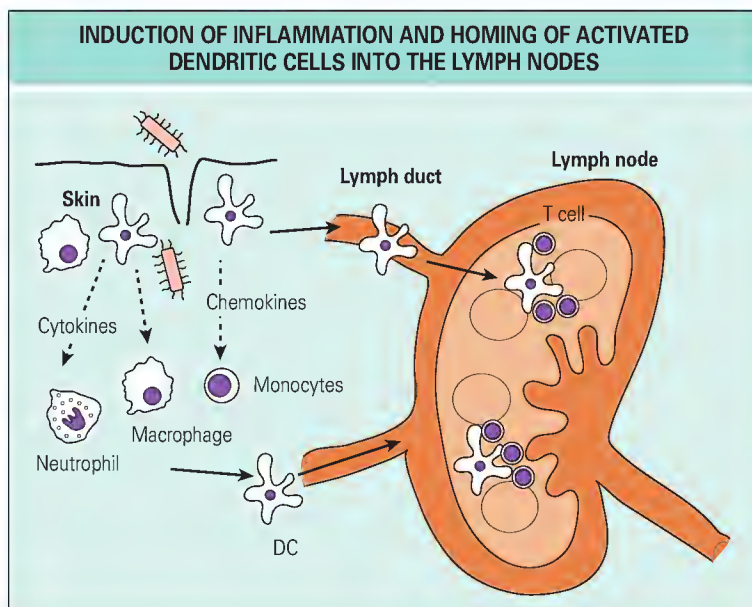


Fig. 16.5 Macrophages or dendritic cells (DCs) detect invasion of microorganisms through innate immune sensors and produce chemokines or cytokines, thereby inducing inflammatory reactions. Activated DCs migrate into lymph nodes and provoke T-cell activation.

fungi, whereas Toll-deficient flies succumb to infection with both organisms. This indicates that the discrimination of fungi and bacteria happens upstream of Toll. Thus flies detect pathogens in the hemolymph, not on the plasma membrane. In mammals, the complement system, rather than the TLR system, is similar to Toll when one considers recognition in the fluid and activation of protease cascades.

CRITICAL FUNCTIONS OF INNATE IMMUNITY

Induction of inflammation

Innate immunity detects microbial infection and induces inflammatory reactions in local peripheral tissues such as the skin (Fig. 16.5). TLRs expressed on macrophages or DCs play major roles in this process. TLR signaling can induce robust production of proinflammatory cytokines including IL-6 and tumor necrosis factor- α (TNF- α), chemokines, and adhesion molecules and thereby recruit or activate various inflammatory cells at the sites of infection. Recruited and activated macrophages or neutrophils then ingest, through internalizing sensors, and subsequently kill invading pathogens by producing nitric oxide, reactive oxygen species, or defensins. NLR signaling can induce generation of proinflammatory cytokines such as IL-1 β and IL-18 through the activation of inflammasome (see later) and contributes to inflammatory reactions. Inflammation is a critical local response to resolve infection. However, inflammation is a double-edged sword, because excessive amounts of cytokines can be lethal for the host, as is the case in endotoxin shock.

Activation of adaptive immunity on infection

Locally activated APCs mature to express a distinct set of chemokine receptors. Then they are transported to the lymph nodes, where they interact with and activate T cells (see Fig. 16.5). Thus an innate immune response subsequently leads to the activation and establishment of adaptive immunity. Clonal T-cell expansion requires not only T-cell receptor-mediated but also costimulatory molecule-mediated signaling (Fig. 16.6). Internalizing sensors facilitate antigen presentation, and signaling sensors such as TLRs can enhance expression of costimulatory molecules, including CD80 and CD86. Thus innate immune sensors directly contribute to the activation of adaptive immunity.

A CD4⁺ T cell differentiates into a type 1 helper T (Th1), type 17 helper T (Th17), or type 2 helper T (Th2) cells.²⁰ Th1 cells produce interferon- γ (IFN- γ) and mediate antiviral or antibacterial immunity. Th17 cells produce IL-17 and are involved not only in antibacterial immunity but also in various inflammatory conditions such as autoimmune disorders. Th2 cells secrete IL-4 or IL-13 and are involved in immunity against helminths, but excessive

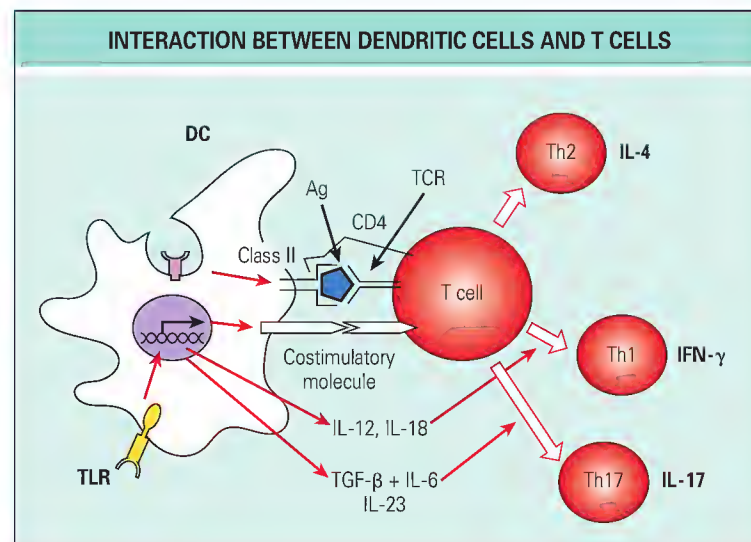


Fig. 16.6 Activated dendritic cells (DCs) induce proliferation of antigen-specific T cells and instruct them in differentiating into type 1 helper T (Th1), Th2, or Th17 cells depending on the DC activation stimuli. Ag, antigen; IFN- γ , interferon- γ ; IL, interleukin; TCR, T-cell receptor; TGF- β , transforming growth factor- β ; TLR, Toll-like receptor.

activation of these cells may cause allergic reaction. APCs are critically involved in regulating Th cell differentiation. This activity depends on tissue origin, cell subsets, or maturation stage of the APCs. But the nature of the stimuli activating the APCs is most important. Most TLR ligands can activate APCs to produce Th1- or Th17-inducing cytokines such as IL-12, IL-18, IL-6, or IL-23. Although Th2-inducing sensors are not well characterized yet, certain helminths or their products can enhance the ability of APCs to support Th2 cell differentiation.

Antiviral responses

Innate immunity responds to viral infection by producing type I IFNs.²¹ Type I IFNs consist of more than 10 IFN- α proteins and a single IFN- β protein. However, all type I IFNs use IFN- α/β receptor (IFNAR), composed of IFNAR1 and IFNAR2 subunits, as a common receptor. The signaling can induce expression of a number of antiviral molecules including 2'-5'-oligoadenylate synthases or IFNs themselves. It can also upregulate expression of the major histocompatibility complex (MHC) and induce DC maturation. These effects contribute to antiviral immune responses.

Type I IFN production is triggered by innate immune signaling sensors. Cytosolic sensors such as RLRs are potent type I IFN-inducing sensors and are expressed in a variety of cells, including macrophages and fibroblasts. Among TLRs, TLR7 and TLR9 can induce both IFN- α and IFN- β . The other TLRs, except TLR3 and TLR4, fail to induce type I IFNs. TLR3 and TLR4 can induce only IFN- β but not IFN- α . TLR4-induced IFN- β plays a critical role in shock induction and bacterial infection, but, as a principle, in viral infection TLRs that recognize nucleic acids are more critical than TLR4 in production of type I IFNs.

Plasmacytoid dendritic cells (PDCs) are a DC subset and also are known as IFN- α -producing cells.²² PDCs look like plasma cells and exhibit poor antigen-presenting activity owing to low levels of expression of MHC class II and costimulatory molecules. PDCs express TLR7 and TLR9 exclusively among TLRs and are involved in antiviral immunity by secreting copious amounts of type I IFNs, especially IFN- α , in a TLR7/9-dependent manner.

Cross-presentation is also important in antiviral immunity.²³ Cross-presentation is defined as exogenous antigen presentation through MHC class I to generate CD8⁺ T-cell responses (Fig. 16.7). Virally infected cells are ingested by APCs. Antigens are processed and transported to MHC class II-containing endolysosomes, where antigens associate with MHC class II molecules. The antigen-MHC class II complex then becomes competent for presentation to CD4⁺ T cells. Exogenous antigens can also be subjected to the association with MHC class I. Antigens can be transported to the cytosol, processed by proteasomes, and then incorporated into the endoplasmic reticulum in a transporter associated with antigen processing (TAP)-dependent manner. Then antigens bind to MHC class I molecules and are presented to CD8⁺ T cells. Alternatively, antigens can be transferred

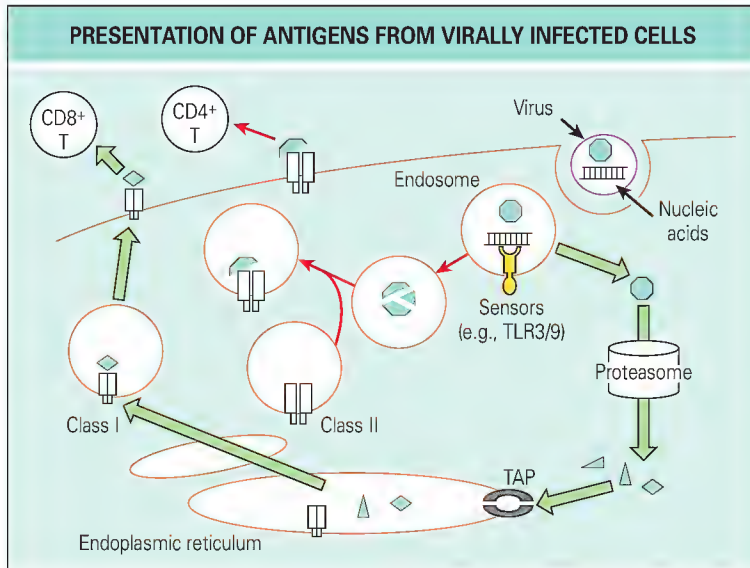


Fig. 16.7 Virally infected cells are incorporated into antigen-presenting cells, and antigens are presented with major histocompatibility complex (MHC) class I or class II molecules. Toll-like receptors (TLRs) can promote cross-presentation, which depends on MHC class I. TAP, transporter associated with antigen processing.

directly to the MHC class I-containing compartment, not via the cytosol. The cross-presentation system ensures that virally infected cells, which do not always possess the ability to present antigen by themselves, can be targets for cytotoxicity. Cross-presentation also should be critical in cancer surveillance, because most cancer cells show poor antigen presentation ability. Several immune sensors such as TLRs can facilitate the cross-presentation, and one DC subset defined by the presence of CD8 α , CD103, or the chemokine receptor XCR1 features a high ability to phagocytose dying cells and cross-present the antigens.²³

MOLECULAR MECHANISM OF SENSOR SIGNALING

TLR carries the intracytoplasmic TIR region.²⁴ This region associates with cytoplasmic adapters that also possess the TIR region. This association is critically involved in stimulating various pathways leading to activation of NF- κ B or interferon regulatory factors (IRFs). There are five TIR domain-containing adapters, and four of them—myeloid differentiation primary response gene 88 (MyD88), TIR domain-containing adapter protein (TIRAP)/MyD88-adaptor-like (MAL), TIR domain-containing adapter protein-inducing IFN- β (TRIF), and TRIF-related adapter molecule (TRAM)—are involved in the pleiotropic function of TLRs (Figs. 16.8 and 16.9). MyD88, characterized first among the TLR adapters, associates with all TLRs except TLR3. MyD88 is essential for TLR-induced cytokine production. TIRAP cooperates with MyD88 downstream of TLR2 and TLR4. MyD88 is critical for all TLR7/9-induced effects, including type I IFN induction (see Fig. 16.9). Meanwhile, TRIF, but not MyD88, is essential for TLR3- or TLR4-induced type I IFN production (see Fig. 16.8). TRAM is required for TLR4 to associate with TRIF. TLR3 can directly associate with TRIF and does not require TRAM for its signaling. Notably, the MyD88-TIRAP and TRIF-TRAM pathways are initiated at the plasma membrane and endosome, respectively. These adapters differentially stimulate signaling cascades that involve IL-1R-associated kinases (IRAKs) or an adapter molecule, tumor necrosis factor receptor-associated factor 6 (TRAF6), and induce the activation of various transcription factors. Activation and nuclear translocation of NF- κ B, IRF-3, and IRF-7 can cause gene expression of proinflammatory cytokines and type I IFNs (see Figs. 16.8 and 16.9).

Inhibitor of κ B kinase (IKK) family members play critical roles in linking TLR signaling and activation of transcription factors (see Figs. 16.8 and 16.9). NF- κ B activation depends on IKK β . IRF-3 activation is induced by a heterodimer of IKK κ /t and TANK-binding kinase 1 (TBK1). The TLR7/9 signaling mechanism in PDCs is peculiar in that the MyD88-mediated pathway leads to IRF-7 activation via IKK α and interleukin-1 receptor-associated kinase 1 (IRAK1).

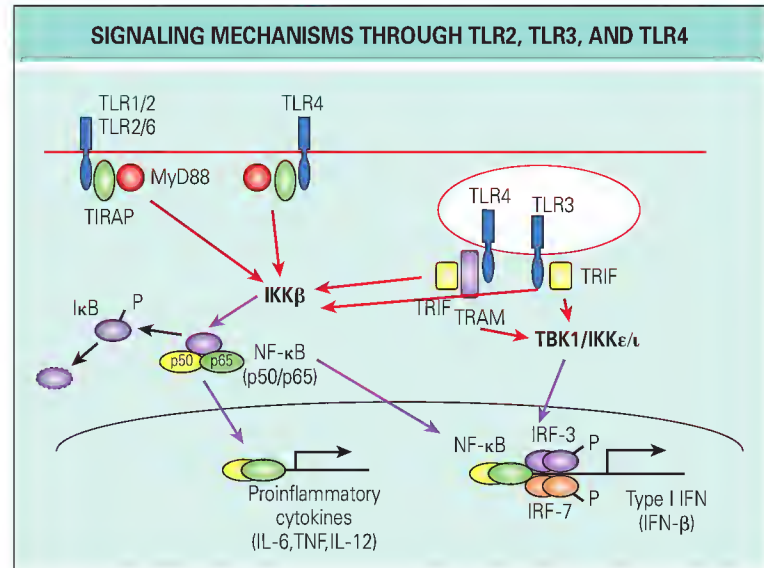


Fig. 16.8 Toll-like receptor 2 (TLR2), TLR3, and TLR4 can induce production of proinflammatory cytokines. TLR3 and TLR4 can also induce production of interferon- β but not of IFN- α . MyD88 is critical for TLR2/4-induced production of proinflammatory cytokines, whereas TRIF (TIR domain-containing adapter protein inducing IFN- β) is required for TLR3/4-induced production of IFN- β . In TLR3/4 signaling, TRIF also contributes to induction of proinflammatory cytokines. IL, interleukin; TNF, tumor necrosis factor.

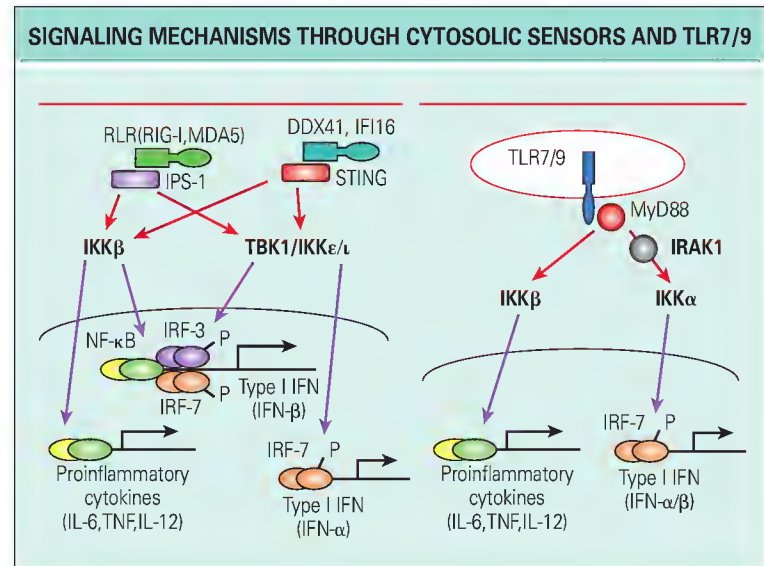


Fig. 16.9 Cytosolic sensors and Toll-like receptors 7 and 9 (TLR7/9) have potent ability to induce type I interferons (IFNs), including IFN- α and IFN- β , as well as proinflammatory cytokines. The TLR7/9-induced type I IFN induction pathway functions mainly in plasmacytoid dendritic cells. IL, interleukin; RLR, retinoic acid-inducible gene I (RIG-I)-like receptors; TNF, tumor necrosis factor.

RLRs do not use adapters with the TIR region but require a CARD-like domain-carrying adapter, IFN- β promoter stimulator 1 (IPS-1; also known as CARD adapter-inducing IFN- β [Cardif], mitochondrial antiviral signaling [MAVS], or virus-induced signaling adapter [VISA]) (see Fig. 16.9). IPS-1 can induce production of proinflammatory cytokines and type I IFNs through the activation of NF- κ B and IRF-3/7 via IKK β and IKK κ /t-TBK1, respectively. The TLR3/4-mediated pathway also converges this cascade by activating IKK β and IKK κ /t-TBK1 complex via TRIF, but not via IPS-1 (see Fig. 16.8). Some cytosolic sensors such as DDX41 and IFI16 activate TBK1 and induce type I IFNs through the association with stimulator of IFN genes (STING).

Inflammasome is a molecular platform that is activated mainly by NLRs (see Fig. 16.3).^{25,26} Inflammasome is activated in several ways, depending

on NLRs or NLR-related molecules such as NLRP3, NAIP5, NAIP2, NLRP1, or AIM2. Each inflammasome requires apoptosis-associated specklike protein containing a caspase activation and recruitment domain (ASC, also known as *pyrin domain and CARD domain containing* [PYCARD]) or NLR family CARD domain-containing 4 (NLRC4) as a CARD-containing molecule. ASC and NLRC4 are critically involved in recruiting caspase-1, which can convert pro-IL-1 β and pro-IL-18 to biologically active cytokines IL-1 β and IL-18, respectively.

SENSORS AND DISEASES

Toll-like receptors and autoimmunity

As noted earlier, nucleic acid-sensing TLRs cannot distinguish between host- and microorganism-derived nucleic acids. Unmethylated CpG motifs, which are TLR9 ligands, and ssRNA, which is a TLR7 ligand, can be found in the host. Host cells are phagocytosed after they die, and nucleic acids from ingested cells are then released to endosomes or phagosomes. Thus hosts potentially expose themselves to the risk of an autoimmune response. However, this risk is contained by several factors. First, these nucleic acids are very unstable and easily degraded. Second, TLR7 and TLR9 are expressed in the endosome or endoplasmic reticulum and segregated from nucleic acids released in the serum. Furthermore, the host possesses some DNA sequences that can inhibit TLR9 signaling.²⁷ Such sequences can be found in the telomere. Thus several fail-safe mechanisms prevent unwanted adjunct effects of host-derived nucleic acids.

The break of this tolerance seems to contribute to the pathogenesis of certain autoimmune diseases, such as systemic lupus erythematosus (SLE).²² In SLE, anti-nucleic acid antibodies are produced, and immune complexes containing nucleic acids are retained as a stabilized form in the serum. The immune complexes are then incorporated into and activate PDCs to produce type I IFNs by coengaging TLRs and Fc receptors. In addition to anti-nucleic acid antibodies, endogenous proteins also can bring out the autoimmune potential of host-derived nucleic acids. Upon massive cell necrosis, nuclear proteins such as high-mobility group box 1 (HMGB1) are released. These proteins bind nucleic acids and facilitate TLR9-induced immunostimulatory effects. One of these, the cationic antimicrobial protein LL37, can also form a complex with DNA. This complex formation facilitates the incorporation of DNA by PDCs and its retention in the early endosome, which thereby activates the PDCs to produce type I IFNs via TLR9. Production of LL37 is elevated in the skin lesions of persons with psoriasis.²⁸ Chromatin proteins and LL37 are included in neutrophil extracellular traps (NETs), which are released from neutrophils. NETs were originally identified as the mechanisms for killing invading microorganisms, but accumulating evidences suggest that NETs are also involved in the pathogenesis of autoimmune diseases.²⁹ Thus not only anti-nucleic acid antibodies but also endogenous molecules contribute to bypassing the fail-safe mechanisms that would normally block the immunopathologic potential of TLR7/9 signaling (Fig. 16.10).

Rheumatoid factor (RF) is an immunoglobulin that can bind to certain types of immunoglobulin G and is often found in the sera of patients with autoimmune disorders. Immune complexes containing nucleic acids can activate RF+ B cells by dual engagement of a B-cell receptor and TLR9.³⁰ Thus TLR signaling is critically involved in both PDC and B-cell activation in autoimmunity.

Toll-like receptors and metabolic diseases

Innate immune sensors also play major roles in the pathogenesis of metabolic diseases that so far have been considered to be nonimmunologic diseases. During the course of obesity, adipocytes secrete chemotactic factors and recruit macrophages. Adipocytes also produce saturated fatty acids, which activate recruited macrophages via TLR4 to produce TNF- α . TNF- α then further activates adipocytes to produce saturated fatty acids. Thus obesity is associated with a low-grade chronic inflammation caused by the loop between adipocytes and macrophages.³¹ Furthermore, mitochondrial DNA can cause myocarditis and dilated cardiomyopathy when it escapes degradation by autophagy.³² TLR9 is required for induction of this inflammatory state leading to heart failure.

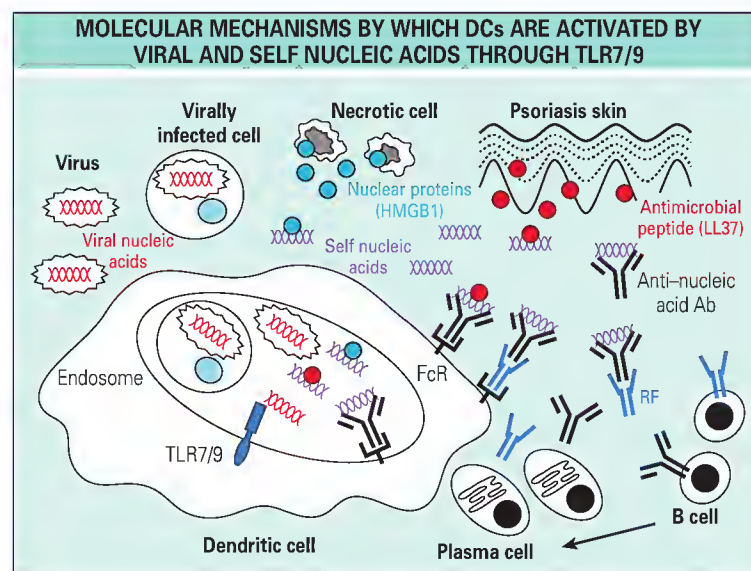


Fig. 16.10 Viral and self nucleic acids activate dendritic cells (DCs) through Toll-like receptors 7 and 9 (TLR7/9). Virus or virally infected cells are incorporated and viral nucleic acids are released in the endosome, where nucleic acid-recognizing TLRs are localized. Self nucleic acids also gain access to the endosome through the association with anti-nucleic acid antibodies, rheumatoid factor (RF), nuclear proteins, or antimicrobial peptides. On binding of TLR9 to its ligand, the extracellular domain of TLR9 is cleaved to be activated. Ab, antibody; FcR, Fc receptor; RF, rheumatoid factor.

NOD-like receptors and inflammation

Excessive activation of the inflammasome can provoke various inflammatory conditions. Hyperuricemia leads to precipitation of uric acid crystals (monosodium urate) in the joints and causes gout arthritis through NLRP3 activation. Pneumoconiosis is a pulmonary inflammatory disease induced by long-term inhalation of particulate dust such as asbestos or silica, which can activate the NLRP3 inflammasome. Furthermore, autosomal dominant mutations in NLRP3 are associated with a group of autoinflammatory disorders that include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystemic inflammatory disease. Clinical symptoms of these diseases include recurring episodes of fever, rash, and arthropathy. Notably, these manifestations are ameliorated by treatment with an IL-1R antagonist (see Chapter 165).

CONCLUSION

The innate immune system efficiently uses a combination of signaling, internalization, and soluble sensors to establish host defense. Intense research over the past few years has led to the clarification of the basic molecular mechanism of innate immunity, and several clinical applications that target innate immune receptors are now in development. Notably, innate immune sensors detect not only MAMPs but also DAMPs, and their recognition of DAMPs contributes to the pathogenesis of various metabolic disorders that have not been considered to be immunologic diseases. Therefore further understanding of how innate immune cells function may potentially lead to the development of new treatment strategies for a variety of disease conditions beyond the immune disorders.

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17

Systems biology

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- Analyses at the systems level deal with emergent properties of normal (healthy) and abnormal (pathologic) systems resulting from the interplay of all their molecular components. The advent of systems biology and the knowledge from systems-level studies on inflammatory processes can uncover complex molecular mechanisms and foster innovative patient- or group-specific treatments.
- Integration of technologies and data types is imperative for systems approaches to gain holistic insights into networks and whole biologic systems. At the same time it represents a serious challenge that must be addressed not only by information technology solutions but also by significant methodologic and cultural changes in the investigational approaches of the scientific and medical communities.
- Reconstruction of signaling and transcriptional networks enhances the understanding of biologic systems. Superposition of computational methods associating specific network behaviors with genomic makeups and downstream clinical outcomes will enable genome-informed diagnostics and identify therapeutic approaches using single agents or combinations of agents that correct network malfunctions.

INTRODUCTION

This chapter discusses systems biology and associated technologies and focuses on answering the following two questions:

1. Can the molecular processes underlying inflammation be characterized in a comprehensive fashion?
2. Would such characterizations go beyond the descriptive surface and reveal insights into disease mechanisms that could inform diagnosis or choice of therapy?

Genomics, transcriptomics, proteomics, metabolomics, and any other “-omics” approaches should be of interest to the rheumatology scholar because they represent global and systematic, as opposed to focused or anecdotal, molecular descriptions of a healthy or pathologic process in biology (Fig. 17.1). These “-omics” perspectives, which can be grouped as elements of what is collectively termed *systems biology*, stem from recognition that knowledge of the human and other genomes obliges us to consider the roles of all possible molecular players in the process under investigation, and not just the role of individual genes and gene products.

WHAT IS SYSTEMS BIOLOGY?

Systems biology aims at understanding biologic and pathologic processes as integrated entities. This requires understanding the properties of the entire system from the whole molecular pathway through to the target organelle, cell, organ, and ultimately the whole body—a sort of bird’s-eye view or wiring plan. The analogy to a car engine can be useful here. For example, consider dealing with individual engine parts, such as a spark plug. With this approach, the spark plug is discovered to be essential for the engine to start, but relatively little is understood beyond that. The first rough assembly of the human genome sequence published in the year 2000 allowed us access to a more complete “parts list” (i.e., the genome). Other parts lists (e.g., the proteome) have since followed, delivered by “-omics” technologies. Yet systems are more than the sum of their parts. Their properties are

a consequence of the interplay of their elements. Thus, to fully understand an engine in its entirety, the assembly plan as well as a model of how the engine works is needed. Using this analogy, therefore, one could include what fuels it, what sort of performance can be expected, and what is the waste it generates. This higher-level understanding is the essence of systems biology. It involves quantitation as well as networks and mathematical modeling, as discussed below. This makes systems biology very different from the analysis of single elements of a system and represents a great challenge for investigators. Physiology has traditionally been the biomedical area in which the function of the body parts has been investigated in the context of the next level of organization (cells within organs within bodies) to determine interdependencies and higher-order function. For most purposes, it is fair to consider systems biology a modern, molecularly savvy type of traditional physiology that takes for granted a knowledge of the tiniest building blocks of individuality, the genes in the genomes.

EXAMPLE OF SYSTEMS BIOLOGY IN PRACTICE

An early example of how such a systems-level perspective can help us understand the underlying principles of entire systems involves the analysis of genes regulated by serum. For the two decades preceding the new millennium, scientists studied serum-stimulated gene-regulatory elements of individual genes, such as the c-Fos transcription factor or collagenase. Serum stimulation was assumed to induce the same response as growth factor stimulation, and therefore these individual gene products were assumed to regulate cell growth. When Iyer and colleagues, using cultured fibroblasts, set out to study the response to serum addition not of an individual gene but of some 9000 human genes in parallel, they observed unique and unexpected patterns.¹ Rather than being involved in cell growth, many of the genes that were turned on by serum were known to be involved in wound healing, that is, tissue remodeling and repair. Suddenly, the serum response element in the collagenase gene, for example, made sense, also in physiologic terms. Since then, hundreds of biologic processes have been studied with the aim of understanding the properties of systems or subsystems (i.e., smaller units with unique properties). In an era in which pathophysiologic variations between individual humans need to be interpreted on the basis of their genomic composition and epigenetic state, the systems perspective is the only existing route to translate molecular information into physiologic meaning and should therefore be important for all physicians.

KEY TECHNOLOGIES EMPOWERING SYSTEMS BIOLOGY

Traditional hypothesis-driven research is being bypassed by data- or systems-driven research for the unbiased exploration of the properties of a system that can then be used to generate novel hypotheses. Systems biology typically studies biologic systems by systematically perturbing them (biologically, genetically, or chemically), monitoring the gene, protein, metabolite, and informational pathway responses, integrating these data, and ultimately formulating mathematical models that describe the structure of the system and its response to individual perturbations (Fig. 17.2).² It is important to note for the medical reader that a genomic alteration from the norm, such as a mutant gene or a rare allele, in this context represents a perturbation of the system. Hood and Flores have described this systems approach as the virtuous cycle of “biology drives technology drives computation and mathematics.”³ Technology advancements lead to new data types that in turn require new computational and mathematical tools giving rise to a better understanding of the system in an iterative cycle.

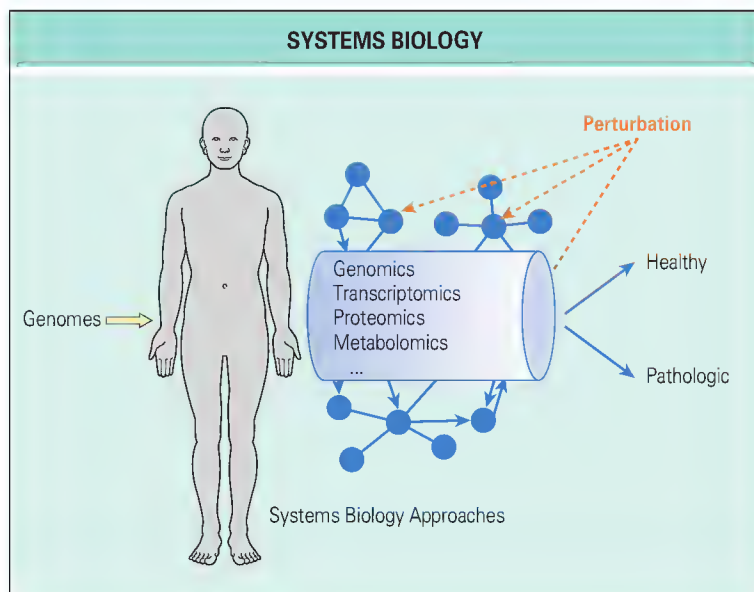


Fig. 17.1 Systems biology is understanding the wiring of whole molecular pathways and organisms. Systems approaches include “-omics” technologies to make informed decisions regarding a healthy or pathologic process in a patient.

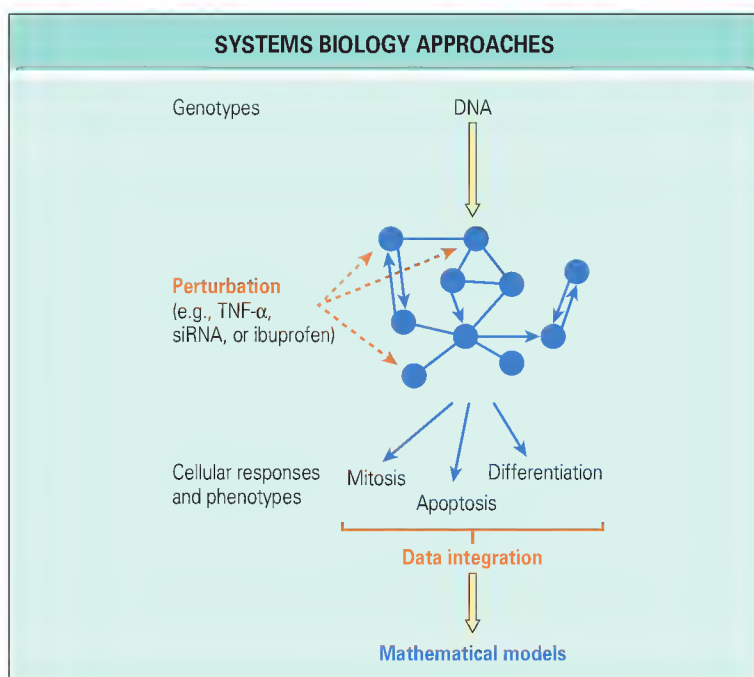


Fig. 17.2 In systems biology, networks of interacting molecules are placed between genotype and phenotype. Each node (depicted as a circle) represents either a gene, protein, or metabolite. Gene, protein, metabolite, and pathway responses are monitored following biologic, genetic, or chemical perturbation. Computational and mathematical tools eventually aid in better understanding the system. siRNA, small interfering RNA; TNF- α , tumor necrosis factor- α .

In Table 17.1 the key data-gathering techniques for generating quantitative and qualitative data for systems studies are described. For a more in-depth review of the concepts of systems biology and its impact on human biologic research, the authors highly recommend further reading in the *Handbook of Systems Biology*.⁴ A complete description of methods used to create computational models and conduct simulations of immune function is discussed in detail elsewhere.⁵ The “-omics” technologies such as those presented in Table 17.1 have the potential to transform medicine from traditional symptom-oriented diagnosis and treatment of diseases toward disease prevention and early diagnostics.⁶

Analysis tools and data management

Systems biology research projects often create data sets of enormous size and diversity. Biologic systems display complex behaviors that can seldom be interpreted in terms of linear relationships between the elements that compose them. Rather, these components are highly connected and in complex, nonlinear relationships with each other, such as feedback mechanisms and other regulatory loops and relays. Therefore bioinformatics and modeling skills have become essential elements in systems approaches. Large data sets can be sorted by applying statistics, algorithms, and software developed by mathematicians and computational scientists. The aim is to make testable predictions about the system, for example, how the overall system will be affected by alterations in the concentration of a component that influences the efficiency of a certain element. An important point is that the software solutions being developed must be driven by the needs of the systems biologists actually interested in understanding the human physiologic process. Furthermore, there is a need to make both data generation and data analysis tools accessible to all scientists to better catalyze worldwide scientific progress. This requires standardization efforts and widespread data sharing. In addition to rewarding researchers by offering publication-like citations (in the form of digital object identifiers, or DOIs) for voluntarily publishing data or by providing attractive data management systems supporting their work, the best way to promote a culture of data sharing is by making data management and sharing a condition for funding. Besides policies and incentives, development of appropriate data management systems is indispensable.

The basic requirements for a large-scale systems biology data management system are the following:

- Automated data collection approaches: providing data storage and data security
- Data integration: providing metadata and data standardization to make data comparable
- Data delivery: making data publicly available, thereby facilitating systems biology research

This is true for the clinical laboratory setting as well as for the basic large-scale biologic research laboratory. Further requirements are the extensibility to new data types and functionality as well as carefully designed interfaces for integration with other systems in a continuously changing environment. Support for modeling of data and uploading to public repositories, such as the National Center for Biotechnology Information Gene Expression Omnibus, European Bioinformatics Institute ArrayExpress, PeptideAtlas, or BioModels, are equally important. A comprehensive review and a more detailed discussion of data management systems successfully employed in large-scale systems biology projects is available elsewhere.¹²

Data standardization and integration

As mentioned earlier, two major challenges in systems biology are data standardization and integration. Data come in different formats, metrics, and degrees of statistical significance. Often data have been obtained using different systems, protocols, and/or reagents (e.g., cell type, species, growth conditions, biochemical handling). Biologic objects, be they genes, proteins, or tissues but also diseases, suffer from an international lack of standardized language and nomenclature. This is a fundamental impediment to data comparison and integration that is often dealt with by making compromises, which affect the reliability of observations.

Data standardization

A multitude of initiatives have been taken in recent years to assign non-equivocal nomenclature to biologic objects as well as to create computational modeling languages that can deal with nonuniform data sets. Data comparison and exchange are considerably easier within a technologic area (e.g., genomics) than between different areas (genomics vs. metabolomics). The Minimum Information for Biological and Biomedical Investigations recommendations represent the agreed international community standards in the field needed to reproduce experiments and are complemented by many other standards, such as the proteomics standards initiative—molecular interactions in the proteomics field, the mass spectrometry markup language in the mass spectrometry area, BioPax as the exchange format for pathway data, and the systems biology markup language for the description of systems biology models in xml.

Data integration

Data intersection and integration are nevertheless very powerful in unearthing patterns that would otherwise be difficult to discern. For example, the

TABLE 17.1

Three questions on the key technologies empowering systems biology

What is it?	How is it done?	What is it good for?
Genomics		
Comprehensive characterization of whole-genome sequences of individuals (patient groups, ethnic groups)	High-throughput parallel sequencing by next-generation sequencing (NGS) technologies	Determine correlation with disease through statistics, computational modeling (e.g., the International Cancer Genome Consortium efforts in cancer genomics) ⁷
Epigenomics		
Characterization of changes in chromatin states and gene regulation that can be inherited on top of the genomic DNA sequence	Determination of whole-genome DNA methylation profile by bisulfite sequencing, mapping of chromatin domains associated with particular modifications (histone acetylation, methylation, etc.), characterization of noncoding RNAs	Essential to explain the environmental context-dependent genotype-to-phenotype transition (as addressed, e.g., by the International Human Epigenome Consortium and the ENCODE [ENCyclopedia of DNA Elements] projects) ^{8,9}
Metagenomics		
Characterization of the genomic information present in particular samples (e.g., feces, hair follicles, saliva) to determine the composition of the human microbiota	Genomics technology followed by computational deconvolution, with avoidance of human sequencing by filtering	Represents critical interface between body and environment and can be also causally associated with human disease (e.g., inflammatory bowel disease) as reflected by the initiative of the Human Microbiome Project ¹⁰
Transcriptomics		
Characterization of genomes in action, mapping of all coding and noncoding RNAs in a given tissue under a given condition	NGS technologies of RNA converted to DNA by reverse transcriptases and if necessary amplified by polymerases; NGS enables whole transcriptome sequencing (RNA-seq) and provides a high resolution and more quantitative alternative to microarrays	Reveals "fingerprint" and gene expression program of particular state of cells and tissues
Proteomics		
Parallel characterization of proteins (presence thereof, their interactions, modifications)	Mass spectrometry (mostly), protein arrays, or indirect genetic tools (yeast two-hybrid methods)	Measures endpoints of gene expression and their properties; identifies targets and receptors of agents and characterizes biomarkers
Metabolomics		
Parallel profiling of selected groups of metabolites (lipids, sugars, amino acids, etc.)	Selective enrichment by biochemical means followed by mass spectrometry (mostly) or chromatography	Provides powerful measurements of gene activity integration within environmental context
Phenomics		
Integration of all quantifiable molecular and nonmolecular features of a biologic system, including aspects of cell, tissue, organism shape, and appearance	All of the technologies above as well as high-content small interfering RNA screening and computer-assisted imaging	Allows for integration of many features not currently standardized (e.g., cell shape) but reflective of molecular action (cytoskeletal proteins)
Systems pharmacology		
Characterization of single or combination pharmacologic agents (small molecules, drugs, and biologics) by ability to perturb biologic systems	Integration of the approaches above, medicinal chemistry, chemoinformatics, and computational tools	Used for prediction of adverse effects, second medical use, strategic use of combination therapy and polypharmacology
Systematic single-cell analysis		
Use of all technologies above at single-cell resolution	Computer-assisted multiparameter microscopy (confocal, other), mass cytometry (fluorescence and mass spectrometry detected), ¹¹ as well as chip and microfluidic technologies	Avoids confounding averaging of molecular parameters over heterogeneous populations; allows detection of stochastic processes
Network analysis		
Organization of components of biologic systems in networks of physical interaction or other measurable relationships (clustering of properties, temporal order of expression of genes, etc.)	Graph theory and topologic analysis borrowed from mathematics	Detects functional relationships among molecules or among properties, predicts function of network members and regulatory properties of subnetworks
Computational modeling		
Use of computer and mathematics to imitate and predict the behavior of biologic systems	Algebraic or probabilistic mathematical tools, differential equations, flow analysis to obtain quantitative and dynamic biologic models	Allows one to test depth of mechanistic understanding of a process and ultimately to obtain tools predictive of diagnostic reliability or therapeutic outcome

combination of data on gene expression at the messenger RNA (mRNA) level (resulting from, e.g., quantitative sequencing of the ensemble of mRNAs in cells) and the protein level (resulting from, e.g., quantitative proteomic analysis) can synergize in conferring significance to observed changes. The ability to additionally obtain corroborating evidence by using

corresponding changes in metabolite composition or drug sensitivity, or by using a different cellular system, enhances the importance of the observed changes dramatically. Simple computational algorithms are used to parse or screen for synonyms and infer data from other species using gene orthology, whereas probabilistic statistical models are often used to deal with

incomplete data sets. There are advantages to keeping different experimental models (e.g., different cell lines or animal models) despite the trends toward standardization. It is critical, however, to maintain a high degree of normalization and controlled, defined language, particularly in medicine when sampling and processing patient tissues for analysis, to unleash the true potential of approaches at the systems level.

Models and networks

Essential to the discovery cycle of systems biology is the ability to derive and test models that should mimic physiologic events, such as the prediction of a molecular pathway to convey a signal or turn over a metabolite.¹³ For this, data that can be computed are a prerequisite, thus quantitative biology must go hand in hand with systems biology. This dovetails in a more medical sense with accurate parameters from laboratory medicine and genomic medicine. Two types of data can be distinguished. One is numerical and represents the quantity of a particular property, such as the affinity of one protein for another, the turnover rate of an enzyme, or the concentration of a metabolite or an mRNA. The other is topologic and represents the relationship of one biologic entity to another, such as the position in a greater network—for example, being “upstream” or “downstream” in a process. Additionally, the dimensions of time and space, as both numerical and topologic parameters, may vary. The ability to model actual physiologic situations necessitates gathering knowledge about both the “hierarchy” of a process and the architecture of the possible information flow associated with it, as well as values that quantify the individual components. Thus most systems biology models are based on molecular networks. When the networks are large, such as gene-regulatory networks and protein-protein interaction networks, useful information can be inferred from the structure of the network; for example, whether particular nodes (in network language, objects are “nodes” and connections or relationships are “edges”) represent bottlenecks, or how central they are in the process. This may indicate that particular genes, for instance, are master regulators. In the case of protein-protein interactions, preferred protein partners may always be found together, and together combine with alternate additional partners, which suggests modularity in the organization of proteomes. When the system under investigation is characterized well enough in terms of quantitative parameters such as enzyme kinetics, it has been useful to model its ability to process biologic matter or information. The intermediate metabolism of entire organisms, the sequence of events in cell cycle regulation, and even the oscillatory pattern of certain transcriptional processes have all been modeled successfully. Large research consortia are now tackling orders of magnitude more complex processes, such as the functions of a human liver.¹⁴

CASE STUDIES

Four selected global analyses are described in detail in the following sections as a first step toward a systems-level view of the complexity of biologic processes.

Host factors regulating infection across mammalian viruses

High-content small interfering RNA (siRNA) screens have been successful in systematically identifying new disease genes and in gaining insights into signaling networks. Currently, the two largest technical problems with this technology are the inconsistencies between the phenotypes generated by different siRNAs targeting the same gene, and weak comparability of similar siRNA screens performed by different laboratories or in different cell lines or using different siRNA libraries. A striking example is the largely nonoverlapping hit list (less than 7% overlap) produced in three published screens that identify host factors required for human immunodeficiency virus infection.¹⁵ Applying single-cell and computational analysis, Lucas Pelkmans and colleagues could significantly improve the reproducibility of siRNA screens when the population heterogeneity of cell lines was considered.¹⁶ More than 40 siRNA screens analyzing 17 different mammalian virus infections and related physiologic processes such as lipid homeostasis, endocytosis, and cell size regulation in two different cell lines were performed in this complex study. Measuring virus uptake as well as 200 cellular features at the single-cell level improved the reproducibility of hit lists of host factors required for the uptake of the same virus across different cell lines and between siRNAs required for the uptake of different viruses in the same cell line. With these hit lists, systems-level insights into host signaling networks involved in viral infection could be gained. Two distinct envelope-dependent

strategies by which viruses hijack regulation of protein translation can be deduced from this study. For example, of the 49 human kinases tested that have previously been shown to play a role in virus infection and endocytosis, DYRK3 and FRAP1 (also known as *mTOR*) had the most global effects on virus infection. More than half of all enveloped virus infections were more sensitive to DYRK3 silencing than to FRAP1 silencing, whereas most of the nonenveloped virus infections were more sensitive to FRAP1 silencing. Interestingly, FRAP1 is known to regulate protein translation, and the yeast homologues of FRAP1 and DYRK3 are known to play opposite roles in protein translation, which suggests that virus particle structure and type constrain the host cellular mechanisms that can be hijacked for infection.

Model of a mammalian transcriptional network mediating the differential response to pathogens

Amit and colleagues¹⁷ developed one of the first transcriptional networks for the mammalian innate immune system. As a case study they used the innate immune response of dendritic cells through Toll-like receptors. First, RNA microarrays were applied as a global profiling technology to measure the component states. Primary mouse dendritic cells were stimulated with Toll-like receptor ligands and genomewide mRNA levels were profiled over time. Second, a provisional network model was devised based on the coexpression of transcription factors and their putative targets. This included the nomination of 144 candidate regulators and the identification of 120 reporter or signature genes for monitoring the effects of perturbing regulators. In a third step, predictions of the resulting model were experimentally tested using a genetic network perturbation approach. Lentiviral small hairpin RNAs were used to silence the expression of the selected candidate transcriptional regulators, and a multiplex mRNA detection system was used to quantify the effect of each gene knockdown on the expression of the chosen signature genes. This allowed the construction of a network model that linked candidate regulators with specific target genes. The core network consists of 24 regulators encompassing both the inflammatory response (enriched for nuclear factor- κ B [NF- κ B] and other inflammation-responsive genes) and the antiviral response (enriched for interferon response factors and viral and other interferon-responsive genes). In the inflammatory response, several feed-forward loops were identified that may ensure response only to persistent and not to sporadic signals. In the antiviral response, a two-tiered circuit was discovered involving feedback and feed-forward loops, implicating a new module of cell cycle regulators not previously associated with this response. Further, over 75 additional genes were identified to fine-tune the regulation of target genes. From a biomedical perspective, identification of entire regulatory arms (viral vs. inflammatory) allows therapeutic targeting of specific pathways to control disease or enhance vaccine efficacy. To gain an even deeper understanding of the specific network components, this approach can be complemented by using proteomics and phosphoproteomics to select and test additional candidate regulators with mRNA levels that are unchanged in the immune response under study.

Topologic insight into the tumor necrosis factor- α /nuclear factor- κ B subnetwork

Affinity purification (AP) of proteins and identification of co-purified interactors by mass spectrometry (AP-MS) has become the preferred method for the analysis of protein-protein interaction networks because it produces data that better reflect the physiology of the system and the multidirectional complexity of a network. A systems approach was applied using AP-MS to map a protein-protein interaction network around 32 known and candidate tumor necrosis factor- α (TNF- α)/NF- κ B pathway components, and functional RNA interference (RNAi) perturbation assays to identify key modulators of the pathway.¹⁸ More than 200 molecular interactions were identified, about 70% of which were already known. A further 80 proteins not previously implicated in NF- κ B signaling were also identified, including 10 modulators of the pathway as shown by the combined loss-of-function analysis. Combining RNAi perturbations with AP-MS to map the physical and functional interactions of human signaling pathways is a paradigm for future studies, providing plenty of data to be followed up by more directed investigations. Another pathway relevant to human disease elucidated by AP-MS and RNAi is the autophagy pathway.¹⁹

Mathematical model for tumor necrosis factor- α -induced nuclear factor- κ B signaling

Whereas the previous example provides a wealth of topologic data about a signaling pathway relevant to human disease, this example contributes

quantitative data to this pathway. NF- κ B dynamics were measured in high throughput with a microfluidic cell culture system and live-cell imaging. The response of thousands of single cells was measured for a wide range of TNF- α concentrations. NF- κ B-dependent gene expression was also measured, and a model was presented to explain these findings.²⁰ In contrast to population studies, NF- κ B activation was shown to be heterogeneous at the single-cell level and is a digital process with fewer cells responding at lower TNF- α doses. Cells also encode a set of analogue parameters to modulate the signaling outcome, such as the timing, intensity, and number of transcription factor oscillations, to create digital outputs, such as activation and early gene expression. Early gene expression is not dependent on the inducing signal intensity, whereas the expression of later genes requires persistent nuclear localization of NF- κ B, which exists only at the highest input signal levels. Elucidation of NF- κ B activation as a case study in systems biology has been very productive, leading to the study of NF- κ B dynamics in response to different TNF- α concentrations and time-varying TNF- α stimulation, as well as with different ligands, on drug perturbations, and in response to bacteria. The example described here represents one of several model-driven studies performed in the last 10 years.

FUTURE OF SYSTEMS BIOLOGY IN RHEUMATOLOGY

A surge of systems-level studies of inflammatory processes can be envisaged. Over the next 3 to 5 years, genomic sequences will likely be available for all patients seeking treatment for serious inflammatory conditions. There will be the potential for patients to increasingly sample both data on their own health state and information from Internet resources. Yet what will be critical is the ability to interpret the somatic epigenetic changes associated with the diseased state in the diseased tissue in the context of particular environments (e.g., microbial, dietary, smoking). Possibly this will be inferable from data obtained using serum samples or directly from biopsy

specimens. Computer models based on the molecular networks of the inflammatory process and on the mechanism of action of the available therapeutics will triangulate data on therapeutic outcome from large databases and suggest patient- or group-specific treatments. The following are areas of activity in which particular progress can soon be expected:

- Creation of comprehensive diagnostic and prognostic profiles of cytokines, chemokines, and other secreted factors based on systems-level evaluations (away from individual levels and combinations) through application of the recently developed mass cytometry approach
- Appreciation of differences between large groups of responders compared with nonresponders to signaling network responses to antiinflammatory single and combination therapies
- Single-cell-resolution mapping of differential healthy and nonhealthy expression profiles of most cell types involved in inflammation (including new cell types soon to be discovered by molecular profiling)
- Exhaustive characterization of human proteins of the innate immune system devoted to antimicrobial detection and their potential role in autoimmunity
- Comprehensive characterization of the human body-associated microbiome (intestine, oral cavity, skin) and its association with inflammatory conditions

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18

Epigenetics in rheumatology

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- Epigenetic modifications consist of DNA methylation and modifications of histone tails.
- Epigenetic modifications can be changed by environmental influences and can be restored after mitosis and meiosis.
- Epigenetic modifications of chromatin render it more or less accessible for transcription factors and thereby define which genes in a cell are transcribed.
- Even though DNA methylation always leads to gene silencing, histone modifications can enhance or suppress gene transcription, depending on the modification.
- Global DNA hypomethylation and hypomethylation/hypermethylation at specific promoters occur in immune and stromal cells in rheumatic diseases.
- Changes in histone acetylation, methylation, and SUMOylation have been found in rheumatic diseases.
- MicroRNA is small inhibitory RNA whose expression is regulated by epigenetics and which in turn regulate the expression of epigenetic enzymes.

WHAT IS EPIGENETICS?

Expression of genes in a cell is regulated on three different levels. First, the genetic code determines which proteins can potentially be made by an organism. Second, the epigenetic code modifies chromatin so that it is accessible for transcription or not. Third, transcription factors bind and initiate the transcription of a gene.

All proteins made by a cell are encoded in the genetic code. The sequence of the DNA determines the genotype, which is unique for each individual. However, even though each cell of the body contains the full and identical genetic code, different proteins are made by different cells according to their functions. This specific pattern of transcribed genes is the basis for the different phenotypes of the cells in the body and is maintained by the epigenome. Epigenetic modifications of chromatin render it more or less accessible to transcription factors and thereby define which genes in a cell are transcribed.

To ensure that each daughter cell has the same gene expression pattern as its predecessor and can thus fulfill the same function, the epigenetic code, just as the genetic code, must be heritable. In contrast to the genetic code, however, the epigenetic code must also be modifiable so that the changes in gene expression needed during development and differentiation can occur. Heritable epigenetic modifications are restored after mitosis and also after meiosis and thus are passed not only to daughter cells but also to following generations. Transient epigenetic changes are placed and removed, depending on the current requirements of the cell. Accordingly, changes in the epigenetic code can be introduced by environmental conditions. By these means the cell can adapt to changes in its environment by stable alterations in its gene expression pattern.

An impressive example of the interaction of the environment with the epigenome is maturation of the queen bee in a bee hive. The contents of the royal jelly are able to influence epigenetic modifications such that only the larva that is fed royal jelly can express the genes necessary to grow into the queen bee.¹ Similarly, nutrition can also influence the epigenetic code in mammals. Key experiments by Waterman and colleagues showed

that feeding pregnant agouti mice a special diet of folic acid and vitamin B₁₂ changes the fur color of their offspring.² These remarkable phenotypic changes are induced by epigenetic silencing of the agouti gene. In addition, environmental influences can introduce epigenetic changes in humans that are still visible in the offspring. For example, epigenetic modifications that silence expression of the insulin-like growth factor II gene have been found in children whose mothers were pregnant during the Dutch Hunger Winter of 1944/1945.³

Already in 1957 a strong influence of the environment on the epigenome and thus on cellular differentiation and function was propagated by Conrad Waddington.⁴ However, only in recent years has epigenetic research been widely acknowledged. The more the field advances, the more diseases are found in which the epigenome is affected and possibly contributes to the development and persistence of disease. In parallel, drugs that modify the epigenome are developed in the hope that pathologically changed gene expression can thus be permanently corrected.

THE BASIC MECHANISMS

Epigenetic modifications are placed directly at the DNA base cytosine or at the protruding tails of the histones. They can directly and indirectly affect gene transcription. Direct effects are induced by changes in the packing of chromatin and thus alter its accessibility for transcription factors; indirect effects are mediated by the recruitment of effector molecules.⁵

Histone modifications

The five histone proteins H1, H2A, H2B, H3, and H4 keep the DNA packed within the nucleus so that the positively charged amino acids of the histone tails interact with the negatively charged phosphate backbone of the DNA. If negatively charged epigenetic modifications are placed at the histone tails, they induce a conformational change that loosens the chromatin structure and thus induces the formation of transcribed euchromatin. Other modifications tighten the packaging of the DNA, which results in inactive heterochromatin. In addition, effector molecules are bound that lead to stabilization or inhibition of the transcription machinery.⁵

A variety of different modifications of histone tails are known, namely, acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, and adenosine diphosphate (ADP) ribosylation. These modifications are not isolated but are interconnected and influence gene transcription in combination or sequentially. Even though all these histone modifications are assumed to modulate transcriptional activity, they vary greatly in their stability and impact. Up to now, however, no direct evidence has shown that these histone modifications themselves initiate changes in gene expression. Instead of being activating or repressing by themselves, histone modifications might also be installed at active or silent chromatin to stabilize the current status.⁶ Nevertheless, certain acetylation and methylation marks strongly correlate with euchromatin and heterochromatin, respectively.⁷ Other modifications, however, could not so clearly be connected to a transcriptional activity state.

Histone acetylation

Histone acetylation is a rather transient histone modification that is not heritable. Histones are acetylated by histone acetyltransferases (HATs) and deacetylated by histone deacetylases (HDACs). HATs and HDACs are promiscuous enzymes that in addition to acetylation of histones, also catalyze the acetylation of transcription factors, oncoproteins, and tumor suppressors.⁸ HDACs have come into focus in recent years because of the development of HDAC inhibitors and their successful application in cancer therapy. The HDAC family consists of 18 members that are classified into 4 groups.

The HDACs in group III, the sirtuins, are nicotinamide adenine dinucleotide dependent, whereas the rest of the family is zinc dependent. The commonly used HDAC inhibitors work by blocking the Zn activity site and accordingly inhibit the function of all class I, II, and IV HDACs, but not the Zn-independent sirtuins. How much the therapeutic action of HDAC inhibitors stems from the resulting increase in histone acetylation or acetylation of nonhistone proteins has not been clarified to this point.

Histone tails are acetylated at lysines. Acetylated lysines are found in histone tails at sites of actively transcribed DNA. Acetylation neutralizes the positive charge of the histone tails and thus decondenses the chromatin.^{9,10} Proteins with a bromodomain can recognize acetylated histone tails and bind to them.¹¹ The bromodomain is commonly found in proteins that are known to remodel chromatin and regulate transcription. Thus, acetyl residues placed at lysines in the histone tails support gene transcription by conformational changes in chromatin and by attraction of activating effector proteins.

Histone methylation

Histone methylation is much more stable than histone acetylation and is preserved during cell division. It plays a crucial role in embryogenesis and initiates silencing of the inactive X chromosome in female cells.¹² Methyl residues are placed mainly at arginines or lysines of the histone tails by histone methyltransferases (HMTs). Methylation of histidines has also been described, but its function is largely unknown.¹³ Depending on the HMT, arginines are monomethylated or dimethylated, whereas lysines are monomethylated, dimethylated, or trimethylated.¹⁴ Even though methylation at lysines can be removed by demethylases, no enzyme that directly removes methyl residues from arginines has been found thus far. However, monomethylated arginine can be deaminated to citrulline by peptidylarginine deiminase 4 (PAD4). Citrullination is associated with transcriptional repression.¹⁵ Demethylation of methylated lysine is catalyzed by proteins that contain an amine oxidase or a Jumonji C (JmjC) domain.

Methylation can enhance as well as repress transcription. The effect on gene transcription depends on the location and quantity of methyl residues placed at the amino acids. For example, three-methyl residues (trimethylation) at lysine number 4 of the tail of histone 3 (H3K4me3) are found at sites of active gene transcription, whereas trimethylation of lysine number 27 (H3K27me3) suppresses gene transcription.^{16,17} Importantly, a combination of different methyl marks, as well as a combination of methyl marks with other histone modifications, can largely influence the outcome. The effect of these combinatorial histone modifications on gene transcription is mediated by the binding of different effector complexes. Additionally, these effector complexes can lead to further modifications (e.g., deacetylation if they have HDAC activity), which reinforces the effect of a methyl mark.¹⁸

Methyl marks on histones are bound by proteins with methyl-binding properties like plant homeodomain (PHD) fingers and by the Royal superfamily of chromatin-binding proteins containing, among others, chromodomain, Tudor domain, and malignant brain tumor (MBT) domain.^{5,19,20} The proteins that recognize methyl marks can either directly activate or repress transcription or can recruit chromatin-remodeling complexes.^{19,21}

Histone methylation has also been suggested to induce chromosomal looping, which brings gene elements such as promoters in close contact with genes of a different genomic region.²²

Phosphorylation

Phosphorylation is a histone modification that is induced rapidly (e.g., after stress stimuli) but is equally removed rapidly.²³ A longer-lasting effect of histone phosphorylation is, however, achieved by interconnection with other, more stable histone modifications. Phosphorylation can, for example, entail histone acetylation and methylation.^{24,25} In particular, phosphorylation and acetylation work in synergy since both of them negatively charge histones and thereby loosen their connection to the DNA. Furthermore, phosphoacetylated histones are bound by 14-3-3 proteins, which initiate transcription. Phosphate groups on histone tails are also recognized by proteins with BRCA1 C-terminal (BRCT) domains.⁵

As other proteins, histones are phosphorylated by histone kinases at their serines and threonines and are dephosphorylated by phosphatases.

SUMOylation

Addition of the small ubiquitin-related modifier (SUMO) to lysines in the histone tail is called SUMOylation. SUMOylation is considered a counter player to acetylation since it occurs preferably at acetylated lysines and, by attracting HDACs, leads to removal of acetylation and repression of gene transcription.²⁶ Transcriptional repression can then be further reinforced by binding of heterochromatin protein 1 (HP1). HP1 works together with HMTs to induce stable repression via histone methylation.²⁷

SUMO is conjugated to lysines by E1 SUMO-activating enzymes, E2 SUMO-conjugating enzymes, and E3 SUMO ligases and removed by isopeptidases.²⁸

Ubiquitination

Even though SUMO and ubiquitin share structural features and both are conjugated to lysines, their function in transcriptional control is different. In particular at H2A, monoubiquitination is found at sites of active transcription, whereas in H2B it is associated with transcriptional repression.^{29,30} H3 and H4 have been shown to carry polyubiquitin marks, but their effect on gene transcription is not known yet.³¹ Ubiquitination exerts its effect by induction of other histone modifications, for instance, methylation and the formation of effector complexes that promote or inhibit transcription.³² Recent reports also suggest loosening of chromatin packaging as a result of the concerted action of ubiquitin and acetyl residues.³³

Ubiquitin ligases mediate monoubiquitination and polyubiquitination of histone lysines, which can be again deubiquitinated by deubiquitinating enzymes.

Adenosine diphosphate ribosylation

ADP ribosylation is probably the least studied histone modification. Although glutamic acid was described primarily as an acceptor site for ADP ribose in histones, it was later shown that histones are ADP-ribosylated at lysines.³⁴

Histones are mono-ADP-ribosylated by mono-ADP ribosyltransferases (MARTs) or poly-ADP-ribosylated by poly-ADP ribosyltransferases (PARPs).²⁴ Similar to histone ubiquitination, cooperation of ADP ribosylation with acetylation is assumed.³⁵

DNA methylation

The most common and best studied epigenetic modification of DNA is methylation of the cytosine ring resulting in 5-methylcytosine. Recently also, 5-hydroxymethylcytosine has been found in DNA.³⁶ The functional role of this modification, however, still has to be clarified. Since up to now no enzyme has been found that demethylates DNA, even though active DNA demethylation takes place in the genome, it has been proposed that the formation of hydroxymethylcytosine is an intermediate of the demethylating process.^{37,38} During development, DNA is globally demethylated in the paternal and at a later time also in the maternal pronucleus. In addition, changes in the methylation pattern occur in the fully developed organism, for instance, at the promoter of estrogen-responsive genes.^{39,40} Demethylation can occur either actively by removal of methyl marks or passively by lack of restoration of methylation marks after cell division.

Nevertheless, DNA methylation is the most stable epigenetic modification and is typically restored after mitosis and also meiosis. Although de novo methylation is accomplished by DNA methyltransferase 3a (DNMT3a) and DNMT3b, restoration of methyl marks after mitosis is catalyzed by DNMT1. Usually, these enzymes catalyze the addition of methyl marks to the cytosine ring at genomic locations with a high content of cytosine-phosphatidylguanine (CpG) dinucleotides, so-called CpG islands. In addition, regions that border CpG islands, which are called CpG shores, are methylated. This methylation pattern occurs mostly at sites of tissue-specific methylation.⁴¹

Apart from CpG methylation, DNA can also be methylated in a CHG or CHH context, where H can stand for adenine, cytosine, or thymidine.⁴² CHG or CHH methylation is found in pluripotent stem cells and disappears during cellular differentiation.

DNA methylation always represses gene transcription. Gene silencing by DNA methylation works by interference with transcription factor-binding sites or by recruitment of transcriptional repressors. Repressor proteins can also bind histone-modifying enzymes such as HDACs and thus lead to changes in the histone code.

DNA methylation is absolutely necessary for the repression of repetitive sequences such as *Alu* sequences and retrotransposons, genomic imprinting, X chromosome inactivation in female mammals, and tissue-specific gene expression. Accordingly, disturbances in DNA methylation have profound consequences on cell physiology.

A summary of epigenetic marks is provided in Figure 18.1.

EPIGENETICS IN DISEASE

Along with knowledge of the epigenetic mechanisms in healthy cells, more knowledge about epigenetic changes in disease has been gained. There are diseases in which alterations in the epigenetic machinery were found to be

Fig. 18.1 Epigenetics in the regulation of gene expression. AAA, poly A tail; Ac, acetylation; ADP, ADP ribosylation; Me, methylation; P, phosphorylation; SUMO, SUMOylation; Ub, ubiquitination.

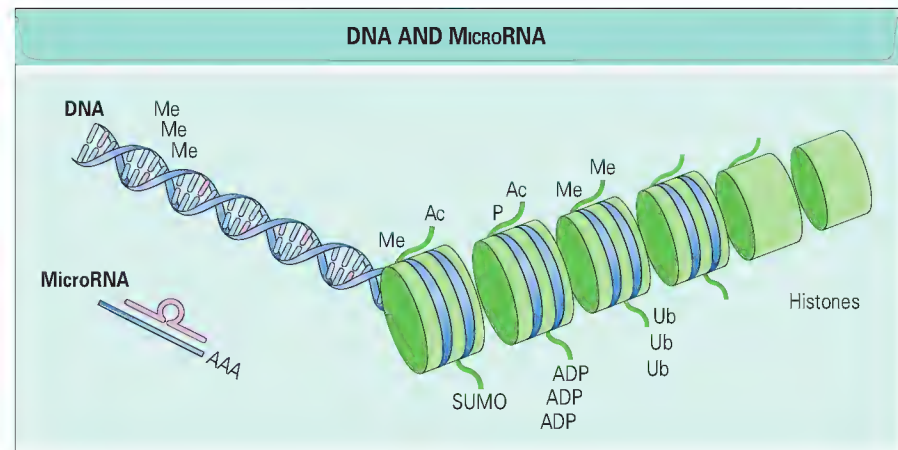
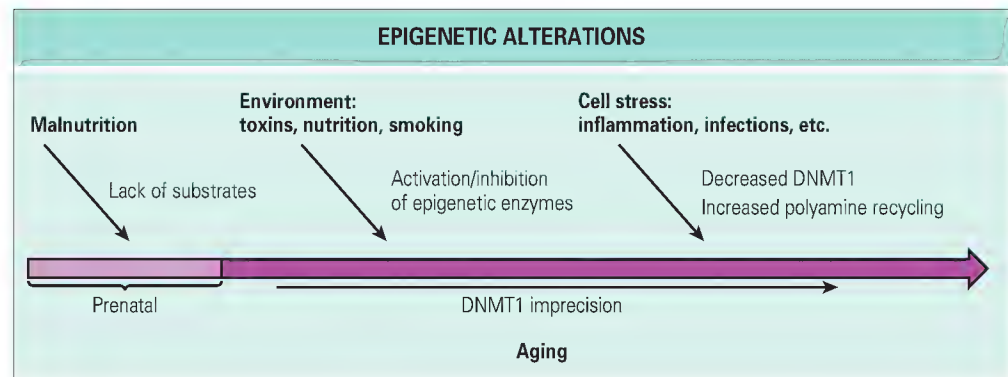


Fig. 18.2 Events that can cause changes in the epigenome. DNMT1, DNA methyltransferase 1.



causative, in most diseases, however, changes in the epigenome were found to be associated with just the disease state, but it is not yet clear whether these changes are a cause or a consequence of the disease.⁴³

As mentioned earlier, epigenetic silencing of genomic regions is crucial for the proper formation of heterochromatin. In some cases, correct silencing of maternal or paternal parts of the genome is needed for a balanced expression of gene products. This is true not only for the X chromosome in female organisms but also for a variety of specific genes called imprinted genes.⁴⁴ In contrast to the normal diploid expression of genes, imprinted genes are haploid-expressed, which leads to a physiologic reduction in gene dosage. Currently, approximately 80 of these genes have been described in which physiologically only the maternal or the paternal allele is transcribed, but not both. On chromosome 15q11-13, for instance, certain genes are known to always be transcribed from the maternal chromosome and others only from the paternal. Disturbances in imprinting at this location, which leads to incorrect silencing or expression of the imprinted genes, are known to be one cause of Angelman syndrome and Prader-Willi syndrome.^{45,46} Similarly, disturbance in the imprinting process is one cause of the increased risk for tumor in patients with Beckwith-Wiedemann syndrome. In these patients, either the *H19* gene is totally silenced by hypermethylation of both alleles or methylation is lost at the IFG-II locus, which leads to diploid expression of this gene.^{47,48} In fragile X syndrome a CGG stretch in the 5' untranslated region of the fragile X mental retardation 1 (*FMR1*) gene is transformed into a CpG island by repeated duplication. By methylation of this newly formed CpG island the *FMR1* gene is silenced during development, which leads to mental retardation.⁴⁹

The early detection of epigenetic changes in some tumors suggests that epigenetic alterations can be causative in cancer.^{50,51} The genome of transformed cells is generally hypomethylated.⁵² In particular, loss of methylation at repetitive sequences leads to genomic instability (e.g., via gene disruption and genomic deletion).⁵³ Additionally, pathologic hypomethylation or hypermethylation occurs at gene promoters. As described earlier for Beckwith-Wiedemann syndrome, silencing of tumor suppressor genes or activation of oncogenes can confer a critical growth advantage to tumor cells. Changes in DNA methylation give rise to changes in histone modifications by recruitment of the respective enzymes. Accordingly, changes in histone acetylation and methylation are induced in many cancers.⁵⁴⁻⁵⁶

Changes in DNA methylation and histone modifications have also been found in neurodegenerative and neurologic diseases and in autoimmune and chronic inflammatory diseases.⁵⁷⁻⁶⁰ However, thus far it is mostly not clear

how and when altered epigenetic marks contribute to the pathogenesis of these diseases.

The origin of epigenetic alterations

Given that the epigenome can be modulated by the environment, it is tempting to assume that environmental risk factors induce epigenetic changes that lead to disease. Studies of monozygotic twins indeed show that the epigenome of these genetically identical individuals differs more and more over time.⁶¹ Different environmental influences could be the reason for this divergence. Increasing evidence, for instance, has shown that lipoproteins can influence the epigenome, which might be the first step toward the development of cardiovascular disease.⁶²

Another reason for changes in the epigenome over time might be failure of proper restoration of epigenetic marks after cell division. DNMT1, for instance, is not as accurate as DNA polymerase, which means that especially in highly proliferating tissues, mistakes in the restoration of methyl marks can accumulate.⁶³ Also, increased consumption of metabolites during fast proliferation can influence DNA methylation. The production of polyamines, for example, is increased in response to cellular stress, and accordingly, polyamine synthesis and, more importantly, recycling are activated in chronic inflammatory diseases.^{64,65} Polyamine recycling and DNA methylation, however, are both dependent on *S*-adenosylmethionine (SAM) as a donor for methyl groups. If the demand for polyamines is high, SAM is used mainly for polyamine recycling, thus leaving too little SAM for proper DNA methylation.

Another important point regarding the role of epigenetics in disease development is its fundamental role in embryogenesis and cell differentiation. Limitations of the epigenetic machinery early in life could lead to pathologic conditions at a later time. Studies examining patients who were exposed to prenatal malnutrition suggest that such disturbances in development of the central nervous system lead to mental illness.^{66,67} The mechanisms that can lead to epigenetic changes are summarized in Figure 18.2.

Rheumatic diseases and epigenetic changes

Several aspects of rheumatic diseases make this field interesting for epigenetic research. The risk for development of a rheumatic disease is increased with age, smoking is an environmental risk factor for most of the rheumatic diseases, and the inflammatory process leads to an increase in cellular stress,

which can be an initiator of epigenetic changes, as mentioned previously. Furthermore, concordance rates for rheumatic diseases in monozygotic twins are often low, thus pointing to nongenetic factors influencing the incidence of these diseases. Changes in DNA methylation and histone modifications have been found in the immune and stromal cells of patients with rheumatic diseases. They might be the basis for dysfunctions of the immune system, as well as for the chronicity of rheumatic diseases.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is currently the most studied rheumatic disease with respect to epigenetic changes. In SLE, heritability explains around two thirds of cases.⁶⁸ Interestingly, DNA methylation differs significantly between monozygotic twins when one twin is healthy and the other has SLE.⁶⁹ DNA hypomethylation is found in SLE T cells, which was speculated to be caused by a defective ras mitogen-activated protein kinase (MAPK) signaling pathway leading to diminished levels of DNMT1.^{70,71} Several studies have convincingly shown that on hypomethylation, T cells change their gene expression pattern and become autoreactive.^{72,73} In particular, hypomethylation induces the expression of CD70 and CD11b in lupus T cells, which has been implicated in the initiation of autoreactivity.⁷⁴⁻⁷⁶ Also, expression of perforin is induced by hypomethylation in the T cells of lupus patients.⁷⁷ Perforin promotes macrophage cell death, which in conjunction with the disturbed clearing of cell debris in SLE, was proposed to promote the formation of autoantibodies against DNA. In vitro, demethylation induces the expression of human endogenous retrovirus (HERV) sequences in peripheral blood cells.⁷⁸ Since in vivo peripheral blood cells from patients with SLE aberrantly express HERV, it has also been assumed that the loss of silencing of these repetitive sequence is due to hypomethylation.⁷⁹ Expression of HERV has been suspected to induce autoimmune reactions either by altering gene expression or by acting as superantigens.⁸⁰ Accordingly, expression of HERV transcripts correlates with the presence of the antinuclear antibodies anti-U1 ribonucleoprotein and anti-Sm.⁸¹ A strong argument for a causative role of hypomethylation of T cells in the subsequent changes in gene expression comes from mouse models, where transfer of in vitro hypomethylated T cells leads to an autoimmune response similar to that seen in human patients with SLE.⁸²

Regarding histone modifications, the histones H3 and H4 in lupus T cells have been found to be globally hypoacetylated but hyperacetylated at specific sites (e.g., the CD70 locus).^{83,84} At the CD70 promoter an increase in the active H3K4me2 mark was also found.⁸⁴ A genome-wide study discovered significant changes in the active H4K4me3 mark when comparing blood

cells from SLE patients with those from healthy individuals and patients with rheumatoid arthritis (RA).⁸⁵

Rheumatoid arthritis

In RA, studies of monozygotic twins have shown that only about two thirds of cases of disease can be explained by genetics.⁸⁶ This is significantly lower than, for instance, in celiac disease, where the concordance rate for monozygotic twins is higher than 80%.^{87,88} Epigenetic changes that arise over time or in response to environmental influences might explain why RA develops in one twin whereas the other stays healthy. In patients, changes in the epigenome are found in peripheral blood cells, as well as in resident cells of the joints (i.e., synovial fibroblasts). Most studies have looked at DNA methylation, whereas studies investigating histone modifications in RA are still rare.

Global demethylation was found in T cells and in particular in CD4+CD28- cells of RA patients.^{70,89} In patients with chronic inflammatory diseases, as well as in the elderly, expansion of CD4+ T cells that lack CD28 expression is commonly seen.^{90,91} Along with the loss of CD28, these cells are also characterized by a different functional profile. The specific gene expression pattern seen in these cells can partly be explained by decreased levels of DNMTs and consequent loss of methylation at specific gene promoters.^{89,92} Apparently, continuous proliferative stress inhibits extracellular signal-regulated kinase (ERK) and Jun N-terminal kinase (JNK) signaling, which in turn downregulates the expression of DNMTs.⁹² Other studies analyzing peripheral blood cells found loss of methylation at the promoters of interleukin-6 and ephrinB1 to be a cause of the increased expression of these genes in patients with RA.^{93,94}

In parallel to the hypomethylated state in peripheral blood cells, synovial fibroblasts of RA patients were found to be globally hypomethylated.⁹⁵ Also, the lack of DNMT1 during proliferation in this case is assumed to cause improper restoration of methyl marks after cell division.⁹⁵ Additionally, an increase in polyamine recycling could be shown in RA synovial fibroblasts, which as mentioned earlier can aggravate DNA demethylation.⁹⁶ Loss of methylation in RA synovial fibroblasts leads to the expression of LINE-1 retrotransposons, as well as to increased levels of CXCL12.^{97,98} Similar to what is found in cancer cells, in RA synovial fibroblasts, hypomethylated and hypermethylated genomic sites are also found.⁹⁹ For instance, death domain receptor 3 (DR-3) expression is low in RA synovial fibroblasts because of hypermethylation.¹⁰⁰

Data describing histone modifications in patients with RA are scarce. HDAC activity was found to be higher in peripheral blood cells and HDAC1

TABLE 18.1 Overview of epigenetic changes in rheumatic diseases

Disease	Cell type	Modification	Affected genes	Consequences	References
SLE	CD4+ T cells	DNA hypomethylation	Global, CD70, CD11a, perforin, HERV (?)	Increased expression, autoreactivity, macrophage death, autoantibody formation (?)	70, 74, 75, 77, 79
	CD4+ T cells	Histone H3 and H4 deacetylation	Global		83
	CD4+ T cells	H3 hyperacetylation	CD70	Increased expression	84
	CD4+ T cells	Increase in H3K4me2	CD70	Increased expression	84
	PBMCs	Increase in H3K4me3	Global		85
RA	CD4+ T cells	DNA hypomethylation	Global		70
	CD4+CD28- T cells	DNA hypomethylation	Global		89
	PBMCs	DNA hypomethylation	IL-6, ephrinB1	Increased expression	93, 94
	Synovial fibroblasts	DNA hypomethylation	Global, LINE-1, CXCL12	Increased expression	95, 97, 98
	Synovial fibroblasts	DNA hypermethylation	DR-3	Decreased expression	100
	PBMCs	Increased HDAC activity	Global		101
	Synovial fibroblasts	Increased HDAC1	Global		102
	Synovial tissue	Increased /decreased HDAC activity	Global		103, 104
Scleroderma	CD4+ T cells	DNA hypomethylation	Global		110
	Skin fibroblasts	DNA hypermethylation, histone deacetylation	FLI1	Decreased expression, increased collagen synthesis	111
ANCA vasculitis	Neutrophils	Loss of H3K27me3	Proteinase 3, myeloperoxidase	Increased expression, autoantibody formation (?)	112
Osteoarthritis	Chondrocytes	DNA hypomethylation	MMP-3, MMP-9, MMP-14, ADAMTS4	Increased expression	113
	Chondrocytes	Increased HDAC7	Global	Increased MMP-13	114

ANCA, antineutrophilic cytoplasmic antibody; HDAC, histone deacetylase; HERV, human endogenous retrovirus; IL-6, interleukin-6; MMP, matrix metalloproteinase; PBMCs, peripheral blood mononuclear cells; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

expression higher in synovial fibroblasts of RA patients.^{101,102} Findings on the activity of HDACs in RA synovial tissues are inconsistent; such activity was described to be higher as well as lower than in osteoarthritis synovial tissues.^{103,104} Since acetylation is a rather transient histone modification that responds rapidly to environmental changes, such as levels of tumor necrosis factor, selection of patients could be a decisive bias in this type of studies. It is notable, however, that pan-inhibitors of HDACs have a beneficial effect in various arthritis animal models, and trials in humans are eagerly awaited.¹⁰⁵⁻¹⁰⁸ Also, SUMOylation seems to be affected in RA synovial fibroblasts, which in connection with HDAC4 changes the expression of matrix metalloproteinase 1 (MMP-1).¹⁰⁹

Other rheumatic diseases

Even though epigenetic studies are much more advanced in SLE and RA, changes in the epigenetic machinery have also been found in other rheumatic diseases. An overview of the findings is provided in Table 18.1. In general, it can be said that global DNA hypomethylation evolves in peripheral blood and stromal cells. In parallel, either key pathogenic genes lose their epigenetic repressive marks, or counterregulatory genes are silenced by aberrant cytosine methylation.

EPIGENETICS AND MICRORNA

MicroRNA is small noncoding RNA molecules that silence their target genes by transcriptional or translational inhibition. In many conditions, including rheumatic diseases, microRNA expression has been found to be disturbed, with some microRNA upregulated and others downregulated.¹¹⁵ In RA synovial fibroblasts, for instance, expression of microRNA 155, 146a, 203, 323, and 124 was found to be dysregulated.¹¹⁶ MicroRNA is encoded in the genome in intergenic regions and overlapping introns or in the exons of other genes.¹¹⁷ From studies of tumor cells it is known that deletions, translocations, and amplifications often occur in microRNA-encoding regions.¹¹⁸ In addition, approximately 50% of the microRNA-coding genes are estimated to be affected by disturbances in DNA methylation.¹¹⁹ In turn, microRNA can also modulate the expression of genes that are important for the epigenetic machinery. Disturbances in this microRNA consequently lead to epigenetic changes. In SLE, for instance, microRNA 21 and 148a are overexpressed in T cells. Both these microRNA molecules target DNMT1 and thus contribute to the lack of DNMT1 and DNA hypomethylation in lupus T cells.¹²⁰

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19

The microbiome in rheumatic diseases

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- Many rheumatic and autoimmune diseases are categorized as complex and polygenic disorders. Genes have a clear role in their pathogenesis, but environmental factors appear to be required for the development of disease.
- Multiple lines of epidemiologic and clinical investigation have implicated several microorganisms in inflammatory rheumatic disorders; however, causation could not be established.
- The microbiome is defined as the totality of microbial communities and their genes in a defined community or biologic niche; the human microbiome is vast and complex and outnumbers the host genome by several orders of magnitude.
- Culture-independent, high-throughput DNA-sequencing technologies—coupled with deeper insight into mucosal immunology—have significantly advanced our understanding of the role of microorganisms in modulating health and disease.
- Germfree and gnotobiotic experiments have provided a deeper understanding of host-microbial interactions and have shown the ability of gut bacteria to induce both local and systemic autoimmunity in genetically predisposed animal models.
- The role of the oral, gut, and skin microbiome in human autoimmunity has recently been recognized as a potential contributor to disease mechanism.

INTRODUCTION

All mammals, including humans, are home to trillions of bacteria from the instant that they are born. Immediately afterward, a massive, complex and dynamic community of microorganisms rapidly begins to populate most cavities and surfaces of our body (including the skin, airways, and genitourinary and gastrointestinal tracts) and coexists with us rather harmoniously for the rest of our lives. This microbiome represents the totality of the ecologic communities of symbiotic, commensal, and pathogenic microorganisms (and their genomes) that we necessarily procure from the environment.¹ This interdependent, synergistic biologic bond is based on a mutually beneficial exchange. Humans provide an appropriate nutritional environment for bacteria, fungi, and viruses, which in return help shape the mucosal immune system, degrade complex polysaccharides, and produce vitamins and other factors essential for our survival.²

Until very recently, however, most of these microorganisms have been all but ignored as determinants of health and disease. Many rheumatic and connective tissue disorders are currently categorized as complex polygenic autoimmune diseases. Despite recent advances in molecular pathogenesis and treatment, most arthritides can be ameliorated but not cured, and their etiology remains elusive. Genes have a clear contribution to susceptibility, but these genetic effects appear to require environmental factors to explain differences in incidence of the disease.

Characterizing the microbiota inhabiting humans is now possible because of exponential advances in bacterial DNA-sequencing technologies. Largely as a result of the National Institutes of Health (NIH) Human Microbiome Project (HMP) and the European Metagenomics of the Human Intestinal Tract (MetaHit) consortium, an almost complete catalogue of intestinal, periodontal, and skin microbial communities is now in existence.^{3,4} This knowledge, coupled with renewed interest in mucosal immunology, provides important insight suggesting that the human microbiome

represents an environmental factor capable of influencing autoimmune disease manifestations.

THE MICROBIOME

Humans undergo embryonic maturation within a naturally protected, sterile habitat. Immediately after birth, vaginal- or skin-derived bacteria (depending on the delivery technique) colonize the neonate's gastrointestinal tract and other body surfaces.⁵ For several months there is a period of relative taxonomic instability. Over time, however, phylogenetic richness and species diversity increase, and by the end of the first year of life, particularly with the introduction of solid foods, the gut microbiota expands, stabilizes, and adopts the characteristics of the adult communities.⁶ At this stage the human microbiome is quantitatively vast and complex. In total, 100 trillion microorganisms live in our body spaces and outnumber the amount of human cells by a factor of 10⁷. The adult human gut alone contains on average 2 kg of bacteria, whose collective genome encodes approximately 3.3 million different genes—100 times more than that of its human host. Although more than 1000 different species from a dozen divisions colonize the gastrointestinal tract, the microbiome of healthy humans is dominated by four major bacterial phyla: Firmicutes, Bacteroidetes (which combined represent about three quarters of the total gut community), and to a lesser degree, Proteobacteria and Actinobacteria.⁸ More importantly, humans can be clustered into three groups (or enterotypes) according to the composition of their gut microbiome.⁹ In healthy individuals from industrialized nations, these enterotypes appear to be independent of host factors, thus arguing for the existence of three stable core human microbiomes.¹⁰

MUCOSAL BARRIERS AND HOST-IMMUNE INTERACTIONS

Physiologic intestinal inflammation and homeostasis in health

Dietary patterns and antibiotic use are certainly able to alter the composition of the microbial community in the intestine.¹¹ However, the mechanism by which the microbiome is selected, established, and maintained within a given individual remains uncertain. Nevertheless, the symbiotic processes and bidirectional crosstalk between the microbiome and host immune system are becoming better understood. Indeed, the idea that commensal bacteria are merely a group of passive organisms that obtain nutritional benefit at the host's expense has become untenable. Compelling recent evidence has demonstrated that cells from both the innate and adaptive immune systems in the lamina propria actively cooperate to maintain a state of homeostasis (Fig. 19.1, left panel). In this healthy state, a massive amount of antigenic material derived from the diet and commensal flora is actively tolerated by mucosal-associated lymphoid tissue to mutually benefit the microbiota and its host.¹² Through evolution, several biologic check points have been established to keep these two “biologic universes” separate and prevent microorganisms from accessing the lamina propria and, eventually, the peripheral organs and tissues. A physicochemical and immune barrier represents the first line of defense. A thick mucus layer,¹³ enteric antimicrobial proteins,¹⁴ and high levels of secretory immunoglobulin A¹⁵ are all designed to prevent a flood of undesired flora (or any of their components) into the host. Tightly adherent epithelial cell columns that further contain bacterial invasion provide a second protective strategy. Enterocytes not only function as a strict anatomic boundary but also have

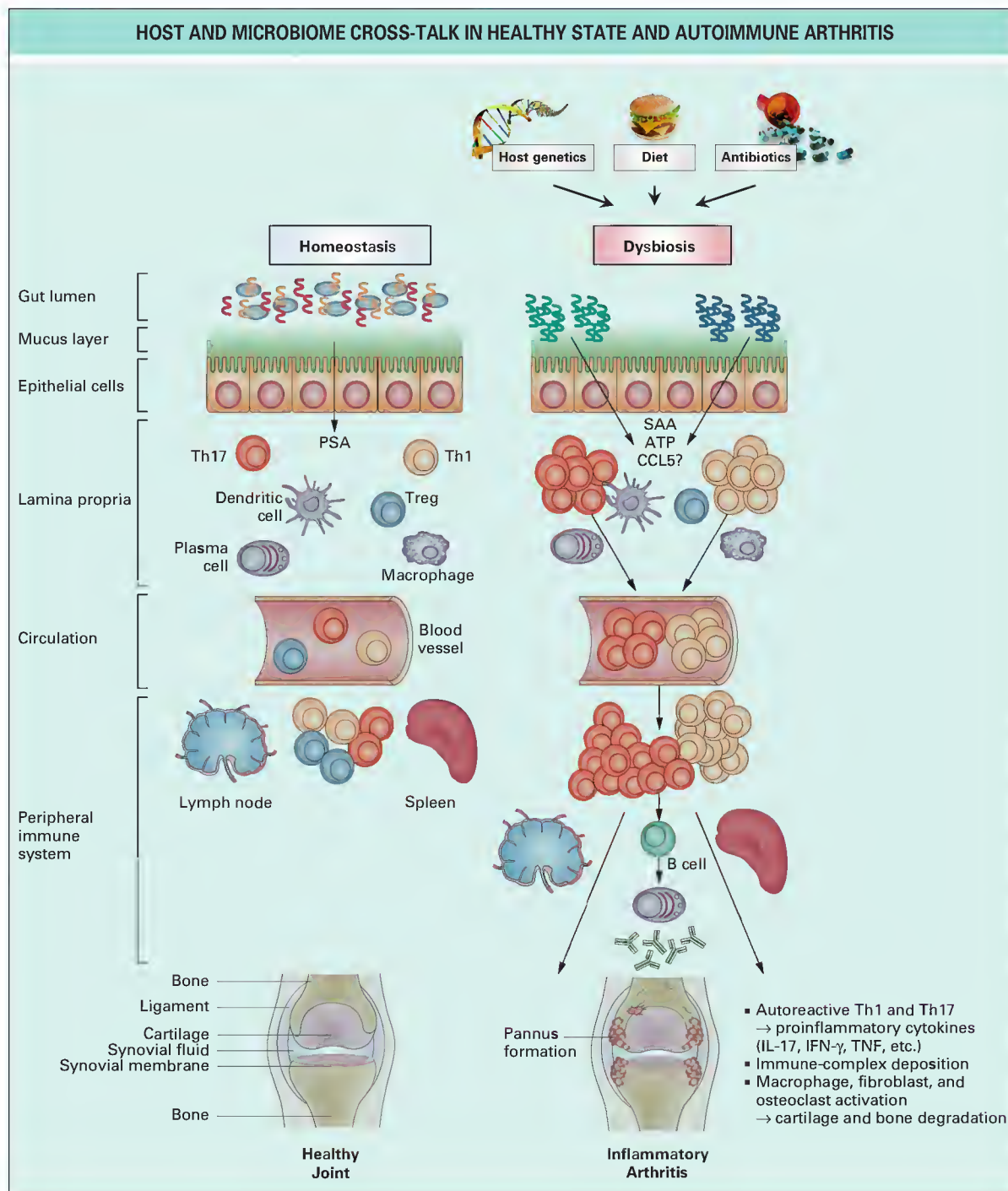


Fig. 19.1 (Left panel) In the healthy state, balanced host-microbial interaction is essential for maintenance of homeostasis. A thick mucus layer, epithelial cells, and secretory IgA form a physicochemical barrier that prevents direct contact with gut-associated lymphoid cells, which constantly survey the contents of the intestinal lumen and eliminate undesired antigens. Commensal bacteria such as *Bacteroides fragilis* can activate pro-tolerogenic machinery. A specific cell wall component, polysaccharide A (PSA), is sufficient to induce activation of regulatory T cells (Tregs), production of interleukin-10 (IL-10), and repression of type 17 helper T cells (Th17) to avoid uncontrolled inflammation. (Right panel) When either genetic, dietary, or environmental factors alter the balance in composition of the microbiota, a state of dysbiosis ensues. Potentially harmful bacteria (such as segmented filamentous bacteria or *Lactobacillus*) predominate and promote local activation and expansion of proinflammatory cells (Th17 cells, Th1 cells, and others) through several molecules (such as adenosine-5'-triphosphate [ATP], serum amyloid A [SAA], or CCL5 signaling). These autoreactive T cells migrate to peripheral immune compartments and activate B cells to differentiate into autoantibody-producing plasma cells. These cells and antibodies then migrate to synovial tissue, where the inflammatory cascade is amplified through the activation of effector components, including macrophages, fibroblasts, osteoclasts, cytokines, and proteinases. If self-perpetuating, this process can lead to arthritis and joint destruction. IFN- γ , interferon- γ ; TNF, tumor necrosis factor. (Adapted with permission from Scher JU, Abramson SB. *The microbiome and rheumatoid arthritis*. *Nat Rev Rheumatol* 2011;7:569-78.)

functional antimicrobial properties.¹⁶ These cells produce a variety of bactericidal proteins such as defensins, cathelicidins, and C-type lectins. Furthermore, epithelial cells express Toll-like receptors (TLRs) in their cellular membrane that allow recognition of pathogen-associated molecular patterns in microorganisms, activation of the signaling adaptor molecule MyD88 (myeloid differentiation primary-response protein 88), and induction of downstream inflammatory responses. If still insufficient, the intestinal lamina propria harbors the largest and most varied immune armamentarium

in mammals. Bacterial proteins and surface molecules such as lipopolysaccharides and other microbe-associated molecular pattern factors interact with TLRs and related pattern recognition receptors in the host innate immune cells.¹⁷ Dendritic cells, macrophages, and natural killer cells continuously survey the lumen to process and phagocytose antigens to trigger an appropriate response.

What ultimately defines this homeostatic state between the host and microbiome is a delicate balance in the type and predominance of CD4⁺ T

cells in the lamina propria.¹⁸ A necessary state of “physiologic” gut mucosal inflammation is driven by a permanent but low-level activity of effector cells, including the helper T cells Th1, Th2, and Th17 and their respective signature cytokines interferon- γ , interleukin-4/13 (IL-4/13), and IL-17/22. Regulatory T cells (Tregs), a tolerogenic subset of T cells, produce IL-10 and transforming growth factor- β to proactively counterbalance the potentially exaggerated proinflammatory effects. A fundamental aspect in maintenance of this equilibrium directly relates to the way that the adaptive immune system reacts. Recent paradigm-changing work in mucosal immunology has altered the way in which we understand the dichotomy between innate and adaptive immunity.¹⁹ Surprisingly, even a single intestinal commensal taxon is sufficient to activate CD4+ T cells and shift the balance toward proinflammatory or antiinflammatory responses. Segmented filamentous bacteria (SFBs), commensal gram-negative anaerobes, are able by themselves to activate Th17 cells,²⁰ whereas a specific polysaccharide of *Bacteroides fragilis*—polysaccharide A (PSA)—can stimulate Tregs and promote broad tolerogenic effects through the TLR2 signaling pathway.²¹ These Treg-inducing properties have also been demonstrated for indigenous gut *Clostridium* species.²²

Dysbiosis as a trigger for autoimmunity

An imbalance in the composition of the microbiota (a state called *dysbiosis*) may ensue if potentially pathogenic bacteria expand or beneficial bacteria become less abundant (Fig. 19.1, right panel).¹⁹ This leads to an alteration in the local immune response, typically dominated by proinflammatory cells and their products. When this reaction is self-regulated, the result is beneficial for both the host and the microbiome since detrimental microorganisms are eliminated. When this state of dysbiosis perpetuates, uncontrolled local inflammation is expected, as has been demonstrated in the case of inflammatory bowel disease (IBD; see later). However, the notion that an altered microbiome could influence systemic immune activation (or even lead to distal extraintestinal autoimmunity) is novel. Several studies have now shown that unique commensal species can initially affect the local adaptive immune response and subsequently trigger (or prevent) tissue-specific systemic autoimmunity. In experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, manipulation of the gut microbiome exacerbates the incidence and severity of EAE.^{23,24} In the non-obese diabetic mouse model of type 1 diabetes, colonization by commensal microbes reduces pancreatic inflammation and autoantibody production and abrogates disease.²⁵

RESEARCH METHODS FOR STUDY OF THE HUMAN MICROBIOME

The vast majority of existing microorganisms simply cannot be isolated in culture, either because they are fastidious growers or because of a lack of understanding of their nutritional or oxygen requirements. This leaves about 80% of all bacteria unidentified. Recent advances in DNA-sequencing technologies now permit these microbiologic challenges to be circumvented. A component of prokaryotes’ small ribosomal subunit, 16S ribosomal RNA (16S rRNA), is now used to establish phylogenetic analyses in microbiome studies.²⁶ This gene is uniquely found in bacterial cells and has highly conserved primer binding sites, and it is therefore very useful for determining which members of a given community are present without prior knowledge. The gene is also advantageous because it does not amplify human DNA. Yet at the same time, the 16S gene possesses several hypervariable regions that provide specific sequences unique to each species, thereby allowing extensive bacterial taxonomic identification without the need for culture.^{27,28}

Bacterial DNA is typically extracted from the human samples of choice and further amplified by using universal 16S primers. Pyrosequencing is then performed and the sequences obtained are aligned, trimmed, and subsequently classified. Ultimately, this approach provides an overall understanding of which bacterial species are represented in a given community and their relative abundance. Such studies have, for example, established associations among patients with autoimmune disorders (i.e., psoriasis, IBD, and type 1 diabetes). This methodology, though useful for establishing correlative associations, does not consider the functional enzymatic capabilities of the microbiome. The physiologic activities of these “second genomes” can provide insight into mechanisms of disease as well.²⁹ For example, a seminal study comparing the gut microbiota of monozygotic twins discordant for obesity revealed a similar taxonomic content among groups. However, there was a significant (and constant) variation in enzymatic pathways that differentiated obese from lean individuals.³⁰ This approach, known as whole-genome shotgun sequencing, complements the 16S studies

and requires the complete DNA sequencing of genes found in a given community. Beyond functionality, alignment of full genomes can also provide knowledge about potential islands of pathogenicity or even antigenic structures embedded in the microbiome, which may in turn help in the discovery of factors triggering local and systemic autoimmunity.

Aside from DNA sequencing, the study of proteomics and metabolomics is also of high relevance for understanding microbiome behavior and its impact on the host. Unique molecular components of bacteria rather than entire genetic or enzymatic structures may be sufficient to alter the mammalian immune response. This has been illustrated recently in the case of the periodontopathic bacterium *Porphyromonas gingivalis* and its relationship with the pathogenesis of rheumatoid arthritis (RA). *P. gingivalis*-derived enzymes such as α -enolase seem to be sufficient for triggering inflammatory joint disease in predisposed murine models³¹ (see the RA microbiome section). Similarly, PSA-containing *B. fragilis* (but not the PSA knockout variant) is able to protect against EAE, an animal model of multiple sclerosis.³² This is of importance because it promotes the notion that (at least hypothetically) specific parts of unique microorganisms could serve as biomarkers of autoimmune disease or even be the target of therapeutic approaches.

In 2007 the NIH established the HMP³³ and the European Commission launched the MetaHit consortium. Their central objective, perhaps complementary to the Human Genome Project, is to characterize the microbial communities found at several different sites on the human body and to analyze the role of these microbes in human health and disease.

THE MICROBIOME IN ANIMAL MODELS OF INFLAMMATORY ARTHRITIS

The physiologic and metabolic importance of the gut microbiome and its role in maturation of the host immune system has been studied with the use of gnotobiotic experiments. In a gnotobiotic animal, only certain known strains of bacteria and other microorganisms are present. Because these gnotobionts are normally reared in a sterile (germfree [GF]) or microbially controlled environment, they are a unique tool to study symbiotic relationships between a host and one or more microorganisms of interest.³⁴ In a similar experimental fashion, several studies have assessed the influence of intestinal bacteria as triggers for inflammatory arthritis (Fig 19.2). Since the 1970s, multiple animal models have been described as being susceptible to arthritis only when exposed to microorganisms, particularly those from the intestinal flora. The original report showed a protective effect of germs in an adjuvant-induced arthritis rat model in which severe inflammatory arthritis developed in the totality of animals raised in a GF state, as opposed to a significantly lower incidence in conventionally reared rats.³⁵ Research involving the streptococcal cell wall-induced rat arthritis model illustrates another classic example of these interactions. In this model too, conventionally raised animals are typically resistant to joint inflammation, whereas GF rats become susceptible to arthritis.³⁶

Many more studies using similar approaches were reported in the 1980s. These studies revealed that specific gram-negative enterobacteria were either protective³⁷ or inducers³⁸ of inflammatory arthritis in GF rats, thus raising the possibility of the intestinal microbiota as a triggering factor. In one of the most elegant set of experiments in the field of spondyloarthritis, Taurog and colleagues³⁹ described the need for commensal (and not necessarily pathogenic) intestinal bacteria in the development of both local intestinal inflammation and peripheral arthritis in HLA-B27 transgenic rats (a spontaneous model of spondyloarthritis in which multiple copies of HLA-B27 and human β_2 -microglobulin transgenes are microinjected). In GF rats, in turn, signs of mucosal or joint damage do not develop. Taken together, these results provided initial support for the hypothesis of an interrelationship between alterations in the gut microbiome (dysbiosis) and the development of systemic inflammatory arthritis. The original literature was indeed ambiguous about whether the intestinal flora was protective of or detrimental to joint physiology, but mechanistic insight had been scarce. Clearly, the host’s genetic background and even gender may modulate susceptibility to arthritis after exposure to a given microbiome. This was elegantly illustrated in a recent study of collagen-induced arthritis in mice in which HLA genes were differentially expressed.⁴⁰ Using 16S rRNA gene pyrosequencing, arthritis-susceptible HLA-DRB1*0401 mice were found to have an intestinal microbiota dominated by a *Clostridium*-like bacterium, whereas the guts of *0402 mice were enriched with members of the Porphyromonadaceae family and *Bifidobacterium* genus. Even though DRB1*0402 mice contained a dynamic sex- and age-influenced gut microbiome, only DRB1*0401 mice had altered mucosal immune function and increased gut permeability.

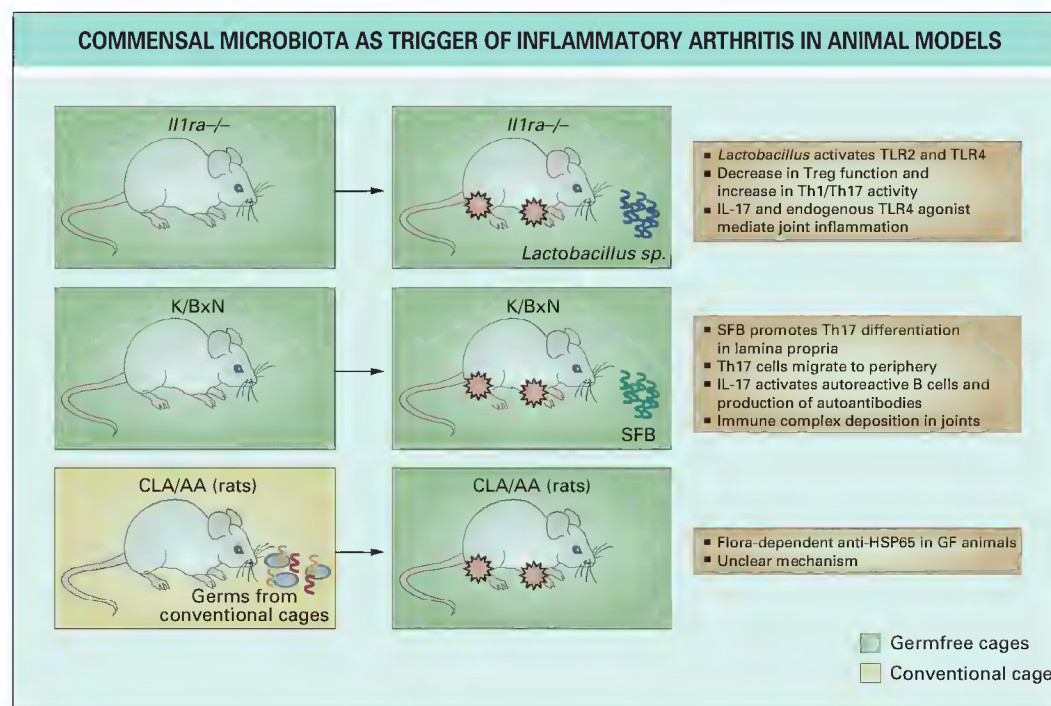


Fig. 19.2 Gnotobionts are animals that are kept germfree (GF) until known specific microorganisms are introduced in a controlled setting. Use of this experimental approach has advanced our understanding of how local changes in the intestinal microbial community (dysbiosis) are capable of producing an imbalance in the proinflammatory and antiinflammatory immune response and ultimately trigger autoimmunity at distal sites. Segmented filamentous bacteria (SFB) are sufficient to activate lamina propria type 17 helper T cells (Th17) cells in the K/BxN model of inflammatory arthritis. These cells migrate to the periphery, produce interleukin-17 (IL-17) (their signature cytokine), and stimulate plasma cells to produce arthritogenic autoantibodies. However, when kept in GF conditions, arthritis does not develop in these animals. *Lactobacillus* is also a proarthritogenic microorganism in the *IL1rn*^{-/-} model. An increase in Th17 cell activity and a decrease in regulatory T cell (Treg) function are key to the development of joint inflammation. Colitis or arthritis does not develop in the HLA-B27 transgenic rat in the GF state. Inflammation is activated by gut commensals such as *Bacteroides*. AA, adjuvant arthritis; CIA, collagen-induced arthritis; TLR2, Toll-like receptor 2. (Adapted with permission from Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. *Nat Rev Rheumatol* 2011;7:569-78.)

Since the late 2000s, the use of gnotobiotic mice has expanded our knowledge about the role of the gut microbiome in inflammatory arthritis (see Fig. 19.2). Autoimmune T-cell-mediated arthritis develops spontaneously in IL-1 receptor antagonist knockout (*IL1rn*^{-/-}) mice, for example, unless the animals are kept under GF conditions. When these mice are monocolonized with a strain of the commensal *Lactobacillus bifidus*, rapid and severe arthritis develops, comparable to that of conventionally raised mice.⁴¹ An imbalance in the Treg/Th17 cell response and subsequent TLR activation seems to explain the mechanism behind *Lactobacillus*-triggered arthritis in this model.

The K/BxN T-cell receptor transgenic mouse is another well-studied model of inflammatory arthritis that is caused by autoreactive T-cell-driven production of autoantibodies against glucose-6-phosphate isomerase.⁴² Here again, the incidence and severity of arthritis are decreased in GF animals, largely because of lower activation of peripheral Th17 cells. However, the introduction of a single gut-residing commensal SFB restores the disease phenotype,⁴³ and arthritis is abrogated when the mice are treated with SFB-targeting antibiotics from birth. Gut and joint inflammation in the SKG mice, another Th17-driven model characterized by a single point mutation in ZAP-70, is also flora dependent, although mostly fungal in origin.⁴⁴

Taken together, these data suggest that a particular intestinal microbiota is required to trigger (if not drive) systemic autoimmunity and subsequent inflammatory arthritis in animal models. It also ascribes to the notion that a state of dysbiosis may require genetic host susceptibility, as illustrated by the inability of wild-type animals to mount an inflammatory response even in the presence “proarthritogenic” gut flora.

THE MICROBIOME IN HUMAN INFLAMMATORY ARTHRITIS

The relevance of enteropathic arthritis to human rheumatic disease can be found in the pathogenesis of several arthritides. Spondyloarthritis, particularly enteric reactive arthritis and IBD-related arthropathy, are the most prevalent examples. Other notable entities include jejunoileal bypass-arthritis syndrome, celiac disease, the microscopic colitis spectrum, and Whipple disease, which are discussed in their respective chapters. The skin,

gut, and periodontal microbiomes have also been implicated in the etiopathogenesis of psoriasis and RA.

Spondyloarthritis

Spondyloarthritis (SpA) is a continuum of a spectrum of multiple related but phenotypically distinct disorders, including psoriatic arthritis (PsA), reactive arthritis, IBD-related arthropathy, and ankylosing spondylitis (AS).^{45,46} There is a constellation of several potential clinical manifestations ranging from axial and peripheral arthritis to psoriasis, uveitis, and bowel inflammation. The link between joint and gut inflammation in the SpA spectrum is well established in both murine models (i.e., HLA-B27 transgenic rats)^{46,47} and humans. The strongest association has been found between IBD and AS—AS develops in as many as 16% of patients with IBD, almost 50% of whom exhibit some compromise of their sacroiliac joints.⁴⁸ Conversely, up to two thirds of SpA patients show signs of subclinical microscopic gut inflammation, most notably in 60% of those with AS and 90% of those with enterogenic reactive arthritis.⁴⁹ This mucosal inflammation affects both the terminal ileum and the colon and could be either acute (bacterial enterocolitis-like) or chronic (Crohn-like). The acute form is associated with transient arthritis, whereas the chronic type is seen in patients with persistent joint inflammation who are at higher risk for full-blown IBD. Notably, gut inflammatory changes fluctuate with the activity of arthritis and vice versa.⁵⁰ Interestingly, circulating antibodies against the enteric microbes present in IBD patients, such as anti-I2, are also found in the plasma of AS patients.⁵¹ Moreover, the efficacy of sulfasalazine for both IBD and SpA (a drug that is poorly absorbed from the gut) represents another manifestation of the gut-joint linkage. Using low-throughput denaturing gradient electrophoresis and polymerase chain reaction (PCR) methods, one study showed a significant decrease in intestinal sulfate-reducing bacteria (i.e., *Desulfovibrio* spp.) in AS patients versus controls,⁵² an alteration also found in IBD patients. This has led to the use of a cocktail of commensal bacteria for the treatment of SpA. Even though this randomized clinical trial did not demonstrate significant benefit over placebo,⁵³ there is a clear need for further diagnostic and therapeutic exploration with novel DNA-sequencing techniques and more defined microbial communities.

Inflammatory bowel disease–related arthropathy

IBD is a spectrum of autoimmune disorders affecting the gastrointestinal tract, more commonly the colon and small intestine. The major types of IBD are Crohn disease (CD) and ulcerative colitis (UC). Concomitant nonaxial joint inflammation develops in about a third of all patients. Two forms of peripheral arthropathy have been described. Type I is typically found in UC, is oligoarticular in nature, and usually follows IBD activity. Type II IBD–related arthritis tends to be chronic and polyarticular and has a course independent of that of gut mucosal inflammation.⁵⁴ In addition, as discussed, axial arthropathy is significantly higher in those with IBD. AS is reported in 1% to 16% of patients, whereas asymptomatic sacroiliitis occurs in up to 45% of patients with IBD. Although no single taxon has ultimately been implicated, most reports confirm a state of dysbiosis with an overall decrease in phylogenetic diversity. Both CD and UC patients have decreased biodiversity, a lower proportion of Firmicutes, and an increase in Gamma-proteobacteria.⁵⁵ Microbial clades differentially abundant in IBD include *Roseburia* and *Phascolarctobacterium* (decreased in CD and UC) and Ruminococcaceae (decreased in CD only), along with a significant increase in Enterobacteriaceae (specifically, *Escherichia* and *Shigella* genera).⁵⁶ A dramatic reduction in the relative abundance of Firmicutes, one of the two major phyla along with Bacteroidetes, has consistently been reported. Several members of this group are known producers of potent antiinflammatory short-chain fatty acid metabolites, such as acetate (Ruminococcaceae) and butyrate (*Roseburia*). In CD patients, a specific decrease in *Faecalibacterium prausnitzii* (another potent butyrate producer) has also been described and validated.⁵⁷ Permanent reductions in all of these clades, coupled with an increase in pathobionts from the *Escherichia/Shigella* group, may ultimately have functional consequences on the ability of the host to repair the gut epithelium and regulate local inflammatory responses. Whether these IBD-associated alterations in the gut microbiome differ in patients with articular manifestations is unknown. Intriguingly, mice deficient in any step of the inflammasome pathway involving NLRP6, ASC, caspase-1, or IL-18 show an alteration in gut microbial ecology. This shift in microbiota is dominated by members of the Prevotellaceae family and is associated with an IBD-like phenotype that is transmissible to cohoused wild-type mice.⁵⁸

Psoriasis and psoriatic arthritis

PsA is a chronic inflammatory arthritis that affects individuals with psoriasis of the skin (Ps). The prevalence of Ps is approximately 2% to 3% in the general population, whereas the incidence of PsA in patients with Ps is about 30%.⁵⁹ For reasons that are unclear, PsA typically occurs after the onset of skin disease. The pathogenesis of PsA remains poorly understood, and the current paradigm posits that in the presence of strong genetic risk factors (e.g., major histocompatibility complex class I molecules such as HLA-B*27 and B*39),⁶⁰ PsA will develop in individuals with Ps after exposure to currently unidentified environmental factors and that arthritogenic antigens may trigger innate immune responses that secondarily drive adaptive immunity and lead to systemic and joint inflammation. Although genes are important in the pathogenesis of PsA, there are apparent limitations to this contribution, as demonstrated by a modest concordance rate in first-degree relatives and monozygotic twins. Proposed environmental triggers have included viruses, vaccinations, bacterial infections, trauma, and stress. PsA has specifically been associated with changes in the gut microbiota. As described, PsA develops in HLA-B27–overexpressing rats only in the presence of intestinal microbes, whereas subclinical gut mucosal inflammation has also been found in patients with active PsA,⁶¹ mostly in those with predominantly axial disease. Furthermore, a history of infections that required antibiotic treatment was associated with the occurrence of arthritis in patients with Ps.⁶² Most recently it was shown that dendritic cells from PsA patients (but not from those with Ps) have an impaired immune response to bacteria.⁶³ These data reinforce the notion of an altered bacterial clearance mechanism in PsA that eventually leads to chronic systemic inflammation in joints, entheses, skin, and even the gut.

The human skin microbiome has also recently been studied with high-throughput DNA-sequencing techniques. Surprisingly, its diversity is much greater than anticipated from the original culture-based reports.⁶⁴ Four different phyla predominate: Actinobacteria, Firmicutes, Bacteroidetes, and Proteobacteria. However, the relative abundance of the skin microbiome is directly dependent on the physiologic condition of a given topographic region and is associated with factors such as moisture (high abundance of *Staphylococcus* and *Corynebacterium* species) and sebaceous content (predominance of *Propionibacterium* spp.). Poststreptococcal psoriasis, which could evolve into chronic psoriasis in 40% of cases, is a well-established

bacterial-associated mechanism.⁶⁵ Moreover, the composition of the cutaneous microbiota in patients with psoriasis was studied recently.⁶⁶ Striking differences could be demonstrated at both the phylum and species level. For instance, Actinobacteria and *Propionibacterium acnes* were both underrepresented in untreated psoriatic plaques when compared with unaffected skin from the same psoriasis patients and normal controls. This may be the result of an inhospitable microenvironment for these organisms, or equally possible, they may play a protective role against psoriasis. The role of the gut and cutaneous microbiota in the passage from Ps to PsA is an attractive hypothesis and a matter of intense research. It is conceivable that alterations in microbial composition herald (or even promote) the advance from skin disease to a more disseminated phase in which joints and entheses are also affected.

Rheumatoid arthritis and the microbiome

Since the discovery of the microscope and microorganisms by Antony van Leeuwenhoek in the 18th century, successive hypotheses attempted to link the oral and intestinal microbiome with the etiology of RA. Notably, Sir William Osler described *arthritis deformans* as being due to tuberculosis,⁶⁷ the *focal sepsis* hypothesis attributed periodontal flora as the cause of RA,⁶⁸ and the *toxemic factor* theory proposed that substances produced by intestinal microorganisms are ultimately responsible for the joint inflammation in rheumatoid patients.⁶⁹ Paleopathologic and epidemiologic evidence, though debatable, suggests that RA is a transmissible New World disease that spread to the rest of the planet after the conquest.⁷⁰ This is based on the lack of skeletal remnants with RA-like erosions outside the Americas and a higher prevalence of the disease in Native Americans than in other populations. Moreover, until very recently, the incidence of RA appeared to be declining.⁷¹ Because genetic changes occur over several generations, this decrease has been attributed to a possible “birth cohort” effect or “hygiene hypothesis.” These theories propose a role for an infectious agent that was presumably highly prevalent a century ago but has been slowly eradicated by introduction of the modern lifestyle and dietary modifications. Exposure to this agent by subsequent generations may therefore have decreased along with the incidence of the disease. Several clinical reports have implicated specific pathogenic microorganisms as triggers for RA, mostly through indirect evidence (serologic and PCR methods) and circumstantial observations. These microorganisms include several viruses and retroviruses, bacteria, and mycoplasmas (see Chapter 107). However, a precise causal effect could not be established.

The intestinal microbiome in rheumatoid arthritis

The idea that intestinal microorganisms are associated with the development of RA is not novel. Classic examples at the beginning of the 20th century include the albuminous putrefaction therapies of Andrews and Hoke and the toxemic factor hypothesis of Carl Warden.

Beyond convincing animal model data on the role of intestinal bacteria in RA-like disease, there is also evidence that therapeutic regimens seemingly targeting the enteroarthropathy connection work in the clinic. Many of these drugs have been classified as disease-modifying antirheumatic drugs (DMARDs) and are still in use today. This notion was originally developed in the 1940s, when sulfasalazine became the first rationally designed compound for the treatment of rheumatic diseases. Because RA was thought to be caused by streptococci found in milk,⁷² sulfasalazine was created in a deliberate effort to combine a sulfonamide antibiotic (against enteric bacteria) with a salicylate (as antiinflammatory agent) through an azo bond.⁷³ Sulfasalazine, as well as the antimalarial agent hydroxychloroquine, are currently used for mild cases of RA. Moreover, triple DMARD therapy (a combination of sulfasalazine, hydroxychloroquine, and methotrexate) remains one of the few first choices for all patients with RA who have poor prognostic features and moderate or high levels of disease activity, regardless of disease duration,⁷⁴ and it appears to be equivalent in efficacy to the combination of methotrexate and a biologic agent for early RA.⁷⁵ Furthermore, tetracycline antibiotics have also been proved to be efficacious in the treatment of early seropositive RA,⁷⁶ which has led to the approval of minocycline as a DMARD. Despite these encouraging clinical outcomes, the underlying mechanisms of action for all these drugs—particularly their specific antibiotic properties—have never been completely elucidated.

The community composition of intestinal bacteria in patients with RA has been studied with low-throughput technologies. Via gas-liquid chromatography or limited oligonucleotide probing, RA patients were found to have a decrease in *Bacteroides* groups in comparison to controls.⁷⁷ These approaches, however, remain inadequate and nonspecific for characterization of the entire gut microbiota. Efforts using high-throughput DNA sequencing are currently under way.⁷⁸

The oral microbiome in rheumatoid arthritis

At the turn of the 20th century, the widely prevalent oral sepsis hypothesis led to the use of teeth extraction as a widespread treatment of RA. It lasted for several decades and was eventually deemed ineffective. In the last decade, a vast body of published literature has shown epidemiologic associations between the presence of periodontal disease (PD) and RA. PD was more common and severe in patients with RA than in those with osteoarthritis.⁷⁹ In another study, subjects with RA had an eightfold increased likelihood of periodontitis in comparison to controls.⁸⁰ Others have found a less robust correlation, thus suggesting that study methodologies and the definition of PD have been variable.

Multiple lines of investigation have also implicated *P. gingivalis*, a common periodontopathic bacterium, as a possible triggering factor for joint inflammation.⁸¹ *P. gingivalis* is a gram-negative anaerobe that contains a unique enzyme—peptidyl arginine deiminase (PADI)—that is capable of citrullinating arginine peptide residues in a calcium-dependent posttranslational modification process. According to this model, these citrullinated residues turn into neopeptides that are recognized by antigen-presenting cells in the appropriate genetic context (i.e., HLA); this leads to the activation of T and B cells, which ultimately stimulates the production of anti-citrullinated peptide antibodies (ACPAs) by plasma cells and unfolding inflammatory responses within the joint. Evidence to support this model is derived from *in-vitro* and *in-vivo* studies. PADI-sufficient *P. gingivalis*—but not other periodontal bacteria or a PADI knockout strain—is able to citrullinate human fibrinogen and α -enolase.⁸² Intriguingly, in susceptible DR4-IE transgenic mice, both autoimmunity and inflammatory arthritis develop when immunized with *P. gingivalis* enolase (both citrullinated or uncitrullinated), thus suggesting a pathogenic role in the initiation of disease.³¹ Citrullination of proteins occurs as a part of physiologic cellular processes, particularly in apoptosis. The joints of patients with RA, however, have abnormally high levels of both citrullinated proteins and ACPAs.⁸³ There is

limited evidence that ACPAs are responsible for the initiation of RA since these antibodies (along with rheumatoid factor) can be found several years before any clinical manifestation become evident.⁸⁴ Several recent human studies have established a positive serologic correlation between *P. gingivalis* exposure, ACPA titers, and RA,^{85,86} with first-degree relatives demonstrating an intermediate antibody profile when compared with healthy controls.⁸⁵ The first study that directly looked at the presence of oral microorganisms was recently conducted and used multiplexed pyrosequencing to compare the bacterial composition of the subgingival microbiota in those with new-onset, DMARD-naïve RA and controls.⁸⁷ Notably, RA patients exhibit a high prevalence of PD at disease onset, and their subgingival microbiota is similar to that of patients with chronic RA and healthy subjects with comparable PD severity. Overall, *P. gingivalis* is found in 55% of RA patients versus 27% of controls, thus suggesting a potential common pathway for RA and PD and a potential role for *P. gingivalis* in a subset of RA patients.

CONCLUSION

New DNA-sequencing technologies and experimental approaches have brought novel insight into the potential mechanisms of disease behind autoimmune processes. It is now possible to taxonomically characterize thousands of bacteria (and their function) in exquisite detail. Animal models of inflammatory arthritis have shown the capacity of specific oral and intestinal commensal bacteria to activate proinflammatory cells, which then initiate and perpetuate deleterious effects in the joint. The clinical implications of these discoveries, along with the notion that humans harbor distinct enterotypes, open a new perspective in rheumatic and autoimmune research. Identification of “arthritogenic” commensal organisms could provide insight into the “in-virionmental” trigger of these diseases and lead to a new understanding of disease pathogenesis that could result in novel preventive therapies.

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20

Tissue destruction and repair

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- Cartilage is made up of collagens, proteoglycans, and minor glycoproteins. Bone consists of a mineralized collagen matrix. Both tissues can be degraded by active proteinases.
- Different classes of proteinases play a part in connective tissue turnover, but the proteinase that predominates varies with different tissues and the resorptive situation.
- Matrix metalloproteinases (MMPs) are produced in proforms and, once activated, can degrade connective tissue. MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs), and the balance between active MMPs and TIMPs determines the extent of degradation. Pro-MMPs can be activated by metalloproteinases and serine proteinases. ADAM (a disintegrin and metalloproteinase) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) proteinases are also upregulated in diseased joints and cleave proteoglycans. Serine proteinases have likewise been implicated in cartilage breakdown, and cysteine proteinases initiate collagen breakdown in bone.
- Various cytokines and growth factors, alone or in combination, inhibit matrix synthesis and stimulate proteinase production and matrix destruction. Tissue destruction occurs in both rheumatoid arthritis and osteoarthritis.
- Some growth factors increase the synthesis of matrix and proteinase inhibitors. Growth factor combinations can be used in conjunction with stem cells and chondrocytes within artificial matrices to promote the repair of small cartilage defects in large joints.

INTRODUCTION

Cartilage and the underlying subchondral bone are destroyed in severe cases of arthritis, and this limits normal joint function. Cartilage contains different types of collagen, which are composed of rod-shaped molecules that aggregate in staggered arrays to form cross-linked fibers that give connective tissue strength and rigidity.¹ Entrapped within these collagen fibers are the proteoglycans,² predominantly aggrecan, which consists of three globular domains interspersed with heavily glycosylated and sulfated polypeptide. In the presence of hyaluronic acid, these form highly charged aggregates, attract water into the tissue, and allow cartilage to resist compression. Chondrocytes in normal adult cartilage maintain a steady state in which the extent of matrix synthesis equals that of degradation. Any change in this steady state will affect the functional integrity of cartilage. During growth and development, synthesis of matrix components exceeds degradation, whereas in pathology there is an increase in the rate of degradation that is often associated with a reduction in matrix synthesis.

The primary cause of cartilage and bone destruction in the arthritides is elevated levels of active proteinases, secreted from a variety of cells, that degrade collagen and aggrecan. The sources of these proteinases depend on the type of disease. In osteoarthritis (OA), the proteinases produced by chondrocytes play a major role. In contrast, in a highly inflamed rheumatoid joint, chondrocytes, synovial cells, and inflammatory cells all contribute to the proteolytic loss of tissue matrix.

Joint tissues are capable of repair; although aggrecan can be readily resynthesized, replacement of collagen after its destruction is more difficult.³

A variety of growth factors and cytokines present in the joint are able to promote matrix synthesis, and these factors have been studied to determine whether cartilage and bone defects can be repaired *in vivo*.

PROTEOLYTIC PATHWAYS OF CONNECTIVE TISSUE BREAKDOWN

Extracellular matrix proteins are broken down by different proteolytic pathways. The five main classes of proteinases⁴ are grouped according to the chemical group that participates in the hydrolysis of peptide bonds. Cysteine and aspartic proteinases are predominantly active at acidic pH and act intracellularly; threonine proteinases, the proteasome being the most characterized, also act intracellularly at nearly neutral pH; and the serine proteinases and metalloproteinases, active at neutral pH, mostly act extracellularly. Other enzymes, such as elastase, are stored and released when neutrophils are stimulated. Some enzymes, such as furin, may not participate in the proteolysis of matrix proteins but activate proenzymes that subsequently degrade the matrix. Membrane-bound proteinases are associated with cytokine processing, receptor shedding, and removal of proteins that are responsible for cell-cell or cell-matrix interactions.

The complete repertoire of human proteases (defined as the degradome)⁵ comprises approximately 569 proteinases, and all classes of proteinases have roles in the turnover of connective tissue. One proteinase pathway may act in concert with or precede another, and the pathway that predominates varies with different resorptive situations. Turnover of the extracellular matrix often involves complex interactions between different types of cells. The osteoid layer in bone is removed by osteoblast metalloproteinases before the attachment of osteoclasts, which secrete predominantly cysteine proteinases such as cathepsin K. These proteinases degrade bone matrix after removal of the mineral. An intricate series of interactions between T cells, macrophages, synovial fibroblasts, and chondrocytes occur in the rheumatoid joint. In septic arthritis, both serine proteinases and metalloproteinases released from neutrophils exceed the local concentration of inhibitors, which results in rapid removal of the cartilage matrix from the joint cavity. In OA, the inflammation is typically less marked but nevertheless is thought to contribute to pathology.⁶ Other mechanisms also contribute to joint tissue destruction, especially in OA, including abnormal mechanical loads inducing mechanosensitive genes and age-related changes in the cartilage matrix (such as advanced glycation end products) altering cellular responses by engaging alternative receptors (e.g., Toll-like receptors) and resulting in the expression of different genes.

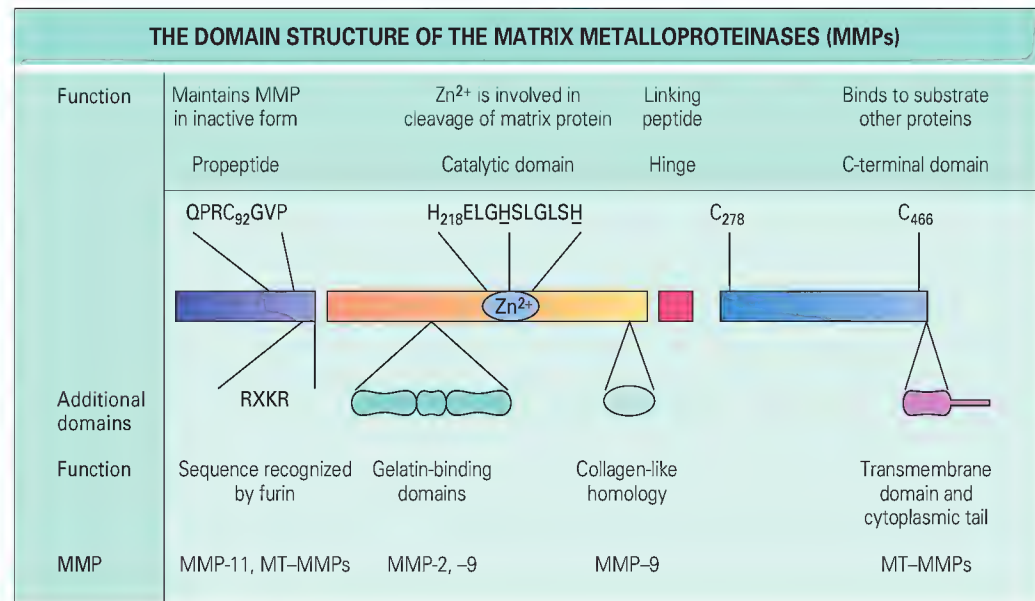
EXTRACELLULAR PROTEOLYSIS—NEUTRAL PROTEINASES

Matrix metalloproteinases

The matrix metalloproteinase (MMP) family, when activated and acting collectively, can degrade all the components of the extracellular matrix. MMPs are zinc-dependent endopeptidases, and all contain common domains (Fig. 20.1).⁷ All are produced as latent (inactive) proenzymes, and proteolytic loss of the propeptide leads to activation. The membrane-type MMPs (MT-MMPs) and stromelysin-3 (MMP-11) have a short peptide insert between the propeptide and the N-terminal domain, a sequence recognized by furin, a serine proteinase located in the Golgi apparatus; these MMPs are therefore secreted as active enzymes. Zinc is present at the catalytic center within the N-terminal catalytic domain, which is joined to the C-terminal



Fig. 20.1 All matrix metalloproteinases (MMPs) contain a similar domain structure with a zinc-binding domain (yellow), and most contain the C-terminal domain (blue). All are secreted with a propeptide (purple) that maintains the latency of the MMP by a conserved cysteine binding to the active site zinc. Other groups of MMPs build on this core structure. The gelatinases have additional domains inserted (green). The membrane-type MMPs (MT-MMPs) have a transmembrane domain (pink) that locates the MMP at the cell surface. The MT-MMPs and stromelysin-3 have a sequence of basic amino acids inserted between the prodomain and catalytic domain that are specifically recognized by furin, a serine proteinase that activates these enzymes intracellularly. Varying the domains ensures that individual MMPs can bind to the matrix components that they cleave.



hemopexin domain by a flexible linking peptide. For efficient collagenolysis, cooperation between the catalytic domain and an exosite in the hemopexin domain that specifically binds the C-terminal to the scissile bond is critical for conferring substrate specificity.⁸ MMP-8 and MMP-9 are found stored within the specific granules of the neutrophil, whereas most other MMPs are produced by different connective tissue cells after stimulation with a variety of mediators.

MMPs are divided into four main groups called the stromelysins, collagenases, gelatinases and MT-MMPs.⁹ The stromelysins have broad substrate specificity, and the natural substrates of these enzymes are probably proteoglycans, fibronectin and laminin.¹⁰ Stromelysin-1 (MMP-3) is not normally widely expressed but can readily be induced by growth factors and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α). The three stromelysins have similar substrate specificity but their expression patterns are often quite distinct.

There are three mammalian collagenases: MMP-1, MMP-8, and MMP-13. These enzymes, once activated, cleave fibrillar collagens at a single site to produce fragments three fourths and one fourth the original size. The enzymes differ in their specificity for different collagens, with MMP-13 having much broader substrate specificity than the other collagenases. Both MMP-1 and MMP-13 are synthesized by macrophages, fibroblasts, and chondrocytes when these cells are stimulated by inflammatory mediators. MMP-8 is predominantly released from neutrophils on stimulation of the cell, but this MMP can also be produced by chondrocytes, and all three collagenases are present in diseased cartilage (Fig. 20.2). MMP-13 is often controlled in a different way from MMP-1; retinoic acid, which downregulates MMP-1, is known to upregulate MMP-13 in some cell types.

The two gelatinases cleave denatured collagens, type IV and V collagen, and elastin. Expression of MMP-2 is the most widespread of all the MMPs; MMP-9 is expressed in a wide variety of transformed and tumor-derived cells. Both MMP-2 and MT1-MMP (MMP-14) have also been shown to have collagenolytic activity, and the cell-surface location of MT1-MMP ideally situates it for the pericellular proteolysis that is often evident in cartilage affected by OA.

Levels of different MMPs are increased in rheumatoid synovial fluid, in conditioned culture media from rheumatoid synovial tissues and cells, in synovial tissue at the cartilage-pannus junction in rheumatoid joints, in cartilage with OA, and in animal models of arthritis.^{11,12} These proteinases are implicated in the pathologic destruction of joint tissue and are involved in the normal turnover of connective tissue matrix that occurs during growth and development. In OA, rates of both matrix synthesis and breakdown are increased, which leads to the formation of excess matrix in some regions (osteophytes) with focal lesions (loss of matrix) in other areas.

The MMPs therefore need careful control,¹⁰ which occurs at a number of critical steps (Fig. 20.3); these include synthesis and secretion, activation of the proenzymes, and inhibition of the active enzymes.

Synthesis and secretion

IL-1, TNF- α , and IL-17 stimulate numerous cell types to produce proinflammatory and degradative molecules. The synthesis and secretion of MMP-1, MMP-3, and other MMPs are stimulated by such mediators.¹³

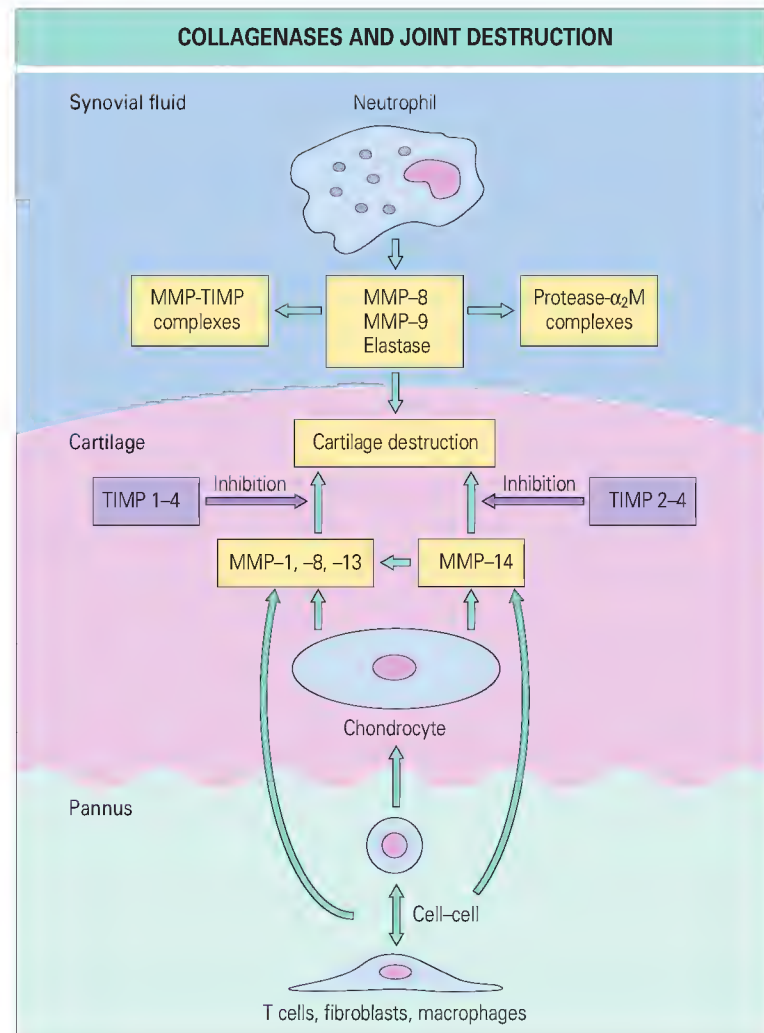


Fig. 20.2 Cell-cell interactions between T cells, synovial fibroblasts, and macrophages within the pannus tissue give rise to a mixture of cytokines and growth factors that act on these cells and on chondrocytes to increase procollagenase-1 (matrix metalloproteinase-1 [MMP-1]), procollagenase-2 (MMP-8), procollagenase-3 (MMP-13), or membrane type 1 (MT1)-MMP (MMP-14). After activation, if local levels exceed the available tissue inhibitor of metalloproteinases (TIMPs), collagen destruction ensues. MMP-14, located at the cell surface, can initiate activation cascades, as can serine proteinases that activate the procollagenases. Within the joint cavity, neutrophils can also release collagenase-2 (MMP-8), gelatinase B (MMP-9), or elastase at or close to the cartilage surface where degradation will occur unless α_2 -macroglobulin (α_2 M) or TIMPs bind and inactivate the enzymes.

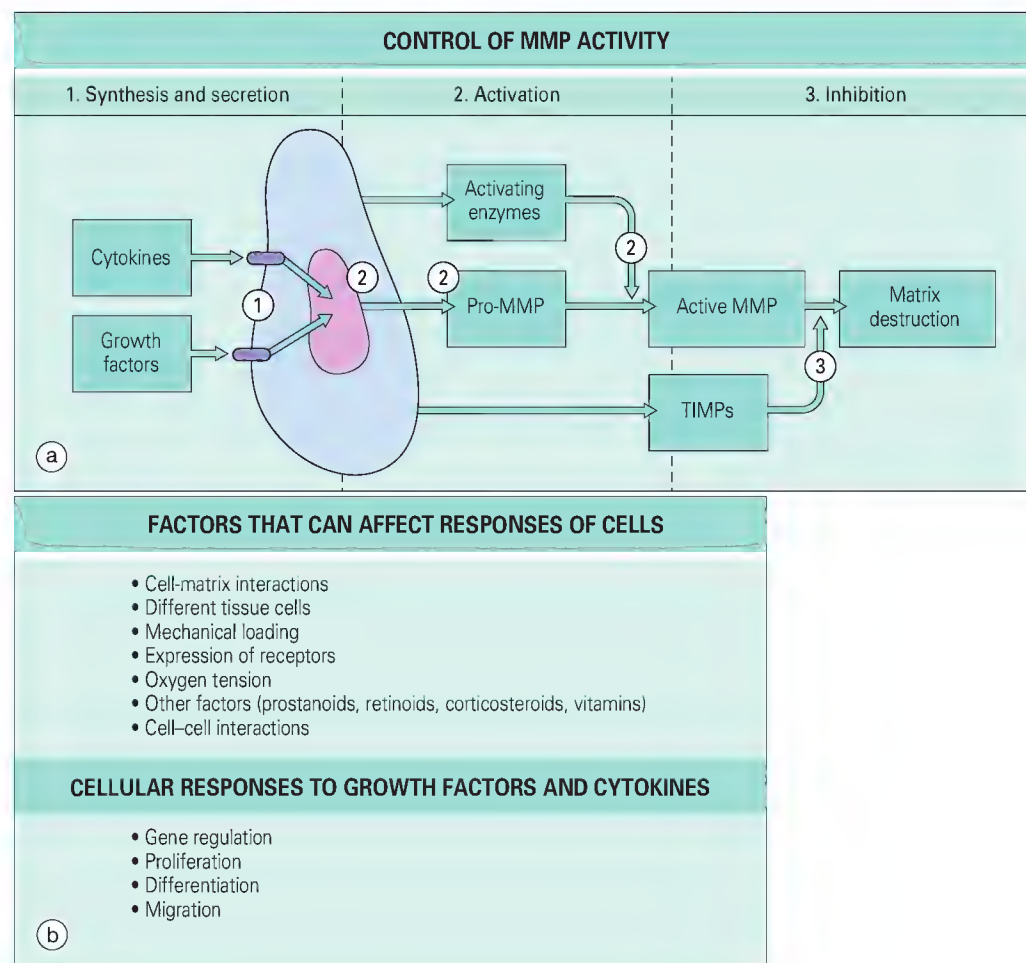


Fig. 20.3 (a) The matrix metalloproteinases (MMPs) are controlled by mechanisms that include upregulation by combinations of cytokines and growth factors, activation of the secreted enzymes, and inhibition by tissue inhibitors of metalloproteinases (TIMPs). (b) Other factors often alter the cellular response to these stimuli, and different cells can respond to growth factors and cytokines in a number of ways.

Arthritic joints have large numbers of different cell types that produce specific cytokines and growth factors that often differ in their action on individual cell types (see Fig. 20.3b). It is also likely that multiple cytokines will be present within such an inflammatory milieu, thus making it difficult to predict the outcome of blocking the action of an individual cytokine to prevent tissue destruction. TNF- α blockade in some patients with rheumatoid arthritis (RA) successfully reduces inflammation and joint destruction, whereas some studies suggest that blocking other cytokines such as IL-6, IL-17, or oncostatin M (OSM) may confer similar benefit, especially in patients unresponsive to a given biologic agent. Cytokines and growth factors mediate their effects on cells by binding to specific cell-surface receptors. A “signal” is transduced to the nucleus via specific intracellular signal transduction pathways that culminate in the activation or repression of target genes. Signaling in inflammation is complex, and multiple signaling cascades are often activated by a given cytokine in different cell types. A further level of complexity is that interactions, or “crosstalk,” between different signaling pathways can occur and mediate the gene expression of degradative molecules.¹⁰ The key components of signaling pathways are an attractive therapeutic target because they allow small molecules to be used as drugs, and specific inhibitors of the JAK/STAT pathway have been tested successfully in trials.^{14,15} Recent work has also suggested that metalloproteinases are regulated epigenetically, both at the transcriptional level (i.e., by promoter DNA methylation) and post-transcriptionally by microRNA.¹⁶

Activation of proenzymes

Activation of latent pro-MMPs is an important and understudied control point in connective tissue breakdown. The propeptide is removed proteolytically, which allows the enzyme to hydrolyze peptide bonds, and activation is likely to be achieved in a tightly controlled environment close to the cell surface. Active MMP-3 activates procollagenases and other MMPs. Recent data implicate MT1-MMP, which itself is activated by the serine proteinase furin, as an important initiator of MMP activation cascades. Plasmin, matriptase, and other serine proteinases activate some members of the MMP family (see later), and *in vitro* studies have demonstrated that inhibitors of furin, matriptase, and plasmin can block cartilage breakdown.¹⁷

Inhibition of active enzymes

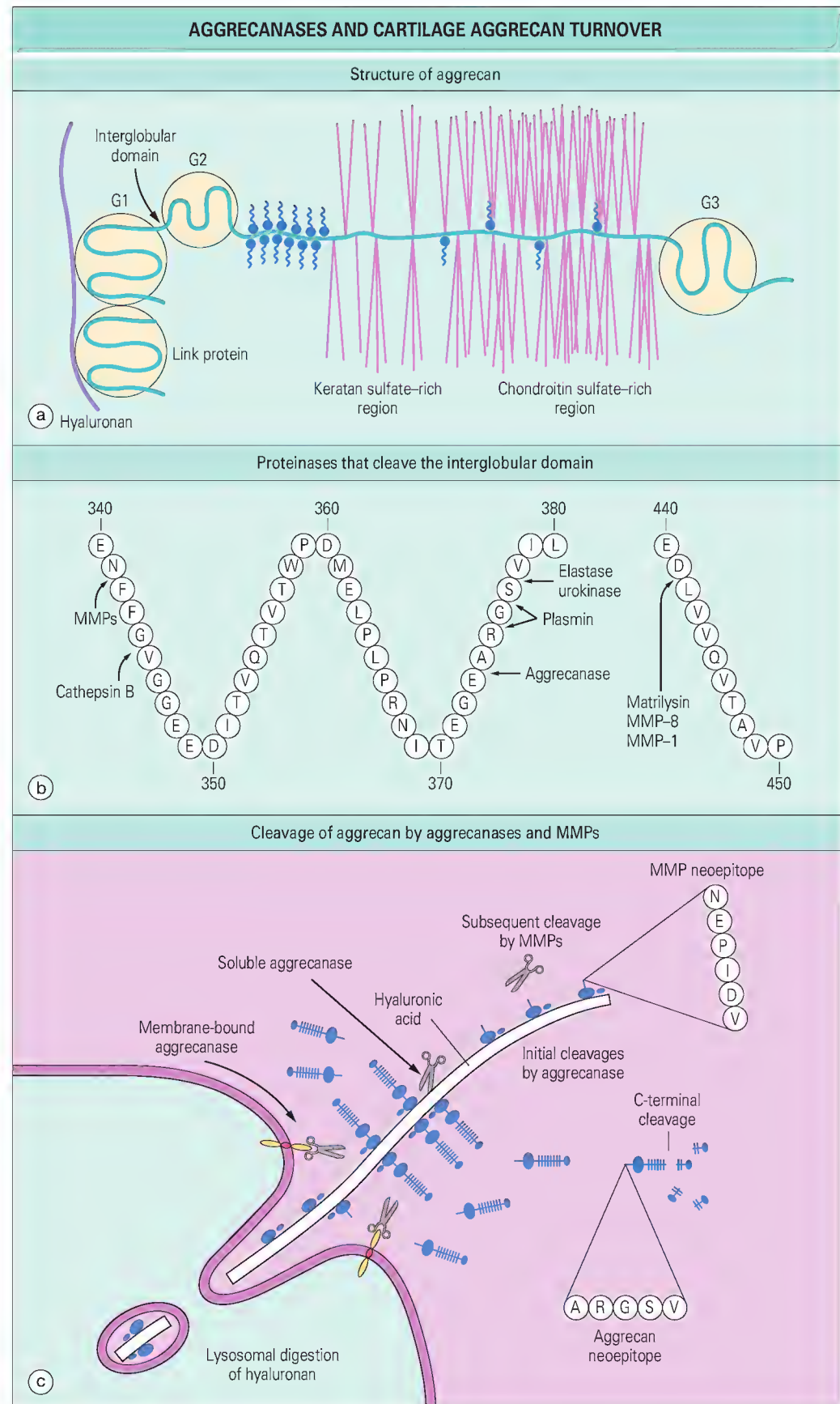
All active MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs),¹⁸ which are highly stable proteins that bind tightly to active MMPs in a 1:1 ratio. TIMPs play an important role in controlling connective tissue breakdown by blocking activated MMPs (see Figs. 20.2 and 20.3). If TIMP levels exceed those of active enzymes, connective tissue turnover is prevented. TIMP-3 is bound by the extracellular matrix after secretion and also inhibits members of the ADAM (a disintegrin and metalloproteinase) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) families (see the next section). TIMP-4 is predominantly localized in heart tissue but can be produced by joint tissues. TIMP-1 and TIMP-3 are upregulated by growth factors such as transforming growth factor- β (TGF- β), insulin-like growth factor 1 (IGF-1), and OSM; these agents also upregulate matrix synthesis. The mechanisms that control the extracellular activity of the MMPs are illustrated in Figure 20.3.

ADAM and ADAMTS proteinase families

Two additional families of proteinases, both closely related to MMPs, are also implicated in cartilage biology, particularly in relation to proteoglycan turnover. ADAMs are usually membrane-anchored proteinases with diverse functions conferred by the addition of different protein domains. The disintegrin domain can bind to integrins and prevent cell-cell interactions; cysteine-rich, epithelial growth factor (EGF)-like, transmembrane, and cytoplasmic tail domains are also found. Some members are associated with the cleavage and release of cell-surface proteins. For example, ADAM-17 is known for its ability to release TNF- α from the cell surface. Other ADAMs have also been described in cartilage, including ADAM-10, ADAM-12, and ADAM-15.

ADAMTS family members are distinguished from the ADAMs in that they lack these latter three domains but have additional thrombospondin-like domains (which can number up to 13 and are located predominantly at the C-terminus); they are thought to mediate interactions with the extracellular matrix.¹⁹ Some ADAMTS proteinases can, under certain circumstances, be produced as alternatively spliced forms that differ primarily in the number of their thrombospondin repeats and may give rise to differences

Fig. 20.4 (a) Structure of aggrecan. The major proteoglycan in human cartilage is aggrecan, a protein with three globular domains: G1 to G3. Between G2 and G3 there is a linear region of polypeptide to which charged sugars are attached that attract water and cause the aggrecan to swell. (b) Proteinases that cleave the interglobular domain. Both ADAMTS-4 and ADAMTS-5 and matrix metalloproteinases (MMPs) can cleave aggrecan at specific amino acid sequences between the G1 and G2 domains. Cleavage in this region by ADAMTS-4 and ADAMTS-5 is thought to be key to the pathologic loss of aggrecan from cartilage. (c) Cleavage of aggrecan by aggrecanases and MMPs. ADAMTS-4 and ADAMTS-5 are metalloproteinases that belong to the ADAMTS family. They are either associated with the chondrocyte membrane or released into the extracellular space where aggrecan is cleaved between the G1 and G2 domains, as well as at several sites close to the G3 domain. A specific neoepitope is released and is found in diseased synovial fluids. The G1 domain, which is bound to hyaluronic acid, can be subsequently cleaved by MMPs, with a specific MMP neoepitope being left that can be detected in arthritic cartilage in late-stage disease. TIMP-3 inhibits the release of aggrecan.



in their substrate specificity and localization within the extracellular matrix. Several members of this family are recognized as aggrecanases,¹⁹ and some of these enzymes, most notably ADAMTS-4 and ADAMTS-5,²⁰ are thought to be responsible for the cleavage of cartilage proteoglycan (Fig. 20.4). Recent studies suggest that an enzyme is present on the surface of chondrocytes that also cleaves aggrecan and is distinct from ADAMTS-4 or ADAMTS-5; however, it remains unclear whether it is an ADAMTS family member that is attached tightly via thrombospondin domains or whether a separate

enzyme is present. Interestingly, many of the ADAM and ADAMTS family members are inhibited by TIMP-3, which in *in vitro* studies, effectively blocks release of aggrecan from cartilage.

Serine proteinases

There are almost as many serine proteinases (31%) in the human degradome as there are metalloproteinases (34%),⁵ which makes this proteinase class

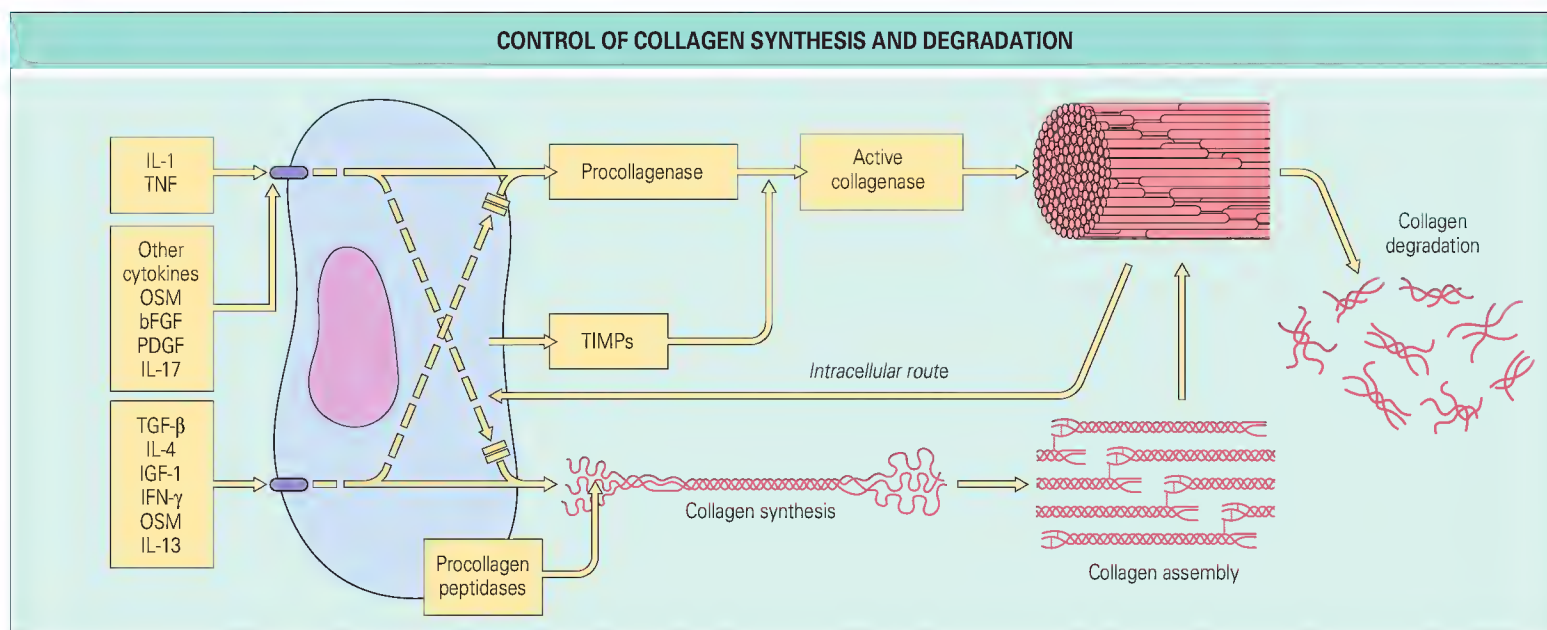


Fig. 20.5 Many growth factors (e.g., transforming growth factor-β [TGF-β], interferon-γ [IFN-γ], insulin-like growth factor 1 [IGF-1], interleukin-4 [IL-4], IL-13) increase the synthesis of collagen, increase proteinase inhibitors, and often reduce the production of proteinases. IL-1 and tumor necrosis factor-α (TNF-α) increase the production of proteinases and can reduce collagen synthesis. Other agents, such as oncostatin M (OSM), IL-17, basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF), can further influence these processes. TIMP, tissue inhibitor of metalloproteinase.

increasingly interesting in terms of joint destruction. Indeed, both direct and indirect roles for serine proteinases have been described, including regulation of cell signaling and modulation of the biologic activity of growth factors; these events can significantly alter inflammatory responses.¹⁷ The complement serine proteinase C1s can degrade IGF-binding protein-5 (IGFBP-5) to release active IGF-1, a growth factor integral in controlling cartilage damage. Complement activation components are elevated in the synovial fluid, synovium, and cartilage of patients with arthritis, and targeted deletion or inhibition reduces disease severity in murine arthritis models.²¹ Interactions between TNF-α and the complement system may contribute to disease pathogenesis, and therapeutics that target complement components are now being developed for the treatment of RA.²² As well as a pro-MMP activator, plasmin can activate TGF-β, release IGF-1 from IGFBPs and activate the complement cascade. The serine proteinases neutrophil elastase and cathepsin G are stored in azurophil granules and released after exposure of the neutrophil to inflammatory stimuli. In mice deficient in both neutrophil elastase and cathepsin G, experimental arthritis is less severe with reduced inflammatory cell infiltration, thus suggesting that these neutrophil serine proteinases are important in promoting the inflammatory process by establishing chemotactic gradients that recruit immune cells and enhance inflammation. Modulation of the biologic activity of chemokines is another important role,¹⁷ and it is now apparent that serine proteinase activators of protease-activated receptor-2 (PAR-2), such as mast cell β-tryptase and chondrocyte matriptase, contribute to joint swelling and synovial vasodilatation, as well as MMP expression and activation.^{23–25} Moreover, the protective phenotype of PAR-2-deficient mice in experimental RA and OA^{24,26} strongly suggests these proteolytic activators could be therapeutic targets. Conversely, some serine proteinases are thought to be protective, such as fibroblast activation protein-α (FAP-α) and dipeptidyl peptidase IV (DPPIV). These transmembrane enzymes have unusual catalytic activity in that they hydrolyze postproline bonds two or more residues from the N-terminus of target substrates, which makes them important regulators of biologically active peptides/neuropeptides and chemokines. Inhibition of FAP-α and DPPIV increases cartilage invasion by RA synovial fibroblasts²⁷ and, because FAP-α is elevated during inflammation as well as in OA cartilage, and α₂-antiplasmin is a physiologic substrate of FAP-α, these findings suggest an important protective feedback mechanism for these enzymes in maintaining cartilage homeostasis.

INTRACELLULAR PATHWAYS—ACID PROTEINASES

Levels of cathepsin D (an aspartic proteinase) and cathepsin B (cysteine proteinase) are increased in OA cartilage and increased levels of cathepsins

B, H, and L (cysteine proteinases) are reported in antigen-induced rat arthritis models and within rheumatoid joints.²⁸ Incubation of resorbing cartilage with specific cathepsin B inhibitors blocked the release of proteoglycan fragments, an action suggesting the involvement of an intracellular route for cartilage proteoglycan breakdown. Cathepsin K can also cleave collagen, albeit at a different site from the MMPs, and the presence of chondroitin sulfate increases the activity and stability of this enzyme. A correlation of cathepsin K-generated collagen fragments with increasing age in OA cartilage has been reported.²⁹ Cathepsin K is now a drug target for the treatment of osteoporosis in which bone resorption is excessive (see later). The relative contribution of intracellular and extracellular pathways to collagen breakdown is controversial. Tissues with high matrix turnover (e.g., periodontal ligament) or that have been stimulated to resorb have increased numbers of collagen-containing vacuoles, which suggests that these vacuoles are linked to resorption. Some work suggests that the intracellular pathway predominates in normal turnover whereas the extracellular route is prevalent only in pathologic conditions.³⁰ Close apposition of the intracellular and extracellular pathways will be found in many situations characterized by connective tissue turnover (Fig. 20.5).

OSTEOCLASTIC BONE RESORPTION

Bone is also destroyed in RA,³¹ and both the MMPs and cysteine proteinases are involved.³² For details see Chapter 22 and the online supplement.

MODEL SYSTEMS OF CARTILAGE BREAKDOWN

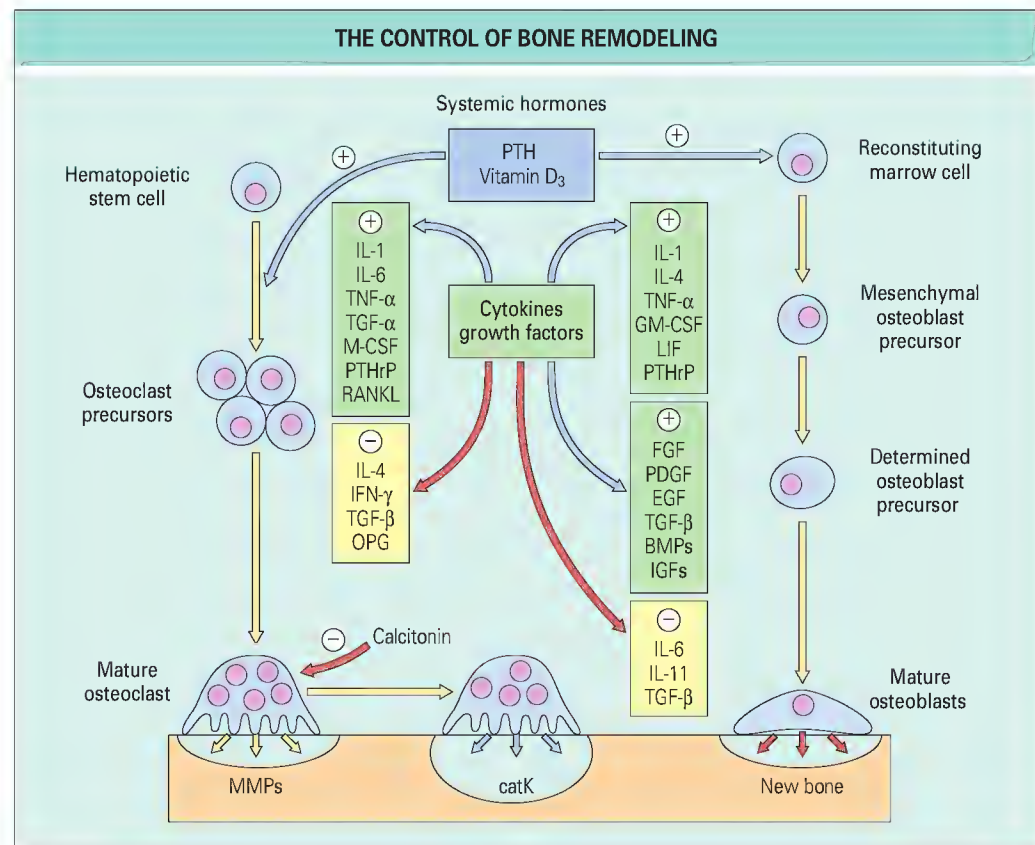
A large number of *in vitro* and *in vivo* models are used to study the mechanisms of joint destruction. Initiation of cartilage breakdown can be induced with IL-1, TNF-α, IL-17, retinoic acid, or other proinflammatory cytokine combinations in model systems.³⁶ Specific proteoglycan fragments are released first from resorbing cartilage (see Fig. 20.4). TIMP-3 blocks such release of proteoglycans, thus supporting a role for ADAMTS enzymes, particularly ADAMTS-5, and possibly other chondrocyte membrane metalloproteinases. Cysteine proteinase inhibitors can also block the release of proteoglycans from cartilage, thus indicating that they could be involved in upstream activation pathways.³⁷

The loss of collagen from cartilage is viewed as the final phase of tissue destruction and is essentially irreversible; attempts at repair do not lead to restoration of normal cartilage. Before the loss of collagen, many of the minor components of the extracellular matrix are first degraded, including molecules that are closely associated with the collagen fibrils, such as cartilage oligomeric matrix protein (COMP), decorin and type IX collagen. It

Osteoblasts respond to parathyroid hormone and other agents that induce bone resorption, such as IL-1 and TNF- α , by increasing the secretion of MMPs to remove the osteoid layer on the bone's surface. Osteoclast precursors then adhere to the exposed bone surface, differentiate, and form a low-pH microenvironment beneath their lower surface. This removes mineral, and lysosomal proteinases then resorb the exposed matrix (Fig. e20.1). Cathepsins B and L cleave collagen types II, IX, and XI and destroy cross-linked collagen matrix at low pH. Osteoclasts produce cathepsin K, which cleaves type I collagen at the N-terminal end of the triple helix. This enzyme plays a key role in the degradation of bone collagen and its expression correlates with bone resorption. It is also produced by synovial fibroblasts and is thought to contribute to synovium-initiated bone destruction in the rheumatoid joint.³³ Bone resorption is impaired in situations in which cathepsin K is deficient, evidence that has made cathepsin K a drug target for the treatment of osteoporosis in which bone resorption is excessive.

There is clear evidence for a central role of receptor activator of nuclear factor- κ B ligand (RANKL) in the bone destruction seen in RA. This member of the TNF ligand family of cytokines is abundantly produced by T cells and synovial fibroblasts in RA synovial membrane and it stimulates the formation of multinucleated osteoclasts. It is upregulated by a variety of cytokines, including IL-1, TNF- α , IL-11, OSM, parathyroid hormone-related peptide (PTHrP), macrophage colony-stimulating factor (M-CSF) and IL-17. It binds to a specific receptor, RANK on the surface of osteoclast precursors. Increased levels of RANK and RANKL, as well as multinucleated cells, are evident in arthritis models associated with bone erosions. The potent activity of IL-17 in osteoclastogenesis is mediated by the upregulation of RANKL and its action is antagonized by the decoy receptor osteoprotegerin (OPG). OPG is effective in blocking bone resorption³¹ and in rat adjuvant-induced arthritis and the arthritis of TNF transgenic mice³⁴; it protects against the development of bone and cartilage destruction. Studies have investigated the use of antisclerostin antibodies as a treatment to prevent osteoporotic bone loss because reduced sclerostin levels are associated with high bone mass.³⁵

Fig. e20.1 Hematopoietic stem cells are induced to differentiate into osteoclast precursors by systemic hormones such as parathyroid hormone (PTH), as well as vitamin D₃; various cytokines and growth factors have stimulatory or inhibitory effects on this differentiation. These precursors mature into osteoclasts, which first remove the mineral component of bone via acidification of an extracellular zone on the bone surface and then mediate the breakdown of protein components through the production of matrix metalloproteinases (MMPs) and cathepsin K (catK); calcitonin inhibits osteoclast function. Osteoblasts are derived from reconstituting bone marrow cells that differentiate under certain stimuli into osteoblast precursors, which then further differentiate into mature osteoblasts. These cells model and repair bone by producing new mineralized bone matrix. Pathways that promote differentiation are in blue; pathways that inhibit it are in red. EGF, epidermal growth factor; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGF, insulin-like growth factor; IL-1, interleukin-1; M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; PDGF, platelet-derived growth factor; PTHrP, parathyroid hormone-related peptide; RANKL, receptor activator of nuclear factor- κ B ligand; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α .



is not known whether this disassembly of the matrix occurs in a defined sequence, but it is evident that a matrix as complex as articular cartilage requires numerous proteolytic activities to effect complete tissue destruction. Although IL-1 and TNF- α are sometimes able to initiate cartilage collagen resorption alone, when these cytokines are combined with OSM, rapid and reproducible release of collagen is found in bovine and porcine cartilage. Synthetic MMP inhibitors and TIMP-1 are able to prevent this release,³⁶ a finding that strongly implicates the collagenolytic MMPs in this process.

Murine models of RA include collagen-induced arthritis. Implantation of RA synovial fibroblasts with normal articular cartilage under the renal capsule of mice with severe combined immunodeficiency leads to maintenance of the aggressive phenotype of the synovial fibroblasts that invade the cartilage, whereas OA synovium does not.³⁸ Adenoviral delivery of proinflammatory cytokines intraarticularly can also lead to RA-like tissue destruction with concomitant synovial hyperplasia.³⁹ These models emphasize the role that synovial fibroblasts play in destroying both bone and cartilage in RA, and methods have also been developed in which synovium and cartilage can be cocultured *in vitro*. The interplay between cartilage, bone, and synovium and the different points at which joint destruction can be blocked are illustrated in Figure 20.6. A role of inflammation and factors such as IL-1 in the progression of OA is now proposed. Although spontaneous OA animal models are available, surgical instability models are most

common in laboratory animals, including dog, guinea pig, rabbit, rat, mouse, sheep and goat.⁴⁰ Advantages of surgical models over spontaneous models include a significantly faster onset of disease with a decrease in both variability and dependence of genetic background.⁴¹ The two most common models are generated via either anterior cruciate ligament transection or destabilization of the medial meniscus (DMM), with DMM being the model of choice in the mouse.⁴¹ These models in the mouse have allowed the use of transgenic knockout (KO) or knock-in (KI) animals to provide insight into the mechanisms that regulate OA pathology.^{6,42} Despite these developments, no single model fully replicates human disease and it is unclear how well any of these models resemble idiopathic OA in the older human population.^{6,40}

METALLOPROTEINASE-DEFICIENT MICE IN MODELS OF DISEASE

Targeted gene disruption or KO experiments in mice have allowed investigation of the contribution of individual MMPs to many physiologic and pathologic processes, including arthritis.⁴³ All MMP KO mice are embryonically viable, but the MMP-9 KO exhibits an abnormal pattern of skeletal development, the MMP-20 KO shows severe abnormalities in tooth development, and the MMP-14 KO displays severe defects in skeletal development and dies within 3 to 16 weeks of age.

MMP-9 KO mice show developmental abnormalities that involve growth plate and endochondral ossification. Hypertrophic chondrocytes develop normally but apoptosis, vascularization, and ossification are delayed. MMP-9 appears to be important in the invasive activity of osteoclasts at resorption sites and mice deficient in MMP-9 exhibit a delay in osteoclast recruitment, although osteoclastic resorption of mineralized matrix still occurs.

MT1-MMP KO causes severe defects in both endochondral and intramembranous bone formation and gives rise to severe connective tissue defects and the development of arthritis. Bone marrow stromal cells from MT1-MMP KO mice show decreased bone formation, thus suggesting that MT1-MMP may influence the differentiation and activity of osteoblasts. MT1-MMP KO mice also have increased numbers of osteoclasts, thus suggesting that MT1-MMP may influence the differentiation and recruitment of these cells.

MMP-13 KO mice show only transient abnormalities in cartilage resorption during long-bone growth and fracture healing; however, when subjected to a surgical model of OA (DMM), cartilage erosion is inhibited in these mice even in the presence of aggrecan depletion, which supports the potential for therapeutic intervention in established OA with MMP-13 inhibitors. Furthermore, MMP-13 expression correlates with elevated hypertrophy-associated genes. The recapitulation of growth plate-like hypertrophic differentiation of chondrocytes has suggested an important role in the pathogenesis of OA. However, in the MMP-13 KO DMM animals, hypertrophy markers were still detected in cartilage that did not erode, which suggests that it is not the hypertrophic differentiation of chondrocytes *per se* that results in degradation of cartilage but rather the hypertrophy-associated expression of MMP-13. Of further interest was the observation that osteophytes still formed in the MMP-1 KO mice subjected to DMM, thus suggesting that osteophyte formation is not linked to articular cartilage destruction but to other factors, potentially joint instability.⁴⁴

In the development of antibody-induced arthritis (AbIA), an animal model of RA, MMP-2 KO mice showed significantly exacerbated arthritis in comparison to wild-type mice. Recovery from AbIA could be achieved in the MMP-2 KO mice by injection of wild-type fibroblasts. This suggests a suppressive role for MMP-2 in the progression of AbIA even though MMP-2 is overproduced in the AbIA joint in wild-type mice. In contrast to MMP-2 KO mice, MMP-9 KO mice show reduced levels of AbIA, an observation indicating that MMP-9 enhances arthritis in this model. The double-KO mice showed no significant difference from the wild-type mice, probably reflecting the net effects of both exacerbated arthritis by MMP-2 deficiency and reduced arthritis by MMP-9 deficiency. In cartilage with AbIA, erosion was mild even in severely arthritic mice; therefore the roles of MMP-2 and MMP-9 in cartilage erosion could not be determined. Somewhat counterintuitively, however, in DMM-induced OA, MMP-9 disruption resulted in more severe OA.

Disruption of the MMP-3 gene has been investigated in several models of arthritis: antigen-induced arthritis (AIA), collagen-induced arthritis (CIA), and induction of OA by both a collagenase-induced instability model of OA⁴⁵ and surgical transection of the medial collateral ligament and partial medial meniscectomy. All studies show no significant differences in either inflammation or proteoglycan depletion between the MMP-3 KO mice and controls. The major MMP cleavage site in aggrecan generates

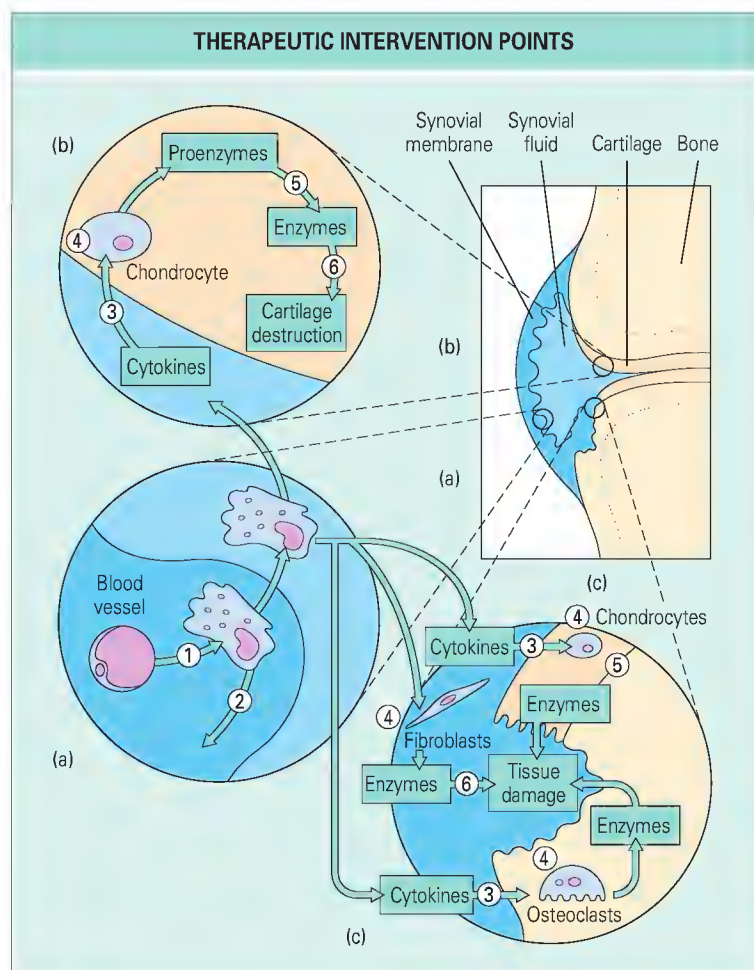


Fig. 20.6 Therapeutic intervention points for preventing connective tissue destruction and cellular mechanisms involved in tissue damage. The destructive cycle of events can be broken in a number of ways, including (a) (1) blocking the entry of harmful cells, (2) removal of harmful cells from the joint, (b and c) (3) blocking or mimicking cytokine or growth factor action, (4) blocking the intracellular signaling pathways involved in the production of proteinases, (5) preventing the activation of proteinases, and (6) direct inhibition of the destructive proteinases degrading bone or cartilage. (c) Within the joint, mixtures of cytokines stimulate chondrocytes to release and activate enzymes that damage the cartilage matrix. Within the synovium, fibroblasts, macrophages, and T cells interact to produce tissue damage in bone and cartilage. The cytokines released also activate osteoclasts, which leads to the destruction of bone.

the C-terminal neopeptide VDIPEN. In the AIA model and in collagenase-induced instability models, VDIPEN staining was eliminated or significantly reduced in MMP-3 KO mice but in CIA and meniscectomized mice, VDIPEN staining was the same as in wild-type mice. MMP-mediated aggrecan cleavage has been further assessed via a KI mouse in which the wild-type cleavage site was altered so that it was impervious to MMP activity. These mice have no developmental problems, which implies that MMP-mediated aggrecanolysis is not important in growth plate remodeling. In addition, lack of a growth plate phenotype in KOs for ADAMTS-1, ADAMTS-4, or ADAMTS-5, as well as a KI engineered to resist aggrecanase-mediated aggrecanolysis (the N-terminal ARGSV neopeptide), supports nonproteolytic mechanisms of aggrecan remodeling in the growth plate.⁴⁶ The ADAMTS-4 and ADAMTS-5 KO mice have revealed that ADAMTS-5, at least in mice, plays a major part in tissue turnover in models of OA and inflammatory arthritis.^{20,47}

The COL2-3/4C neopeptide (generated by collagenases) was used to detect collagen cleavage, and this was eliminated in the AIA model in MMP-3 KO mice versus wild-type controls but was unchanged in the meniscectomized model. In the AIA model, MMP-3 appears to have an important role in the mechanisms leading to cleavage of type II collagen. In contrast, the meniscectomized MMP-3 KO mice exhibited accelerated formation of OA lesions when compared with wild-type mice. These results could suggest that MMP-3 plays an important role in homeostasis in healthy cartilage by balancing anabolism and catabolism of the cartilage matrix or, alternatively, that the MMP-3 gene is compensated by another similar gene such as MMP-10.

Mice deficient in either TIMP-1 or TIMP-2 exhibit no major phenotype, whereas a mild but transient OA with increased proteoglycan loss and increased generation of the VDIPEN neopeptide develops in TIMP-3 KO mice. As TIMP-3 KO mice age, there is evidence of increased cartilage catabolism; lack of TIMP-3 will lead to an altered metalloproteinase/TIMP balance and the higher levels of TNF- α could also be due to lack of inhibition of the metalloproteinase TNF- α -converting enzyme (TACE).⁴⁸

Studies in KO mice are therefore a powerful approach for defining protein function and application of these KO experiments in mouse models of diseases has shown that MMPs serve specific roles in a variety of pathologic processes. These data need to be interpreted carefully because of significant differences between mice and humans in MMP expression (e.g., MMP-1), gene redundancy, and the distribution of load across joints. However, novel targets for therapeutic intervention can be investigated by using these models.

THERAPEUTIC INHIBITION OF PROTEINASES

The use of synthetic proteinase inhibitors as drugs to prevent joint destruction in the arthritides has been unsuccessful to date. Compounds that inhibit MMPs are the most studied¹⁰ with the aim of treatment being to shift the balance away from matrix degradation to prevent the loss of connective tissue matrix without leading to excess synthesis. Initial problems with the oral availability of MMP inhibitors have been overcome. Despite favorable results in the treatment of some cancers, trials of compounds that inhibit the collagenases in patients with RA have not been successful. It may be that the compounds used were unsuitable or that collagenases are not the best target. It is not known whether sufficient penetration of cartilage by these compounds was achieved or whether their specificity was altered during absorption.

The antibiotic doxycycline and derivatives with no antibiotic activity weakly inhibit MMPs, and these compounds have been licensed for the treatment of periodontal disease. They are also effective in animal models of arthritis and have therefore been proposed as a treatment to prevent cartilage damage. In a randomized placebo-controlled trial of overweight women with unilateral radiographic knee OA, those randomized to doxycycline 100 mg twice daily had a 33% reduction in the mean amount of joint space narrowing over a period of 30 months.⁴⁹ It is possible that specific TIMPs could be used successfully in the future to halt the progressive and chronic destruction of connective tissue seen in the arthritides. It may be necessary to combine different proteinase inhibitors, either in sequence or with other agents that target different but specific steps in the pathogenesis, before the chronic cycle of joint destruction found in these diseases can be broken (see Fig. 20.6).

Recent interest has begun to focus on compounds that target events before the induction of these destructive genes. Some compounds that block specific signal transduction pathways have been shown to prevent cartilage destruction *in vitro* and compounds are in development that specifically inhibit the Janus kinases as an oral disease-modifying therapy.⁵⁰

REPAIR OF CONNECTIVE TISSUE MATRIX

Cartilage metabolism may be altered by effects on cellular proliferation, migration or differentiation and the control of individual genes (see Fig. 20.3b). The effect of any particular growth factor also depends on the differentiation state of the cell. Various types of cells in tissues may respond differently to particular cytokines and growth factors. Other local conditions will affect these responses, such as mechanical loading, oxygen tension, and the presence of other factors (see Fig. 20.3b).

Diseased joints have areas of cartilage in which new matrix synthesis occurs, as well as net loss of the extracellular matrix. Growth factors play major roles in regulating normal matrix synthesis and in the processes that protect cartilage in disease. Growth factors such as TGF- β and bone morphogenic proteins (BMPs) have direct effects on chondrocytes and are known to be involved in matrix deposition in OA (e.g., osteophyte generation).⁵¹ However, TGF- β is also known to induce MMP-13 expression under some circumstances, and lack of TGF- β responsiveness with increasing age may be an important caveat for effective tissue repair in disease. Other factors, such as hormones, corticosteroids, prostaglandins, peptides or retinoids, may also influence cellular responses to these growth factors.

TGF- β and IGF-1 have profound effects on the synthesis of matrix components by chondrocytes.⁵² TGF- β can downregulate the production of several matrix-degrading proteinases and upregulate proteinase inhibitors such as TIMP-1 or plasminogen activator inhibitor, thus suggesting that it may prevent cartilage destruction by both stimulating synthesis and blocking degradative pathways. TGF- β is locally synthesized by chondrocytes, affects protein synthesis, and potentiates the stimulation of DNA synthesis achieved with other growth factors rather than initiating this itself. IGF-1 mimics many of the actions of TGF- β and has a significant effect on matrix synthesis but does not have the same mitogenic properties or affect protein synthesis to the same extent. Within cartilage, TGF- β and IGF-1 are stored in considerable quantities bound to different matrix components. More recently, connective tissue growth factors and members of the BMP family have been shown to have anabolic effects on cartilage and bone. The source of growth factors will vary. They can be produced by cells outside the cartilage and diffuse in, or they can be produced locally by chondrocytes. The control mechanisms are complex and growth factors also exist in a latent form; other proteins, such as IGFBPs, may be present that sequester the factors and prevent them from binding to cellular receptors. The activity of some MMPs can cause the release of growth factors as matrix is degraded. This provides positive feedback mechanisms that redress the balance between degradation and synthesis of matrix components.

Growth factors are recognized as being protective of cartilage, stimulating matrix synthesis, and blocking the effects of proinflammatory cytokines. Other factors also protect joint tissues. Interferon- γ inhibits cytokine-stimulated bone resorption and IL-1- or TNF- α -stimulated collagenase production by chondrocytes, as well as reduces IL-1-stimulated release of prostaglandin from cartilage. IL-4, IL-13 and IL-10 have all been shown to oppose the effects of these proinflammatory cytokines by blocking MMP secretion or activation or increasing inhibitor production and matrix synthesis. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) can also affect cartilage homeostasis by inducing cells to migrate, differentiate or proliferate. In addition, bFGF stimulates the production of plasminogen activator inhibitors and TIMP-1 in fibroblasts and endothelial cells. All these growth factors are likely to stimulate cartilage repair, and many do not act alone but rather synergistically to promote the synthesis of new matrix.

MODELS OF MATRIX REPAIR

Considerable progress has been made in cartilage repair. Defects found in diseased or damaged cartilage can be repaired in model systems after the delivery of agents that will stimulate chondrocytes to synthesize new matrix.⁵³ Different approaches have been used, including the following:

- Isolation of autologous chondrocytes or stem cells, which are grown and differentiated in culture and then implanted into defects at high density
- Grafting of cartilage into large defects
- Filling of defects with various natural or synthetic polymers
- Addition of growth factors to encourage migration into the defect and subsequent synthesis of matrix components

Defects in cartilage have been filled with biodegradable matrices that contain low concentrations of a chemotactic or mitogenic factor that is

slowly released, such as TGF- β . Many growth factors have been shown to be effective including bFGF, PDGF, EGF, growth hormone, TGF- β and IGF-1. A cartilage-like matrix is produced within defects after 6 weeks. Successful induction of cartilage is now being achieved in experimental models and could be adapted for clinical use to allow intervention in the disease process. A key issue here is the “quality” of the cartilage matrix generated, and there is an emphasis on ensuring an appropriate ratio of types I and II collagen, where type II should predominate. The potential use of mesenchymal stem cells (nonhematopoietic progenitor cells found in various adult tissues) for tissue engineering to generate replacement tissues for repair of joint damage in arthritis is an attractive area of research,⁵⁴ but

it will still be some time before such stem cell therapies are used clinically. However, successful integration of such matrices with host tissue is often problematic, although advances in regenerative medicine, especially in the area of nanotechnology, have led to novel surface scaffolds for implants that provide specific biofunctionality to better encourage biointegration of implants.⁵⁵

These techniques remain limited because they rely on surgical intervention, which may be practical only in large joints. However, when traumatic injury has resulted in damage to cartilage or when large joints have a discrete and well-defined injury, this procedure may benefit patients by increasing the chance of cartilage repair.

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Principles of tissue engineering and cell- and gene-based therapy

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- Tissue engineering is an interdisciplinary research approach that combines the principles and methods of engineering sciences, cell and molecular biology, and clinical medicine with the aim of replacing injured or degenerated human tissues.
- The central dogma of tissue engineering states that a target tissue-specific template for replacing injured tissue relies on three principal components: cells, cell carriers (scaffolds), and external stimuli (e.g., growth factors or mechanobiologic stimuli).
- Mesenchymal stem cells are the most promising cell candidate for musculoskeletal tissue engineering because they can easily be obtained from mesodermally derived tissues (i.e., bone marrow), possess high expansion capacity, are able to differentiate into a number of mesenchymal lineages, and exhibit immune suppressive effects.
- Innovative production methods (i.e., electrospinning) allow the fabrication of biomimetic, target tissue-specific three-dimensional templates build up from synthetic or natural polymers (or from both).
- Various gene products (i.e., interleukin-1 receptor antagonist [IL-1ra], IL-4, IL-10, nuclear factor κ B) have been identified as potential therapeutic agents for treating rheumatic disorders, whereas gene delivery can be realized via viral (transduction) and nonviral (transfection) gene therapy technologies.

INTRODUCTION

Tissue engineering and cell-based therapies are emerging disciplines that constitute the principal technologies in the relatively new field of regenerative medicine. These technologies are directed toward self-regeneration and involve the use of biomaterials or biologically active molecules, application of differentiated or undifferentiated cells, functional tissue engineering, organ transplantation, and process technologies, as well as the development of regulatory standards (Fig. 21.1). In orthopedic surgery, autologous chondrocyte implantation (ACI) has become an established technique for the repair of focal articular cartilage defects in young adults. On the other hand, repair of degenerated cartilage lesions arising from diseases such as osteoarthritis (OA) or rheumatoid arthritis (RA) remains one of the greatest orthopedic challenges. The key underlying cause of this challenge is the inflammatory environment that drives the competing anabolic and catabolic processes toward extensive joint and cell transplant degeneration. As a result of intensive research in the past 2 decades, adult mesenchymal stem cells (MSCs) have emerged as a promising candidate cell type for the treatment of rheumatic diseases, principally because of their well-characterized ability to differentiate along the chondrogenic pathway and their recently demonstrated antiinflammatory and immune suppressive properties through trophic mediators.

TISSUE ENGINEERING

Tissue engineering is an interdisciplinary research approach with the goal of replacing injured or degenerated human tissues to restore their form, structure, and function by combining the principles and methods of engineering sciences, cell and molecular biology, and clinical medicine.^{1,2} From its beginning in the early 1990s, “tissue engineering” has developed into its own scientific and clinical discipline, with potential application for almost every tissue of the human body. The central dogma of tissue engineering

states that a target tissue-specific template for replacing injured or degenerated tissue relies on three principal components: cells, cell carriers (scaffolds), and external stimuli (e.g., bioactive molecules, including growth factors and genes, or mechanobiologic stimuli) (Fig. 21.2).

In the context of tissue engineering, the basic function of the scaffold is to provide a temporary structure for the seeded cells or migrating host cells to adhere to and subsequently to synthesize new native extracellular matrix (ECM) in a shape and form guided by the scaffold. The main criteria for scaffold design include controlled biodegradability, suitable mechanical strength, and appropriate surface chemistry, as well as the ability to regulate cellular activities, such as proliferation, cell-cell and cell-matrix interactions, and directed differentiation.^{3,4} Scaffolds can be manufactured from native or synthetic polymers, with native materials exhibiting optimal biocompatibility and biodegradability and synthetic polymers having higher primary stability and being more accessible for macrostructure and microstructure formation. A key requirement for a tissue-engineering scaffold is optimal porosity to facilitate nutrition, proliferation, and migration of cells and to ensure cell colonization of the entire carrier. Although primary, tissue-specific cells (i.e., chondrocytes) are inherently the most suitable source of cells for cartilage tissue engineering, they have limitations in practice because of the shortage of supply, loss of phenotype during expansion culture, and potential donor site morbidity after harvest.^{3,5}

AUTOLOGOUS CHONDROCYTE IMPLANTATION

An established procedure for the treatment of symptomatic chondral or osteochondral defects of the knee joint guided by the principles of tissue engineering is the first generation of ACI, originally developed by Brittberg and coworkers⁶ 2 decades ago. First, a cartilage biopsy sample is taken arthroscopically from a small, non-load-bearing area. After enzymatic isolation and chondrocyte expansion in culture *in vitro*, a second surgical procedure is performed that involves exposure of the knee joint via arthrotomy, débridement of the cartilage defect, and suturing of a periosteal patch or collagen membrane over the defect to obtain a cavity in which the culture-expanded chondrocytes can be injected and secured by sealing with fibrin glue. This technique achieves predominantly good to very good long-term clinical results in more than 70% of patients,⁷ and the results are superior to those of sole débridement or osteochondral cylinder transplantation.⁸

However, ACI has several disadvantages that need to be addressed. The use of periosteum can result in transplant hypertrophy, calcification, and delamination,⁹ and the cell suspension has the potential to leak and thus compromise the development of sufficient neotissue at the defect site. Recent experimental and clinical research has been directed toward the development of matrix-associated procedures for ACI whereby biocompatible scaffolds are used as a vehicle for secure delivery of primary chondrocytes to the defect site. Today, clinical experience and promising clinical outcome data using collagen type I membranes or hydrogels,¹⁰ a copolymer of polyglycolic acid (PGA), polylactic acid (PLA), and polydioxanone, and hyaluronic acid have been reported.³ For example, use of a collagen type I hydrogel, which minimizes potential chondrocyte dedifferentiation, as seen in a monolayer, by providing a three-dimensional environment subsequent to enzymatic cell isolation, results in homogeneous cell distribution and promotes cartilage-specific cell differentiation and ECM deposition within the scaffold.¹¹

In contrast to the surgical treatment of focal articular cartilage lesions, which can result from acute injury or osteochondrosis dissecans, regenerative approaches to the treatment of OA or RA must take into consideration the fact that the cartilage damage arises from an underlying disease process. It is noteworthy that acute cartilage injury and osteochondrosis dissecans

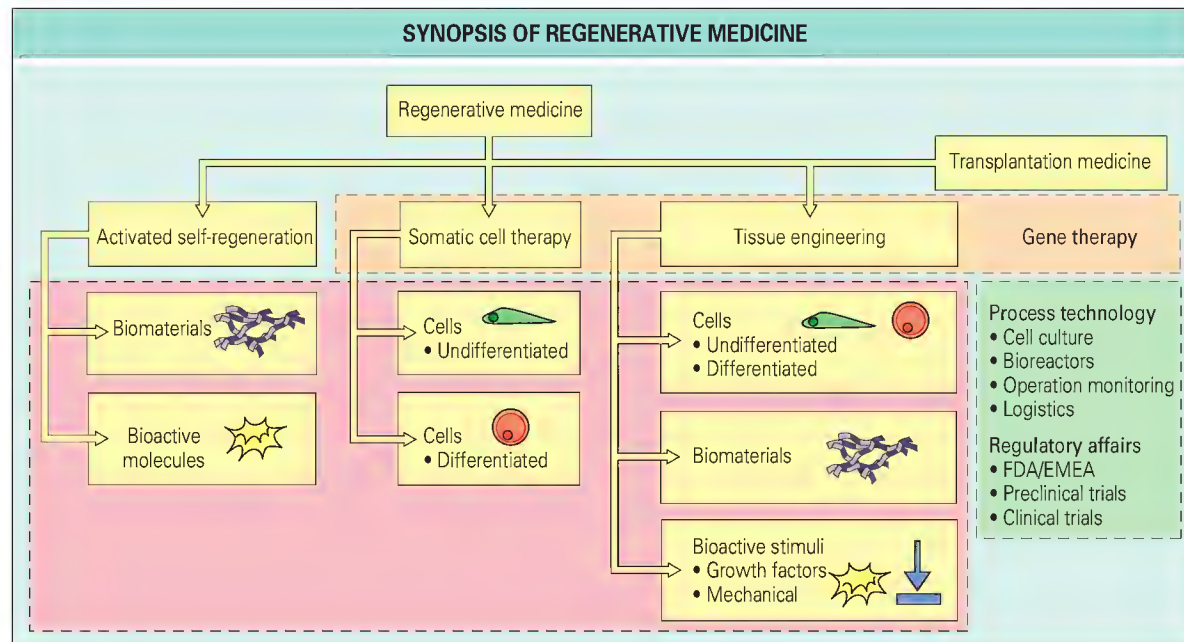


Fig. 21.1 Principal technologies of regenerative medicine targeting the reconstruction of damaged or diseased human tissue and organ function. EMEA, European Medicines Agency; FDA, Food and Drug Administration.

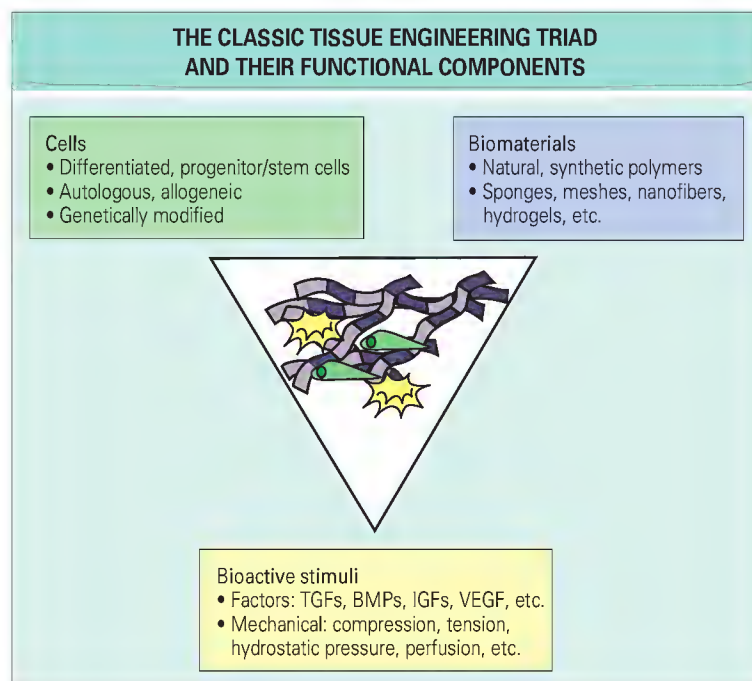


Fig. 21.2 Functional components of the classic tissue engineering triad. BMPs, bone morphogenetic proteins; IGFs, insulin-like growth factors; TGFs, transforming growth factors; VEGF, vascular endothelial growth factor.

often take place in an otherwise healthy joint. The patient may be young, and thus a localized treatment may be sufficient to repair the focal defect. On the other hand, with OA and RA the patient is likely to be older and thus requires treatment of at least one compartment or the entire articulating surface. In addition, inflammatory conditions in the joint are likely to result in degradation of any engineered cartilage.¹² Consequently, unless the underlying disease is treated effectively and technologies are available to restore whole compartments, any cell-based treatment of OA and RA is unlikely to be of long-term benefit.

MESENCHYMAL STEM CELLS

The advantage of adult MSCs, which can potentially overcome the shortcomings of chondrocytes, is that they can easily be obtained from a bone marrow aspirate or other mesodermally derived tissues, possess high expansion capacity, and are able to differentiate into a number of

mesenchymal lineages.^{4,13} In particular, MSCs have been shown to undergo efficient chondrogenic differentiation *in vitro* and *in vivo*.^{4,14} MSCs are commonly isolated from a tissue-derived cell mixture by virtue of their avid adherence to cell culture plastic substrate or by density-gradient fractionation and are therefore intrinsically a heterogeneous cell population. Although no definitive MSC marker or markers have been identified, an immunophenotype positive for STRO-1, CD73, CD146, and CD106 and negative for CD11b, CD45, CD34, CD31, and CD117 has been shown to most reliably characterize the MSC population.^{4,13,14} For the purpose of cartilage regeneration, extensive analyses of microenvironments that promote chondrogenesis in MSCs *in vitro* have been performed. Conditioning the culture medium with growth factors such as fibroblast growth factor-2 or transforming growth factor- β (TGF- β) during monolayer expansion enhances positive selection for chondroprogenitor cells.¹⁵ The development of effective methods to maintain an articular cartilage phenotype without hypertrophy, ossification, or fibrinogenesis and a delivery system to localize the cells within a lesion without compromising their chondrogenic differentiation or the integrity of the repair tissue are additional requirements for the use of MSCs in articular cartilage regeneration.^{3-5,16}

Intraarticular injection of mesenchymal stem cells

Intraarticular injection of MSCs into the joint space is, at least conceptually, the simplest approach for their application to rheumatic diseases (Fig. 21.3a). Because the synovium lines all the internal surfaces of the joint space, except for cartilage and the meniscus, and is highly cellular, it is likely to be a primary tissue for interaction with MSCs.

Only few studies on direct intraarticular injection of MSCs into animal models of OA have been performed thus far. One study described the delivery of autologous MSCs via a dilute solution of sodium hyaluronan into the knee joints of a goat OA model induced by total medial meniscectomy and resection of the anterior cruciate ligament.¹⁷ The cell-treated joints showed evidence of marked regeneration of the medial meniscus, and implanted cells were detected in the newly formed tissue. Articular cartilage degeneration, osteophytic remodeling, and subchondral sclerosis were also reduced. Whether the changes observed in the MSC-treated joints resulted from repair tissue formation by the transplanted cells or the interaction of MSCs with host synovial fibroblasts at the site of injury remains unclear.

In another study, a freshly created partial-thickness cartilage defect in the knee joint of the mini-pig was treated by direct intraarticular injection of MSCs suspended in sodium hyaluronan.¹⁸ The results demonstrated that the cell-treated group showed improved cartilage healing in comparison to the control group without cells. The authors postulated that sodium hyaluronan might facilitate the migration and adherence of MSCs or MSC-like cells, probably derived from the synovium, to the defect. However, this repair tissue was of inferior quality, possibly because of insufficient MSCs localized to the site of injury, and it was shown to further deteriorate by 12 weeks.

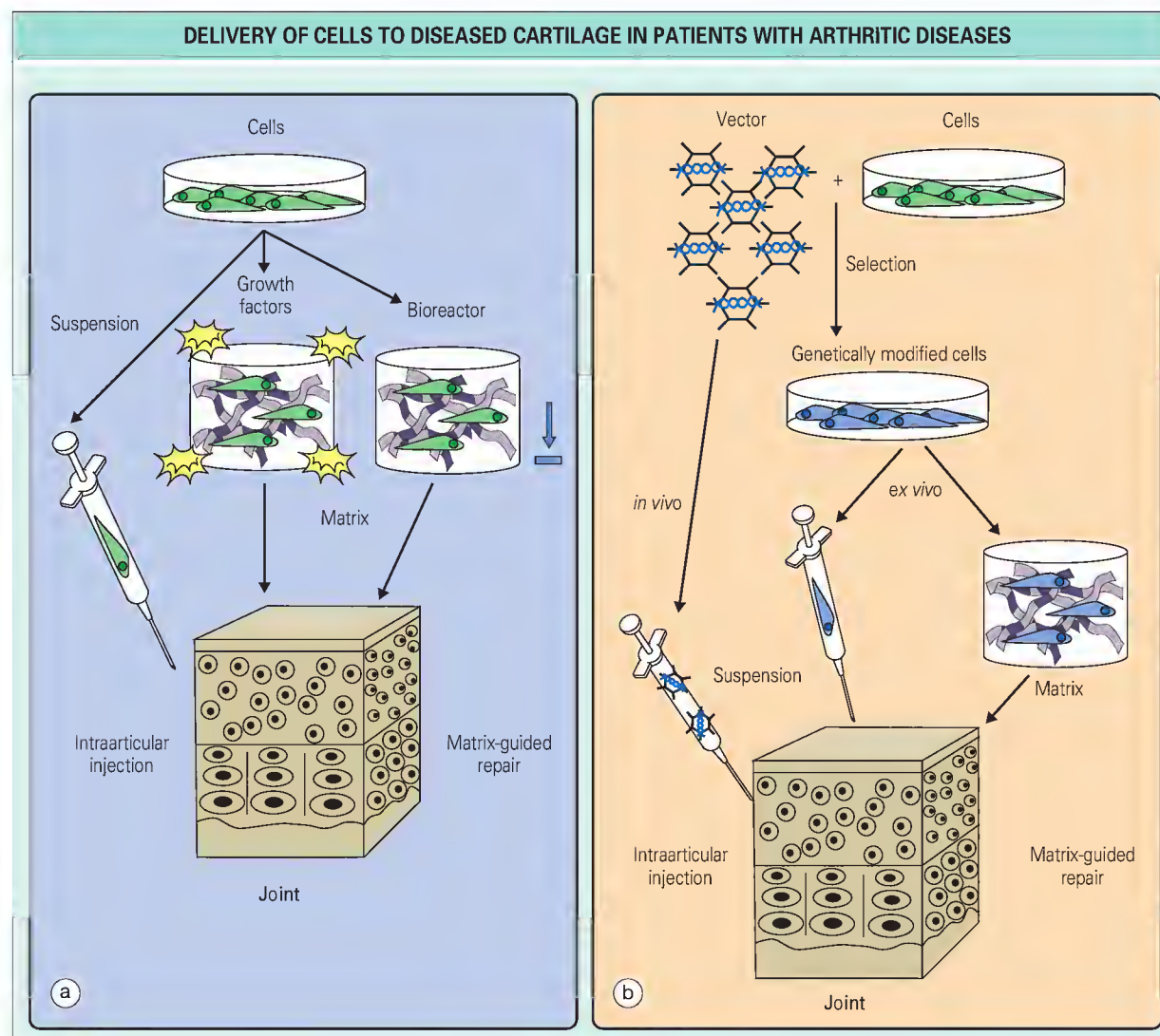


Fig. 21.3 (a) Cell-based therapy for cartilage tissue engineering. Cells in suspension can be injected directly into the joint cavity, where they encounter all intraarticular tissues and might function via trophic mediators and exhibit chondroprotective or regenerative effects. Otherwise, cells (i.e., mesenchymal stem cells, chondrocytes) can be implanted in a matrix-guided manner into the cartilage defect after *ex vivo* conditioning with biochemical or biomechanical stimulation (or both). (b) Gene therapy approach for cartilage tissue engineering. Vectors can be directly injected in an intraarticular mode for *in vivo* gene delivery, or primary cells can be used as vehicles for *ex vivo* gene delivery. In the latter, successfully transduced cells can be applied to the joint cavity either by intraarticular injection as a suspension or by seeding within a matrix that can be implanted into a cartilage defect. Depending on which delivery approach is chosen, ubiquitous or local transgene expression is induced by the *ex vivo* genetically modified cells or by resident cells that are transduced via intraarticular vector application.

Matrix-guided application of mesenchymal stem cells

A more controlled method of cell application to restore the eroded cartilage surface is via a scaffold (see Fig. 21.3a). Seeding MSCs onto or into a scaffold, such as a biodegradable template, for proliferation and matrix production offers the advantage of providing an accessible, easy-to-manipulate, self-renewing source of otherwise spatially limited progenitor cells.

Synthetic scaffolds

Synthetic scaffolds offer the advantage of design manipulation, such as fiber diameter, pore size, degradation time, and reproducible fabrication. Many commonly studied synthetic scaffolds in cartilage repair are fabricated from α -hydroxy polyesters, including PGA, PLA, their copolymer poly(lactic-co-glycolic acid), and poly- ϵ -caprolactone.^{3,16,19,20} The topography and material properties of these scaffolds play an important role in their ability to support MSC differentiation; for example, a nanofibrous scaffold of biodegradable polymers demonstrates enhanced support of MSC proliferation and multilineage differentiation activities.^{20,21}

Natural scaffolds

In contrast to synthetic scaffolds, native biomaterials, including collagen type I, hyaluronic acid, chitosan, and alginate,^{3,22} offer the advantage of presenting a more natural microenvironment. These matrices are biodegradable, can be metabolized by cells via the action of endogenous collagenases,

elicit very limited if any inflammatory reaction, and offer a three-dimensional surrounding with material properties similar to those of hyaline cartilage. In particular, collagen gels may be formed to adapt to any desired defect shape. When compared with meshes or fleeces, in which cell seeding is often limited to mostly the superficial regions of the scaffold material, seeding in hydrogels permits even distribution of MSCs, thus promoting homogeneous ECM production.^{11,12}

The first clinical results of transplantation of MSCs seeded with collagen type I hydrogels for the repair of isolated full-thickness cartilage defects were reported by Wakitani and associates.²³ Two patients with patellar defects were treated with collagen gel–MSC constructs; the constructs were covered with a periosteal flap, and fibrocartilaginous filling of the defect was noted after 1 year, as well as significantly improved patient outcomes at 1-, 4-, and 5-year follow-up. In another case report from the same group,²⁴ a full-thickness cartilage defect in the weight-bearing area of the medial femoral condyle was treated. Histologically, the defect was filled with a hyaline-like type of cartilage tissue that stained positively with safranin O. One year after surgery, the clinical symptoms had improved significantly.

It is noteworthy that these pilot studies have been performed on isolated or focal articular cartilage defects in an otherwise healthy joint. A very different tissue microenvironment exists as a result of loss of joint homeostasis in OA and thus will influence MSC engraftment and differentiation.¹² The potential role and success of matrix-based cell transplantation in a joint diseased with RA are still unclear, as is the impact of the influence of this procedure on the development and progression of disease.²² In general, the

cartilage lesions in OA and RA are large, unconfined, and often opposed (“kissing lesion”) and affect more than one location. Thus, it is important to point out that current biologic and technologic developments are as yet inadequate to indicate sufficient retention of cell-loaded scaffolds in OA or RA lesions.¹²

Trophic and immune suppressive effects of mesenchymal stem cells

Even though the exact mechanisms that guide homing of the implanted or mobilized cells are not known, it is clear that MSCs themselves secrete a broad spectrum of bioactive molecules that have immunoregulatory^{25,26} or regenerative activities (or both).²⁷ The secreted bioactive factors have been shown to inhibit tissue scarring, suppress apoptosis, stimulate angiogenesis, and enhance mitosis of tissue-intrinsic stem or progenitor cells. Because of the complex, multifaceted secretory activity of MSCs, these cells have also been referred to as “medicinal signaling cells,” distinct from their differentiation capacity.²⁸

MSCs are potent modulators of the immune response and exhibit anti-proliferative capacity. They inhibit the proliferation of T lymphocytes induced by allogens, mitogens, or anti-CD3 and anti-CD28 antibodies. T-cell proliferation is inhibited by cell cycle arrest in the G0/G1 phase.²⁹ They also modulate the function of the major immune cell populations, including CD8+ cytotoxic T lymphocytes, B lymphocytes, and natural killer (NK) cells.³⁰ The immunosuppressive activity of MSCs is induced by a combination of inflammatory cytokines, including interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin-1 α (IL-1 α) or IL-1 β .³¹ In addition, MSCs exert significant effects on dendritic cell function by altering the generation and maturation of dendritic cells and skewing their function toward a regulatory phenotype.³² Two other key mechanisms are based on expression of the inducible nitric oxide synthase and indoleamine-2,3-dioxygenase enzymes.³³ Another important mediator of immunosuppression secreted by MSCs is HLA-G. HLA-G is a nonclassical HLA class I molecule that has been shown to suppress the proliferation of CD4+ T cells, induce apoptosis of CD8+ T cells, and inhibit NK cells.³⁴ MSCs can also modulate B-cell responses, depending on the ratio of both cell types. Indeed, at low ratios, MSCs inhibit the proliferation and activation of B cells, similar to their effect on T cells.³⁵

GENE TRANSFER STRATEGIES

The formation of tissues and elements of the skeletal system is the product of an exquisite biologic program that involves the regulated expression of genes and spatiotemporally specified activities of the gene products. Recent advances in cellular, molecular, and developmental biology have led to the identification of various gene products that might serve as therapeutic agents for treating rheumatic disorders, some of which are listed in Table 21.1.

Because exogenous DNA is not spontaneously taken up and expressed by cells in an efficient manner, genes have to be transferred to cells with the aid of vehicles or vectors. These can be assigned to two broad categories: those derived from viruses and those that are not. Viral gene delivery is known as transduction, and virus vectors being used in human clinical trials include retrovirus, adenovirus, adeno-associated virus (AAV), and herpes simplex virus. Overall, it can be stated that no good universal vector exists; instead, the choice of vector depends on the target application. Nonviral gene transfer is known as transfection and may be as simple as delivery of naked, plasmid DNA or via polymers or delivery by applying biophysical methods, such as electroporation. In general terms, nonviral vectors are less expensive, safer, and simpler than viral vectors, but they are considerably less efficient. Some of the specific advantages and disadvantages of each available vector system are listed in Table 21.2 and have been reviewed extensively elsewhere.³⁶ Of note in this context is the occurrence of insertional mutagenesis during human gene therapy trials, which has impeded further use of oncoretroviruses for nonlethal and nonmendelian diseases.³⁷

Regardless of the vector, genes may be transferred to their targets by *in vivo* or *ex vivo* strategies, the principles of which are illustrated in Figure 21.3.

Rheumatoid arthritis

The application of gene transfer to joints was pioneered by Evans and coworkers^{38,39} as a means of treating arthritic disorders. For the treatment

TABLE 21.1

Gene products for cartilage restoration and protection in arthritic/rheumatic diseases

Therapeutic target	Gene product (examples)
Chondrogenic induction	Growth factors (e.g., TGF- β s, BMPs, Wnts) Signal transduction molecules (e.g., Smads) Transcription factors (e.g., SOXs, brachyury)
Osteogenic inhibition	Osteogenic inhibitors (e.g., noggin, chordin) Inhibitors of chondrocyte terminal differentiation (e.g., PTHrP, IHH, SHH, DHH) Signal transduction molecules (e.g., Smad6, Smad7, mIAP-1)
Inhibition of apoptosis	Caspase inhibitors (e.g., Bcl-2, Bcl-XL) FasL blockers (e.g., anti-FasL) NO-induced apoptosis inducers (e.g., Akt, PI-3-kinase) TNF- α , TRAIL inhibitors (e.g., NF- κ B)
Inhibition of senescence	Inhibitors of telomere erosion (e.g., hTERT) Free radical antagonists (e.g., NO antagonists, SOD)
Cartilage matrix synthesis	Growth factors (e.g., TGF- β s, BMPs, IGF-1) Extracellular matrix component (e.g., collagen type II) Enzymes for glycosaminoglycan synthesis (e.g., GlcAT-1)
Protection against inflammation	Cytokine antagonists (e.g., IL-1ra, sIL-1R, sTNFR, anti-TNF-Abs) Proteinase inhibitors (e.g., TIMP1, TIMP2) Antiinflammatory cytokines (e.g., IL-4, IL-10, IL-11, IL-13) Enzymes inhibiting IL-1 (e.g., GFAT)

TABLE 21.2

Vector systems for gene delivery applications for arthritic/rheumatic diseases

Vector	Characteristics
Nonviral	Overall weak efficiency, transient, many inflammatory
Adenovirus	High efficiency, transient, inflammatory
Adeno-associated virus	Moderate efficiency, safe, clinical trial for rheumatoid arthritis
Herpes simplex virus	High efficiency, cytotoxic, transient
Retrovirus	Long-term expression, clinical trial for rheumatoid arthritis, safety concern
Lentivirus	High efficiency, safety concern
Spumavirus	Moderate efficiency, no known disease in humans, not yet used in joints

of RA, biologic therapies that suppress the activities of proinflammatory cytokines such as TNF- α or IL-1 β have shown efficacy. However, such therapies are expensive and require repeated administration, only fewer than half of patients achieve a robust therapeutic response, and the issue of side effects remains of concern. Thus far, most attention has focused on local, intraarticular administration via *ex vivo* and *in vivo* modes of gene delivery (see Fig. 21.3). Genes encoding certain antiinflammatory cytokines such as IL-4, IL-10, and IL-13, antagonists of IL-1 and TNF, or antiangiogenic proteins have shown efficacy in several animal models of RA (see Table 21.1).⁴⁰⁻⁴³

Collectively, these studies have established a convincing proof of principle that has led to the development of human gene therapy protocols for the treatment of RA.⁴⁴ The first clinical protocol selected an IL-1 blocker, the IL-1 receptor antagonist (IL-1ra), as the transgene,³⁹ which was delivered in *ex vivo* fashion via a retrovirus to the metacarpophalangeal joints of nine individuals with severe RA. This phase 1 trial was completed successfully without incident, and the procedure was well tolerated by all nine patients included.³⁸ Another phase 1 protocol, largely similar to the protocol just mentioned, that included one patient has been completed in Düsseldorf, Germany,⁴⁵ with results comparable to those from the trial in Pittsburgh. A phase 1 trial of 15 individuals that involved direct, intraarticular injection of a recombinant AAV2 vector carrying cDNA encoding a fusion protein

consisting of two TNF soluble receptors (sTNFRs) combined on an immunoglobulin molecule was closed and converted into the first phase 2 clinical trial using the same vector.⁴⁴ It was temporarily halted by the U.S. Food and Drug Administration (FDA) because of the death of one individual enrolled in the study as a result of severe histoplasmosis.³⁷ However, the FDA determined that the vector was not responsible for the outcome and has allowed the trial to continue.⁴⁴ The only clinical trial of gene therapy for RA that involved nonviral gene delivery used the genetic synovectomy approach with DNA encoding the herpes simplex thymidine kinase gene, with one individual being treated.⁴⁶ Two other phase 1 trials in Korea and the United States involved the use of *ex vivo* delivery of TGF- β_1 via retrovirus vectors, and 16 individuals have been enrolled without any adverse events thus far.³⁷

Osteoarthritis

Because IL-1 is also an important mediator of cartilage breakdown in OA, its inhibitors have likewise been considered useful targets for gene

intervention. Several animal studies have confirmed the promise of IL-1ra gene delivery in treating OA.⁴⁷ *Ex vivo* delivery of IL-1ra cDNA via retrovirus vectors and direct delivery of IL-1ra via plasmid DNA to the osteoarthritic knee joints of dogs⁴⁸ and rabbits, respectively, were shown to slow cartilage degeneration. Remarkably, in a similar study in horses in which the effects of adenoviral-mediated gene delivery of IL-1ra for experimental OA were explored, reduced lameness of the horses receiving gene therapy was observed.⁴⁹ Of note, because of the localized pathology in OA, it is better suited for local, intraarticular delivery of gene transfer vectors than RA is, in which a systemic condition is typically present. However, in the late stages of human OA, substantial structural defects have already resulted from long-term cartilage degeneration. It is thus highly unlikely that arresting the progress of the disease with an antiinflammatory and chondroprotective gene such as IL-1ra would be sufficient. Structural repair of the damaged cartilage (e.g., via cell-based tissue-engineering approaches, possibly in combination with gene therapy approaches) will be needed to restore full joint function, as extensively reviewed elsewhere.^{3,5,50}

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22

Osteoimmunology

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INTRODUCTION

Two major aspects determine the clinical picture of rheumatic diseases. The first is that inflammation is a central component of many, especially the most severe forms of rheumatic diseases. Some rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, or Sjögren syndrome, are considered classic systemic autoimmune diseases based on the observation of autoantibody formation and accumulation of cells of the adaptive immune system at sites of inflammation. Chronic immune system activation is regarded as a central triggering factor for inflammatory rheumatic diseases. The second key aspect is that the consequences of the immune disturbances affect musculoskeletal tissue, which is the common target of this disease group. Indeed, musculoskeletal tissue experiences progressive local and systemic damage, which is the basis for functional impairment and a high disease burden. Thus, the combination of chronic immune system activation and musculoskeletal tissue damage is the hallmark of rheumatic diseases. Detailed understanding of the pathophysiologic processes of rheumatic diseases requires comprehension of the mutual interactions between the immune system and musculoskeletal tissue. These interactions are the basis for osteoimmunology.

CURRENT CONCEPTS IN OSTEOIMMUNOLOGY

Osteoimmunology is a field of research that focuses on the crosstalk between the immune and musculoskeletal systems.¹ This field is particularly relevant for understanding rheumatic diseases, which are characterized by profound alterations in bone architecture as a consequence of activation of the immune system. The term *osteoimmunology* was created after landmark observations in the late 1990s demonstrated T lymphocytes triggering bone loss by inducing the differentiation of bone-resorbing cells, termed *osteoclasts*.²⁻⁴ These concepts put two, at first sight fundamentally different, organ systems—the immune system and the skeleton—in a much closer relationship to each other than one would ever expect.

Current concepts of osteoimmunology that are of relevance for rheumatology involve (1) regulation of bone degradation by the immune system, (2) the interaction between inflammation and bone formation, and (3) the role of bone and bone marrow as a niche for immune cells. The first concept, immune-mediated regulation of bone loss, has been studied intensively in recent years and has become a well-developed concept that is instrumental in understanding the different forms of bone loss in the course of rheumatic diseases. In contrast, the second concept, interactions between inflammation and bone formation, is still much less developed but is important for defining the mechanisms of repair of structural damage in the joint and the mechanisms driving general bone loss, as well as for explaining the pathophysiology of bony ankylosis. Similarly, the third concept, the bone marrow niche, is currently being highly investigated and is particularly relevant to understanding the deregulation of immune cell trafficking during inflammatory diseases (i.e., the triggers for recruitment of immune cells from bone marrow into inflammatory sites) and to explaining the formation of a stable microenvironment, which allows longevity and antibody production by long-lived plasma cells.

OSTEOCLASTS AS TRIGGERS OF ARTHRITIC BONE EROSIONS

Erosion of periarticular bone is a central feature of RA and psoriatic arthritis.^{5,6} Bone erosion mirrors the destructive process in joints affected by arthritis because it reflects the damage triggered by chronic inflammation.

Visualization of bone erosions by imaging techniques is important not only for the diagnosis of RA but also for defining the severity of disease and response to antirheumatic therapy.⁷ Osteoclasts are bone-specialized macrophages and are the only cell type capable of removing calcium from bone and, consequently, degrading bone matrix. This bone-resorbing function is an essential component of the bone-remodeling process that allows not only normal bone development and skeletal growth but also bone maintenance and repair throughout life. Osteoclasts are also required for the bone erosions observed in rheumatic joints. Indeed, osteoclasts are part of the inflamed synovial tissue of human RA and psoriatic arthritis, as well as all major experimental models of arthritis. Preliminary evidence for osteoclasts in the synovial tissue of RA patients was gathered in the 1980s before Gravallese and colleagues first described that mature osteoclasts are localized at the site of bone erosions in RA joints by using modern molecular tools for characterization of these cells.^{8,9} Later, the essential function of osteoclasts in triggering inflammatory bone erosions was shown by blocking essential molecules for osteoclastogenesis or by using mice deficient in osteoclasts.^{10,11} In all these models no bone erosions occurred when osteoclasts were either effectively blocked or genetically depleted despite clear synovial inflammation. These findings clearly placed osteoclasts as the effector cells for bone erosions and structural damage downstream from the inflammation in the affected joints.

MOLECULAR AND CELLULAR MECHANISMS OF INFLAMMATORY BONE EROSION

What are the mechanisms leading to osteoclast formation at a site since they are not usually present in the joints? Two key mechanisms are essential to form osteoclasts in joints: (1) accumulation of osteoclast precursor cells in the joint and (2) stimulation of their differentiation into the osteoclast lineage. Osteoclast precursors are mononuclear cells belonging to the monocyte/macrophage lineage.¹² Early monocytic precursor cells have the potential to differentiate into macrophages, dendritic cells, osteoclasts, and other more organ-specific cell lineage types such as Kupffer cells in the liver or microglia in the brain. It is not fully clear whether some monocytes already committed to the osteoclast lineage are entering an inflamed joint or whether monocytes “decide” locally within the inflamed synovium on receiving the appropriate signals to switch to the osteoclast lineage. Nonetheless, experimental evidence supports the observation that the peripheral monocytic pool changes during inflammation. For instance, the fraction of CD11b+ cells that serve as osteoclast precursors increases, thus suggesting that an increased number of cells entering the joint can differentiate into osteoclasts.¹³ Moreover, cytokines such as tumor necrosis factor- α (TNF- α) induce the expression of receptors on the monocyte surface, such as osteoclast-associated receptor (OSCAR), which is important for osteoclast differentiation.¹⁴ However, in actuality much less is known about surface receptors on monocytes that can negatively regulate their differentiation into osteoclasts. In fact, one such molecule is CD80/CD86, which effectively blocks osteoclast formation when bound to CTLA4, a negative regulator of T-cell costimulation by monocytes.^{15,16} This could link regulatory T cells that are highly expressing CTLA4 on their surface to bone homeostasis because these cells can suppress osteoclast formation independently of the receptor activator of nuclear factor κ B (NF- κ B) ligand (RANKL), which is one of the major regulators of osteoclast differentiation.

The second mechanism is that monocytic osteoclast precursors that have already entered the inflamed joints find the ideal environment there to further differentiate into osteoclasts because of the presence of RANKL and monocyte colony-stimulating factor (M-CSF/CSF-1), essential stimulating signals for osteoclastogenesis. Both are also involved in the activation of mature osteoclasts (Fig. 22.1). M-CSF, which binds to CSF-1R encoded by

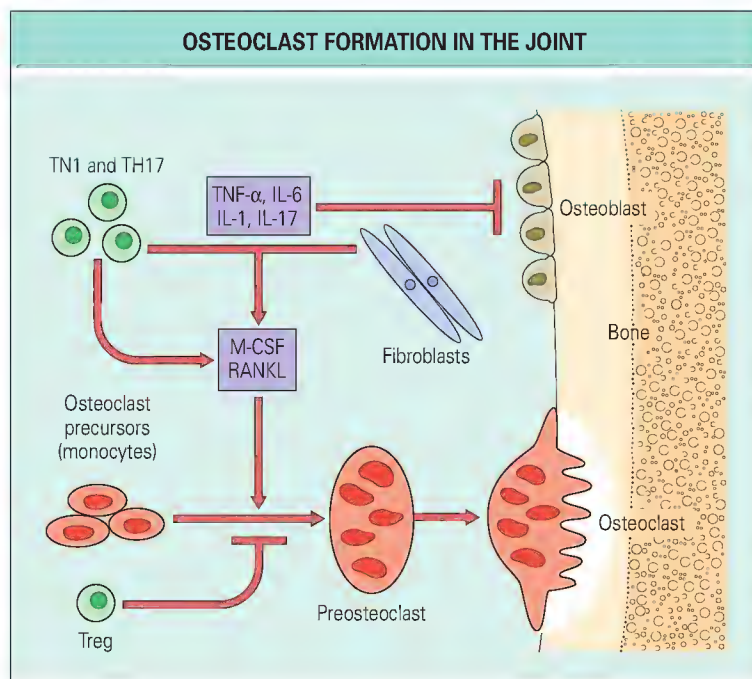


Fig. 22.1 Monocytic cells in the synovium serve as osteoclast precursors. On exposure to monocyte colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κ B ligand (RANKL) synthesized by T cells and synovial fibroblasts, they fuse to polykaryons, termed *preosteoclasts*, which then undergo further differentiation into mature osteoclasts and acquire specific features such as the ruffled membrane. Inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, and IL-17 increase the expression of RANKL and thus support osteoclastogenesis in the joint while inhibiting systemic bone formation by the osteoblasts. In contrast, Treg blocks osteoclast formation via CTLA4.

the protooncogene *C-FMS*, promotes both proliferation and survival of osteoclast precursors. RANKL binds a surface receptor on the precursor cells named RANK that induces signaling essential for osteoclast differentiation via NF- κ B and the activator protein 1 (AP-1) transcription factor family.^{2,3} In the joint this process requires intensive crosstalk with other cells, particularly fibroblast-like synoviocytes and activated T cells. Among T cells, both type 1 and type 17 helper subsets are of importance in this process. Indeed, both cell types inducibly express RANKL.^{3,17} This essential osteoclastogenic cytokine is expressed in the synovium of patients with RA, thus suggesting that it actively contributes to formation of osteoclasts in the synovium.^{18,19} A high level of RANKL expression in the synovium is apparently not balanced by the expression of regulatory molecules such as osteoprotegerin (OPG), a decoy receptor of RANKL that blocks osteoclast formation,²⁰ which suggests that this imbalance is of importance in yielding a negative net effect on local bone mass in the case of arthritis. This concept is supported not only by data obtained from animal models of arthritis showing effective protection from structural damage when blocking RANKL with OPG despite clear synovial inflammation but also by a recent clinical study showing that an antibody against RANKL (denosumab) protects against the progression of bony structural damage in patients with RA.²¹

Apart from RANKL, the osteoclastogenic properties of the inflamed synovial membrane are further enhanced by expression of M-CSF, which is essential for osteoclast formation as well.²² Moreover, proinflammatory cytokines such as TNF- α , interleukin-1 (IL-1), IL-6, IL-17, and vascular endothelial growth factor (VEGF) are all potent inducers of RANKL expression and thus enhance osteoclast differentiation as well. Some of these cytokines additionally exert direct effects on osteoclast precursors; in particular, TNF- α engages TNF receptor type I on the surface of osteoclast precursors, which increases their differentiation into osteoclasts.²³ This link between proinflammatory cytokines and osteoclast formation is most likely the explanation why cytokine-targeted therapy, particularly blockade of TNF- α , is highly effective in retarding the structural damage in RA. Indeed, TNF-blocking agents virtually arrest the radiographic damage in RA and are considered excellent agents for achieving structural protection of joints.²⁴⁻²⁹ Furthermore, several studies have shown that anti-citrullinated protein antibodies (ACPAs) are among the strongest predictors of bone-erosive disease in RA, thus linking autoantibody response in RA and the ability of the disease to elicit structural bone damage. Recently, autoantibodies against

citrullinated vimentin have been reported to bind to osteoclasts, induce their differentiation into bone-resorbing cells, and promote bone loss. This effect was based on the inducible release of TNF- α from osteoclast precursors.³⁰

Apart from TNF- α -blocking therapies, one can anticipate a similar effect of the IL-6 antagonist tocilizumab in addition to its well-established anti-inflammatory effect^{31,32} based on the observations that anti-IL-6R antibody therapies reduce VEGF in synovial fibroblast cultures and that IL-6 drives RANKL expression and hence supports osteoclastogenesis.^{33,34}

PERIARTICULAR AND SYSTEMIC BONE LOSS IN RHEUMATIC DISEASE

Periarticular bone loss has been long known as a radiographic sign of RA and has been explained by the paracrine effects of inflammatory tissue on periarticular bone. Still, periarticular bone loss (also termed *periarticular osteoporosis*) has been poorly defined so far. Apparently, periarticular bone loss is based on a substantial decrease in bone trabeculae along the metaphyses of bones close to inflamed joints, thus suggesting that the bone marrow cavity along inflamed joints is also part of the disease process of arthritis. This is supported by data from magnetic resonance imaging (MRI) studies in patients with RA, which have unraveled a high frequency of signal alterations in the juxtaarticular bone marrow in addition to synovitis outside the cortical bone barrier.^{35,36} These lesions are water-rich lesions with a low fat content, which suggests that bone marrow fat is locally replaced by water-rich tissue. Histologic examination of bone marrow lesions has been carried out in joints of patients with advanced-stage RA undergoing joint replacement surgery. They have revealed that the bone marrow lesions visualized on MRI contain (water-rich) vascularized inflammatory infiltrates that replace bone marrow fat and harbor aggregates of B cells and T cells. Importantly, very similar, if not identical MRI changes are found early in the disease process of RA and have shown a link to subsequent bone erosions in the same joints.³⁷ Bone marrow lesions are often linked to cortical penetration of inflammatory tissue either by means of bone erosions or by small cortical bone channels that connect the synovium with the juxtaarticular bone marrow. Moreover, bone marrow lesions are associated with an endosteal bone response since they coincide with the accumulation of osteoblasts and deposition of bone matrix in the endosteum.³⁸ These novel data have enhanced our view of arthritis as a disease that is confined not solely to the synovial membrane but also to bone marrow.

It has long been known that inflammatory diseases, including RA and ankylosing spondylitis (AS), lead to osteoporosis and increased fracture risk. Data obtained in recent years have supported these concepts and have shed more detailed light on osteoporosis and fracture risk in RA patients. Osteopenia and osteoporosis are frequently observed in patients with RA and are even observed in rather high frequency before any disease-modifying antirheumatic drug (DMARD) or glucocorticoid therapy is started. Roughly 25% of patients with RA have osteopenic bone mineral density at the spine or hip before the onset of therapy in early RA, and 10% have osteoporosis, thus suggesting these symptoms to be an intrinsic component of the diseases.³⁹ Consequently, RA patients are at high risk for the development of complications from systemic bone loss because of the increased prevalence of low bone mass at the onset of disease. The reason for this risk appears to be based on the coincidence of standard risk factors for osteoporosis, such as older age and female sex, with the onset of RA. Another explanation is the possibility that low-grade inflammation often long precedes the onset of clinical symptoms of RA. Indeed, even a small elevation in C-reactive protein as a sign of low-grade inflammation in the normal healthy population dramatically increases the risk for fractures, as independent population-based studies have shown.⁴⁰ Fracture risk is in fact higher in RA patients and has been confirmed by a recent meta-analysis of nine prospective population-based cohorts in which it was shown that fracture risk doubles with the diagnosis of RA independent of whether glucocorticoids are used.⁴¹ Similarly, a large case-control study based on the British General Practice Research Database has shown that RA doubles the risk for hip and vertebral fracture, which clearly supports the concept that inflammation is an independent risk factor for osteoporosis.⁴²

OSTEOIMMUNOLOGIC ASPECTS OF BONE FORMATION IN RHEUMATIC DISEASE

To gain a balanced view of the interaction between the immune system and bone it is important to better define how activation of the immune system controls bone formation. Given the observation that inflammatory arthritis induces profound changes in joint architecture—covering the whole

spectrum from an almost purely erosive disease such as RA, to a mixed pattern with erosions and bone formation side by side, to a prominent bone-forming pattern as observed in AS—regulation of bone formation becomes an interesting aspect of rheumatic diseases. In RA, there is little sign of repair of bone erosions, which is astonishing considering that bone formation is usually coupled to bone resorption and that an increased rate of bone resorption should thus increase bone formation. This, however, is by no means the case in RA, which is virtually a purely erosive disease. Recent data suggest that bone formation is actively suppressed by inflammation. Interestingly, TNF- α suppresses bone formation very potently by enhancing the expression of Dickkopf-1 (DKK1), a protein that negatively regulates the wntless/int (Wnt) signal transduction pathway.⁴³ Wnt signals are key triggers for bone formation by enhancing the differentiation of bone-forming cells (i.e., osteoblasts) from their mesenchymal cell precursors. Wnt proteins are also involved in the regulation of osteoclastogenesis because they enhance the expression of OPG, which blocks osteoclast formation.⁴⁴ Thus, influencing the balance of Wnt proteins and their inhibitors is a very potent strategy for disturbing bone homeostasis: a low level of Wnt activity yields low bone formation and high bone resorption, whereas a high level of Wnt activity increases bone formation and simultaneously blocks bone resorption. In RA, the former scenario appears to be relevant because bone resorption is increased and bone formation is decreased. Inhibitors of Wnt, such as DKK1, are expressed in the synovial tissue of RA patients, thus suggesting a suppressive effect on bone formation. This concept is further supported by the paucity of fully differentiated osteoblasts within arthritic bone erosions, which indicates that no major bone formation is indeed occurring in these lesions.

Pure degradation of bone during arthritis is the exception rather than the rule in joint disease. Psoriatic arthritis, AS, and osteoarthritis and metabolic arthropathies such as hemochromatosis arthropathy are partly or even predominantly characterized by bony spurs along joints and intervertebral spaces. These lesions are based on new bone formation. We have recently perceived that osteophyte formation cannot easily be compared with the erosive structural damage observed in RA and that therapies blocking bone erosions such as TNF- α blockade do not influence the formation of osteophytes/syndesmophytes.⁴⁵ Areas prone to osteophyte formation are (1) periarticular sites of the periosteum in the vicinity of the articular cartilage, (2) edges of vertebral bodies, and (3) the insertion sites of tendons. These sites are particularly rich in fibrocartilage, which is considered a tissue from which osteophyte formation emerges given the interplay of certain triggering factors.⁴⁶ Triggers are certainly mechanical factors because osteophytes often emerge at entheses along the insertion sites of the tendons. Usually, osteophytes are based on endochondral ossification, which first leads to differentiation of hypertrophic chondrocytes from mesenchymal cells and abundant deposition of extracellular matrix before rebuilding into bone occurs, a process that requires invasion and resorption of the mineralized cartilage by osteoclasts and then differentiation of osteoblasts that deposit the bone. The molecular signals involved in osteophyte formation have recently been defined: transforming growth factor- β (TGF- β) and bone morphogenetic proteins (BMPs), along with active BMP signaling through SMAD3 proteins, facilitate human osteophyte formation.⁴⁷ Moreover, noggin, an inhibitor of BMPs, effectively blocks osteophyte formation, thus suggesting that this protein family plays a key role in the formation of bony spurs by facilitating osteoblast differentiation.⁴⁷ Another essential protein family involved in osteophyte formation is the Wnt protein family. These proteins bind to surface receptors such as low-density lipoprotein-related protein (LRP) 5/6 and frizzled proteins on the surface of mesenchymal cells, and such binding leads to signaling through β -catenin, which translocates to the nucleus and activates genes involved in bone formation. Nuclear translocation of β -catenin is observed at sites of bony spurs, thus suggesting its activation by Wnt proteins. There appears to be tight crosstalk between Wnt proteins and BMP proteins because these two protein families act synergistically on bone formation. Moreover, crosstalk to the RANKL-OPG system occurs as well because Wnt proteins induce the expression of OPG, which shuts down bone resorption.⁴⁸ It thus appears that the balance between bone-forming factors, such as Wnt and BMP proteins, and bone-resorbing factors, such as RANKL and TNF, is crucial for how a joint remodels during arthritis.

BONE MARROW AS A NICHE FOR B-CELL DIFFERENTIATION AND AUTOANTIBODY FORMATION

Mechanisms that explain the influence of the immune system on bone homeostasis have thus far dominated osteoimmunology research; however,

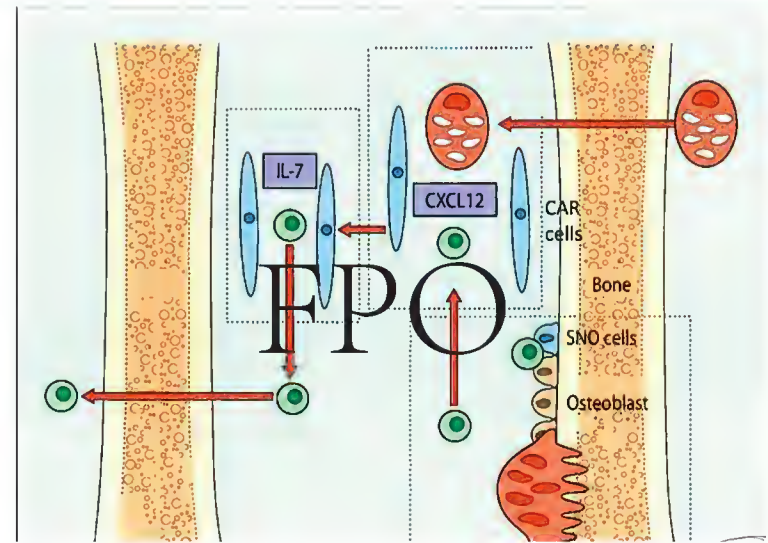


Fig. 22.2 Bone marrow niche. Maintenance and renewal of hematopoietic stem cells (HSCs) depend on a subset of osteoblasts forming the HSCs' niche, which are defined as spindle-shaped N-cadherin+CD45⁺ osteoblastic (SNO) cells. HSCs are mobilized by the activity of osteoclasts and differentiate. Pre-pro-B cells share a common niche with plasma cells based on the expression of CXCL12 by bone marrow stromal cells, also known as CAR (CXCL12-abundant reticular) cells. On further differentiation into pro-B cells, the cells switch to a different niche that is based on bone marrow stromal cells that express interleukin-7 (IL-7). Further differentiation of B cells into pre-B cells makes them independent of bone marrow niches before leaving the bone marrow to secondary lymphatic organs. Plasma cells reentering the bone marrow share the CXCL12-triggered bone marrow niche with pre-pro-B cells.

bone-immune system interactions also play an important role in other areas. Bone is a hematopoietic organ that provides the microenvironment, also called niches, for the maintenance and mobilization of hematopoietic stem cells (HSCs); it is the site of early B-cell differentiation and homing of the long-lived plasma cells. Despite a high number of studies describing osteoblastic and vascular niches, a novel concept suggests that mesenchymal cells and HSCs form a unique bone marrow niche that is regulated by the local surrounding environment and by long-distance signals such as hormones.⁴⁹ Bone-forming cells, or osteoblasts, have been shown to be required for establishing formation of the HSC niche, and osteoblastic development is regulated by osteoclasts.⁵⁰ These factors appear to be important in early B-cell differentiation, as well as for the survival of long-lived B cells and plasma cells.⁵¹ B cells contribute to RA through antigen presentation and the production of antibodies, autoantibodies, and cytokines. Both the earliest precursors (pre-pro-B cells) and end-stage B cells (plasma cells) require CXC chemokine ligand 12 (CXCL12) to home to bone marrow (Fig. 22.2). CXCL12-abundant reticular (CAR) cells are a small population of bone marrow stromal cells that are the main reason why peripheral HSCs always home to bone marrow. CAR cells are distinct from the mononuclear spindle-shaped N-cadherin+CD45⁺ osteoblastic (SNO) cells that express IL-7 and adjoin more mature pro-B cells.⁵² SNO cells not only allow homing of memory B cells and plasma cells to bone marrow but also provide survival signals that allow longevity of these cells and prevent apoptosis. Thus, long-lived memory B cells and plasma cells are dependent not only on affinity maturation but also on an acquired ability to survive. Successful competition for survival niches therefore appears to be a key factor explaining the longevity of these cells. Plasma cells apparently traffic into these survival niches in bone marrow by CXCL12-induced chemotaxis, where they produce antibodies and persist. If bone marrow homing of plasma cells is disturbed, which is seen in murine lupus models in which plasma cells are unresponsive to CXCL12, a marked accumulation of plasma cells in the spleen is observed.⁵¹ Also, circulating B cells might become only memory B cells if they find appropriate survival conditions outside restimulating secondary lymphoid organs.

CONCLUSION

Osteoimmunology has considerably refined our insights into the pathogenesis of rheumatic diseases, particularly arthritis. It appears that one of the

reasons for the preferential targeting of bone by inflammatory arthritis is a disturbance in the natural interaction of the bone and immune systems. This idea gives credence to the old concept of bone remodeling as a controlled inflammatory response despite clear synovial inflammation.⁵³ With the help of osteoimmunology, we are now starting to understand the molecular interactions between immune activation and the skeletal system, which

links inflammatory diseases with bone loss. Knowledge of these pathways will allow tailoring of drug therapies to target skeletal damage more specifically and thus more effectively. In addition, further insight in the role that bone and bone marrow play in shaping the immune responses, particularly in maintaining plasma cells in the bone marrow niche, will open a new perspective in autoimmune diseases.

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23

Inflammation and its mediators

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- Inflammation is the primary process by which the body attacks and destroys microbial invaders, heals wounds, and damages its own tissues.
- The acute, or early, phase of inflammation is characterized by microvascular changes and activation of granulocytic cells (neutrophils, mast cells, eosinophils). Cells from the monocytic lineage predominate in the mature or chronic inflammatory response.
- Activation of platelets and endothelial cells is an essential element of the inflammatory response in tissues.
- Among the most important plasma-derived mediators of inflammation are complement components that provoke vasodilation, granulocyte chemotaxis, and the secretion of inflammatory cell mediators.
- Soluble mediators released from activated cells promote inflammation and provoke tissue injury. Such mediators include histamine and serotonin, prostaglandins and leukotrienes, superoxide anion, and nitric oxide.
- The inflammatory response involves a complex interaction between the nervous system and inflammatory cells.

INTRODUCTION

Inflammatory processes are necessary for survival and regulate both homeostasis of the organism and defense against pathogens. Best recognized as a localized response to injury (e.g., from microbial pathogens, trauma, neoplasia, toxins), inflammation is also important in tissue remodeling during development and in clearance of cellular debris during tissue turnover.

For two millennia, inflammation has been clinically recognized by the four cardinal signs of Celsus: calor (heat), rubor (redness), dolor (pain), and tumor (swelling). A fifth sign, *functio laesa* (loss of function), was proposed by the 19th century pathologist Virchow to underscore inflammation's potential to cause damage. At the cellular level, inflammation begins with vasodilation and increased microcirculation, which leads to transmigration of leukocytes into the injured tissue.¹ Inflammation involves interplay of the innate and adaptive immune responses, the immunologic and nervous systems, and the coagulation and fibrinolytic cascades. Inflammatory responses are regulated, in a complex and integrated manner, by the effects of a wide range of molecular mediators. These inflammatory mediators are highly diverse but can be grouped loosely as (1) growth factors and cytokines, (2) arachidonic acid (AA) derivatives and lipid mediators, (3) the complement system, (4) proteases, (5) neuropeptides, and (6) free radicals and reactive oxygen species (ROS).

In health, inflammation is a self-limited response to a specific injury; once the injury is repaired, the inflammatory focus clears and homeostasis is restored. On occasion, however, the inflammatory response is triggered inappropriately or excessively or it fails to resolve after the trigger is removed. Excessive inflammation may result, for example, in response to a persistent host antigen being misinterpreted as foreign (e.g., in rheumatic fever or poststreptococcal glomerulonephritis) or from a decreased ability to clear immune system stimulants such as apoptotic cells or immune complexes (as in systemic lupus erythematosus [SLE]); in these cases, autoimmune responses drive undesirable and frequently destructive inflammation. In other, so-called autoinflammatory syndromes (e.g., familial Mediterranean fever), inflammatory cells themselves may have defects that lead to persistent or recurrent undesirable inflammation. In many cases we do not fully understand what causes pure inflammatory diseases. Nonetheless, our understanding of inflammatory processes has increased remarkably, which

has led to targeted therapies for inflammatory diseases, including agents that block the proinflammatory cytokines tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and IL-6, as well as agents targeted to other inflammatory mediators. The more that we learn about the processes of inflammation, the more likely that effective therapies will be developed for rheumatic and other inflammatory diseases.

Here we summarize the major cellular participants in inflammation and provide an overview of the mediators that drive inflammatory responses.

THE CELLS OF INFLAMMATION

Acute versus chronic inflammation

Inflammation can be either acute or chronic. The acute, or early, phase of inflammation is characterized by microvascular changes and neutrophilic infiltration, whereas monocytic cells predominate in the chronic inflammatory response. These distinctions are somewhat arbitrary, however, with many exceptions. For example, cells of the monocytic lineage may dominate from the beginning of an inflammatory response (as in tuberculosis), and neutrophils persist in some forms of chronic inflammation (as in polyarteritis nodosa). Resident tissue macrophages from the monocytic line may also provide the early sentinel signals that initiate acute inflammation, as is the case with gout and pseudogout.²

Endothelial cell activation

Many of the leukocytes that participate in inflammation circulate in the bloodstream. To localize to extravascular tissue, they must exit the vasculature (diapedesis) and migrate to the extravascular space (chemotaxis). These processes require a complex sequence of events, beginning with the (micro)vascular response. Arterioles vasodilate and endothelial cells contract, thereby exposing the basement membrane; blood flow slows and plasma extravasates. In turn, leukocytes concentrate and increase their contact with the endothelium.³

In response to bacteria or other affront, resident tissue immune cells (macrophages, dendritic cells, and fibroblasts) generate mediators such as IL-1 β and TNF- α . These cytokines (Greek for "cell movers") induce local vascular endothelial cells to express surface molecules that contact and bind leukocytes, which permits their egress from the vasculature.⁴ Diverse pairs of adhesion molecules sequentially mediate leukocyte rolling, tight adhesion, and diapedesis (Fig. 23.1). The first step, leukocyte rolling, occurs mainly via interactions of the adhesion molecules E-selectin on endothelial cells and L-selectin on leukocytes with mucin-like sialylated glycoproteins on leukocytes and endothelial cells, respectively.⁴ Selectins are expressed constitutively on both leukocytes and endothelium, and their interactions are strong but short-lived, with the result that a percentage of leukocytes are always transiently adherent, or marginated, to the endothelium and roll along with a tumbleweed-like progression. At sites of inflammation, after exposure to stimuli such as IL-1 β and TNF- α , expression of E-selectin on endothelial cells increases markedly, which leads to an increase in the percentage of leukocytes that marginate and roll. The next step, leukocyte tight adhesion, results from the interaction of leukocyte adhesion molecules known as integrins (e.g., CD11a/CD18 or LFA-1, CD11b/CD18 or CR3, $\alpha_5\beta_1$, or VLA-4) with endothelial cell counterligands (e.g., intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]). Tight adhesion requires the *de novo* expression of adhesion molecules on endothelium and activation of preexisting integrins on leukocytes, both in response to inflammatory mediators. Specific integrin-ligand pairing, in turn, establishes specific cell-cell adhesion events that contribute

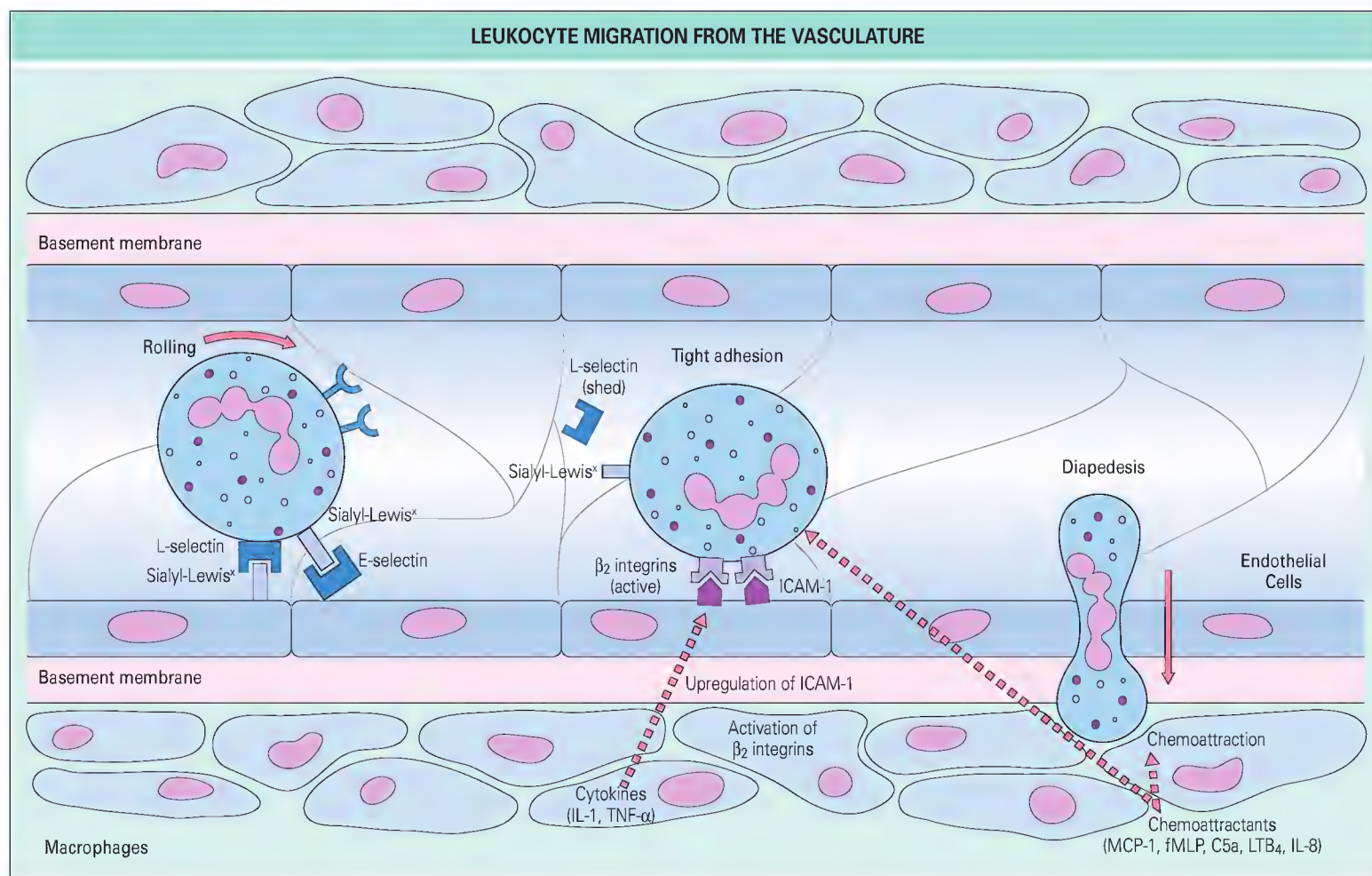


Fig. 23.1 Leukocytes exit the vasculature through a sequence of interactions with the vascular endothelium. The first step, rolling, guarantees leukocyte-endothelial contact through transient interactions between selectins and sialylated glycoproteins (sialyl-Lewis^x) on cognate cells. Leukocyte tight adhesion results from the interaction of leukocyte adhesion molecules known as integrins with counterligands on endothelial cells, such as intercellular adhesion molecule 1 (ICAM-1). In contrast to selectin/glycoprotein interactions, integrin/ICAM interactions are dependent on activation and expression. Once tightly adherent to the endothelium, leukocytes transmigrate through the vasculature and into tissues. Activation of leukocytes, as well as their transmigration through the endothelium and basement membrane, is mediated by chemoattractants such as monocyte chemoattractant protein 1 (MCP-1), C5a, *N*-formyl-methionyl-leucyl-phenylalanine (fMLP), leukotriene B₄ (LTB₄), and interleukin-8 (IL-8). TNF- α , tumor necrosis factor- α .

to the distribution and homing of leukocytes; common integrin-ligand pairs include CD11a/CD18 with ICAM-1 (lymphocytes-endothelium), CD11b/CD18 with ICAM-1 (neutrophils-endothelium), and VLA-4 with VCAM-1 (monocytes-endothelium). Importantly, many of these adhesion molecules are not inert binders of their cognate ligands; for example, CD11b/CD18 (also known as macrophage 1 antigen and complement receptor 3) is not only an adhesion molecule but also a receptor for the “inactive” form of the C3b complement component (C3bi), as well as a transmembrane signaling receptor in its own right. Finally, transmigration of leukocytes through the endothelium and basement membrane is driven by chemokines such as monocyte chemoattractant protein-1 (MCP-1), C5a, and IL-8.¹

Granulocytes

Neutrophils, eosinophils, and basophils constitute a group of leukocytes known as granulocytes, so named for the presence of highly visible granules—actually highly developed vacuolar structures—in their cytoplasm (Fig. 23.2). Mast cells are similarly equipped with specialized granules but are classified separately. The contents of the granules vary with cell type and can be distinguished under routine staining (hematoxylin-eosin) with light microscopy. Granulocytes, also called polymorphonuclear leukocytes because of their multilobed nuclei, form a part of the innate immune system and are crucial to the acute inflammatory response.

Neutrophils

Polymorphonuclear neutrophils are the body's first-line defense against most foreign invaders and are the major cell type in most acute and some chronic inflammatory diseases. The importance of neutrophils in bacterial defense is demonstrated by patients with hereditary defects in neutrophil

function, who are prone to repeated and often life-threatening infections. Neutrophils are the most prevalent leukocyte in the bloodstream and account for more than 50% of all circulating white blood cells; in acute inflammatory conditions (e.g., bacterial infection), the percentage of neutrophils in the bloodstream increases to 80% or greater. Unlike most other leukocytes, however, neutrophils are not normally present in significant numbers in the extravascular spaces. Neutrophils are also remarkable for their short half-life, approximately 7 hours inside the bloodstream and slightly longer in extravascular spaces.

Neutrophil granules contain an impressive arsenal of microbicidal weaponry that is unleashed on cell activation (Figs. 23.3 and 23.4). As identified by routine staining, neutrophil granules consist of two classes: primary (or azurophilic) granules develop first, followed by secondary (or specific) granules. *Azurophilic granules* are functionally similar to the lysosomes of other cells. Like other lysosomes, azurophilic granules contain a variety of proteases, in this case including elastase, matrix metalloproteinase-3 (MMP-3), MMP-8, MMP-9, cathepsins, and lysozyme (Table 23.1). In addition, azurophilic granules contain myeloperoxidase (MPO), a key enzyme for both microbicidal activity and mediation of tissue injury in inflammatory disease. In response to phagocytosis of a bacterium or other foreign body, azurophilic granules fuse with the phagosome to direct their contents at the ingested target. In addition, a membrane-bound reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is assembled and activated, which results in rapid oxygen consumption (the “respiratory burst”) and the generation of potent ROSs within the phagolysosome. Coordinated discharge of MPO from the azurophilic granule into the phagolysosome catalyzes the reaction of ROSs and chloride to form hypochlorous acid (HOCl, or chlorine bleach). HOCl and its derivatives are powerful oxidizing agents that can, among other things, disrupt bacterial electron transport

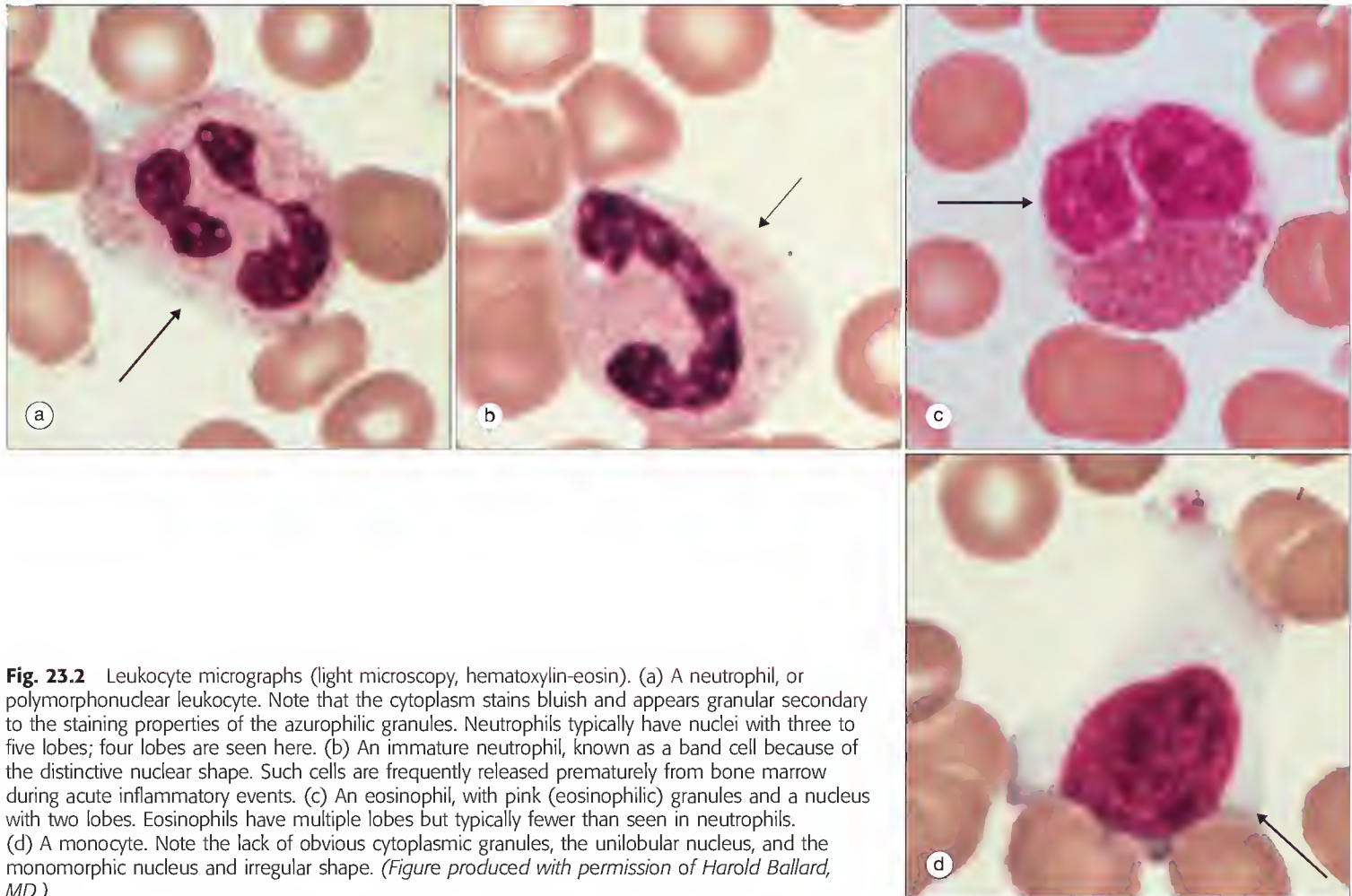


Fig. 23.2 Leukocyte micrographs (light microscopy, hematoxylin-eosin). (a) A neutrophil, or polymorphonuclear leukocyte. Note that the cytoplasm stains bluish and appears granular secondary to the staining properties of the azurophilic granules. Neutrophils typically have nuclei with three to five lobes; four lobes are seen here. (b) An immature neutrophil, known as a band cell because of the distinctive nuclear shape. Such cells are frequently released prematurely from bone marrow during acute inflammatory events. (c) An eosinophil, with pink (eosinophilic) granules and a nucleus with two lobes. Eosinophils have multiple lobes but typically fewer than seen in neutrophils. (d) A monocyte. Note the lack of obvious cytoplasmic granules, the unilobular nucleus, and the monomorphic nucleus and irregular shape. (Figure produced with permission of Harold Ballard, MD.)

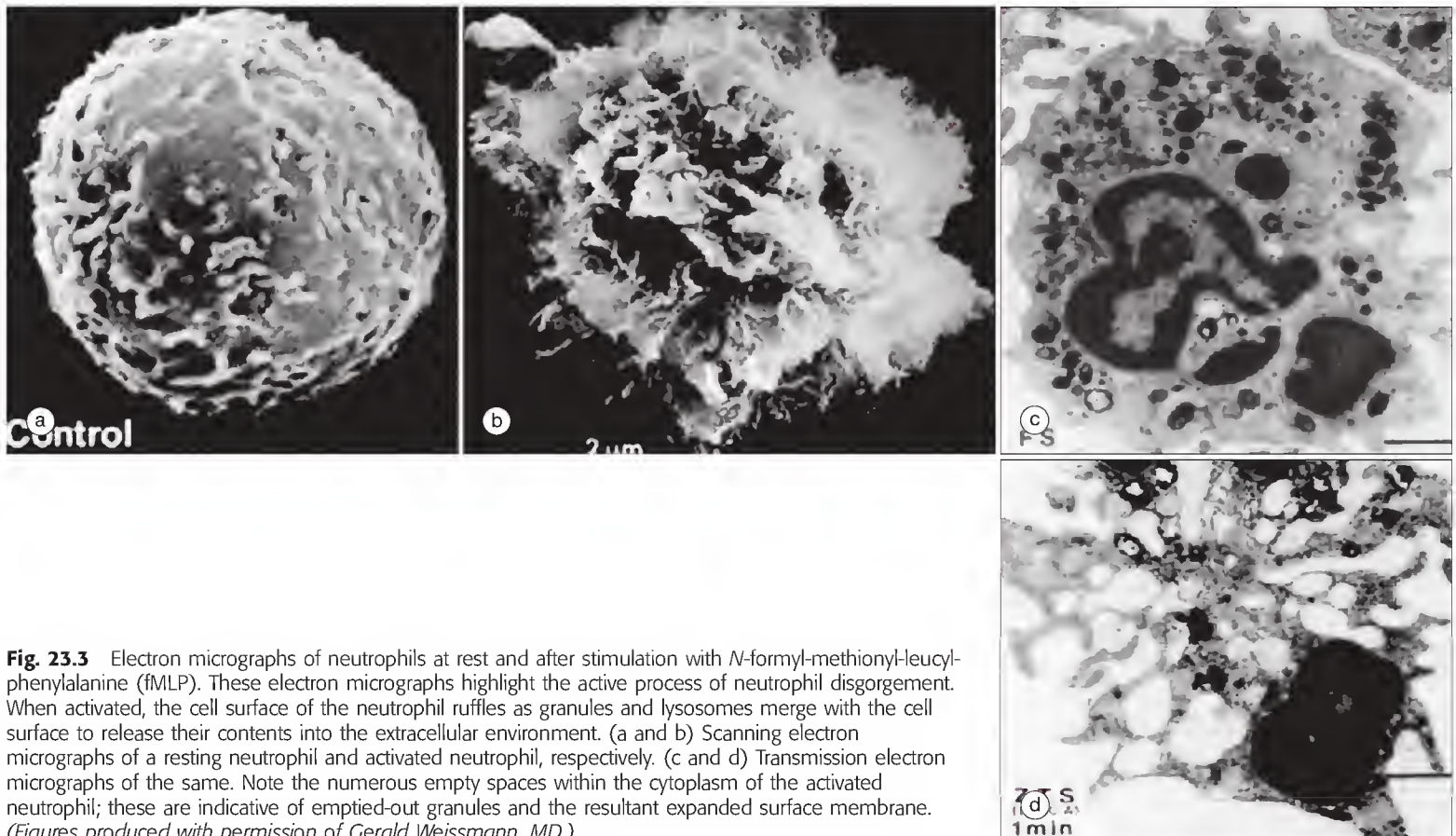


Fig. 23.3 Electron micrographs of neutrophils at rest and after stimulation with *N*-formyl-methionyl-leucyl-phenylalanine (fMLP). These electron micrographs highlight the active process of neutrophil disorgement. When activated, the cell surface of the neutrophil ruffles as granules and lysosomes merge with the cell surface to release their contents into the extracellular environment. (a and b) Scanning electron micrographs of a resting neutrophil and activated neutrophil, respectively. (c and d) Transmission electron micrographs of the same. Note the numerous empty spaces within the cytoplasm of the activated neutrophil; these are indicative of emptied-out granules and the resultant expanded surface membrane. (Figures produced with permission of Gerald Weissmann, MD.)

chains and disturb DNA synthesis. Azurophilic granules thus provide potent mechanisms through which microorganisms are destroyed; when released inappropriately into the extracellular environment, however, the contents of these granules can cause significant tissue damage.

Specific granules also contain lysozyme, but their contents generally differ greatly from those of azurophilic granules. Specific granule proteases include collagenase (MMP-1) and plasminogen activator; they also contain proteins with poorly defined function, such as lactoferrin and β_2 -microglobulin. In contrast to azurophilic granules, specific granules possess an extensive array of membrane-associated proteins, including cytochromes, signaling

molecules, and receptors; thus, specific granules constitute a reservoir of proteins destined for the topologically external surfaces of both phagocytic vacuoles and the plasma membrane.³

In addition to primary and secondary granules, studies have identified two other types of neutrophil granules. *Gelatinase granules*, similar to specific granules in size, are notable for their high concentrations of gelatinase, a latent enzyme with the capacity for tissue destruction. *Secretory vesicles* are smaller than the other granules and do not appear to contain proteolytic enzymes. In contrast to the other granules, which typically fuse with phagolysosomes, secretory granules fuse with the cell membrane and appear to serve as a reservoir for surface membrane lipids and surface membrane-associated proteins.

Because neutrophils have such destructive capacity, localization and activation of them must be carefully regulated. Chemoattractants for neutrophils include leukotriene B₄ (LTB₄), platelet-activating factor (PAF), IL-8, and the complement split product C5a. At low concentrations and when distributed in a gradient, these molecules lead neutrophils to migrate toward regions of higher concentration. At high concentrations, however (i.e., at the bacterial source of the gradient), these same molecules cause neutrophils to cease migration and become activated. Receptors for soluble ligands other than chemoattractants have also been identified on neutrophils, including receptors for growth factors, colony-stimulating factors, and cytokines (see Fig. 23.4); these ligands may modulate neutrophil function. For example, pretreatment of neutrophils with either insulin or granulocyte-macrophage colony-stimulating factor results in the amplification of subsequent neutrophil responses to chemoattractants.³

Once localized to their target tissue and activated, neutrophils are intrinsically inefficient at phagocytosing unmodified targets. Optimal neutrophil phagocytosis depends on opsonization (from the Latin “to prepare for eating”) and modification of a target via adornment of it with immunoglobulin, complement components, or both. Neutrophils express the complement receptors CR1 and CR3, which promote phagocytosis by binding the target-adherent complement components C3b and C3bi, respectively. In addition, neutrophils express two families of receptors for the Fc portion of bound or aggregated IgG: low-affinity Fc γ RIIa and high-affinity Fc γ RIIIb. During some infections or after *in vitro* stimulation with interferon or granulocyte colony-stimulating factor, neutrophils also express the high-affinity receptor Fc γ RI, which binds monomeric IgG (for an overview of leukocyte receptors see Table 23.2).

Recently, a completely novel neutrophil function has been identified. In some instances, neutrophils confronted with bacterial invasion may choose to die and in so doing release neutrophil extracellular nets (NETs), which are composed of decondensed chromatin associated with antimicrobial proteins. NETs have the capacity to trap and kill bacteria and serve both as a physical containment structure to prevent bacterial spread and as an antibacterial delivery system. NETs may also serve as a “catalytic” surface on

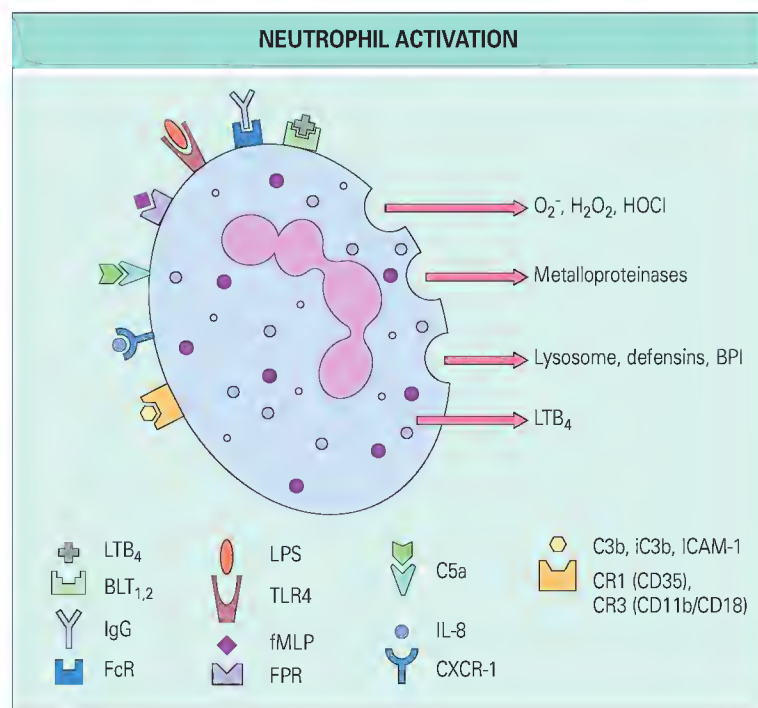


Fig. 23.4 Various signals stimulate neutrophil activation via ligation of cell-surface receptors. On activation, neutrophils both degranulate and produce a number of inflammatory mediators. See text for details. BLT, leukotriene B₄ receptor; BPI, bactericidal/permeability-increasing protein; fMLP, *N*-formyl-methionyl-leucyl-phenylalanine; FPR, formyl peptide receptor; ICAM-1, intercellular adhesion molecule 1; IL-8, interleukin-8; LPS, lipopolysaccharide; LTB₄, leukotriene B₄; TLR4, Toll-like receptor 4.

TABLE 23.1

Products of neutrophils, macrophages, and eosinophils

Cell	Granule contents	Cytokines produced	Other inflammatory mediators
Neutrophil	<i>Primary (azurophilic) granules:</i> Elastase, MMP-3, MMP-8, MMP-9, cathepsins, defensins, bactericidal/permeability-increasing protein, proteinase 3, lysozyme, myeloperoxidase <i>Secondary (specific) granules:</i> Collagenase, plasminogen activator, lysozyme, lactoferrin, β_2-microglobulin <i>Gelatinase granules:</i> Gelatinase	IL-1, L-6, IL-8, TNF- α , GM-CSF	ROS, PAF, PGE ₂ , LTB ₄
Macrophage	Lysozyme (aside from many others mentioned in text)	IL-1 β , TNF- α , IL-6, IL-8, IL-12, MCP-1, MCP-2, RANTES, PDGF, TGF- β , IFN- γ	Complement components, ROS, iNOS, PGE ₂ , TxA ₂ , PGI ₂ , LTB ₄ , LTC ₄ , PAF, MMP-1, tissue factor, plasmin inhibitor
Eosinophil	<i>Specific granules:</i> Charcot-Leyden crystal protein, major basic protein, eosinophil peroxidase, eosinophil cationic protein, eosinophil-derived neurotoxin, secretory PLA₂ <i>Small granules:</i> Arylsulfatase B	IL-4, IL-5, IL-8, IL-10, IL-12, GM-CSF, TNF- α , TGF- β , LTB ₄ , LTC ₄ , PAF, PGE ₂ , ROS, collagenase, PDGF, VEGF, MCP-1	

GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon- γ ; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; LTB₄, leukotriene B₄; MCP-1, monocyte chemoattractant protein-1; MMP-3, matrix metalloproteinase-3; PAF, platelet-activating factor; PDGF, platelet-derived growth factor; PGE₂, prostaglandin E₂; RANTES, regulated on activation, T cell expressed and excreted; ROS, reactive oxygen species; TNF- α , tumor necrosis factor- α ; TXA₂, thromboxane A₂; VEGF, vascular endothelial growth factor.

TABLE 23.2
Leukocyte receptors, ligands, and their functions

Receptor type	Examples	Examples of ligands	Functions
FcγR	FcγRI, FcγRIIa, FcγRIIIb	Immunoglobulins	Recognize and bind Fc portions of immunoglobulins
Toll-like receptors	TLR1 to TLR11	Pathogen-associated molecular patterns (PAMPs; e.g., LPS)	Recognize pathogens and activate immune responses
Formyl peptide receptors	Formyl peptide receptor 1	Bacterial <i>N</i> -formyl-methionyl peptides	Mediate chemotaxis and activation of neutrophils and monocyte-macrophages
Scavenger receptors	Scavenger receptor A	Numerous targets on bacteria, apoptotic cell structures	Stimulate phagocytosis of bacteria and apoptotic cells, adhesion
Mannose receptor	Mannose receptor C type 1	Mannose (on pathogens)	Mediates endocytosis of glycoproteins by phagocytes
Complement receptors	CR1, CR2, CR3, CR4 C5aR	Complement components C5a	Aid in opsonization and phagocytosis Activates inflammatory cells
Integrins	Mac-1 (CD11b/CD18) LFA-1 (CD11a/CD18)	ICAM-1	Bind to cell adhesion molecules and extracellular matrix, which results in strong adhesion
Chemokine receptors (CR, CCR, CXCR, CXXCR classes)	CCR: CCR1 CCR3, CCR5 CXCR: CXCR1, CXCR2	CC: MCP-1, RANTES, MIP-1α CXC: IL-8	Recognize chemoattractants, mobilize and activate leukocytes

ICAM-1, intercellular adhesion molecule-1; LFA-1, lymphocyte function–associated antigen-1; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; TLR1, Toll-like receptor 1.

which neutrophil elastase can inactivate tissue factor pathway inhibitor, which promotes clotting and possibly contributes to the role of neutrophils in acute coronary syndromes. How neutrophils “decide” whether to use their more classic defense systems or to die and produce NETs remains an area of intense study.⁵

Eosinophils, basophils, and mast cells

Other granulocytes important in inflammatory responses include eosinophils and basophils. Like neutrophils, these cells also contain a variety of lipid and peptide mediators (see Table 23.1). In contrast to neutrophils, however, these cells are less common in the bloodstream but are found in greater numbers in extravascular tissue. Eosinophils typically do not phagocytose their targets but are thought to discharge their contents after adhering to larger surfaces. Eosinophils are considered to be important in combating parasitic infection and are also involved in the inflammatory response generated by allergic or immediate hypersensitivity reactions; the latter role is shared by mast cells and basophils. Abnormal eosinophil activity has been implicated in several inflammatory diseases, including asthma, eosinophilic pneumonia, Churg-Strauss vasculitis, and idiopathic hypereosinophilic syndrome. Basophils also play a role in allergic reactions.

Mast cells are most commonly localized to perivascular locations within tissues. Their granular contents are similar to those of basophils, and like basophils, mast cells may play a role in allergic reactions. Recent data from animal models suggest that mast cells may also be important in the pathogenesis of rheumatoid arthritis (RA).

Macrophages

Macrophages play multiple roles in inflammation and immunity by serving both as antigen-presenting cells (APCs) that drive adaptive immune responses and as primary inflammatory cells in chronic diseases such as atherosclerosis and RA. Tissue macrophages are derived from circulating monocytes but differentiate and become activated on entering peripheral tissues. Although the process of monocyte adhesion to and diapedesis through blood vessels is similar in many respects to that of neutrophils, monocytes respond to a different set of chemotactic factors, including the chemokines RANTES, MCP-1, macrophage inflammatory protein-1α (MIP-1α), and MIP-1β and the growth factors transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) (see Table 23.1).⁶ Once in tissues, macrophages can live for up to several months.

As actors in the innate immune system, macrophages are stimulated to phagocytose nonencapsulated bacteria via recognition of evolutionarily conserved motifs on bacterial surfaces. To do so, macrophages express surface receptors for pathogen-associated molecular patterns, including Toll-like receptors, formyl peptide receptors, and scavenger receptors, many of which are also found on neutrophils (Table 23.2).⁷ After phagocytosis, macrophages destroy microbes through mechanisms similar to those used by neutrophils: lysosomal enzymes, reactive oxygen and nitrogen intermediates, toxic radicals, and chloramines. As with neutrophils, macrophage phagocytosis and killing of pathogens are greatly enhanced by opsonization

of the pathogens. Macrophages have surface receptors for multiple opsonins, including the mannose receptor (which directly recognizes glycoproteins on microbial surfaces), CR1, CR3, CR4, FcγRI, FcγRII, and FcγRIII (see Table 23.2).^{8,9} Although the function of the majority of macrophage products is primarily to augment inflammation and repel external threats, macrophages, like neutrophils, have the capacity to damage host tissue via release of their digestive and degradative contents.

Macrophages differ from neutrophils in their capacity to serve as “professional” APCs. After phagocytosis, APCs degrade foreign antigens in protease-containing endosomes; vesicles containing major histocompatibility complex (MHC) class II molecules then fuse with the endosomes, which allows membrane-bound MHC class II complexes to become loaded with antigenic peptide fragments. The MHC class II/peptide complexes are then delivered to the cell surface, where they present antigen to T cells to stimulate the highly specific responses of adaptive immunity. In this and other examples, the past decade of research has underlined the direct connection between inflammation and innate immunity and their influence on adaptive immune processes.

One of the earliest steps in most inflammatory responses is activation of resident tissue macrophages, whose subsequent production of cytokines alters vasomotor tone and endothelial adhesiveness (as described earlier). Through ligation of various surface receptors, macrophages may be activated by interferon-γ (IFN-γ), complement components, immune complexes, lipopolysaccharide (LPS), and cytokines such as IL-1β, TNF-α, and IL-6.⁷ Once activated, macrophages secrete a dazzling variety of proinflammatory products (see Table 23.1), including proteases (e.g., lysozyme, elastase, and collagenase), inflammatory cytokines (IL-1β, TNF-α, IL-6, IL-12, and others), chemokines (IL-8, MCP-1, MCP-2, RANTES, and others), and several complement cascade proteins (C1, C2, C3, and C4).⁶ Indeed, a vigorous acute-phase response driven by cytokine production and characterized by high serum levels of acute-phase reactants is typical of diseases with extensive macrophage involvement. Activated macrophages also produce multiple eicosanoids (e.g., prostaglandin E₂ [PGE₂], thromboxane A₂ (TXA₂), prostacyclin [PGI₂], LTB₄) that can contribute to the propagation of inflammation. In addition, activated macrophages produce procoagulant factors such as tissue factor and plasmin inhibitor, thereby linking the inflammatory and clotting responses. Indeed, local intravascular coagulation in response to infection is thought to play a role in limiting the spread of infection; when unchecked, coagulation in the presence of inflammation leads to disseminated intravascular coagulation, a potentially life-threatening condition.

Lymphocytes

For a discussion of lymphocytes, please refer to Chapter 15.

Platelets

Platelets are small, anucleated circulating cellular fragments that function to maintain hemostasis. In response to vascular injury, platelets adhere to

the subendothelial matrix of the vascular wall, become activated, and rapidly induce platelet aggregation and thrombus formation. The almost explosive nature of thrombotic events is largely due to platelet degranulation, wherein platelets disgorge preformed factors from α -granules and dense granules into the surrounding microvasculature. In addition to procoagulant factors such as von Willebrand factor, fibrinogen, and factor V, platelet granules also contain inflammatory mediators, including chemokines (e.g., RANTES, MCP-3, MIP-1 α , and platelet factor 4), growth factors (e.g., PDGF and TGF- β), histamine, and serotonin.¹⁰ Further underscoring the link between inflammation and coagulation, platelets are themselves activated on exposure to inflammatory mediators.

Activated platelets not only release preformed inflammatory mediators but also participate in inflammatory processes via plasma membrane activity. Signaling molecules upregulated on activated platelets include P-selectin, which adheres to and activates neutrophils, and CD40L, which induces inflammatory responses in many cell lines, including the endothelium.¹¹ On activation, platelets also rapidly produce eicosanoids, such as TXA₂ from membrane-derived AA, and other lipid membrane-derived inflammatory products, such as PAF. As discussed below, platelets may also participate in some antiinflammatory activities.

Other links between coagulation and inflammation

Inflammation promotes coagulation through additional means. Tissue factor, which stimulates thrombin formation, is produced by macrophages in inflammatory conditions such as sepsis and atherosclerosis.¹² Systemic inflammation also inhibits the function of the natural anticoagulant pathways of antithrombin and protein C. Additionally, systemic inflammation inhibits fibrinolysis via generation of plasminogen activator inhibitor type I (PAI-I). Inhibition of fibrinolysis is permissive for microvascular thrombosis; PAI-I inhibition prevents both endotoxin-induced microthrombosis and experimental coronary thrombosis. Conversely, studies by Salmon and Girardi have implicated complement activation (see later) as a key player in the evolution of antiphospholipid syndrome.¹³ In short, inflammation and coagulation are intimately related processes, and the role of coagulation needs to be considered when treating systemic inflammatory illnesses.

INFLAMMATORY MEDIATORS

A myriad of soluble mediators coordinate the inflammatory process. These mediators are derived from a number of sources, including the inflammatory cells described earlier, plasma proteins, and resident tissue cells such as nerves and endothelium. Some of the more important molecular components are described here.

The complement cascade

Complement was discovered by Bordet in 1899 and described as a heat-labile component of fresh plasma that “complemented” the ability of antibodies to lyse red blood cells and bacteria. More than 30 serum proteins and cell-surface receptors are now collectively recognized as the complement system. A primary function of complement is to coat and opsonize cell membranes and soluble antigens for recognition and digestion by phagocytic cells. Other components generated during complement activation independently generate an inflammatory response. These so-called anaphylatoxins (C3a, C5a) rapidly induce vasodilation, leukocyte activation, and chemotaxis. A third function of the system is to directly lyse unencapsulated, gram-negative bacteria.

Three distinct complement cascades—the classical, alternative, and mannose-binding lectin pathways—differ in their mechanisms of target recognition and initial activation but converge at the C5 convertase (Fig. 23.5). Many complement plasma proteins are zymogens (proteases that become active after proteolytic cleavage) and generally circulate in a dormant state. Once active, many complement components participate in cleavage or activation of subsequent components. Thus, each successive enzymatic step results in rapid and dramatic amplification. In response to this potential for explosive activation, complement regulatory molecules exist to dampen the cascades. Given the importance of complement activation to rheumatic disease, a more detailed understanding of the three complement cascades is important for both researchers and practicing rheumatologists.

Classical pathway

Although it was the first of the three complement pathways to be discovered, the classical pathway was the last to evolve and largely depends on a preceding humoral immune response for its activity. Activation of the classical

pathway occurs when the C1q component of the multimeric complement 1 complex (C1) binds to the Fc tails of multiple IgG or IgM antibodies complexed to antigen. When at least two of the six C1q globular heads have bound, the remaining components of the complex (two molecules each of C1r and C1s) undergo a conformational change that unleashes the autocatalytic enzyme activity in C1r. Active C1r cleaves C1s to its active form. C1s in turn cleaves soluble C4 and then C2 to C4a and C4b and C2a and C2b, respectively.¹⁴ (By convention, cleaved components are designated with the letter “a” for the smaller, soluble fragment and “b” for the bigger, enzymatically active fragment. Complement molecules in the classical pathway are numbered in the order in which they were discovered, which in almost all cases corresponds to their place in the complement sequence. Unfortunately for students, C4 acts before C2 but was discovered after C3.) C4b and C2b combine to form C4b2b (the C3 convertase of the classical pathway), which cleaves C3 to C3a and C3b. C3b combines with C4b2b to form C4b2b3b (C5 convertase), which in turn cleaves C5 to C5b and C5a. Subsequent assembly of the C5b, C6, C7, C8, C9 membrane attack complex (MAC) can form a pore in the cell membrane of some pathogens and most host cells and lead to their death. C3 performs double duty: although some portion of C3b joins with C4b2b to form the C5 convertase, the majority of C3b (as C3b or C3bi) serves as an opsonin; minutes after activation of the complement cascade, millions of C3b molecules are covalently attached to a single bacterium’s surface to facilitate its phagocytosis by macrophages and neutrophils.

Mannose-binding lectin pathway

The mannose-binding lectin (MBL) pathway evolved before the classical pathway and appears to have given rise to the latter. In contrast to the classical pathway, the MBL pathway does not require immunoglobulin but is activated by contact with bacterial surface mannose residues. Because these residues are inaccessible on vertebrate cells, the MBL pathway distinguishes “self” from “other” on the basis of a generic pattern rather than a specific antigen. When a C1q-like component of the MBL complex engages mannose on a pathogen, it activates the mannose-associated serine proteases MASP-1 and MASP-2 (analogous to C1r and C1s); thereafter, the MBL complex functions identical to activated C1: it cleaves C4 and C2 to form the classical C3 convertase.¹⁵

Alternative pathway

The alternative pathway is unique in that its activation is not initiated by binding; instead, the alternative pathway is always undergoing activation via the spontaneous hydrolysis of C3 in plasma. C3(H₂O) binds the alternative pathway component factor B, which is then converted by the associated factor D into Ba and Bb. The C3(H₂O)-Bb complex that results is an alternative C3 convertase and converts fluid-phase C3 into C3a and C3b, the latter of which is quickly inactivated by hydrolysis unless it is deposited on a cell surface. Once covalently bound to a cell surface (or indeed, any surface), however, C3b binds factor B; cleavage of factor B by factor D then results in formation of the membrane-associated C3bBb convertase, which is functionally equivalent to the classical C3 convertase (C4b2b).¹⁶ Because this primitive pathway fails to distinguish self from other, its specificity resides not in any intrinsic property of foreign particles but in the ability of host cells (but not bacteria) to defend themselves against indiscriminate complement activation (see the later section on complement regulation).

C3a and C5a anaphylatoxins

Release of the soluble fragments C3a and C5a, known as anaphylatoxins, accelerates the inflammatory response in multiple ways: anaphylatoxins engage mast cell and basophil receptors, which triggers the release of vasoactive mediators such as histamine and the cysteinyl leukotrienes LTC₄ and LTD₄. C5a and C3a also induce vasodilation and capillary permeability, upregulate adhesion molecule expression on leukocytes and endothelium, and cause smooth muscle contraction. C5a is a powerful chemoattractant and activator of neutrophils and can stimulate both neutrophil degranulation and the respiratory burst.

Complement regulation

When C3bBb binds to host cells, the host complement regulatory proteins CR1 and decay-accelerating factor (DAF) rapidly bind C3b and displace Bb. CR1 and DAF, in combination with the membrane cofactor of proteolysis, also catalyze the cleavage of C3b by plasma protease factor I to produce inactive C3b. In contrast to host cells, bacterial surfaces lack these regulatory proteins and instead permit binding of properdin, which stabilizes rather than degrades the alternative C3 convertase. Thus, bacteria are vulnerable to attack by the alternative pathway by virtue of their inability to defend themselves against complement deposition.

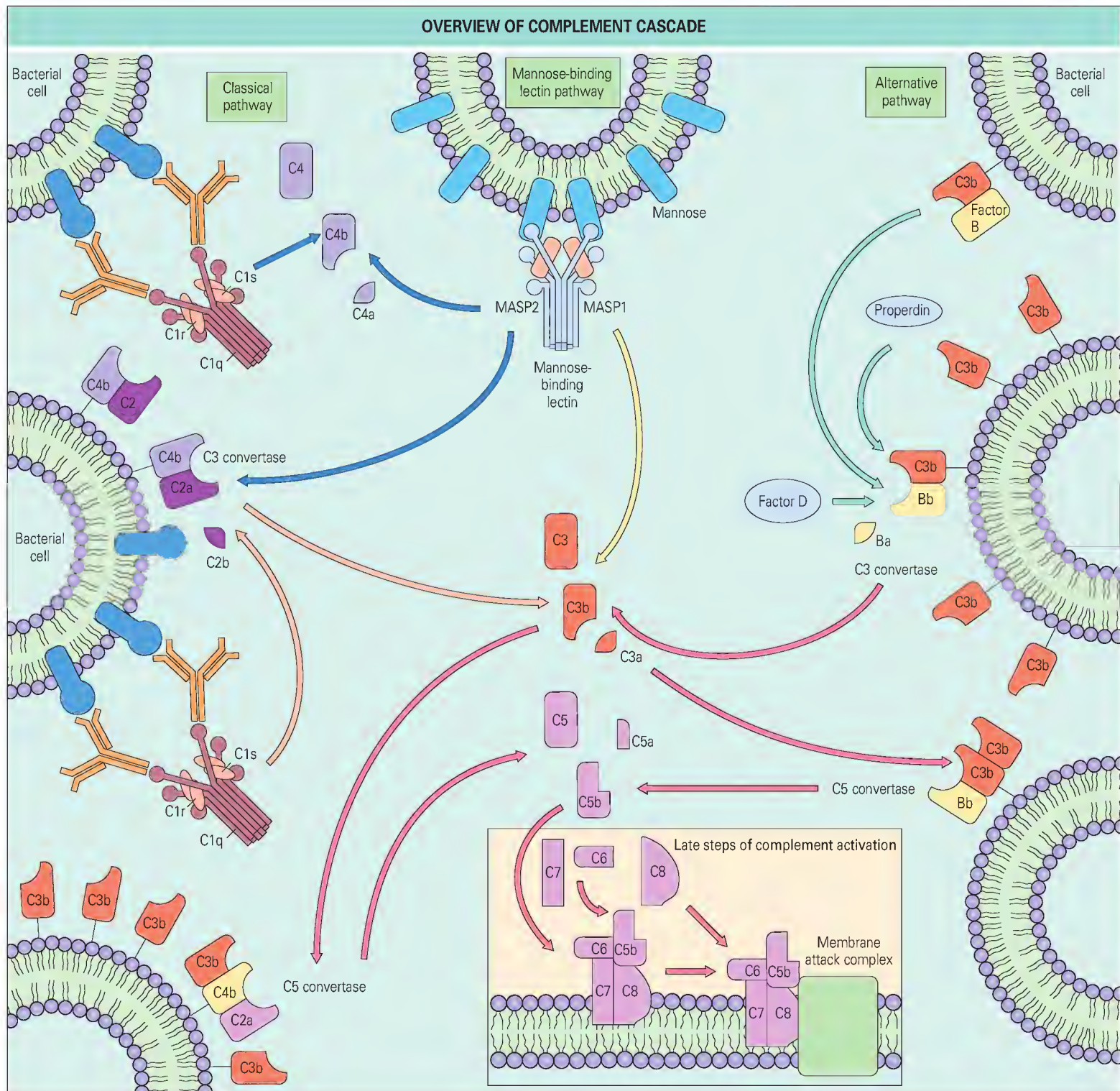


Fig. 23.5 Three distinct complement cascades—the classical, alternative, and lectin pathways—differ in their mechanisms of target recognition and initial activation but converge at the C3 convertase. Activation of the classical pathway occurs when the C1q component of C1 (which consists of C1q, two molecules of C1r, and two molecules of C1s) binds to multiple Fc portions of IgG or IgM antibodies complexed to antigen. Binding of C1q activates C1r, which in turn cleaves C1s to its active form. C1s then cleaves soluble C4 and C2 to C4a and C4b and C2a and C2b, respectively. C4b and C2b combine to form C4b2b (the C3 convertase of the classical pathway), which cleaves C3 to C3a and C3b. C3b combines with C4b2b to form C4b2b3b (C5 convertase), which then cleaves C5 to C5b and C5a. Subsequent assembly of the C5b, C6, C7, C8, C9 membrane attack complex occurs. The mannose-binding lectin pathway is a primitive version of the classical cascade. When the mannose-binding lectin (MBL) component of the MBL complex (analogous in form and function to the C1 complex) binds mannose on a pathogen, it activates the mannose-associated serine proteases MASP-1 and MASP-2 (akin to C1r and C1s); thereafter, the MBL complex functions as activated C1 does by cleaving C4 and C2 to form C3 convertase. The alternative pathway is initiated by the spontaneous hydrolysis of fluid-phase C3. C3 (H₂O) binds the alternative pathway component factor B, which is then converted by the associated factor D into Ba and Bb. The C3(H₂O)-Bb complex that results is an alternate C3 convertase and converts fluid-phase C3 into C3a and C3b, the latter of which is quickly inactivated by hydrolysis unless it is deposited onto a cell surface. If bound to a cell surface, however, C3b can bind factor B; factor D then cleaves factor B, thereby resulting in formation of the C3 convertase C3bBb, which is equivalent to the C3 convertase (C4b2b) of the classical and lectin pathways. (Adapted from Walport MJ. *Advances in immunology: complement (first of two parts)*. *N Engl J Med* 2001;344:1058–61.)

TABLE 23.3
Complement regulatory proteins

Protein	Complement regulatory function	Comments
C1 inhibitor (C1 INH)*	Membrane-bound serine protease inhibitor that inactivates the C1 complex by binding to C1r and C1s	Deficiency associated with hereditary and acquired angioedema, systemic lupus erythematosus
C4-binding protein (C4BP)	Plasma protein that displaces C2b and binds to C4b; cofactor for cleavage of C4b by factor 1	
CD35 (complement receptor 1)*	Membrane-bound glycoprotein that displaces Bb and binds C3b or displaces C2b and binds C4b; promotes C3b and C4b inactivation by factor 1	
CD55 (decay-accelerating factor [DAF])*	Membrane-bound protein that regulates the formation of C3 convertase by displacing Bb from C3b and C2b from C4b	Deficiency associated with paroxysmal nocturnal hemoglobinuria
CD59 (protectin)*	Prevents formation of the membrane attack complex on host cells	Deficiency causes paroxysmal nocturnal hemoglobinuria
CD46 (membrane cofactor protein, MCP)*	Membrane-bound protein that binds C3b and C4b and promotes their inactivation by factor 1	
Factor H	Plasma protein cofactor for factor 1; displaces Bb and binds C3b in plasma and on host cell surfaces	Deficiency leads to recurrent pyogenic infections, hemolytic-uremic syndrome
Factor I	Plasma protease that inactivates C3b and C4b; requires CR1, factor H, CD46, or C4BP as cofactor	Deficiency results in recurrent bacterial infections

*Present on host but not microbial cell surfaces.
MCP, manocyte chemoattractant protein.

Other proteins that have evolved to inhibit complement activation (Table 23.3) include fluid-phase proteins such as C1 inhibitor and the C3 and C5 convertase inhibitors, C4-binding protein and factor H, membrane-bound proteins such as the C3 and C5 convertase inhibitors, and CD59, a glycolipid that prevents insertion of the MAC into plasma membranes.¹⁷

Complement in disease

Complement deficiencies cause susceptibility not only to bacterial infection but also to autoimmune disease. Patients with specific complement deficiencies are especially prone to SLE; lupus develops in approximately 90% of C1q-null, 75% of C4-null, and up to 30% of C2-null individuals. Why complement deficiency predisposes to autoimmune disease is not entirely clear, but it may result from inefficient clearance of apoptotic cells and immune complexes.¹⁸ Deficiencies of later complement components may have other effects. For example, C5 deficiency results in susceptibility to *Neisseria* infections, thus testifying to the importance of the MAC in responding to these organisms.

Complement activation almost inevitably results in some degree of tissue destruction, as seen in rheumatic diseases such as SLE, RA, vasculitis, and antiphospholipid antibody syndrome. Interest in complement in inflammatory disease has led to the development of pharmacologic complement inhibitors such as eculizumab, a humanized monoclonal anti-C5 antibody approved for paroxysmal nocturnal hemoglobinuria.

Inflammatory conditions also result from hereditary or acquired deficiencies of complement regulatory proteins. For example, deficiency of the C1q inhibitor protein leads to undue complement activity under metabolic stress and the development of intermittent and potentially life-threatening angioedema.

Lipid mediators of inflammation

Given the ubiquity of membrane lipids, it is not surprising that nature has evolved strategies to exploit them for roles in addition to membrane structure. Among the most important roles of membrane lipids is their ability to serve as substrates for the generation of proinflammatory and antiinflammatory mediators.

Arachidonic acid derivatives

Many bioactive lipid mediators are produced through the oxidation of AA, including prostaglandins, leukotrienes, and the more recently recognized lipoxins (Fig. 23.6). AA is a polyunsaturated fatty acid covalently associated with cell membrane phospholipids; phospholipase A₂ catalyzes its release (phospholipase C₂ liberates diacylglycerol [DAG] from membrane triglycerides and can also produce AA via the action of lipase on DAG). In any given cell, the products formed from AA are determined by factors such as the cytokine milieu, specific expression of AA-modifying enzymes, and tissue type.

Cyclooxygenase products

Prostaglandins, so named because they were originally identified in sheep seminal fluid (i.e., from the prostate gland), result from the action of cyclooxygenases (COX-1 or COX-2) on AA. COX enzymes are heterobifunctional: they first incorporate oxygen into AA to form the five-carbon ring common to all prostaglandins and produce the intermediate PGG₂. A second COX reaction reduces PGG₂ to PGH₂ (hence the alternative designation of COXs as PGH synthases). PGH₂ is further converted into stable prostanoids by a variety of specific terminal synthases, which are expressed with some tissue specificity; differentiated cells tend to produce only one prostaglandin type in abundance.

COX-1 and COX-2, encoded on separate chromosomes, are structurally similar and perform the same enzymatic functions, but they are differentially expressed. COX-1 is generally expressed constitutively and is abundant in many tissues and cell types, including the renal collecting tubules, gastric epithelial cells, endothelial cells, macrophages, and platelets. COX-1 products typically participate in homeostasis of the organism and basic physiologic processes (e.g., protection of the gastric mucosa). In contrast, COX-2 is inducible and expressed primarily in inflammatory cells (macrophages, fibroblasts, endothelial cells) in response to stimuli such as IL-1 β , TNF- α , PDGF, and epidermal growth factor.¹⁹ COX-2 products generally contribute to the inflammatory processes that initially drive COX-2 expression. Moreover, COX-2 expression is elevated in many pathologic conditions, including inflammatory arthritis and some neoplasms. On this basis, selective COX-2 inhibitors were developed that were shown to have less gastrointestinal toxicity than nonselective COX inhibitors. However, COX-2 inhibition also appears to convey an increased risk for myocardial infarction, possibly by disturbing the balance between COX-1 and COX-2 products in the vasculature.

The bioactive prostanoids generated from PGH₂ include PGD₂, PGE₂, PGF₂, PGI₂ (prostacyclin), and TXA₂, each of which is produced by the action of one or more specific isomerases (terminal synthases). In contrast, PGJ₂ is derived nonenzymatically via dehydration of PGD₂. Prostaglandins are short-lived and generally act in an autocrine or paracrine manner. The effects of prostaglandins are generally mediated through specific G protein-coupled, seven-transmembrane-domain receptors, which have been classified into five types according to their responsiveness to selective agonists and antagonists. DP, EP, FP, IP, and TP receptors are preferentially engaged by PGD₂, PGE₂, PGF₂, PGI₂, and TXA₂, respectively.

Prostaglandin E₂

PGE₂ is the most common prostanoid and the one most critical for inflammation. PGE₂ induces fever, smooth muscle contraction, and T-cell migration and, along with PGI₂, induces the vasodilation and vascular hyperpermeability of early inflammation.²⁰ Elevated PGE₂ levels have been reported in the serum and synovial fluid of patients with RA and osteoarthritis (OA) and probably contribute to joint damage by promoting osteoclastic bone resorption and inhibiting proteoglycan synthesis. Not all of the effects of PGE₂ are proinflammatory, however; PGE₂ inhibits T-lymphocyte activation and proliferation, downregulates antibody production, and has variable effects on the secretion of MMPs.

PGE₂ is generated from PGH₂ by three different isoforms of PGE synthase (PGES)—cytoplasmic PGES (cPGES), microsomal PGES-1 (mPGES-1), and mPGS-2. Like COX-1, with which it is functionally coupled, cPGES is constitutively and ubiquitously expressed, whereas mPGES-1 is upregulated by proinflammatory stimuli and is functionally coupled with COX-2. mPGES-2 has a less clearly defined role and is linked to both COX isoforms.²¹ In

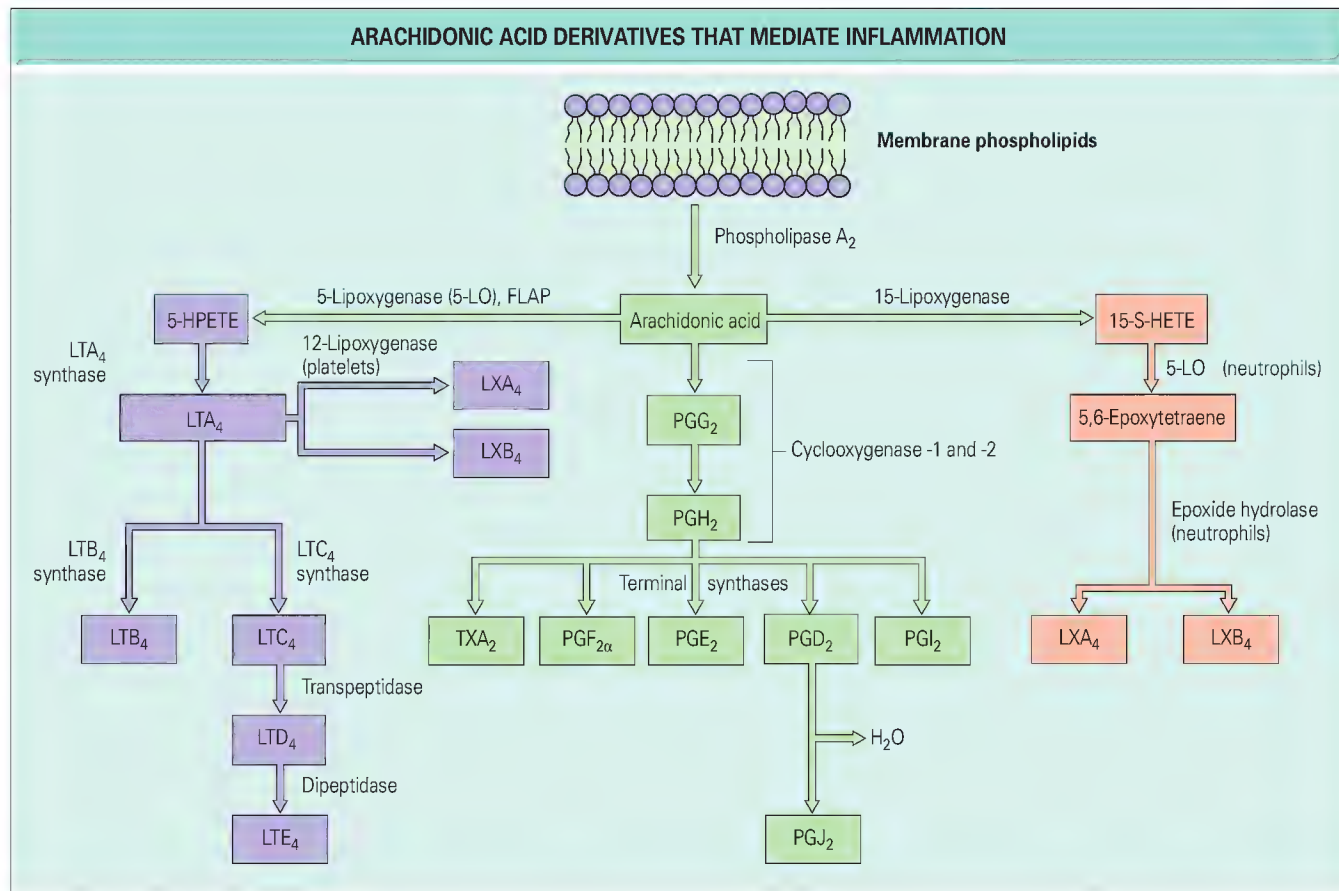


Fig. 23.6 Arachidonic acid (AA) is liberated from cell membrane phospholipids via phospholipase A_2 activity. Three distinct classes of products—prostanoids, leukotrienes, and lipoxins—may subsequently be generated by the action of distinct enzyme systems. *Prostanoid formation:* cyclooxygenase-1 (COX-1) and COX-2 convert AA sequentially into PGG_2 and PGH_2 . Specific terminal synthases generate all other prostanoid products from PGH_2 , with the exception of PGJ_2 , which is formed from PGD_2 through a dehydration reaction. *Leukotriene formation:* 5-lipoxygenase (5-LO) in concert with 5-lipoxygenase-activating protein (FLAP) act on AA to generate 5-hydroxyeicosapentaenoic acid (5-HPETE) and, subsequently, leukotriene A_4 (LTA_4). LTB_4 is formed from LTA_4 via LTA_4 hydrolase. In contrast, LTC_4 synthase converts LTA_4 into LTC_4 . Subsequently, transpeptidase and dipeptidase convert LTC_4 into LTD_4 and LTD_4 into LTE_4 , respectively. *Lipoxin formation:* Lipoxins are formed through cell-cell interactions during inflammation; two of the several pathways leading to lipoxin formation are shown here. Cells such as airway epithelium produce and release AA-derived 15-S-HETE. 15-S-HETE then diffuses into leukocytes, where it is first converted into 5,6-epoxytetraene by 5-LO and then into LXA_4 or LXB_4 by the action of epoxide hydrolase. Alternatively, when adherent platelets interact with activated leukocytes in the vascular lumen, the LTA_4 released from leukocytes diffuses into platelets, where it is converted to LXA_4 and LXB_4 by 12-LO. In contrast to prostanoids and leukotrienes, lipoxins appear to have largely antiinflammatory effects. Not shown are the aspirin-triggered lipoxins, which form when acted on by aspirin-acetylated COX-2.

experimental systems, COX-2 and mPGES-1 increase in tandem and co-localize to the same subcellular fraction. In human rheumatoid synovial fibroblasts, mPGES-1 expression is induced by IL-1 β and TNF- α and inhibited by dexamethasone.^{22,23} mPGES-1-null mice are resistant to both adjuvant- and collagen-induced arthritis.²⁴ mPGES-1 is therefore an attractive potential therapeutic target.

Other prostaglandins

PGI_2 (prostacyclin) induces vasodilation and inhibits platelet aggregation, qualities that have been exploited in the treatment of pulmonary hypertension. PGD_2 can also produce vasodilation and probably plays a role in allergic inflammation and asthma; on antigenic stimulation, it is released in large amounts by mast cells. In the central nervous system (CNS), PGD_2 regulates sleep. PGF_2 , a powerful uterine constrictor, is not known to participate in inflammatory events.

In contrast, PGJ_2 exerts a number of antiinflammatory effects. Unlike conventional prostaglandins, which signal via cell-surface receptors, PGJ_2 is transported into cells, where it acts on the intranuclear peroxisome proliferator-activating receptor- γ (PPAR- γ). Activated PPAR- γ inhibits the activation of nuclear factor κB (NF- κB), an important transcription factor for proinflammatory genes. In some cell types, PGJ_2 may also directly inhibit NF- κB . *In vitro*, addition of PGJ_2 to human macrophages inhibits the production of IL-1 β , TNF- α , IL-6, IL-12, and inducible nitric oxide synthase (iNOS). In an animal model of arthritis, intraperitoneal administration of PGJ_2 suppressed pannus formation and inflammatory infiltration.²⁵

Thromboxane A_2

TXA_2 is formed from PGH_2 via the enzyme thromboxane synthase. In contrast to prostaglandins, it contains a six-member carbon ring. TXA_2 is a

platelet activator and a potent vasoconstrictor. Platelet TXA_2 production is dependent on COX-1 and unaffected by COX-2 inhibitors, thus suggesting that the prothrombotic effects of selective COX-2 inhibitors may be a consequence of TXA_2 production unopposed by PGI_2 . Although TXA_2 is conventionally thought of as being derived from platelets, thromboxane synthase can be upregulated in other cell types in response to cytokines, and thromboxane production has been implicated in the pathogenesis of murine lupus nephritis.²⁶

Leukotrienes

Leukotrienes are important AA-derived inflammatory mediators as well (see Fig. 23.6 for how they are generated).

LTB_4 is the most important leukotriene in acute inflammatory responses; it activates leukocytes and prolongs their survival. Additionally, LTB_4 is a powerful chemoattractant for neutrophils and macrophages and stimulates leukocyte adhesion to vascular endothelium by upregulating integrin expression.²⁷ LTB_4 is present in high levels in the synovial fluid and sera of RA patients, and LTB_4 antagonism inhibits inflammatory arthritis in several animal models. In a phase 2 clinical trial, however, an LTB_4 receptor antagonist was not efficacious for RA.²⁸

LTC_4 , LTD_4 , and LTE_4 , known as the Cys leukotrienes, are produced principally by eosinophils, basophils, macrophages, and mast cells and have significant biologic effects. They induce vasodilation and increased microvascular permeability; increase bronchoconstriction, wheezing, and mucus secretion; and decrease mucociliary clearance.

Antiinflammatory lipids

Resolution of inflammation depends on an organism's ability to produce antiinflammatory mediators. Among these are AA-derived lipids known as

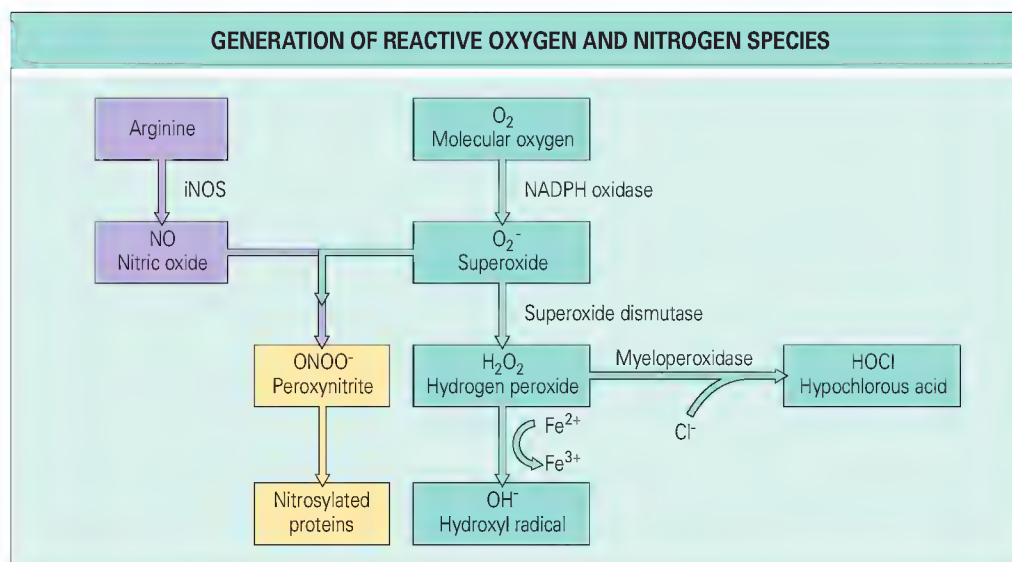


Fig. 23.7 As shown on the right side of the figure, molecular oxygen is converted to superoxide (O_2^-) by the action of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Superoxide dismutase subsequently converts superoxide to hydrogen peroxide (H_2O_2). In the presence of molecular iron, H_2O_2 is spontaneously converted to the hydroxyl radical ($OH^\cdot$), an extremely unstable and reactive oxygen product. Alternatively, reaction of H_2O_2 with molecular chloride is catalyzed by myeloperoxidase in the phagolysosomes of macrophages and neutrophils; the product, hypochlorous acid (HOCl), is an extremely potent antibacterial agent. As shown on the left side of the figure, inducible nitric oxide synthase (iNOS) liberates nitric oxide from the side chain of arginine. Interaction of nitric oxide and superoxide results in the formation of highly reactive peroxynitrites, which can modify and potentially alter the function of a wide range of proteins.

lipoxins (LXs). LXs are formed during the cell-cell interactions that occur during inflammation (see Fig. 23.6).²⁹ The requirement for the presence of two different inflammatory cells for LX formation may be a mechanism for delaying LX production until inflammation has already taken hold, consistent with a role for LX in the resolution phase of inflammation. LXs and their analogues exert multiple antiinflammatory effects, including inhibition of cytokine expression (e.g., IL-1 β , TNF- α , and IL-8), neutrophil chemotaxis/interaction with endothelial and epithelial cells, activation of monocytes, and proliferation of inflammatory cells. LXs also promote macrophage clearance of apoptotic leukocytes.²⁹ *In vivo*, LXs inhibit inflammatory disease in several animal models, including experimental colitis, asthma, and peritonitis³⁰; their role in human inflammation is less well established.

Resolvins and docosatrienes are non-AA-derived lipid molecules that are potent endogenous antiinflammatory mediators. These lipid products are generated from the essential ω -3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); like LXs, they are produced during the later phases of inflammation and hasten its resolution.³¹ Resolvin E1 significantly inhibits leukocyte infiltration in murine models of inflammation and protects against the development of sulfonic acid-induced colitis.^{32,33} A recent systematic review demonstrated a consistent (albeit modest) benefit of EPA and DHA supplementation in RA.³⁴

Vasoactive amines

Low-molecular-weight amines that are important inflammatory mediators include histamine and serotonin. Histamine is the decarboxylation product of the amino acid histidine. It is released from mast cells and basophils during cell stimulation, most particularly after surface IgE binding and cross-linking of Fc ϵ receptors. Histamine interacts with its receptors to promote immediate hypersensitivity reactions, including vasodilation and enhanced permeability of postcapillary venules.

In addition to its role as a neurotransmitter, serotonin is stored in the dense body granules of platelets. Serotonin is a vasoconstrictor and also enhances microvascular permeability. In addition, serotonin promotes fibrosis by enhancing collagen synthesis by fibroblasts and may therefore play a role in periaortitis-associated retroperitoneal fibrosis.

Reactive oxygen species and nitric oxide

ROSs and nitric oxide (NO) are small molecules containing unpaired electrons that are highly reactive with cellular components. Inappropriate activation of macrophages and neutrophils during acute and chronic inflammation can lead to the release of ROSs into the extracellular milieu and result in damage to extracellular and cellular components. The major ROSs formed by cells are, in descending order of stability, superoxide,

hydrogen peroxide, and the hydroxyl radical (Fig. 23.7). The hydroxyl radical has a half-life of less than 10^{-6} second and is probably responsible for much of the havoc wreaked by oxidative intermediates.³⁵

Phagocytes generate ROSs in large amounts in the form of superoxide via phagocyte oxidases (PHOXs), which include an NADPH oxidase complex. (NADPH oxidases are also found in other cells, where they are termed NOXs [nonphagocytic oxidases].)³⁶ In contrast to the ROSs generated by phagocytes for inflammation and host defense, ROSs produced by NOX tend to influence homeostatic cellular events, including cell proliferation and apoptosis.³⁶ The proinflammatory transcription factors activator protein 1 and NF- κ B were among the first intracellular complexes discovered to be substrates for ROS signaling.³⁷ These spur the production of dozens of proinflammatory mediators, including collagenase, IL-1 β , and TNF- α , as well as lead to increased adhesion molecule expression on endothelium and leukocytes.

Nitric oxide

NO is synthesized via oxidation of arginine by one of three distinct NOS isoforms (see Fig. 23.7). The neuronal (nNOS) and endothelial (eNOS) isoforms are constitutively expressed, with activity regulated by intracellular calcium levels and the calcium-binding protein calmodulin. In contrast, the inducible (iNOS) isoform is induced by stimuli such as LPS, IL-1 β , TNF- α , and IFN- α ; its activation leads to sustained generation of NO.³⁸ NO production plays vital roles in regulating physiologic processes, host defense, inflammation, and immunity. Its proinflammatory effects include vasodilation, edema, cytotoxicity, and mediation of cytokine-dependent processes that lead to tissue destruction. NO-dependent tissue injury has been implicated in a variety of rheumatic diseases, including SLE, RA, and OA. Conversely, the production of NO by eNOS may serve a protective, or antiinflammatory, function by preventing adhesion and the release of oxidants by activated neutrophils in the microvasculature.³⁹

NO, a gaseous free radical, is labile (half-life <5 seconds) and in the presence of oxygen is rapidly metabolized to nitrate and nitrite.⁴⁰ Given the short half-life of NO itself, its biologic activity in tissues is usually determined by its alteration of target molecules. One important reaction of NO is with free thiols to form S-nitrosothiol compounds. S-nitrosothiol derivatives, formed both extracellularly and intracellularly, are significantly more stable (half-life >2 hours) and retain NO-like vasodilating properties with less cytotoxicity.⁴¹ The reaction of NO with superoxide anion yields peroxynitrite, a highly toxic free radical that nitrosylates proteins and thereby leads to the accumulation of injurious intracellular oxidants and DNA damage (see Fig. 23.7).

NO and its derivatives play complex roles in immunoregulation. Low NO levels promote lymphocyte activation and proliferation, whereas high concentrations suppress APC activity and T-cell proliferation.^{42,43} There is

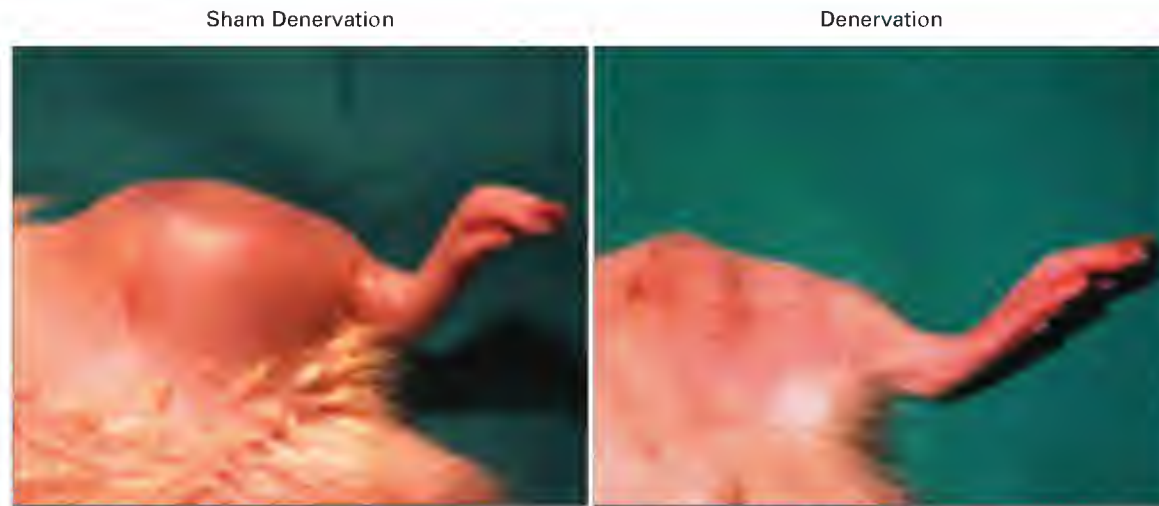


Fig. 23.8 Joint denervation prevents arthritis. Sensory denervation of the rat knee joint prevents the development of arthritis. (a) Normal rat knee 24 hours after the injection of carrageenan. Note the intense inflammation. (b) Denervated rat knee 24 hours after the injection of carrageenan. (Reproduced with permission from the BMJ Publishing Group.)

evidence that NO exerts different effects on discrete subpopulations of T cells: inhibition of secretion of IL-2 by murine type 1 helper T (Th1) cells and an increase in the secretion of IL-4 by Th2 cells. At high concentrations, NO promotes apoptosis in macrophages, CD4+CD8+ thymocytes, and chondrocytes.^{44,45} At lower concentrations (<1 mM), NO inhibits the apoptosis of hepatocytes, B lymphocytes, and eosinophils via the inhibition of caspases.⁴⁶

Although excessive NO production is generally associated with tissue injury, it is important to note that NO constitutively produced by endothelium is thought to play a protective role in the microvasculature. This protection is afforded by the capacity of NO to inhibit platelet and neutrophil adhesion to endothelial monolayers, as well as to inhibit superoxide anion production by leukocytes.⁴⁷

Nitric oxide in rheumatic diseases

NO has been implicated in the pathogenesis of lupus in murine models.⁴⁸ Splenic and renal tissues from MRL/lpr mice demonstrate increased iNOS mRNA expression and increased amounts of material immunoreactive for iNOS. Administration of NG-monomethyl-L-arginine (L-NMMA), an NOS inhibitor, prevents the development of glomerulonephritis and reduces inflammatory arthritis in this model.⁴⁸ In human SLE, serum nitrite is elevated during active disease, and levels correlate with disease activity and autoantibody titers.^{49,50}

The importance of NO in experimental arthritis models is also well documented. Adjuvant-induced arthritis is suppressed by the NOS inhibitor L-NMMA.⁵¹ Elevations of NO and amelioration of disease by nonselective NOS inhibitors have also been demonstrated in collagen-induced arthritis and streptococcal cell wall arthritis.⁵¹⁻⁵³ Inhibition of NO production also attenuates OA in animal models.^{54,55} In human arthritis, increased nitrite levels have been demonstrated within the joint fluid of patients with OA and RA.^{56,57} iNOS expression has been demonstrated in both RA and OA synoviocytes and chondrocytes.⁵⁸ St. Clair and colleagues⁵⁹ reported increased expression of iNOS in blood mononuclear cells in RA patients. In these studies the degree of nitrite production by peripheral mononuclear cells *ex vivo* correlated with disease activity, and this group demonstrated that the increased expression of iNOS and iNOS enzyme activity by peripheral blood mononuclear cells was reduced with anti-TNF therapy. Changes in NOS activity after treatment correlated significantly with changes in the number of tender joints.

THE NERVOUS SYSTEM IN INFLAMMATION

The immune and nervous systems are in constant communication, and the inflammatory response involves a complex bidirectional interaction between the two such that the nervous and immune systems together constitute a unified defense mechanism against internal and external threats. The nervous system registers inflammation in the periphery via sensory nerves and directs the immune system through a variety of messengers ranging from autonomic neurotransmitters (e.g., acetylcholine) to peripherally synthesized neuropeptides such as substance P (SP), which can be either

proinflammatory or antiinflammatory. The CNS also controls inflammatory responses through the release of neuroendocrine hormones such as melanocyte-stimulating hormone (MSH) and corticotropin-releasing factor (CRF), which dampen inflammation. Conversely, the immune system regulates the CNS through the release of cytokines, growth factors, and other mediators; release of cytokines in the periphery, for instance, can induce the hypothalamic-pituitary-adrenal axis to release glucocorticoids.

Both clinical and experimental evidence support the finding that the peripheral nervous system modulates inflammatory arthritis. As early as 1965 it was observed that peripheral nerve transection attenuates distal inflammation in rats with adjuvant-induced arthritis.⁶⁰ Carrageenan-induced joint inflammation is also inhibited by joint denervation (Fig. 23.8). Clinically, hemiparetic patients in whom RA later develops are largely spared from disease on the paralyzed side. That RA is characteristically symmetric (indicating cross-spinal reflexes) and predominantly distal (where dense sensory innervation occurs) also suggests possible CNS involvement.

Joint innervation

Joints are heavily innervated with sensory nerve branches terminating in the joint capsule, synovium, entheses, subchondral bone, and periosteum. Normal synovial tissue is richly innervated with both sensory and sympathetic nerves. Type C sensory nerve fibers containing neuropeptides such as SP or calcitonin gene-related peptide (CGRP) are present in the synovial lining and sublining tissue and in the vascularized peripheral parts of the joint menisci. Mast cells and afferent nerve terminals are frequently observed in all parts of the normal synovium.

Autonomic influences on inflammation

The autonomic nervous system is hard-wired into the immune system; parasympathetic branches from the vagal nerve and sympathetic nerve fibers synapse on the major organs of immunity, including the spleen, lymph nodes, thymus, bone marrow, and the gut's mucosa-associated lymphoid tissue. Thus, there exists a dense established network that provides direct lines of communication between the immune and autonomic nervous systems, which permits rapid and robust responses when stimulated.

The parasympathetic nervous system: an antiinflammatory pathway

Leukocyte-derived inflammatory mediators activate parasympathetic sensory nerve fibers that ascend in the vagus nerve. Afferent parasympathetic signals trigger efferent parasympathetic responses in the nucleus tractus solitarius that result in the release of acetylcholine, which has potent local antiinflammatory effects on both macrophages and endothelium.⁶¹

In vitro, acetylcholine inhibits production of TNF- α , IL-1 β , and IL-18 by macrophages while permitting synthesis of the largely antiinflammatory cytokine IL-10. Acetylcholine also inhibits the release of a recently recognized inflammatory mediator, high-mobility group box-1 (HMGB-1), by macrophages exposed to TNF- α .⁶² The antiinflammatory effects of acetylcholine appear to be due to engagement of $\alpha 7$ nicotinic receptors

TABLE 23.4
Inflammatory effects of selected neuropeptides

Neuropeptide	Where produced (outside the CNS)	Effects on inflammation	Evidence for involvement in arthritis
Substance P (SP; neurokinin)	C-type nerve fibers Lymphocytes Macrophages Eosinophils	Arteriole vasodilation Increased microvascular permeability Chemoattraction and activation of macrophages, polymorphonuclear neutrophils, lymphocytes, and eosinophils Mast cell degranulation	Elevated SP in synovial fluid of RA joints RA synovial fibroblasts (RASFs) overexpress SP receptor (NK-1R) Stimulates RASFs to proliferate and secrete inflammatory products
Calcitonin gene-related peptide (CGRP)	C-type nerve fibers	Potent arteriole and venous vasodilator	CGRP overexpressed in entheses of animals with adjuvant-induced arthritis Elevated CGRP levels in synovial tissue from OA joints
Neuropeptide Y (NPY)	Sympathetic nerve fibers	May favor Th2 response: inhibits IFN- γ and stimulates IL-4 production in lymphocytes	RA synovium has paucity of NPY-containing nerve fibers
Vasoactive intestinal peptide	Peripheral nerves Mast cells Lymphocytes Polymorphonuclear neutrophils Macrophages	Antiinflammatory peptide Inhibits chemotaxis and activation of macrophages and T cells Stimulates production of IL-4, IL-10, and IL-1ra	Therapeutic in collagen-induced arthritis

CNS, central nervous system; IFN- γ , interferon- γ ; IL-1ra, interleukin-1 receptor antagonist; OA, osteoarthritis; RA, rheumatoid arthritis; Th2, type 2 helper T cell.

on macrophages, which results in decreased synthesis of TNF- α .⁶³ This intimate connection between the nervous and immune systems can thus profoundly modulate the inflammatory response. The selective cholinergic agonist nicotine improves survival in experimental sepsis and has been associated with improvement of ulcerative colitis.^{40,62} Stimulation of the vagal nerve suppresses carrageenan-induced arthritis and endotoxemic shock. These findings may lead to newer and safer cholinergic agonists that may be used to treat inflammatory disease.

Sympathetic nervous system

Sympathetic nerve fibers release norepinephrine, which acts on target cells, including most immune cell types, by engaging α_1 -, α_2 -, and β -adrenoreceptors. The effects of the sympathetic nervous system on immunity and inflammation are mixed and vary with the cell and clinical context. For instance, the effects of norepinephrine on macrophages depend on which receptors are being expressed and engaged. Ligation of macrophage β -adrenoreceptors inhibits TNF- α secretion, whereas α_2 -receptor engagement induces the release of TNF- α and binding of the α_1 -receptor stimulates complement production.⁶⁴ In addition to inhibiting macrophage function, activated β -adrenergic receptors also inhibit neutrophil and NK cell function. β -Adrenoreceptor ligation can also cause a Th2 shift, largely by increasing IL-10 production.⁶⁴ Furthermore, norepinephrine is often released in sync with release of corticotropin, and glucocorticoids are potentiated in the presence of norepinephrine. On the other hand, stimulation of β -adrenoreceptors also drives IL-8 secretion by monocytes, and localized, neurogenic inflammation is promoted by the activation of β -adrenoreceptors.⁶⁴ In contrast to the mixed effect of β -adrenoreceptors on macrophages, the function of α -adrenergic receptors on immune cells is largely proinflammatory.

Consistent with these somewhat confusing *in vitro* observations, animal studies have shown that disrupting sympathetic nervous system signaling can either worsen or improve inflammatory disease, depending on context. Sympathectomy ameliorates early, but exacerbates late inflammation in collagen-induced arthritis. In contrast, β -adrenergic agonists improve late-stage experimental arthritis. The distinct proinflammatory and antiinflammatory effects of norepinephrine may in part relate to dose because much higher concentrations of norepinephrine are required to activate the β -adrenergic receptor; a low density of sympathetic fibers may therefore dictate a primarily α -adrenergic response in arthritic joints. In this context, it is interesting to note that RA patients have a relative paucity of sympathetic nerve fibers in the synovium.⁶⁵ Moreover, RA CD8+ T cells have fewer β -adrenoreceptors, thus suggesting that they may be resistant to inhibition by norepinephrine.⁶⁶ In one very small 14-day randomized clinical trial in the 1980s, guanethidine was used to achieve regional sympathetic blockade in a group of 24 RA patients, which resulted in decreased symptoms and improved grip strength.⁶⁷

Neuroendocrine mechanisms

The hypothalamus continuously receives data about the body's environment and, in response to stress signals such as IL-1 β , releases CRF. CRF activates the pituitary to secrete adrenocorticotrophic hormone (ACTH), which in turn stimulates the adrenal glands to produce and secrete glucocorticoids, potent endogenous antiinflammatory immunomodulators. MSH, which derives from the same precursor as ACTH, is also secreted by the pituitary gland and can suppress inflammation. Systemic administration of MSH improves inflammatory arthritis, experimental colitis, and experimental allergic encephalomyelitis.⁶⁸ Recent studies of crystal-induced arthritis suggest that the antiinflammatory effects of MSH are mediated through engagement of a specific receptor, MSH-R3.

Peripheral nervous system

Peripheral sensory nerves, on stimulation by noxious agents such as bradykinin, histamine, or inflammatory cytokines such as IL-1 (nerves can also directly respond to pathogen-derived factors via membrane-bound pattern recognition receptors),⁶⁹ not only transmit pain signaling but also secrete inflammatory mediators known as neuropeptides. Neuropeptides are neurotransmitters that are generally thought to mediate neuron-to-neuron communication, but they also act on (and are produced by) cells outside the nervous system, such as macrophages, dendritic cells, and lymphocytes. Neuropeptides have pleiotropic effects and can both contribute to and help resolve inflammation. Early in the acute inflammatory response, neuropeptides trigger a number of critical events, including arteriolar vasodilation, increased microvascular permeability, and leukocyte recruitment (Table 23.4). In recognition of this role of neuropeptides, the edema, warmth, and redness seen in early inflammatory lesions are sometimes collectively referred to as neurogenic inflammation.

Conversely, neuropeptides may hasten the resolution of inflammation by induction of regulatory T cells.⁷⁰

Neuropeptides

Substance P

SP was first discovered and purified in powder form (hence its name "substance powder") in 1931. It is widely distributed throughout the peripheral and central nervous systems, where it functions largely as a transmitter of pain signaling. Unmyelinated C-type nerve fibers release SP in response to noxious stimuli, and a variety of proinflammatory effects are produced by acting on target cells through binding and activation of the NK-1 receptor (NK-1R). SP ligation of NK-1R on postcapillary endothelium increases microvascular permeability and causes edema; it also induces vasodilation in arterioles.⁷¹ SP acts as a chemoattractant and activator for macrophages, lymphocytes, neutrophils, and eosinophils. Mast cells also possess NK-1R and degranulate in response to SP, which leads to the release of histamine

and serotonin. Lymphocytes proliferate and differentiate when stimulated with SP, and some leukocytes (e.g., lymphocytes, macrophages, and eosinophils) are themselves capable of SP expression.⁷²

Substantial evidence supports a role for SP in inflammatory arthritis. In animal models, more severely affected joints have higher levels of SP.⁷² Exogenous SP directly infused into joints exacerbates experimental arthritis, whereas neural depletion of SP by pretreatment with capsaicin ameliorates joint inflammation.^{73,74} In a mouse model of adjuvant-induced arthritis, NK-1R knockout mice experienced less joint swelling and plasma extravasation.⁷⁵

Increased levels of SP are found in a number of human inflammatory diseases, including RA, inflammatory bowel disease, and asthma.⁷⁰ *In vitro*, RA synovial fibroblasts (RASFs) respond to nanomolar concentrations of SP by releasing PGE₂ and MMP-1 and proliferating.⁷⁶ At these same concentrations, SP also stimulates the production of IL-1, TNF- α , and IL-6 in peripheral whole blood from RA patients. Increased levels of both SP and NK-1R are found in the synovial fluid of RA joints, and RASFs overexpress NK-1R mRNA. NK-1R antagonists have not yet been studied for the treatment of RA, but anti-TNF therapies reduce serum levels of SP in patients with RA.⁷⁷

Calcitonin gene-related protein

CGRP, an alternative splice product of calcitonin, is a widely distributed neuropeptide that is released primarily from small peripheral sensory nerves. It acts on the complex of the G protein-coupled calcitonin receptor-like receptor (CLR), which is expressed by smooth muscle, endothelial cells, macrophages, and lymphocytes. CGRP is co-localized and released with SP in afferent nerves and is a potent arterial and venous vasodilator, particularly in the microvasculature.⁷⁸

It is overexpressed at the nerve endings of animals with adjuvant-induced arthritis and in sensory neurons in rats with collagen-induced arthritis.^{72,79} Synovial tissue from OA joints also contains nerve endings with high

concentrations of both SP and CGRP,⁸⁰ consistent with a role in inflammation. However, CGRP may be a mixed proinflammatory and antiinflammatory agent because it inhibits T-cell and pre-B-cell differentiation, macrophage antigen presentation, IL-1 production,⁷⁸ and RASF activity *in vitro*.⁸¹

Neuropeptide Y

Neuropeptide Y is a tachykinin released from sympathetic nerve endings. Unlike SP, neuropeptide Y exerts both proinflammatory and antiinflammatory effects. Neuropeptide Y inhibits IFN- γ and stimulates IL-4 production in rat lymphocytes,⁸² thus suggesting that it may favor Th2 responses and therefore modify Th1-predominant diseases such as RA and multiple sclerosis. Neuropeptide Y ameliorates disease severity in experimental allergic encephalomyelitis (the animal model of multiple sclerosis) but has not yet been tested in models of inflammatory arthritis.⁸³ The spinal fluid of patients with multiple sclerosis shows depressed levels of neuropeptide Y, and the synovium of RA patients has a paucity of neuropeptide Y-containing nerve fibers, which may help maintain the Th1 response.

Vasoactive intestinal peptide

Vasoactive intestinal peptide (VIP) is a neuropeptide synthesized and released by immune cells, as well as by nerve endings that synapse on central and peripheral lymphoid organs. VIP is a potent antiinflammatory peptide that inhibits chemotaxis and activation of macrophages and T cells. Consequently, it inhibits the production of TNF- α , IFN- γ , IL-6, and IL-12 and stimulates production of the antiinflammatory cytokines IL-10 and IL-Ra.⁸⁴ VIP may additionally shift T cells to a Th2 phenotype because it increases IL-4 production, and it may promote regulatory T-cell production. VIP has been shown to be therapeutic in several inflammatory models, including sulfonic acid-induced colitis, sepsis, and collagen-induced arthritis, and a recent clinical trial demonstrated immunoregulatory effects in a cohort of patients with pulmonary sarcoidosis.^{84,85}

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24

Scientific basis of pain

■ HANS-GEORG SCHAIBLE

- Nociception is the encoding and processing of noxious stimuli in the nervous system; the subjective sensation pain is evoked by nociception and influenced by psychological and social factors.
- Clinically relevant pain is classified as nociceptive when tissue is inflamed or damaged or as neuropathic when nerve fibers or nerve cells are affected.
- Peripheral nociceptors are slowly conducting, thinly myelinated or unmyelinated nerve fibers that respond to tissue-damaging mechanical, thermal, and chemical stimuli.
- The central nociceptive system consists of neurons in the spinal cord, brain stem, thalamus, and cortical areas that process noxious stimuli; the conscious pain sensation with its sensory-discriminative and affective components is generated at the thalamocortical level.
- During inflammation, peripheral nociceptors are sensitized to mechanical or thermal stimuli (or to both) by inflammatory mediators (peripheral sensitization).
- Damaged nerve fibers may show action potentials that are evoked at the site of the lesion and in neuronal cell bodies (ectopic discharges).
- Peripheral sensitization and ectopic discharges may induce a state of hyperexcitability in the central nociceptive system (central sensitization) that increases the gain of central nociceptive processing.
- Nerve fibers originating in the brain stem can enhance or inhibit spinal nociceptive processing (descending facilitation or inhibition).

NOCICEPTION AND PAIN

Pain is an unpleasant sensory and emotional experience that is evoked by actual or potential noxious (i.e., tissue-damaging) stimuli or by tissue injury or is described in such terms. Because pain is a subjective experience, it cannot be measured objectively. *Nociception* is the encoding and processing of noxious stimuli in the nervous system and can be measured objectively (e.g., with electrophysiologic recordings). Under normal conditions the relationship between nociception and pain is relatively precise and predictable. A stimulus that is noxious will usually evoke a subjective pain response. However, under clinically relevant conditions the relationship between nociception and pain may not be strict, particularly when the pain is chronic (see later).

Neurons in the peripheral and central nociceptive system that encode noxious stimuli form the nociceptive system. A simplified scheme of the nociceptive system is shown in [Figure 24.1](#). Peripheral nociceptive neurons (nociceptors) innervate the skin, deep tissue, and most visceral organs. They encode noxious stimuli applied to the tissue. The central nociceptive system consists of sensory nociceptive neurons in the spinal cord, spinal reflex pathways, and ascending tracts that activate the brain stem and supraspinal structures in the thalamus and cortex. Corticothalamic networks produce the conscious pain response.^{1,2}

Types of pain

Application of a noxious stimulus to *normal* tissue elicits *acute physiologic nociceptive pain*. This pain protects tissue from being damaged further because withdrawal reflexes are usually elicited. Inflammation or injury causes *pathophysiologic nociceptive pain*. It may appear as spontaneous

(resting) pain, hyperalgesia, allodynia, or any combination of these types of pain. *Hyperalgesia* is higher pain intensity felt on noxious heat stimulation (thermal hyperalgesia) or noxious mechanical stimulation (mechanical hyperalgesia). *Allodynia* is pain elicited by stimuli that are normally below the pain threshold.¹

Whereas *nociceptive pain* is elicited by noxious stimulation of the sensory endings of nociceptors in tissues, *neuropathic pain* is caused by injury or disease of nociceptive neurons in the peripheral or central nervous system. This pain does not primarily signal tissue damage. It often has an abnormal burning or electrical character and can be persistent or episodic (e.g., trigeminal neuralgia). It may be combined with hyperalgesia and allodynia. Thus, even touching the skin with a soft brush can cause intense pain. Causes of neuropathic pain include nerve or plexus damage, metabolic diseases such as diabetes mellitus, and herpes zoster. Damage to central pain-processing neurons (e.g., in the thalamus) can cause central pain.^{1,3}

Usually, pain is called “chronic” when it lasts longer than 6 months. Chronic pain may result from persistent nociception (with a chronic disease), but it is often significantly influenced by psychological and social factors. It can be accompanied by neuroendocrine dysregulation, fatigue, dysphoria, and impaired physical and even mental performance.⁴

THE PERIPHERAL BASIS OF PAIN

Structure and dual function of peripheral nociceptors

Nociceptors are sensory neurons with thinly myelinated A δ - or unmyelinated C-fiber axons. The cell bodies of nociceptors are located in the dorsal root ganglia. Their peripheral branches form sensory endings (“free nerve endings”) in the innervated tissue, and their central branches terminate in the dorsal horn of the spinal cord or in the brain stem, where they activate synaptically nociceptive dorsal horn neurons (see [Fig. 24.1](#)).⁵

Many nociceptors have a dual function. They encode noxious stimuli and transmit this information to the spinal cord (sensory function). In addition, they transport neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) from the cell body to the periphery and release these mediators in the tissue on stimulation. There, these neuropeptides induce vasodilatation, plasma extravasation, attraction of macrophages, degranulation of mast cells, or other processes that elicit *neurogenic inflammation*. Such neurogenic components contribute significantly to many inflammatory diseases.⁶

Sensory function of nociceptors

Most nociceptors respond to noxious *mechanical* stimuli (painful pressure, squeezing or cutting the tissue), noxious *thermal* stimuli (heat or extreme cold), and *chemical* stimuli and are therefore called *polymodal*. Noxious stimuli evoke a sensory potential in the sensory ending (transduction). When the depolarization is sufficiently strong, action potentials are triggered and conducted by the axon to the spinal cord or the brain stem ([Fig. 24.2](#)).⁵

In joints, nociceptors innervate mainly the fibrous capsule, ligaments, adipose tissue, menisci, and the synovial layer. The cartilage is normally not innervated. A typical joint nociceptor is activated by strong pressure on the joint (e.g., hitting the joint) and by noxious movements (i.e., painful rotation against resistance of the tissue). It is not usually activated by movements and positions in the working range.⁷ Nociceptors in muscle are located in the muscle belly and in the tendon. They respond to noxious (painful) compression of the muscle, they may be activated by muscle

SCHEME OF THE NOCICEPTIVE SYSTEM WITH NOCICEPTIVE FREE NERVE ENDINGS IN THE PERIPHERAL TISSUE, AFFERENT NERVE FIBERS AND THEIR SYNAPSES IN THE DORSAL HORN OF THE SPINAL CORD, AND ASCENDING TRACTS

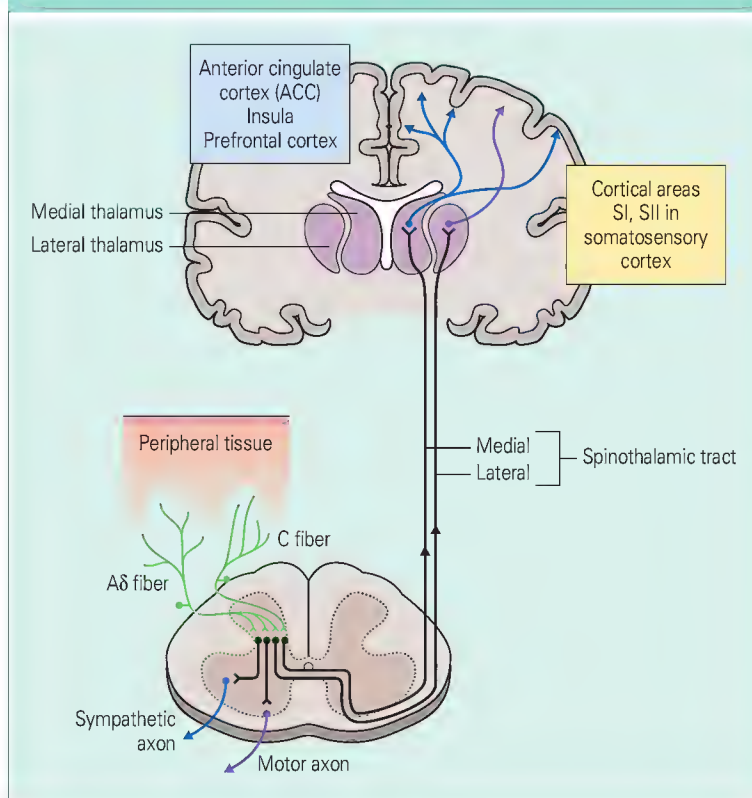


Fig. 24.1 The nociceptive system consists of nociceptive free nerve endings in peripheral tissue, afferent nerve fibers, and their synapses in the dorsal horn of the spinal cord. From there the medial and lateral spinothalamic tracts ascend to the medial and lateral thalamus, and interneurons project into motor and sympathetic reflex pathways. Note: Other ascending pathways such as the spinoreticular tract and dorsal column pathways are not displayed.

contraction under ischemic conditions, and some of them are activated by noxious thermal stimuli. Normally, they do not respond to innocuous pressure and to contractions of the muscle.⁵ Cutaneous nociceptors respond to noxious heat (in the range of 42°C to higher than 50°C), and they encode noxious mechanical stimuli such as squeezing.⁵ Visceral nociceptors respond to a variety of mechanical, thermal, and chemical stimuli.⁵

Notably, not all nociceptors are polymodal. An important group of nociceptors is relatively mechanoinensitive and, in the skin, heat insensitive. Because these nociceptors do not respond to noxious stimuli applied to normal tissue, they were initially called *mechanoinensitive* or *silent* nociceptors.^{1,7} These nociceptors are “recruited” during inflammation (see later).

With repetitive or strong noxious stimulation of the tissue, nociceptors are often *sensitized* to stimuli. The excitation threshold of polymodal nociceptors drops such that even light, normally innocuous stimuli activate the fibers, and silent nociceptors become excitable by innocuous and noxious stimuli.^{1,7} This *peripheral sensitization* produces enhanced input to the spinal cord and induces *central sensitization* there (Fig. 24.3). Both peripheral sensitization and central sensitization cause *primary hyperalgesia* and *allodynia* at the site of inflammation. In addition, central sensitization causes *secondary hyperalgesia*, or enhanced pain sensitivity in healthy tissue surrounding the site of inflammation (Fig. 24.4).

Molecular mechanisms of peripheral stimulus transduction and peripheral sensitization

The sensory endings of nociceptors express ion channels and membrane receptors that transduce the mechanical, thermal, and chemical stimuli into a sensory potential (see Fig. 24.2). Some sensory molecules have been identified.⁸ The best known is transient receptor potential vanilloid 1 (TRPV1), a ligand-gated ion channel that is expressed in nociceptors but not in other peripheral neurons. On opening, cations, in particular, Ca^{2+} , flow into the cell and depolarize it. TRPV1 is opened by temperatures higher than 43°C, which are felt as painful heat by humans; by chemicals that elicit burning pain, such as capsaicin and ethanol applied to a wound; and by low pH (less than 5.9), which occurs in inflamed tissue. TRPV1 is activated by metabolites of arachidonic acid produced by lipoxygenases such as 12-hydroperoxyeicosatetraenoic acid (12-HPETE) and by endocannabinoids such as anandamide and N-arachidonoyl-dopamine (NADA). Furthermore, TRPV1 is sensitized via second messengers by the inflammatory mediators bradykinin, prostaglandin E_2 (PGE_2), extracellular adenosine triphosphate, glutamate, proteases, cytokines, and nerve growth factor (NGF).

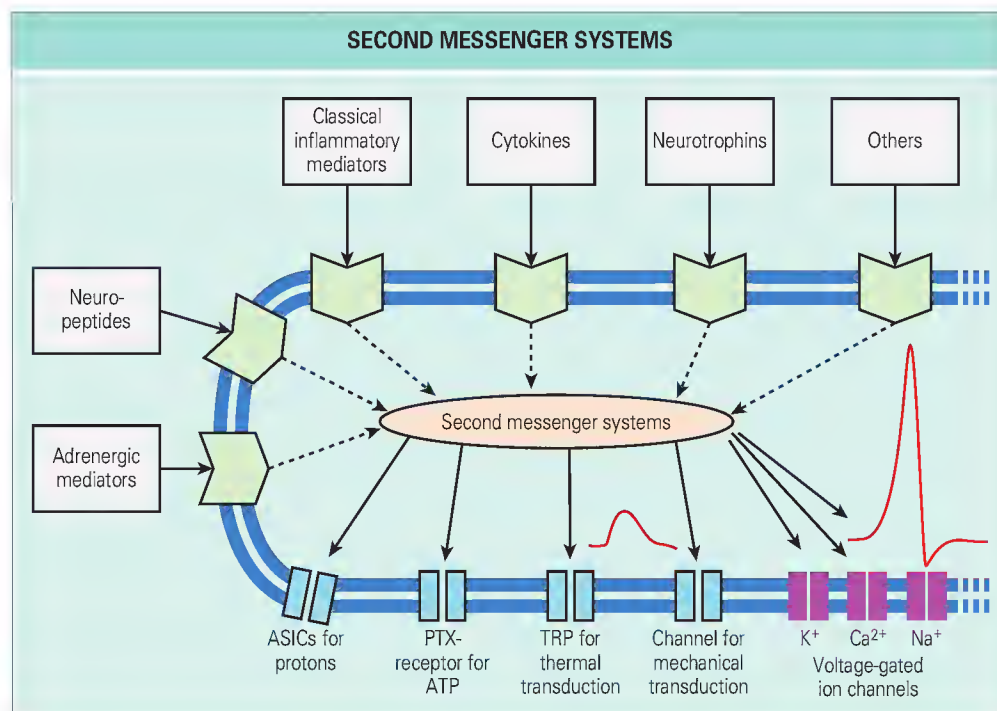


Fig. 24.2 Sketch of the enlarged sensory ending of a nociceptor in tissue. At the bottom is shown ion channels for the transduction of thermal, mechanical, and chemical stimuli (they produce a sensory potential) and voltage-gated ion channels (opening of Na^+ channels produces action potentials). At the top and the left side are displayed metabotropic receptors for chemical mediators. ASIC, acid-sensing ion channel; TRP, transient receptor potential; TTX, tetrodotoxin. Classic mediators are bradykinin, prostaglandin E_2 , and others. (From Schaible H-G, Ebersberger A, Natura G. Update on peripheral mechanisms of pain: beyond prostaglandins and cytokines. *Arthritis Res Ther* 2011;13:210.)

Thus, TRPV1 is one transducer of noxious heat, and it is the crucial ion channel for inflammatory *thermal hyperalgesia*.⁸

Other TRP channels such as TRPV2, TRPV3, TRPV4, TRPM8, and TRPA1 are also expressed in a proportion of primary sensory neurons. Some of them are coexpressed with TRPV1, whereas others are expressed in non-nociceptive neurons. For example, TRPM8 is opened by temperatures that are felt to be cool—hence TRPM8 is assumed to be the transducer in non-nociceptive cold fibers. In general, the role of these other TRP channels is less clear. TRP ion channels such as TRPA1 and TRPV4 may also be involved in the transduction of mechanical stimuli and in mechanical hyperalgesia, which is more important than thermal hyperalgesia. However, the ionic basis of mechanonociception is poorly understood.⁸

When the sensory ending is sufficiently depolarized through the ion channels of transduction, voltage-gated Na^+ channels are opened and action potentials are triggered (see Fig. 24.2). Nociceptive sensory neurons express mainly the sodium channel types $\text{Na}_v1.7$, $\text{Na}_v1.8$, and $\text{Na}_v1.9$, whereas large-sized nonnociceptive neurons express mainly $\text{Na}_v1.1$, $\text{Na}_v1.6$, $\text{Na}_v1.7$, and some $\text{Na}_v1.8$. $\text{Na}_v1.7$ and $\text{Na}_v1.8$ channels are directly involved in generation of the action potential, and $\text{Na}_v1.9$ influences the threshold for action

potentials. These channels can be upregulated or downregulated by second messenger pathways involving protein kinase A, protein kinase C, sphingomyelinase, calmodulin, and p38 mitogen-activated protein kinase. The excitability of neurons may also be controlled by K^+ channels (e.g., of the KCNQ family) and Ca^{2+} channels. Excitability is increased when voltage-gated K^+ channels are closed (this evokes sustained depolarization of neurons) or when Ca^{2+} flows into the neuron through voltage-gated T-type channels.⁹

In addition, nociceptors express receptors for inflammatory mediators in the membrane (see Fig. 24.2); Box 24.1 shows which particular mediator receptors are expressed in subgroups of sensory neurons.^{9,10} Inflammatory mediators sensitize nociceptors to mechanical and thermal stimuli. Ligand binding of these membrane receptors activates second messenger systems, which then render both transduction molecules and voltage-gated ion channels more excitable (e.g., by phosphorylation). For instance, PGE_2 acts on G protein-coupled EP receptors to increase cyclic adenosine monophosphate. This activates protein kinase A, which finally leads to phosphorylation of TRPV1 and voltage-gated Na^+ channels. In the long term, some mediators may also regulate the expression of such ion channels in the membrane. In addition, sensory nerve endings possess Toll-like receptors that signal molecular patterns of infectious agents, thus indicating an important role of nociceptive nerve fibers in the context of innate immunity.

“Classic inflammatory mediators” such as bradykinin and prostaglandins activate or sensitize neurons within minutes, and the effects are quite short-lived (minutes only). By contrast, injection of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) into the joint leads to slowly developing, but persistent sensitization of nociceptive afferents (i.e., an increase in the number of action potentials in response to a stimulus) that lasts at least several hours. In addition, cytokines regulate the expression of molecules of nociception (e.g., TNF- α upregulates TRPV1 receptors).¹¹ These effects of cytokines can be blocked by anticytokine

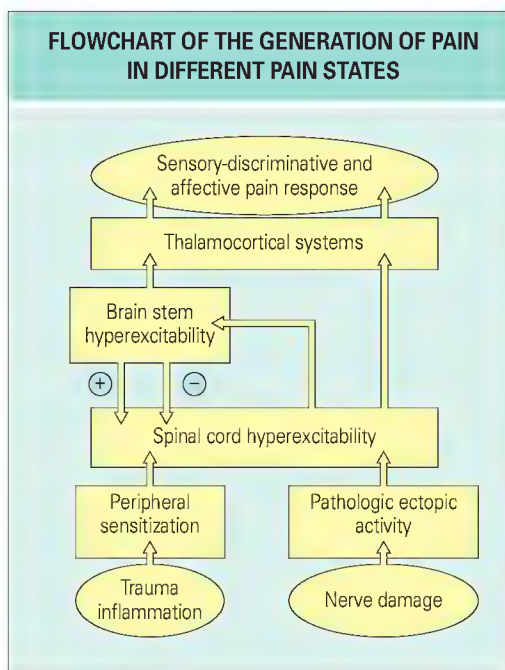


Fig. 24.3 Spinal cord hyperexcitability (central sensitization) can result from both peripheral sensitization and ectopic pathologic discharges in the afferent nerve fiber. The brain stem (also rendered hyperexcitable) provides feedback to the spinal cord that is either inhibitory or facilitatory.

BOX 24.1 RECEPTORS FOR MEDIATORS IN SUBGROUPS OF SENSORY NEURONS

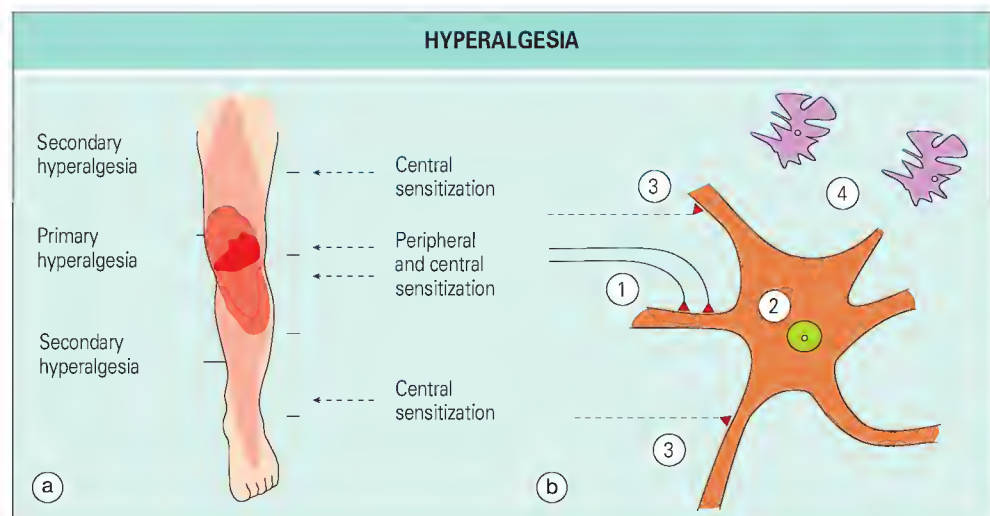
Ionotropic receptors for

- Adenosine triphosphate (ATP), H^+ (acid-sensitive ion channels [ASICs]), glutamate (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], kainate, *N*-methyl-D-aspartate [NMDA] receptors), acetylcholine (nicotinic receptors), serotonin (5-HT₃)

Metabotropic receptors for

- Acetylcholine, epinephrine, serotonin, dopamine, glutamate, γ -aminobenzoic acid, ATP
- Prostanoids (prostaglandins E_2 and I_2), bradykinin, histamine, adenosine, endothelin
- Neuropeptides (e.g., substance P, calcitonin gene-related peptide, somatostatin, opioids)
- Proteases (protease-activated receptors PAR1 and PAR2)

Fig. 24.4 Central sensitization. (a) Regions of primary and secondary hyperalgesia produced by peripheral and central sensitization. (b) Mechanisms of spinal sensitization: (1) enhanced release of transmitters from sensitized nociceptors, (2) enhanced excitability of postsynaptic neurons, (3) suprathreshold synaptic activation by afferents from remote regions (in the normal, nonsensitized state insufficient), and (4) spinal release of mediators from glial cells and other cells.



therapy with biologic agents, and it is expected that this also inhibits release of proinflammatory substance P and other neuropeptides.

NGF is an essential neurotrophin for the development of sensory nerve fibers. In adults, a large proportion of sensory nerve fibers remain dependent on the trophic effect of NGF. These neurons express tyrosine kinase receptor A (TrkA) (specific for NGF), and NGF is required for their structural and functional integrity. However, substantial amounts of NGF are also produced at inflammatory sites, where NGF acts as an inflammatory mediator. It enhances currents through TRPV1 channels and reduces the threshold for thermal excitation. Long-term exposure to NGF increases the expression of TRPV1, bradykinin, and P2X receptors and Na⁺ channels, as well as the synthesis of substance P and CGRP. In addition, NGF stimulates inflammatory cells to release inflammatory compounds. Thus, NGF is a key molecule in nociceptor biology, and neutralization of it has proved to be highly analgesic in humans.⁹

Nociceptors also express receptors for neuropeptides. Substance P and CGRP sensitize part of the neurons, whereas opioid peptides and somatostatin inhibit the neurons. Thus, actual receptor sensitivity is due to a balance between excitatory and inhibitory influences.⁹

Peripheral mechanisms of neuropathic pain

In healthy sensory nerve fibers, action potentials are generated in the sensory endings on stimulation of the innervated tissue. By contrast, damaged nerve fibers often show pathologic *ectopic discharges*—action potentials generated at the site of nerve injury or in the cell bodies of impaired fibers in dorsal root ganglia. Neuropathic pain may also be generated by intact nerve fibers in the vicinity of injured nerve fibers that are affected by the process of wallerian degeneration.³ Pathologic discharges may cause a state of central sensitization (see Fig. 24.3).

Different mechanisms can produce ectopic discharges. First, after nerve injury, changes in the expression of Na⁺ channels may alter the membrane properties of the neuron such that rapid firing rates (bursting ectopic discharges) are favored. Changes in the expression of K⁺ channels in neurons have also been shown. Second, injured axons of primary sensory neurons may be excited directly by inflammatory mediators (e.g., by bradykinin, nitrous oxide, and cytokines) released from white blood cells and Schwann cells around the damaged nerve fibers. Third, injured nerve fibers may be affected by the sympathetic nervous system. Although the latter does not activate primary afferents in normal tissue, injured nerve fibers may become sensitive to adrenergic mediators because neuronal adrenergic receptors are upregulated. A direct connection between afferent and efferent fibers (so-called ephapses) is thought to be the cause. Furthermore, after nerve injury, sympathetic nerve fibers may sprout in the dorsal root ganglion.^{1,3} Currently, the best treatment of peripheral neuropathic pain consists of drugs that reduce the excitability of neurons (e.g., carbamazepine or gabapentin).

THE CENTRAL BASIS OF PAIN

Nociceptive spinal cord neurons

Nociceptors activate synaptically nociceptive dorsal horn neurons (see Fig. 24.1). The latter are either spinothalamic or spinoreticular tract neurons that ascend to supraspinal sites or are local interneurons that are part of the segmental motor or vegetative reflex pathways. A noxious stimulus applied to normal tissue causes a withdrawal reflex that removes the threatened part of the body from the damaging source. Under inflammatory conditions the inflamed tissue is kept in a position that activates nociceptors as little as possible.

Typically, nociceptive spinal cord neurons receive convergent input from numerous sensory neurons in one organ or different organs. Part of the nociceptive dorsal horn neurons are activated by input only from the skin, whereas others are activated by input only from deep tissue (i.e., muscles, tendons, and joints). A large proportion of dorsal horn neurons receive input from both the skin and deep tissue, and others are excited by cutaneous, deep tissue, and visceral stimulation. As a consequence, pain may be poorly localized (especially in deep somatic tissue) and may be even projected. In particular, noxious stimulation of the viscera leads to projection of pain into the skin and deep tissues that are supplied by nociceptors of the same segment.^{1,5}

The spinal cord is under the influence of descending tracts that inhibit or facilitate the spinal nociceptive processing. These descending pathways originate from brain stem nuclei (in particular, the periaqueductal gray matter and nucleus raphe magnus) and descend in the dorsolateral funiculus of the spinal cord.^{12,13}

Generation of the conscious pain response in the thalamocortical system

The conscious pain response is produced in the thalamocortical system (see Fig. 24.1). Different aspects of pain are produced by different networks. Analysis of the noxious stimulus with respect to its location, duration, and intensity (the *sensory-discriminative aspect* of pain) is performed in the *lateral thalamocortical system*, which consists of relay nuclei in the lateral thalamus and primary and secondary somatosensory cortices (SI and SII) in the postcentral gyrus. In these regions, innocuous and noxious stimuli are discriminated.¹⁴ The *affective aspect* of pain (i.e., the noxious stimulus is felt to be unpleasant and causes aversive reactions) is produced in the *medial thalamocortical system*, which consists of relay nuclei in the central and medial thalamus and the anterior cingulate cortex, the insula, and the prefrontal cortex.² These brain structures are part of the limbic system, and the insula may be an interface between the somatosensory and the limbic system. Notably, the limbic regions are involved not only in pain processing. Specifically, the anterior cingulate cortex is activated during different emotions, including sadness and happiness, and parts of the anterior cingulate cortex are also involved in the generation of autonomic responses (they have projections to regions that command autonomic output systems). Other cingulate regions are involved in response selection (they have projections to the spinal cord and the motor cortices) and in orientation of the body toward or away from innocuous and noxious somatosensory stimuli. A role in the process of memory formation/access has also been discussed.¹⁵

Central sensitization

Strong pathologic nociceptive input causes spinal cord hyperexcitability (*central sensitization*) (see Fig. 24.3). Central sensitization amplifies the synaptic processing of nociceptive input in the spinal cord, and thus the thalamocortical system is more strongly activated. Together with peripheral sensitization at the site of inflammation, the spinal hyperexcitability produces *primary hyperalgesia* at the inflamed region. Furthermore, central sensitization generates a zone of *secondary hyperalgesia* in regions adjacent to and remote from the inflamed region, even though the latter areas are in a healthy condition (see Fig. 24.4a). For example, patients with advanced-stage osteoarthritis (OA) often report widespread pain far beyond the OA joint and exhibit lowered pressure pain thresholds in cutaneous and subcutaneous structures of the entire leg.¹⁶ Thus, central sensitization leads to an increase and spread of the pain beyond the site of origin.

Central sensitization can last as long as the nociceptive input persists and disappear when the peripheral input is reduced. However, central sensitization may also outlast the peripheral nociceptive process. In these cases, nociceptive input has probably triggered *long-term potentiation*, a persistent increase in synaptic efficacy.¹⁷ Such a process could account for pain states that persist even when the peripheral nociceptive input has disappeared.

Spinal sensitization is influenced by tracts descending from the brain stem (see flowchart in Fig. 24.3). Experimental evidence suggests that *descending inhibition* of neurons with input from inflamed areas is increased, at least in the acute stage of inflammation, with spinal sensitization being kept under control.¹² However, in severe chronic pain states such as OA or rheumatoid arthritis, some forms of descending inhibition (descending noxious inhibitory control [DNIC]) are almost absent, thus indicating that the endogenous pain control systems became insufficient.^{13,16} Interestingly, this form of descending inhibition is restored after replacement of the OA hip joint.¹⁶ In contrast, *descending facilitation* may support the expansion of receptive fields into healthy areas and thereby promote secondary hyperalgesia¹²; in the case of neuropathic pain, mainly descending facilitation has been observed. Thus, spinal/supraspinal/spinal loops are quite important in the generation of pathologic pain.¹²

Mechanisms of spinal sensitization

Important mechanisms of spinal sensitization are displayed in Figure 24.4b. First, sensitized nociceptors from the inflamed site create stronger input into the spinal cord; that is, they release more transmitters at synapses at the spinal neuron.^{1,7} This is a presynaptic mechanism of spinal sensitization. The main transmitter of sensory afferents is glutamate, and peptidergic C fibers in addition release substance P and CGRP.⁵ Second, enhanced transmitter release from sensitized nociceptors renders the postsynaptic neuron more excitable. This constitutes a postsynaptic mechanism of spinal sensitization. Mechanistically, glutamate activates N-methyl-D-aspartate (NMDA) and non-NMDA receptors (both are ion channels) and metabotropic glutamate receptors in spinal cord neurons.⁵ During noxious stimulation both non-NMDA and NMDA receptors are opened by glutamate, and in particular,

influx of Ca^{2+} through the calcium-permeable NMDA receptors triggers biochemical changes in the neurons that enhance the sensitivity of the neurons. Administration of NMDA receptor antagonists prevents central sensitization and reduces established hyperexcitability. In addition, many spinal nociceptive neurons express receptors for substance P and CGRP, and through activation of these receptors the enhanced release of substance P and CGRP contributes to spinal sensitization.^{1,5} Third, the hyperexcitability of the spinal neuron makes it possible for the neuron to now be activated even by primary afferents that are normally not able to cause suprathreshold excitation of the neuron (dashed lines). Hence the total receptive field of the neuron is enlarged. As a consequence of this sensitization a higher proportion of neurons respond to stimulation of peripheral tissue.^{1,7} Together, these changes produce the areas of secondary hyperalgesia or spreading pain.

Fourth, synaptic processing is further modified by mediators that are produced in the spinal cord and create a change in the milieu there. Numerous spinal neurons (and other cells) produce prostaglandins (mainly PGE_2 and PGD_2).¹⁴ During peripheral inflammation, more PGE_2 is released in the spinal cord and contributes to spinal sensitization. In particular, cyclooxygenase-2-selective inhibitors reduce spinal hyperexcitability by inhibition of spinal prostaglandin synthesis and, as proposed, by enhancing spinal endocannabinoids.¹⁸ By contrast, spinal PGD_2 instead inhibits spinal sensitization during peripheral inflammation.⁷ Glial cells in the spinal cord can significantly contribute to the generation of pain states, particularly

neuropathic pain¹⁹ but also experimental models of OA.¹⁵ On stimulation, neuroglia secrete a number of mediators such as nitrous oxide, neurotrophins, and proinflammatory cytokines, and neutralization of such mediators may attenuate hyperalgesia.¹⁹

Importantly, inhibitory transmitters such as γ -aminobutyric acid (GABA) and opioids are able to reduce spinal sensitization by decreasing release of transmitters and depolarization of postsynaptic neurons. An important mechanism of spinal sensitization may be the loss of segmental inhibition that is normally provided by GABAergic interneurons.⁵

CONCLUSION

Pain is an important component of suffering from disease, and therefore treatment of pain is an absolute necessity in clinical medicine. In a wider sense, pain is also an important element of the so-called illness response. The symptoms of diseases result not only from local disease processes but also from mechanisms in the central neurons system that respond to challenges such as inflammation, infection, and injury in a coordinated fashion. In fact, plenty of evidence has shown autonomic/endocrine/immune interactions to be related to acute and chronic pain.²⁰ In this respect, pain therapy may not only just attack a clinical symptom but also modify the further course of disease.

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25

Effects of the neuroendocrine system on development and function of the immune system

■ MAURIZIO CUTOLO ■ RAINER H. STRAUB

- The function of the hypothalamic-pituitary-adrenal (HPA) axis is not completely normal in patients with chronic inflammatory diseases.
- Levels of HPA axis hormones are inadequately low in relation to levels of circulating proinflammatory cytokines.
- Serum concentrations of adrenal androgens are mostly decreased.
- The influence of estrogens on immunity is rather complex depending on many different factors; estrogens can be proinflammatory and antiinflammatory but enhance B-cell immunity (autoimmunity).
- The steroid hormone vitamin D modulates many aspects of innate and adaptive immunity.
- The cortisol nadir at midnight and the parallel increase in immunostimulatory hormones such as melatonin and growth hormone drive the nightly increase in tumor necrosis factor and interleukin-6 concentrations and thus morning clinical symptoms in rheumatoid arthritis.
- Many alterations of neuroendocrine pathways and chronic inflammatory disease sequelae can be explained by an evolutionarily selected program that redirects energy-rich fuels from stores (liver, muscle, fat tissue) to the activated immune system during the night.

INTRODUCTION

Independent observations already being made in the 19th century by Trousseau, Charcot, and Bannatyne indicated that pregnancy is favorable in rheumatoid arthritis (RA), as summarized in the Nobel Prize lecture of the rheumatologist Philip S. Hench on December 11, 1950.¹ Dr. Hench wrote as follows²:

after 1931, records of these cases [of pregnancy with RA] were more carefully made and assembled ... because of my growing belief that this phenomenon of relief [from arthritic disability] was analogous to, if not identical with, that which may occur during jaundice, and that the same agent might be responsible for the relief both during pregnancy and jaundice.

These observations linked for the first time immune/inflammatory diseases to hormones, and this was firmly established by the enormous treatment success achieved through administration of endogenous glucocorticoids during the 1950s.³ In addition, the obvious female preponderance in the prevalence and incidence of autoimmune diseases spoke for the role of sex hormones (e.g., estrogens).⁴ This female predominance is particularly evident in the reproductive years, when sex hormone levels are highest in women (estrogens) and men (androgens).

Furthermore, the induction of ovulation by gonadotropin, a gonadotropin-releasing hormone analogue, or clomiphene can result in flares, embryonic losses, or fetal deaths in patients with systemic lupus erythematosus (SLE) or antiphospholipid syndrome.⁵ Again, this indicates that generally an increase of female sex hormones can worsen autoimmune diseases. In sharp contrast seems to be the finding that some women develop an autoimmune disease such as RA after menopause when serum sex hormone levels fall dramatically. This is not an unresolvable paradox considering the

mentioned role of sex hormones, as will be demonstrated later, because sex hormones have very different effects on different types of immune cells; in addition, their peripheral metabolism plays an important role.⁴ This is particularly true in menopause with the increased physiologic activity of the aromatase complex in peripheral tissues (e.g., adipose tissue). Increased activity of this enzyme complex leads to higher peripheral synthesis of estrogens from androgens, which has a stimulating effect on B-cell immunity.⁶

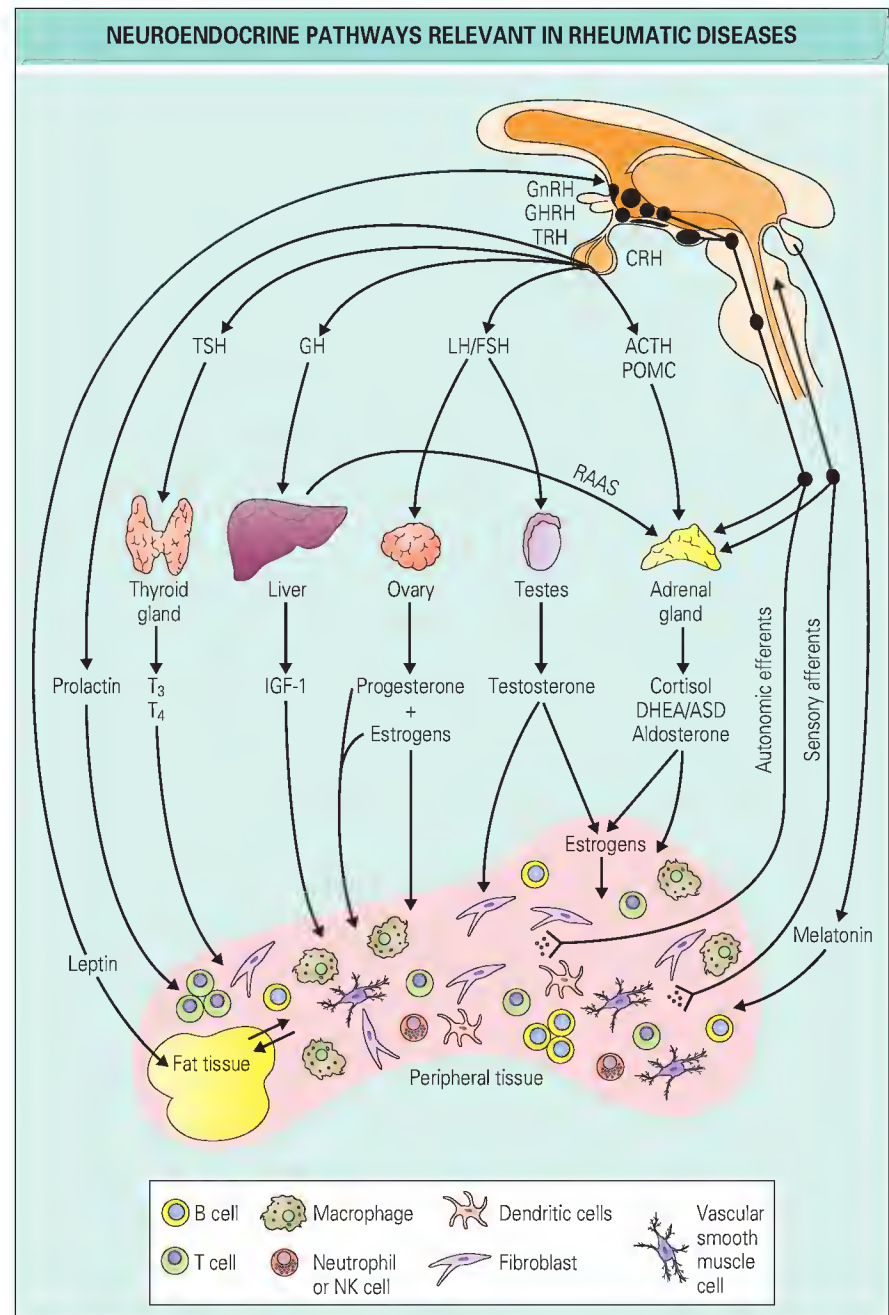
The clear connection between stressful life events on the one hand and exacerbations of autoimmune diseases on the other demonstrates a role for steroidal hormones or neurotransmitters in these diseases (e.g., cortisol and noradrenalin).^{7,8} Similarly, the phenomenon that in different diseases hemiplegia spares the paretic side from inflammatory signs and symptoms supports an important propagating role for the nervous system.⁹ Moreover, the circadian undulation of symptoms in autoimmune diseases links the rhythms of the central nervous and neuroendocrine systems to immunologically mediated phenomena. In recent years, we have started to recognize that the neuroendocrine system is important in providing energy-rich fuels to the activated immune system,¹⁰ the long-standing supply of which in chronic inflammatory diseases leads to many unwanted disease sequelae.¹¹ These clinical findings have opened up totally new avenues for understanding the impact of the neuroendocrine system on the development and function of the immune system in chronic inflammatory diseases.

NEUROENDOCRINE SYSTEM

Fig. 25.1 is a representation of the different endocrine and neuronal axes relevant to the neuroendocrine system. The hypothalamic-pituitary-adrenal (HPA) axis influences many immunologic mechanisms (see later). Progesterone, dehydroepiandrosterone (DHEA), and androstenedione are precursor hormones of the HPA axis that can be converted to downstream sex hormones. Sex steroid action can take place in the same cells where conversion occurs (intracrinology).¹² In postmenopausal women, nearly 100% of sex steroids are synthesized in peripheral tissues from precursors of adrenal origin, as mentioned earlier (in older men peripheral conversion depends on age and can be up to 80%). After menopause and during aging, the HPA axis can take over various functions of the hypothalamic-pituitary-gonadal (HPG) axis (Fig. 25.2), and this can and have an effect on immune/inflammatory reactivity. Peripheral conversion can be influenced by local cytokines, hormones, and neurotransmitters.¹³ The well-known undulation of symptoms of autoimmune diseases during the menstrual cycle demonstrates the influence the HPG axis. In this situation, gonadally produced estrogens and androgens can bypass the conversion steps via progesterone and DHEA (see Fig. 25.2, yellow box). Beyond steroid hormones, vitamin D (or, better, D hormone as active metabolite), prolactin, melatonin, growth hormone, insulin-like growth factor 1, and other hormones demonstrate immune-modulating properties.¹⁴⁻¹⁶

The central neuroendocrine system is activated upon peripheral inflammation that stimulates the HPA axis. In recent years, this stimulation has been recognized as part of the energy appeal reaction and water retention reaction,^{10,11} while the HPG axis and the somatotrophic axis are switched off. The major immune stimuli for the HPA axis and the sympathetic nervous system are circulating interleukin-6 (IL-6), interferon- γ (IFN- γ), and tumor necrosis factor (TNF) and local cytokines such as IL-6, TNF, IL-17, and IL-1 β , which directly activate sensory afferents.¹⁷ It is important to mention that acute stimulation of neuroendocrine centers can lead to markedly

Fig. 25.1 Neuroendocrine pathways relevant in rheumatic diseases. Neuroendocrine pathways link the central nervous system with the periphery by way of hormones and nerve fibers (neurotransmitters). Some important cells are shown to indicate some targets in inflamed tissue and lymphoid organs. Autonomic efferents comprise sympathetic and parasympathetic nerves with the main sympathetic neurotransmitters noradrenaline (plus neuropeptide Y, adenosine triphosphate, and endogenous opioids) and with the main parasympathetic neurotransmitter acetylcholine. The sensory nervous system bears vesicles with substance P and calcitonin gene-related peptide. ACTH, adrenocorticotropic hormone; ASD, androstenedione; CRH, corticotropin-releasing hormone; DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; NK, natural killer; POMC, pro-opiomelanocortin-derived proteins (other than ACTH); RAAS, renin-angiotensin-aldosterone system; T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (or thyrotropin).



different behavior of these axes compared with chronic stimulation due to the relative insufficiency of stress axes (exhaustion).

Hypothalamic-pituitary-adrenal axis Influence of hypothalamic-pituitary-adrenal axis hormones on the development of the immune system (animal models)

There are tight connections between the HPA and somatotrophic axes and the thymus.¹⁸ For example, glucocorticoids have long been known to inhibit thymocytes, and thymocytes possess all enzymes to generate glucocorticoids in the thymic microenvironment.¹⁹ Adrenocorticotropic hormone (ACTH) inhibits mitogenesis of immature and mature thymocytes,²⁰ DHEA suppresses proliferation of thymocytes,²¹ and DHEA induces thymocyte apoptosis by upregulation of Fas and FasL.²² Inversely, thymic factors such as thymulin or cytokines influence the hypothalamic-pituitary axis (e.g., growth hormone secretion), which led to the concept of a reciprocal feedback loop between the hypothalamic-pituitary axis and the thymus.¹⁸

In addition, growth hormone and prolactin were shown to be important connectors of the pituitary gland and the thymus.¹⁸ These interconnections between the hypothalamic-pituitary axis and the thymus most probably play an important role in the aging process, in which the integration of this network is disrupted and the thymus undergoes involution.²³ Because the thymus is the primary T-lymphopoietic organ during ontogenesis, its

age-related involution with morphologic alterations is, in part, responsible for the decline in antigen-specific T-lymphocyte immune functions. It is still unclear whether the neuroendocrine connection between the hypothalamic-pituitary axis and the thymus is altered in human chronic inflammatory autoimmune disease.

Progesterone inhibits differentiation of bone marrow-derived dendritic cells, and it also influences maturation of dendritic cells.^{24,25} In addition, progesterone might influence B-lymphocyte development because progesterone receptors have been demonstrated in premature B cells.²⁶ The inhibiting role of glucocorticoids on B-lymphocyte development has been demonstrated in the mouse.²⁷ Although most of these findings play relevant roles in the immunophysiology of rodents, their impact has never been demonstrated in humans with or without a chronic autoimmune disease.

Influence of hypothalamic-pituitary-adrenal axis hormones on the immune system

Although corticotropin-releasing hormone (CRH), as a major hormone of the hypothalamus, has a strong antiinflammatory role in the general regulation of the HPA axis, CRH produced locally exerts many proinflammatory effects.²⁸ The use of a CRH receptor type 1 antagonist has been found to ameliorate adjuvant arthritis.²⁹ Similarly, local administration of the pituitary hormone ACTH exerts some stimulatory activities on cytotoxic T lymphocytes,²⁰ and T lymphocytes, B lymphocytes, and macrophages possess melanocortin receptors.³⁰ ACTH can bind to all melanocortin

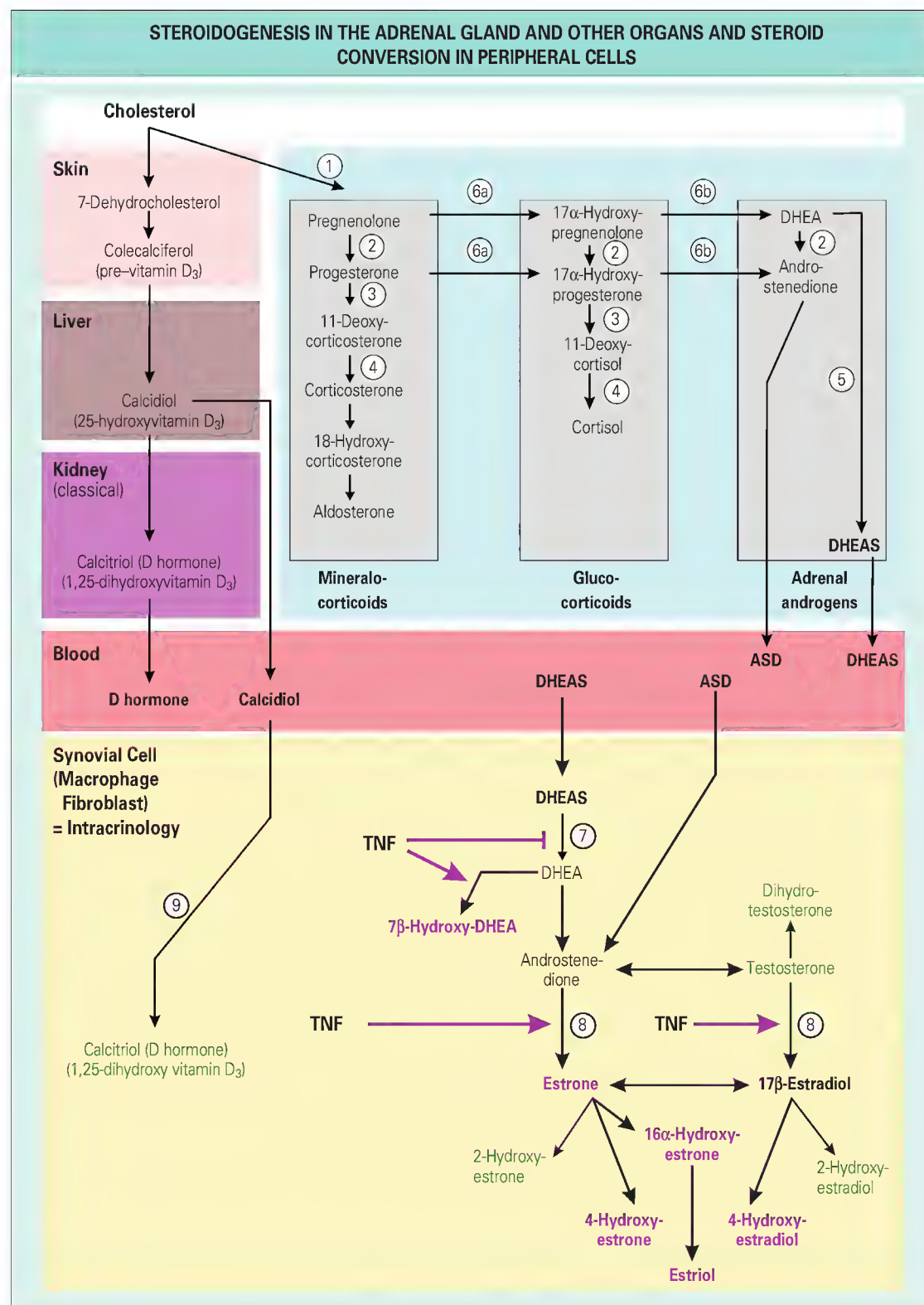


Fig. 25.2 Steroidogenesis at the level of different organs and steroid conversion at the level of peripheral cells. The size of the font indicates availability, production, and concentration of the respective factors (small font = little; big font = much). The large grey box on the upper right shows steroidogenesis in the adrenal gland under healthy conditions. The small brown and violet boxes on the upper left show vitamin D pathways in different organs. The bottom section (yellow box) depicts the conversion of steroid hormones in peripheral cells such as the macrophage or fibroblast (intracrinology). The violet and green colors in the yellow box indicate a proinflammatory and an antiinflammatory influence, respectively. DHEAS is converted to downstream androgens and estrogens. The proinflammatory tumor necrosis factor (TNF) interferes with several hormonal conversion steps (a line with a bar at the end indicates inhibition, whereas an arrow indicates stimulation). Circled numbers: 1, P450 side-chain cleavage enzyme; 2, 3β-hydroxysteroid dehydrogenase; 3, P450c21 (21-hydroxylase); 4, P450c11 (11α-hydroxylase); 5, DHEA sulfotransferase; 6a and 6b, P450c17, an enzyme with two activities (17α-hydroxylase and 17/20-lyase); 7, DHEAS sulfatase; 8, aromatase complex; 9, α1-hydroxylase (occurs in cells equipped with this enzyme, i.e., macrophages). ASD, androstenedione; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.

receptors type 1 to 5, and signaling via type 4 and 5 receptors leads to proinflammatory events via phosphoinositol hydrolysis, protein kinase C activation, and stimulation of the JAK/STAT pathway.³¹

In contrast, glucocorticoids possess antiinflammatory effects *in vitro* on almost all immune cells and inflammatory bystander cells studied. This is particularly true if concentrations of cortisol or corticosterone are equal to or above 10^{-7} mol cortisol per liter and if, *in vivo*, this elevation lasts for a longer period of time (days to weeks). In contrast, if, *in vivo*, glucocorticoids rise for only a short period of time (hours), they might exert overall immunostimulatory effects by inducing redistribution and migration of immune cells.^{32,33}

Glucocorticoids and progesterone shift the T-cell immune response to a helper T cell type 2 (Th2) immune reaction.³⁴ This phenomenon is most probably an important factor during pregnancy to save the semiallogeneic embryo from the maternal immune system.³⁵ In addition, this cytokine shift is also an important factor for pregnancy-related amelioration of diseases such as RA and multiple sclerosis, but it can be a stimulating factor in SLE in the second trimester.

Finally, adrenal androgens were found to have several antiinflammatory effects by inhibiting cytokines such as IL-2, IL-6, TNF, interferon- γ , and others.³⁶ These antiinflammatory effects are attributed to the biologically active DHEA but not its biologically inactive precursor DHEA sulfate (DHEAS). In the circulation, DHEAS is the pool for DHEA, which is converted from DHEAS in peripheral cells.

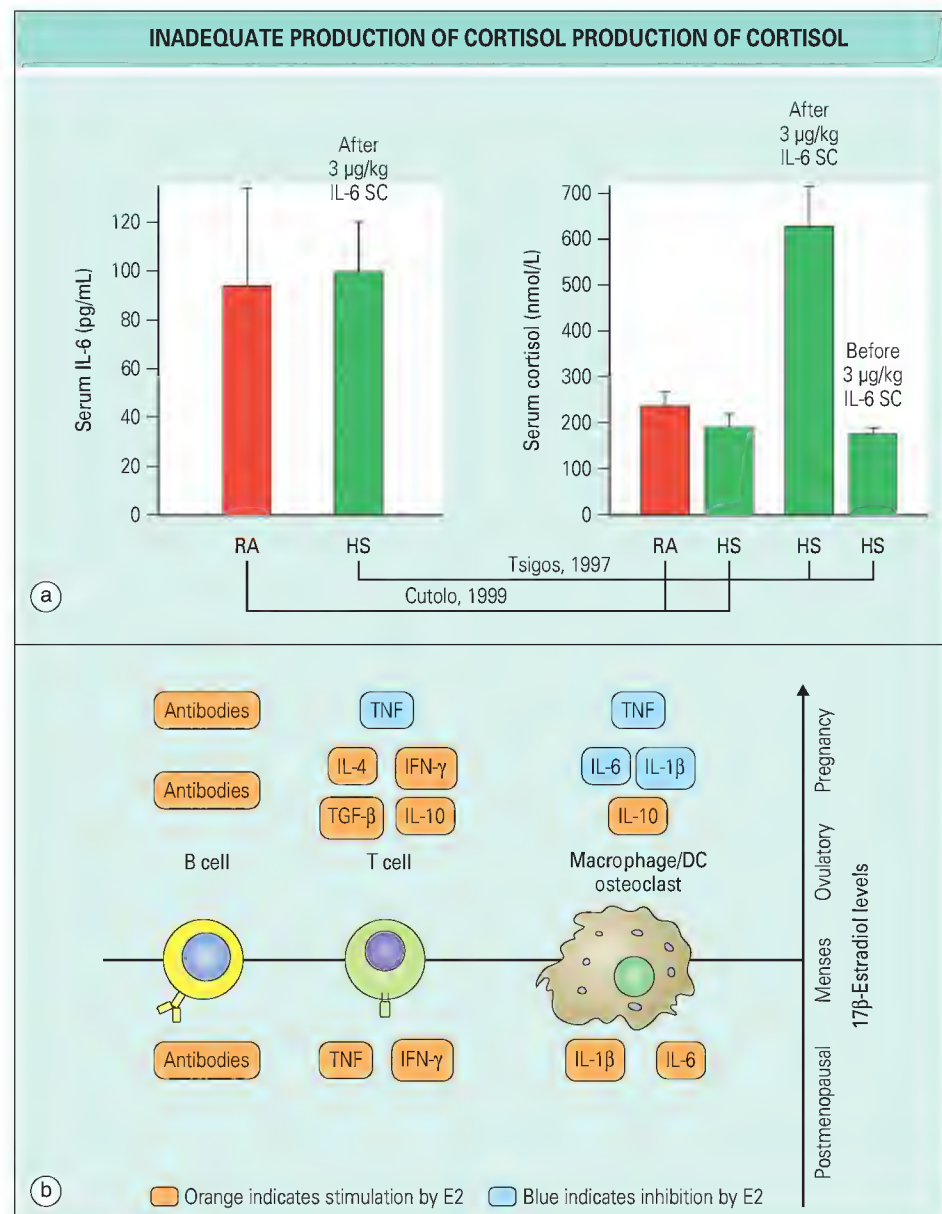
It was thought that biologically active DHEA has effects opposite to those of cortisol. This DHEA effect prompted several therapeutic studies in patients with SLE (characterized by low serum DHEA levels), which

demonstrated a mild beneficial effect in this disease.^{37,38} A similar positive role of DHEA was not demonstrated in RA, which most probably depends on conversion of DHEA to proinflammatory 7 β -hydroxy-DHEA and other proinflammatory pathways³⁹ (see Fig. 25.2, yellow box). The importance of all these hormones in influencing T regulatory cells or T effector cells is still a matter for further study.

Hypothalamic-pituitary-adrenal axis hormones and the pathophysiology of chronic inflammatory diseases

The lack of HPA axis hormones worsens inflammatory diseases, both in animal models and in patients.^{40,41} Every acute inflammatory event—for example, simulated by injection of IL-6⁴²—increases circulating levels of HPA axis hormones, but in patients with chronic inflammatory diseases, hormone levels are not increased although IL-6 levels are continuously elevated⁴³ (Fig. 25.3a). Importantly, the function of the HPA axis is not completely normal in patients with chronic inflammatory diseases, and levels of HPA axis hormones are inadequately low in relation to circulating and stimulating cytokines.^{44,45} Habituation phenomena accompanied by cytokine-induced blockade of hormone synthesis lead to their inadequate levels in chronic inflammatory diseases.⁴⁶ In addition, concentrations of adrenal androgens are mostly decreased due to reorganization of adrenal steroidogenesis, which leads to a preponderance of cortisol relative to other adrenal hormones. This is most probably due to inhibition of adrenal 17,20-lyase activity of P450c17 (see enzyme 6b in Fig. 25.2). Importantly, the preponderance of cortisol relative to adrenal androgens is a feature of nearly all chronic inflammatory diseases.¹⁰ This preponderance was recently explained by a new theory as a reallocation program of energy-rich fuels

Fig. 25.3 Inadequately low levels of cortisol in relation to cytokine levels and influence of 17 β -estradiol on target immune cells. (a) Inadequate secretion of cortisol in relation to inflammation. The right panel shows that subcutaneous (SC) injection of interleukin-6 (IL-6) leads to a large increase in serum cortisol in healthy subjects (HS).⁴² The left panel shows that injection of IL-6 leads to very similar serum levels of IL-6 in healthy individuals compared with patients with rheumatoid arthritis (RA).⁴³ However, serum cortisol levels are not increased in patients with RA compared with healthy individuals as demonstrated in the right panel.⁴³ (b) Influence of estrogens on important proinflammatory and antiinflammatory pathways in different cell types. The concentration of 17 β -estradiol is given on the y-axis. Depending on the concentration of 17 β -estradiol (E2), factors in orange boxes are stimulated and factors in blue boxes are inhibited by estrogens. DC, dendritic cell; IFN- γ , interferon- γ ; TGF- β , transforming growth factor- β ; TNF, tumor necrosis factor.



(amino acids) from muscle to the activated immune system, which is supported by a loss of androgens.¹⁰

Not only is HPA axis organ function altered, but conversion and degradation of secreted hormones in peripheral tissue are altered. In cells of inflamed tissue, activation of the biologically inactive DHEAS to the biologically active DHEA is inhibited by TNF⁴⁷ (see Fig. 25.2, yellow box), and TNF activates the aromatase complex, which leads to the formation from androgens of proinflammatory estrogens, such as 16-hydroxylated estrogens (see Fig. 25.2, yellow box).⁴⁸ All these peripheral phenomena lead to a more proinflammatory environment in inflamed tissue and might explain otherwise unexpected immune/inflammatory reactions and therapeutic results, even in the presence of normal serum hormonal concentrations.

Hypothalamic-pituitary-gonadal axis

Influence of hypothalamic-pituitary-gonadal axis hormones on the development of the immune system (animal models)

In animal studies, 17 β -estradiol at high concentrations leads to a suppression of B-lymphocyte lineage precursors. In addition, IL-7-responsive B-lineage precursors are greatly expanded in genetically hypogonadal female mice. Estrogen replacement in these mice resulted in a dose-dependent reduction in B-cell precursors.⁴ At pregnancy levels, 17 β -estradiol induced a downregulation of B-lymphopoietic cells in bone marrow of young ovariectomized mice mediated through both estrogen receptors.⁴

In addition to their effects on B cells, estrogens have a strong influence on the development and maintenance of T cells. In estrogen receptor-intact animals, 17 β -estradiol (pregnancy levels) induced profound thymus involution.⁴ Treatment with 17 β -estradiol (pregnancy levels) for 4 weeks decreased thymus cellularity and the percentage of CD4+ cells in the spleen, which was not observed in double estrogen receptor-deficient mice.⁴ Thus 17 β -estradiol inhibits B-cell and T-cell precursor development. Whether the 17 β -estradiol-induced changes are positive or negative in human chronic inflammation remains to be established because autoaggressive but also autotolerant regulatory B and T cells might be eliminated.

Finally, 17 β -estradiol has been shown to promote the differentiation of dendritic cells from bone marrow precursors *in vitro*, and this effect is mediated via estrogen receptor- α .⁴⁹ Raloxifene and tamoxifen, two estrogen antagonists, inhibited the differentiation of estrogen-dependent dendritic cells from bone marrow precursors *ex vivo* in competition experiments with physiologic levels of 17 β -estradiol.⁵⁰

In conclusion, these experiments in animals and with cells of rodents demonstrate that 17 β -estradiol has inhibitory effects on the development of B cells and T cells. Similar inhibitory effects were demonstrated for testosterone with regard to the thymus.²¹ It is currently unclear how these sex hormones influence development of immune cell precursors in patients with autoimmune diseases. This can be an important line of research, because sex hormones might bias the immune response toward an aggressive autoimmune response already many years before outbreak of the disease.⁵¹

Influence of androgens and estrogens on the function of the immune system (studies in humans)

In general, in physiologic concentrations androgens suppress the immune responses.⁵² Fig. 25.3b summarizes the most important effects of high and low concentrations of estrogens on different types of cells involved in chronic inflammation.⁴ At pregnancy levels (increase), 17 β -estradiol inhibits important proinflammatory pathways such as TNF, IL-1 β , IL-6, MCP-1, inducible nitric oxide synthase expression, production of matrix metalloproteinases (MMPs), and activity of natural killer cells, whereas 17 β -estradiol at the same concentration stimulates antiinflammatory pathways such as IL-4, IL-10, transforming growth factor- β (TGF- β), tissue inhibitors of MMP (TIMPs), and osteoprotegerin (see Fig. 25.3b). At lower concentrations, 17 β -estradiol stimulates TNF, IFN- γ , IL-1 β , and the activity of natural killer cells. This dichotomy of 17 β -estradiol at high versus low concentrations is not observed for B cells, because antibody production is still stimulated throughout the full concentration range (see Fig. 25.3b). Consequences of these 17 β -estradiol effects for chronic inflammation are summarized in the next section.

Hypothalamic-pituitary-gonadal axis hormones and the pathophysiology of chronic inflammatory diseases

B cells, T cells, and antigen-presenting cells (macrophages/dendritic cells and B cells) are decisive for the initiation of autoimmune diseases. One might separate two clinically important phases of an autoimmune disease: (1) an asymptomatic phase, and (2) a symptomatic phase (after disease outbreak). Disease outbreak means involvement of a target organ and target

tissue leading to the classical clinical signs of visible and functionally relevant inflammation. Recent important work in the field of RA has shown that autoimmune phenomena are already present and initiated more than 10 years before disease outbreak.^{53,54}

In the asymptomatic phase, T cells, B cells, and antigen-presenting cells play an important hidden role because clonal expansion of autoreactive T cells and B cells happens without overt disease symptoms. Because the influence of estrogens on these players is different from that on other cell types, estrogens can have quite opposite roles depending on the involved cells. If B cells play a central role by antigen presentation, autoantibody production, and/or bystander cytokine production, they will speed up the outbreak of the disease in the early reproductive years. Because men never experience these high estrogen or progesterone levels and counteract these hormones by testosterone, the apparent gender dimorphism of autoimmune diseases during the reproductive period of women can be explained. However, the differences between men and women do not exist in peripheral inflammatory tissues (e.g., synovial tissue in RA) because estrogens are produced locally by an activated aromatase complex in both sexes (see earlier).

If tissue-destructive T cells and B cells play an equally important role in initiation of a chronic inflammatory disease, it is hypothesized that the onset of disease in a woman will be delayed because 17 β -estradiol may inhibit T-cell autoimmunity but always stimulates B-cell autoimmunity. In such a situation, the onset of the disease might be shifted to the late reproductive phase or postmenopausal period. If tissue-destructive T cells play the most important role (no role for B cells), the onset of the disease should be expected in the postmenopausal phase when serum concentrations of 17 β -estradiol but also progesterone decline.⁴ Thus ovariectomy in animal models or menopause in women is stimulatory for autoimmune arthritis and other autoimmune diseases of late onset and T-cell dominance.

The location of tissue inflammation in an autoimmune disease is defined by a tissue autochthonous autoantigen (or several autoantigens). Once a disease has entered the highly inflammatory symptomatic phase, many other cell types become involved depending on the major location of the autoimmune disease (in the brain, in the joint, in the kidney, in the liver, etc.). For example, in the joint, macrophages, fibroblasts, osteoclasts, osteoblasts, adipocytes, endothelial cells, and many more gradually become involved in the inflammatory process. Depending on the predominant cell types involved, 17 β -estradiol and also progesterone might have quite different effects on these bystander inflammatory activities of participating cells.⁴

All players (including B cells, T cells, and antigen-presenting cells) might have very different capacities to take up and to metabolize estrogens.⁴⁸ Metabolism of estrogens depends on transport into cells, desulfation of sulfated estrogens, sulfatation of nonsulfated estrogens, androgen aromatization, and estrogen conversion to downstream hydroxylated or methylated estrogens (see Fig. 25.2, yellow box). In addition, upregulation or downregulation of estrogen receptors α and β (in cells or on the cell surface), of coactivators, and of corepressors might well depend on involved cells and microenvironmental conditions such as accompanying hypoxia and the surrounding cytokine cocktail. In addition, it has been nicely demonstrated, but in one animal model, that 17 β -estradiol accelerates immune complex glomerulonephritis but may ameliorate focal sialadenitis, renal vasculitis, and periarticular inflammation.⁵⁵ This might suggest that quite different pathologic conditions might even be present in the same human individual so that estrogens (or their peripheral metabolites) may have beneficial effects on one aspect of the disease but a different influence on other mechanisms. This depends most probably on involved cell types, on concentrations, and notably on peripheral estrogen metabolism rate.^{4,13}

Studies in the last decade also demonstrated that the small change in estrogen or progesterone levels during therapy with oral contraceptives or hormone replacement therapy has variable power to increase the risk or severity of a B cell-related autoimmune disease (with more clear effects on overt disease).⁴ One understands that at postmenopausal levels estrogens can even stimulate several immune mechanisms due to their bimodal role (see Fig. 25.3b).

In addition, there are important similarities between chronic inflammatory diseases and inflammatory reactions in certain types of cancer, such as breast cancer and prostate cancer. In inflammatory tissue of patients with RA, steroid hormone precursors are converted mainly into 16-hydroxylated estrogens, which are proliferative and covalently bound to estrogen receptor- α .⁵⁶ In contrast, generation of antiproliferative 2-hydroxylated estrogens is blocked. Conversion can happen in synovial macrophages and fibroblasts (see Fig. 25.2). Similarly, macrophages in breast cancer tissue can convert precursor hormones to 16-hydroxylated estrogens with a similar increase of estrogenic effects.⁵⁷ Like 17 β -estradiol, the converted

16-hydroxylated estrogens can stimulate important growth factors such as TGF- β , basic fibroblast growth factor, keratinocyte growth factor, and bone morphogenetic proteins.⁴ This is in agreement with the important growth-supporting role of 17 β -estradiol during pregnancy. In both chronic inflammatory disease and cancer, in which overshooting growth responses play a decisive pathogenic role, the 17 β -estradiol-stimulated increase in these growth factors is most probably harmful.

VITAMIN D IN CHRONIC INFLAMMATORY AUTOIMMUNE DISEASES

Vitamin D is a steroid hormone because it is generated from the steroid backbone of cholesterol, which is converted to the active D hormone (see Fig. 25.2). Epidemiologic evidence clearly indicates a significant association between low levels of serum vitamin D (25-hydroxyvitamin D₃ [25(OH)D₃]) and increased incidence of autoimmune diseases (role as a risk factor), including RA, SLE, type 1 diabetes mellitus, and multiple sclerosis.⁵⁸ In addition, it has also been demonstrated that lower levels of vitamin D are associated with higher disease activity in RA. Likewise, vitamin D supplementation is associated with a reduced risk of RA, type 1 diabetes mellitus, and multiple sclerosis.⁵⁸

The presence of vitamin D receptors in cells of the immune system and the fact that several of these cells produce the active vitamin metabolite (1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]) (intracrinology) justify the view that vitamin D could have immunoregulatory effects on dendritic cells, Th1 and Th17 cells, as well as B cells.⁵⁸ With respect to B lymphocytes, it was shown that 1,25(OH)₂D₃ does exert direct effects on B-lymphocyte homeostasis.⁵⁹ In addition to confirming direct vitamin D receptor-mediated effects on B-lymphocyte proliferation and immunoglobulin production, this study also highlighted the ability of 1,25(OH)₂D₃ to inhibit the differentiation of B lymphocytes into plasma cells and class-switched memory B cells, which suggests a potential role for vitamin D in B-lymphocyte-related disorders such as SLE (characterized by severe deficiency).⁵⁹

Vitamin D, like cortisol and sex hormones, regulates both innate and adaptive immunity, mainly potentiating the innate immune response and suppressing the adaptive immunity.⁶⁰ Potentiation of the innate immune response at surfaces exposed to the environment establishes an excellent first-line defense against pathogens. Thus vitamin D would be expected to enhance resistance to acute infections in the skin, lungs, gastrointestinal tract, bladder, and other epithelial surfaces. In fact, vitamin D is synthesized at an increased rate inside monocytes/macrophages in the presence of bacterial and viral infections, and stimulates the synthesis of antimicrobial peptides such as cathelicidins, which contribute to bacterial killing and initial defense against pathogens like *Mycobacterium tuberculosis*.⁶¹ Those mechanisms might underlie the beneficial effects exerted by graded sun exposure, which was used to treat chronic tuberculosis in sanatoriums at the beginning of the 20th century. Interestingly, a systematic review of data for the period between 1971 and 2006 for 11 countries and regions around the world confirmed a seasonal pattern of tuberculosis, with the most prominent peak during winter and spring.⁶¹ If infections represent a risk factor for development of RA, seasonality of infections and vitamin D serum levels might play an important role.

Furthermore, at normal serum concentrations, vitamin D downregulates Th1-dependent immune responses, and its intake or increased synthesis during UV light exposure has been found to be inversely associated with the risk of RA. Interestingly, significantly lower serum levels of 1,25(OH)₂D₃ were observed in patients with RA from the north of Europe (less UV exposure higher incidence of RA) than in those from the south, linked to a different duration of sunshine.⁶² These effects of vitamin D indicate an important role for this hormone in autoimmune diseases.

CIRCADIAN RHYTHMS AND THE IMMUNE SYSTEM

The term *circadian rhythm* refers to the 24-hour cycles in the physiologic processes of living organisms. In RA it is observed that symptoms are worse in the very early morning hours, and a similar pattern has been described for asthma, gout flares, angina pectoris, and others. It is remarkable that the improvement of morning stiffness in RA induced by prednisolone after 6 months is similar in magnitude to the improvement of morning stiffness during a single day (from morning to evening). Over both time periods—the term of a clinical trial and the course of 1 day—an improvement of 40% to 50% can occur. Imagine, therefore, a situation in which an investigator in a clinical trial did not pay attention to the specific time of examination and

recorded improvement that reflected the diurnal variation as much as a sustained treatment effect. Circadian rhythms are a basis for variations in the immune/inflammatory response.

Both IL-6 (Fig. 25.4a) and TNF display a circadian rhythm, with maximum levels in the very early morning hours.⁶³ In healthy subjects, the peak value of IL-6 is found at about 6 AM. In patients with RA, the peak value of IL-6 appears at 7 AM. In healthy subjects, IL-6 serum levels are approximately 2 to 4 pg/mL, whereas in RA patients these levels are 20 to 40 pg/mL. Thus the amplitude of the curve of cytokine production is higher and the curve is broadened in RA compared with control subjects.⁶⁴ In healthy subjects, serum levels of IL-6 usually decrease by 9 AM, whereas in RA patients, these levels can remain elevated until 11 AM. The increased amplitude and the broadened curve in the morning hours are important for the morning symptoms. In view of these observations the key question is what is driving the circadian oscillation of serum levels of cytokines.

The cycle of the HPA axis has a maximum in the early morning hours at 8 AM and a nadir at midnight (see Fig. 25.4a). Detailed analyses of the circadian curves of cytokines and cortisol have revealed a lag time between the cortisol rise compared with the increase in cytokine of approximately 60 to 120 min.⁶⁵ From this study and a recent analysis of the results of several independent investigations,⁶³ it appears that morning cytokine levels can drive the increase in cortisol. The cortisol rhythm in healthy subjects does not differ from that in patients with RA when disease activity is relatively low to moderate. This similarity holds for the period, the amplitude, and the time of the minimum and peak of the cycle (see Fig. 25.4a).

Although levels of cytokine 10 times higher than normal should drive a stronger cortisol response (see Fig. 25.4a), it is notable that the serum levels of cortisol are similar in healthy control subjects and patients with RA. This phenomenon was discussed earlier and was called *inadequate secretion of cortisol in relation to inflammation* (relative insufficiency). The reasons for this inadequacy relate in part to inhibition (or exhaustion) of the HPA axis by chronically elevated levels of cytokines. In other words, secreted cortisol is unable to dampen the proinflammatory response. For this reason, cytokine levels stay high.

At present, it is thought that the cortisol nadir at midnight and the parallel increase of the immunostimulatory hormones melatonin, prolactin, and growth hormone drive the increase of nightly TNF and IL-6.⁶⁴ Subsequently, these two cytokines drive cortisol, and the later cortisol increase finally dampens the cytokine surge, and so on. Because the circadian rhythm is generated in higher brain centers of the endocrine and nervous systems (in the hypothalamus), the circadian rhythms of cytokines mirrors the activity of neuroendocrine centers in the brain. This provides a strong indication that neuroendocrine pathways influence disease-related pathophysiology and might suggest new options for therapeutic interventions.

A recent theory explained nighttime activation of the immune system as an evolutionarily selected circadian program that allocates energy-rich fuels to brain and muscle during the day (daytime consumers) and to the immune system and growth-related pathways during the night (nighttime consumers) (see Fig. 25.4b).¹⁰ This circadian program is tightly coupled to the function and action of the neuroendocrine system (see Fig. 25.4b).

The theory further explains that continuous use of energy reallocation programs to support the activated immune system leads to disease sequelae such as sickness behavior, anorexia, malnutrition, muscle wasting and cachexia, cachectic obesity, insulin resistance with hyperinsulinemia, dyslipidemia, increase of adipose tissue near inflamed tissue, alterations of steroid hormone axes, elevated sympathetic tone and local sympathetic nerve fiber loss, decreased parasympathetic tone, hypertension and volume overload, inflammation-related anemia, and osteopenia.^{10,11}

Translational studies: circadian or circannual therapies

One would think that a therapeutic increase in circulating glucocorticoids should alleviate symptoms in patients with RA. Glucocorticoids are usually given after the patient awakes in the morning at a time when gelling and stiffness are already at a maximum, but this is not the optimal moment during the day. Recent data from a double-blind, placebo-controlled, randomized study involving hundreds of patients with RA demonstrated a more marked and significant effect on morning stiffness and serum IL-6 level when glucocorticoids are given at 2 AM in the night.⁶⁶ The question is why immunosuppressive treatment with glucocorticoids can inhibit proinflammatory sequelae better when given at 2 AM.

These observations are very important in understanding antiinflammatory counterregulation of immune responses. It has been demonstrated that glucocorticoids induce the transcription of the inhibitor of κ B (I κ B α) gene, which results in an increased rate of I κ B α protein synthesis and inhibition

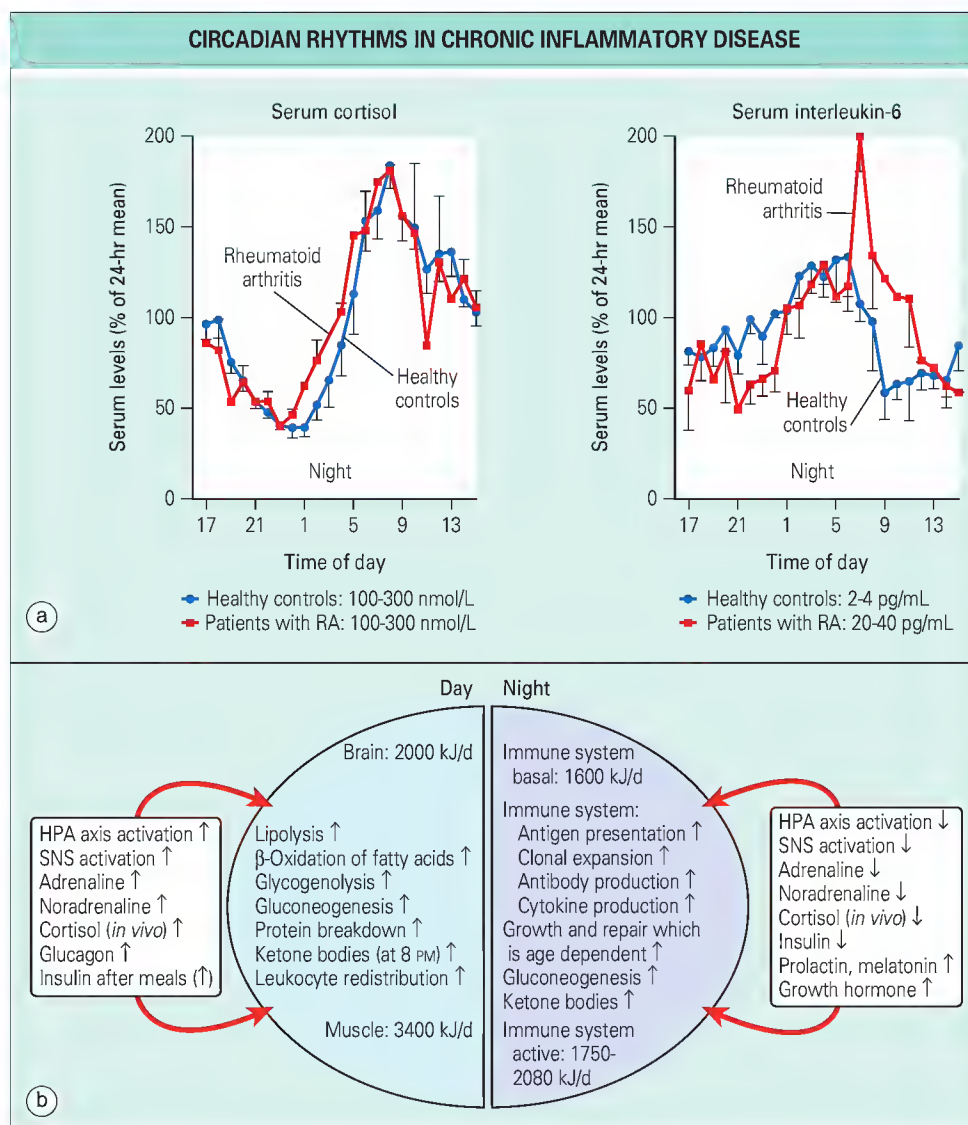


Fig. 25.4 (a) Circadian rhythm of cortisol and interleukin-6 (IL-6) in healthy subjects and patients with rheumatoid arthritis (RA). The data are given in percent of the 24-hour mean. Despite the markedly increased serum levels of IL-6 in RA compared with healthy subjects, the circadian rhythm of cortisol is similar in both groups (in amplitude and period). This phenomenon is termed *inadequate secretion of cortisol in relation to inflammation*. (b) Allocation of energy-rich fuels follows the circadian rhythm. During the day, fuels are provided to muscles and brain (daytime consumers), whereas during the night energetic substrates are directed toward an activated immune system and growth-related pathways (nighttime consumers). Nightly activation of the immune system stimulates immune/inflammatory responses leading to more disease-related problems in the early morning. Neuroendocrine pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) control daytime and nighttime energy allocation via distinct regulators as indicated by the bold red arrows.

of proinflammatory nuclear factor- κ B (NF- κ B) effects. Other studies have shown that glucocorticoids can interfere with the transcriptional activation potential of DNA-bound NF- κ B complexes leading to antiinflammatory effects. These effects appear very early in the turning-on phase of a proinflammatory response (early stimulation of immune cells). The turning-on phase of a proinflammatory reaction is much more vulnerable to immunosuppressants than the turning-off phase. Therefore the regulation of an important proinflammatory factor such as a TNF increase must occur very early because otherwise an overwhelming secretion of this harmful cytokine would occur.

In view of the circadian rhythms and the impact of the timing of immunosuppressive administration on efficacy, there is great interest in exploring timed-release forms of cytokine neutralizers (based on small molecules) or cronobiologic administration of antiproliferative drugs such as methotrexate as a therapeutic modality in RA.^{67,68} Reformulation of old drugs like glucocorticoids (nocturnal hormone) in new circadian drug delivery forms has recently optimized the clinical efficacy and improved immunosuppressant activities in RA.⁶⁶

In a 12-week multicenter, randomized, double-blind trial, 288 patients with active RA were randomly assigned to receive either a modified-release prednisone tablet that released prednisone at 2 AM ($n = 144$) (following the night circadian synthesis of the endogenous glucocorticoids) or an immediate-release prednisone tablet ($n = 144$). The modified-release tablet was taken at bedtime (10 PM) and prednisone was released with a delay of 4 hours after ingestion. This treatment (night available prednisone) was compared with morning administration of immediate-release prednisone as an active comparator and showed significant superiority to the immediate-release formulation.^{66,69}

On the other hand, vitamin D levels show a circannual rhythm with troughs in winter and peaks in summer and demonstrate a significant negative association with clinical RA severity as assessed using the 28-joint

Disease Activity Score.⁶² In addition, the onset of arthritis symptoms during the winter or spring has been associated with greater radiographic disease progression at 6 and 12 months.⁷⁰ Thus seasonality of first symptoms seems to be an independent predictor of radiographic outcome and disease severity, which might be related to the seasonal lack of the immunosuppressive action of vitamin D.⁷¹

In healthy individuals, downregulation of Toll-like receptor 4-mediated production of IL-1 β , IL-6, TNF, IFN- γ , and IL-10 by peripheral blood mononuclear cells was observed only in summer and not in winter (vitamin D effect?).⁷² Because high-dose oral therapy with the vitamin D₃ analogue alfacalcidol exerted a positive effect on disease activity in 89% of 19 patients with RA,⁷³ one can speculate that circannual administration of vitamin D in wintertime can improve the disease status in RA patients. Recent data suggest that calcitriol [1,25(OH)₂D₃] may downregulate proinflammatory cytokine production in activated macrophages in humans by significantly decreasing aromatase activity, especially in an estrogenic milieu such as RA synovial tissue.^{48,74}

CONCLUSION

Clinical observations indicate a strong influence of the neuroendocrine system on immune function in chronic inflammatory and immune-mediated diseases. In addition, these neuroendocrine pathways influence the development of the immune system by interfering with the thymus in that almost all hormones of the HPA and HPG axes support the gradual involution of the thymus. Similarly, hormones of these two axes also hinder B-cell lymphopoiesis, which was demonstrated for 17 β -estradiol in particular. On the other hand, CRH, ACTH, and 17 β -estradiol exert some immunostimulating effects, whereas glucocorticoids and androgens generally suppress immune responses.

The action of the different hormones is influenced by (1) the immune stimulus (foreign antigens or autoantigens) and subsequent antigen-specific immune responses; (2) the cell types involved during different phases of the disease (e.g., T cells, B cells); (3) the target organ with its specific microenvironment; (4) the timing of hormone increase in relation to the disease course (and the reproductive status of a woman); (5) the serum and local concentration of hormones; (6) the variability in expression of hormone receptors depending on the microenvironment and the cell type; and (7) intracellular and extracellular peripheral metabolism of hormones leading to important biologically active metabolites with quite different antiinflammatory and proinflammatory function (common pathway in men and women).

The circadian rhythm of disease-related symptoms with a peak in the early morning hours confirms that the neuroendocrine system has a strong

influence on these chronic immune/inflammatory diseases. The influence is transferred by the circadian undulation of the activity of hormonal and neuronal pathways linking the brain to immune cell activation.

New therapeutic strategies are based on circadian rhythms and generally on a more detailed understanding of the complex neuroendocrine immune system. In addition, circannual therapy with vitamin D might be a new treatment strategy. A new theory explains pathophysiology and disease sequelae as an evolutionarily selected program to allocate energy-rich substrates to the activated immune system. The continuous use of this neuroendocrine program leads to unwanted disease sequelae that have been recognized in recent years. These pathophysiologic considerations can lead to new therapeutic strategies that interfere with cellular energy metabolism, possibly in a circadian or circannual way.

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26

Interpreting the medical literature for the rheumatologist: study design and levels of evidence

■ ROBERT B.M. LANDEWÉ

- Randomized controlled trials are not necessarily the best solution for every clinical question; many relevant clinical questions are better addressed in well-designed and appropriately analyzed observational studies.
- Statistical significance is not a goal *per se*. Statistical testing ideally is only a minor part of the analysis of clinical research, and the merits of a “significant *P* value” are all too often overrated.
- It is very important that trial designers make a clear distinction between trials with a superiority design and trials with a noninferiority design. It is even more important that readers of the trial reports are aware of the differences between the two, and interpret them accordingly.
- Only appropriate communication about the internal and external validity of trials will ultimately result in appropriate implementation of trial data and improvement of patient care.

INTRODUCTION

In medicine there is a strong belief that randomized controlled trials (RCTs) are superior to observational studies. Randomization does provide indisputable strengths, but data show that RCTs and observational studies often arrive at the same conclusion. Furthermore, there are theoretic and practical problems that preclude the acceptance of RCTs as the only source of useful information: (1) RCTs often address research questions that do not serve the main interest of clinicians, (2) many research questions cannot be solved by RCTs, and (3) an RCT has methodologic requirements that should be met to optimally favor its benefits. Large observational studies are frequently considered second rate; however, observational cohort studies are sometimes the only source of data available and can often supply useful information to complement RCTs.

Although the fundamental theory underlying an RCT—and the primary analysis of an RCT—is relatively simple, practical trial conduct faces many potential pitfalls that may eventually result in violation of prognostic similarity and introduce bias. Examples are inadvertent unblinding of a study drug (e.g., if the study treatment is very effective but the placebo is not), unbalanced nonrandom discontinuation (e.g., if the study drug is responsible for adverse drug reactions that cause selective dropout), or simply poor trial conduct or overt misconduct (e.g., if patients do not show up for visits, assessors do not measure outcomes with scrutiny, or at worst, nonexistent or virtual patients with faked response patterns are reported). It is the investigators' responsibility to optimize trial conduct and data collection, to perform a correct analysis of the data, and to transparently describe the process and results of the trial in the medical literature—this is “good clinical practice.” The consumers of these reports, peer reviewers, scientists, rheumatologists, workers in the pharmaceutical industry, regulatory authorities, and others have their own responsibility. They have the obligation to interpret the data carefully by weighing their integrity and importance, unprejudiced with respect to the investigators' interpretations, and to translate trial data into useful, clinically applicable information. This process has gained attention as “critical appraisal,” and the literature provides superb guidance on how to critically appraise the report of an RCT.^{1,2} Medical journals have agreed on guidelines with respect to trial report (e.g., CONSORT guidelines³), thus tremendously improving critical appraisal. Good clinical practice and critical appraisal are applicable to observational

research without prejudice, although the focus may be slightly different. Recently, for example, the checklist for STrengthening in Reporting of OBservational Studies in Epidemiology (STROBE) was published in an attempt to improve the quality of reports in this field.^{4,5}

In this chapter the focus is primarily on methodologic elements that in my opinion are the most important in critically appraising the results of clinical trials and observational studies with respect to application to clinical practice. Because some of these elements specifically pertain to RCTs, others primarily refer to observational studies, and there is also a generic category pertaining to both types of research, three categories of critical appraisal will be discussed: one primarily referring to RCTs, one referring to observational studies, and one referring to both.

LEVELS OF EVIDENCE

During the past decade the accessibility of medical literature has tremendously improved. It is safe to say that the majority of practicing rheumatologists at present can almost immediately get access to (abstracts of) just about every medical study that has been reported in the literature. In addition, meta-analysis and systematic literature review, in which the available literature is weighed and judged in a systematic manner and the data are pooled, have become an art of science. In an attempt to bring some order to the quality of epidemiologic research and consequently to prioritize types of research with respect to methodologic rigor, several scales have been developed. One of the more comprehensive scales (with most differentiation) is the Oxford Centre for Evidence-Based Medicine scale, which applies levels of evidence to five different study scenarios (therapy, prognosis, diagnosis, differential diagnosis, and economic analysis).⁶ In general, such scales rate systematic reviews and appropriately conducted meta-analyses higher than individual RCTs, followed by observational studies and then case series, with expert opinion at the lowest level. Although level-of-evidence scales can be very helpful in prioritizing (the quality of) studies, a note of caution is needed. Frequently, a study is inappropriately rated. An unplanned subgroup observation in the context of an RCT, for example, should not be rated level 1 because the result is not obtained in an unbiased manner (see later), whereas a methodologically weak RCT also does not deserve a rate of 1. Sometimes, “low-grade evidence” is the only kind of evidence that can be obtained, for instance, if the disease under study is very rare or if an RCT is considered unethical. Those who have been involved in the development of guidelines realize that a lot of what physicians do on an everyday basis is based on “expert opinion” and not substantiated by any study at all.

Instead of relying entirely on levels of evidence, readers of the medical literature rather should rate the studies themselves and try to obtain some insight on what the aim of the study is, how the study has been performed, and what the impact of the results should be with regard to their own patients.

RANDOMIZED CONTROLLED TRIALS OR OBSERVATIONAL STUDIES?

A typical RCT investigates whether a new drug, strategy, or intervention is efficacious and safe in comparison to an equivalent treatment or placebo. The trial involves patient selection and randomization before the treatment begins and, thereafter, a predetermined follow-up time to establish whether the primary endpoint (measure of the treatment effect) has been met. The most characteristic feature—and the major advantage of an RCT—is

randomization. Technically, this process divides patients according to all known and unknown prognostically important factors across treatment groups at baseline and thereby creates a situation of similarity with respect to the probable prognosis. In other words, treatment groups are similar in everything except allocated treatment. Prognostic similarity at baseline is important for attributing an observed effect to a particular treatment rather than to an imbalance in an unrelated, but prognostically important factor.

RCTs also have important drawbacks. They might lack external validity or generalizability. Inclusion criteria and exclusion criteria ensure that the trial population is a particular selection of the entire population with a certain disease. An RCT includes patients who are “prone to change,” who might have a high level of adherence to the protocol to ensure retention, or who have a low probability of adverse reactions from comorbidity, comedication, or both. Consequently, such a trial population comprises highly motivated, often educated individuals who have a high level of disease activity but are otherwise healthy. This scenario does not usually appropriately reflect the normal clinical situation.

Another disadvantage of RCTs is their often relatively short follow-up time. There are several trivial explanations, but probably the most important argument is that true prognostic similarity exists only at baseline and becomes increasingly disparate over time. Take, for example, comedication or other coincident interventions. A short follow-up period is methodologically advantageous (see the later section “Internal Validity and External Validity”) but may in rheumatology reflect only a small proportion of the entire duration that a patient is under observation for a chronic disease in real practice. As a consequence, RCTs often use surrogate endpoints rather than those that truly reflect the clinical outcome of the disease. An appropriate example in this respect is the use of bone mineral density as a surrogate outcome measure for fractures in osteoporosis trials. It depends largely on the study question whether an RCT will provide the most appropriate answer. RCTs do provide a reliable impression of the short-term efficacy and safety of drugs in the selection of patients. They do not, however, provide information about an individual patient’s prognosis, long-term results or relevant outcomes, and data about rare events. It is here that observational studies, with many patients and long follow-up, might prove their value.

CRITICAL APPRAISAL I: ISSUES PERTAINING TO RANDOMIZED CONTROLLED TRIALS

Internal validity and external validity

A trial is a rather artificial construct that usually serves one main purpose: to investigate whether a particular treatment is efficacious. In general, elements of trial design, such as selection of patients, sample size, choice of the comparative intervention, and duration of the trial, are chosen in such a manner that the trial can optimally demonstrate a treatment effect, that is, a difference in efficacy between the new treatment and the control intervention. The methodologic rigor of a trial, which is dependent on these elements of trial design, is referred to as *internal validity*.

Understandably, trials often do not resemble clinical practice. Rheumatoid arthritis (RA) trials, for example, frequently include patients with a high level of disease activity, which may form only a minority in clinical practice. The extent to which clinical trial results can be extrapolated to common clinical practice is referred to as *external validity*. External validity is much more diffuse than internal validity. It depends on how the consumer of the data interprets the results, how these results are presented, how convincingly the investigators have argued their message, and how credible they are in the eyes of the beholder. It depends on whether the reader thinks that the data from the trial are applicable to an individual patient in the reader’s own practice. Undoubtedly, external validity will be judged unsatisfactory if internal validity falls short. The opposite is not necessarily true, however. A trial with high internal validity can easily have insufficient external validity. An increasingly common example in RA is an RCT with 1000 patients who have high disease activity that tests a new treatment against the “currently best available disease-modifying therapy for RA” and finds a small, statistically significant difference in favor of the new treatment that is not very clinically relevant. Such a new treatment will probably be approved by drug registration authorities if it is considered safe because it has proven superiority in a well-conducted trial with high internal validity. Needless to say, this effective treatment with doubtful advantage over existing treatments should not be broadly applied in common clinical practice without further consideration (external validation). Readers of trial reports should weigh the balance between internal and external validity: which prevails when one falls short of the other and which elements are important in translating the trial result into clinical practice.

Efficacy versus effectiveness

It is obligatory to be informed about the underlying aim of the trial, which is not necessarily the same as the primary study objective. Drug registration trials under the auspices of the pharmaceutical industry serve a different purpose than do investigator-initiated trials with treatment strategies. The former are often referred to as explanatory or efficacy trials and are characterized by a high level of internal validity, whereas the latter—pragmatic trials or effectiveness trials—more closely resemble clinical practice, often find their basis in questions emerging from clinical practice, and as a consequence have a higher level of external validity.⁷

The results of explanatory trials are frequently very robust and confirm the efficacy of the drug tested beyond statistical doubt but may fall short in terms of clinical significance. Examples are numerous and include any trial that presents the results of a “new drug” tested against placebo or an active comparator.

Effectiveness trials often have a more understandable trial result that is more easily applicable to individual patients, but the results may be biased, for example, by imperfections in blinding and changes in the type and intensity of treatment during the trial. An interesting type of trial that belongs to this group is the *benchmark trial* in RA. The essential characteristic of a benchmark trial is that treatment (type, intensity, or both) is not kept constant during the course of the trial but is dependent on the clinical response of the individual patient (whether the benchmark is met). Such a trial mimics everyday clinical practice very well but is in conflict with the fundamental theory underlying RCTs, namely, that patient groups in a trial are prognostically similar during the trial. The methodologic robustness of the trial is to some extent jeopardized by increased clinical face validity. Readers should have knowledge of these elements because they are relevant for interpreting the results and deciding about their usefulness for application to individual patients.

Superiority trials and noninferiority trials

Textbooks in clinical trial design teach that the underlying null hypothesis should be carefully formulated during the design phase of the trial. The formulation of the null hypothesis, which in theory is the hypothesis that is challenged by experimentation (the trial), tells immediately whether the basic design of the RCT is aimed at proving superior efficacy of a new treatment (the superiority design) or at proving that a new drug treatment is as effective as a comparator drug, for ethical reasons frequently the current standard of therapy (the noninferiority design). The RCTs that we have seen during the past decade in rheumatology most often have had a superiority design, with the null hypothesis being that the new treatment is as efficacious as placebo or a comparator treatment. The design of the trial and the sample size are dependent on a *minimally important difference*, which is determined in advance by the investigators and serves as the basis for calculations of sample size. In rheumatology, many consecutive RCTs have resulted in a number of treatments that have proven efficacy against placebo or against the standard-of-care therapy.

An affluence of effective treatments such as in RA has its other side of the coin. First, there is increasing sympathy for the ethical argument that progress in the treatment of rheumatic diseases should have its consequences for the standard of care in this disease. The immediate implication with regard to trial design is that conventional RCTs with placebo as therapy in the control group will be considered unethical. The more effective the therapy in the control group, the more difficult it is to surpass the effect in the control group with a new treatment—the classic superiority trial will be increasingly unfeasible.

Second, even though we have an affluence of effective drugs for conditions such as RA, there is a knowledge gap with respect to drug efficacy in mutual comparisons. Using previous argumentation, these pregnant clinical questions cannot be solved with classic trial designs. Therefore, we will probably see an increasing number of noninferiority trials in rheumatology in the near future.⁸ Such trials have the null hypothesis that the new drug is inferior to the effective treatment in the control arm and embark on determination of an appropriate *noninferiority margin*. More than the choice of a minimally important difference in superiority trials, the choice of a noninferiority margin in a noninferiority trial is a highly subjective decision that includes elements of efficacy, safety, and cost and can make or break the interpretability of such a trial. It is crucial that readers know about elements of the null hypothesis, such as choices and considerations related to the design type of the trial (superiority vs. noninferiority) and to levels of minimally important difference and noninferiority margin.

Statistical power

Every RCT should technically be able to reject the null hypothesis if the alternative hypothesis reflects the truth—it should have sufficient statistical power. One could justifiably argue that trials with insufficient power should not have been executed. It is unethical to expose patients to potentially harmful drugs if the trial is not able to demonstrate superiority or noninferiority of that drug; if it fills the medical literature with data that are inconclusive and, consequently, poses a risk for misinterpretation and inappropriate application to patient care; and if it is extremely cost-ineffective to conduct trials that do not meet their goals. So it seems obvious that the reader of a trial report should ascertain whether the statistical power was appropriate. Many do not realize that statistical power is more than sample size alone. Although the latter is of most importance, statistical power is, among other factors, dependent on the outcome measure (the responsiveness and discriminatory capacity) and the expected effect size (the anticipated difference between the new treatment and the control treatment). The wording justifying the sample size of the trial provides, to some extent, resolution of the power considerations. In sample size calculations, patient numbers are calculated for a given primary outcome measure with an assumption for its variability, for given values of *beta* (1 – statistical power), and for a pre-defined effect size. Sometimes the anticipated effect size is based on realistic assumptions stemming from previous studies, but all too often an effect is chosen that has no scientific precedent (“20% between-group difference”). Some investigators want 80% statistical power, others choose 90% power as preference, and all too often the reader is left with the impression that convenience outweighs theoretic arguments about power: “the calculation should fit.” Rather than only describing the sample size calculation *per se* (which is often done inappropriately), the trial report should include argumentation for the chosen assumptions, such as the level of the minimal clinically important difference, the noninferiority margin, the level of *beta*, the historic precedents, and so on, and the reader should try to interpret this cautiously.

Intention-to-treat analysis

Every investigator, every trial designer, and every clinician knows about the dogmatic character of the intention-to-treat (ITT) principle underlying the main analysis of a clinical trial. Although occasionally a paper mentions a surrogate of ITT (e.g., “modified ITT analysis”), the definition of ITT is crystal clear. It means that all patient in the trial are considered to belong to the group that they were originally allocated to by randomization, regardless of what has happened to them during the trial. The justification for this somewhat dogmatic principle is that the ITT analysis is the most conservative analysis because it preserves at least the prognostic similarity that was created at baseline by randomization. All other types of analyses, including “modified ITT,” are second rate because they allow retrograde patient selection at baseline. The typical *completers analysis*, for example, includes only patients who have done well with the allocated study treatment and ignores those who have discontinued treatment and may differ from the completing patients in terms of prognosis (prognostic dissimilarity). In fact, completers of an RCT form a selected group of patients and should be considered an observational cohort rather than a trial group (see later).

ITT is not a certificate for an appropriate trial analysis. The trial report should spell out how patients who do not provide actually measured trial data are handled (see the later section “Missing Data”). It should mention how data generated by patients who discontinued the trial medication but showed up at visits are handled. Last but not least, there is no generic means of data manipulation in this regard. For example, considering every dropout to not have changed (improved) in a clinical trial involving RA patients and ACR20 (American College of Rheumatology 20% improvement criteria) as the primary outcome measure is probably conservative because a proportion of these patients will have had a clinical response. However, considering these dropouts as not having changed in a clinical trial with radiographic progression as the outcome measure is all but conservative because it looks as though the dropouts do not exhibit progression, and a trial arm with a high proportion of premature discontinuations may show spurious benefit.

In summary, ITT together with appropriate handling of data, including appropriate imputation, works conservatively in that it tends to reduce a treatment contrast.

Conservatism, however, is not necessarily a guarantee for a more truthful trial result. In a noninferiority trial, ITT may spuriously lead to a conclusion of noninferiority, whereas in truth, unbalanced withdrawal, poor trial conduct, or unintended cointerventions may be responsible for the absence of a difference between treatment groups. An example may clarify this statement (Table 26.1). Suppose that two analgesic drugs (A and B) are compared

TABLE 26.1
Example of intention-to-treat analysis

	Treatment A (n = 100)	Treatment B (n = 100)
Number of patients who discontinued the trial	15	15
Number of patients who completed the trial	85	85
With clinical response	25	20
Number of patients taking rescue medication	10	30
With clinical response	2	20
Response percentages based on:		
Intention-to-treat analysis	25% (25/100)	20% (20/100)
Completers analysis	29% (25/85)	24% (20/85)
Per-protocol analysis	31% (23/75)	9% (5/55)

with respect to their ability to relieve pain in an RCT and that drug A is in truth more effective than drug B (which of course you do not know in reality). The primary outcome measure is the number of patients with a 40% decrease in pain on a visual analog scale. Suppose also that patients take additional acetaminophen if they experience too much pain (“rescue analgesia”). Expectedly, the proportion of patients taking additional medication is lower in group A (the better treatment) than in group B (10 patients vs. 30 patients). Also expectedly, only 2 of these 10 patients in group A needing additional drug experienced a response (the severe cases), whereas 20 of the 30 patients needing additional drug (the milder cases) in group B experienced a response (attributable to comedication). Table 26.1 shows how different types of analysis (ITT vs. per-protocol design) work with regard to response percentages and treatment effect. Keep in mind that in reality drug A is more efficacious than drug B. The unbalanced use of comedication resulted in (only) 5% more responses in group A than in group B if analyzed by ITT. This is a small difference, probably not compatible with a conclusion of superiority of drug A in a trial with a superiority design but easily compatible with a conclusion of noninferiority of drug B in a trial with a noninferiority design. The picture changes, however, if the analysis is repeated on a per-protocol basis. Now, the treatment effect consists of almost 20% more responders in group A than in group B, probably compatible with the superiority of drug A in a trial with a superiority design and incompatible with the noninferiority of drug B in a trial with a noninferiority design: ITT analysis is conservative with respect to concluding superiority of a drug in a superiority design (even if in reality superiority exists). Per-protocol analysis is conservative with respect to concluding noninferiority in a noninferiority design.

Analysis of noninferiority trials is not yet a closed book, but experts are in favor of simultaneously presenting ITT and per-protocol analyses so that readers can judge for themselves. It is always wise to be careful with interpretation if both analyses differ importantly (such as in this example).

Subgroup analyses

The issue of subgroup analysis in clinical trials is controversial. Proponents of subgroup analysis point to its hypothesis-generating potential. Opponents argue that subgroup analysis is irresponsible data mining that involves looking for statistically significant differences by splitting up the trial population into smaller subgroups. Both parties are right to some extent. Subgroup analysis can sometimes help disentangle incomprehensible trial results and can raise attention about new, previously unacknowledged phenomena. However, inappropriate subgroup analysis can also provide spurious results, either by coincidence (multiple testing effects) or by unintended patient selection mechanisms. An example of the latter is as follows: the investigators of an RCT compare radiographic progression in a subgroup of patients with an early clinical response and a subgroup of patients without an early response and find that progression is significantly lower in the first subgroup. This result, however, may easily be confounded by less severe disease at baseline in the favorable subgroup.

It is relevant to some extent to divide subgroup analysis into preplanned and *post-hoc* subgroup analysis. The former refers to the design phase of the trial and includes analyses in subgroups that are of potential relevance, such as the treatment effect in men and women separately or in patients who are rheumatoid factor positive and negative. Importantly and in contrast to *post-hoc* subgroup analysis, the decision to perform and report such an analysis

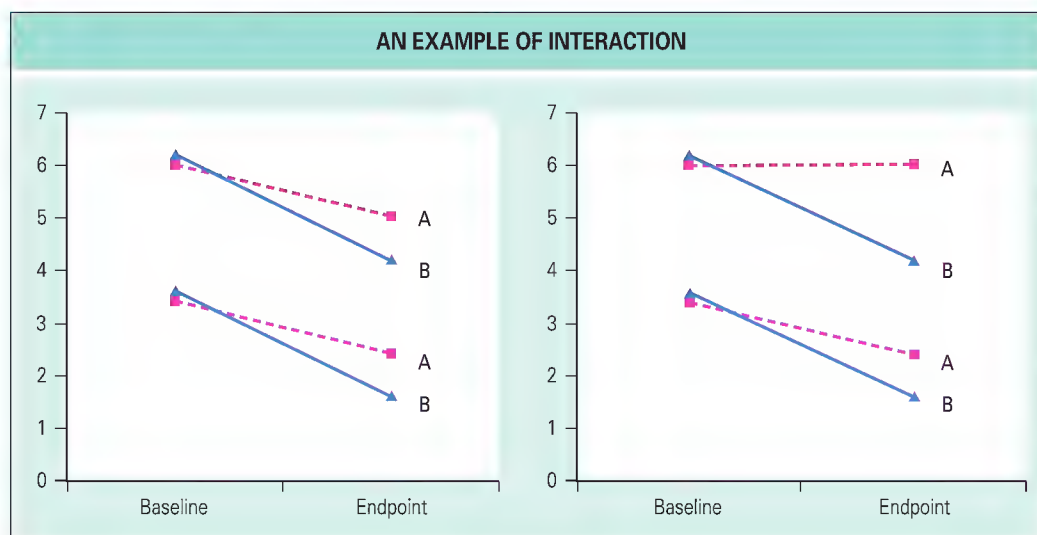


Fig. 26.1 Results of subgroup analysis of an imaginary clinical trial comparing two treatments (dashed line with squares, treatment A; solid line with triangles, treatment B) in a subgroup with high baseline disease activity and a subgroup with low baseline disease activity. See text for clarification.

cannot be driven by knowing the data. In practice, however, it is often difficult to discern whether a preplanned subgroup analysis is truly preplanned. Methodologically, preplanned subgroup analysis is superior to *post-hoc* analysis only if the subgroups of interest were created by *stratified randomization*, which means randomization within the subgroups. It is hoped that stratified randomization creates prognostic similarity within the strata (a trial within a trial) and, that if performed appropriately, provides sufficient statistical power to detect a meaningful difference within the subgroup.

Usually, subgroup analysis is not performed in subgroups created by stratified randomization. If subgroup analysis is performed and the question of interest is whether a particular treatment performs differently in subgroup X than in subgroup Y, it is important to realize that the analytic translation of this question refers to testing statistical interaction.

Figure 26.1 shows an example of such an interaction. In the first panel, treatment A is less effective than treatment B, both in the subgroup of patients with high disease activity and in the subgroup of patients with low disease activity. The treatment effect is similar in both subgroups: no interaction.

In the second panel, however, the treatment effect is dependent on the subgroup of disease activity. Although treatment A seems to be effective in patients with low disease activity though less effective than treatment B, it seems to be completely ineffective in patients with high disease activity even though treatment B is still effective in this subgroup: interaction. Very often, absence of efficacy in the subgroup of patients with high disease activity is found and reported while the other subgroup is ignored, so it is not clear whether a presumed effect is truly attributable to a specific subgroup. This type of subgroup analysis makes sense only if the interaction is demonstrated and confirmed statistically. The issue of how to statistically test interaction is beyond the scope of this chapter.

In summary, subgroup analysis can be informative, but there are certain rules of play, among which the most important is probably interpretation of subgroup analyses cautiously and with reservation.

CRITICAL APPRAISAL II: ISSUES PERTAINING TO OBSERVATIONAL STUDIES

Types of cohorts

Usually, observational research involves the prospective follow-up of a group of individuals (cohort) with regard to a particular outcome. That outcome can be an event (e.g., death, clinical remission) but can also be a disease activity state over time (e.g., time-averaged disease activity state, mean swollen joint count). The types of cohorts that may be encountered in literature can grossly be divided into two: healthy cohorts and clinical cohorts. It is relevant for the reader of an article to realize what type of cohort is being studied.

Healthy cohorts

Healthy cohorts are large cohorts of individuals who are healthy with respect to the outcome of interest (although possibly not in other aspects).

Frequently, study subjects belong to some group of easily traceable individuals (e.g., nurses or physicians). The outcome of interest is usually simple and unequivocal (e.g., mortality), cohorts are large, and follow-up is typically long. The research question of interest might refer to an intervention but also to a potential risk factor or an exposure. Famous examples of healthy-cohort studies are the Baltimore Longitudinal Study of Aging, the Framingham study, the Johns Hopkins Precursors Study, and the Nurses Health Cohort. Very often and understandably, these large cohorts are used to address multiple different study questions and are sometimes therefore referred to as “multipurpose cohorts.”

Clinical cohorts

Clinical cohorts include patients with one or more features in common who are observed for a definite or indefinite time with respect to one or more primary outcomes. There are several types of clinical cohorts. Inception cohorts include and follow all patients in whom a particular disease is diagnosed (disease duration at baseline = 0). Prevalence cohorts include and follow patients with a particular disease at a certain point in time (disease duration at baseline ≥ 0). Patient registries include and follow patients with a particular disease and a particular feature (e.g., patients with RA who start a particular treatment). The distinction between cohorts and registries is subtle and frequently, but not always relates to the time of follow-up. A cohort generally has a previously defined (limited) follow-up (although this follow-up duration is often adjusted over time); a registry has, in principle, an undefined (unlimited) follow-up duration.

A special form of observational prevalence cohort that is frequently seen in rheumatology is the follow-up cohort of an RCT, the purpose of which is often to investigate whether a particular effect seen in an RCT can be maintained over a longer period. Occasionally, trial arms of the original RCT are preserved during the follow-up period, but often they are not. Importantly, results from follow-up studies of RCTs should not be interpreted as though they have the same scientific rigor as the RCT itself. The prognostic similarity created by randomization exists only at baseline and is increasingly lost over time, particularly when trial blinding is unveiled and patients are asked to continue in a follow-up study. The type of longitudinal bias that might arise is discussed in the next section. One specific limitation of such cohorts with regard to generalizability is that patients in the cohort stem from a clinical trial and reflect a population with relatively severe disease, high disease activity at baseline, and so on. One should keep in mind that relatively mild cases are by definition not included in the cohort, which has implications for the interpretability of prognostic variables derived from such cohorts.

Selection bias

Looking at the characteristics of observational studies as outlined earlier, it is obvious that they are a better reflection of common clinical practice than RCTs are, perhaps with the exception of follow-up studies of RCTs. This is also their major advantage. However, cohorts and registries are not unselected populations. A number of selection mechanisms might influence the interpretation of results, and three well-known examples will be discussed.

Left-censorship bias

Left-censorship bias can occur if patients with particular characteristics are inadvertently excluded from the observational cohort because they are simply not available. Suppose that you want to investigate the relationship between cyclooxygenase-2 (COX-2) inhibitors and cardiovascular morbidity in a database of 10,000 patients, including all prevalent patients with osteoarthritis. The study does not include patients who were at such high risk for cardiovascular death that the outcome (death) has already occurred before entry into the study. As a consequence, the observed mortality rate in this cohort might be an underestimate of the truth, especially if COX-2 inhibitors are particularly dangerous in high-risk patients.

In general, left-censorship bias occurs at formation of the cohort or before the cohort is formed, it refers to selection based on differences in disease severity, and it is important only if severity is related to the outcome of interest. By definition, its influence is difficult to quantify and it is impossible to adjust for left-censorship bias in the analysis.

Right-censorship bias

Right-censorship bias is also known as “selective dropout” or “attrition.” Suppose, in an RCT using a COX-2 inhibitor, that patients at higher risk for adverse gastrointestinal events had a higher dropout rate than did those at low risk. This would lead to a spuriously low rate of adverse gastrointestinal events in the patients who remain in any open follow-up. A type of right-censorship bias that most readers will be familiar with is bias by trial completion, or “completers” bias, which is often seen in follow-up studies of RCTs. Only patients who perceive that their treatment is effective or who tolerate it best (or both) remain in the study, which provides favorable study results for that drug.

Right-censorship bias occurs when the composition of the cohort is determined during follow-up, refers to selection based on differences in disease severity or disease activity, and is important if severity or activity is associated with outcome. Right-censorship bias can be quantified and adjusted for in the analysis to some extent.

Confounding by indication

Confounding by indication refers to the question of which patients begin treatment with which drug. Suppose, in a clinical practice setting, that patients at high risk for gastrointestinal events are initially given COX-2 inhibitors whereas those at lower risk are given conventional nonsteroidal antiinflammatory drugs (NSAIDs). A higher event rate is found in patients treated with COX-2 inhibitors than in those treated with NSAIDs; however, the rate in these high-risk patients might still be lower than it would have been if they had been treated with conventional NSAIDs.

Confounding by indication can occur before as well as after composition of the cohort; it refers to situations in which the severity of the disease determines the choice of treatment, and it is important if treatment and disease severity are both related to outcome. There are techniques that quantify the severity of disease, so it is possible to adjust for confounding by indication.

CRITICAL APPRAISAL III: ISSUES PERTAINING TO RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES

Generalizability

As argued earlier, the type of patients included in a study is of pivotal importance with respect to interpretation of the trial results. In efficacy trials, statistical power—the probability that the trial confirms the superiority of a new treatment if such superiority truly exists—is of eminent importance. Discriminatory ability and sensitivity to change in the outcome measures are determinants of statistical power. The outcome measures propagated for clinical trials in RA, such as the ACR⁹ and European League Against Rheumatism (EULAR)¹⁰ response criteria, perform best—and have been validated—in patient groups with high levels of disease activity, which is why most efficacy trials include such patients. In the spectrum of patients with RA, however, these patients do not constitute a majority, which may have implications for interpretation of the trial results. It is possible, if not likely, that many RA patients with less active disease do not necessarily need the “new treatment” that tested most effectively in the efficacy trial but can do very well with the comparator drug.

Another discrepancy between observational studies (clinical practice) and RCTs is the paucity of clinically relevant comorbid conditions in RCTs

as compared with clinical practice because patients with relevant comorbidities are usually excluded. Similar reasoning can be followed regarding compliance or, in general, any reason that increases the probability of premature discontinuation, nonresponse, or both.

It is very important when appraising a report of a clinical trial to realize that the patients in the trial do not necessarily resemble individual patients in clinical practice and that such discrepancies may have consequences for translation of the trial results. Study reports should include all necessary information about disease activity, severity, and prognosis (which they often do), as well as information about relevant comorbidity and comedication (which they often exclude), to allow the reader an appropriate interpretation of generalizability.

Missing data

Ideally, RCTs and observational studies should provide complete data. In practice, however, studies without missing data do not exist: patients miss planned visits for whatever reason and do that more frequently than any investigator would consider acceptable; patients withdraw consent, lose motivation, and drop out; patients report adverse events to the investigator, who decides to discontinue the patient from the study; the investigator and patient are disappointed with regard to a drug effect and decide to stop; or a patient moves and gets lost to follow-up. All these examples create missing data. Although the examples given here are very familiar to every reader (and will be considered inherent to clinical practice), the methodology, statistical analysis, and interpretation of the study results do not very well comply with the problem of missing data. It is crucial to realize the issue of missing data before the study starts and to consider scenarios on how to handle missing data. There is not one acceptable generic solution, but by far the worst solution is to entirely withdraw the patient from the analysis. Usually, discontinuation is a nonrandom process, which means that the reason why patients withdraw is somehow associated with disease severity and therefore with the probability of achieving an outcome or a treatment response (confounding). Ignoring these patients means that in a trial, treatment groups cannot be considered prognostically similar anymore, which is probably the most important violation of trial methodology that can be committed, and that in observational studies, the results may be biased by selection.

Data imputation is the only alternative. Imputation means that an imaginary value is attributed to missing assessments so that the patient with missing data remains in the analysis, but the question obviously is what to impute. *Nonresponder imputation* is a popular and conservative means of data imputation in clinical trials with a response measure (e.g., ACR20) as primary outcome variable. It simply attributes nonresponse to every patient who discontinues participation in the trial, irrespective of the reason for discontinuation. *Last observation carried forward (LOCF)* and *baseline observation carried forward (BOCF)* are popular means of imputing continuous data in which the last value or the baseline value that was actually measured, respectively, are imputed as a substitute for subsequent missing assessments. *Worst-case scenarios* impute the worst group value or the value representing the 95th percentile. Imputation of group means or group medians is also used. *Linear interpolation* can be useful if in-between data points are missed, and *linear extrapolation* is used if the expected time course follows an approximately linear trend. Finally, sophisticated computer algorithms (e.g., bayesian, Markov chain, Monte Carlo multiple imputation procedure) exist that use multiple imputation techniques. Discussion of such techniques is beyond the scope of this chapter.

As argued, there is not a single acceptable means of imputation. Nonresponder imputation usually works well if a predefined response is the outcome of interest, and LOCF seems to be a reasonably conservative approach for imputation of missing continuous data in a setting in which treatment should improve a preexistent state (e.g., disease activity, physical function). Linear extrapolation is frequently used to impute missing radiographic data because the natural course of radiographic damage is compatible with worsening and LOCF would result in spurious inhibition of progression. In theory, trial results (i.e., the treatment contrast) should not be dependent on what means of data imputation is used for missing data. The only transparent way of confirming the robustness of the study result is to perform and show sensitivity analyses for the missing data. This means that different means of imputation are performed and the consequences checked with regard to the outcome of interest.

Data interpretation

Probably the most important means of communicating study results is by graphs. A well-designed graph provides far more information than does a table with comprehensive descriptive data, such as means, standard

deviations, and so on. An appropriate graphic representation of the treatment results can provide a good idea about the relative efficacy of a new treatment in comparison to a control drug at first glance. Every reader of RA clinical trial articles will be familiar with the informative bar graph representation of ACR20/50/70 responses per group. More cumbersome is the graphic representation of radiographic progression. The most frequently used Sharp-van der Heijde progression score usually has a skewed distribution, which means that the data are not normally distributed. Very often, a data set of radiographic progression scores includes a high number of zero scores and a relatively low number of positive scores, with a minority of extreme progression scores at the right side of the spectrum. This feature means that the usual parametric descriptive statistics such as means and standard deviations do not appropriately reflect what has actually happened in the group. Medians and percentiles (25%, 75%) do a better job in that respect, but median progression in modern clinical trials of RA is often zero in the intervention and the control group, whereas progression is statistically significantly different. Recently, probability plots have been proposed to fill in this gap in communication.¹¹ A probability plot shows every individual change in score per trial arm; it is ordered from the lowest through the highest observed value and is plotted against its cumulative probability. By superposing the plots of the trial arms in one graph, it is clear at first glance how the groups have performed with respect to radiographic progression.

Tabulation of data is important for several reasons: (1) to underscore the authors' conclusions and make them transparent to critical appraisal, (2) to make additional inferences for data interpretation (examples are calculations for the *number needed to treat* and *effect sizes* for researchers interested in the performance of outcome measures), and (3) as a source for the meta-analyst. It is critical that the authors of a trial report realize that their data may be used for several scientific purposes, and they should provide sufficient information. It is difficult to give exact guidelines because the prerequisites are different for different outcome measures, but a few examples may help. When the ACR response is used as an outcome measure, it is crucial to report not only proportions but also crude numbers (numerator as well as denominator). When continuous outcome measures (e.g., swollen joint count, disease activity state) are reported, data about status, as well as change, should be provided as means and appropriate standard deviations (rather than standard errors of the mean), in addition to the actual number of patients used in the analysis. When distributions of continuous outcome measures are overtly skewed (e.g., radiographic progression scores), the investigators should present not only means and standard deviations but also medians and key percentiles (e.g., 25th, 75th). With regard to reporting on radiographic progression, there is consensus that—in the interest of the meta-analyst—logarithmically transformed progression scores should also be reported in the tables.¹²

The statistical test

The main goal of statistical analysis in the report of a trial or an observational study is to challenge the null hypothesis or, in other words, to find probabilistic support for a difference observed between treatments (trial) or for a (predictive) association (observational study). A second aim of statistical testing is to determine the robustness of a demonstrated effect.

In flagrant contrast to what is often done, in reality, statistical analysis should take only a modest place in the report of a study. However, many authors cannot resist the attractiveness of " $P < .0001$ " and build their article around the statistical test result rather than the opposite. Unfortunately, many of these authors are unable to reproduce the correct interpretation of $P < .0001$ and counter critical questions about the relevance of the effect with, "It is highly statistically significant, though, isn't it?," thus implying that the effect is clinically important.

The P value is a probability, namely, the probability that even if it is assumed that the null hypothesis is correct, it is nevertheless rejected. This sentence is comprehensible only if one realizes that the clinical trial one is looking at is just one (random) example of many, let us say 1000, imaginary similar trials. Whoever accepts this will also accept that all 1000 imaginary trials will have 1000 different results. The majority differ only slightly, a few will have more deviant results simply by coincidence, and a very few will even have extremely deviant results in either direction, whereas in truth the difference should be zero! In theory, such differences could be of such a magnitude that they lead to rejecting the null hypothesis. We talk about erroneous rejection of the null hypothesis, or a type I error. The P value is the probability of a type I error. $P < .0001$ means that there is very, very small chance of a type I error. It could be said that the result is very robust and that such a P value adds to the credibility of the trial (internal validity). It does not say that the difference that was found is a relevant difference or that an effect is meaningful. Current efficacy trials are often so powerful in

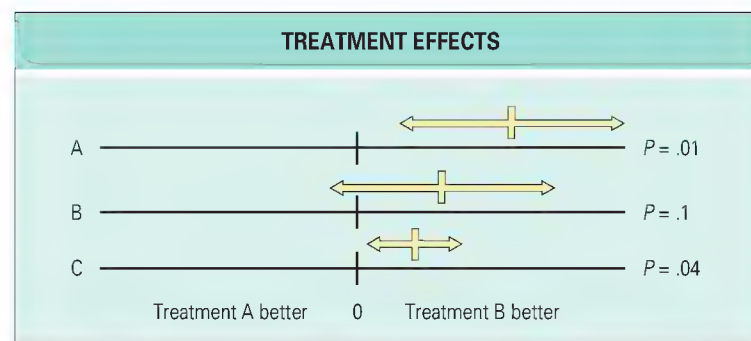


Fig. 26.2 Treatment effects and 95% confidence intervals of three potential scenarios (A, B, and C) for an imaginary clinical trial comparing treatment A and treatment B. See text for clarification.

statistically underscoring small differences that very good P values can be obtained with treatment effects that are negligible when considered in the context of patient care. So, statistically significant does not imply clinically relevant. The opposite is also true: not statistically significant does not mean not relevant or in other words, "the absence of evidence is not the same as evidence of absence (of a meaningful effect)," a statement referring to type II error (see later).

The second aim of statistical analysis is to determine how robust the trial results are. Actually, one is interested in the implications with respect to the size of the treatment effect. Usually, a 95% confidence interval (CI) is used to describe the bandwidth for estimates of the treatment effect. Elaborating on the discussion about P value, the 95% CI is best understandable by imagining that a particular trial is done 1000 times. Ninety-five percent of the time the trial result (the estimate of the treatment effect) will lie between the limits of the 95% CI, but 5% of the time the treatment effect will take a more extreme value. The relationship between P value and 95% CI is further clarified in Figure 26.2. Suppose a clinical trial in RA patients with two treatment arms (A vs. B) and (improvement in) disease activity state as the outcome measure. Three possible treatment effects are plotted in a diagram that a reader of meta-analyses may be familiar with. The zero treatment effect reflects the level of equivalence. All three scenarios represent a trial result in which treatment B is better than treatment A (more improvement in disease activity state with B than with A). The P values are presented per scenario. The arrows represent the 95% CIs around the mean improvements in disease activity state. Note that the 95% CIs of scenarios A and C lie entirely to the right of zero. Both treatment effects are statistically significant ($P < .05$); the null hypothesis of "no difference" is rejected. Note that the 95% CI in scenario B crosses zero. The treatment effect is not statistically significant ($P = .05$); the null hypothesis is not rejected. Note also that notwithstanding a *smaller* treatment effect in scenario C than in scenario B, the treatment effect in C is statistically significant, as represented by a narrower 95% CI. We say that the trial result is more *precise*. It is the combination of statistical information and information about the preciseness of the treatment effect that makes 95% CIs such attractive tools in clinical trials. To improve information exchange and interpretation of trial results, it is almost mandatory to present 95% CIs around the mean treatment effects and not only P values. As with many generic rules, the balance occasionally dips to the other side: it is not particularly useful and often confusing to present 95% CIs of variables not related to treatment effects (or related to hypothesis testing). An example is the presentation of 95% CIs around the mean 28-Item Disease Activity Score (DAS28) at baseline.

CONCLUSION

In this chapter a wide array of points to consider in the critical appraisal of RCTs and observational studies have been addressed. Emphasis is placed on issues referring to external validity or generalizability because that is what most rheumatologists need to know. As mentioned in the introduction, the choice of issues addressed is subjective and the chapter is by no means intended to cover everything that is important in appraising study data.

It is hoped that the points raised will increase awareness of the importance of the interplay between the clinical investigator responsible for the study report and the consumer of the data, often the clinician, who has to decide about application of the study results to the area of clinical medicine, which affects individual patients. Only appropriate communication in this area will ultimately improve patient care.

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27

Ethics in clinical trials

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- The objective of clinical research is the acquisition of generalizable knowledge to increase understanding of human biology or to improve health.
- Research subjects may be placed at risk for the good of others.
- An ethical framework has been developed to ensure that research subjects are not exploited and are treated with respect.
- Ethical challenges vary according to the phase of development of the experimental therapy.
- Conflict of interest is a multifaceted challenge in the modern age of medicine.
- Two cases illustrate the ethical issues in drug research involving human subjects.

The objective of clinical research is the acquisition of generalizable knowledge to increase understanding of human biology or to improve health. Although the participation of human subjects is required to achieve these ends, the attainment of the goals of clinical research does not ensure benefit to those who participate. Indeed, it is self-evident that the research subject may be placed at some risk for the good of others, a reality at the core of the ethical dilemmas in human subject research. It is therefore incumbent on those who formulate, conduct, and report such research that their work adhere to the highest standards. This chapter reviews the ethical dilemmas arising in the research setting and presents principles that should guide this activity.

GENERAL ETHICAL PRINCIPLES

Extensive literature and experience serves to inform the philosophical and practical paradigms that guide current human subject's research.¹⁻⁷ Theoreticians interested in this area have looked to the field of moral philosophy and ethical theory to derive principles that provide a foundation for ethical judgments concerning research involving human subjects.⁸ Rooted in the Nazi experimentation revealed in Nuremberg, these efforts have been bolstered by a number of seminal documents beginning with the *Nuremberg Code* (1947),⁹ the *Declaration of Helsinki* (1964),¹⁰ the *Belmont Report* (1979),¹¹ the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*,¹² and most recently *Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products* of the World Health Organization.¹³ Malfeasance and ethical lapses typified by the Tuskegee study have also provided a potent stimulus for change.^{1,2,14} Ethically designed and conducted research now rests on principles articulated in these foundational documents. The *Belmont Report*, a particularly influential statement in the current era, added the notions of respect for persons, beneficence, and justice to the enduring principle of informed consent established in Nuremberg over 30 years before. Indeed, these core ethical tenants provide the foundational elements guiding the current regulation of human subjects research.

WHAT IS ETHICAL RESEARCH?

A useful framework developed by Emanuel and colleagues¹⁵ incorporates seven requirements whose purpose is to ensure that research subjects are not exploited and are treated with respect (Table 27.1). The ethical

considerations inherent in these requirements can be framed in the form of the following questions^{6,15}:

1. Does the anticipated societal and scientific value of the research justify the resources required to conduct the research?
2. Does the research employ valid scientific methodology and is it practically feasible?
3. Is the selection of subjects fair and equitable?
4. What potential harms and risks are imposed on the research subjects? Are the risks minimized? Are the potential societal benefits in proportion to the risks imposed on the participants?
5. Has the study undergone independent review?
6. Is informed consent sought from the research subjects?
7. Are there safeguards to ensure respect for research subjects during their participation in the research?

The intent of these requirements is to provide a methodology for the evaluation of the ethics of clinical research.

ETHICAL CONSIDERATIONS IN CLINICAL TRIALS

In the setting of drug trials, the traditional stages (phases 1 to 4) of scientific development present phase-specific ethical challenges^{3,5} that vary in importance as a drug (or device) works its way through the approval cycle.

Phase 1 trials represent the first testing in human subjects. Typically small in size, these trials usually, but not always, involve healthy volunteers. Safety and toxicity in contrast to efficacy are the primary concerns, and for this reason informed consent, risk-benefit, and scientific validity are particularly relevant. Participants receive no benefit—indeed they may experience significant adverse consequences—and hence are dedicating themselves to the “greater good.” Phase 2 clinical trials include more affected subjects and thus may include efficacy as an active endpoint but have similar ethical considerations. Phase 3 trials involve not only larger numbers of patients but also an ever-widening range of participants, which brings the ethical construct of fair subject selection to the forefront. Clinical trials at this stage of development focus on efficacy and safety. With both phase 3 and 4 clinical investigations, the latter conducted after the drug has been approved, respect for enrolled subjects becomes a primary consideration raising concerns such as allowing voluntary withdrawal from participation, protecting privacy, and informing subjects of new risks and benefits as well as the results of the research. Phase 4 clinical trials are the postmarketing investigations conducted by the pharmaceutical industry. Although a subject of some criticism, such studies are considered justified because they provide important data on serious but low-prevalence adverse events.

RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials (RCTs) remain the gold standard methodology for the demonstration of efficacy and safety in the development of new therapies. This format is defined by a number of design characteristics including randomization, blinding, and the comparison of two (or more) interventions, used to demonstrate therapeutic equivalence or superiority of one treatment over another. Despite its advantages, this research design presents a unique spectrum of ethical challenges for the investigator.^{3,15} These include such matters as the treatment versus research distinction (often referred as the *therapeutic misconception*),¹⁶⁻²⁰ equipoise (the lack of convincing evidence that one intervention is superior to another),^{6,21} the choice of comparators (the use of a placebo is important),^{3,5,22-25} randomization (which does not allow for autonomous preferences in treatment),³

TABLE 27.1

Ethical requirements for ethical research

REQUIREMENT	ETHICAL VALUES
1. Social or scientific value	Scarce resources, nonexploitation
2. Scientific validity	Scarce resources, nonexploitation
3. Fair subject selection	Justice
4. Favorable risk-benefit ratio	Nonmaleficence, beneficence, and nonexploitation
5. Independent review	Public accountability, minimizing influence of potential conflicts of interest
6. Informed consent	Respect for autonomy
7. Respect for potential and enrolled subjects	Respect for autonomy and welfare

blinding,³ and the sharing of preliminary information. Each of these ethical challenges warrants commentary.

Levine defines *practice* as activities “designed solely to enhance the well-being of an individual patient,” whereas the intent of *research* is to contribute to a base of knowledge that can be generalized to all those who suffer from the disease under investigation.²⁰ In the setting of clinical research, this distinction is easily blurred, especially when existing treatments for the disease in question are unsatisfactory or when the proposed new treatment is highly innovative. In these circumstances, research subjects often fail to appreciate the difference between research and treatment, a phenomenon known as *therapeutic misconception*.¹⁶⁻²¹ The way to resolve this dilemma is to ensure that research subjects understand that the purpose of clinical research is to produce generalizable knowledge, regardless of whether or not they derive benefit from their participation in the study. Five dimensions have been suggested as safeguards to ensure the subject’s comprehension of the research (Table 27.2).²¹ Thus in contemporary medicine, where practice and research may coexist, it is virtually instinctive that physicians might wish to employ pioneering therapy despite a lack of formal validation. In such circumstances, the line that demarcates research from treatment can be easily breached, which reinforces the need for attention to these ethical issues.

Of the defining principles, the physician’s duty to the individual patient remains a central doctrine. Dating back to Hippocrates, this notion is deeply embedded in how medicine expresses its professionalism. This fiduciary duty is communicated primarily through the clinical transaction, a patient-centered endeavor that relies on physician-based attributes often characterized as virtuous.²⁶⁻²⁸ Against this backdrop, there is the contrasting duty of the researcher—the promotion of human welfare through the rigorous application of the scientific methods (research). An important and problematic feature of the RCT arises from the randomization, a method in which treatment is apportioned by chance rather than by physician recommendation. A patient’s needs and values thus become subverted, even sacrificed, for the greater good of others. An approach to resolving this dilemma is the concept of *equipoise*,²⁹ which requires a researcher to have no justifiable reason for preferring one treatment over another in a clinical trial. *Clinical equipoise* simply expands this concept. Instead of being a requirement that the treatments exist in exact balance (the researcher would have no preference), *clinical equipoise* is based on an honest disagreement among knowledgeable professionals concerning the superiority of one treatment. For this reason an RCT can be considered permissible because it shifts the responsibility from the researcher to the greater community of physicians.

Another problematic aspect of clinical trials is the use of placebos. When new therapies are being examined, or when current treatment is ineffective or unsatisfactory, the use of placebos does not raise ethical concern. However, a problem arises when new therapies are being compared with established treatment. The *Declaration of Helsinki* states that the “benefits, risk, burdens, and effectiveness of a new method should be tested against those of the best current . . . methods.”¹⁰ The Food and Drug Administration, however, has generally been supportive of the use of placebos because such studies may produce more “purified” knowledge.²² One approach toward reconciliation is that the burden of proof lies with those who propose depriving patients of standard care.²² Alternatively, a middle ground has been advocated²⁵ in which the *placebo orthodoxy*, which promotes the use of placebos based on methodologic considerations, is contrasted with an *active-control orthodoxy* in which placebos are viewed as sacrificing the rights and welfare of patients in the name of scientific rigor. For example, in situations in which life-saving therapy is available, placebo-controlled studies are *prima facie* unethical. The justification for placebos becomes blurred in conditions in which

TABLE 27.2

Dimensions of research that should be understood by research subjects

1. Scientific purpose

Clinical research is designed to produce generalizable knowledge and to answer questions about the safety and efficacy of intervention(s) under study to determine whether or not they may be useful for the care of future patients.

2. Study procedures

Participation in a trial may involve procedures or tests, in addition to the intervention(s) under study, that are intended only or primarily to generate scientific knowledge and that are otherwise not necessary for patient care.

3. Uncertainty

For intervention(s) under study in clinical research, there often is less knowledge and more uncertainty about the risks and benefits to a population of trial participants than there is when a doctor offers a patient standard interventions.

4. Adherence to protocol

Administration of the intervention(s) under study is typically based on a strict protocol with defined dose, scheduling, and use or avoidance of concurrent medications, compared to administration of standard interventions.

5. Clinician as investigator

Clinicians who are in health care settings provide treatment; in a clinical trial setting, they are also investigating safety and efficacy of an intervention.

From Henderson GE, Churchill LR, Davis AM, et al. *Clinical trials and medical care: defining the therapeutic misconception*. *PLoS Med* 2007;4:1735–8.

effective treatments do exist but some potential for harm may arise as a consequence of using a placebo. In these circumstances, compelling methodologic advantages must exist. Examples of such conditions include those with high placebo response rates; those with a waxing and waning course or frequent spontaneous remissions; those for which existing therapies are only partly effective or have produced serious side effects; and those for which the low frequency of occurrence means that an equivalency trial would have to be so large as to compromise enrollment and completion of the trial.²⁵ Many of these characteristics are germane to chronic rheumatic diseases, osteoporosis being a good example.

With the advent of effective therapies for the treatment of osteoporosis, specifically the prevention of fracture, the ethical implications arising from the use of placebos have sparked considerable controversy.³⁰⁻³² The question raised is whether individuals who are highly susceptible to osteoporotic fracture should be enrolled in a placebo-controlled clinical trial. Various approaches to this ethical conundrum include enrolling only patients who have no fracture history or, alternatively, patients who have experienced side effects or failed to show a response to current therapy. Most clinical trials involving this condition employ an add-on approach in which the nontreatment group receives calcium and vitamin D. Methodologic solutions have been considered including the use of noninferiority and superiority trials with the placebo group replaced by a group receiving established therapy.³³ Although this may seem to solve the ethical problem, such trials require much larger numbers of participants to demonstrate a reduction in fracture. In addition to the logistical and cost implications, there is also the observation that such trials, given their larger size, ultimately result in more study subjects’ developing fractures over the study period than if a placebo arm had been employed.³⁴ Thus one ethical dilemma is simply replaced by another. Last are the studies that employ various biomarkers of bone turnover as fracture surrogates.³⁵ This approach reduces the number of study participants but is suboptimal, because it does not directly address the most important clinical endpoint (fracture).

Other methodologic features of the RCT also raise ethical concerns. For instance, randomization is usually performed blinded, either single blind (subjects do not know what treatment or intervention they are receiving), or double blind (neither subjects nor investigators know the treatment or intervention). Random assignment and blinding minimize bias and enhance validity. Such procedures are not necessarily compatible with the patient’s best interests or desires, however, nor do they respect the subject’s autonomy.⁵ Two ethical concerns are readily apparent: (1) preferences and information concerning what intervention the subject is receiving is necessary for autonomous decision-making; and (2) information pertaining to which intervention the subject is receiving may be important in the assessment of adverse events or in the setting of medical emergency. Informed consent

addresses the first concern. Providing the appropriate safeguards concerning adverse events, however, requires specification in the research protocol of the conditions, thresholds, and consequences of breaking the code (unblinding the study). A related ethical problem is the sharing of information as it accumulates in a clinical trial, because the risks and benefits of the study therapy may change and thus alter equipoise. Study monitors and independent data safety monitoring boards make decisions regarding the early study termination, thus taking the decision away from the investigator. In the context of international research, a more recent problem is the investigator's (and sponsor's) obligation to ensure ongoing access to the investigational therapy to study subjects upon completion of the clinical trial.^{5,36}

Another recent phenomenon of relevance to clinical trials is the role of contract research organizations (CROs) in drug development.³⁷ CROs are commercial organizations that, as independent contractors, offer clients (usually drug companies) a wide range of pharmaceutical research services in the path of drug development. They offer an important outsourcing function to the pharmaceutical industry, which provides cost savings while bypassing the academic medical center, the traditional (and possibly safer) site for the conduct of clinical trials. CRO-industry revenues have grown dramatically since their inception in the early 1990s.³⁷ Problems such as the preferential enrollment of the economically disadvantaged (through pretrial monetary inducements), "backloading" payment approaches in which the largest payments are made to study subjects at the end of the trial (which inhibits patients from terminating their participation), disquiet pertaining to the comprehension of non-primary-English-speaking subjects (which raises concerns regarding informed consent), inadequate monitoring of adverse events, and concerns about the depth, diversity, and medical knowledge of the workforce that makes up the CRO. Whether or not this model, premised mainly on the desire to reduce costs, compromises ethical oversight remains open to question. Further uncertainty exists with respect to the role and scope of the regulatory mechanisms that oversee the activity of the CROs—that is, do these entities answer to the regulatory agencies responsible for monitoring clinical trials (a mandated requirement for academic medical centers) or to the drug companies that hire them? Few data exist on the degree to which clinical trials involving the rheumatic diseases may have been affected by the CRO phenomenon. However, reliance on this model remains strong and this practice is likely to grow.

CONFLICT OF INTEREST

The term *conflict of interest* encompasses a spectrum of behaviors and actions involving personal gain, usually but not always limited to financial benefit.³⁸⁻⁴¹ Arising over the last two decades from the complex relationships among industry, investigators, and the academic institutions where they are employed, such conflicts raise a variety of ethical issues. That financial and other inducements might influence, and at times overpower, professional judgment comes as no surprise given the pressures accompanying modern life, yet the circumstances and determinants of such behavior are not fully understood. Barnes and Florencio conclude that conflict of interest increases as the value of the secondary interest rises, as professional judgment becomes more specialized and less amenable to supervision, as the decision-making process becomes less transparent, and when there is a long-standing relationship between the participants.⁴² It is well documented that financial and other incentives influence physicians in the clinical environment.⁴³⁻⁴⁵ Although their influence in other arenas of academic medicine may be less appreciated, such influences are pervasive and affect virtually every corner of the academic medical enterprise: physician-industry interactions, investigator-industry relationships, and the academic center itself. Journal publication and continuing medical education likewise are not immune.^{46,47}

Academic institutions have attempted to manage these conflicts. Initially, simple disclosure—for example, of outside financial interests—was considered sufficient. More recently institutional committees review reported conflicts and on occasion require the divestment of equities, the termination of consulting relationships, and the imposition of methods of monitoring. Medical journals have also followed suit, requiring disclosure and implementing other methods such as the rejection of medical reviews by those believed to have conflicts of interest.⁴⁶ Despite these safeguards, breaches are often seen, which supports the need to be ever vigilant.

CASE STUDIES

Modulation of immune responses with biopharmaceuticals such as the monoclonal antibodies (mAbs) has become an important therapeutic strategy for the autoimmune diseases. Because many of these new therapies have

potentially significant toxicities, patient safety and the ethical considerations arising in the context of clinical trial participation will remain at the forefront of the effort to find more effective treatment for this disease. As examples illustrating some of the important ethical considerations arising in this research setting, two recent clinical trials involving such agents are relevant. The clinical details of these cases are summarized in Boxes 27.1 and 27.2.

As a consequence of the experiences in these trials, both protocols have undergone intense scrutiny by the lay press^{48,49} and the scientific community,^{50,51} an assessment that has included an examination by the National Institutes of Health (NIH) Recombinant DNA Advisory Committee and the European Medicine Agency (EMA).⁵² Numerous questions have arisen: Was the science underlying the proposed therapy flawed? What factors or conditions associated with each clinical trial contributed to the outcome? Were the patients adequately informed about the risks of participation? Were the patients sufficiently protected against these risks?

An ethical analysis of these events begins with the informed consent. Under the current guidelines for research participation in the United States, all research subjects must be informed of the risks and the benefits of their participation in a research study, a requirement fulfilled by the process of

BOX 27.1 CLINICAL CASE

The patient was a 36-year-old white female enrolled in an open-label phase 1/2 clinical trial (safety/efficacy study) of a genetically engineered adenovirus encoded with a tumor necrosis factor receptor construct under development by a biotech company as an intra-articular injection for rheumatoid arthritis (RA). The patient had developed RA 15 years before her enrollment, had previously been treated with etanercept (2002 to 2004), and at the time of her recruitment to the study had been managed with adalimumab, methotrexate, and prednisone. She previously had surgery on her toe but not her knee, although she had been treated with multiple (10) knee injections of corticosteroids. Randomly assigned to the highest-dose group, she received her first dose of the study drug on February 26, 2007, without incident. Her second intra-articular injection was administered on July 2, 2007, and on the same evening the patient developed fever and diarrhea. Due to the persistence of the fever, Levaquin was prescribed (July 5, 2007), but over 48 hours she remained febrile (40° C) and was experiencing nausea and vomiting. By July 9, 2007, her knee had become tender, and she was tachycardic, had a white blood cell of 29,000/mm³ (predominantly lymphocytes) and exhibited mild liver function abnormalities. Her fever persisted despite aggressive antibiotic therapy, and subsequently (July 16, 2007) her liver function was further deteriorating, she remained febrile, and the hemoglobin level was noted to be dropping to a low of 4.6 g/dL. Hypotension and respiratory distress ensued, and she was transferred to another center.

By July 19, additional laboratory and radiologic testing revealed a coagulopathy, retroperitoneal hemorrhage, and further deterioration in liver function. At this time the question of liver transplantation was raised but dismissed. Serologic tests for herpes simplex virus 1 showed negative results, as did nasopharyngeal cultures. On July 19 a liver biopsy was performed; the biopsy specimen revealed small areas of acute necrosis and inflammatory lesions and tested positive for *Histoplasma*. Her deterioration continued, and she expired on July 24, 2007. An autopsy revealed disseminated *Histoplasma capsulatum* involving all organs without granuloma (a feature typical of histoplasmosis in the immunocompromised), a large retroperitoneal hematoma, and a minimal swelling of the knees.

BOX 27.2 CLINICAL CASE

Six healthy young male volunteers were enrolled in a phase 1 study of the safety of TGN1412, a superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes of receiving a single intravenous dose of the drug, all six volunteers developed a severe systemic inflammatory response secondary to the rapid induction of proinflammatory cytokines. Patients reported headache and myalgia and developed nausea, diarrhea, vasodilatation, and hypotension. Over the ensuing 24 hours, all patients became critically ill with diffuse pulmonary infiltrates, renal failure, and disseminated intravascular coagulation. All patients were admitted to the intensive care unit, where they received aggressive supportive therapy including dialysis, high-dose intravenous corticosteroids, and an anti-interleukin-2 receptor antagonist antibody. Prolonged shock and respiratory distress syndrome developed in two patients, who required intensive support for 8 and 16 days, respectively. All patients ultimately survived.

informed consent as discussed earlier.⁵³ Three primary elements support this requirement: information, comprehension, and voluntariness. Once these elements are achieved, the subject's authorization is sought.^{11,53} Information provided to the research subject should be adequate to explain the rationale for and the procedures involved in the study and should meet a *reasonable volunteer* standard. To do this, the investigator may need to consider factors such as the subject's age and educational level, and other barriers to communication such as language. Informed consent continues throughout the subject's participation in the research.

There have been indications suggesting possible problems with respect to the informed consent process in one of the cases described (see Box 27.1). For example, it has been reported that the subject participated in the clinical trial because of a perceived benefit, primarily the alleviation of her knee pain.^{48,49} This problem, an example of *therapeutic misconception*, has been discussed earlier. Such beliefs are strong inducements to participation and have to be adequately tempered by the primary investigator through a thoughtful, considered process of informed consent. Statements such as "You cannot expect to benefit directly from your participation in this study," so often found on consent forms, are not sufficient to mitigate the problem of therapeutic misconception.

Another important consideration relates to the prestudy risk assessment of the developers of the drug and the primary investigators. Although this subject's death is not believed to have been a direct consequence of the adenovirus vector employed to deliver the anti-tumor necrosis factor medication, the patient's immunosuppression, a consequence of the totality of her therapy, as well as the risk of histoplasmosis in a patient living in an endemic region for this condition may not have been sufficiently appreciated by the investigators.^{54,55}

Concerns pertaining to the ethical oversight of this investigation are compounded by the circumstances of its approval. Ethical review was conducted by an independent institutional review board (IRB), one unaffiliated with an academic medical center. Two issues are raised in this context. The first is the quality of scientific review given the complexities of therapy in this disease setting. Was there sufficient rheumatologic, immunologic, and infectious disease expertise on the IRB to adequately assess the potential for adverse outcomes with this new therapy? The second concern pertains to the for-profit nature of this IRB. Could the approval process have been influenced by circumstances in which the IRB was being paid directly by the company seeking approval for the drug?

In this study a third issue, coercion, is also of concern. The study sponsor had agreed in principle to the use of a neutral party in the recruitment of patients, a protocol that was not employed.⁵⁶ Indeed the research subject was approached directly by her rheumatologist, a practice that may place undue influence on the patient to agree to enroll in the study. To reduce this form of influence, the NIH recommends that physicians not recruit their

own patients into clinical trials they are conducting. In circumstances in which this cannot be avoided, it has been suggested that an impartial third party explain the study and obtain informed consent.⁵⁷ This practice is particularly relevant in studies involving novel therapies that are deemed risky and in circumstances in which the individual's condition is not life threatening, and is especially of interest in studies in which the investigator has a financial interest (as was the case in the rheumatoid arthritis [RA] trial discussed here).

A final concern has to do with the assumption of risk. As in the case of an earlier and now well-documented study involving gene therapy with fatal consequences,^{58,59} the RA study subject had relatively well-controlled disease with standard therapy. Thus the degree of assumed risk may have been out of proportion to the potential benefit, which provokes concern in general as to which subsets of diseases should even be considered for innovative therapies that employ emerging technologies.⁵⁶

In the second example (see Box 27.2), the investigation was a phase 1 study of the safety of a novel immunomodulatory therapy using healthy volunteers. In phase 1 investigations the ethical accountability to the (healthy) study participant is especially high, a responsibility magnified by the difficulty in quantifying risks. Indeed, one of the major impediments to drug development in this arena (mAbs) is the risk of adverse immune-mediated reactions in humans that include immunosuppression, autoimmunity, and, in the case presented, cytokine storm, a topic extensively reviewed recently.³² Dosing for such "first-in-human" clinical trials is based on preclinical safety studies, primarily in nonhuman primates, combined with *ex vivo* studies. Dose selection nonetheless remains challenging because of differences between the primate and human systems, species selection, scientific considerations pertaining to the receptor model employed, calculations based on what is known as the *minimal anticipated biological effect level* (MABEL), and a number of additional considerations relevant to mAbs and their pharmacology and immunology.⁵² The TGN1412 experience, coupled with a growing science pertaining to safer dosage predictions in mAbs therapy, should have addressed this important safety consideration. Although these challenges will require scientifically based solutions, the problems associated with this inexact science just compound the ethical challenges.

An important practical matter arising in this study was the decision to administer the drug to all six participants virtually simultaneously. Clearly, had the administration of the drug been performed in a sequential fashion, thus allowing for observation of each patient individually, fewer of the six study participants would have been subjected to the life-threatening adverse effects of the study drug. This methodologic caution has obvious ethical implications concerning the safety of the study participants and appears to have been recognized in the recently published EMEA guidelines concerning first-in-human clinical trials.⁶⁰

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CLINICAL BASIS OF
RHEUMATIC DISEASE

28

History and physical examination

■ ANTHONY D. WOOLF

- History taking is the most important skill in rheumatology.
- The physical examination is pivotal in confirming the cause and effect of musculoskeletal problems.
- Assessment of the musculoskeletal system should form part of any general medical examination.
- The consultation involves a patient-centered phase for the patient's story; a physician-centered phase to clarify the story by interrogation and examination; and an interactive phase during which the patient and physician discuss their concerns, findings, conclusions, and plans.
- The consultation must meet the expectations of the patient.
- Musculoskeletal conditions cause a broad range of problems that need to be assessed by a multidisciplinary team to develop an appropriate plan of management.

INTRODUCTION

Musculoskeletal complaints are among the most common symptoms, and their cause and effect need to be established. Physicians evaluating such patients need to characterize the problem and its impact, establish the cause, and develop a management plan. If unable to identify the cause, physicians must at least be able to describe the abnormality and recognize whether it is important and requires a more skilled assessment. When the person is reviewed, the physician must be able to assess response to treatment and be able to recognize the lack of expected response. Musculoskeletal conditions are also frequent comorbid conditions that need to be identified and treated.

Many common musculoskeletal problems can be managed effectively in the community by the primary care team, but other less common or more serious problems will require specialist management, often within the context of a multidisciplinary team. Different competencies are needed for these different levels of care. All physicians should be able to recognize an abnormality of the musculoskeletal system and whether it is important by being able to perform a screening assessment in combination with basic knowledge of musculoskeletal conditions. More expert management will require greater competency in clinical assessment and more detailed knowledge of the possible causes; such an assessment will be made by a specialist physician (rheumatologist).

In this chapter a basic screening assessment of the musculoskeletal system is described that is appropriate as part of a general examination to identify whether any abnormality is present. A more detailed evaluation of a person with a musculoskeletal problem is also presented. From such assessment the syndrome that the person is complaining of should be identified, and with appropriate knowledge and investigation, a differential diagnosis should be possible.

SCREENING ASSESSMENT

Musculoskeletal conditions should always be sought by routine screening as part of any general history and examination. Once an abnormality has been identified, a more detailed assessment is necessary. This screen takes only a few minutes. It has been validated in a general medical setting and within undergraduate training.¹

Screening history

The common symptoms of any musculoskeletal condition are pain, stiffness, and limitation of function. Joint disease is often associated with swelling. Sensitive functional tests are (1) the ability to dress without difficulty, including socks and shoes, which is a complex activity that uses both the upper and lower limbs, and (2) the ability to ascend and descend stairs without difficulty, which is sensitive in detecting abnormality in the lower limbs. The following screening questions will quickly establish the presence or absence of major musculoskeletal problems.

- Do you suffer from any pain or stiffness in your arms, legs, neck, or back?
- Do you have any swelling of your joints?
- Do you have any difficulty washing and dressing?
- Do you have any difficulty going up or down stairs or steps?

Musculoskeletal conditions are often associated with systemic features, and general inquiry should be made about the person's health.

Screening examination

Any significant abnormalities of the spine, arms, or legs should be identified by inspection at rest and during certain movements and with brief palpation and stress tests of selected joints. Normality is looked for in the appearance, posture, and resting position of the joints and in smooth movement through the expected normal range. Whenever any joint is affected by a musculoskeletal condition, one movement is usually nearly always affected, and it is these movements that are assessed in this screening. For such screening to be part of the routine examination of all patients, it has to be quick, simple, and easy to annotate. This screening was developed to meet these criteria.¹ The gait, arms, legs, and spine (G, A, L, S) should be assessed.

- *Gait.* Observe the patient walking forward for a few feet, turning, and walking back again. Abnormalities in the different phases should be recognized: heel strike, stance phase, toe-off, and swing phase (Fig. 28.1). Look for abnormalities in movement of the arms, pelvis, hips, knees, ankles, and feet during these phases.
- *Inspection of the standing patient.* View the patient from the back, side, and front to look for any abnormalities, in particular, abnormalities in posture and symmetry. Examine for tenderness by applying pressure at the midpoint of each supraspinatus muscle and rolling an overlying skinfold.

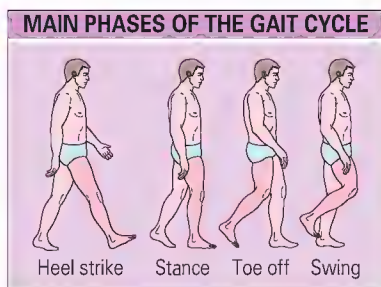


Fig. 28.1 The main phases of the gait cycle are heel strike, stance, toe off, and swing. The phases relate to the shaded leg.

- **Spine.** Ask the patient to flex the neck laterally to each side. Place several fingers on the lumbar spinous processes, ask the patient to bend forward and attempt to touch the toes while standing with the legs fully extended, and observe and feel for normal movement.
- **Arms.** Ask the patient to place both hands behind the head with the elbows fully back. This is a sensitive test for many components of the shoulder apparatus. Straighten the arms down to the side of the body and then inspect with the patient's elbows bent to 90 degrees, palms down, and fingers straight. Turn hands over and make a tight fist with each hand. Place, in turn, the tip of each finger on the tip of the thumb. Squeeze the metacarpals from the second to the fifth.
- **Legs.** With the patient reclining on an examination table, flex each hip and knee in turn while holding and feeling the knee. Then passively rotate the hip internally. With the patient's leg extended and resting on the couch, examine for tenderness or swelling of the knee by pressing down on the patella while cupping it proximally. Squeeze all the metatarsals and finally inspect the soles of the feet for callosities.

Any abnormalities identified should be documented so that they can be assessed more completely.

G	✓	
	A (appearance)	M (movement)
A	✓	X
L	✓	✓
S	✓	X
Restricted movement of the left shoulder		
Restricted movement of the cervical spine with crepitus		

ASSESSING A MUSCULOSKELETAL PROBLEM

General aims

When someone has or is identified at screening as having a musculoskeletal problem, the aim of consultation is to fully characterize the problem that the person is complaining of to identify the syndrome and then make a clinical diagnosis or at least offer a differential diagnosis. This next step needs basic knowledge of musculoskeletal conditions and may require investigations. Assessment of a person's musculoskeletal problem therefore requires not just good clinical skills but also knowledge of functional anatomy, the features of common musculoskeletal conditions, their differential diagnosis, the role of investigations, risk factors and complications, and their probable prognosis. Musculoskeletal conditions are common and can coexist. It should not be assumed that each symptom relates to a single diagnosis.

The impact of the musculoskeletal problem must be identified in terms of symptoms such as pain, physical disability, depression, and fatigue, as well as with respect to its effect on activities of daily living and how it affects the person's ability to participate in what that person wants and needs to do. In addition, interpersonal relationships with family, caregivers, and friends may be affected, and the person often expresses fear of the future.

The patient's concerns must also be identified if the consultation is to fulfill the expectations of the patient, as well as those of the physician (Table 28.1). They must have a full understanding of the treatment plan and what

TABLE 28.1

What is the expectation of the consultation?

Patient expectation	Clinician expectation
What is wrong?	Is any abnormality present?
What will happen? <i>Will I get better? Will I become worse and unable to do what I want and need to do?</i>	What is the abnormality? What is the cause? What effect is it having?
What can you do about it? <i>Can it be cured or just relieved?</i>	Are any predisposing or risk factors present?
What can I do about it? <i>Will a diet or complementary therapies help? Should I exercise?</i>	Have any complications occurred? What treatment is indicated? What has been the response to previous treatment?
Am I getting better?	Has the patient responded to current treatment? What is the prognosis?
If I am not improving, am I receiving the best treatment?	

expectations to have. If the condition is chronic, the patient must have the ability to actively participate in management of the condition, and for this the patient requires knowledge and support. It is important for the physician to show empathy and gain the confidence of the person to establish a relationship of trust and understanding.

If a person is being reassessed, response to treatment needs to be determined both in terms of the disease process and in terms of the impact that it has on the person. It must be compared with the expected response to determine whether any modification of the treatment plan is needed. Many standardized assessments for musculoskeletal conditions can be used to measure impact² and monitor response to treatment³; such assessments are considered within the relevant disease area elsewhere in this book.

The consultation to assess a musculoskeletal problem

The consultation consists of several phases: listening and observing, inquiring, performing an examination, ordering investigations, and making and communicating the conclusion. History taking is by far the most important part of the evaluative process, complemented by physical examination, to confirm the nature of the musculoskeletal problem. One should listen throughout the consultation to understand the patient's concerns, needs, and expectations. Observe the patient's overall appearance, movements, and manner. In the majority of cases it is necessary to make a complete assessment of the entire person, particularly since an apparently simple local problem may be the manifestation of a more generalized condition or the symptoms may be referred from a distant site. When dealing with a musculoskeletal problem, investigations are usually necessary only to confirm clinical suspicion regarding the diagnosis and to help gauge disease activity, prognosis, and choice of treatment. They should follow logically from the findings of the consultation and be performed only if the results will influence decision making.

Any consultation should close with a full discussion of the findings and conclusions so that the person understands the cause, the treatment, and its probable benefits and risks; what can be done by the person themselves, and the probable outcome. Such discussion needs to consider the patient's needs and expectations. Because many musculoskeletal conditions are chronic or recurrent, the patient will need a detailed explanation to enable active participation in care. Further support can be given by other health care professionals or be obtained from written material, the Internet, and patient support groups.

History

First clarify what has brought the patient to the consultation and what the patient's expectations are. Characterize the nature of the condition and its impact. Explore other potentially relevant factors such as the medical history, risk factors related to lifestyle or occupation, and factors that may influence its impact, such as the patient's expectations and socioeconomic environment (Box 28.1).

What are the symptoms?

Symptoms specifically related to musculoskeletal conditions are most often pain and stiffness, frequently accompanied by loss of function, which can

BOX 28.1 CHARACTERIZATION OF A MUSCULOSKELETAL PROBLEM

- What are the symptoms?
- Site and distribution of the symptoms
- Chronology
- Associated symptoms
- Preceding illnesses or injuries and other relevant clues
- Response to health interventions
- Its impact on activities, participation, and quality of life

BOX 28.2 SYMPTOMS OF A MUSCULOSKELETAL PROBLEM**Specific symptoms**

- Pain
- Stiffness
- Swelling
- Deformity
- Weakness
- Instability
- Loss of function

General symptoms

- Fatigue and malaise
- Emotional lability—fear, anxiety, depression
- Sleep disturbance
- Symptoms of systemic diseases

Red flags

- Weight loss
- Fever
- Temple headache/pain with scalp tenderness/visual disturbance
- Loss of sensation
- Loss of motor function
- Difficulties with urination or defecation

Other possible symptoms

- Color changes or coldness of digits or limbs
- Altered sensation

limit activities and restrict participation. Mobility and dexterity are most often limited. Nonspecific symptoms may be present as well. Red flags for potentially serious conditions must be recognized (Box 28.2).

Characterization of these symptoms helps the physician differentiate a musculoskeletal complaint into one of several "syndromes":

- Joint problem, including inflammatory and noninflammatory (osteoarthritis)
- Regional pain problem (including periarticular and soft tissue problems)
- Neck or back pain problem
- Generalized pain (and/or stiffness) problem
- Muscle problem (pain, stiffness, or weakness)
- Bone disorder
- Systemic problem with musculoskeletal symptoms

Pain

The characteristics of the pain can help identify its cause. Nociceptive pain results from a stimulus or lesion in peripheral tissues that causes a painful impulse to be transmitted by an intact nervous system, whereas neuropathic pain arises as a direct consequence of a lesion or disease affecting the nervous system. These types of pain need to be distinguished, and different causes of nociceptive pain have their own characteristics. Pain may also be referred from another site. Also identify the effect of pain on the person with respect to function and quality of life.

What is the site and distribution of the pain?

Ask the patient to demonstrate where the pain is felt and where it is most severe. Is the pain generalized or localized? How easily can it be localized? Articular and periarticular pain often radiates widely and presents far from its origin. Such referred pain is felt in the dermatome related to the myotomal or sclerotomal origin of the affected structure (Table 28.2). Pain from bone and periosteum radiates little and is localized more reliably.

TABLE 28.2**Common patterns of referred pain**

Source of pain	Pattern of referral
Cervical spine	Occiput, shoulders
Shoulder	Lateral aspect of the arm
Lateral epicondyle	Midforearm region
Carpal tunnel	Radial fingers, occasionally the forearm or arm
Lumbar spine	Sacroiliac joints, buttocks, posterior aspect of the thigh, lower part of the leg, foot
Hip joint	Groin, medial aspect of the thigh, medial aspect of the knee, greater trochanter, buttock above the gluteal fold
Trochanteric bursa	Lateral aspect of the thigh, buttock

TABLE 28.3**Patterns of pain**

Type	Pain pattern	Cause
Bone pain	Pain at rest and at night	Tumor, Paget disease, fracture
Mechanical joint pain	Pain related to joint use only	Unstable joint
Osteoarthritic joint pain	Pain on joint use, stiffness after inactivity, pain at the end of the day after use	Osteoarthritis
Inflammatory joint pain	Pain and stiffness in the joints in the morning, at rest, and with use. Acuteness and severity can indicate the probable cause	Inflammatory, infective, crystal induced (acute, exquisite tenderness)
Periarticular and soft tissue pain	Pain on selective movements, localized periarticular or soft tissue tenderness	Bursitis, tenosynovitis, tendinitis, enthesitis
Neuropathic	Diffuse pain and paresthesia in the dermatome worsened by specific activity	Root or peripheral nerve compression
Referred	Pain unaffected by local movement	

Widespread pain can be due to fibromyalgia or polymyalgia rheumatica, whereas pain in several joints suggests an arthropathy. Myeloma or metastatic malignancy must be considered in those with multiple sites of pain that are related not just to joints. Examination of the patient is necessary to clarify the anatomic site of origin of the pain.

What are its characteristics and pattern?

The features of the pain, the time and mode of onset, and its diurnal pattern provide diagnostic clues. Severity is subjective and is not diagnostic alone, although its perceived severity indicates the probable impact that it is having. Certain musculoskeletal conditions are characterized by specific patterns of pain (Table 28.3). For example, gout usually begins in the middle of the night with a pricking sensation in the great toe and quickly escalates into an intolerable persistent burning pain, whereas osteoarthritis is characterized by use-related pain and stiffness of the affected joints with inactivity. Mechanical pain is generally related to use. Inflammatory joint pain is present at rest and with use and is usually worse at either end of the day. Neuropathic pain is diffuse and described as superficial burning, stinging, or pricking pain; as deep aching pain; or as paroxysmal, electric shock-like pain. It is often evoked by a specific activity such as skin stimulation, pressure over affected nerves, and changes in temperature or emotion and is associated with paresthesia in the dermatome. It may include allodynia (pain caused by a stimulus that does not normally provoke pain), hyperalgesia (when there is an increased sensitivity to pain), and hyperesthesia (when a non-noxious stimulus causes the sensation of pain). Bone pain is typically present at rest and at night. These types of pain give clues but are not diagnostic.

The pattern of evolution of the pain should be established in conjunction with the development of any other symptoms—how the patient has arrived at the present situation.

What precipitates, worsens, or improves the pain?

Periarticular problems are often induced by a specific type of repetitive activity. Spinal stenosis can be suspected from a history of activity-related buttock and leg pain that improves rapidly with rest only to recur after further activity, and walking downhill (which extends the spine) causes more pain than walking uphill or cycling. The response to exercise in contrast to rest is a typical feature of sacroiliitis or spondylitis. Rest usually improves the pain from osteoarthritis but has little effect on inflammatory pain. The response to antiinflammatory analgesics versus simple analgesics can help distinguish an inflammatory cause of the symptoms, such as ankylosing spondylitis, from mechanical back pain; the response of polymyalgia rheumatica to glucocorticosteroid therapy is characteristic.

What is its effect on the person?

Pain is a subjective sensation that cannot be felt by others. It can be measured with a visual analog scale, but the degree to which it disrupts the person's life in terms of activities and participation that the person needs and wants to do gives a more meaningful indication of its severity and impact. Pain frequently disturbs sleep, which magnifies its impact.

Stiffness

People often describe a generalized “stiffness” after prolonged rest or the day after an unusual level of exercise, which is more common as people age. More specifically, people frequently describe stiffness related to symptomatic joints. An inflammatory joint disorder is generally associated with prolonged morning and evening joint stiffness, whereas osteoarthritis is associated with short-lived stiffness after inactivity. Morning stiffness of the girdle muscles is characteristic of polymyalgia rheumatica, which can be so severe that it is virtually impossible to roll out of bed and dress, although a few hours after getting up the patient may be virtually asymptomatic. The duration of morning stiffness can indicate the activity of rheumatoid arthritis or polymyalgia rheumatica.

Stiffness of movement of the fingers can relate to tenosynovitis (sometimes with triggering), joint disease, or tightening of the soft tissues, such as with systemic sclerosis or Dupuytren contracture. “Stiffness” can also be used to describe a reduced or limited range of movement or by the patient to describe the difficulty in movement associated with muscle diseases such as inflammatory myositis, Parkinson disease, and motor neuron disease. A careful examination is necessary to be certain about correct attribution of this symptom.

“Locking” describes the sudden inability to perform a particular movement and suggests a specific mechanical event in which some internal derangement actually causes the joint to lock in one position until a trick movement or help is used to free it. This is a classic symptom of a loose body or torn meniscus of the knee joint, but it also occurs in the finger with triggering secondary to stenosing tenosynovitis.

Swelling and deformity

Swelling may involve soft tissues, the joint, or bone. Did it follow an injury? Did it appear rapidly or slowly? Is it painful? Does it come and go, or is it gradually enlarging? Any swelling needs careful examination to establish its nature and cause. Joint swelling is a sign of disease, and examination is necessary to confirm whether it is related to the joint or a periarticular structure and to establish whether it is due to an effusion, synovial proliferation, or bony growth. Imaging such as ultrasound may be required. Recognition of any deformity requires familiarity with the musculoskeletal system to distinguish normal variation from abnormal findings.

Weakness and instability

Weakness can indicate a muscle disorder such as inflammatory myositis or a neuropathy. The pattern of muscle weakness, whether generalized or in a central or peripheral distribution, should be established. Regional weakness is more likely to have a specific cause. However, “weakness” may be used by a patient to describe different things, such as general fatigue, difficulty with movement because of joint disease or pain, or regional weakness of a joint or limb caused by the local muscle wasting that can accompany joint damage. A sensation of “giving way” and general instability of the lower limbs can result from knee pain or weak quadriceps muscles. A joint may be unstable and suddenly give way because of muscle weakness, or it may be related to the ligaments being ruptured or lax in hypermobility. Examination is needed to characterize what is being described.

Loss of movement or function

Musculoskeletal conditions often cause difficulty performing various activities, which may be the main complaint. Establish whether any particular movements and functions are restricted and whether such restriction relates to pain and stiffness or is a primary problem. Painless loss of movement suggests tendon rupture or a neurologic cause.

Fatigue and malaise

Fatigue is a manifestation of most generalized rheumatic disorders, including rheumatoid arthritis, systemic lupus erythematosus (SLE), and most notably, fibromyalgia. Fatigue is sometimes related to depression. It may also be the consequence of poor sleep, which is often related to pain. Fatigue may be severely disabling and is very distressing to the person. The fatigue associated with rheumatoid arthritis or SLE is a good indicator of systemic disease activity.

People with inflammatory arthritis are often able to function well for several hours but then suffer overwhelming fatigue. The fatigue of fibromyalgia is usually associated with lack of concentration and poor-quality sleep. Polymyalgia rheumatica is frequently accompanied by a feeling of sudden aging, with rejuvenation occurring rapidly after a moderate dose of corticosteroid.

Emotional lability

Fear and anxiety are common accompaniments of a musculoskeletal problem and are influenced by factors such as knowledge of the possible diagnosis, expectations for prognosis, future aspirations, and fear of losing independence. Emotional lability, depression, and other psychiatric disturbances can also be the direct result of a rheumatic disease such as SLE. In addition, sleep disturbance secondary to pain can affect mood.

What is the pattern and chronology of the symptoms?

The distribution and chronologic pattern of each symptom need to be established. How did the patient arrive at the present situation? When and how did it start—was the onset sudden or gradual, spontaneous, or after some specific event such as trauma or an infection? What was the subsequent course with respect to time and the pattern of distribution of the symptoms? If articular, does it involve peripheral small joints or large joints or have an axial distribution? Has it followed an additive, intermittent, or flitting course? Is it symmetric or asymmetric? What associated symptoms or signs have developed and when? Do the symptoms fit some recognized pattern? It is important, however, to avoid forcing the symptoms into a pattern—musculoskeletal conditions are common, and different conditions can coexist.

The pattern is important in identifying the possible cause. For example, a traumatic condition obviously relates to a specific event, whereas a degenerative pathology is usually manifested in a slow, insidious fashion. Crystal-related inflammation is particularly rapid in onset and severe, but self-limited, whereas untreated sepsis causes a steadily worsening situation over a few days. Many of the idiopathic inflammatory or immune-mediated rheumatic diseases have a variable course with spontaneous remissions and exacerbations, whereas others, such as reactive arthritis, follow a more predictable course with the sequential development of mucocutaneous and joint inflammation over a period of a few weeks after the initiating event, which gradually subsides over months. Other specific patterns include palindromic rheumatism, which as the word implies, involves episodes of arthritis affecting one or two joints that come and go spontaneously over a few days.

Associated symptoms, preceding factors, red flags, and other clues

Musculoskeletal conditions often have systemic features, and systemic disorders often have musculoskeletal symptoms. It is therefore important to ask about the patient's general health and inquire about the presence of systemic symptoms, such as fever, night sweats, or weight loss and other “red flags” (see [Box 28.2](#)), which may indicate the presence of a serious systemic disorder such as a malignancy, infection, or active inflammatory disease. Review the patient's general health—current, recent, and past. Questions should be directed by knowledge of associated symptoms of the conditions under consideration ([Table 28.4](#)). For example, one should inquire about a recent diarrheal illness, urethritis, or psoriasis and mucocutaneous problems with the seronegative spondyloarthritides. Did any preceding trauma or repetitive or unusual use take place? The previous medical history may include past events that give clues to the present problem, such as a previous attack of unexplained epilepsy in someone with SLE or fetal loss or thrombosis with antiphospholipid syndrome. In other cases, relevant

TABLE 28.4
Associated symptoms, signs, and conditions

	Symptom	Possible diagnosis
Neurologic	Headaches	SLE, temporal arteritis
	Numbness or paresthesia	Neuropathy—compression
	Weakness	Myositis, neuropathy
	Stroke	Antiphospholipid syndrome
	Epilepsy	SLE
Mouth	Dry mouth	Sjögren syndrome
	Mouth ulcers	Reactive arthritis, Behçet disease, inflammatory bowel disease
Eyes	Dry eyes	Sjögren syndrome
	Red eyes	Spondyloarthritis
	Visual loss	Temporal arteritis
Skin	Rash	
	Psoriasis	Psoriatic arthritis
	Livedo reticularis	SLE
	Erythema nodosum	Acute sarcoid or erythema nodosum arthropathy
	Telangiectasia	Systemic sclerosis
	Other	Viral—rubella, human parvovirus
	Photosensitivity	Connective tissue disease
	Ulcers	Behçet disease, vasculitis
	Raynaud phenomenon	Connective tissue disease
	Nodules	Osteoarthritis, rheumatoid arthritis, gout, hyperlipidemia, SLE, rheumatic fever, polyarteritis nodosa, multicentric histiocytosis
	Alopecia	SLE
Respiratory	Pleuritis	Connective tissue disease
	Breathlessness	Pulmonary involvement with inflammatory disease, e.g., systemic sclerosis, rheumatoid arthritis
Gastrointestinal	Indigestion, history of peptic ulcer	Nonsteroidal-associated gastritis or ulceration
	Diarrheal illness	Reactive arthritis, inflammatory bowel disease
Genitourinary	Renal stones	Gout
	Dysuria	Reactive arthritis, Behçet disease, acute gonococcal arthritis
	Genital ulcers	Reactive arthritis, Behçet disease, acute gonococcal arthritis
	Vaginal discharge	Reactive arthritis, Behçet disease, acute gonococcal arthritis
Trauma	Fracture	Osteoporosis
	Ligament rupture	Osteoarthritis in the future
	Sprains and strains	Hypermobility syndrome
Nonspecific symptoms	Malaise	Inflammatory disease, malignancy
	Fever	SLE, septic arthritis
	Weight loss	Inflammatory disease, malignancy
	Fatigue	Inflammatory disease
	Anorexia	Inflammatory disease, malignancy
Hematologic	Aging	Polymyalgia rheumatica
	Thrombosis/thromboembolism	Antiphospholipid syndrome
Obstetric history	Anemia	Inflammatory disease
	Fetal loss—early and late	Antiphospholipid syndrome
	Intrauterine growth retardation	Antiphospholipid syndrome
	Preeclampsia	Antiphospholipid syndrome

SLE, systemic lupus erythematosus.

previous medical events may relate to the associations between disorders, such as hypermobility in childhood or past joint trauma as risk factors for osteoarthritis.

The family history can help in the differential diagnosis in some situations, although almost everyone has a relative with arthritis and familial associations are seldom predictive. Importantly, a family history gives personal experience of the potential impact of a rheumatic condition and affects the person's anxieties about the diagnosis and prognosis. Useful clues include a recent flulike illness in the family or other close contacts, which raises the possibility of a viral arthritis; nodal arthritis affecting the mother when deciding whether small-joint polyarthralgia of the hands is early rheumatoid arthritis or nodal osteoarthritis; or a family history of ankylosing spondylitis, iritis, or psoriasis in a young man with back pain.

Recognized risk factors for the development and outcome of musculoskeletal conditions include obesity, lack of physical activity, poor diet, smoking, and excess alcohol intake, as well as activities that expose people to sprains and strains, such as sports or occupation. Recognized “yellow flags” for chronicity of back pain include job dissatisfaction, unavailability

of light work, depression, and low educational level. All this information may need to be considered when fully evaluating someone's musculoskeletal condition.

Previous health interventions and symptom response

Previous and present management should be reviewed. What has the patient been told and what knowledge and understanding does the patient have? What interventions have been tried—prescription and over-the-counter pharmacologic treatments, physiotherapy, supplements, or complementary therapies? What was the response to them? Did the patient benefit or sustain any adverse effects? What is the patient's attitude to and probable compliance with any treatment?

The response to treatment can be of great relevance in understanding the nature of the problem, such as the response of many inflammatory disorders such as ankylosing spondylitis to antiinflammatory therapy or the rapid and almost miraculous response to corticosteroids that is typical of polymyalgia rheumatica. Drugs themselves may also be the cause of the problem, as in drug-induced lupus and thiazide diuretics in gout.

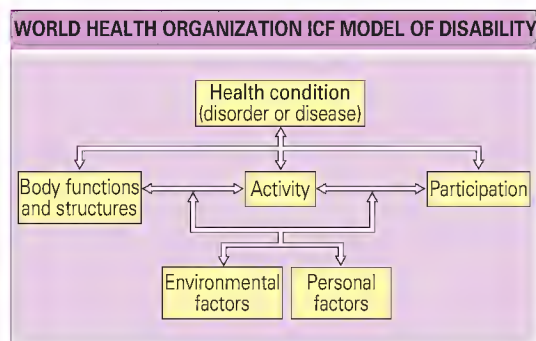


Fig. 28.2 World Health Organization's International Classification of Functioning, Disability, and Health model of disability. (Adapted from World Health Organization. *International classification of functioning and health*. Geneva: WHO; 2001.)

What is its impact?

The impact of the musculoskeletal condition must be assessed in relation to the patient's needs and aspirations. The framework of the World Health Organization's International Classification of Functioning, Disability, and Health⁴ (Fig. 28.2) provides a useful way to look at the effect of any health condition on the functioning of an individual in terms of loss of function, limitation of activities, and restriction of participation within the personal and environmental context of the person's life.

Explore what the patient needs to do and would like to do in everyday activities, including personal care; the home environment; tasks for others, whether paid or unpaid; and personal, social, and leisure activities. Musculoskeletal problems often affect mobility and dexterity. Pain disturbs sleep. What is difficult, requires assistance, or has become impossible to do? Talk a patient through a typical day and also remember to ask about any problems participating in work or leisure activities, as well as personal activities such as toileting or sexual activity. Find out the patient's frustrations and concerns.

Learn whether and how the patient has coped with the limitations. Establish the amount of physical and emotional support that the patient has from family, friends, other caregivers, or social services. Does this support meet the patient's needs? How has the condition affected the patient's economic situation? Helping the patient problem-solve is an important part of the management plan.

The effect on health-related quality of life can be formally assessed by using various validated generic and disease-specific questionnaires such as the Health Assessment Questionnaire.²

Social history and occupation

Knowing the patient's social history is important in assessing the condition and its impact and in planning management. The personal and environmental context plays an important role in the impact. Occupation is also important because it may have a causal role or an effect on the symptoms, or alternatively, the symptoms may have an effect on occupation. Understanding the person's occupation can also give a clearer idea of the person's needs and how to help the person return to the occupation.

Examination

A careful examination is necessary to confirm clinical suspicions gained from the history. It also complements a screening assessment by characterizing any abnormality of the musculoskeletal system that has been identified. Examination of the musculoskeletal system is principally an exercise in applied anatomy. Is the pain originating from the bone, muscle, joint, or periarticular structures? Is the joint pain inflammatory or mechanical in origin? Is the origin of the pain local with tenderness or pain on movement, or is it referred? How painful is it to touch or move, and is this consistent with the history? The examination may focus on the symptomatic structures, but it is usually most informative to do this as part of a general examination of the musculoskeletal system and the entire patient.

Aims of examination

The aim of examination of the musculoskeletal system is to answer four questions:

1. Are the findings normal?
2. What is the abnormality?



Fig. 28.3 Testing for warmth by using the back of one's hand.



Fig. 28.4 Redness as seen in gout. This is a valuable indicator of the intensity of underlying joint inflammation.

3. What is the pattern of distribution?
4. What other features are of diagnostic importance?

These, in combination with the history, should establish the differential diagnosis.

Are the findings normal?

The expected appearance and ranges of movement of the musculoskeletal system need to be recognized. Abnormalities observed may be an abnormal resting position, swelling, deformity, muscle wasting, or abnormal movement. Warmth, crepitus, tenderness on palpation, instability, or weakness may be present.

What is the abnormality?

The nature of the abnormality needs to be established. What structures are involved? What are the characteristics of the abnormality? Is evidence of inflammation, damage, deformity, or biomechanical abnormalities present? These abnormalities are not mutually exclusive; a combination of them may be found.

Inflammation. An inflamed joint is characterized by pain, tenderness, warmth, redness, and swelling. Pain is often apparent by observing movement, and tenderness is elicited by gentle palpation. Warmth is detectable mainly in medium-sized and large joints, for example, the knee, ankle, and wrist joints (Fig. 28.3). Redness is uncommon but is seen with gout, especially around the big toe (Fig. 28.4), and with sepsis. Swelling of an inflamed joint is characterized by its articular origin, is fluctuant because of synovial proliferation or effusion, and is tender, whereas in osteoarthritis, bony swelling along the joint line may be apparent. A number of specific techniques can be used for detection of synovitis and effusion at different joints (Fig. 28.5). One must identify the inflamed structure. Inflammation of periarticular structures such as bursae or entheses must be carefully distinguished from inflammation of the joint. Inflammation of muscle is characterized by tenderness.

Damage. Joint damage is recognized by the presence of deformity, crepitus, movement in an abnormal plane, and loss of joint range of movement not secondary to pain and in the absence of features of current inflammation. Crepitus is an audible and palpable sensation resulting from the movement of one roughened surface over another. In osteoarthritis, the crepitus has a fine quality. This should be distinguished from the coarser, clicking sensation encountered in normal joints.

Deformity. Joint deformity usually refers to malalignment or subluxation of two articulating bones in relation to one another and is identified by abnormal posture, often more apparent on weight bearing or with certain movements, such as occurs with developmental scoliosis of the spine. A severely damaged joint from rheumatoid arthritis or osteoarthritis may cause

movement in an abnormal plane. For example, the elbow is a simple hinge joint; hence its normal range is flexion/extension only, and any other movement, such as elbow abduction, is abnormal and likely to indicate gross joint disruption. Paget disease may be accompanied by bone deformity.

Biomechanical abnormalities. Every joint has a normal posture and spectrum of normal range of joint motion, which varies with age, gender, genetics, and ethnic origin. Motion outside this range may be considered hypermobility or hypomobility. Biomechanical abnormalities can result in symptoms such as scoliosis and back pain, joint hypermobility syndrome is associated with joint pain, and foot pain is often caused by abnormal biomechanics. Joint range is reduced by joint inflammation (the bulk of the inflamed synovium and the effusion) or by irreversible damage to the joint structures (articular cartilage and subchondral bone). Movement is first lost from the extremes of the range. Complete loss of movement is described as ankylosis.

What is the pattern of distribution?

The distribution of involvement of the musculoskeletal structures is important in the diagnosis of musculoskeletal conditions because certain patterns are characteristic (Table 28.5 and see Chapter 29). Several different problems may affect an individual; the apparent pattern may be a false clue to the diagnosis. Examination is needed to confirm the pattern of distribution and to establish whether the various problems relate to a single diagnosis or to several coincident problems, such as the coexistence of nodal osteoarthritis and rheumatoid arthritis.



Fig. 28.5 Testing for swelling. (a) The bulge sign in the knee. The back of the hand gently pushes the fluid from one side of the knee to the other to fill out the "dimples" on either side of the patella. This is most helpful in detecting small knee effusions. (b) The patellar tap. One hand is used to cup the patella and compress the suprapatellar pouch, and the fingers of the other hand press down on the patella to feel for cross-fluctuation. (c and d) Swelling/fluctuation of the small joints of the hand. Detect cross-fluctuation at the joint line with the index fingers and thumbs by squeezing and feeling each side of the joint (as illustrated) or by squeezing and feeling from side to side with one index finger/thumb and squeezing and feeling from the palmar to the dorsal aspect with the other index finger/thumb ("interlocking C").

What other features are of diagnostic importance?

Some systemic features (see Table 28.4) may be of diagnostic importance or of value in assessing severity. Many of these features are easily visible skin signs such as psoriasis, nail fold capillary abnormalities, or telangiectasia, whereas others, such as pulmonary fibrosis or neuropathy, will need to be identified by careful general examination.

Method of examination

One should look at the entire person, including posture and movement, and each region is then examined by comparing one side with the other. It is usually necessary to examine the full musculoskeletal system to correctly assess the problem, but most emphasis is placed on the probable origins of the symptoms while remembering that pain is frequently referred and that any examination must consider all possible causes. Explain to the patient what you are about to do and ask whether the patient thinks that any part of the examination is likely to be painful.

The key elements of the examination to identify the clinical signs of musculoskeletal conditions (Box 28.3) are to look, feel, move, and stress (Table 28.6). These steps are usually performed in an integrated manner. Special tests may be necessary to identify specific problems.

Look

Attitude and spontaneous movement. Observe the person when sitting and undertaking various functional movements during the consultation for any abnormalities associated with musculoskeletal conditions. An inflamed joint is most comfortable when the periarticular structures are at greatest laxity and intracapsular pressure is least. Pain is most severe when intracapsular pressure is greatest. An indication of the severity of the pain is given by the protection with which the person treats the affected region. Is ease of movement in keeping with the severity of pain described?

Swelling and deformities. Look for swelling, but palpate to characterize whether it is due to synovial thickening, joint effusion, bony enlargement, or a combination of these features. Ultrasound is often used to better characterize swelling. Look for any deformities of the joints, bones, or spine. A number of terms are in common use to describe deformities:

- **Kyphosis:** forward curvature of the thoracic spine
- **Scoliosis:** lateral curvature of the spine
- **Dislocation:** articulating surfaces displaced so that they are no longer in contact with one another

BOX 28.3 CLINICAL SIGNS OF MUSCULOSKELETAL CONDITIONS

- Attitude
- Deformity
- Swelling
- Skin changes
- Muscle wasting
- Tenderness
- Restricted movement
- Crepitus
- Warmth
- Muscle weakness
- Instability
- Limited function

TABLE 28.5

Characteristic patterns of involvement of the musculoskeletal system

Diagnosis	Symmetry	No. of joints involved*	Large or small	Distribution	Upper or lower limbs
Rheumatoid arthritis	Symmetric	Polyarthritis	Large/small	Peripheral	Upper/lower
Ankylosing spondylitis	Asymmetric	Oligoarthritis	Large	Central and peripheral	Lower
Psoriatic arthritis	Asymmetric	Oligo/polyarthritis	Large/small	Peripheral	Upper/lower
Reactive arthritis	Asymmetric	Oligo/polyarthritis	Large/dactylitis	Peripheral	Lower
Gout	Asymmetric	Mono/oligoarthritis	Large/small	Peripheral	Lower/upper

*With oligoarthritis, five or fewer joints are affected; with polyarthritis more than five joints are affected.

- **Subluxation:** partial dislocation
- **Fixed flexion:** loss of extension so that the joint is permanently flexed
- **Valgus:** a lower limb deformity in which the distal part is directed away from the midline (e.g., hallux valgus)
- **Varus:** a lower limb deformity in which the distal part is directed toward the midline (e.g., genu varum).

Examination is necessary to determine whether these deformities are correctable. Commonly encountered specific deformities of the hand are shown in Figure 28.6.

Skin. Look at the skin, both that overlying the affected region for redness indicating marked inflammation and for other skin changes, including

TABLE 28.6
System for examination of the musculoskeletal system

Look	At rest for Swelling Deformity Wasting Attitude Skin
Feel for	During movement Tenderness Swelling Movement—crepitus Temperature
Move	Active Passive Resistance Listen
Stress	Stability
Tests	

psoriasis, ulceration, livedo reticularis, and nodules such as tophi, erythema nodosum, and rheumatoid nodules (Table 28.7). Look carefully at the hands and nails because of the many abnormalities that can occur.

Wasting. Look for loss of muscle bulk. Arthropathy can cause widespread wasting around the joint. More localized wasting suggests a tendon, muscle, or peripheral nerve lesion. Swelling of a joint can give a false impression of adjacent loss of muscle.

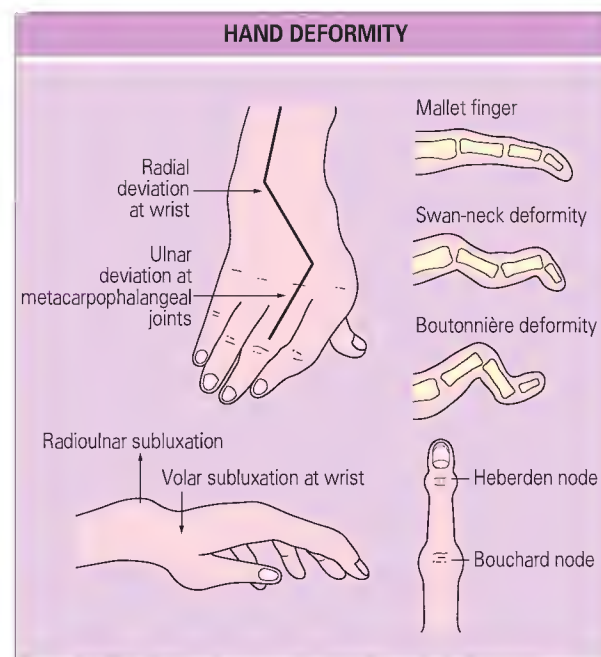


Fig. 28.6 Common deformities of the hand.

TABLE 28.7
Associated skin lesions

Region	Type of skin lesions	Associated conditions
Torso/limbs	Livedo reticularis Erythema ab igne Erythema migrans Palpable purpura Psoriasis Erythema nodosum Nodules Ulcers Calcinosis cutis	SLE, antiphospholipid syndrome, vasculitis Sign of external heat applied to relieve pain Lyme arthritis Leukocytoclastic vasculitis Psoriatic arthritis Acute sarcoid Heberden nodes, rheumatoid arthritis, gout, hyperlipidemia, SLE, rheumatic fever, polyarteritis nodosa, multicentric histiocytosis, sarcoidosis Vasculitis, Behçet disease, Crohn disease? Limited cutaneous systemic sclerosis
Face and mouth	Butterfly rash Psoriasis Heliotrope discoloration Oral ulcers Telangiectasia	SLE Psoriatic arthritis Dermatomyositis SLE, reactive arthritis, Behçet disease Limited cutaneous systemic sclerosis
Nails	Clubbing Pitting Onycholysis Splinter hemorrhages	Hypertrophic pulmonary osteoarthropathy Psoriatic arthritis Psoriatic arthritis Small-vessel vasculitis, endocarditis
Hands	Raynaud phenomenon Nail fold capillary abnormalities Palmar erythema Gottron papules Telangiectasia Sclerodactyly Vasculitic lesions	SLE, scleroderma, mixed connective tissue disease Scleroderma, dermatomyositis Active rheumatoid arthritis, SLE Dermatomyositis Limited cutaneous systemic sclerosis Limited cutaneous systemic sclerosis Rheumatoid arthritis, connective tissue diseases
Feet	Keratoderma blennorrhagica	Reactive arthritis

SLE, systemic lupus erythematosus.

TABLE 28.8

Possible causes of tenderness

Site	Possible cause
Muscular: localized	Myofascial lesion
Muscular: generalized	Fibromyalgia, myositis
Joint line: generalized	Arthropathy, capsular disease
Joint line: localized	Abnormality of intracapsular structure, e.g., medial knee joint line tenderness with a meniscal tear
Periarticular	Bursitis, enthesopathy, sarcoid
Bone	Bone pathology: osteoporotic fracture or invasive lesion
Vertebral	Bone pathology: osteoporotic fracture or invasive lesion

Feel

Warmth. First feel gently for warmth, which is best evaluated by using the backs of the fingers and comparing the finding with that of a normal structure (see Fig. 28.3). Warmth is a cardinal sign of inflammation but may be detected only over large joints.

Tenderness. The presence and localization of tenderness are important in identifying the cause of the problem (Table 28.8). Examine carefully to establish whether it is the joint line or periarticular region. Is the tenderness muscular, either generalized, such as in myositis, or localized, such as the characteristic tender spots of fibromyalgia? Does it involve the temporal artery or temporomandibular joint? Is tenderness absent despite pain? Feel for tenderness by gradually increasing pressure while watching the person for any reaction and releasing as soon as the presence of tenderness is established. Apply pressure only until blanching of the nail of the examining fingers occurs. Percuss the vertebrae to detect localized tenderness.

Swelling. Determine the precise location and anatomic associations of the swelling, whether it is tender, and whether it involves fluid, soft tissue, or bone. Different types of swelling have typical characteristics. Swelling of a joint is confined by the capsule and is most apparent with any weaknesses in the capsule; for example, an effusion in the knee may be associated with a popliteal cyst. Fluid and soft tissue are ballotable; this is the principle of the patellar tap and the interlocking-C examination of the interphalangeal joints (see Fig. 28.5).

Movement. Palpating the joint and periarticular structures while moving gives further information about the pain and tenderness, as well as crepitus from the joint or tendon sheaths.

Move

Three methods can be used to assess joint movement—active, passive, and against resistance.

- To examine joints, a combination of active and passive movement is recommended.
- To detect lesions in tendons or at tendon-osseous junctions, the against-resistance method is principally of use.
- To measure muscle power, the against-resistance method is the principal technique.

First establish the active range, and if reduced, see whether it is greater with passive movement, but be cautious because this may be painful. Familiarity with the normal ranges and planes of movement of the joints is needed. If the problem is unilateral, compare the affected with the unaffected side. Formal measurement of range of motion is of limited value. Involvement of the joint, in particular, synovitis, usually restricts all movement. Restriction of movement in one plane is characteristic of periarticular lesions, tenosynovitis, or internal derangement of the joint. Pain in all directions of movement is associated with synovitis. Pain in just one plane of movement indicates a localized articular or periarticular problem. Pain throughout the range of movement is more characteristic of mechanical problems such as osteoarthritis.

Resisted active movement is valuable in identifying problems related to the muscle tendon or enthesis. This should be performed with the joint in neutral position. Reproduction of pain indicates that it is originating from the muscle, tendon, or tendon insertion related to that movement. Passively stretching the tendon or ligament may also reproduce the pain.

BOX 28.4 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM**Gait**

- Observe the patient walking forward for a few feet, turning, and walking back again.

Posture

- Observe the patient from the back, side, and front to look for any abnormalities, in particular, abnormalities in posture and symmetry.

Listening during joint movement may detect fine crepitus secondary to cartilage damage, crackling associated with hypermobility, or clonking caused by a loose body or irregular surfaces such as severe damage. Audible tendon friction rubs may be heard in patients with systemic sclerosis.

Stress

Joint stability should be assessed by stressing a joint. Stability may be abnormal because of generalized hypermobility, ligament rupture subsequent to trauma or inflammation, capsular inflammation, or loss of articular cartilage and changes in bone as a result of osteoarthritis or rheumatoid arthritis.

Special tests

Various special tests are used for specific diagnoses that are not within the scope of this overview but are considered elsewhere in this text (see Chapters 71-82, as appropriate).

General examination

A full general examination forms an important part of the assessment of a person with a musculoskeletal problem. More frequent problems relate to the skin and nails, neurologic system, and eyes (see Tables 28.4 and 28.8).

Regional examination of the musculoskeletal system

A systematic approach to examination should be taken, but be sure to address any questions raised by the history or screening examination. The sequence can vary, but in general it is easiest to look at the patient as a whole and during walking and standing to observe gait and posture. Then work from the head downward, first with the patient standing to examine the upper limbs, spine, and pelvis and then supine to complete the examination of the pelvis and spine and to examine the lower limbs by comparing one side with the other (Boxes 28.4 through 28.7).

Gait

Gait demonstrates the integrated function of the lower limbs and will reveal abnormalities in the musculoskeletal system (see Fig. 28.1). Further assessment of the lower limbs will be necessary to identify the specific cause of any abnormality in gait.

Certain abnormal patterns of gait are well recognized. Pain in one limb causes avoidance of weight bearing by that limb and shortening of that phase of the gait cycle. The cycle is asymmetric, with shorter steps on the painful limb, and is described as an antalgic gait. Weakness of the hip adductors results in dipping of the pelvis to the other side when bearing weight on the affected limb. During the gait cycle the person leans the upper part of the body over the weak hip to compensate for this and maintain balance. This Trendelenburg gait is apparent as side-to-side movement of the shoulders when walking. Such movement of the shoulders is also seen with an inequality in leg length, which leads to tilting of the pelvis during the gait cycle. An alternative gait with leg length inequality is to flex the knee of the longer leg to clear the ground during the swing phase, with consequent dipping of the person up and down. A dropfoot results in a high-stepping gait to avoid tripping on the toes during the swing phase.

Posture

The normal symmetry of the body helps identify abnormalities in posture. Observe the whole person while standing and dressed only in underwear, and look for equality of height of landmarks—the tips of the shoulders, the scapulae, the pelvic brim, and the crease of the buttocks. Inspect the spine carefully for its normal curves and identify any scoliosis. Look at the feet during normal posture.

Documentation

The history and examination need to be documented. The history should form a clear story that another clinician can read, assess, and interpret. The

Text continued on p. 223

BOX 28.5 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM—HEAD, SPINE, AND PELVIS**Cervical spine**

- Look** Look for hyperextension caused by thoracic kyphosis or loss of normal lordosis.
- Feel** Percuss the vertebrae for tenderness.
Palpate the paraspinal muscles for spasm or tenderness.
- Move** Actively turn the head to the right, left, flexion, extension, rotation to the left and right, and lateral flexion to the left and right with the examiner gently guiding the head to ensure that maximum range is reached.
- Tests** Problems related to the cervical spine are often associated with neurologic symptoms and signs, which should be elicited.

Posture and alignment of the head and neck.



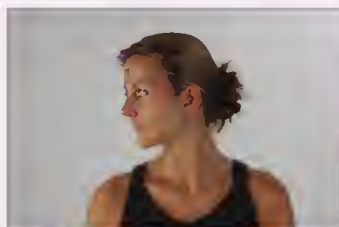
Extension.



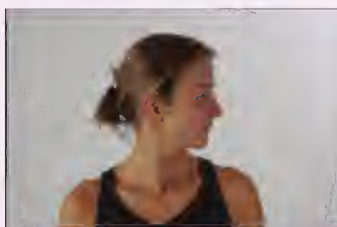
Flexion.



Right rotation.



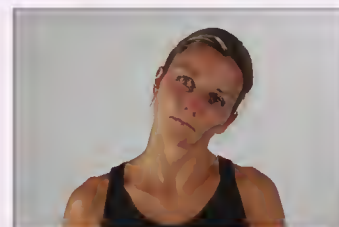
Left rotation.



Right lateral flexion.

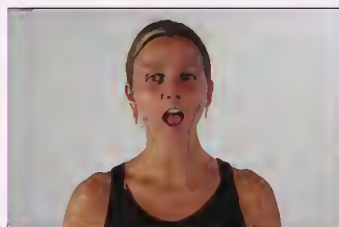


Left lateral flexion.

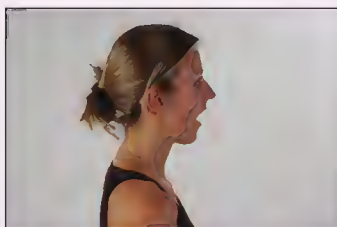
**Temporomandibular joints**

- Feel** Palpate over the joint line for tenderness, crepitus, or clicking. The joint can be palpated anterior to the tragus or from within the external auditory meatus. Feel for crepitus or clicking on movement.
- Move** Open the mouth wide. Deviate the lower jaw side to side.

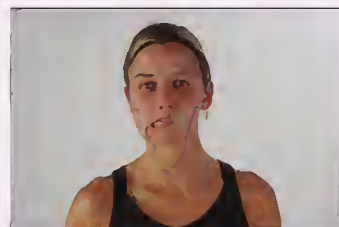
Mouth opening.



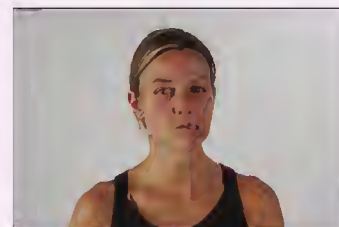
Mouth opening.



Side-to-side movement of the jaw.

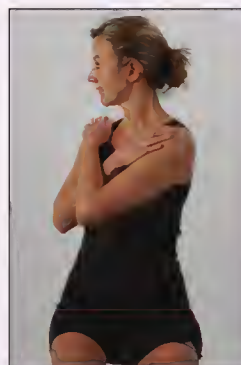


Side-to-side movement of the jaw.

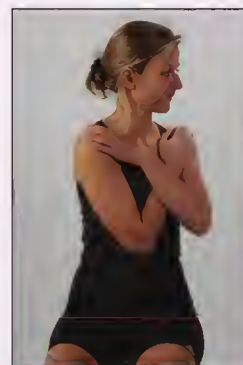
**Dorsal spine**

- Look** Look for any kyphosis or scoliosis. Look for any asymmetry of the scapulae.
- Feel** Percuss the vertebrae for tenderness.
Palpate the paraspinal muscles for spasm or tenderness.
- Move** Fix the pelvis by sitting and rotate the upper part of the body to the right and left with the examiner gently guiding the shoulders to ensure that maximum range is reached.

Right rotation.



Left rotation.



BOX 28.5 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM—HEAD, SPINE, AND PELVIS—cont'd**Lumbar spine**

Look	Look for a normal lordosis or any scoliosis. Look for any asymmetry of the pelvic brim or the crease of the buttocks.
Feel	Percuss the vertebrae for tenderness. Palpate the paraspinal muscles for spasm or tenderness.
Move	While standing in an erect posture, bend forward as though trying to touch the toes, bend backward to arch the back, and bend from side to side. The person may be able to place the hands flat on the ground if hypermobile. Flexion can be more formally assessed with the Schober test by measuring extension of a line drawn when upright between 10 cm above and 5 cm below the level of the posterior iliac spines as identified by the dimples of Venus.
Stress	Tests for tension of the lumbar roots should be performed when patient is lying down. <i>Femoral nerve stretch test:</i> With the person lying prone, hold the ankle and passively flex the knee as far as it will go. The test is positive if pain is felt in the isolateral anterior aspect of the thigh. <i>Sciatic nerve stretch test:</i> With the person lying supine, gently raise the straight leg to the maximum angle achievable without significant pain and then dorsiflex the ankle. An increase in pain indicates sciatic nerve root tension.
Tests	The lumbar spine houses the lumbar spinal nerve roots, and neurologic symptoms and signs should be elicited.

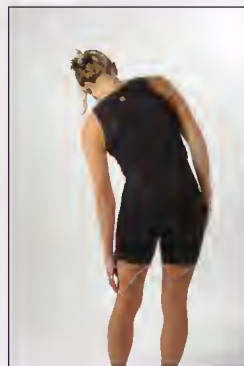
Lumbar flexion.



Lumbar extension.



Left lateral flexion.



Right lateral flexion.

**Pelvis and sacroiliac joints**

Look	Look for asymmetry of the pelvic brim and the lower part of buttocks.
Feel	Palpate for tenderness in the buttocks. Palpate the sacroiliac joints for tenderness.
Stress	Stress the sacroiliac joints for tenderness. Various methods can be used to compress or distract the joint to elicit tenderness, such as pushing on both iliac wings when the person is lying supine.

Test for cruralgia.



Test for sciatica.



Test for sciatica.



BOX 28.6 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM—UPPER EXTREMITY**Shoulder**

- Look** Look for any asymmetry in the scapulae and posture or muscle wasting.
- Feel** Palpate over the midpoint of each trapezius and the supraspinatus to identify tender spots. Palpate over the acromioclavicular joint line, glenohumeral joint line, and bicipital groove.
- Move** Actively elevate the arms into the air.
Actively place the hands behind the head.
Actively place the hands behind the back.
Steady the scapula and, with the elbow at 90 degrees, rotate internally and externally; then passively abduct, flex, and internally and externally rotate the shoulder.
- Tests** Several methods can be used to establish whether impingement is present.

Abduction and external rotation.



Adduction, extension, and internal rotation.



External rotation.



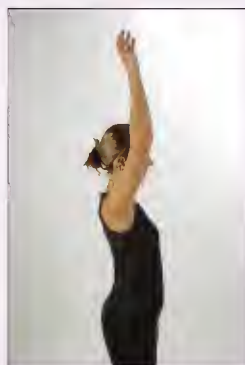
Internal rotation.



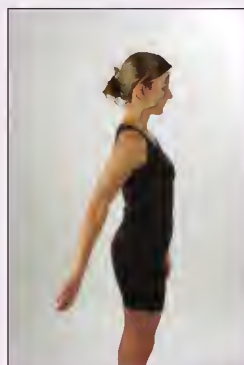
Flexion.



Elevation.



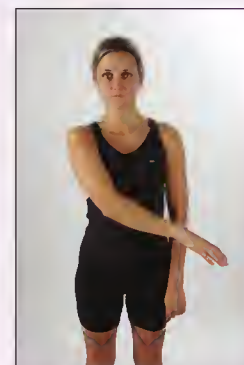
Extension.



Abduction.



Adduction.

**Elbow**

- Look** Look for any swelling or deformity. Joint swelling is first apparent in the para-olecranon groove. The olecranon is a common site for bursitis and rheumatoid nodules.
- Feel** Palpate over the para-olecranon groove for synovial swelling or tenderness. Palpate over the medial and lateral epicondyles for tenderness. Assess the laxity of the skin if considering hypermobility.
- Move** Passively extend and flex the elbow and look for hyperextension.

Palpate over the medial and lateral epicondyles for tenderness.



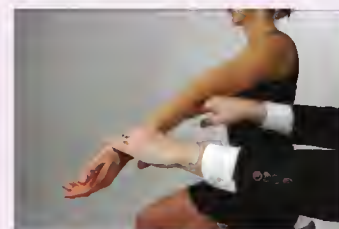
Elbow flexion.



Elbow extension.



Assess for elbow hyperextensibility.

**Wrist**

- Look** Look for any swelling or deformity.
Swelling over the dorsum involves the joint or extensor tendon sheath. With active extension of the fingers, swelling of the extensor tendon sheath moves—the tuck sign.
Look for squaring of the base of the palm because of swelling of the carpometacarpal joint seen in osteoarthritis. Typical deformities in established rheumatoid arthritis are volar subluxation and radial deviation at the wrist with dorsal subluxation of the ulnar styloid.
- Feel** Palpate over the joint line for tenderness or synovial swelling.
- Move** Passively flex and extend the wrist.
Assess for hypermobility by passively moving the thumb toward the volar aspect of the forearm with the wrist in full flexion.
Use resisted flexion, extension, or pronation if assessing epicondylitis at the elbow.
- Stress** Assess stability of the inferior radioulnar joint by demonstrating movement when pressing down on the radial head—the piano key sign.

BOX 28.6 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM—UPPER EXTREMITY—cont'd

Wrist flexion.



Wrist extension.



Resisted active wrist extension to test for lateral epicondylitis.



Resisted active wrist flexion to test for medial epicondylitis.



Wrist ulnar movement.



Wrist radial movement.



Assess supination.



Assess pronation.

**Hand****Look**

Look for any swelling or deformity. Is the swelling specific to joints or tendons or is it diffuse?

Look for any associated clues. Much can be learned from the hand. Look for wasting of the small muscles; inspect the skin, nails, and nail beds.

Typical deformities in established rheumatoid arthritis are ulnar deviation of the fingers at the metacarpophalangeal joints, hyperextension at the proximal interphalangeal joint with flexion at the distal interphalangeal joint (swan-neck deformity), or flexion at the proximal interphalangeal joint with hyperextension at the distal interphalangeal joint (boutonnière deformity). A Z-deformity of the thumb can be seen in systemic lupus erythematosus.

Feel

Palpate over each joint line for tenderness or bony or synovial swelling. Squeezing across all the knuckles together can be used as a composite assessment for tenderness of the metacarpophalangeal joints.

Move

Palpate the tendon sheaths during movement to detect crepitus or tendon nodules. Feel the quality of the skin for induration, thickening, or laxity.

Actively make a tight fist with palmar aspect uppermost to see whether all fingers fully flex and estimate strength of grip by observing blanching of the palmar surface of the hand on release of the fist.

Actively make a firm pinch grip between the thumb and fingers individually.

Passively extend the fifth finger to assess for hypermobility.

Actively make a fist.



Release the grip and observe the palm for blanching.



Palpate the metacarpophalangeal joints.



Palpate the proximal interphalangeal joints.



Squeeze across the metacarpophalangeal joints.



Palpate the tendon sheaths.



Assess grip strength.



Assess pinch grip.



Assess for hypermobility of the thumb and wrist.



Assess hyperextensibility of the fifth finger.



BOX 28.7 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM—LOWER EXTREMITY

Observing gait is an important part of assessing the lower limbs. Examination should be done with the person lying on a bench. Measure leg length if a pelvic tilt when standing suggests shortening or with a discrepancy in the position of the medial malleoli with a straightened pelvis. Pain in the hindquarter is often called “hip pain” but can have many origins that need elucidation by examination.

Hip**Look**

Observation of the person walking will have given some information about the hips. Wasting of the buttock or thigh muscles from disuse may be apparent.

Feel

Palpation should be used to clarify the origin of any symptoms. The word *hip* is used to describe symptoms anywhere in the hindquarter.

Tenderness is usually related to tendinitis or bursitis.

Move

With the person supine, actively and then passively flex the hip as far as possible with the knee in flexion to look for contralateral movement.

With the hip passively flexed to 90 degrees, rotate it internally and externally by holding the foot, supporting the thigh, and moving the lower part of the leg inward and outward while being careful to not inflict pain.

Internal rotation is often affected first in disorders of the hip joint.

With the person lying supine and the leg fully extended, hold the contralateral anterior superior iliac spine to prevent movement of the pelvis and passively abduct and adduct the leg.

With the person lying prone or on the side, passively extend the straightened leg.

Assess leg length by the relative position of the medial malleoli with the pelvis straightened.



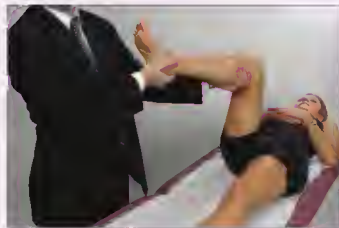
Hip flexion-active.



Hip flexion-passive-to look for contralateral movement.



Internal rotation.



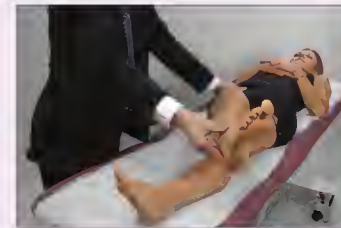
External rotation.



Abduction.



Adduction.

**Knee****Look**

Observation of the person walking will have given some information about the knees. Wasting of the thigh muscles from disuse may be apparent. Instability may be present. Look for any swelling and its exact site because it may relate to the joint or periarticular structures. Look for any deformity. Typical deformities are fixed flexion, valgus, or varus.

Feel

Palpate for tenderness or swelling and establish the affected structures. Palpate the joint line for tenderness. Assess for articular swelling and effusion by the bulge sign or patella tap (see Fig. 28.5). Palpate for a popliteal cyst.

Move

With the person supine, passively flex the knee as far as possible with the hip in flexion. If the hip is also abnormal, hang the leg over the side of the bench to examine flexion of the knee without hip flexion.

With the person lying supine, fully extend the leg in an attempt to touch the back of the knee onto the bench. Assess passively if the knee will hyperextend.

Stress

Anterior and posterior stability should be tested to assess the cruciate ligaments.

Medial and lateral stability should be tested to assess the collateral ligaments and for loss of joint space.

Knee flexion.



Knee extension.



Stress the cruciate ligaments.



Stress the collateral ligaments.



BOX 28.7 REGIONAL EXAMINATION OF THE MUSCULOSKELETAL SYSTEM—LOWER EXTREMITY—cont'd**Foot and ankle**

- Look** Observe the feet when standing and during walking. Look for a normal longitudinal arch and, during the gait cycle, look for normal heel strike and take-off from the forefoot. Look for any callosities beneath the metatarsal heads and for any swelling and redness of the toes. Swelling of the metatarsophalangeal joints can separate the toes so that daylight becomes visible between them. Look for any deformities. Deformities include pes planus (flattening of the longitudinal arch); pronation of the foot; valgus deformity of the hindfoot (eversion of the subtalar joint); pes cavus (high longitudinal arch); talipes equinovarus; hallux valgus; subluxation of the metatarsophalangeal joints; and "claw," "hammer," and "mallet" deformities of the toes.
- Feel** Symptoms may relate to the joint, periarticular bone, tendons and their sheaths and insertions, or bursae. Palpate for tenderness or swelling and establish the affected structures. Squeeze across the metatarsus, and if tenderness is noted, examine the metatarsophalangeal joints individually.
- Move** Actively flex and extend the ankle. Actively invert and supinate and then evert and pronate the foot. Passively deviate the heel medially (inversion) and laterally (eversion) by grasping the heel between the thumb and index finger of one hand and moving it while anchoring the lower part of the leg with the other hand. Passively rotate the forefoot on the hindfoot by grasping the forefoot between the thumb and fingers while anchoring the heel with the other hand to assess the midtarsal joint. See whether the patient is able to stand on the toes, which requires an intact posterior tibialis tendon.

Metatarsal squeeze.



Ankle flexion.



Ankle extension.



Inversion and supination.



Eversion and pronation.



Subtalar inversion.



Subtalar eversion.



Midtarsal rotation.



Assessing the first metatarsophalangeal joint.



examination is documented most easily on a homunculus. A standardized approach is recommended to denote deformities, restricted movement, joint swelling, and joint tenderness (Fig. 28.7).

Various disease-specific standardized assessments can be used to evaluate conditions such as rheumatoid arthritis, ankylosing spondylitis, or SLE. These conditions are considered elsewhere in this text.

CONCLUDING THE CONSULTATION

Interpretation

The aim of the consultation is to identify the cause of the person's problems, assess their impact and response to any treatment, plan management, and fully discuss this and the expected outcome with the patient.

Making a diagnosis requires integration of the history and findings on examination with knowledge of the possible causes and results of appropriate investigations. Pattern recognition plays a key role (see Chapter 29). Knowing what is likely at different stages of life in different individuals and looking for clues throughout the consultation are important. Because musculoskeletal conditions are common, it must be remembered that multiple pathologic processes are possible.

ANNOTATING THE EXAMINATION FINDINGS

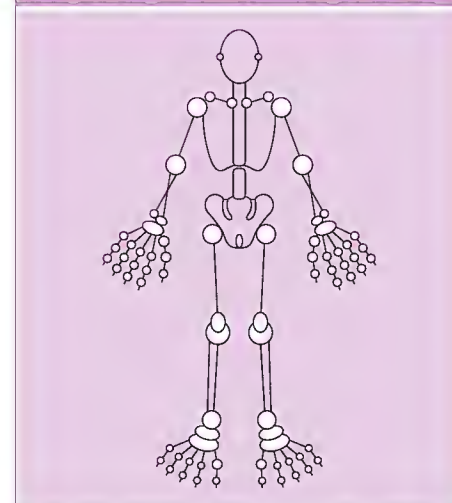


Fig. 28.7 A homunculus can be used to annotate abnormal findings during examination.

Communicating the findings

The most important part of the consultation, especially for the patient, is communication of the findings and conclusions. Ensure that the person feels that all the problems have been listened to, questions answered, and expectations met as far as possible. It is sometimes difficult to explain all of a person's symptoms with precise tissue-based causes, and this can cause

concern and loss of confidence in the physician. Concepts of mechanical back pain and fibromyalgia can be difficult for the person to grasp. This part of the consultation needs the most time but is usually the most hurried part. A specialist nurse can supplement the information that the person wants, and a lot of material about musculoskeletal conditions is available from support organizations such as the Arthritis Foundation or Arthritis Care and through the Internet.

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29

Pattern recognition in arthritis

■ OSVALDO HÜBSCHER

- Pattern recognition is the key to diagnosis of the rheumatic disorders; central questions that need to be asked are as follow:
 - Is a musculoskeletal problem or disease present in another system?
 - Is the condition articular or periarticular?
 - Is the condition mechanical (arthrosis) or inflammatory?
 - Does it affect appendicular or axial structures, or both?
- These questions can be answered from synthesis of data from the history and physical examination:
 - *From the history:* mode of onset, sequence of development of the different features, and the duration and pattern of the symptoms
 - *From the physical examination:* the number, distribution, and pattern of the affected joints or periarticular structures and the nature of any systemic involvement

INTRODUCTION

The history and physical examination are the two most important components of the diagnostic process for patients complaining of musculoskeletal pain, stiffness, or other symptoms.¹ Clinical judgment in interpreting the findings elicited from the history and physical examination should allow the physician to answer several key questions:

- Do the symptoms originate in the musculoskeletal system or in other systems (e.g., neurologic disorders, vascular disease, Pancoast syndrome)?
- Is it an articular or nonarticular process? A substantial number of patients will have localized mechanical problems or nonspecific soft tissue conditions. Muscular syndromes or pain originating in periarticular foci can often mimic an articular origin (sometimes affecting more than one site). Examples are unilateral or bilateral anserine bursitis resembling an intraarticular knee joint disorder and extensor tendinitis of the thumb (de Quervain tenosynovitis) mimicking wrist involvement. Primary bone conditions (e.g., Paget disease, osteoid osteoma, osteomalacia), as well as infiltrative (e.g., lymphomas) and lytic (e.g., metastatic disease, osteitis fibrosa cystica) lesions, may also provoke pain referred to a joint.
- Does the patient have arthralgia or arthritis? Arthralgia refers to pain localized to a joint, whereas arthritis refers to objective evidence of an inflammatory change in the joint. Arthritis is a much more specific sign of an articular disorder.
- Is evidence of other organ involvement present (e.g., systemic connective tissue disorders), or does it appear to be a disorder restricted to the musculoskeletal system (e.g., osteoarthritis)?
- Is the articular problem inflammatory, mechanical, degenerative, or something else?
- Does the disease affect axial or appendicular structures, or both?

Once the physician has established that the disorder originates in the joints, several other aspects of the history and physical examination should be considered to delineate a diagnostic pattern of arthropathy. The attributes of joint involvement that are considered in this section focus on those dominating the clinical picture during the early phases of rheumatologic

disorders, when treatment could be of greater benefit. Moreover, the diagnostic value of pattern recognition will be considered without taking into account other characteristics of the patient (e.g., gender, age, family history, or the presence or absence of extraarticular features of disease) normally contributing to diagnostic certainty.

MODE OF ONSET AND DURATION OF SYMPTOMS

Some arthropathies typically cause an acute onset of pain with the peak intensity being reached within hours or a few days, whereas in others maximum severity is attained gradually (over a period of several weeks or months). The same disorder may have a sudden onset in some patients but be gradual in others. Rheumatoid arthritis (RA), for instance, may be manifested as an acute polyarthritis (especially in the elderly) and psoriatic arthritis as an acute monoarthritis resembling gout, but in most cases both disorders begin insidiously. Examples of disorders with an acute onset also include bacterial arthritis, rheumatic fever, reactive arthritis, sarcoidosis, palindromic rheumatism, and crystal-induced arthritis (the best example being nocturnal attacks of gout). An arthritogenic virus (e.g., rubella virus and hepatitis B virus) may also cause acute synovitis. An insidious pattern is common with osteoarthritis (OA), early-onset pauciarticular juvenile idiopathic arthritis (EOPA-JIA) and the polyarticular-onset type, mycobacterial and fungal arthritis, and most cases of neuropathic arthropathy (Charcot joints).

Arthritic disorders lasting less than 4 to 6 weeks are considered to be self-limited in practical terms, whereas those lasting longer are considered to be chronic. In self-limited arthritic disorders the duration of symptoms and signs may be a valuable discriminating feature. Early episodes of monoarticular gout tend to subside spontaneously after 7 to 10 days and resolution is complete, acute or subacute attacks of pseudogout (calcium pyrophosphate dihydrate crystal deposition disease [CPPD]) may last from 2 to 3 days to 3 to 4 weeks, and most articular or periarticular episodes of palindromic rheumatism disappear within hours to several days with no articular sequelae. Steady inflammation in an individual joint for more than a few days or a week in children is highly unlikely to be due to rheumatic fever.

THE NUMBER OF AFFECTED JOINTS

The clinical pattern may be monoarticular, oligoarticular, or polyarticular, as reflected by involvement restricted to a single, a few, or several joints, respectively.

Although almost any individual arthropathy may begin as monoarthritis, the initial pattern of some disorders is characteristically monoarticular regardless of the subsequent course. In particular, patients with an acute painful synovitis of a single joint and varying degrees of overlying redness represent a challenging subset in clinical rheumatology.^{2,3} Although redness may occur with any acute monoarthritis regardless of the cause, its presence usually evokes a restricted list of possible diagnoses (Table 29.1). The most common are crystal-induced synovitis (including acute calcific periarthritis),⁴ bacterial infectious arthritis (Fig. 29.1), traumatic conditions, psoriatic arthritis, and palindromic rheumatism (in which the joint may have a dark, bluish redness).

Chronic monoarthritis is often the initial manifestation of a variety of joint disorders (Table 29.2) and may or may not spread with time to other joints; histologic elucidation may be necessary to make the correct diagnosis. In a substantial number of patients the cause remains undetermined.⁵

TABLE 29.1

The red-hot joint

Type	Subtypes/examples (if applicable)
Infectious	Bacterial Neisserial (may be preceded by transient polyarticular disease) Mycobacterial Virus Lyme disease
Crystal induced	Gout Calcium pyrophosphate dihydrate crystal deposition disease (pseudogout type) Hydroxyapatite (acute calcific periarthritis)
Traumatic/fracture	
Palindromic rheumatism	
Psoriatic arthritis	
Reactive arthritis	
Bacterial endocarditis	
Sarcoidosis	

TABLE 29.2

Selected causes of chronic monoarthritis

Type	Subtypes/examples (if applicable)
Infectious arthritis	Mycobacterial, fungal, bacterial, viral, Lyme disease
Inflammatory arthritis	Crystal induced Monoarticular rheumatoid arthritis Early-onset pauciarticular juvenile idiopathic arthritis Seronegative spondyloarthritis (ankylosing spondylitis, reactive arthritis, colitic arthritis, undifferentiated spondyloarthritis) Psoriatic arthropathy Foreign body synovitis (e.g., plant thorn synovitis) Sarcoidosis
Noninflammatory arthritis	Osteoarthritis Internal derangement Osteonecrosis Synovial osteochondromatosis Reflex sympathetic dystrophy Hemarthrosis (e.g., coagulopathy, anticoagulants) Neuropathic (Charcot joint) Paget disease Stress fracture Transient regional osteoporosis Juvenile osteochondroses
Tumors	Pigmented villonodular synovitis Lipoma arborescens Synovial metastasis from solid tumors Synovial sarcoma Osteoid osteoma
Undiagnosed	

Involvement of two to four separate joints is referred to as oligoarthritis. In general, rheumatologic disorders manifested as monoarthritis may also be oligoarticular. Despite this overlap, in some cases involvement of two or three joints (rather than one) may significantly narrow the diagnostic spectrum. As an example, lower limb oligoarthritis (especially of the knees and ankles) in an asymmetric fashion is reminiscent of the HLA-B27-associated seronegative spondyloarthropathies.⁶ An asymmetric oligoarthritis affecting scattered distal interphalangeal (DIP), proximal interphalangeal (PIP), and metacarpophalangeal (MCP) joints of the hands characterizes a common subgroup of patients with psoriatic arthritis.

The third articular pattern is one in which polyarticular involvement dominates the clinical picture. A wide variety of inflammatory and noninflammatory disorders, both common and uncommon, may be manifested as polyarthritis (Table 29.3).⁷

TABLE 29.3

Distribution of selected oligoarthritis and polyarthritis

Symmetric	Asymmetric
Inflammatory	
RA, JIA (systemic and polyarticular types) Adult-onset Still disease Systemic lupus erythematosus Mixed connective tissue disease Polymyalgia rheumatica Rheumatic fever (adult onset) Jaccoud arthritis	Ankylosing spondylitis Reactive arthritis Psoriatic arthritis (oligoarticular type) Enteropathic arthritis Undifferentiated spondyloarthritis JIA (pauciarticular types) Palindromic rheumatism
Degenerative/crystal induced	
Osteoarthritis (primary generalized, erosive, and nodal types) CPPD (pseudo-RA type) "Milwaukee shoulder" Hemochromatosis arthropathy	Gout (especially oligoarthritis) CPPD (pseudogout type)
Infectious	
Viral arthritis	Bacterial arthritis Bacterial endocarditis Lyme disease (late phase)
Miscellaneous	
Hypertrophic osteoarthropathy Amyloid arthropathy Myxedematous arthropathy Sarcoid arthritis (acute type) Cancer-associated arthritis	Cancer-associated arthritis Pancreatic disease-associated arthritis

Most asymmetric arthritides may be or are characteristically initially monoarticular. CPPD, calcium pyrophosphate dihydrate crystal deposition disease; JIA, juvenile idiopathic arthritis; RA, rheumatoid arthritis.



Fig. 29.1 The red-hot joint. Septic arthritis of the ring finger metacarpophalangeal joint has resulted in swelling and intense redness of the skin.

IS THE ARTHRITIS SYMMETRIC OR ASYMMETRIC?

This distinction is very helpful in the differential diagnosis of oligoarticular and polyarticular conditions, with RA being the classic example of symmetric arthritis, which denotes simultaneous inflammatory signs in pairs of peripheral joints. Symmetry is not necessarily strict in the hands; the same MCP or PIP joint may not be equally affected in both extremities of patients with RA. Erosive inflammatory OA, pachydermodactyly, parvovirus arthritis, and many cases of systemic lupus erythematosus (SLE) may resemble RA, whereas reactive arthritis, psoriatic arthritis, and polyarticular gout are usually characterized by asymmetric involvement of appendicular joints.

Fig. 29.2 Rheumatic disorders affecting the distal interphalangeal (DIP) joints. (a) Psoriatic arthropathy of two DIP joints and the interphalangeal joint of the thumb, together with nail dystrophy. (b) Osteoarthritis is the most common disorder affecting this segment (Heberden nodes).

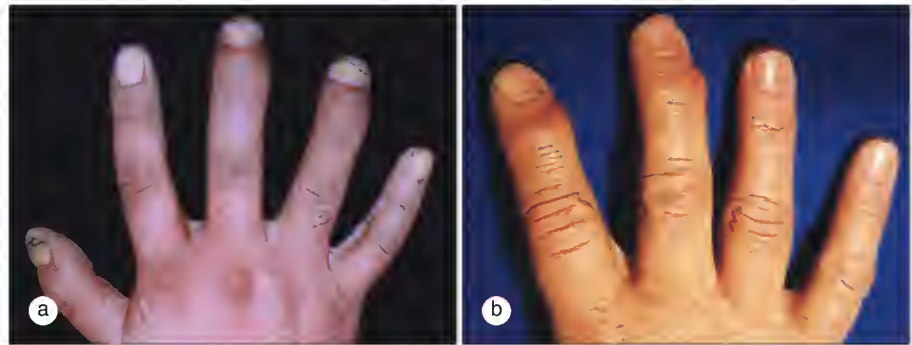


TABLE 29.4
Chronic arthropathies with peripheral and axial involvement

Type	Subtypes/examples (if applicable)
Inflammatory	
Spondyloarthritis	Ankylosing spondylitis Reactive arthritis Psoriatic arthropathy (a subset of patients) Enteropathic arthritis Undifferentiated
Juvenile idiopathic arthritis	Systemic and polyarticular onset
Adult-onset Still disease	
SAPHO syndrome	
Noninflammatory	
Osteoarthritis	
Diffuse idiopathic skeletal hyperostosis	
Acromegaly	
Ochronosis	
Spondyloepiphyseal dysplasia	
<i>SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis.</i>	

Both symmetric and asymmetric seronegative oligoarthritis and polyarthritis have been described in association with neoplasia in rare cases.⁸

This feature of the articular pattern has obvious limitations: every patient with a symmetric disorder may have an initial asymmetric phase. Table 29.3 lists a number of conditions classified according to the most characteristic pattern.

LOCALIZATION OF AFFECTED JOINTS

Axial involvement

Axial structures include, apart from the spine, centrally located joints such as the sacroiliac, sternoclavicular, and manubriosternal joints and the rest of the chest wall and sometimes the shoulders and hips.

In the presence of peripheral arthritis, one of the most helpful clues in the differential diagnosis is to determine the presence of concomitant axial involvement. Whereas some rheumatologic conditions rarely affect the axial segments (e.g., crystal-related syndromes, systemic connective tissue disorders), a combined pattern is often seen in others (Table 29.4). OA of the spine frequently coexists with appendicular involvement. Diffuse idiopathic skeletal hyperostosis affects mainly the dorsal and lumbar spinal segments and may be accompanied by OA in atypical upper limb joints (elbow, shoulder, MCP).⁹ Patients with ankylosing spondylitis, psoriatic arthritis, reactive arthritis (after both enteric and sexually transmitted infection), and arthritis accompanying inflammatory bowel disease may also exhibit varying degrees of combined axial and peripheral involvement. Polyarticular and systemic-onset juvenile idiopathic arthritis, as well as adult-onset Still disease, commonly affects the apophyseal joints of the cervical spine in addition to peripheral joints. SAPHO syndrome (synovitis, acne,



Fig. 29.3 Acute gout. The first metatarsophalangeal joint is involved at some time in approximately 75% of patients. Desquamation of the skin often occurs.

pustulosis, hyperostosis, and osteitis) is a further example among the much less frequent arthritides.¹⁰

Peripheral involvement

Individual joints, tendon sheaths, and bursae may be affected by a large number of rheumatic disorders. Involvement of some joints, however, may be closely associated with the early phases of a particular disease or group of diseases and thereby facilitate the diagnostic process. Common examples in clinical rheumatology include the following:

- Bilateral and symmetric involvement of small and large joints is typical of RA. The MCP and PIP joints of the fingers and wrists are commonly affected. Distal joints are less frequently involved.
- Exclusive inflammatory DIP joint involvement of the fingers is a relatively infrequent, though important clue to the diagnosis of a subset of patients with psoriatic arthritis. Nodal OA (Heberden nodes) is the most frequently encountered disorder affecting this segment (Fig. 29.2).
- Bilateral bony enlargement of the second and third MCP joints with restricted motion is characteristic of hemochromatosis-related arthropathy.¹¹
- Severe proximal pain (neck, shoulders, and buttocks) with minimal objective findings in an appropriate setting is highly indicative of polymyalgia rheumatica, although the onset of RA in the elderly may be difficult to differentiate from this entity.¹²
- Bilateral shoulder disease with striking joint enlargement (shoulder pad sign) is very typical of amyloid arthropathy.¹³
- Podagra: the metatarsophalangeal joint of the big toe is typically affected during acute gouty attacks (Fig. 29.3). Less frequently, CPPD and other crystalline disorders,¹⁴ as well as OA, psoriatic arthritis, and a wide variety of conditions, may mimic the podagra of gout.¹⁵ The occurrence of “pseudopodagra” is one of the best examples of how the specific site of the index joint, though helpful, can only suggest the diagnosis.



Fig. 29.4 Sausage fingers and toes. (a) Psoriatic arthropathy/dactylitis of the third finger. (b) Reactive arthritis/dactylitis more evident in the second and third toes. Note the nail dystrophy.

- Pain and swelling in the knees and ankles (often asymmetric) may be seen in seronegative spondyloarthritis, including reactive arthritis after infection with *Chlamydia* and enteric organisms.¹⁶ In both of the latter conditions, involvement of the toes is also frequent, and the clinical appearance of dactylitis (“sausage toe”) is most typical. Dactylitis is also very reminiscent of psoriatic arthritis (Fig. 29.4).

SEQUENCE OF JOINT INVOLVEMENT

Clinical involvement of joints may follow three major patterns: additive, migratory, and intermittent. An additive pattern refers to the involvement of additional joints while the previous joints remain symptomatic. Polyarticular OA, reactive arthritis, and RA are typical examples of this progressive sequence.

A migratory pattern means that the process ceases or abates in one joint while simultaneously or immediately thereafter starting in a previously normal joint. Whipple disease and neisserial arthritis may be manifested as a migratory arthritis and tenosynovitis, and the fleeting arthritis of rheumatic fever in children is a classic example.

The intermittent rheumatologic disorders are characterized by complete remission of symptoms and signs until the next recurrence in the same or other joints. No evidence of active disease or residual signs can be detected during intervals. Crystal-induced arthritis, familial Mediterranean fever, Muckle-Wells syndrome, the arthritis seen in Whipple disease, and palindromic rheumatism usually follow this pattern for years with asymptomatic periods that vary in length. Adult-onset Still disease may also run a polycyclic clinical course.¹⁷

LOCAL PATTERN OF JOINT DISEASE

Some local signs may be of great diagnostic help. In the same manner as the presence of redness often suggests a particular group of diagnoses (see earlier), the occurrence of skin desquamation when the inflammation declines is suggestive of acute gouty monoarthritis. Additional findings that may be of diagnostic value include the following:

- Enlargement of a given individual joint may be symmetric or asymmetric (more obvious in the fingers). Fusiform swelling of the PIP joints is typical of RA, as opposed to Heberden nodes, erosive OA, chronic sarcoidosis, and tophaceous gout, which often produce asymmetric enlargement of the affected joint.
- The local signs of inflammation may extend beyond the anatomic limits of the joint. This feature may be a major diagnostic contribution, as illustrated by the presence of dactylitis. A diffusely painful swollen hand or foot may indicate reflex sympathetic dystrophy syndrome in that extremity (Fig. 29.5). Bilateral symmetric puffy swelling of hands and fingers (and sometimes the feet) may be seen in the early phases of systemic sclerosis and mixed connective tissue disease (Fig. 29.6). In a totally different clinical context, diffuse swelling of both hands with pitting is a conspicuous feature of the syndrome of “remitting seronegative symmetric synovitis with pitting edema” (Fig. 29.7).¹⁸



Fig. 29.5 Reflex sympathetic dystrophy syndrome. Diffuse edematous swelling of the entire right hand is evident.



Fig. 29.6 Swollen hands in mixed connective tissue disease. The presence of symmetric puffy hands is a common early finding. Similar changes are often seen in the early stages of scleroderma.



Fig. 29.7 Remitting seronegative symmetric synovitis with pitting edema. Note the massive acute painful edema of both hands in an 80-year-old man.



Fig. 29.8 Flexion contractures of all fingers in carcinoma-associated fasciitis. Painful swelling and contractures of both hands developed in a 50-year-old woman secondary to marked hardening and thickening of the palmar fascia. Palmar erythema is also present. Investigations revealed ovarian carcinoma, the most commonly associated neoplasm in these patients.

- Symmetric enlargement of the hands and feet associated with variable degrees of pain is seen from time to time by rheumatologists. Digital clubbing and local signs of inflammation may or may not be prominent. Primary or secondary hypertrophic osteoarthropathy,¹⁹ acromegaly, and the rare thyroid acropachy should be considered when encountering these cases.
- Flexion contractures of the fingers (plus other segments in some cases) as a result of structural changes in soft tissues lead to a number of clinical diagnoses apart from systemic sclerosis and eosinophilic cutaneous fibrosis. β_2 -Microglobulin amyloidosis, nephrogenic systemic fibrosis (both entities occurring in patients undergoing hemodialysis), diabetic cheiroarthropathy, and the syndrome of cancer-associated palmar fasciitis are among the diagnostic options (Fig. 29.8).²⁰

THE CLINICAL VALUE OF PATTERNS OF ARTHROPATHY

Evidence of some distinct articular patterns focuses the spectrum of diagnostic options and reduces unnecessary diagnostic testing.²¹ These patterns are not diagnostic per se, and they must always be viewed only as a rough guide for various reasons.

First, unrelated arthropathies may share one or more clinical patterns. As an example, EOPA-JIA, tuberculous arthritis, and foreign body arthritis



Fig. 29.9 Early-onset pauciarticular juvenile idiopathic arthritis in a young girl with monoarthritis. This patient had associated asymptomatic iridocyclitis. In some cases, synovial biopsy is mandatory to exclude other disorders.



Fig. 29.10 Gouty attack superimposed on a Heberden node. The clinical combination may be found in elderly patients treated with diuretics, as seen in the distal interphalangeal joint of the right index finger in this 78-year-old woman. Note the mild desquamation of the overlying skin.

(e.g., plant thorn synovitis)²² may all give rise to a chronic monoarthritis of the knee (Fig. 29.9). Both gout and pseudogout can mimic septic arthritis in the setting of febrile acute monoarthritis or polyarthritis.²³

Second, some major arthritides have more than one mode of onset. It should be remembered, for example, that chronic or intermittent monoarthritis and oligoarthritis (with no involvement of the small joints of the hands) may occasionally dominate the early course of RA before symmetric polyarthritis evolves. The same finding may also precede the appearance of typical inflammatory low back pain in patients with ankylosing spondylitis. Moreover, CPPD has many clinical patterns, with pseudogout and pseudoosteoarthritis being the most frequent.²⁴

Third, the articular pattern may change with time in the course of a single disorder. In these cases the correct diagnosis is facilitated when the patient is seen during the “typical” phase of the disease and may be hampered during the “atypical” phases. Early monoarticular gout is easy to suspect. In late stages it may be manifested as a chronic additive, relatively symmetric polyarticular disease, thereby leading to confusion with RA.²⁵ Finally, a single clinical pattern of joint disease may correspond to more than one diagnosis. Chronic gout superimposed on Heberden nodes²⁶ and the coexistence of crystals and infection in cases of subacute monoarthritis²⁷ are examples of this clinical situation (Fig. 29.10).

Fourth, a significant number of patients with peripheral arthritis do not fall into a specific diagnosis and may be described as having an undifferentiated peripheral arthritis (UPIA). Patients may persist with UPIA, progress to a specific diagnosis, or enter remission. An algorithm has been proposed to provide an approach to reach a diagnosis.²⁸

The combination of features just analyzed can often contribute to accurate diagnosis of an arthropathy. Diagnostic refinement may require the addition of laboratory studies, joint fluid examination, imaging techniques, and other methods. The more varied the articular patterns possible in a

given arthropathy, the more necessary complementary studies become. Systemic vasculitis, SLE, bacterial endocarditis, human immunodeficiency virus infection, solid tumors and leukemia, Behçet syndrome, sarcoidosis, relapsing polychondritis, and pancreatic-associated arthritis are examples of disorders in which several patterns of arthropathy have been described and a panoply of investigations may be required in addition to the physical findings. However, a careful history and physical examination remain the cornerstone of diagnostic evaluation of all patients with rheumatologic complaints.

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30

Role of laboratory tests in rheumatic disorders

■ EUGEN FEIST ■ GERD-RÜDIGER BURMESTER

- In rheumatic diseases laboratory tests contribute significantly to diagnosis, which should always be based on clinical findings. Measurement of biomarkers can also be useful for monitoring of treatment efficacy and safety as well as for stratification of patients to predict prognosis and treatment response.
- Sensitivity and specificity of virtually all biomarkers is limited, and therefore the laboratory diagnostics should be guided by the clinical picture.
- Laboratory markers provide different positive or negative predictive values; thus they can be used to exclude a disease in cases of a normal result or to support the clinical diagnosis in cases of a pathogenic result.

INTRODUCTION

In this chapter the focus is on commonly used laboratory tests that are relevant to major disorders seen by rheumatologists. Because laboratory test results are commonly part of the classification and diagnostic criteria, it is important to understand some key conceptual issues before using these tests in making diagnostic and treatment decisions.

Sensitivity is the percentage of *true positives* correctly identified. For example, if 60% of patients with rheumatoid arthritis (RA) have a positive result on a test for rheumatoid factor (RF) immunoglobulin M (IgM), the sensitivity of RF IgM for RA is 60%.

Specificity, on the other hand, is the percentage of *true negatives* correctly identified. For example, if 80% of patients without RA do not have RF IgM, then the specificity of RF IgM for RA is 80%.

The **likelihood ratio** (LR) incorporates both the sensitivity and specificity of a given test and provides a direct estimate of how much a test result will change the odds of having a disease. The likelihood ratio for a positive result (LR+) indicates the increase in the odds of having the disease when a test result is positive. The likelihood ratio for a negative result (LR-) indicates the decrease in the odds of having the disease when a test result is negative. The pretest odds is the likelihood that the patient has a specific disease before testing and is usually related to the prevalence of the disease. The likelihood ratio can be combined with information about the prevalence of the disease, characteristics of the patient pool, and information about the particular patient to determine the posttest odds of disease.

The more frequently a given condition, or a positive laboratory test result, occurs in the healthy population, the more likely that the condition will be diagnosed. Clinicians only seldom appreciate the importance of disease frequency (the pretest probability in Bayesian terms) in making a diagnosis.¹ The prevalence of positive results on a certain blood test in the healthy population must be known for the results of any rheumatologic screening test to be interpreted correctly (Table 30.1).

The concepts of false-negative and false-positive results are the converse of sensitivity and specificity, respectively, but are useful in clinical decision-making. False-positive results on antinuclear antibody (ANA) tests are one frequent reason for rheumatology consultations. For example, the prevalence of systemic lupus erythematosus (SLE) in the general population depends on the geographic region and is around 1 in 2000 to 1 in 10,000, whereas 1 in 20 healthy individuals have a usually weakly positive result in

ANA screening. Thus, given the frequency of nonspecific musculoskeletal symptoms in the general population, only a minority of such patients, even if they test positive for ANA, have SLE (Table 30.2).^{2,3}

Problems with false-negative results are more unusual but may have serious consequences. For example, patients with vasculitis and other life-threatening rheumatic diseases may develop irreversible end-organ damage because the diagnosis has been erroneously ruled out just on the basis of negative laboratory results.

Finally, there is always the risk of measurement error in any test, and this applies to all laboratory tests in rheumatic diseases. Whenever clinical signs and symptoms do not match the laboratory test results, the tests should be considered possibly in error and should be repeated.

LABORATORY TESTS IN RHEUMATIC DISEASES

The most common use of blood cell counts and measurements of biochemical markers is to monitor adverse effects of the various immunosuppressive medications used for the treatment of rheumatic conditions. In this context, detailed guidelines for monitoring treatment with various traditional as well as biologic disease-modifying antirheumatic drugs (DMARDs) were developed by different rheumatologic societies. Markers of the acute-phase response are mainly useful for evaluation of disease activity and differentiation of infectious complications.⁴

Blood panel**White blood cells**

Increased concentrations of neutrophils typically are seen in bacterial infections (e.g., infectious arthritis, septicemia, pneumonia) but also in active phases of rheumatic diseases such as RA and vasculitides. In patients undergoing immunosuppressive treatment, the presence of neutropenia should always raise suspicion of drug-related bone marrow suppression. In contrast, neutropenia in association with splenomegaly is a characteristic feature of active Felty syndrome. Lymphocytosis is present during several viral infections, whereas lymphopenia is commonly seen in active phases of SLE as well as with immunosuppressive drug treatment.

Eosinophilia, commonly seen in patients with allergies and parasitic infections, also is a typical feature of eosinophilic granulomatosis with polyangiitis (formerly known as *Churg-Strauss syndrome*) and eosinophilic fasciitis (Shulman syndrome). Of note, eosinophil blood counts are very sensitive to glucocorticoid treatment and show a rapid normalization.

Platelets

Thrombocytosis can accompany active phases of autoimmune diseases such as RA, whereas thrombocytopenia can be related to the presence of anti-thrombocyte antibodies, for example, in active SLE. Furthermore, decreased thrombocyte counts raise suspicion of drug-induced toxicity. To differentiate these conditions, examination of a peripheral blood smear and ultimately bone marrow aspiration are useful. Examination of bone marrow aspirates reveals the number and appearance of megakaryocytes and is the definitive test for many disorders causing marrow failure. However, normal number and appearance of megakaryocytes does not always indicate normal platelet production. For example, in patients with immune thrombocytopenic purpura, platelet production frequently is decreased, or not appropriately increased, despite the presence of normal-appearing megakaryocytes.⁵ If the bone marrow is normal but the spleen is enlarged, increased splenic sequestration is the likely cause of thrombocytopenia; if the bone marrow is normal and the spleen is not enlarged, excess platelet destruction is the

■ TABLE 30.1

Laboratory tests used in inflammatory rheumatic diseases: likelihood of disease in patients with positive test results

Blood test	Suspected disease	Patients with positive result	Prevalence of positive result in normal persons	Disease prevalence	Likelihood of disease if result is positive	Likelihood of disease if result is positive and joint pain is present
Rheumatoid factor	Rheumatoid arthritis	80/100	2/100	1/100	1/2	1/1.5
Antinuclear antibodies	Systemic lupus erythematosus	99/100	1/100	1/2000	1/20	1/5
HLA-B27	Ankylosing spondylitis	90/100	6/100	1/300	1/18	1/4.8 (1/3 for back pain)
Elevated uric acid	Gout	80/100	5/100	1/200	1/10	1.3

Adopted from Pincus T. A pragmatic approach to cost-effective use of laboratory tests and imaging procedures in patients with musculoskeletal symptoms. *Prim Care* 1993;20:795-814.

■ TABLE 30.2

Diagnosis of rheumatic diseases

Diagnosis	History and physical examination	Blood tests	Radiographs	Synovial fluid
Rheumatoid arthritis	Synovitis Morning stiffness	RF or ACPA in ~80% Elevated ESR in 50%-60%	Demineralization Erosions Joint space narrowing	Inflammation WBC > 10,000/mm ³
Systemic lupus erythematosus	Multisystem disease	ANA in >99% DNA antibodies in 60%-75%	Generally nondestructive arthritis	Mild inflammation
Axial spondyloarthritis	Back pain Axial involvement	HLA-B27 in ~90%	Sacroiliitis Vertebral squaring	Inflammation WBC 5000-20,000/mm ³
Gout	Recurrent attacks	Uric acid elevated in 75%-90%	Erosions, cysts	Negatively birefringent crystals on microscopy
Osteoarthritis	Pain ± swelling ± limited motion	Nonspecific abnormalities	Joint space narrowing Osteophytes	Noninflammatory WBC < 10,000/mm ³
Systemic sclerosis	Skin tightness proximal to metacarpophalangeal joints Facial skin tightening	ANA in >90% with HEp-2 cells	± Pulmonary fibrosis ± Esophageal dysmotility ± Calcinosis	Nonspecific
Polymyositis	Muscle weakness ± pain	CPK elevated in 80%, ANA and myositis-specific antibodies	Not helpful	Nonspecific

ACPA, anti-citrullinated peptide antibodies; ANA, antinuclear antibodies; CPK, creatine phosphokinase; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; WBC, white blood cell count. Adopted from Pincus T. Laboratory tests in rheumatic disease. In: Klippel JH, Dieppe PA, editors. *Rheumatology*. 2nd ed. London: Mosby International; 1997, p. 10.1-10.8.

likely cause. Some patients may have platelet dysfunction; a drug cause is suspected if symptoms began only after patients started taking a potentially causative drug. Some medications such as nonsteroidal antiinflammatory drugs (NSAIDs) can interfere with platelet function and lead to bleeding complications.

A hereditary cause is suspected if there is a lifelong history of easy bruising and bleeding after tooth extractions or surgery. In the case of a suspected hereditary cause, von Willebrand antigen and factor activity studies are performed.

Hemoglobin

Anemia in rheumatic diseases most commonly reflects decreased production of red blood cells in the bone marrow due to continued inflammation, with increased hepcidin production leading to disturbed iron metabolism. Anemia of chronic disease is commonly normocytic and normochromic; however, microcytic hypochromic anemia also can be associated with chronic disease. Microcytic hypochromic anemia is commonly seen with iron deficiency and other conditions such as thalassemia and lead poisoning. Macrocytic anemia, commonly caused by vitamin B₁₂ deficiency, folate deficiency, liver disease, and hypothyroidism, is not common in rheumatologic conditions except with methotrexate treatment. Hemolytic anemia is not uncommon, especially in active SLE with detection of antierythrocyte antibodies and in other immune complex-mediated conditions. Anemia due to chronic or acute gastrointestinal bleeding is also a frequent adverse effect of NSAIDs, with glucocorticosteroids contributing to an increased risk.

BIOCHEMICAL TESTING

Liver function tests

Liver function tests should be ordered before and after initiation of treatment with certain antirheumatic drugs (including NSAIDs as well as traditional and biologic DMARDs) to monitor for adverse effects. Measurement of aspartate aminotransferase and alanine aminotransferase is included in guidelines or recommendations for monitoring treatment with all immunosuppressive medications.⁶ Albumin levels can also be measured when chronic liver disease or damage to the liver from medications is suspected. There is evidence to suggest that abnormal results on liver function tests seen with methotrexate therapy in RA may not be as frequent as previously suggested, with very few patients discontinuing methotrexate treatment because liver function test result abnormalities over 10 to 15 years of use.^{7,8}

Alkaline phosphatase

Alkaline phosphatase is made mostly in the liver and in bone, with some produced in the intestines and kidneys. It also is made by the placentas of pregnant women. Conditions that cause rapid bone growth (puberty), bone disease (osteomalacia or Paget disease), hyperparathyroidism, or liver cell damage can lead to increases in alkaline phosphatase levels. Values of 1.5 to 3.0 times the upper limit of normal are consistent with a hepatocellular cause (viral infection, drug toxicity, alcohol), whereas values more than 3.0

times the upper limit of normal are usually associated with biliary involvement. Bone involvement can be found at any alkaline phosphatase level.

Kidney function tests and urinalysis

Kidney function tests are routinely performed before and after initiation of treatment with antirheumatic drugs (including NSAIDs as well as certain traditional and biologic DMARDs) to monitor for adverse effects. For this purpose, creatinine levels or creatinine clearance provides sufficient information. Of note, disturbed kidney function is associated with a high risk of methotrexate accumulation causing toxic effects. Connective tissue diseases and systemic vasculitides are frequently associated with kidney involvement causing glomerular and interstitial nephritis. In cases of suspected nephritic or nephrotic syndrome, urine tests and frequently kidney biopsy are standard procedures. Urinalysis is also useful for monitoring of kidney involvement and should include detection and quantification of proteins as well as of hematuria and leukocyturia.

Uric acid

Uric acid measurement is commonly included in the workup of patients with arthritis, and level may be elevated in 90% of patients with gout. Yet healthy people can have elevated levels as well, and the definitive diagnosis of gout depends on demonstration of uric acid crystals in synovial fluid (Fig. 30.1). In monitoring response to uric acid-lowering therapy, low levels of uric acid (usually less than 5 to 6 mg/dL) should be the goal to reduce the risk of recurrent gout attacks.

Calcium and vitamin D

Determination of calcium and vitamin D levels is part of the workup for osteoporosis and high or low bone turnover states and may be considered in patients at risk of these conditions and for monitoring of treatment. Calcium absorption, use, and excretion are regulated and stabilized by a feedback loop involving parathyroid hormone and vitamin D. Conditions and diseases that disrupt calcium regulation can cause inappropriate acute or chronic elevations or decreases in calcium and lead to symptoms of hypercalcemia or hypocalcemia. Renal insufficiency or failure, symptoms of hypercalcemia (e.g., fatigue, weakness, loss of appetite, nausea, vomiting, constipation, abdominal pain, urinary frequency, and increased thirst) or hypocalcemia (e.g., muscle cramps or tingling in the fingers), gastrointestinal disease leading to poor absorption, thyroid disease, malignancies, and poor nutrition may be reasons for monitoring calcium levels. Monitoring may also be needed during vitamin D supplementation.

In the past 25 years, more than 50 metabolites of vitamin D have been described. To date, only a few of these have been quantified in blood, but this has widened our understanding of the pathologic role that altered vitamin D metabolism plays in the development of diseases of calcium homeostasis. Currently, awareness is growing of the prevalence of vitamin D insufficiency in the general population in association with an increased risk of several diseases. However, for many researchers, it is not clear which vitamin D metabolites should be quantified and what the information gained from such an analysis tells us. Two metabolites—25-hydroxyvitamin D and 1,25-dihydroxyvitamin D—have received the most attention. The need for measuring serum levels of 1,25-dihydroxyvitamin D is limited, and this metabolite therefore should not be considered as part of the standard vitamin D testing regimen. On the other hand, serum levels of 25-hydroxyvitamin D provides the single best assessment of vitamin D status, and thus measurement of this metabolite should be the only vitamin D assay typically performed.⁹

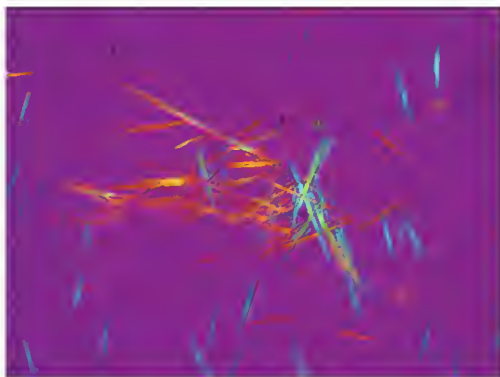


Fig. 30.1 Uric acid crystals in synovial fluid.

Acute-phase reactants

The acute-phase response occurs in a wide variety of inflammatory conditions, including various infections, trauma, malignancies, inflammatory rheumatic disorders, and certain immune reactions to drugs.¹⁰ Currently, the most widely used laboratory tests to monitor inflammation are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Of note, ESR levels are usually physiologically higher in females and also increase with age and during pregnancy. CRP levels in particular have been reported to be higher among obese patients.

The acute-phase proteins are mainly produced by hepatocytes upon stimulation by cytokines (e.g., interleukin-6, interleukin-1, and tumor necrosis factor). The most important acute-phase proteins whose levels increase during inflammation (positive reactants) are CRP, fibrinogen, α_1 -antitrypsin, ferritin, haptoglobin, ceruloplasmin, serum amyloid protein A, and several complement components, especially C3. In inflammatory conditions, increased plasma levels of fibrinogen and immunoglobulins as well as a frequently associated anemia can increase the ESR. In patients with polycythemia or chronic lymphocytic leukemia, a lower ESR is typical.

Serial measurements of ESR and CRP are valuable for monitoring the level of inflammation in patients with disorders such as RA. However, in RA some patients can show signs of clinical disease activity but have normal CRP and ESR values.¹¹ In addition, up to 40% of patients with RA have a normal ESR and/or CRP level at initial presentation.¹² In each instance, the clinical picture should be the determining factor in decision-making regarding treatment. It is essential to note that ESR is an indirect measure of acute-phase protein concentrations. Although CRP concentrations may increase and decrease very rapidly, ESR values change slowly upon control of inflammation.

In patients receiving immunosuppressive treatment, CRP levels may not show an adequate increase when infection is present. Clinicians should be aware of this problem, which seems to be more marked with treatment involving biologics such as the interleukin-6 receptor antagonist tocilizumab, and should rely on clinical examination and imaging tools.

SEROLOGIC TESTING

Autoantibodies

Testing for autoantibodies is frequently used in the diagnosis of rheumatic conditions and sometimes for monitoring of disease activity. Some of these autoantibodies are more specific for one disease, whereas others can be found in several diseases. Both of these categories of autoantibodies may be valuable tools in the clinical workup. Research into autoantibodies has yielded considerable information about the pathogenesis of various rheumatic conditions, but serologic testing for autoantibodies in clinical practice generally remains more an adjunct to diagnosis and management rather than a precise clinical guide.

Rheumatoid factor

Rheumatoid factor (RF) is the traditional designation for autoantibodies directed at the Fc γ chains of IgG molecules. In clinical practice, laboratories tend to test only for IgM RF, but RF can belong to all major immunoglobulin classes (IgG, IgA, IgM) and in some cases IgD and IgE as well. In peripheral circulation, however, the main immunoglobulin classes of RF that can be easily detected are IgA and IgM RFs.

Today enzyme-linked immunosorbent assay (ELISA) and nephelometric assays have become the most common methods for quantifying RF. IgM RF is produced in many chronic inflammatory conditions (long-standing infections such as bacterial endocarditis, hepatitis B and C, tuberculosis, and chronic bronchitis, but also in fibrosing alveolitis and silicosis). Thus RF is not specific for a particular rheumatic disease such as RA. It can also be seen in 5% to 6% of the elderly in the normal population.

The main indications for RF testing in diagnosis are suspicion of RA or Sjögren syndrome, but RF also commonly appears in mixed connective tissue disease, SLE, cryoglobulinemia, and the polyarticular-onset form of juvenile inflammatory arthritis. It is thus apparent that the specificity of RF in differentiating RA from some other rheumatologic conditions is poor. However, with higher titers of RF the specificity increases, and RF testing becomes a more useful laboratory tool. Higher titers are also associated with more aggressive and erosive disease. Of note, 20% to 30% of RA patients test negative for RF and yet have the clinical picture with a potentially poor prognosis when not treated. RF may appear up to several years before the onset of clinical RA. With effective treatment, RF titers can decrease, which is especially typical for B cell-directed therapy with rituximab.

Antibodies to citrullinated protein and peptide antigens

In 1964 antibodies directed to keratohyaline granules of human buccal mucosa cells were described as a specific marker for RA. They were termed *antiperinuclear factor* (APF). Several years later antibodies reacting with upper mucosal cells of the esophagus, so-called antikeratin antibodies (AKAs), were found that had a prevalence in and specificity for RA similar to those of APF. In the late 1990s anti-citrullinated vimentin (anti-Sa) antibodies were described in Canada and anti-citrullinated peptide antibodies (ACPAs) were described in Holland and France. All these antibodies (APF, AKA, anti-Sa, ACPA) have now been shown to target citrullinated parts of proteins such as filaggrin in buccal mucosa, keratin in esophagus, vimentin in macrophages, and fibrin in the RA-affected joint.

Citrullination is the result of deimination of arginine residues in these proteins by activation of Ca^{2+} -dependent peptidylarginine deiminase enzymes during inflammation-induced apoptosis (programmed cell death). Leakage of these active enzymes into cells or onto synovial structures causes citrullination of proteins in many types of synovial inflammation. However, typically only RA patients react to such modified proteins by producing significant amounts of ACPAs. This is likely to depend on the specific presentation of citrullinated peptides to T cells by shared epitope motifs on HLA-DR molecules.

ACPAs can be detected by ELISA and immunoblotting methods using citrullinated proteins or peptides.¹³ The use of a cyclic citrullinated peptide has become the most widely used surrogate antigen for detection of ACPA. Other identified citrullinated autoantigens in RA, such as citrullinated vimentin or mutated citrullinated vimentin, can also be used for detection of ACPA. The sensitivity of the ACPA test is around 50% to 60% at the onset of RA and can rise as high as 85% later in the course of the disease. Several studies have demonstrated the presence of ACPAs up to a decade before the onset of clinical disease.¹⁴ When found in patients with early undifferentiated arthritis, ACPAs predicts later development of classic erosive RA. They are especially prevalent in RF-positive patients but can be found in around 25% of RF-negative RA patients as well.

The ACPA test is helpful in discriminating between RA and psoriasis with erosive arthritis and also between RA-associated and hepatitis C-associated polyarthritis. Yet in the setting of a positive RF test result and typical clinical findings of RA, a positive ACPA test result adds little,¹⁵ especially once a decision to treat has been made, which should be the course of action for any patient suspected of having RA (Table 30.3). Accumulating data suggest that patients seropositive for ACPAs and/or RF may respond better to rituximab. Recently an association between ACPA positivity, HLA-DR alleles, and smoking has been shown in different cohorts.¹⁶

Antinuclear antibodies

ANA testing serves as a screening tool for connective tissue diseases. However, ANAs are seen in individuals with many rheumatologic conditions as well as in many healthy people (Table 30.4). They are generally detected by indirect immunofluorescent (IIF) techniques using monolayers of HEP-2 cells. Subsequently, differentiation of a positive ANA result should be performed using solid-phase immunoassays such as ELISA. ANAs are reported in terms of titers (e.g., 1:320, which is usually also the cutoff for positive results) and staining patterns (e.g., homogeneous or speckled).

The presence of ANAs is a serologic hallmark of connective tissue disorders such as SLE, Sjögren syndrome, mixed connective tissue disease, systemic sclerosis, and undifferentiated connective tissue disease, as well as of autoimmune hepatitis. However, finding antibodies by itself does not

signify disease, because healthy people (especially family members of patients with connective tissue diseases, elderly individuals, and patients using drugs such as sulfasalazine and isoniazid) can show clinically irrelevant positive ANA reactivity.

A high titer increases the likelihood that the presence of antibodies is related to an autoimmune disease. In such cases further workup with testing for the specific antigenic target such as anti-double-stranded DNA (dsDNA), anti-Ro (SS-A), anti-La (SS-B), and antiribonucleoprotein is indicated. In patients in whom a diagnosis cannot be made based on clinical symptoms, watchful waiting is recommended.

ANAs also produce a wide range of staining patterns, which should guide the further serologic differentiation (Figs. 30.2 to 30.4).

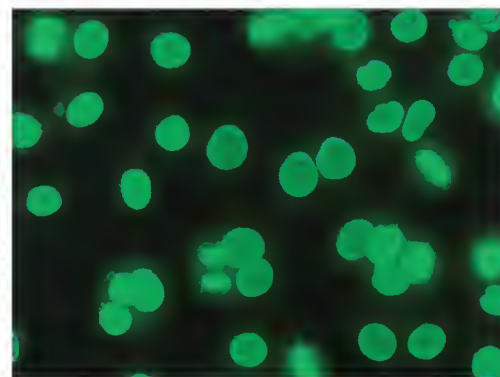


Fig. 30.2 Antinuclear antibody homogeneous staining.

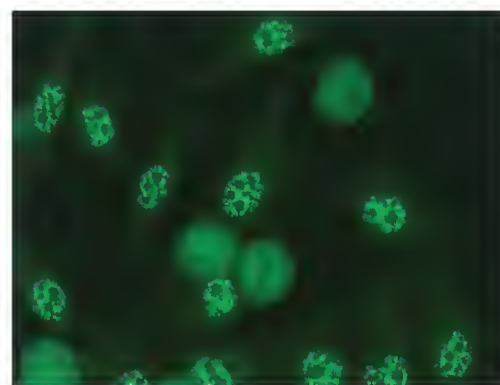


Fig. 30.3 Antinuclear antibody speckled staining.

TABLE 30.4
Frequency of antinuclear antibodies in autoimmune and nonrheumatic diseases

	Sensitivity (%)
Autoimmune disease	
Systemic lupus erythematosus	95-100
Systemic sclerosis	60-80
Mixed connective tissue disease	100
Polymyositis/dermatomyositis	60
Rheumatoid arthritis	50
Rheumatoid vasculitis	30-50
Sjögren syndrome	40-70
Drug-induced lupus	90
Discoid lupus	15
Pauciarticular juvenile chronic arthritis	70
Nonrheumatic diseases	
Hashimoto thyroiditis	45
Graves disease	50
Autoimmune hepatitis	50
Primary pulmonary hypertension	40

TABLE 30.3
Rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) sensitivity comparisons

	RA (n = 102)	Non-RA (n = 98)	Sensitivity (%)	Specificity (%)	PPV (%)	LR+
RF > 20 U/mL	56	11	55	89	84	5.0
RF ≥ 50 U/mL	46	4	45	96	92	11.3
ACPA+	42	2	41	98	96	20.5
RF < 50 U/mL and ACPA+	14	2	25	98	88	12.5

PPV, positive predictive value; LR, likelihood ratio.

Adapted from Nell VP, Machold KP, Stamm TA, et al. Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. *Ann Rheum Dis* 2005;64:1731-6.

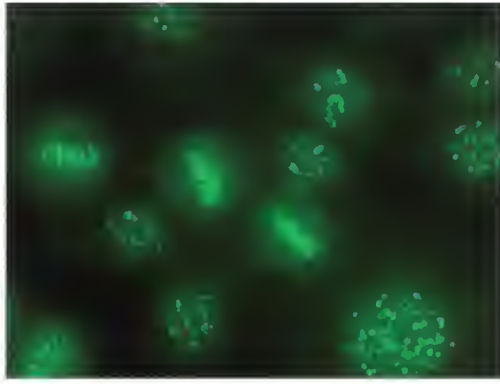


Fig. 30.4 Antinuclear antibody centromere staining.

Anti-double-stranded DNA antibodies

Anti-DNA antibodies target complexes of single- or double-stranded DNA and protein, producing a homogeneous pattern in ANA IIF with positively reacting chromosomes in metaphase. Although anti-dsDNA antibodies are a specific marker for SLE, anti-single-stranded DNA (ssDNA) antibodies represent a nonspecific finding. A positive result for anti-dsDNA antibodies in ANA or ELISA screening must be confirmed by *Crithidia luciliae* IIF or Farr assay, which provides higher specificity.

Anti-dsDNA antibody testing is very specific (95%) but not as sensitive (70%) for SLE, which makes the test result part of the classification criteria for SLE. Anti-dsDNA antibodies also might have a pathogenic role in SLE nephritis and are commonly associated with disease activity in lupus nephritis. The usual picture in active SLE nephritis is increased anti-dsDNA antibody along with decreased C3 and C4, with levels of all tending to normalize with control of active kidney disease.

Anti-Sm and anti-U1 ribonucleoprotein antibodies

Anti-Sm and anti-U1 ribonucleoprotein (RNP) antibodies are directed against the spliceosome and produce a coarse speckled pattern in ANA IIF, with the nucleoli spared. These antibodies can be confirmed using solid-phase immunoassays such as ELISA. Anti-Sm antibodies are found almost exclusively in SLE patients, are detected in 10% to 40% of these patients, and are part of the ACR classification criteria. When the test result is negative it is not helpful in ruling out SLE, but the presence of these antibodies is a very strong piece of evidence of possible SLE.

The presence of anti-U1 RNP antibodies, especially at high titers, is very typical for mixed connective tissue disease and is a prerequisite for diagnosis. Furthermore, anti-U1 RNP antibodies, usually at lower titer, are found in 40% to 60% of SLE patients.

Anti-Ro (SS-A) and anti-La (SS-B) antibodies

The targets of anti-Ro (SS-A) and anti-La (SS-B) antibodies are nuclear and cytoplasmic RNPs. These antibodies produce a fine speckled pattern in ANA IIF, with staining of the nucleoli as well. Anti-Ro and anti-La antibodies are part of the classification criteria for Sjögren syndrome but also are frequently detectable in SLE patients. They have been particularly associated with subacute cutaneous lupus and photosensitivity. Anti-Ro and anti-La antibodies have also been associated with neonatal lupus and congenital heart block because they cross the placental barrier. Therefore, during pregnancy, the fetus should be screened for congenital heart block by ultrasonography, and newborns of antibody-positive mothers should avoid sunlight exposure during the first weeks of life.

Anticentromere and anti-Scl-70 antibodies

Anticentromere and anti-Scl-70 autoantibodies are the specific and most frequent markers for systemic sclerosis, each detectable in up to 40% of patients. Anticentromere antibodies produce a typical pattern in ANA IIF by staining the centromere region of chromosomes. The target of anti-Scl-70 is topoisomerase I, and it shows a nucleolar and nucleoplasmatic staining as well as positively reacting chromosomes in metaphase. The presence of anti-Scl-70 antibodies should be confirmed using solid phase immunoassays, but the ANA pattern of anticentromere antibodies is pathognomonic. Interestingly, these two antibody types do not occur in the same patient and are associated with distinct clinical pictures. Anticentromere antibodies are more frequently observed in the context of slowly progressive scleroderma and pulmonary hypertension. Patients who test positive for anti-Scl-70 typically have systemic sclerosis and pulmonary as well as esophageal organ manifestations.

Antiphospholipid antibodies

Antiphospholipid antibodies bind to certain serum proteins complexed to phospholipid molecules.¹⁷ The assays most widely used to detect antiphospholipid antibodies are the anticardiolipin assay (ELISA) and the lupus anticoagulant (also called *lupus inhibitor*) functional test. One can screen for functionally procoagulant antiphospholipid antibodies by measuring activated partial thromboplastin time, which is abnormally prolonged in their presence.

Antiphospholipid antibodies were originally detected when false-positive results for syphilis were found using the Wassermann reaction. Subsequently, positive reactivity on the anticardiolipin ELISA and the lupus anticoagulant test was shown to depend on binding of autoantibodies to a serum cofactor, which in the case of the anticardiolipin ELISA is β_2 -glycoprotein I and in the lupus anticoagulant assay may be either β_2 -glycoprotein I or prothrombin.

Lupus anticoagulant is an inappropriate name for the procoagulant autoantibodies because they appear not only in SLE but also in other autoimmune diseases and in so-called primary antiphospholipid syndrome. These are patients experiencing venous or arterial thrombotic events, recurrent fetal loss, and thrombocytopenia in the absence of clinical features of another chronic inflammatory rheumatic disorder. The name also is misleading because lupus anticoagulants are not anticoagulants but procoagulants. They block the assembly of the prothrombinase complex, which gives rise to prolonged results on coagulation assays *in vitro* (e.g., prolonged activated partial thromboplastin time, dilute Russell viper venom time, and kaolin clotting time). This abnormality cannot be corrected by mixing the patient plasma 1:1 with normal plasma, whereas this mixing corrects clotting properties in patients with coagulation factor deficiencies.

Anticardiolipin antibodies are detected by ELISA using cardiolipin-coated microtiter plates that are then flooded with diluted bovine serum to secure binding of bovine proteins to the phospholipid. The most important phospholipid-binding protein attaching to the cardiolipin is β_2 -glycoprotein I, which acts as a cofactor in the test. Autoantibodies to β_2 -glycoprotein I and to the cardiolipin- β_2 -glycoprotein I complex give rise to positive results of importance for diagnosing a procoagulant state, whereas antibodies directed at the cardiolipin itself show no such relationship. Antibodies to the naked cardiolipin appear transiently in several infections and permanently in syphilis. The antibodies may belong to all three major immunoglobulin classes, but IgG anticardiolipin antibodies are those most closely related to procoagulant activity and thus the presence of lupus anticoagulant activity. To be able to discriminate between diagnostically important anticardiolipin antibodies, it is now common to search for specific anti- β_2 -glycoprotein I antibodies using ELISA plates coated with purified β_2 -glycoprotein I protein. The presence of anti- β_2 -glycoprotein I antibodies correlates better with a positive lupus anticoagulant test result and with manifestations of antiphospholipid syndrome. The diagnostic criteria of antiphospholipid syndrome are fulfilled by the presence of a clinical criterion (vascular occlusions and/or pregnancy morbidity) and a positive laboratory test result (with confirmation after 12 weeks).

Antineutrophil cytoplasmic antibodies

Antineutrophil cytoplasmic antibodies (ANCA) represent a subgroup of neutrophil-specific autoantibodies. They are commonly directed to the azurophil granule proteins myeloperoxidase (MPO) and proteinase 3 (PR3). ANCAs are characteristic of patients with necrotizing vasculitides such as granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome). In IIF assays, ANCA directed at PR3 typically gives rise to a coarse granular fluorescence pattern in the cytoplasm of neutrophils and monocytes using ethanol-fixed leukocytes, and is therefore called *cytoplasmic ANCA* (c-ANCA) (Fig. 30.5). In contrast, MPO-ANCA produces a perinuclear staining pattern on neutrophils and monocytes (p-ANCA) (Fig. 30.6). A positive result on an IIF screening test for p-ANCA or c-ANCA should be confirmed using a specific ELISA employing MPO and PR3 as antigens.

The usefulness of ANCAs in monitoring disease activity in granulomatosis with polyangiitis has been controversial.^{18,19} They are useful in diagnosing ANCA-associated vasculitides but may not be that helpful in individual patients in predicting remission or relapse, and their measurement is not currently recommended for these reasons.

Complement

The most frequent clinical parameters used for judging complement activation are the protein levels of C3 and C4, although these values are of limited

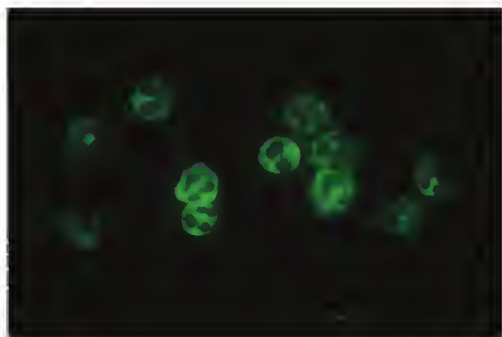


Fig. 30.5 Cytoplasmic staining pattern of antineutrophil cytoplasmic antibodies.

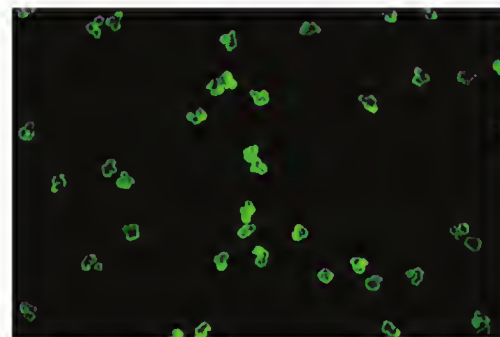


Fig. 30.6 Perinuclear staining pattern of antineutrophil cytoplasmic antibodies.

use because they represent increased production during inflammation (acting as positive acute-phase reactants) and sometimes also consumption by immune complexes. Total hemolytic complement (CH50) is a functional assay used to measure the intactness and consumption of the entire classic pathway; however, it is rarely used nowadays because of its technical complexity. Decreased complement levels are useful in the setting of SLE nephritis, in which low levels are associated with persistent nephritis and normalization is associated with better outcomes. Hypocomplementemia is also a feature of preeclampsia/eclampsia, which is an important point to remember when caring for pregnant patients with SLE with and without antiphospholipid syndrome.

CONCLUSION

Laboratory tests are useful tools for diagnosis and for monitoring of adverse events related to medication use in some rheumatic conditions. Laboratory

results are secondary to clinical signs and symptoms and should not replace or detract from a thorough history and physical examination. As always, any test that will not change the diagnosis, prognosis, or treatment of a rheumatic condition probably should not be performed.

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31

Synovial fluid analysis

■ ANTHONY J. FREEMONT ■ ENGY ABDELLATIF

- Normal synovial fluid is a hypocellular, avascular connective tissue.
- In disease, synovial fluid increases in volume and can be aspirated.
- Changes in synovial fluid cells, noncellular particles, and molecular biomarkers reflect the pathogenesis of the arthropathy.
- Synovial fluid microscopy, which identifies cells and particles, is a simple, cheap, and accurate test that yields information of diagnostic and prognostic significance.
- Cellular and molecular biomarkers of disease processes involving SF are increasingly being studied and may bring about a revolution in understanding and recognizing joint disease.

INTRODUCTION

Normal synovial fluid

Synovial fluid (SF) is a transudate of plasma supplemented with high-molecular-weight, saccharide-rich molecules such as hyaluronans and proteoglycan-4, as well as a host of “structural,” signaling, and effector molecules produced by synovial cells and chondrocytes.¹ Many of these molecules are involved in cartilage nutrition, joint homeostasis, and lubrication. The fluid is kept free of debris by macrophage-derived type A synoviocytes, and formation of SF is balanced by its removal via synovial lymphatics.

Unlike the lining of most body cavities, the surface of synovium consists of an incomplete cell layer with no intact basement membrane. The same is true of articular cartilage. The interfaces between the matrices of the two joint-lining tissues (synovium and cartilage) and joint fluid therefore have no regulatory cell layer to moderate fluid flux and the passage of cells and bioactive molecules. Thus, the chemical environment within the joint is relatively homogeneous, and changes in SF reflect changes within local tissues.

In a normal joint, SF contains few cells ($<200/\text{mm}^3$), mainly chondrocytes and synoviocytes, together with migratory defense cells (e.g., lymphocytes, macrophages). The nature and regulation of the chemical composition of SF are complex and poorly understood.

Synovial fluid in diseased joints

Variation in the volume and composition of SF reflects pathologic processes within the joint. Because of the anatomic relationships of the tissues in the joint, events such as inflammation and enzyme-mediated degradation are reflected by changes in the cellular and chemical composition of SF. Both the cellular and chemical changes have been widely studied to obtain a better understanding of disease processes and to identify aspects of diagnostic and prognostic utility.²

Synovial fluid microscopy

SF microscopy has been carried out as a diagnostic test for many years.³ Histologic and cytologic analysis of human tissues and body fluids is usually the exclusive realm of the pathologist. This is not the case with SF microanalysis, however, because it is possible to perform the test without complex technology. Consequently, it can be carried out close to the patient's bedside

by clinicians. Indeed, many clinicians have had a leading role in development of the science.^{4,5}

Detailed microscopic analysis of SF can yield significant information about the nature of joint diseases and their prognosis.² By comparison with other investigations (e.g., magnetic resonance imaging, serology), SF microscopy combines simplicity, economy, and clinical applicability across the whole spectrum of inflammatory and noninflammatory joint diseases.

SF microscopy gives diagnostic information with different levels of precision, from a single precise diagnosis at one end of the spectrum to simply distinguishing inflammatory from noninflammatory arthropathies at the other. This apparent lack of complete specificity should not be seen as detracting from the value of the test because the clinical question being considered by the rheumatologist may be answered by knowing whether the cause of the joint swelling is inflammatory (e.g., “Does my rheumatoid patient with long-standing disease, who now has a red, hot joint, have a rheumatoid flare or osteoarthritis?”). In the hands of experts, SF microscopy viewed “blindly” (i.e., without knowledge of any patient data) will give a precise diagnosis (e.g., a specific crystal arthritis, rheumatoid arthritis [RA], osteoarthritis [OA], torn meniscus, septic arthritis) in about 50% of cases. In a further 20% it allows relevant and clinically significant differential diagnoses to be made (e.g., 50% of patients with seronegative spondyloarthritis have a specific SF cytology that enables them to be distinguished with certainty from those with other forms of inflammatory arthropathy, including rheumatoid disease, even at initial evaluation,⁶ and in all but 2% to 3% of the remainder, SF microscopy can distinguish inflammatory from noninflammatory arthropathies). If these limitations of SF microscopy are properly considered and applied, the false-positive rate is very low (typically $<5\%$) and the false-negative rate almost zero.

At the same time it has to be acknowledged that access to dedicated laboratories with high throughput and specialized staff is, at best, patchy, and many rheumatologists and pathologists have to resort to SF analysis without expert support. Therefore, the next section of this chapter, which is based on the authors' experience in training young clinicians, technical staff, and nurses, will assist clinicians who find that they need to set up and use a small laboratory for analyzing SF specimens with microscopy to obtain reliable diagnoses.

THE BASIC APPROACH TO SYNOVIAL FLUID MICROSCOPY

SF analysis consists of four elements, with each requiring different types and complexity of equipment. The following approach will yield the maximum information for relatively little outlay and minimal time input. The equipment required is relatively simple: a microscope with polarizers and an interference plate, a hemocytometer chamber, and a cytocentrifuge.

It is important to recognize that SF should be examined unfixed, and consequently it should be treated with the same level of care as all other fresh body fluids. For health and safety reasons the samples should be handled in a biologic safety cabinet and, because fresh samples deteriorate rapidly even if kept refrigerated, should be examined within 24 hours of aspiration. Because SF from inflamed joints has a tendency to clot, it should also be anticoagulated. The best anticoagulant is lithium heparin.

The four elements of SF analysis are

- Visual inspection
- Nucleated cell count
- “Wet preparation”
- Cytocentrifuge preparation

Visual inspection

Synovial fluid should be examined for color and clarity.

Color

Normally, SF is pale yellow. With hemarthroses it will be red or orange and, with inflammatory arthropathies, cream or white. In septic arthritis it may be colored by bacterial chromogens.

Clarity

Normal SF is clear, but with increasing numbers of particles (e.g., crystals) or cells, it becomes cloudy.

Nucleated cell count

The nucleated cell count can be performed manually with a hemocytometer chamber or automatically with automated counters⁷ and even “dipsticks.”⁸ For convenience, the nucleated cell count of SF is expressed as cells/mm³ (directly equivalent to cells/ μ L). Normal SF contains fewer than 200 cells/mm³. In inflammatory joint disease the cell count is greater than 1000/mm³, and in noninflammatory arthropathies it is lower. Cell counts in excess of 50,000/mm³ are virtually restricted to four conditions: acute rheumatoid “flares” (including breakdown of disease control by anti-tumor necrosis factor) and septic, acute crystal, and reactive arthritis.

“Wet preparation”

SF aspirates often contain visible particles, usually fibrin clots or fragments of cartilage. In making the “wet preparation,” the specimen should be agitated and a small aliquot containing as many particles as possible placed on a microscope slide. It can then be gently squeezed flat beneath a cover slip and viewed unstained with a conventional microscope. For optimal results the condenser diaphragm should be closed to produce diffused light in which unstained cells and particles are seen clearly. This preparation is examined for one cell type, the ragocyte,⁹ for several different classes of crystals, and for other noncellular particulate material.

Classes of crystalline material

Several classes of crystalline material are found in joints,² and their detection is not as straightforward as sometimes thought¹⁰ (Fig. 31.1). Monosodium urate monohydrate (“urate”) crystals are needle shaped, 5 to 30 μ m in

length, and highly birefringent. They can be distinguished from other crystals by their properties in polarized light with an interference plate in the system. (For ease, it is useful to have on hand a microscope preparation made by smearing the contents of a tophus onto a slide because this known sample of urate crystals can then be used to standardize the optics of the microscope.) This system gives the microscope image a pink background against which urate crystals appear either yellow or blue, depending on the direction of their long axes. Other crystals, such as calcium pyrophosphate (“pyrophosphate”) crystals, are also yellow and blue, but the direction of the long axes of the yellow- and blue-appearing crystals is reversed. Urate crystals, especially when intraleukocytic, are diagnostic of gout.

Pyrophosphate crystals accumulate within joints with advancing age. In acute pseudogout, the crystals are associated with a high nucleated cell count. The presence of calcium pyrophosphate crystals in association with otherwise typical features of OA¹¹ characterizes hypertrophic OA.

Hydroxyapatite within SF indicates damage to calcified cartilage or sub-articular bone. Loss of cartilage sufficient to expose these structures is seen most commonly in OA¹¹ and RA. Hydroxyapatite crystalloids are too small and amorphous to be seen with the light microscope, but staining with alizarin red produces a birefringent red product that is easily visualized. A specific arthropathy, “Milwaukee shoulder” (and its equivalent in other joints), is associated with larger apatite microspheroids.¹²

Lipids enter SF from the blood in inflammatory joint disease, hemarthroses, and trauma to subsynovial fat. They are usually present either as droplets with a Maltese cross pattern (liquid spherical crystals) or as needle-shaped crystals within a droplet of neutral fat.

Following the intraarticular injection of depot corticosteroids, steroid crystalloids remain within the joint for up to 10 weeks and may mislead the unwary if their true nature is not recognized.

Other crystals are found within SF but are too numerous and rare to describe here. For further description see Freemont and Denton.²

Noncrystalline particles

Synovial joints are lined by cartilage and synovium, and some contain ligaments and fibrocartilage. In disease, small fragments of these structures may appear within SF. Most common are fragments of articular cartilage or, particularly in the knee, internal ligament and meniscal fibrocartilage.²

Articular cartilage has a silken sheen in polarized light. In OA, the most common disorder in which cartilage is found free in the joint, fragments typically show the crimp pattern characteristic of fibrillated cartilage or clusters of chondrocytes.

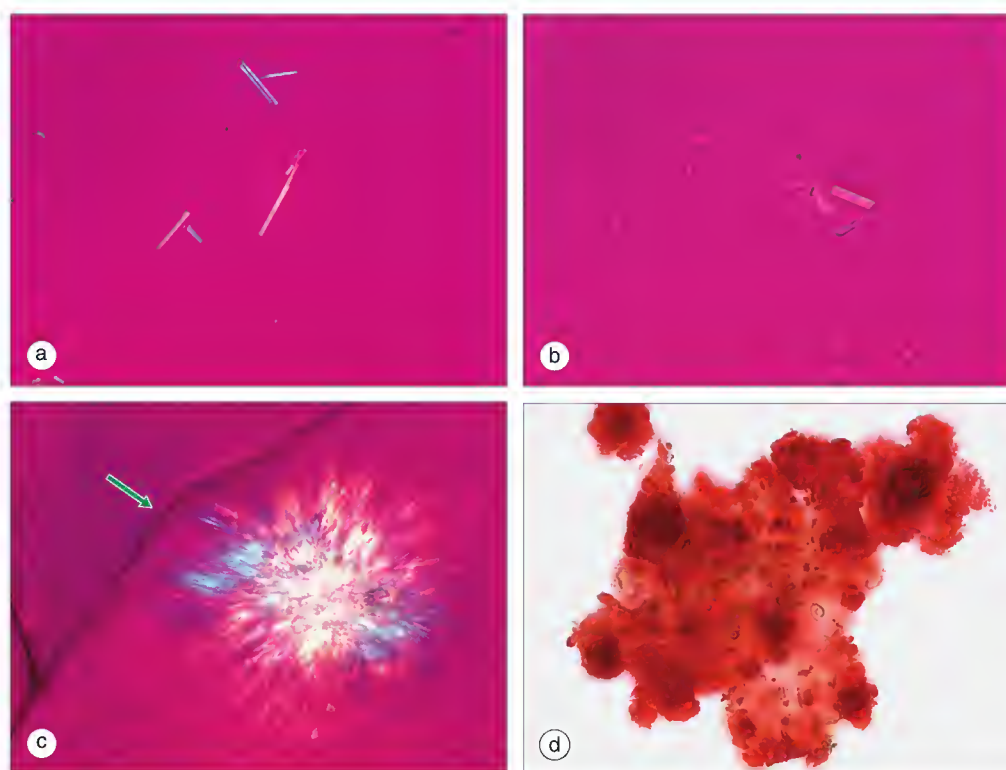


Fig. 31.1 A montage of common crystals. (a) “Urate” crystals viewed in polarized light with a quarter-wave plate. (b) Pyrophosphate crystals viewed in the same system. Note that pyrophosphate crystals appear duller and that the apparent color of the crystal is the opposite of the urate crystals when related to the long axis of the crystal. (c) A lipid droplet (arrow) containing a “beach ball” of needlelike crystals. (d) Hydroxyapatite crystals stained with alizarin red.

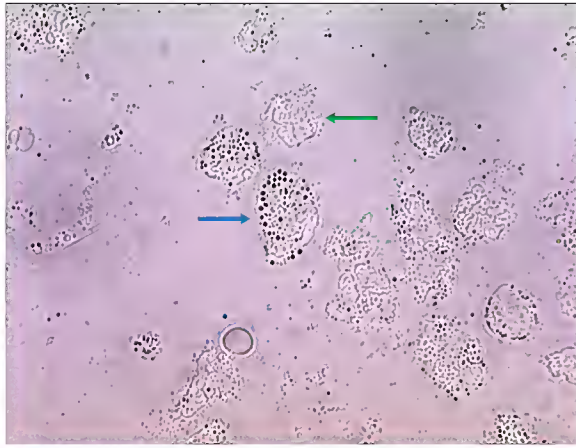


Fig. 31.2 Ragocyte (blue arrow) from a patient with rheumatoid arthritis showing the typical granules. An adjacent cell does not contain ragocyte granules (green arrow). This photograph was taken with a conventional microscope with the condenser iris almost fully closed (pseudophase). The preparation is unstained.

With the increase in arthroplastic surgery, increasing numbers of SF samples are being taken to identify wear, infection, and loosening. Many modern plastics used in prostheses (such as ultrahigh-density polyethylene), methylmethacrylate cement, and composites such as Dacron and carbon fiber mimic crystals if they fragment and can cause diagnostic problems. Metal debris from metal-based prostheses appear as tiny black particles that may exhibit refractivity. Though difficult to recognize, such particles may be important guides to imminent prosthetic failure.

In joints containing metal-on-metal prostheses in which the relatively newly recognized disorder (wrongly) called Aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) is present, characteristic particles resembling worm casts are seen.^{12a}

Ragocytes

Ragocytes⁹ are cells of various lineage that are characterized by the presence of large, refractile cytoplasmic granules (Fig. 31.2). Ragocytes were first described in RA (hence the name), in which they have been shown to contain immune complexes. Some studies indicate that they may form *in vitro*.¹³ They are not restricted to RA but are a feature of all inflammatory arthropathies, so their diagnostic value is somewhat limited. However, with the exception of RA, septic arthritis, gout, and pseudogout, ragocytes rarely account for more than 50% of all nucleated cells. If a crystal arthropathy is excluded, ragocyte counts of 70% to 90% are very strongly suggestive of RA,¹⁴ and if above 90%, they are suggestive of septic arthritis.

Cytocentrifuge preparation

SF cytoanalysis can be conducted adequately only on monolayers made with a cytocentrifuge; smears are unacceptable preparations for this purpose. Optimal preparations are made by diluting the fluid to 400 cells/mm³ with isotonic saline and staining with a Giemsa stain. The one exception is when septic arthritis is suspected, in which case the greatest likelihood of identifying organisms is afforded by diluting the fluid to 1200 cells/mm³ and staining with Gram stain.

Many different cell types are found within SF and reflect differences in the pathogenic mechanisms of joint disease. Although epitope-defined subclasses of inflammatory cells are being characterized by immunocytochemistry and have been found to have disease-specific distributions,¹⁵ this has yet to be fully exploited diagnostically, in part because of problems in performing immunocytochemistry on cytocentrifuge preparations. Therefore, cell recognition in SF preparations is currently based largely on morphologic criteria.

In general, polymorphonuclear leukocytes dominate the cytologic picture in inflammatory arthropathies. Septic arthritis is the only disorder in which both ragocytes and neutrophils account for more than 95% of the nucleated cells.

In noninflammatory arthropathies, lymphocytes, macrophages, and synovocytes are the most commonly encountered cells.

In a patient with RA, SF in which more than 80% of the nucleated cells are small lymphocytes is indicative of less destructive and more slowly

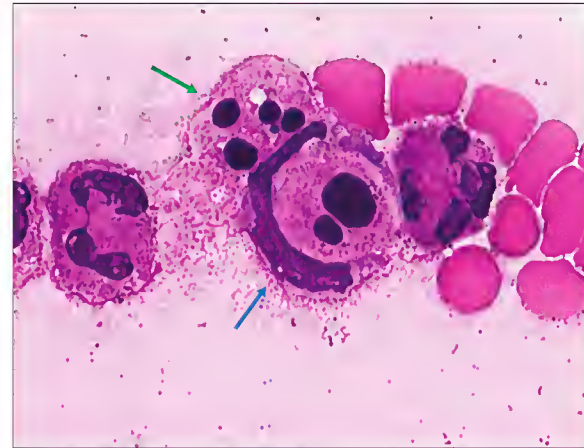


Fig. 31.3 Cytophagocytic mononuclear cell (blue arrow) in which an apoptotic polymorph has been phagocytosed by a macrophage. An apoptotic polymorph is adjacent to it (green arrow).

progressive local disease.¹⁶ If lymphocytes account for more than 70% of the nucleated cells and LE cells are present in the fluid, a diagnosis of systemic lupus erythematosus has to be seriously considered.

Macrophages are the predominant cell (>80% of nucleated cells) in viral arthritis, Milwaukee shoulder, some forms of chronic pyrophosphate arthritis, pigmented villonodular synovitis, and prosthetic debris-induced arthropathy. The presence of macrophages that have phagocytosed apoptotic polymorphonuclear leukocytes (cytophagocytic mononuclear [CPM] cells) (Fig. 31.3) is diagnostic of the seronegative spondyloarthritis.¹⁷

In RA, extensive apoptosis occurs in the absence of CPM cell formation, a feature of such universal occurrence that it can be used diagnostically.

Mast cells, though found in most arthropathies, are seen most commonly in the seronegative spondyloarthritis and in traumatic arthritis.¹⁷

THE PLACE OF SYNOVIAL FLUID MICROSCOPY IN DIAGNOSIS

Synovial biopsy is the investigation of choice for diseases with specific synovial appearances,¹⁸ such as granulomatous inflammation or pigmented villonodular synovitis. However, even experienced histopathologists can sometimes find it difficult to distinguish inflammatory from noninflammatory arthropathies, and very few features in a synovial biopsy specimen will allow a specific diagnosis to be made from within one of these two groups.¹⁹

On this background, SF microscopy is of greatest value for the following:

- Differentiation between inflammatory and noninflammatory arthropathies
- Identification of specific inflammatory and noninflammatory arthropathies even before the full clinical syndrome develops
- Diagnosis of unexplained monoarthritis and oligoarthritis
- Rapid diagnosis of joint disease, particularly in suspected cases of septic arthritis, in which the prognosis is inversely related to the delay in diagnosis

Figures 31.4 to 31.6 present simple algorithms showing how the information obtained from the examinations outlined can feed into the diagnostic process.

DIAGNOSIS OF INTRAARTICULAR INFECTION

Infection in joints is a common cause of joint effusion, a major clinical concern and very difficult to diagnose. SF microscopy has some part to play in the diagnosis of nonseptic infective arthritis, but it is in the setting of septic arthritis that the precision and rapid turnaround times of SF microscopy have their most substantial role, particularly in patients with the following:

- A single red hot joint of sudden onset
- A joint replacement with persistent effusion or pain
- “Immunosuppression” and an effusion (e.g., rheumatoid disease, infection with human immunodeficiency virus [HIV])

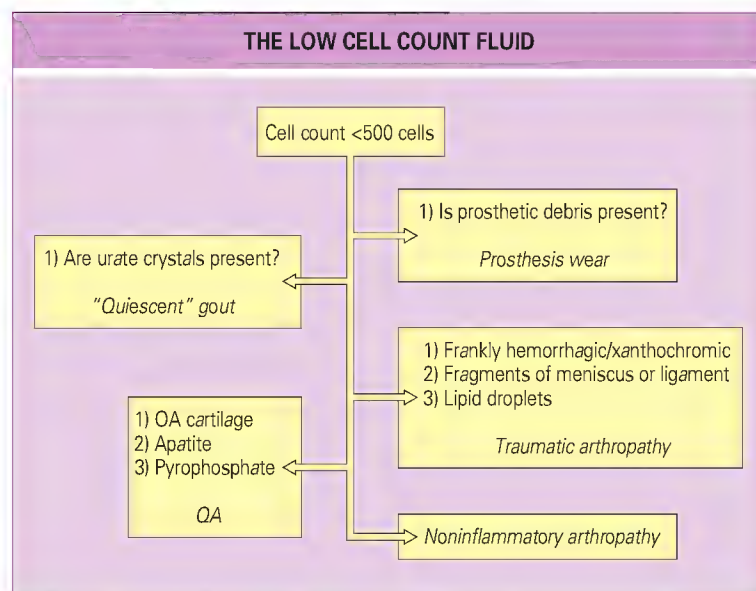


Fig. 31.4 Algorithm for low cell count fluid. OA, osteoarthritis.

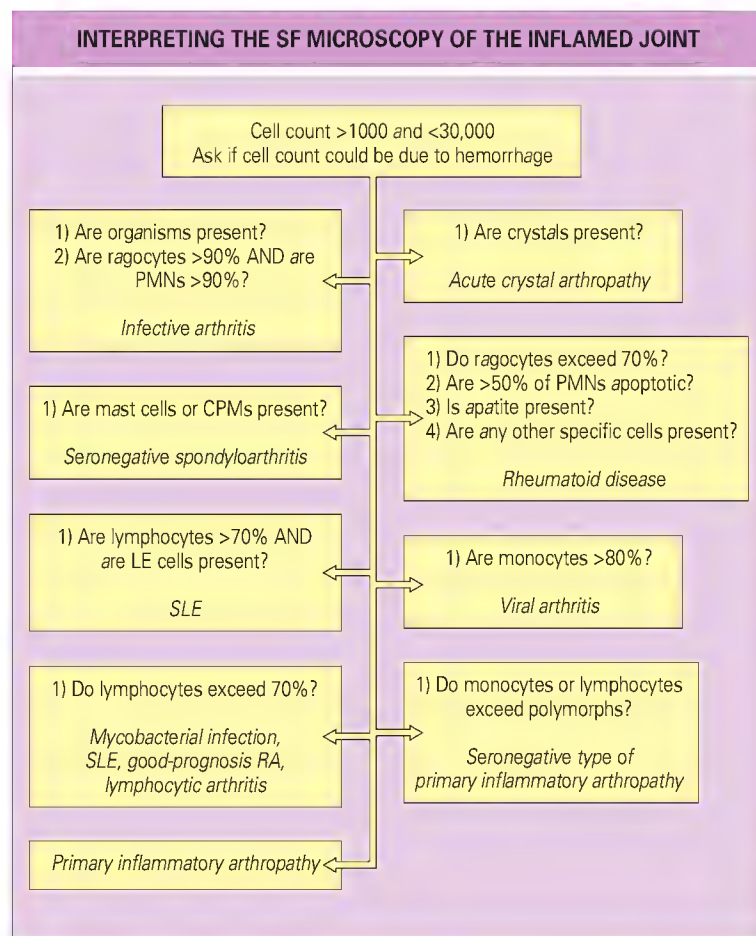


Fig. 31.5 Algorithm for synovial fluid microscopy of the inflamed joint. CPMs, cytophagocytic mononuclear cells; PMNs, polymorphonuclear leukocytes; RA, rheumatoid arthritis; SF, synovial fluid; SLE, systemic lupus erythematosus.

Septic arthritis

Not all bacterial infections lead to septic arthritis.²⁰ By far the most common (75% to 80%) causes of septic arthritis are the gram-positive cocci *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*, the remainder being largely caused by the gram-negative coccus *Neisseria gonorrhoeae* and the gram-negative bacilli *Pseudomonas aeruginosa* and *Escherichia coli*, the latter being more common with immunosuppressed states. In children younger than 2 years, *Haemophilus influenzae*, *S. aureus*, and group A streptococci have been the most common, but the incidence of *H. influenzae*

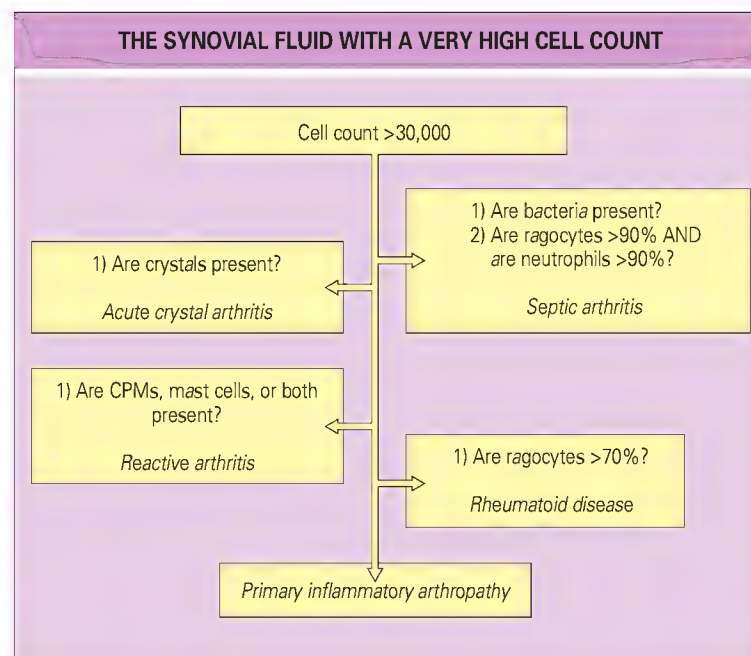


Fig. 31.6 Algorithm for very high cell count fluid. CPMs, cytophagocytic mononuclear cells.

septic arthritis has fallen dramatically since the introduction of type b *H. influenzae* vaccination.

In septic arthritis, careful microscopic examination of SF allows microorganisms to be identified but not classified beyond gram-positive or gram-negative cocci or bacilli. The greatest problems in diagnosing septic arthritis are caused by the relative paucity of organisms in most cases, recognition of gram-negative organisms, and identification of gram-positive cocci rendered gram negative by incomplete antibiotic therapy. In these settings nothing can compensate for patience and experience. Microbiologic culture is also important, but there is little benefit in sending all SF specimens for culture, and in this respect SF microscopy can be used as a rapid screening test for organisms and to exclude other causes of an acutely inflamed single joint, such as a crystal arthropathy or reactive arthritis.

Even in the absence of identifiable organisms, SF microscopy can be very useful in identifying patients with a high probability of having infection. Finding a ragocyte count higher than 95%, total nucleated cells, a nucleated cell count higher than 20,000/mm³, or polymorphonuclear leukocytes accounting for greater than 90% of the nucleated cells should trigger examination of Gram-stained cytocentrifuge preparations or lead to a recommendation for SF and blood samples to be sent for culture (or both).

The reliance on quantitative cytology to make the diagnosis of bacterial infective arthritis in the absence of identification of organisms has been taken further in joints with prostheses following a paper from the Mayo Clinic. It was shown that a nucleated cell count of greater than 1700/mm³ has a sensitivity of 94% and a specificity of 88% in diagnosing prosthetic joint infection in the knee and that a differential count of greater than 65% neutrophils has a sensitivity of 97% and a specificity of 98%²¹; consequently, this has become an area of great interest.²²

Other increasingly common bacterial joint pathogens (e.g., *Neisseria*, *Salmonella*, *Mycobacteria* [including atypical forms]) that do not cause septic arthritis can be identified in SF both by culture and by direct microscopic examination of appropriately stained cytologic preparations.

Nonbacterial infections

Fungal infections are diagnosed by the same approaches suggested for bacteria. By contrast, viral infections are more difficult to diagnose, although an interest in the arthritides associated with HIV infection has shown the diagnostic importance of some features that are seen in no other disorder, such as the coexistence of septic and reactive arthritis in the same joint.

Future techniques

New techniques such as proteomics or polymerase chain reaction using organism-specific primers or amplifying widely expressed bacterial nucleic acid sequences (e.g., 16S ribosomal component) may expand the diagnostic armamentarium in the future.^{23,24}

CHEMICAL CHANGES IN SYNOVIAL FLUID IN DISEASE

The biochemical changes in SF in disease may reflect abnormalities in blood or result from the production of an excess of normal products or the presence of abnormal products in the synovium, cartilage, or fluid itself. In general, because the products of normal or abnormal joint metabolism will be in dynamic equilibrium with serum and be dependent on a complex set of variables such as the hydrostatic and osmotic gradients across the joint, isolated single estimations of a product are not easy to interpret. This is compounded by a lack of availability of normal SF for comparison with disease samples.

Thirty years ago, when biochemical analysis of SF was first studied in earnest, small molecules (e.g., glucose), ions, and pH were the focus of research but, for the reasons given earlier, never gained favor diagnostically. Since then, there have been phases of interest in measuring drug levels and antibodies, which again proved to be of limited value diagnostically.

However, burgeoning recent interest in the discovery and analysis of novel molecular biomarkers (molecules indicative of specific pathologic processes)²⁵ may ultimately help pinpoint specific disease processes within a joint, in much the same way as the cellular and particulate biomarkers discussed earlier.

To date, the range of biomarkers that have been investigated is based on studies of specific molecules predicted to be important from the current understanding of molecular drivers of disease processes. However, many of these findings lack consistency or specificity (or both), particularly as markers of the presence or activity of disease in individuals or specific joints.

There can be little doubt that the advent of widely available proteomics and metabolomics, coupled with robust bioinformatics, will result in a huge increase in the number of biomarkers and peptide/protein “fingerprinting” of disease processes. There is already some evidence of the success of this type of approach when applied to SF, but the opportunities that these technologies open up could herald a revolution in the identification of disease processes and subtypes, a reclassification of joint disease, and advances in diagnosis and prognostication.

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32

Minimally invasive procedures

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- Various minimally invasive procedures ranging from arthrocentesis to synovial biopsy can be used in daily rheumatology practice to determine the diagnosis or to monitor the response to treatment.
- Analysis of joint fluid can distinguish between an inflammatory and noninflammatory cause of arthritis and is especially helpful in the case of monoarthritis, when septic arthritis or crystal-induced arthritis is suspected.
- In the diagnostic workup of patients with rheumatologic disease, especially when systemic disease is suspected, histologic samples can be of great additional value.
- Abdominal fat pad fine-needle aspiration is a relatively noninvasive, simple, and safe technique with excellent specificity and positive predictive value in establishing the diagnosis of amyloidosis.
- When inflammatory myositis syndromes such as polymyositis, dermatomyositis, and inclusion body myositis need to be distinguished from other myopathic syndromes, a histologic sample of the involved muscle or muscles often leads to a definite diagnosis.
- Minor salivary gland biopsy of the sublabial glands is a simple technique that can be performed in an outpatient setting when histologic confirmation of suspected Sjögren syndrome, sarcoidosis, and other infiltrative processes is necessary.
- Synovial tissue biopsy samples can be taken safely on an outpatient basis with blind needle or arthroscopic techniques. Analysis of synovial tissue can be performed for diagnostic reasons in selected cases, to study pathogenetic processes in various types of arthritis, and to evaluate the response to (experimental) treatment in a research setting.

INTRODUCTION

Several minimally invasive procedures can be performed in daily rheumatology practice to determine the diagnosis or monitor the response to treatment. Such techniques include arthrocentesis and biopsy of the skin, muscle and fascia, salivary gland, abdominal fat pad, and synovium. This chapter reviews and describes the processes to be followed for each of these techniques and discusses the indications for and potential complications of the procedures.

ARTHROCENTESIS

Since its introduction in 1951 by Hollander, aspiration of fluid from a joint cavity is performed on a routine basis by rheumatologists for both diagnostic and treatment reasons. Analysis of joint fluid can distinguish between an inflammatory and noninflammatory cause of arthritis and is especially helpful in the case of monoarthritis, when septic arthritis or crystal-induced arthritis is suspected. In addition, arthrocentesis can be used therapeutically when accumulation of fluid in a joint causes painful distention of the joint capsule. Intraarticular therapy with corticosteroids or other preparations can be of adjunctive value in the treatment of several types of arthritis.

Physical landmarks and a thumbnail, ballpoint pen, or marker can be used to carefully determine and indicate the site of puncture. In some cases, such as the hip and sacroiliac joint or when the synovial fluid is loculated, imaging techniques are necessary to ensure correct position of the needle

in the joint cavity. Although the risk of contaminating the joint through the arthrocentesis itself is extremely low, aseptic measures to prevent this complication are necessary. After determining the aspiration or injection site, the skin over this area should be disinfected, which can be done with iodine solution or an alcohol-based disinfectant. It is important to allow the disinfectant fluid to dry. The use of gloves is generally advisable to protect oneself from possibly infected body fluids, but routine use of sterile gloves is unnecessary. When a relatively small joint is to be punctured, use of a local anesthetic—such as a 1% or 2% lidocaine solution without epinephrine—to anesthetize the skin, subcutaneous tissue, and joint capsule can minimize discomfort during the procedure. When rapid insertion of the needle into a joint is possible, use of a local anesthetic is not necessary, or it can be mixed with the corticosteroid or other agent to be injected. The use of local anesthetics can also yield diagnostic information about the exact location and nature of the pain. Most aspirations can be performed with a 21-gauge needle, but a 19-gauge needle can be chosen when large and viscous effusions are being aspirated. Smaller (23-gauge) needles can be used for small joints such as the metacarpophalangeal or interphalangeal joints. If the needle is inserted into the joint correctly but no fluid can be aspirated, the needle might be clogged with fibrin or so-called “rice bodies.” Irrigation of the joint with isotonic saline or some lidocaine can sometimes result in fluid that contains enough crystals or bacteria to establish the diagnosis. If a therapeutic agent is to be injected after the aspiration has been completed, the syringe can be removed and replaced by the syringe with the medication. After ensuring that the needle is still in the joint cavity, the medication can be injected.

Complications of arthrocentesis are extremely rare but include idiopathic infection and bleeding.

BIOPSIES

In the diagnostic workup of patients with rheumatologic disease, histologic samples can be of great additional value. Especially when systemic disease is suspected, combining the clinical symptoms with the characteristic features of the affected tissue gathered with minimally invasive techniques can lead to the correct diagnosis.

Skin and subcutaneous tissue

Technique

Although many skin lesions may directly suggest a diagnosis when combined with the clinical information and the aspect and specific location of the lesion, histologic evaluation of skin abnormalities can help differentiate between different syndromes. Skin biopsy specimens are best taken from a recently developed lesion and should contain normal-appearing skin alongside the edge of the lesion.¹ Using a disposable punch biopsy tool 3 to 6 mm in diameter, diagnosis of dermal and subdermal abnormalities can be determined. After anesthetizing the skin around the biopsy site with 1% to 2% lidocaine, a small cylinder of tissue is removed with a twisting movement of the punch. After achieving hemostasis, the wound can be closed primarily or be left to heal by secondary intention. Both procedures will lead to formation of a small scar. Complications of the procedure are rare and include bleeding, especially when anticoagulants or nonsteroidal antiinflammatory drugs are used, and infection.

If vasculitis or panniculitis is suspected, excision biopsy via scalpel and forceps is more reliable in revealing the diagnosis because a larger amount of tissue that contains panniculus can be examined and thus provide a greater chance of finding abnormalities.¹ A larger amount of tissue also allows additional studies such as immunohistochemistry,

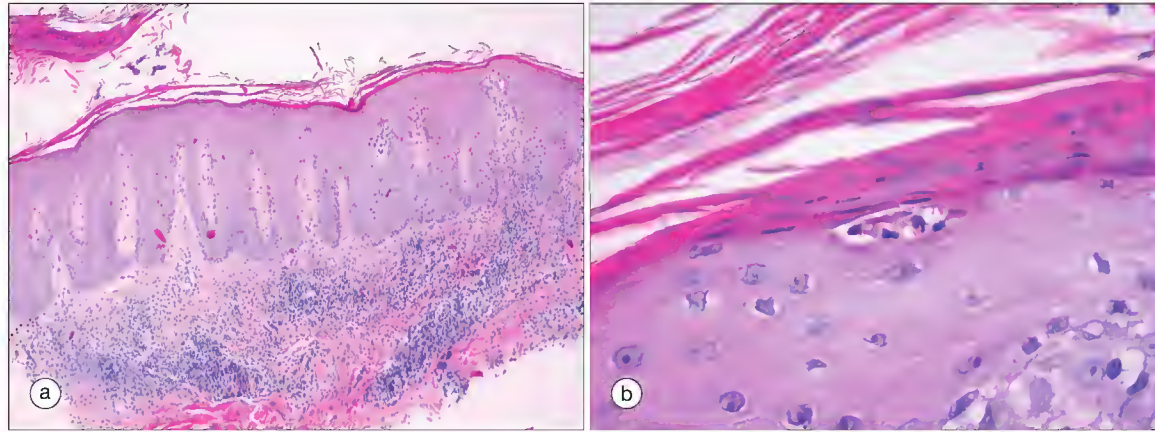


Fig. 32.1 (a) Psoriasis. The epidermis shows regular elongation of the epidermal rete ridges. The cornified layer shows confluent parakeratosis. A superficial perivascular lymphocytic infiltrate is present. (b) Psoriasis detail showing exocytosis of neutrophils.

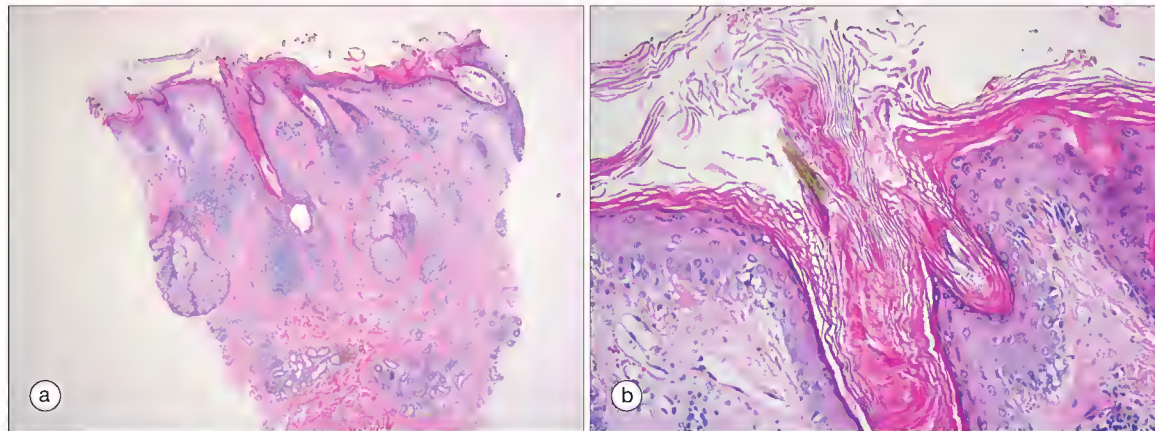


Fig. 32.2 (a) Chronic discoid lupus erythematosus (CDLE). The epidermis shows hyperkeratosis, follicular plugging, atrophy, and basal layer vacuolization. A dense perivascular lymphoid infiltrate is present. (b) CDLE detail.

immunofluorescence, and electron microscopy. For cosmetic reasons, the line of incision should follow the natural lines of the skin.

Skin biopsy for specific rheumatologic disorders

In *psoriasis*, the epidermis is characterized by thickening of the viable cell layers (acanthosis), marked hyperkeratosis (thickening of the cornified layer), loss of the granular layer, and parakeratosis (nuclei in the stratum corneum). In addition, the contorted dermal blood vessels are increased in number and size and extend up to the epidermis. Furthermore, leukocyte infiltration is found in the dermis and epidermis, where some leukocytes form Munro microabscesses underneath the stratum corneum (Fig. 32.1a and b). Immunostaining with anti-CD3 antibodies (a T-lymphocyte marker) has shown that these infiltrates contain many T cells.²

In *lupus erythematosus* (LE), the lesions can be diverse and biopsy can help distinguish between different lesions. Discoid skin lesions show characteristic features: follicular plugs, atrophy, scale, telangiectases, and erythema (“paste” features) (Fig. 32.2a and b).

Direct immunofluorescence (DIF) techniques can be helpful in diagnosing various subsets of LE and vasculitis because the site, morphology, and frequency of deposition vary among these subsets.^{3,4} DIF requires fresh tissue, which can potentially be substituted by immunohistochemical analysis of paraffin-embedded tissue. This latter technique can be used as an adjunct in the assessment of certain inflammatory skin diseases, including vasculopathic conditions and collagen vascular disease.⁵

In *discoid lupus*, immune deposits of mainly IgG and IgM are found in various patterns along the dermoepidermal junction in about 60% to 94% of biopsy samples of lesional skin.⁶ Previous treatment, sun exposure, and duration of the lesion may influence the frequency of positive immunofluorescence. Therefore, the most appropriate biopsy site is an older, untreated lesion that has not been exposed to the sun.

The skin lesions in *systemic LE* may have immune deposits in various sites. Granular deposits of immunoglobulins and complement proteins are found at the dermal-epidermal junction (lupus band).⁷ Other deposition sites include the superficial dermal blood vessel walls, cytotoid bodies in the papillary dermis, and nuclei of the epidermal keratinocytes.⁸

In *scleroderma*, mononuclear infiltrates, mainly consisting of T cells located around blood vessels, and increased collagen, synthesized by activated fibroblasts and leading to tissue fibrosis, can be seen in early lesions.⁹ These findings can be found in localized processes, such as morphea.

Various types of *vasculitis* (leukocytoclastic, eosinophilic, Henoch-Schönlein, polyarteritis nodosa) can be distinguished by histologic analysis of the skin or a subcutaneous lesion in which representative vessels are included. The tissue sample should be of adequate size. When taken from an active lesion, the chance of a false-negative result will be less than when taken from normal skin (Fig. 32.3a and b). Additional immunofluorescent techniques will classically show IgA deposition in *Henoch-Schönlein purpura* (Fig. 32.4), but this can also be seen with other IgA-associated forms of vasculitis such as lymphocytic vasculopathy.¹⁰

Rheumatoid nodules are characterized by palisading fibroblasts surrounding a central area of necrosis. These fibroblasts are in turn surrounded by chronic inflammatory cells, mainly lymphocytes. Various proinflammatory cytokines, components of the complement system, and rheumatoid factor can be found in these granulomas.^{11,12}

Abdominal fat pad fine-needle aspiration

Abdominal fat pad fine-needle aspiration is a relatively noninvasive, simple, and safe technique for establishing the diagnosis of amyloidosis.^{13,14} This technique has excellent specificity and positive predictive value. Using an 18- to 23-gauge needle, aspiration is performed two to five times on different locations from the xiphoid process to the symphysis. The aspirated material is gently distributed on a glass slide and allowed to dry.¹⁵ When stained with Congo red, a specific apple-green birefringence caused by binding to the amyloid can be seen under polarized light. The amyloid deposits are distributed mainly perivascularly and range from massive to subtle (Fig. 32.5). Fluorescent microscopy can improve the detection of amyloid in fat pad smears.¹⁶ Novel proteomic strategies based on mass spectrometry have been proposed to identify the protein constituents of the deposits. Multidimensional Protein Identification Technology is an automated, high-throughput proteomic approach that allows the identification of hundreds of proteins

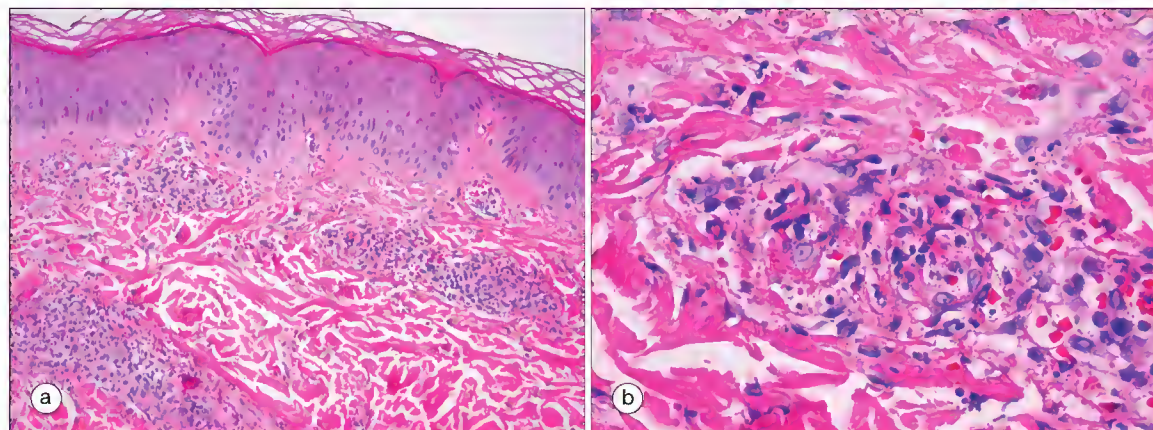


Fig. 32.3 (a and b) Leukocytoclastic vasculitis. Vascular damage with a perivascular neutrophilic infiltrate, nuclear debris, and extravasation of erythrocytes is apparent.

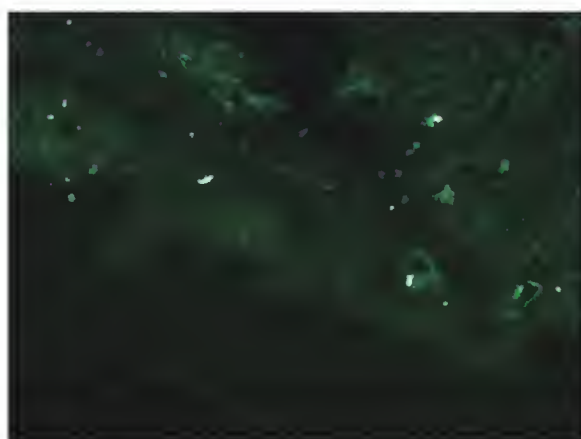


Fig. 32.4 IgA deposition in Henoch-Schönlein disease. Immunofluorescence examination reveals IgA deposits in small vessels.

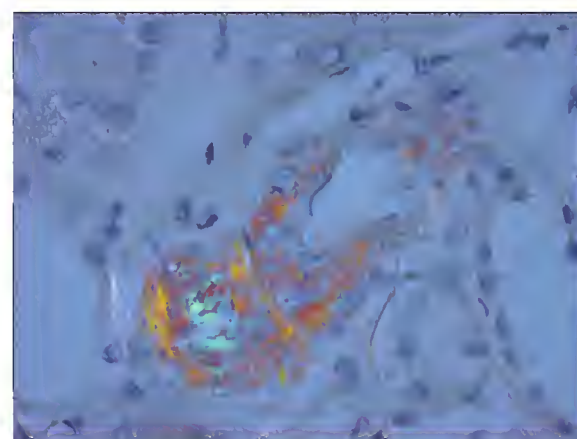


Fig. 32.5 Amyloidosis. Amyloid deposits observed under polarized light show a greenish birefringence of Congo red-stained amyloid fibrils.

in complex samples.¹⁷ The sensitivity and specificity of the fine-needle aspiration technique range from 55% to 75% and up to 92% to 100%, respectively.^{14,18} No complications of this technique have been reported. Variants of the technique include Tru-Cut needle biopsy or excision biopsy. Other possible biopsy sites to confirm amyloidosis are the rectal mucosa, labial salivary gland, and compromised organs (kidney, liver, and endomyocardium). The latter sites should be reserved for patients in whom the aforementioned techniques have failed to establish the diagnosis.

Biopsy of the temporal artery

The “gold standard” for the diagnosis of giant cell arteritis is biopsy of the temporal artery. It should be performed as soon as the diagnosis is suspected, but without delaying treatment. This procedure is usually performed by surgeons.

The suggested sample size is 2.5 to 5 cm because the inflammation is discontinuous, which causes skip lesions (reported in about 10% of cases).¹⁹ Biopsy of the contralateral side is suggested if findings on the first biopsy sample are negative. The sensitivity of a positive biopsy result was reported to not be significantly decreased after 2 weeks of steroid therapy,²⁰ and several case reports have suggested the persistence of histologic abnormalities even after months of treatment.²¹

A meta-analysis of the sensitivity and specificity of clinical signs and symptoms showed various clinical features, such as jaw claudication, diplopia, and the erythrocyte sedimentation rate, to be predictive of a high or low probability of a positive temporal artery biopsy.²² Several other variables influence the reported 3% to 10% incidence of false-negative results: the length and number of biopsy specimens taken, the presence of skip lesions, pathologic sectioning techniques, and the duration of treatment before biopsy.²³ Using bayesian analysis, the sensitivity of a single temporal artery biopsy specimen was calculated to be 89.1% (95% confidence interval, 81.8% to 91.7%).²⁴ The use of imaging techniques, such as B-flow ultrasound and high-resolution magnetic resonance imaging (MRI), may perhaps be of help in defining the arterial segment for biopsy to decrease sampling error.²⁵

Mononuclear infiltrates penetrating all layers of the arterial wall and causing panarteritis can be seen along with activated T cells and macrophages arranged in granulomas.²⁶ In 50% of cases, multinucleated giant cells are found grouped along the fragmented internal elastic lamina (Fig. 32.6a and b). Temporal artery biopsy is a safe procedure with a low complication rate. Complications include postoperative hematoma, wound infection or dehiscence, and facial nerve damage.²⁷

Muscle/fascia

When inflammatory myositis syndromes such as polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) need to be distinguished from other myopathic syndromes, a histologic sample of the involved muscle or muscles often leads to a definite diagnosis. Furthermore, atypical inflammatory myopathies such as pyomyositis, parasitic diseases, and granulomatous myositis in sarcoidosis can be identified.²⁸

Site selection is crucial when performing a muscle biopsy. A muscle biopsy specimen should be taken from an involved muscle identified by physical examination, but from not a fully atrophic or severely weakened one. Also, care should be taken to not obtain samples from a muscle that was injected or has recently been evaluated by electromyography (EMG) because of the chance for focal traumatic myositis. Taking a muscle sample from the side contralateral to the one found to be abnormal on EMG may increase the yield of finding diagnostic abnormalities. The quadriceps or deltoid muscles are involved in most myopathies and are the easiest to access.

Furthermore, the use of MRI to identify affected areas that show increased T2 signal may also help reduce sampling error. The value of fat-suppressive (short tau inversion recovery [STIR]) image signal intensity was studied in 40 patients with idiopathic inflammatory myopathies and correlated significantly with clinical activity and the presence of inflammation on muscle biopsy samples.²⁹ In this study, signal intensity scores were found to be more sensitive in detecting clinical disease activity than was the presence of pathologic changes on muscle biopsy specimens (89% versus 66%).

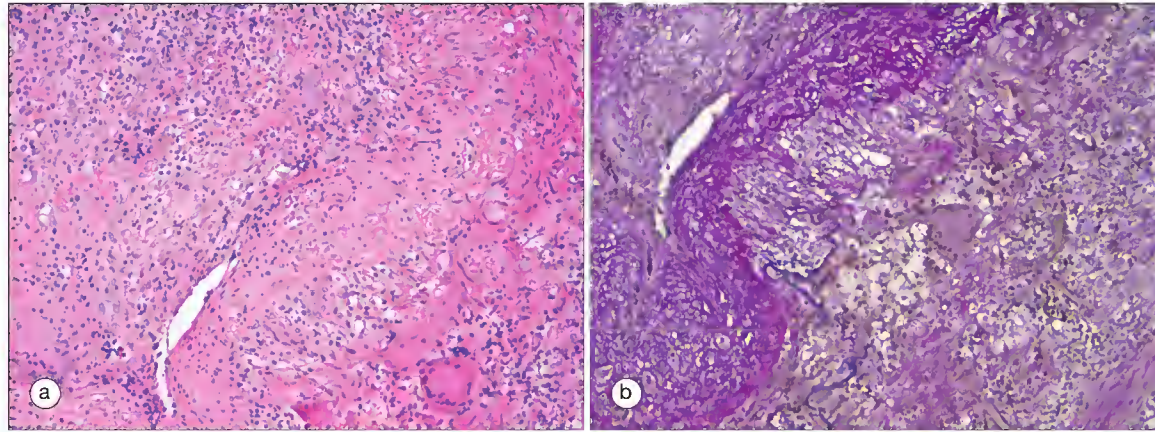


Fig. 32.6 (a) Arteritis temporalis. Low magnification shows partial destruction of the wall by an inflammatory infiltrate containing multinucleated giant cells, which led to fragmentation of the internal elastic lamina and extreme narrowing of the lumen (hematoxylin-eosin). (b) Arteritis temporalis (detail, elastic–Van Gieson stain).

Open biopsy has several advantages because a larger tissue sample can be obtained under direct vision. This reduces the chance of sampling error and allows multiple diagnostic tests.³⁰ Despite these advantages, 25% to 30% of patients with myositis still have negative biopsy results.³¹ With suspected inherited metabolic myopathies, for which multiple quantitative assays need to be performed, open biopsy is recommended.³² This technique, however, requires the assistance of a surgeon and the use of local or regional anesthetics, it can be done only on superficial muscles, it is not suitable for serial biopsy assessment, and it leads to scar formation. Alternatively, the various percutaneous needle muscle biopsy techniques that have been developed are more cost-effective, are more convenient for daily practice, and yield adequate tissue samples for histology, histochemistry, and electron microscopy.³⁰ Some procedures require a skin incision, such as when a disposable Tru-Cut biopsy needle, a suction-assisted reusable device with a side-cutting window and inner cutting cylinder (University College Hospital instrument) (Fig. 32.7), or a sharp-jawed surgical instrument (conchotome) is used.³³

When using the suction-assisted, spring-loaded needles (Bard Biopsy-Cut instrument) originally described by Coté and colleagues,³⁴ more samples can be taken from the same or more than one muscle, which may improve sensitivity.^{31,32,34,35} Additional advantages include the ability to perform this method at the patient's bedside, the fact that no skin incision is required, and the possibility of taking serial biopsy specimens to evaluate treatment. Complications from this technique, such as small hematomas, are rare.

Although the diagnostic value of the specific histopathologic features found in muscle biopsy samples from patients with inflammatory syndromes is somewhat controversial,³⁶⁻³⁸ the combination of clinical information and histologic analysis may result in different therapeutic options and prediction of prognosis.

In inflammatory myopathies, myofiber degeneration, regeneration, and an inflammatory infiltrate consisting of mononuclear cells are usually found. In PM, invasion of cytotoxic T cells into nonnecrotic myofibers can be seen. Typical histologic changes in DM include perimysial perivascular inflammation with B and T cells, capillary involvement, and atrophy of the fibers secondary to ischemia. In IBM, chronic myopathic features, endomysial lymphocytic inflammation, and rimmed vacuoles are present. Filamentous inclusions may be seen on ultrastructural studies. Immunohistochemistry can be of help in determining the diagnosis. With the increasing availability of various antibodies to proteins, both paraffin-embedded sections and (sequential) cryosections can be used for immunohistochemical analysis of the inflammatory infiltrates.³⁹ In most metabolic myopathies, however, immunohistochemistry is not advantageous.

Salivary gland

The main indication for salivary gland biopsy is histologic confirmation of suspected Sjögren syndrome, sarcoidosis, and other infiltrative processes such as amyloidosis and hemochromatosis. Various techniques have been described, each with advantages and disadvantages.

Minor salivary gland biopsy of the sublabial glands is one of the most widely used procedures. It is a simple technique that can be performed in an outpatient setting. The patient is seated or lying with the upper half of

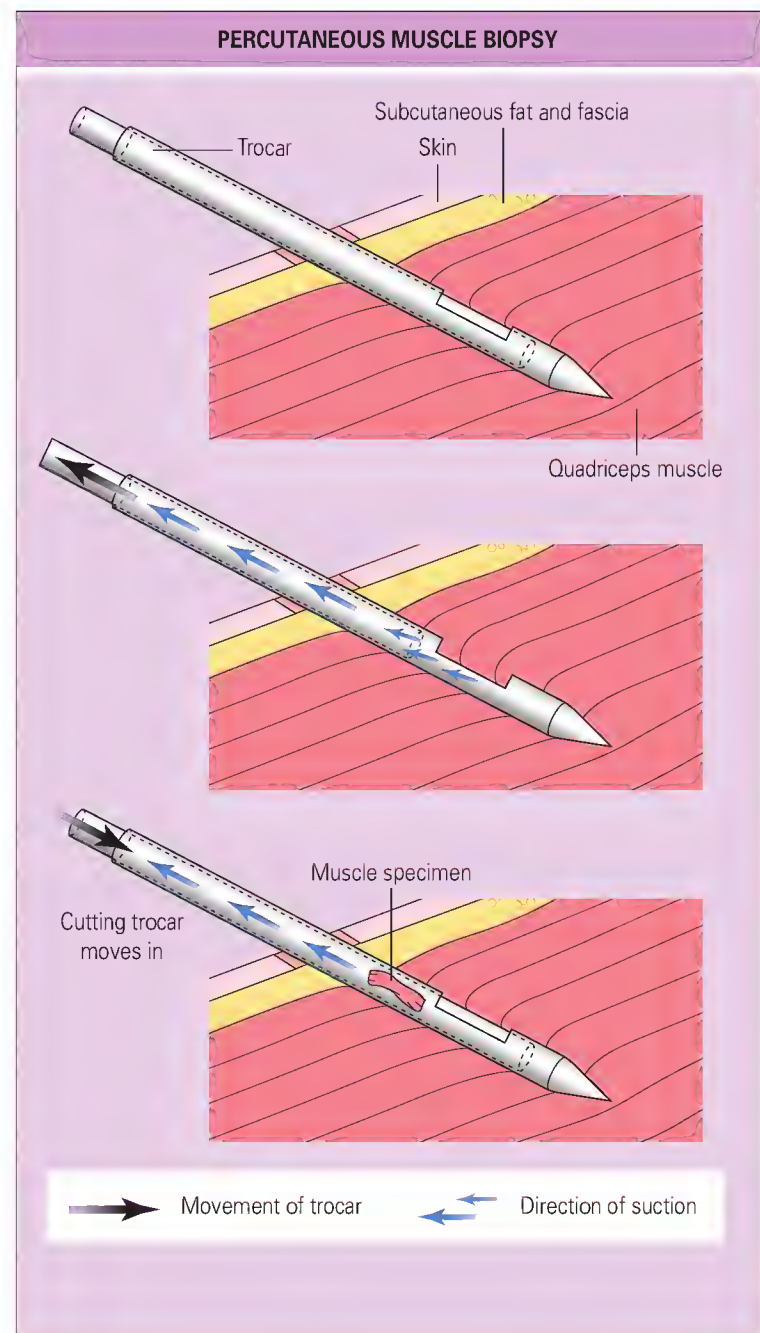


Fig. 32.7 Percutaneous muscle biopsy using a suction-assisted instrument.



Fig. 32.8 (a) Lip biopsy: incision of the lower lip. (b) Biopsy specimen.

the body upright. The lower lip is everted and the mucosa inspected. The biopsy site should contain normal-appearing mucosa and enlarged labial glands (1- to 2-mm firm nodules), as determined by palpation. The area is infiltrated with local anesthetic (e.g., 2% lidocaine with or without epinephrine/adrenaline), and a small superficial 0.1- to 1-cm incision is made (Fig. 32.8a and b). The salivary glands (preferably 5 to 10) are bluntly dissected by grasping them carefully at the base with forceps and applying gentle upward traction.⁴⁰ Light pressure can help bulge the gland from the incision wound.⁴¹ Care should be taken to not damage the sensory nerves, which can easily be distinguished during the procedure. The incision can be closed with dissolvable sutures, but it may be allowed to heal spontaneously. Possible complications include bleeding from an incision that is too deep, damage to the sensory nerve leading to permanent hypoesthesia of the lower lip, and burning of the mouth after the procedure because of drinking hot beverages while still anesthetized.

The glands are fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. For evaluation of the diagnosis of Sjögren syndrome, the inflammatory infiltrate is scored and graded according to the method of Greenspan and Daniels,⁴² which is based on the number of inflammatory cells (foci) within the biopsy section. These foci are usually found perivascularly or periductally, adjacent to the acini of the glands. Classically, a single tissue section is taken to evaluate the infiltrate, but despite standardization of the methodology of sampling, processing, and examining the specimens, reproducibility of histologic scores remains low. To increase the diagnostic accuracy of this test, multilevel sectioning (three different levels at least 200 μ m apart) and use of a cumulative focus score have been recommended.^{43,44} Furthermore, the use of immunohistochemical techniques to quantify the IgA- and IgG-containing plasma cells in the biopsy sample results in higher sensitivity and specificity of the test.⁴⁵

Biopsy procedures on other salivary glands, such as the parotid gland, have also been described. Parotid biopsy for diagnosis of adult and pediatric Sjögren syndrome is safe and accurate.^{46,47} Comparison of parotid and minor salivary gland biopsy shows little added value of the former, especially if other diagnoses such as lymphoma or sarcoidosis are suspected.^{48,49}

Synovium

Because synovial tissue is easily accessible, biopsy samples can be taken safely with blind needle or arthroscopic techniques. Subsequent analysis of synovial tissue can be used for diagnostic reasons in selected cases⁵⁰⁻⁵³ to study the pathogenetic processes in various types of arthritis and evaluate the response to (experimental) treatment in a research setting.^{54,55}

Blind, or closed, needle biopsy has been performed successfully with the Parker-Pearson needle, which is a simplified 14-gauge biopsy needle that does not require a skin incision (Fig. 32.9a).⁵⁶ This technique is safe, well tolerated, technically easy, and inexpensive. After using standard aseptic technique and anesthetizing the skin, subcutaneous tissue, and joint capsule with 1% or 2% lidocaine (see also earlier discussion on arthrocentesis), the trocar is inserted into the joint and the biopsy needle is introduced into the trocar (see Fig. 32.9b and c). Applying suction to a Luer-Lok syringe attached to the biopsy needle helps in obtaining the specimen (see Fig. 32.9d). When the angle of the needle is altered, multiple biopsy specimens can be obtained. Taking six or more biopsy samples from multiple locations reduces the chance of sampling error and leads to a variability of less than 10%.⁵⁷ In patients with minimal or no clinical evidence of inflammation or effusion, the use of 10 to 20 mL of isotonic saline to fill the joint cavity before introducing the trocar may be helpful. Most investigators use this

technique to perform biopsy on the knee joint, but biopsy of other joints such as the ankle, wrist, elbow, and shoulder has also been described. Smaller joints can be approached with a modified short needle.⁵⁸ In most cases this technique yields adequate tissue samples, with signs of inflammation generally being similar to those in samples taken under direct vision via an arthroscopic technique.⁵⁹ It can fail, however, when the joints are not swollen. In a series of more than 800 samples, no complications (such as infection or hemarthrosis) were seen.⁵² Several modifications of this technique have been described, such as use of the Tru-Cut needle for a variety of soft tissue biopsies. This is an inexpensive, disposable item that can retrieve synovial tissue through an action similar to that described earlier.

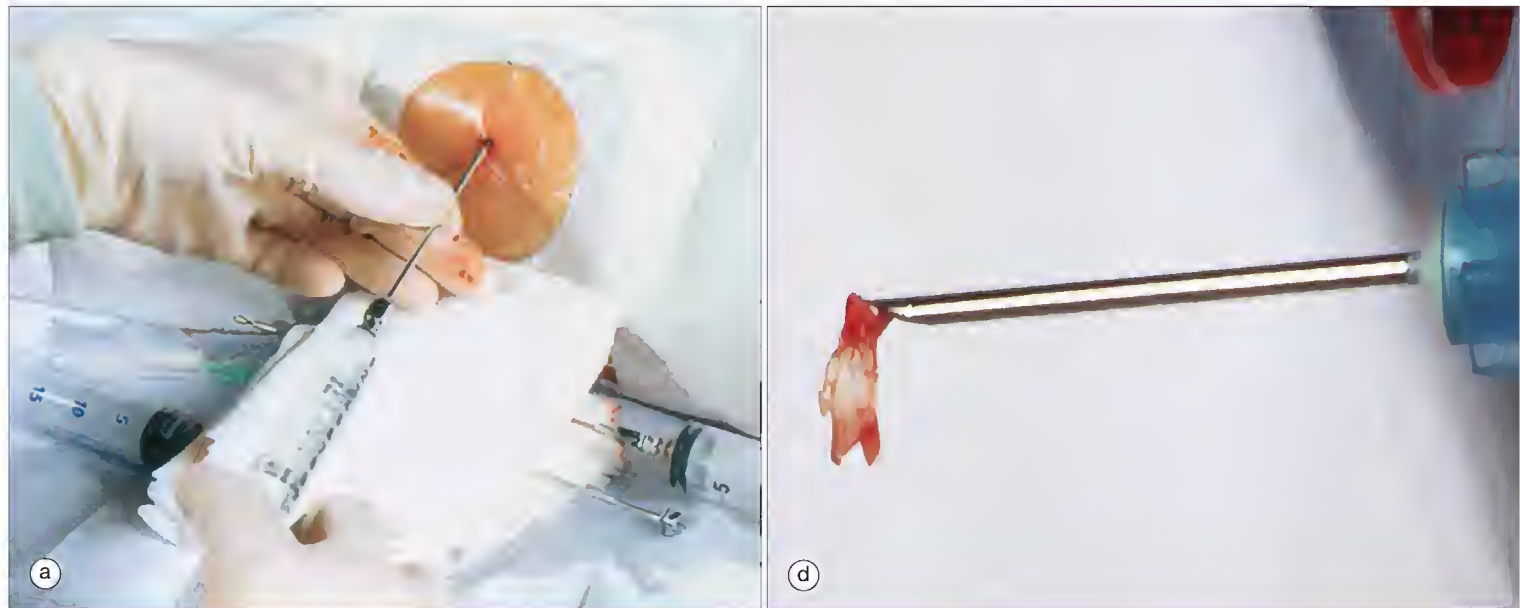
Arthroscopic biopsy

Because blind needle biopsy has limitations (e.g., restriction to larger joints, potential sampling error because of the blind character of the procedure, and difficulty obtaining adequate tissue when the joint is not clinically inflamed), it may be advantageous to obtain synovial tissue with a small-bore arthroscope (Fig. 32.10). Knee arthroscopy can be performed by introducing a small-bore arthroscope or needle arthroscope ranging in size from 4.5 to 2.7 mm into an infrapatellar skin portal, which is created after disinfecting and anesthetizing the skin, subcutis, and knee joint (Fig. 32.11a). A suprapatellar second skin portal is created for the grasping forceps. This technique allows macroscopic examination of the synovial tissue and biopsy of different sites in the joint under direct vision. It can also be used when biopsy samples of an ankle joint are taken through a medial and lateral malleolar portal. A small-bore, 1.9-mm arthroscope can be used for a smaller joint, such as the metacarpophalangeal joint or the wrist through radial and ulnar skin portals (see Fig. 32.11b and c). Inflammatory markers are generally comparable in biopsy samples taken from the knee and a smaller joint such as the wrist.⁶⁰

This technique, performed in an outpatient setting under local or regional anesthesia, is being performed by an increasing number of rheumatologists and is well tolerated by patients. Minimal pain and discomfort during the procedure and minor complications such as vasovagal reactions and temporary swelling of the joint are reported by 35% to 36% and 5% to 10% of patients, respectively.⁶¹ The total complication rate mentioned in a recent survey was 15.1 per 1000 arthroscopies, which is comparable to rates mentioned in the orthopedic literature.⁶² The complications consisted of joint infection (0.1%), deep vein thrombosis (0.2%), and hemarthrosis (0.9%). The amount of irrigation fluid used has been found to correlate with the wound infection and total complication rate, possibly a reflection of the duration of the procedure.

ARTHROSCOPIC JOINT LAVAGE

Joint lavage can be considered for different conditions, such as persistent arthritis after needle aspiration, osteoarthritis, and septic arthritis. The therapeutic effect of joint lavage is attributed to the removal of proinflammatory cells and their destructive enzymes, as well as cartilage degradation products. Although various uncontrolled, retrospective studies have reported a beneficial therapeutic effect of joint lavage for osteoarthritis of the knee joint, a randomized, placebo-controlled trial did not show superiority of this procedure over placebo.⁶³ Moreover, joint lavage alone or combined with infiltration of corticosteroid was similarly effective for symptomatic management of osteoarthritis of the knee; the effects persisted for 3 to 12 months.^{64,65}



CLOSED BIOPSY OF KNEE SYNOVIUM

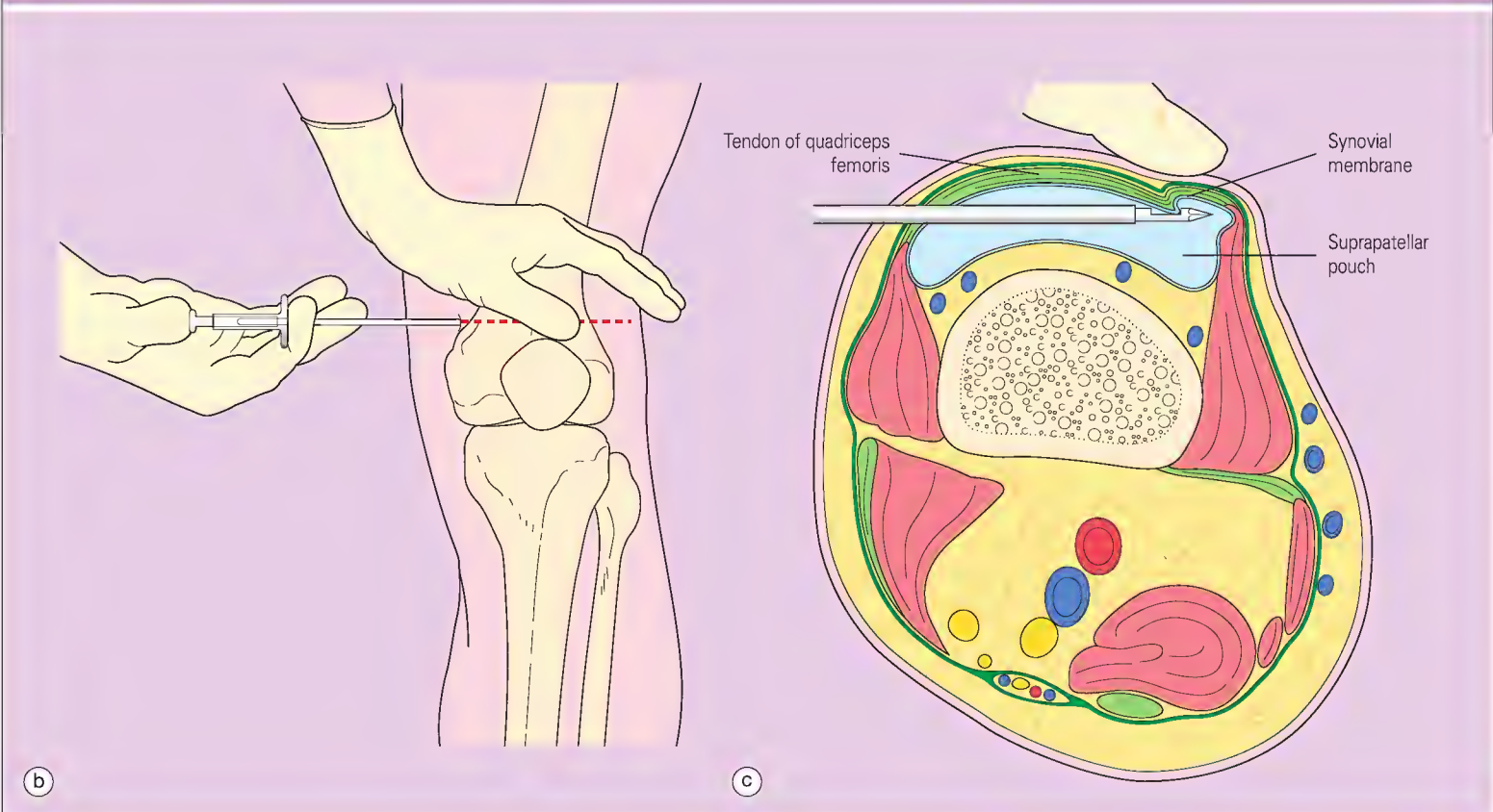


Fig. 32.9 (a) Parker-Pearson needle. (b) Procedure for blind needle biopsy of the knee. (c) Schematic drawing of a blind needle biopsy procedure of the knee. (d) Synovial tissue specimen.



Fig. 32.10 Needle arthroscope.

For inflammatory conditions such as rheumatoid arthritis, the efficacy of joint lavage is still somewhat controversial. Retrospective analysis of the therapeutic effect of needle aspiration and joint lavage in 50 patients revealed that arthroscopic lavage had a superior effect.⁶⁶ This seems to be dependent on the volume of physiologic fluid used during the procedure, with 5 to 10 L giving the best results.^{67,68} Furthermore, the effects of joint lavage are more beneficial in patients with milder disease.

ULTRASOUND-GUIDED SYNOVIAL BIOPSY

Another method increasingly being used to obtain synovial biopsy samples is the recently developed office-based, mini-invasive, ultrasound-guided technique.⁶⁹ This procedure uses ultrasound guidance as an aid to acquire synovial tissue percutaneously by means of a portal and a rigid forceps technique.⁷⁰ This approach combines the advantages of being minimally invasive and being able to sample inflamed synovial tissue under indirect visual inspection. When a multifrequency linear transducer is used, effusion and synovitis can be identified. The sensitivity of this technique can be enhanced by applying power Doppler techniques.⁷¹ Under standard sterile conditions and after infiltrating the skin and subcutaneous tissue with local anesthetic, a 14-gauge needle can be inserted into the designated area under ultrasound guidance. After creating a portal by means of a flexible wire followed by a percutaneous sheath, synovial samples can be acquired with rigid forceps.^{69,70}

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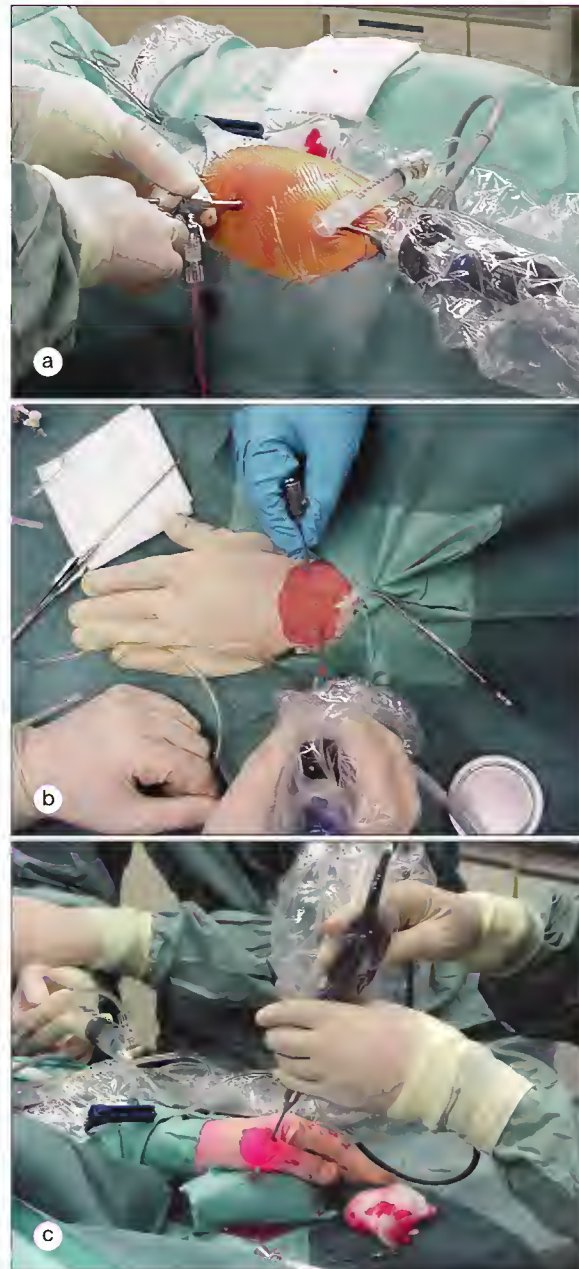


Fig. 32.11 (a) Needle arthroscopy of the knee. (b) Needle arthroscopy of the wrist. (c) Needle arthroscopy of the first metacarpophalangeal joint.

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33

Skin in rheumatic disease

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- Skin is involved frequently in rheumatic diseases.
- Skin manifestations can be hallmark features in some rheumatic diseases, especially lupus erythematosus, dermatomyositis, and systemic sclerosis.
- Skin changes in rheumatic diseases are specific when characterized by a distinct clinical and histopathologic picture.
- Nonspecific skin changes occur in a variety of diseases but not exclusively in a distinct rheumatic disorder.
- Skin involvement can alert the clinician to a different course, therapeutic approach, and prognostic outcome in a patient with rheumatic disease.

INTRODUCTION

Skin changes occur in a variety of rheumatic diseases and are of particular relevance for clinicians dealing with such diseases for several reasons. First, skin can be the initial site of involvement in a rheumatic disease, thereby providing the physician with important clues to the correct diagnosis. Second, skin involvement in a rheumatic disease may serve as an easy-to-access indicator of both systemic involvement and prognostic outcome of the disorder. Third, because of the important psychosocial function of the skin, physicians need to be fully aware of the impact that chronic and often disfiguring skin changes may have on the quality of life of a patient with rheumatic disease. Fourth, skin changes may be induced *de novo* in a patient with rheumatic disease after the initiation of systemic therapy. The rapid advancement in the field of biologics and targeted therapies (e.g., tyrosine kinase inhibitors) for the treatment of rheumatic diseases requires pharmacovigilance for the skin as a frequent site of adverse effects. Finally, elucidation of the pathobiology of skin manifestations will undoubtedly provide important insight into the pathogenesis of rheumatic disorders and allow novel therapeutic approaches.

This chapter describes skin manifestations of the major systemic connective tissue disorders: systemic lupus erythematosus (SLE), dermatomyositis (DM), systemic sclerosis (SSc), and Sjögren syndrome (SJS). This is followed by a heterogeneous group of other systemic rheumatic diseases: rheumatoid arthritis (RA), psoriatic arthritis (PsA), systemic-onset juvenile rheumatoid arthritis (SOJRA), and relapsing polychondritis (RP). It is beyond the scope of this chapter to describe all rheumatic diseases with skin manifestations. The chapter starts with a section describing the general approach to patients with skin manifestations of a rheumatic disease.

APPROACH TO THE PATIENT

To assess skin involvement of a patient with rheumatic disease, a full-body inspection, including the scalp, anogenital area, and mucous membranes, should always be performed because the skin manifestations of rheumatic diseases often have a predilection for distinct body sites that can otherwise easily be overlooked. Examples of such situations are mucosal lesions in the oral cavity of patients with lupus erythematosus (LE) or intertriginous involvement by psoriasis in patients with arthritis. Inspection of all skin appendages (i.e., scalp hair and nails) is also an integral part of any routine dermatologic inspection. Notably, nail changes can be an important indicator of PsA, whereas scarring alopecia may be a troublesome skin manifestation of LE. Full-body inspection also enables the physician to determine the precise extent and severity of skin involvement in a rheumatic disease.

Accordingly, scores to assess the extent and severity of skin involvement have been developed for LE, SSc, and psoriasis and can be used to precisely monitor the efficacy of any treatment.

The skin changes as seen in systemic rheumatic diseases are said to be *specific* when they display characteristic and sometimes even pathognomonic features along with a typical histopathology encountered only in a distinct rheumatic disease. On the other hand, cutaneous manifestations can be *nonspecific* and occur in a diversity of rheumatic and nonrheumatic systemic diseases. It is also well established that some skin diseases have an increased incidence in patients with selected systemic rheumatic diseases. These dermatoses are best referred to as *associated skin diseases*. In some cases only the combination of specific and nonspecific skin changes in the presence of an associated skin disorder may establish the final diagnosis of a rheumatic disease. Description of the skin lesions encountered in patients with rheumatic diseases requires precise terminology. [Box 33.1](#) lists and explains common dermatologic terms encountered in this chapter.

A minimally invasive procedure (e.g., skin biopsy; see Chapter 32) is often helpful to precisely determine the nature of a skin lesion in patients with rheumatic disease. Although most skin lesions can easily be assessed by punch biopsies, involvement of deeper layers of the skin, such as in lupus panniculitis, requires deep incisional biopsies to not miss the diagnosis. Routine processing of skin biopsy specimens with paraformaldehyde fixation is usually sufficient to establish the diagnosis by histopathology, whereas cryopreservation is needed to visualize immunoglobulin deposits by specific staining. It is important to note that immunosuppressive or immunomodulatory treatment (systemic and topical) can severely mask the natural histopathologic picture of a specific skin lesion. Because of the turnover rate of human epidermis, cessation of any such treatment for at least 3 weeks is recommended before skin biopsy.

MAJOR SYSTEMIC CONNECTIVE TISSUE DISORDERS

Systemic lupus erythematosus

Key dermatologic signs of SLE include photosensitivity; malar dermatitis; discoid rash; other forms of specific cutaneous lupus erythematosus (CLE), localized or generalized, involving the epidermis, dermis, or subcutaneous fat of the skin; and oral ulcerations.

Skin involvement is the second most common manifestation of SLE after arthralgias. In approximately 25% of patients with SLE, skin is the first site of disease involvement. According to an Italian study, skin lesions develop in more than 75% of all patients with SLE during the course of their disease.¹ However, patients with SLE may have no signs of skin involvement, a condition called “*lupus sine lupo*.”

Classification of the skin manifestations of LE (CLE) is complex and may be a challenge, especially for novice and nondermatologist physicians. Precise description of the type of CLE is of importance because different subtypes have a different predisposition to systemic involvement of LE. Notably, different subtypes of CLE can occur both in patients with SLE and in patients with no systemic involvement.

The most widely accepted classification of LE was developed by Gilliam and Sontheimer.² It divides LE-specific skin disease into three major clinical subtypes according to their disease acuity: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) ([Box 33.2](#)).³ These subtypes are further specified according to the extent of their skin involvement (local vs. generalized), morphology, and localization of the inflammatory infiltrate in the skin (e.g., LE panniculitis indicating LE-specific infiltration of adipose tissue). It

BOX 33.1 FREQUENTLY USED DERMATOLOGIC TERMS

Erosion—a superficial tangential defect of the epidermis

Erythema—generalized erythema of the skin

Koebner phenomenon—induction of specific skin lesions by nonspecific trauma such as scratching

Macule—a flat localized discoloration of the skin; when the discoloration is red, it is called *erythema*.

Onychodystrophy—disturbed growth of the nail plate

Onycholysis—separation of the nail plate from the nail bed (hyponychium)

Papule/nodule/plaque—a raised, localized, solid skin lesion; when the raised lesion has spread horizontally, it is referred to as a *plaque*.

Pathergy phenomenon—induction of specific skin lesions by intracutaneous injection of sterile NaCl or as a result of venipuncture.

Poikiloderma—a combination of hyperpigmentation, hypopigmentation, telangiectasia, and skin atrophy

Purpura/petechia—localized intradermal hemorrhage; when less than 3 mm in diameter, it is called *petechial*.

Pustule—a vesicle filled with pus

Sclerosis—induration of the skin

Squama—localized area of abnormal shedding of the corneal layer of the epidermis

Ulcer—a substantial defect of the epidermis and deeper layers of the skin (dermis, subcutaneous tissue); it inevitably leads to scar formation.

Urtica/wheal—a transient raised skin lesion attributable to dermal edema; the center of the lesion is pale and the borders are erythematous.

Vesicle/bulla—a localized, raised lesion of the skin filled with exudate, either serous or hemorrhagic fluid; when larger than 0.5 cm in diameter, a vesicle is called a *bulla*.



Fig. 33.1 Generalized acute cutaneous lupus erythematosus. Note the typical distribution with sparing of the knuckles.



Fig. 33.2 Subacute lupus erythematosus (annular subtype). Note the characteristic localization on the upper part of the trunk (V shape).

BOX 33.2 CLASSIFICATION OF LUPUS ERYTHEMATOSUS-SPECIFIC SKIN LESIONS

- A. Acute cutaneous lupus erythematosus (ACLE)
 1. Localized ACLE
 2. Generalized ACLE
 3. Toxic epidermal necrolysis-like ACLE
- B. Subacute cutaneous lupus erythematosus (SCLE)
 1. Annular
 2. Papulosquamous
- C. Chronic cutaneous lupus erythematosus (CCLE)
 1. Discoid lupus erythematosus (DLE)
 - a. Localized
 - b. Generalized
 2. Hypertrophic/verrucous lupus erythematosus
 3. Lupus erythematosus tumidus
 4. Lupus panniculitis/profundus
 5. Chilblain lupus erythematosus
 6. DLE-lichen planus overlap

Modified from Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol* 2004;18:429-62.

is important to note that in patients with SLE (as in patients with CLE only), different forms of LE-specific skin lesions can be present simultaneously (e.g., a butterfly rash as a manifestation of localized ACLE plus chilblain LE as a variant of CCLE).

The hallmark skin lesion of ACLE in patients with SLE is malar dermatitis, which is a reddish maculopapular eruption in a characteristic butterfly distribution on the face (see Fig. 126.1). In most cases patients recall induction or exacerbation of the rash by exposure to ultraviolet (UV) light, thus indicating that photosensitivity is an important diagnostic clue and pathogenetic component. Lesions tend to be transient, last from several hours to weeks, and heal without scarring. Occasionally, poikiloderma (characterized by dyspigmentation, prominent blood vessels, and thinning of the skin) can occur. When generalized, ACLE can involve the trunk with accentuation of the UV-exposed areas but may be localized elsewhere, including the hands, where the knuckles are typically spared (Fig. 33.1). A recently recognized life-threatening variant is toxic epidermal necrolysis-like ACLE. This condition may be regarded as a fulminant form of generalized ACLE in which a massive epidermal injury occurs, possibly because of severe alterations in the dermoepidermal junction and subsequent apoptosis. Another variant is

Rowell syndrome, which was originally described as an erythema multiforme-like eruption in patients with disseminated LE (DLE) and positive anti-Ro/La antibodies. However, subsequent reports and our own observations suggest that similar skin lesions can also develop in patients with SLE and SCLE, as well as in the presence or absence of anti-Ro/La antibodies. Oral lesions are a common mucocutaneous manifestation in patients with SLE and are part of the American College of Rheumatology (ACR) criteria. Typically, they consist of painful aphthoid lesions and ulcerations, especially on the lips and buccal and palatal mucosa, but they may be localized elsewhere in the oral cavity. Some palatal lesions may be asymptomatic.

Patients with clinical features of SCLE usually have circulating anti-Ro and anti-La antibodies and the HLA-B8 and HLA-DR3 haplotype. Notably, SCLE may be induced by drugs, especially antihypertensives and antifungals. This drug-induced type of SCLE does not appear to differ clinically, histopathologically, or immunologically from idiopathic SCLE.⁴ Two variants have been identified: an annular (or arcuate) variant consisting of slightly raised erythema with central clearing and a papulosquamous variant consisting of psoriasis-like or eczematous-like lesions, both typically located on UV-exposed skin, including the lateral aspects of the face, the V of the neck (often with sparing of the area under the chin), the upper ventral and dorsal part of the trunk (Fig. 33.2), and the dorsolateral aspects of the forearms. SCLE lesions never lead to scarring, but hypopigmentation or depigmentation as a result of postinflammatory destruction of epidermal melanocytes is a common complication during the healing process of these skin lesions (Fig. 33.3), especially in patients with darker skin phenotypes. A substantial proportion of patients with SCLE exhibit mild systemic symptoms, especially arthralgias and musculoskeletal complaints. Data from several studies indicate that the proportion of patients with SCLE fulfilling four or more ACR criteria for SLE ranges from 30% to 62%. Therefore,



Fig. 33.3 Residual vitiligo-like skin lesions in a patient with subacute cutaneous lupus erythematosus.



Fig. 33.4 Lupus erythematosus tumidus. Note urticarial plaques on the face and neck.

patients with SLCE need to be monitored closely during the course of their disease to exclude transition into SLE.

The prototypic skin lesion of the classic form of CCLE, also known as discoid CLE, is an erythematous discoid plaque that becomes hyperkeratotic and eventually leads to atrophy and scarring. This subtype of CLE occurs more often in black than in white individuals.³ Dyspigmentation, including hypopigmentation and hyperpigmentation, is common. Discoid lesions have a predilection for the face, ears, and neck but may be widespread without a clear-cut relationship to UV exposure. Disfigurement can be a serious problem, especially in patients with facial involvement. Mucosal membranes, including the lips, mucosal surfaces of the mouth, nasal membranes, conjunctivae, and genital mucosa, may also be involved with characteristic discoid lesions resembling leukoplakia. Although DLE is considered primarily a form of CLE without systemic involvement, patients with SLE may have classic DLE lesions. Long-term follow-up of patients with DLE is also necessary because according to retrospective analysis of a number of studies, SLE will develop in 5% to 10% in the course of the disease.

As outlined in Box 33.2, several other subtypes of CCLE can occur in patients with SLE and nonsystemic LE. In hypertrophic/verruccous CCLE, epidermal hyperkeratosis is prominent and results in lesions with thick scaling. LE tumidus is a rare variant of CLE characterized by photosensitive erythematous, sometimes urticarial plaques and nodules without epidermal hyperkeratosis or follicular plugging.⁶ Lesions are usually located on the face, upper part of the trunk, and extremities (Fig. 33.4). The majority of patients with LE tumidus do not have antinuclear antibodies, and diagnosis relies mainly on the clinical and histomorphologic picture. Because the course and prognosis of LE tumidus are generally more favorable than in other subtypes of CLE, it was suggested that this CLE subtype be labeled “intermittent subtype of CLE.”^{6,7} In contrast, LE panniculitis is a very



Fig. 33.5 Chilblain lupus erythematosus of the toes.

chronic CLE subtype consisting of intense inflammation within the adipose tissue of the skin that results in indurated plaques and lipoatrophy. Lesions are commonly seen on the face, proximal parts of the extremities, upper part of the trunk, and buttocks and can be disfiguring. When the overlying dermis and epidermis are involved in LE panniculitis, it is called *LE profundus*. As shown in a retrospective study of 40 patients with this CCLE variant, few patients (10%) fulfill the ACR criteria for SLE.⁸ Another variant of CCLE is chilblain LE, which denotes pernio-like skin lesions (i.e., red to violaceous plaques located on the distal parts of the extremities—fingertips, toes, and occasionally other parts of the body) that are typically induced and aggravated by exposure to cold (Fig. 33.5). These patients should be monitored carefully because SLE will develop in up to 24% of them.⁹

In the past, SLE disease activity, including some dermatologic criteria, has been assessed by various outcome measurements and scores. Recently, a “Revised CLE Disease Area and Severity Index (RCLASI)” has been introduced.¹⁰ This modified outcome instrument now includes the various CLE subtypes, as well as disease activity parameters (e.g., edema, scaling, hypertrophy, or dyspigmentation). The score had an intraclass correlation coefficient for an interrater reliability of 0.89 for the activity score and 0.79 for the damage score. The RCLASI may be used especially in clinical trials of patients with CLE to precisely assess skin involvement.

Histopathologic examination of a biopsy specimen from specific skin lesions may facilitate the correct diagnosis in a patient with LE. However, it should be noted that proper classification of the various CLE subtypes is based primarily on macroscopic skin morphology whereas the diagnosis of SLE relies on the overall clinical picture, including possible other organ manifestations and laboratory or serologic analysis. In acute forms of cutaneous involvement, LE-specific histologic changes can be subtle.ACLE lesions show vacuolar degeneration of the dermoepidermal junction, dead keratinocytes (“Civatte bodies”), and a sparse lymphohistiocytic infiltrate of the upper dermis. Dermal blood vessels are dilated with extravasation of erythrocytes. In SCLE, these findings are often associated with epidermal atrophy. The lymphohistiocytic infiltrate is located in the upper dermis with an interface and perivascular pattern. Classic DLE lesions have additional epidermal hyperkeratosis and thickening of the dermoepidermal and follicular basement membranes. The lymphohistiocytic infiltrate is often prominent and involves hair follicles, which may also show hyperkeratotic plugging. Mucin may be deposited in the dermis. Deeper forms of CCLE are characterized by a lymphohistiocytic infiltrate situated in the lower dermis, often with mucin deposits (LE tumidus), whereas in lupus panniculitis, the infiltrate is located primarily in the subcutaneous fat tissue. Direct immunofluorescence (DIF) can be used to assess the presence of immunoglobulin (IgG, IgM, and rarely IgA) and complement (C3) along the dermoepidermal junction in frozen sections of CLE lesions. In patients with SLE, this test (“lupus band test”) is typically positive even in nonlesional, sun-protected skin. However, DIF studies currently provide little benefit to the overall diagnosis and classification of LE and may be used only to discriminate between CLE and skin diseases with similar histopathologic findings.

The differential diagnosis of ACLE lesions includes erythema solare (sunburn), photoallergic and phototoxic drug eruptions, DM, atopic eczema, seborrheic dermatitis, contact eczema, and rosacea. SCLE lesions need to be

distinguished from photoallergic and phototoxic drug eruptions, as well as from other forms of annular erythemas (erythema annulare centrifugum, erythema gyratum repens, granuloma annulare, eczema, psoriasis, and tinea). Leukoderma in patients with SLE must not be mistaken for vitiligo, whereas hyperpigmented skin lesions in patients with chronic DLE (CDLE) have to be distinguished from other forms of hyperpigmentary skin diseases.

In addition to the previously described LE-specific skin lesions, a plethora of nonspecific skin signs and associated skin diseases can be present in patients with SLE. These skin signs include harmless vascular changes such as nail-fold abnormalities (large and tortuous capillaries together with areas of avascularity), as well as more serious complications such as vasculitis (leukocytoclastic vasculitis, urticarial vasculitis, nodular vasculitis) and other forms of vasculopathy (atrophie blanche, livedo reticularis, Degos-like lesions, ulcerations, and thromboses), the latter developing especially in patients with antiphospholipid syndrome. Nonscarring alopecia (“lupus hair”) may be seen in patients with SLE, whereas scarring alopecia typically occurs in patients with DLE involving the scalp. Raynaud phenomenon, calcinosis cutis, scleroderma-like changes, and rheumatoid nodules may indicate the presence of an overlap syndrome.

Dermatomyositis

Key dermatologic signs of DM include heliotrope rash, Gottron papules, Gottron sign, poikiloderma atrophicum vasculare, periungual telangiectases, dystrophic cuticles, and calcinosis cutis.

Involvement of the skin is essential in making the diagnosis of DM because characteristic cutaneous lesions belong to the diagnostic criteria for DM according to Bohan and Peter.¹¹ Importantly, skin manifestations precede the clinical symptoms of muscle weakness, electromyopathic abnormalities, or increased levels of creatine phosphokinase in 30% of patients with DM, and in 10% to 20% of all patients with DM, specific skin changes may occur for longer than 6 months without systemic involvement. This group of patients has been referred to as having *amyopathic DM* (DM sine myositis). Although a variety of skin manifestations occur in DM, none of the skin signs allows discrimination between idiopathic DM and the paraneoplastic form.

One highly specific skin sign that can be regarded as the cutaneous hallmark feature of DM is the heliotrope rash (Fig. 33.6). This often pruritic, sometimes burning, violaceous, confluent erythema resembles the color of the heliotrope, a pinkish purple flower that tracks the course of the sun. The heliotrope rash of DM has a characteristic distribution that especially involves the periorbital area. Other sites of predilection are the malar area of the face, the posterior aspect of the neck and shoulders (referred to as the “shawl sign”), and the scalp. DM also often affects the extensor surfaces of the extremities, the knuckles, the dorsal aspects of the interphalangeal joints, and the periungual area of the fingers in a symmetric fashion (see



Fig. 33.6 Heliotrope rash on the face in a man with dermatomyositis.

Fig. 148.1). The characteristic violaceous color and the periorbital distribution of the heliotrope rash distinguish DM from the butterfly rash (malar rash) of ACLE. It is also important to recognize that the skin lesions of DM, when affecting the fingers, tend to be located over the joints and not on the interphalangeal areas, as in patients with generalized ACLE (compare Figs. 33.1 and 148.1).

Depending on the intensity of inflammation, the violaceous macules of DM may evolve into plaques that are often covered with a fine silvery scale, especially on the knees and elbows. When such lesions occur over the knuckles, in the interphalangeal joints, and in the periungual area, they are known as *Gottron papules* (see Fig. 148.1). Violaceous macules developing over the knuckles and the elbows or knees have been referred to as the *Gottron sign* (Fig. 33.7). The intensely inflamed skin lesions of DM may develop into erosions, subepidermal blisters, and ulcers (Fig. 33.8). Recently, the presence of antimelanoma differentiation-associated gene 5 (*MDA5*) has been reported to identify the presence of characteristic skin lesions and musculoskeletal, pulmonary, and prognostic features in Japanese patients with DM.¹² Patients with these antibodies had multiple pustules and ulcers on their fingers and palms. Mortality was independently associated with the presence of anti-MDA5 antibodies.

Furthermore, the term *poikiloderma atrophicum vasculare* has been coined to describe patients with DM and a combination of violaceous erythema, hyperpigmentation, hypopigmentation, telangiectasia, and atrophy.

In addition to the aforementioned skin signs, many patients with DM have prominent nail-fold telangiectases (see Fig. 148.8) and dystrophic (“ragged”) cuticles. Moreover, gingival telangiectases have recently been identified as a sign of juvenile DM. Other, less frequently encountered cutaneous manifestations of DM include panniculitis leading to lipotrophy, papular and pustular lesions, and centripetal flagellate erythema. The term *mechanic’s hands* (see Fig. 148.9) has been applied to the occurrence of



Fig. 33.7 Violaceous plaques on the knees of a patient with dermatomyositis (Gottron sign).



Fig. 33.8 Skin ulcerations in a young female with paraneoplastic dermatomyositis.

chronic eczematous skin lesions on the fingers of patients with myositis.¹³ A high proportion of patients with mechanic's hands turned out to have so-called *antisynthetase syndrome* (an overlap syndrome consisting of anti-synthetase antibodies, erosive polyarthritis, interstitial lung disease, fever, Raynaud phenomenon, and inflammatory myositis). Another subset has anti-PM-SCL antibodies, indicative of a polymyositis-scleroderma overlap syndrome. However, recent observations have questioned the specific association of the previously mentioned antibodies with mechanic's hands, thus suggesting that these skin manifestations may also occur in related systemic connective tissue disorders.

Calcinosis cutis can be an extremely painful and devastating skin manifestation of DM. It occurs most often at sites of friction and trauma, such as on the elbows, trochanters, knees, and fingers, and consists of hard, irregular nodules that eventually drain chalky material to the skin surface. It is more prevalent in juvenile DM than in the adult form. Of note, calcinosis is also a key feature of the calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, telangiectasia (CREST) syndrome and can be a manifestation of overlap syndromes.

Histopathologic examination of a heliotrope erythema typically reveals an interface dermatitis with a sparse lymphocytic infiltrate, epidermal atrophy, vacuolar alteration of the basal keratinocytes, basement membrane degeneration, and interstitial mucin deposition. More inflamed lesions (i.e., Gottron papules) also show lichenoid infiltrate and acanthosis of the epidermis. Immunohistologic studies have demonstrated that the infiltrate in skin and muscle lesions of patients with DM consists mainly of CD8+ lymphocytes, thus supporting the concept of a lymphocyte-mediated disease in the pathogenesis of DM.

The differential diagnosis of DM includes SLE, psoriasis, atopic dermatitis, photoallergic and phototoxic drug eruption, contact dermatitis, cutaneous T-cell lymphoma, SSc, and trichinosis. The skin ulcers in DM need to be distinguished from hemorrhagic-necrotizing vasculitis and from a DM-like eruption with painful ulcerations induced by hydroxyurea.

Systemic sclerosis

Key dermatologic signs of SSc include Raynaud phenomenon, symmetric cutaneous sclerosis, finger swelling, sclerodactyly, digital pits and ulcers, dilated or atrophic nail-fold capillaries, calcinosis cutis, and hyperpigmentation.

The term *sclerosis* describes hardening or induration as a result of excessive deposition of interstitial collagen and subsequent tissue fibrosis. By definition, SSc is a multisystem disorder that involves the skin and internal organs. However, it should be noted that sclerosis of the skin ("scleroderma") is a common reaction pattern of several fibrotic skin disorders, some of which are benign and localized only to the skin whereas others are systemic conditions. Thus, in the context of the clinical pattern, internal organ abnormalities, and laboratory tests, the diagnosis of SSc should always exclude these differential diagnoses (see later).

There is striking heterogeneity within the clinical spectrum of cutaneous thickening in patients with SSc, but two subtypes with distinct clinical, serologic, and prognostic features have been delineated. In patients with *diffuse* SSc, skin thickening involves the trunk and proximal portions of the extremities, whereas in patients with *limited* SSc, the skin induration is confined to the face and distal portions of the extremities. However, there are cases with overlap between these two widely accepted clinical forms of SSc. A distinct form of limited SSc with induration of the fingers ("sclerodactyly") is the CREST syndrome. These patients typically have detectable anticentromere antibodies and a generally favorable prognosis when compared with patients with diffuse SSc. Finally, an unusual variant called *scleroderma sine scleroderma*, in which affected patients have evidence of SSc secondary to SSc-related antibodies and internal organ involvement but no skin involvement, has been described. The prognosis of these patients is similar to those with limited SSc.

Often years before the onset of skin induration, patients with SSc experience Raynaud phenomenon (see Figs. 142.2 and 142.3). Although a non-specific sign that is seen in other connective tissue diseases and closely related overlapping syndromes, Raynaud phenomenon is present in 90% to 99% of patients with diffuse or limited SSc. When cutaneous involvement proceeds, an edematous phase of the affected sites often takes place, especially on the fingers ("puffy fingers"). Similar changes may also be seen on the forearms, legs, feet, face, and trunk. This is followed by gradual thickening of the skin in which the initial inflammation is replaced by interstitial fibrosis caused by abnormal collagen metabolism (indurative phase) and subsequent sclerodactyly and dermatopathic contractures. The impaired acral blood flow in sclerodactyly may lead to digital pits and ulcers (see Fig. 142.4). A recent study further revealed that patients with SSc and digital

ulcers exhibited internal organ involvement 2 to 3 years earlier than did those without digital ulcers.¹⁴

Among the other common cutaneous key signs of SSc are telangiectases, which also form a diagnostic cornerstone in patients with CREST syndrome. The telangiectases seen in patients with SSc are often located on the face, including the lips, but may also be detected on the neck, volar aspects of the fingers, and palms and tend to be matted (see Fig. 142.11). Dilated nail-fold capillaries, often alternating with areas of capillary loss, can easily be detected with a dermatoscope. Calcinosis is another key feature of CREST syndrome and tends to be located on the extremities, especially at the fingertips and over joints (Fig. 33.9).

A relatively unappreciated skin sign in patients with SSc is skin hyperpigmentation. It occurs mostly as a diffuse brownish discoloration resembling a suntan and is usually accentuated in areas of friction and pressure (Fig. 33.10). Variants of skin discoloration in patients with diffuse SSc do occur and include "salt and pepper," which describes a combination of hyperpigmentation and hypopigmentation often found on the upper part of the trunk (see Fig. 33.10).

Although a number of instrumental devices such as a skin durometer and 25-MHz ultrasonography may be useful to determine the extent of skin sclerosis in patients with SSc, the modified Rodnan total skin thickness score remains an essential tool for daily routine, as well as for clinical trials. This score assesses cutaneous thickening on a scale of 0 to 3 in 17 anatomic areas by means of palpation.¹⁵ However, interobserver variability is high (mean, 17.7), and proper application of this tool in patients with SSc still requires some training.

Histopathologic examination of sclerotic skin from patients with SSc demonstrates excessive collagen deposits within the dermis and subcutaneous tissue that often entrap the adnexal structures as the predominant



Fig. 33.9 Calcinosis cutis.



Fig. 33.10 Diffuse hyperpigmentation of the skin in a patient with systemic sclerosis. Note also the depigmentation in the submammary region.

finding. In earlier inflammatory phases (edematous phase), a dense lymphocytic infiltrate may be seen at the interface of the deep dermis and adipose tissue.

The differential diagnosis of SSc includes scleromyxedema; eosinophilic fasciitis (Shulman syndrome); scleredema adutorum and diabeticorum; diabetic thick skin; sclerosing chronic graft-versus-host disease; sclerosing forms of porphyria; polyneuropathy, organomegaly, endocrinopathy, *M* component, and skin changes (POEMS syndrome); nephrogenic fibrosing dermopathy; eosinophilia myalgia syndrome; toxic oil syndrome; carcinoid syndrome; pansclerotic localized scleroderma (morphea); exposure to bleomycin, aromatic chlorinated hydrocarbons, or vinyl chloride; phenylketonuria; various progeria syndromes; and reflex sympathetic dystrophy.

Sjögren syndrome (Mikulicz disease, sicca syndrome)

Key dermatologic signs of SjS include xerostomia, xerosis cutis, angular stomatitis (perlèche), various forms of cutaneous vasculitis, and annular erythema.

Mucocutaneous symptoms are usually the first clinical findings in patients with SjS, a systemic autoimmune disorder that primarily affects the secretory glands. Though a nonspecific sign, dryness (xerosis) of the mucous membranes in context with the other diagnostic criteria is a key component for establishing the diagnosis of this multisystem disease. Xerosis can involve not only the mouth (xerostomia) and the eyes (leading to keratoconjunctivitis sicca) but also the vagina. Regarding the mouth, patients typically complain of dryness, soreness, and burning sensations. Vaginal xerosis can likewise result in dryness, burning, and dyspareunia, but patients frequently do not report these symptoms unless asked specifically about them. Because of diminished salivary production, angular stomatitis (perlèche) of the mouth with *Candida* infection is common. Although dental and gingival problems are said to be more frequent in patients with SjS, a recent study did not indicate any increased risk for caries and gingivitis, probably because of increased awareness and dental care of affected patients.¹⁶

In addition to the aforementioned key signs in the mucous membranes, several *bona-fide* skin manifestations are frequently observed in patients with SjS. All of them are again nonspecific. Xerosis cutis is found in 50% of patients, but the underlying pathomechanism remains obscure. It may lead to generalized pruritus. In the authors' experience, various forms of noncutaneous vasculitis, most likely resulting from an immune complex mechanism, are frequently encountered in patients with SjS. They include palpable and nonpalpable purpura on the legs and buttocks (see Fig. 138.5). This form of cutaneous vasculitis is characteristically induced or aggravated by physical exertion. Other forms of cutaneous vasculitis include lymphocytic vasculitis and urticarial vasculitis (either hypocomplementemic or, less commonly, normocomplementemic). By definition, the urticarial lesions of urticarial vasculitis last longer than 48 hours (in contrast to common urticaria) and often have a purpuric component. Patients frequently complain of burning and painful sensations. The lesions often heal with hyperpigmentation. Histologically, the lesions of lymphocytic vasculitis display a mononuclear cell infiltration with disruption of the architecture of the small blood vessels, whereas those of leukocytoclastic vasculitis, including urticarial lesions, show the expected well-described changes.

An unusual skin manifestation of SjS was originally described in Japanese children and has been coined annular erythema of SjS. It appears to be highly associated with the presence of anti-Ro antibodies. Clinically and histologically, these lesions may be indistinguishable from annular SCL. Recent observations indicate that identical lesions can also occur in white individuals.

Regarding other cutaneous manifestations, it is important to note that SjS can be not only primary but also secondary and therefore associated with a number of other diseases, including LE, DM, SSc, RA, primary biliary cirrhosis, fibromyalgia, and others. The specific skin signs of these associated disorders must therefore be distinguished from the *bona-fide* skin manifestations of SjS.

OTHER SYSTEMIC RHEUMATIC DISEASES

Rheumatoid arthritis

Key dermatologic signs of RA include nodules, often symmetrically distributed, purpura, petechiae, and ulcerations.

The characteristic clinical features of RA are frequently associated with skin manifestations, which may not only serve as helpful diagnostic clues

but also indicate the severity of the disease. Rheumatoid nodules, accelerated rheumatoid nodulosis, rheumatoid neutrophilic dermatosis, and rheumatoid vasculitis are regarded as RA-specific skin manifestations.

Classic *rheumatoid nodules* are present in about 25% of patients with RA and are more frequent in the white male population.¹⁷ Most patients with rheumatoid nodules are rheumatoid factor positive. In seronegative RA, the nodular lesions turned out to be mostly granuloma annulare or other palisading granulomas. Genetic predisposition seems to play a role because patients with the HLA-DR4 haplotype and those with heterozygosity for HLA-DRB1 alleles are at high risk for nodular disease, as well as a severe RA prognosis.¹⁸ Rheumatoid nodules measuring from a few millimeters up to several centimeters generally develop as subcutaneous, firm, and painless lesions. Usually they occur on periarticular locations over extensor surfaces, but they may appear in any location, including the lung, heart, and muscle. Complications that may sometimes occur include infection, ulceration, gangrene, bursitis, and synovial rupture.

The differential diagnosis of rheumatoid nodules includes chronic gouty tophi, rheumatic fever nodules, the subcutaneous nodules found in SLE, nodular or keloidal scleroderma, and the nodules seen in necrobiosis lipoidica and granuloma annulare. In addition, tumoral calcinosis, fibromas, xanthomas, subcutaneous sarcoidosis, metastatic tumors, amyloidosis, ganglion cysts, foreign-body granulomas, basal cell carcinomas, epidermoid cysts, and synovial cysts should be considered.

The characteristic symptomatic complex of arthritis, leukopenia, and splenomegaly, which develops in 1% of patients with RA, is known as *Felty syndrome*. Rheumatoid nodules (76%), hyperpigmentation, and therapy-resistant leg ulcers (22%) may also occur.¹⁹ However, cutaneous hyperpigmentation and leg ulceration may be multifactorial and are often related to underlying chronic venous insufficiency. Importantly, Felty syndrome is associated with an increased risk for cutaneous and systemic infections that may be difficult to treat and be the cause of sepsis. The differential diagnosis includes SLE, drug-induced leukopenia, viral infection, amyloidosis, leukemia, lymphoma, subacute bacterial endocarditis, aplastic anemia, splenic abscess, hemolytic anemia, tuberculosis, and SjS. In addition, cutaneous ulcerations and hyperpigmentation may also be caused by systemic treatment with methotrexate (MTX).

Accelerated rheumatoid nodulosis was initially reported in patients receiving MTX therapy for RA or juvenile rheumatoid arthritis.²⁰ It is characterized by the development of painful nodules mainly on the hands of RA patients being treated with MTX; it has not been found to be associated with other immunosuppressive drugs such as azathioprine. RA patients treated with hydroxychloroquine, D-penicillamine, colchicine, or sulfasalazine were found to be protected against the development of MTX-induced accelerated rheumatoid nodulosis. Interestingly, the occurrence of similar nodules has been observed during MTX therapy in a patient with PsA. Recently, accelerated rheumatoid nodulosis has also been described in patients receiving etanercept,²¹ as well as in one patient receiving an aromatase inhibitor,²² thus indicating that MTX is not the only trigger eliciting such skin manifestations of RA. Like other granulomatous skin manifestations of RA (see later), infections by typical and atypical mycobacteria, as well as by opportunistic or endemic bacteria, have to be excluded, especially in patients taking immunosuppressants.

Rheumatoid vasculitis is a late complication of RA that may involve the skin, as well as other organs, and may affect vessels of any size. Accordingly, rheumatoid vasculitis can result in a variety of cutaneous skin signs (Box 33.3). It occurs in seropositive and mainly male RA patients with longstanding disease.²³ Small-vessel disease clinically represents palpable and nonpalpable purpura, localized petechiae, splinter hemorrhages, nail-fold infarctions (Bywaters lesions), and peripheral neuropathy. In medium-vessel disease, cutaneous findings include nodules, ulcerations, livedo reticularis, and digital infarcts. Because the course of rheumatoid vasculitis is associated with high morbidity and mortality, early and intensive immunosuppressive therapy is required. Biopsy of cutaneous lesions, preferentially nodules, and immunohistochemical examination are often helpful in establishing the diagnosis. Because peripheral neuropathy is frequently observed in cases in which vasculitis cannot be identified, nerve conduction studies and sural nerve or muscle biopsy can be performed. The differential diagnosis of rheumatoid vasculitis includes polyarteritis nodosa, PG, SLE, antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis, and erythema elevatum et diutinum.

In addition to the previously mentioned specific skin manifestations of RA, large numbers of nonspecific skin signs and associated dermatoses have been described (Box 33.4). *Pyoderma gangrenosum* is frequently associated with both seronegative and seropositive RA. Clinically, it begins as a tender erythematous or violaceous papule that expands rapidly into a purulent necrotic ulcer with ragged edematous edges (Fig. 33.11). Usually, PG occurs

BOX 33.3 SKIN MANIFESTATIONS OF RHEUMATOID VASCULITIS

Petechiae or purpura
 Digital infarcts
 Nail-fold telangiectases and infarctions
 Gangrene
 Nonspecific maculopapular or nodular erythema
 Hemorrhagic blisters
 Livedo reticularis
 Erythema elevatum et diutinum
 Atrophie blanche
 Allergic venulitis
 Necrotizing granulomatous vasculitis
 Urticaria vasculitis

BOX 33.4 NONSPECIFIC SKIN MANIFESTATIONS AND ASSOCIATED SKIN DISORDERS IN RHEUMATOID ARTHRITIS

Pyoderma gangrenosum
 Palisaded neutrophilic and granulomatous dermatitis
 Interstitial granulomatous dermatitis
 Atrophic and fragile skin
 Pale and transparent skin
 Palmar erythema
 Livedoid (Raynaud-like) fingertips
 Onychorrhexis and clubbing of the nails
 Onycholysis
 Periungual erythema
 Yellow nail syndrome
 Splinter hemorrhages and nail-fold thromboses
 Pressure ulcers
 Hyperpigmentation
 Transient macular erythema
 Erythromelalgia
 Noninflammatory purpura
 Erythema multiforme
 Urticaria
 Erythema nodosum
 Vitiligo
 Alopecia areata
 Nonmelanoma skin cancer
 Intralymphatic histiocytosis of the skin



Fig. 33.11 Pyoderma gangrenosum. Note the undermined hemorrhagic borders.

as a single painful lesion on the lower extremities. Koebner and pathergy phenomena are characteristic. The presence of chronic relapsing lesions in unusual sites such as the face, upper extremities, or abdomen may indicate another underlying disease such as inflammatory bowel disease or hematologic disorders. The idea that PG is a true skin manifestation of RA has been challenged because it also occurs in other systemic disorders, has no relationship in its clinical manifestation with the course of RA, and involves no



Fig. 33.12 Rope sign in a patient with interstitial granulomatous dermatitis.

histology specific for RA.²⁴ Histologic examination of early lesions demonstrates a neutrophilic infiltrate and small abscesses.

The differential diagnosis of PG includes venous or arterial ulcers, vasculitis, drug reactions, antiphospholipid syndrome, halogenoderma, factitial diseases, deep fungal infections, mycobacterial infections, gummatous syphilis, viral infections, amebiasis, arthropod bites, and tumors.

Rheumatoid neutrophilic dermatosis is a rare cutaneous sign in patients with severe and seropositive RA.²⁵ Clinically, it is manifested as asymptomatic erythematous urticarial papules and plaques that may persist and sometimes ulcerate. They are usually distributed on the forearms and hands. Rheumatoid neutrophilic dermatosis resembles Sweet syndrome.

Palisaded neutrophilic and granulomatous dermatitis, also known as Winkelmann granuloma, represents a condition of unknown cause with a variety of clinical findings in the context of systemic diseases. Skin manifestations usually develop symmetrically on the extensor surfaces of the elbows and fingers and appear as skin-colored, erythematous, or violaceous papules, nodules, and plaques, sometimes with central umbilication and crusts or perforation.²⁶ Histopathologic examination shows granulomatous inflammation in the presence or absence of leukocytoclastic vasculitis. In addition to RA, this condition has been especially associated with Behçet disease, SLE, SSC, ulcerative bowel and celiac disease, sarcoidosis, ANCA-associated vasculitis ("Wegener granulomatosis"), and lymphoproliferative disease.

Another skin sign of RA may be *interstitial granulomatous dermatitis*.²⁷ It consists of multiple well-demarcated erythematous to violaceous papules or plaques, sometimes coalescing to larger areas or linear cords (Fig. 33.12). However, the latter distinctive pattern ("rope sign") is seen in only 10% of all cases.²⁸ Lesions are typically located on the trunk but may also occur on the proximal ends of limbs. They may perforate with extrusion of the necrobiotic collagen. Histopathologically, the lesions consist of a predominantly CD68+ inflammatory infiltrate of macrophages between collagen bundles in the mid and deep dermis. The macrophages are surrounded by degenerated collagen fibers, and no signs of vasculitis or mucin deposition are present. Giant multinucleated histiocytes are detectable in only a subset of cases.²⁸ It is important to note that this condition is associated not only with RA or other forms of arthritis or arthralgias but also with other autoimmune diseases and with cancer.²⁸ The differential diagnosis of the granulomatous dermatitis of RA includes mainly granuloma annulare, necrobiosis lipoidica, granulomatous slack skin, and interstitial granulomatous drug reactions.

Systemic-onset juvenile rheumatoid arthritis (juvenile rheumatoid arthritis, juvenile chronic arthritis, Still disease)

Key dermatologic signs of SOJRA include macular or maculopapular exanthema and rheumatoid nodule-like lesions.



Fig. 33.13 Exanthema in a child with Still disease.

Diagnosis of SOJRA can be challenging. Because skin manifestations can precede the arthralgias by years, early recognition can be crucial in establishing the diagnosis. SOJRA has two clinical manifestations: an acute febrile systemic variant and an oligoarticular variant with low-grade persistent fevers. In the acute-onset variant, in which high episodic fevers with temperatures higher than 38.9° C are characteristic, a nonpruritic transient exanthema that recurs with fevers develops in 90% of patients.²⁹ It consists of discrete macular or maculopapular lesions, often located on the trunk (Fig. 33.13). The color of the lesions is pink to red, and koebnerization is common. The histopathologic findings of the rash are nonspecific and consist of a discrete perivascular mixed infiltrate with edema of the upper dermis. Another skin sign in patients with SOJRA is rheumatoid nodule–like lesions with a predilection for the extensor surfaces of the extremities.³⁰ Lesions can be both clinically and histologically indistinguishable from those in patients with RA.

The differential diagnosis of the typical exanthema of SOJRA in combination with fever and arthralgias includes rheumatic fever, familial Mediterranean fever, hyper-IgD syndrome, tumor necrosis factor receptor–associated periodic syndrome (TRAPS), familial Hibernian fever, autosomal dominant periodic fever with amyloidosis, and benign autosomal dominant familial periodic fever.

Relapsing polychondritis (atrophic polychondritis, systemic chondromalacia, polychondropathia)

Key dermatologic signs of RP include erythema, swelling, and pain in the cartilaginous portion of the ear with sparing of the earlobe, as well as auricular and nasal deformity.

RP is a chronic inflammatory multisystem disorder that can lead to significant morbidity because of destruction of the cartilaginous tissue in many organs. In a significant number of patients with RP, cutaneous involvement is the first clinical manifestation.

The hallmark cutaneous features of RP are erythema, swelling, and pain in the cartilaginous part of the ear that typically spares the earlobe (see Fig. 167.1). The vast majority of patients with RP suffer from auricular involvement during the course of their disease. Persistent inflammation will lead to destruction of the auricular cartilage and result in so-called cauliflower ears. Involvement of the nasal cartilage occurs in 70% of affected patients and eventually leads to a saddle nose deformity.³¹ Glomerulonephritis may accompany RP.

Histopathologic examination of inflamed cartilage shows basophilic staining, loss of the normal lacunar structures, and a neutrophilic infiltrate. At later stages, lymphocytes and plasma cells are more prominent and the cartilage is replaced by granulation tissue and fibrosis.

Several nonspecific skin signs have been reported to occur in 36% of patients with RP.³² However, a significant proportion may be related to associated diseases (myelodysplastic syndrome, Behçet disease, and other systemic disorders) or adverse effects of concomitant systemic treatment. These skin manifestations consist of various forms of vasculitis, including palpable purpura, and erythema elevatum et diutinum, noninflammatory vasculopathies like livedo reticularis, furthermore, panniculitis, and aphthosis (oral or complex).

The differential diagnosis of RP includes primarily traumatic and infectious forms of chondritis and ANCA-associated granulomatous vasculitis,



Fig. 33.14 Psoriasis vulgaris. Note the typical distribution over the extensor surfaces and silvery scales.

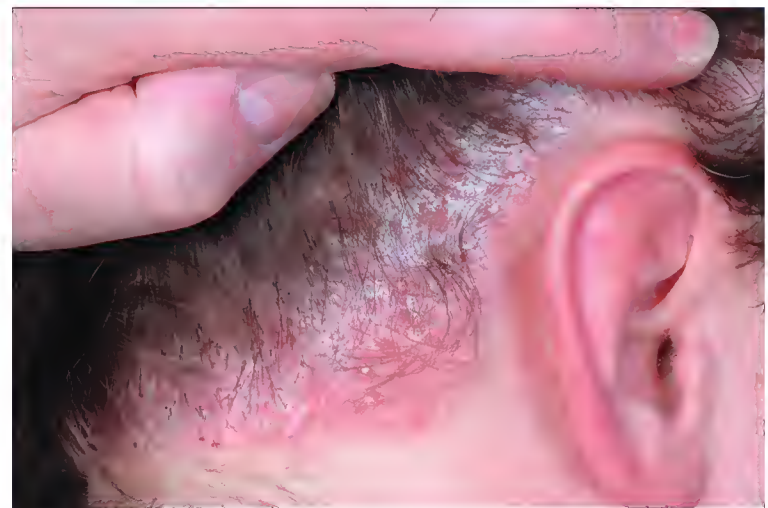


Fig. 33.15 Psoriasis vulgaris involving the scalp (psoriasis capitis).

which may also lead to cartilage destruction, especially of the nose. The combination of features of RP and Behçet disease has led to the designation mouth and genital ulceration with inflamed cartilage (MAGIC syndrome).³³

Psoriatic arthritis

Key dermatologic signs of psoriasis are papulosquamous plaques on the scalp and on the extensor surfaces of the body as well as nail dystrophy. Psoriasis, one of the most common immune-mediated inflammatory skin disorders with an estimated prevalence of 2% in Europe,³⁴ has to be excluded in all patients with arthralgia. Although clinical diagnosis of psoriasis is easy in most cases, it can be challenging in patients with less frequent psoriasis subtypes as well as in those receiving immunosuppressive agents. Moreover, the dermatologic manifestations of psoriasis are quite heterogeneous. Classification of the clinical subtypes of psoriasis is traditionally based on morphology, localization, and extent of the disease, with current concepts also trying to incorporate disease stability and numeric parameters.³⁵

The most common form of psoriasis is known as *psoriasis vulgaris* or *plaque psoriasis*. Its key feature is a sharply demarcated red to pinkish papulosquamous plaque of any size with a noncoherent silvery scale (Fig. 33.14). Involvement of the scalp by psoriasis appears to particularly be associated with PsA (Fig. 33.15).³⁶ On removal of the scale a glossy erythema with blood droplets appears (Auspitz sign). Typically, the elbows, knees, lower part of the back, scalp including the ears, and umbilicus are involved. The palms and soles may be affected as well. Within the psoriasis vulgaris group two subtypes had already been distinguished more than 20 years ago. In the first group (type I), the peak onset of psoriasis occurs at an age of 16 years (females) or 22 years (males), and in the second group (type II) the peak onset occurs at an age of 60 years (females) or 57 years (males).³⁷ Patients



Fig. 33.16 Nail psoriasis. Note the onycholysis, oil spots, and pits.



Fig. 33.17 Psoriasis inversa. Note well-demarcated erythema and absence of scales.

classified as having type I psoriasis vulgaris have a genetic association within the major histocompatibility complex class I region on chromosome 6p (HLA-Cw*0602), whereas patients classified as having type II have no evidence of association with HLA-C alleles.³⁸

Guttate psoriasis (from Latin *guttata*, meaning “droplike”) may be considered a subtype of type I psoriasis vulgaris and is often encountered in children and young adults. In this case the psoriasis develops as an acute eruption of papules and plaques measuring less than 1 cm that most often starts on the trunk but may spread to the proximal parts of the extremities and face. Infections with group B hemolytic streptococci (tonsillitis, pharyngitis) may precede the development of guttate psoriasis, especially in children and young adults. Even though this form of psoriasis is said to be self-limited and resolves within 3 to 4 months, few data are available on the long-term risk for the development of chronic plaque psoriasis after a single episode of guttate psoriasis.³⁹

Nail psoriasis can be considered an important indicator of PsA. Although it occurs in 40% to 45% of patients with psoriasis without joint involvement, its prevalence is 60% to 90% in those with PsA.⁴⁰⁻⁴² Typical features are oil spots (yellow to orange subungual discolorations), pits (punctate nail plate defects), onycholysis, and onychodystrophy (Fig. 33.16). Interestingly, nail psoriasis may be present without additional signs of skin involvement.

In addition to manifestation of psoriasis on the scalp and nails, involvement of the flexural or intertriginous areas may alert the clinician to PsA.³⁶ This type of psoriasis has been coined *psoriasis inversa* and describes the localization of psoriatic lesions in the groin, axilla, submammary region, natal cleft, and genital area. The lesions are typically erythematous with little or no scaling and tend to be associated with maceration and fissuring (Fig. 33.17).

Psoriatic erythroderma describes total involvement of the skin with psoriasis. It is characterized by generalized erythema and various degrees of scaling, depending on the course of development either as an abruptly evolving psoriasis or as a complication of preexisting, slowly progressive plaque psoriasis. Psoriatic erythroderma must be considered a potentially life-threatening condition associated with hypothermia, hypoalbuminemia, and tachycardia. It may lead to high-output cardiac failure, especially in multimorbid patients.

Pustular psoriasis occurs as a limited eruption of sterile pustules on the palms and soles (psoriasis pustulosa palmoplantaris) or as a generalized form (von Zumbusch psoriasis). The latter is an acute, often febrile eruption of multiple monomorphic sterile pustules on erythematous skin, especially over the trunk and extremities, and is associated with systemic illness. Although psoriasis pustulosa palmoplantaris is frequently found in patients with psoriasis vulgaris, genetic studies point toward a different pathogenesis.⁴³

Assessment of the extent, severity, and acuity of skin involvement by psoriasis can be done with various outcome tools, including the Psoriasis Area and Severity Index, Overall Lesion Severity instrument, physician global assessment, and assessment by affected body surface area. Because psoriasis can severely affect quality of life, patient-related outcome tools are likewise important. For nail involvement, a Nail Psoriasis Severity Index has also been developed.⁴⁴

The diagnosis of psoriasis is made primarily clinically, and skin biopsy is not usually required. If biopsied, early psoriasis lesions show a modest lymphocytic perivascular infiltrate with prominent vessels in the upper dermis. Later, extravasation of erythrocytes occurs with mild epidermal hyperplasia. Scalp lesions reveal epidermal parakeratosis and hyperplasia, prominent mitoses in basal keratinocytes, and neutrophilic infiltration. The neutrophils migrate into the epidermis (Munro microabscesses). Fully developed psoriasis lesions show elongation of the rete ridges, mounds of parakeratosis, and more prominent accumulation of neutrophils. Vessels in the papillary dermis are tortuous and dilated with extravasation of both erythrocytes and lymphocytes.

The differential diagnosis of psoriasis vulgaris includes tinea corporis, papulosquamous SCLE, mycosis fungoides, pityriasis versicolor, pityriasis rubra pilaris, secondary syphilis, and eczema. Psoriasis of the scalp must be distinguished from DLE and tinea capitis, whereas nail psoriasis must be differentiated from tinea unguium. Psoriasis inversa may be mimicked by intertrigo, candidiasis, and Hailey-Hailey disease. Psoriatic erythroderma must be differentiated from other forms of primary (drug-induced) and secondary erythroderma (caused by nonpsoriatic immune-mediated inflammatory skin diseases). Pustular psoriasis needs to be distinguished from bacterial skin infections and other noninfectious pustuloses of the skin.

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34

The eye in rheumatic disease

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- Ocular inflammation is common in rheumatic disease and often varies with the rheumatic disease in question.
- The most common ocular manifestations of rheumatic disease are uveitis, scleritis, and keratoconjunctivitis sicca.
- In selected rheumatic diseases (i.e., antineutrophilic cytoplasmic antibody–associated granulomatous vasculitis, Behçet disease), the eye disease may be severe enough to dictate therapy for the systemic disease.

INTRODUCTION

The rheumatic diseases are a heterogeneous collection of immune-mediated, multisystem disorders. Ocular involvement is common and often varies with the rheumatic disease in question.¹ The major manifestations of ocular involvement in rheumatic disease include uveitis, scleritis, retinal vascular disease, neuroophthalmic lesions, orbital disease, keratitis, and sicca disease associated with Sjögren syndrome.¹ The eyes may also be affected by several drugs used for the treatment of inflammatory rheumatic diseases, such as corticosteroids or antimalarial agents; these abnormalities are discussed in the appropriate chapters.

UVEITIS

Uveitis refers to a group of approximately 30 diseases characterized by inflammation inside the eye, some of which are infectious, some associated with systemic diseases, and many of which are eye-limited, immune-mediated disorders. Each disease has its own features, course, treatment, and prognosis. The uveitides are classified by the anatomic site at which the inflammation primarily occurs. Uveitis detected primarily in the anterior chamber is termed *anterior uveitis* (Fig. 34.1), which is also known as *iritis* or *iridocyclitis*. Inflammation primarily involving the vitreous is termed *intermediate uveitis*, and uveitis located in the retina or choroid is called *posterior uveitis*. Uveitis that involves all three compartments but does not have a primary focus of inflammation is termed *panuveitis*. The onset of uveitis may be sudden or insidious, and the duration of the attack may be limited (≤ 3 months' duration) or persistent (> 3 months' duration). The course of uveitis is described as acute, recurrent, or chronic. Acute uveitis has a sudden onset with a limited duration, as in acute anterior uveitis (AAU) seen with seronegative spondyloarthritis. Recurrent uveitis describes a course of multiple attacks of sudden onset and limited duration alternating with periods of remission when the uveitis is inactive and the patient is not undergoing therapy for the disease. Chronic uveitis typically has an insidious onset and a persistent duration, such as chronic anterior uveitis (CAU) associated with juvenile idiopathic arthritis (JIA).^{1,2}

Patients with AAU typically have a red, painful, photophobic eye. Slit-lamp examination reveals inflammatory cells in the anterior chamber. These cells may be deposited on the posterior corneal endothelium and are called *keratic precipitates*. The cellular inflammation in the anterior chamber may be so severe that it produces a *hypopyon* or layering of inflammatory cells within the anterior chamber. Exudation of protein into the anterior chamber, known as *flare*, may also be seen and can be so marked that a fibrin clot forms in the anterior chamber. A complication of anterior uveitis is the formation of adhesions between the posterior iris and the anterior lens surface (posterior synechiae). Posterior synechiae may frequently persist

after the inflammation has settled (Fig. 34.2). Anterior uveitis may also lead to the development of peripheral anterior synechiae, or scar tissue that forms between the peripheral iris and the posterior cornea. The anterior synechiae may be so extensive that the drainage angle of the eye becomes blocked, which can cause an increase in intraocular pressure and secondary glaucoma. Typically, AAU affects one eye at a time, although uncommonly both eyes may be affected simultaneously. Even though only one eye is affected at a time, both eyes may suffer attacks, in which case the uveitis is termed *recurrent, unilateral alternating AAU*.^{1,2}

AAU is most commonly associated with seronegative spondyloarthritis.^{1,3} The estimated annual incidence of AAU is 8.2 new cases per 100,000 population.⁴ Approximately half of these patients will possess the HLA-B27 gene, and 60% will have a diagnosis of seronegative spondyloarthritis.^{3,5} Seronegative spondyloarthritis includes ankylosing spondylitis (AS), reactive arthritis, arthritis with inflammatory bowel disease (IBD), and psoriatic arthritis.^{1,3,5-13} AAU occurs in 25% to 40% of patients with AS.⁶⁻⁸ Conversely, studies of patients with AAU have reported that AS is present in 18% to 34%.^{1,8} AAU is said to occur in 5% to 20% of patients with reactive arthritis at the initial attack and in up to 50% of these patients at long-term follow-up.^{6,7,9} Of patients with arthritis related to IBD, those with AS associated with IBD appear to be at greatest risk for the development of AAU. Spondylitis occurs in 20% of patients with Crohn disease and in 10% to 15% of patients with ulcerative colitis.¹⁰ Approximately 50% to 70% of patients with spondylitis associated with IBD are HLA-B27 positive.^{10,12} Of the HLA-B27–positive patients with IBD, AAU will develop in 50%.^{5,10,12} Among patients with psoriatic arthritis, AAU occurs in approximately 7% to 10%.^{7,8,11,13} Although unilateral, alternating AAU is the most typical type of uveitis associated with seronegative spondyloarthritis, chronic and bilateral uveitis also occurs occasionally and may be seen more frequently in women with IBD or with psoriatic arthritis.^{7,11,12,14}

CAU is less frequent than AAU and may be seen with several disorders, most often sarcoidosis. The rheumatic disease most commonly associated with CAU is JIA.¹⁵ Approximately 12% to 17% of children with JIA have uveitis.^{15,16} A population-based study performed in Finland reported the mean annual incidence and prevalence rates for JIA-associated uveitis to be 0.2 and 2.4 cases per 100,000 population, respectively.¹⁷ Although recurrent AAU is seen with enthesitis-related arthritis, the HLA-B27–associated subgroup of JIA, CAU is more commonly associated with JIA and is seen with antinuclear antibody (ANA)-positive oligoarticular disease at frequencies reported to be approximately 30%.^{18,19} Even though CAU has traditionally been reported in patients with ANA-positive oligoarticular disease, one study suggested a similar frequency in those with ANA-positive polyarticular disease, thus suggesting that the presence of ANA and not the type of arthritis is the key risk factor for CAU.¹⁹ Although it has traditionally been said that cases of JIA-related CAU occur more frequently in girls, one retrospective study of 90 children with JIA found no gender difference in the risk for development of CAU.¹⁵ CAU tends to be insidious and minimally symptomatic (“white eye” uveitis; Fig. 34.3); therefore, it is recommended that patients with ANA-positive JIA be evaluated every 3 months in an effort to detect the uveitis early.²⁰ Two thirds of patients have bilateral disease, and in patients with unilateral disease, uveitis will develop in the other eye within 1 year of diagnosis in the majority.¹ The median time between the onset of arthritis and the development of uveitis has been estimated to be 2 years (range, simultaneous development to 10 years).¹⁶ Chronic uveitis typically requires long-term therapy. Although initial therapy typically consists of topical corticosteroids, increasingly, children with uveitis are treated with systemic agents such as methotrexate or biologics such as infliximab or adalimumab to control the disease.²¹⁻²⁵ A cross-sectional study of 2748 children with JIA demonstrated that approximately 75% had received a nonbiologic disease-modifying antirheumatic drug (DMARD), and the

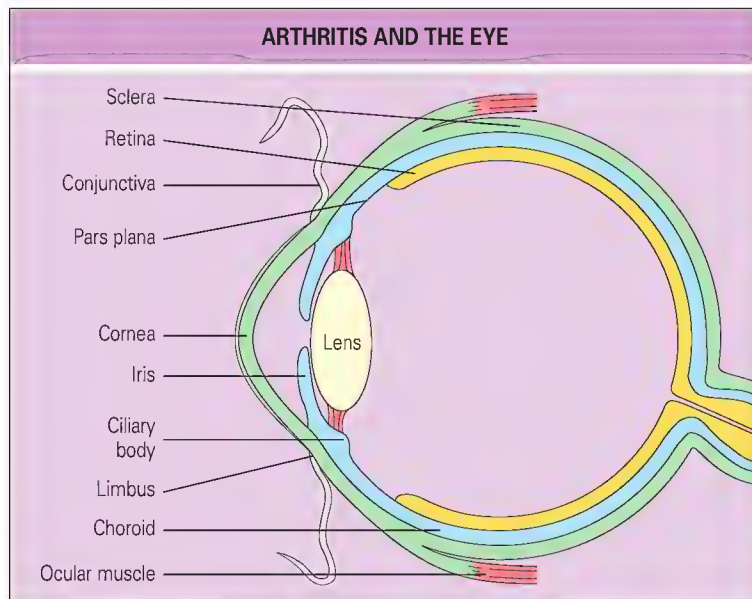


Fig. 34.1 The structural elements of the eye that may be primarily involved in rheumatic disease processes are shown.



Fig. 34.2 Wide-beam slit-lamp view of "old" posterior synechiae (adhesions between the iris and lens) causing distortion of the pupil.

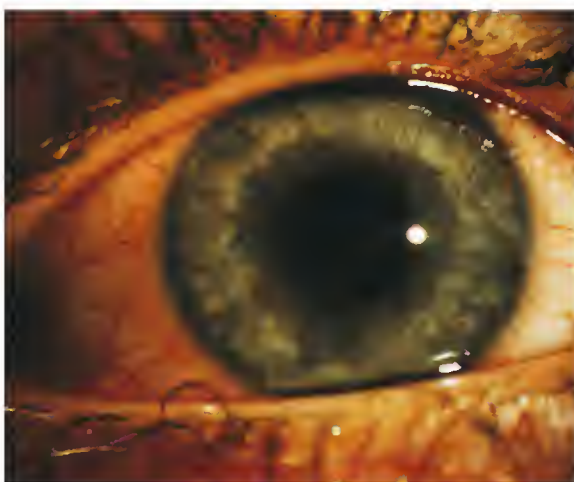


Fig. 34.3 Chronic uveitis in a patient with oligoarticular juvenile idiopathic arthritis: "white eye" uveitis.

presence of uveitis was strongly associated with use of a DMARD, both biologic and nonbiologic (e.g., methotrexate).²⁴

Sight-threatening ocular complications may develop in patients with CAU, with band keratopathy and cataracts each occurring in up to a third of patients.^{1,15,16,21-23,26-33} Secondary glaucoma occurs in 10% to 20% of patients with JIA-associated uveitis and is a poor prognostic finding.^{21-23,26-29} Posterior synechiae are common.^{21,22,28} Other complications include macular edema in 8% to 10% of cases and phthisis in 4% to 10%. Although blindness developed in 40% of patients reported in early series, more recent series have reported a better prognosis, with blindness occurring in about 10%.^{16,21-23,26,29} The improved prognosis appears to be due to earlier detection, better treatment, and better surgical management of the complications.^{28,30,32} Nevertheless, about 25% of patients with JIA-associated CAU will suffer some degree of visual impairment. Furthermore, because the uveitis may persist into adulthood, these children remain at risk for ocular complications from uveitis for decades.³³

Uveitis is a primary manifestation of Behçet disease.^{34,35} The uveitis in Behçet disease may be anterior uveitis (56% to 79% of cases, depending on the series), intermediate uveitis (18% to 66% of cases), posterior uveitis (3% to 29% of cases), or panuveitis with retinal vasculitis (29% to 41% of cases).^{1,34} The presence of retinal vasculitis confers a poor prognosis for vision and is described further in the later section "Retinal Vascular Disease." Anterior uveitis with or without hypopyon is the most common ocular finding in Behçet disease. Although studies from the 1960s and early 1970s reported hypopyon uveitis in up to 88% of patients, more recent studies have shown a decreased frequency of hypopyon to as low as 9%.^{1,34,36} This reported decrease probably represents earlier diagnosis and more aggressive therapy. The uveitis associated with Behçet disease is typically bilateral. In one series, 81% of patients had bilateral uveitis after 1 year and 93% by 2 years.³⁴⁻³⁷

Bilateral CAU may also occur with essential mixed cryoglobulinemia,³⁸ hypocomplementemic urticarial vasculitis syndrome (HUVS),³⁹ and familial juvenile systemic granulomatosis (FJSG).⁴⁰⁻⁴² Essential mixed cryoglobulinemia, or type II cryoglobulinemia, is a small-vessel vasculitis that may result in palpable purpura, arthralgias or arthritis, lymphadenopathy, hepatosplenomegaly, peripheral neuropathy, and hypocomplementemia.⁴³ Renal disease may also be seen in up to 60% of patients with essential mixed cryoglobulinemia.⁴³ Most cases of essential mixed cryoglobulinemia are associated with hepatitis C virus (HCV) infection, with an estimated 85% to 95% of patients having circulating antibodies to HCV.^{44,45} The diagnosis is made by the presence of cutaneous small-vessel vasculitis confirmed by biopsy and the presence of serum cryoglobulins in a patient with the typical clinical features.

An uncommon systemic small-vessel vasculitis, HUVS is characterized by recurrent urticarial lesions associated with cutaneous vasculitis, constitutional symptoms, arthralgias or arthritis, angioedema, and glomerulonephritis.⁴⁶ The joint and kidney disease may be indistinguishable from that found in systemic lupus erythematosus (SLE), and in fact, low ANA titers are often detected in patients with HUVS.⁴⁶ The diagnosis of HUVS is suggested in a patient with recurrent urticaria accompanied by leukocytoclastic vasculitis, constitutional symptoms, arthralgias, and hypocomplementemia. Continuous granular deposition of immunoreactants along the basement membrane zone seen on skin biopsy specimens via a direct immunofluorescence technique helps confirm the diagnosis.⁴⁷ Ocular findings have been reported in HUVS and include conjunctivitis, episcleritis, anterior uveitis, and diffuse anterior scleritis.^{46,47}

FJSG (www.omim.org/entry/186580), also known as *Jabs syndrome* or *Blau syndrome*, is an uncommon autosomal dominant genetic disease characterized by granulomatous polysynovitis, rash, vascular disease, and uveitis.⁴⁰⁻⁴² The syndrome is caused by mutations in the *NOD2* (*CARD15*) gene, which is involved in apoptosis. The uveitis associated with FJSG may be bilateral CAU,^{40,41} a chronic panuveitis with multifocal choroiditis.⁴² FJSG and CAU are often misdiagnosed as JIA or pediatric sarcoidosis. Patients may require aggressive medical therapy to control the uveitis, including immunosuppressive drugs.⁴² Ocular complications such as cataract and macular edema are common.⁴²

Management

Anterior uveitis usually responds to topically applied corticosteroids, which suppress the inflammatory response, and mydriatics, which prevent sequelae of the disease such as posterior synechiae. For the initial flare of uveitis, corticosteroid drops may be required on an hourly basis while awake. Topical corticosteroids have good penetration into the anterior chamber and are therefore useful in treating anterior uveitis. However, because they have limited penetration to the back of the eye, topical corticosteroids are

inadequate for intermediate or posterior uveitis. Periocular corticosteroid injections may provide high concentrations of corticosteroids in the eye and are useful in treating intermediate uveitis and cystoid macular edema, a common vision-threatening complication resulting from uveitis. For patients who do not tolerate periocular corticosteroid injections or if more sustained control of the uveitis is needed, oral corticosteroid therapy is used. Severe acute episodic uveitis may occasionally need treatment with a short course of oral prednisone in addition to intensive topical corticosteroids, as in the case of severe AAU. In patients with chronic posterior uveitis, panuveitis, or anterior uveitis unresponsive to topical corticosteroids, high-dose prednisone (e.g., 1 mg/kg/day) is administered until the inflammation is suppressed, followed by tapering to a lower dose. In many cases, long-term (low-dose) prednisone is needed to suppress the inflammation. If systemic corticosteroids are insufficient to control more severe forms of uveitis, immunosuppressive drug therapy may be required.^{1,34,48}

SCLERAL DISEASE

Scleral disease may be classified as episcleritis or scleritis. Episcleritis is associated with discomfort rather than pain, more superficial ocular inflammation, and less frequent ocular complications and typically has a less frequent association with systemic disease.⁴⁹ The clinical findings depend on whether only the episclera is involved or whether deeper tissue involvement is present. Episcleritis may be nodular or simple and is usually a self-limited condition that often resolves without treatment. Resolution of the inflammation may be expedited by the use of topical corticosteroids. In severe or recurrent cases, nonsteroidal antiinflammatory drugs (NSAIDs) have also been used. Slit-lamp examination is required to differentiate this condition from other causes of “red eye,” such as conjunctivitis and iritis.^{34,49-51}

Scleritis is often characterized by pain, deeper inflammation and edema in the sclera, and frequent ocular complications and is associated with an infectious or systemic disease in approximately 50% of cases.⁴⁹⁻⁵² Unlike episcleritis, which is typically self-limited and remits spontaneously, scleritis generally requires therapy. Scleritis may be classified as diffuse anterior, nodular anterior (Fig. 34.4), posterior, or necrotizing (Fig. 34.5). Scleromalacia perforans is a separate category with an insidious but destructive scleral process that is seen in patients with long-standing rheumatoid arthritis (RA). Any of the previously mentioned types of scleritis may be found in association with RA, although diffuse anterior scleritis is most common.⁴⁹

Approximately 10% of patients with scleritis will have an associated infection, such as syphilis, Lyme disease, or herpes zoster ophthalmicus.⁵⁰ Patients with scleritis appear to have a higher frequency of rheumatic disease.⁵³ Forty percent of patients with scleritis will have a rheumatic disease, the most frequent of which is RA.⁵⁰ Scleritis affects an estimated 1% to 6% of patients with RA and 14% of patients with rheumatoid vasculitis.^{50,54,55} Although estimates of the frequency of scleritis in patients with RA have been as high as 6%, large series have shown that approximately 1% of patients with RA have scleritis.^{49,53} Patients with RA and scleritis tend to have longer-duration and more severe disease and a higher prevalence of extraarticular disease.^{52,54,55} One study of patients with necrotizing scleritis or necrotizing keratitis and RA suggested increased mortality in these patients.⁵⁴

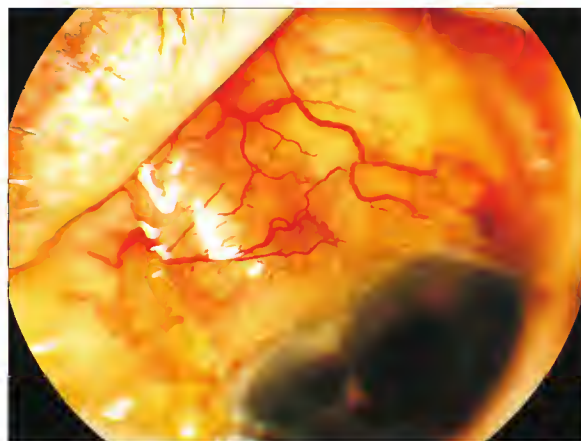


Fig. 34.4 Diffuse and nodular scleritis involving predominantly the upper temporal quadrant of the globe.

The second most frequent systemic disorder associated with scleritis is the systemic vasculitides (most commonly antineutrophilic cytoplasmic antibody [ANCA]-associated granulomatous vasculitis); other associated diseases include SLE, IBD, and relapsing polychondritis.⁴⁹⁻⁵² Any type of vasculitis may be present with scleritis, but half of cases of vasculitis-associated scleritis are due to ANCA-associated granulomatous vasculitis.⁵⁰ Furthermore, in half of patients with vasculitis and scleritis, the scleritis will be the initial feature of the disease.⁵⁰ Scleritis is common in ANCA-associated granulomatous vasculitis, in which it occurs in 16% to 38% of patients, and it is either the first or second most frequent ocular feature, depending on the series.^{34,55-58} The scleritis can be of any type, particularly diffuse anterior or necrotizing scleritis. Marginal corneal ulcers are often seen in association with the scleritis (necrotizing sclerokeratitis) and occasionally without scleritis (see the later section “Corneal Disease”).^{54,57} Posterior scleritis has also been reported.¹

All types of scleritis have been associated with IBD, including necrotizing scleritis and posterior scleritis.^{59,60} The scleral inflammation may parallel the activity of the underlying bowel disease.⁵⁹ Scleral involvement is the most common ocular manifestation of relapsing polychondritis and occurs in approximately 35% to 41% of patients.^{61,62} Most often, diffuse anterior scleritis is the type present, but recurrent episcleritis, necrotizing scleritis, or posterior scleritis may also be seen. An association between scleritis and AS and other forms of seronegative spondyloarthritis has been reported.⁵⁰

Management

Episcleritis can be treated by observation only or a short course of topical corticosteroids because the disease is usually self-limited. Scleritis typically requires systemic therapy and may call for treatment directed at controlling the underlying systemic disease, as in vasculitis.^{49-52,53,58} NSAIDs, particularly flurbiprofen and indomethacin, are effective in the initial management of anterior scleritis in approximately one third of patients.⁴⁹ If NSAID therapy fails to control the anterior scleritis or if posterior or necrotizing scleritis is present, oral prednisone therapy starting at 1 mg/kg/day (60 to 80 mg daily) is needed.^{48,49,63} For cases in which oral prednisone does not control the scleritis or when it cannot be tapered to an acceptably low daily dose, a steroid-sparing immunosuppressive agent may be required.^{48,49} Approximately one third of patients with scleritis require immunosuppressive drug therapy; historically, cyclophosphamide has been the drug used most often.^{49,63} Antimetabolites such as mycophenolate mofetil (CellCept) and biologics have also been reported to be effective.^{64,65} Necrotizing scleritis and scleritis with an underlying systemic vasculitis nearly always require immunosuppressive drug therapy.^{49-52,54,57,63} A standardized grading system has been advocated to help monitor patients during treatment.⁶⁶

RETINAL VASCULAR DISEASE

Ophthalmologists often use the term “retinal vasculitis” to encompass most retinal vascular inflammatory diseases regardless of whether true vasculitis is present. For purposes of this chapter, retinal vasculitis is defined as inflammation of the retinal vessels accompanied by intraocular inflammation and retinal vessel occlusion. Although most ophthalmologists do not distinguish among the different types of retinal vascular disease, we

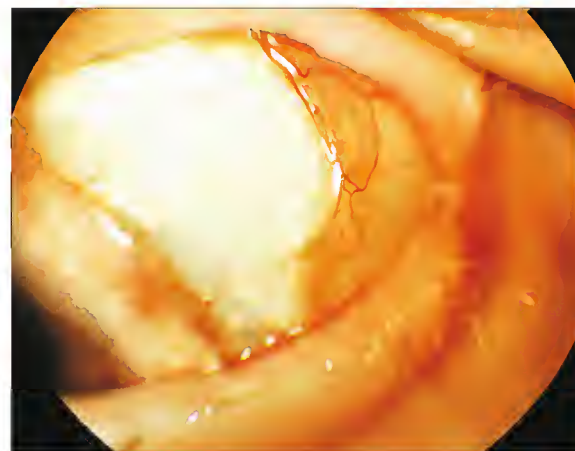


Fig. 34.5 Necrotizing scleritis in a patient with severe rheumatoid arthritis.

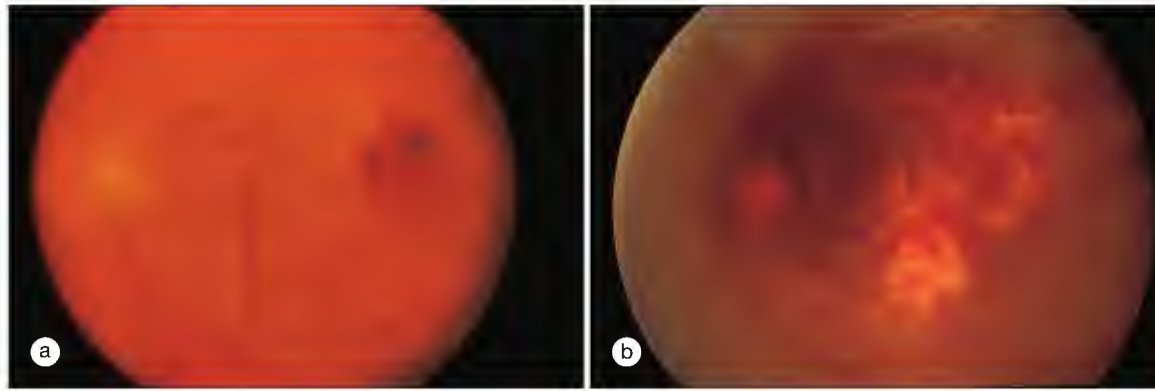


Fig. 34.6 Fundus photographs from a patient with Behçet disease demonstrating retinal vasculitis. (a) Early macular lesion. (b) Progressive disease 1 month later. (From Thome JE, Jabs DA. *Rheumatic diseases*. In: Ryan SJ, editor. *The retina*. 4th ed. London: Elsevier; 2006, p. 1383-408.)

distinguish retinal vasculitis from the occlusive vasculopathies such as the antiphospholipid antibody syndrome associated with SLE (where no intraocular inflammation is present).

Retinal vasculitis may involve the retinal arteries, capillaries, or veins, and it may cause significant visual loss.^{67,68} Retinal vasculitis can be seen in the systemic vasculitides, but it is an uncommon complication except for Behçet disease, in which retinal vasculitis is the most frequent ocular complication in some series.^{34,67-70} In Behçet disease, inflammation may involve both veins and arteries and result in arterial occlusion and retinal necrosis (Fig. 34.6). Occasionally, secondary neovascularization and retinal detachment develop.⁶⁸⁻⁷⁰ The end stage of the disease is a blind, painful eye with secondary glaucoma, rubeosis, and retinal detachment. The natural history of ocular Behçet disease without treatment is poor. The majority of untreated patients will lose all or part of their vision within 5 years, with 74% of eyes in one series having vision worse than 20/200.⁶⁹ For eyes that deteriorated to no light perception, vision declined to this level over a period of 3.6 years.^{36,69} With treatment, clinical outcomes are improved but remain somewhat guarded, with the rate of any ocular complication estimated to be 0.45 per eye-year and rates of vision loss to the 20/200 level or worse being approximately 10% per eye-year.³⁵

Corticosteroid therapy appears to delay progression of the disease but does not alter the ultimate outcome, and therefore immunosuppressive drug therapy is used for the treatment of retinal vasculitis complicating Behçet disease.^{34,48} Initially, chlorambucil was used, typically at a dose of 0.1 to 0.2 mg/kg/day.^{48,71-77} Uncontrolled case series of chlorambucil therapy for Behçet disease have shown long-term, drug-free remissions after 2 years of treatment.^{49,71,72} Fewer published data are available for cyclophosphamide as treatment of ocular Behçet disease, but some clinicians have found it to be as effective as chlorambucil and easier to use.⁴⁹ Cyclosporine and azathioprine have also been reported to be effective in the treatment of ocular Behçet disease, and they have been shown to be efficacious in randomized clinical trials.^{49,75-78} However, nearly 25% of patients treated with azathioprine either had no benefit in terms of the frequency and severity of ocular attacks or required additional therapy, and only 50% of patients treated with cyclosporine had a good response.^{49,75,77,78} Studies of patients with ocular Behçet disease treated with infliximab (Remicade) have suggested that it may be effective, although the dose required appears to be 5 mg/kg/mo or higher.^{79,80}

Microvascular vasoocclusive disease can also affect the retinal vasculature. In SLE the retinal capillaries are involved and primarily result in cotton-wool spots or microinfarcts of the nerve fiber layer of the retina.⁸¹ The prevalence of retinopathy varies widely depending on the patient population studied, from 3% of ambulatory outpatients to 28% of hospitalized patients with SLE having retinal vascular findings.^{82,83} These findings occur in the absence of intraocular inflammation. More extensive retinal and vasoocclusive disease can occur with active SLE or as a result of antiphospholipid antibody syndrome (Fig. 34.7).⁸²⁻⁸⁴ This more severe retinal vasoocclusive disease occurs in less than 1% of patients with SLE, appears to be associated with central nervous system lupus,⁸³ and includes central retinal artery occlusion, central retinal vein occlusion, branch artery occlusion, and diffuse retinal vasoocclusive disease (Fig. 34.8).⁸⁴ With severe retinal vascular disease, the prognosis for vision is poor, and retinal neovascularization commonly develops. Even less common than retinopathy is lupus chorioidopathy (Fig. 34.9).⁸⁵ The clinical changes seen in patients with lupus chorioidopathy involve serous elevations of the retina, most often affecting the neurosensory retina, and serous elevations of the retinal pigment epithelium, and combined elevations may also be seen. These clinical findings

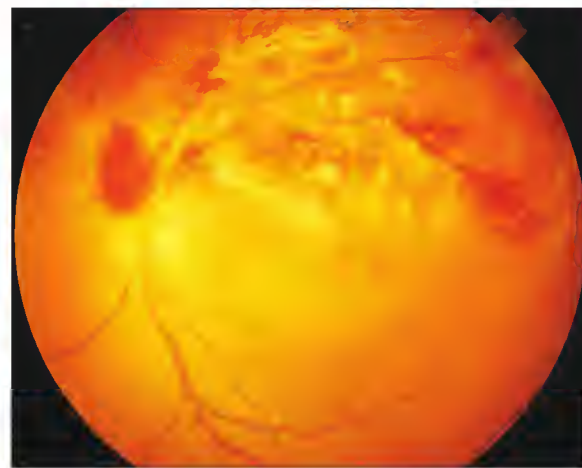


Fig. 34.7 Acute, severe, retinal vasoocclusive disease affecting the upper temporal retinal vessels. A large number of hemorrhages and white choroidal and retinal infiltrates are present.

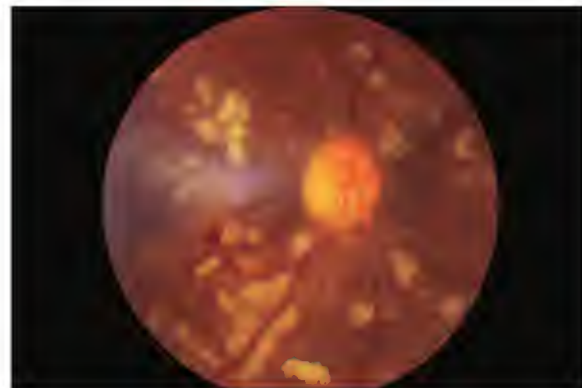


Fig. 34.8 Fundus photograph demonstrating diffuse vasoocclusive disease in a patient with systemic lupus erythematosus. (From Jabs DA, Fine SL, Hochberg MC, et al. *Severe retinal vaso-occlusive disease in systemic lupus erythematosus*. *Arch Ophthalmol* 1986;104:558-63.)

are associated with a systemic vascular disease, either hypertension from lupus nephritis or systemic vasculitis.⁸⁵ Treatment of the underlying disease with systemic corticosteroids and immunosuppressive agents if needed and control of the hypertension can lead to resolution of the serous retinal detachments.⁸⁵

Central retinal artery occlusions can be seen in patients with giant cell arteritis (GCA), although ischemic optic neuropathy is a more classic finding (see later).^{34,67,68,86}

Arteriovenous anastomoses result from shunting of blood from artery to vein without an intervening capillary bed. They are seen commonly in the midperiphery of the retina in patients with Takayasu arteritis.^{1,34,87-89} The arteriovenous anastomoses can shunt blood away from the peripheral retina,



Fig. 34.9 Fundus photograph of a patient with choroidopathy and systemic lupus erythematosus. (From Jabs DA, Hanneken AM, Schachar AP, Fine SL. *Choroidopathy in systemic lupus erythematosus*. *Arch Ophthalmol* 1988;106:230-4.)

which occasionally leads to areas of retinal nonperfusion with subsequent neovascularization of the retina and vitreous hemorrhage.^{1,87-89}

OPTIC NERVE DISEASE

Optic nerve diseases associated with rheumatic disease include ischemic optic neuropathy and optic neuritis.³⁴ The characteristic features of ischemic optic neuropathy are painless sudden loss of vision, decreased color vision, and an altitudinal visual field defect. A relative afferent pupillary defect is present in the affected eye. The optic nerve head may be swollen (as found in anterior ischemic optic neuropathy) or may appear normal initially (as in retrobulbar optic neuropathy). The loss of visual acuity and visual fields is usually permanent, and the optic nerve head becomes atrophic and pale (e.g., optic nerve pallor) over time. In some cases of ischemic optic neuropathy, however, partial recovery of visual acuity has been noted after large doses of pulse intravenous corticosteroids (e.g., 1 g/day of methylprednisolone for 3 days).^{90,91} Although ischemic optic neuropathy may occur with any type of vasculitis, as well as with SLE,⁹² it is seen most commonly in patients with GCA.⁹³

Optic neuritis is characterized by acute or subacute visual loss associated with retrobulbar pain, especially with pain on movement of the affected eye. Examination of the eye reveals decreased vision, a relative afferent pupillary defect, decreased color vision, and visual field loss. The optic nerve head may be swollen or appear normal initially, depending on whether the optic neuritis is anterior or retrobulbar. Visual symptoms result from optic nerve demyelination. Unlike ischemic optic neuropathy, up to 95% of patients with optic neuritis have visual acuity of 20/40 or better 1 year after the event.³⁴ Optic neuritis is most typically associated with multiple sclerosis and responds to pulse intravenous corticosteroids with more rapid improvement of vision. Optic neuritis may also occur in SLE; such patients typically have a steroid-responsive, but also steroid-dependent process.¹

ORBITAL DISEASE

Orbital disease in patients with rheumatic disease may include primary inflammation of the orbital tissue (e.g., orbital pseudotumor or orbital inflammatory syndrome), inflammation of the extraocular muscles (e.g., orbital myositis), or contiguous spread of inflammation from the sinuses, which most typically occurs in ANCA-associated granulomatous vasculitis.⁹⁴⁻⁹⁶ The most common initial sign of orbital disease is proptosis or anterior displacement of the eye caused by a space-occupying lesion or inflammatory process. Associated symptoms and signs include pain, blurred vision, diplopia (double vision) as a result of restriction of eye movement, eyelid swelling, and displacement of the globe. In ANCA-associated granulomatous vasculitis, orbital involvement is common and occurs in 15% to 50% of patients, and in some series it is the most common form of ophthalmic involvement.⁹⁴⁻⁹⁶ Orbital disease may be an extension of granulomatous inflammation from the sinus into the orbit. Such inflammation can lead to compartment syndrome within the orbit, proptosis, orbital apex syndrome, compressive optic neuropathy, and subsequent irreversible visual loss. Orbital pseudotumor separate from the sinus inflammation may also be seen.^{95,96}

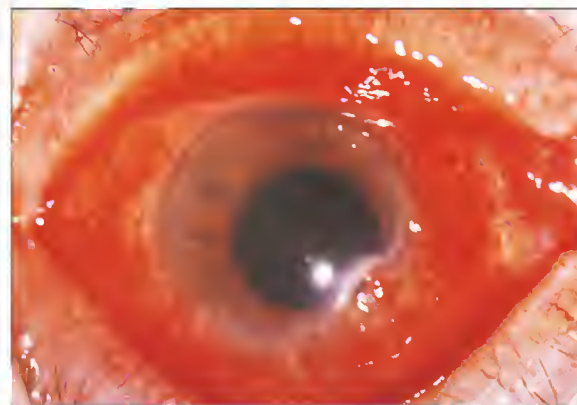


Fig. 34.10 Active corneal ulceration with corneal infiltrates at the "leading edge" of an ulcer and associated conjunctival injection.

Systemic corticosteroids or immunosuppressive drug therapy aimed at controlling the underlying disease can decrease the proptosis, improve mobility, and reduce the associated symptoms, as well as improve visual acuity. Rarely, orbital decompression may be necessary if the inflammatory process has caused proptosis severe enough to compromise the optic nerve (orbital apex syndrome). The orbital disease accompanying ANCA-associated granulomatous vasculitis typically requires immunosuppression and may be difficult to control.

CORNEAL DISEASE

Corneal manifestations of rheumatologic disease include forms of keratitis (inflammation in the cornea) and dry eye disease, or keratoconjunctivitis sicca (KCS; described in the next section). Keratitis is classified as interstitial keratitis (IK) or peripheral ulcerative keratitis (PUK). The diagnosis of IK includes diffuse stromal keratitis, sclerosing keratitis, and deep keratitis. PUK is also known as *marginal keratitis*, *marginal corneal ulceration*, or *limbal guttering*. Limbal vasculitis may also be seen as a rare manifestation and is not discussed further here. Keratitis may occur on its own or in association with scleritis, in which case it is termed *sclerokeratitis*. Although PUK and sclerokeratitis are often associated with rheumatic disease, infectious causes such as herpes simplex and syphilis also need to be considered.

IK is characterized by nonsuppurative inflammation, usually with vascularization of the corneal stroma. It is generally caused by an immunologic response to an infectious agent (e.g., syphilis) but occasionally occurs in systemic disease, with the most common etiology being Cogan syndrome.⁹⁷ It may also occur as a common corneal complication of scleritis.^{49,50,62} The pericorneal or limbal inflammation is accompanied by peripheral corneal vessels that advance across the central cornea preceded by superficial stromal opacities. In nodular scleritis the corneal involvement may be restricted to one segment, but in diffuse scleritis the entire cornea may be involved, with a dense corneal leukoma being produced. Symptoms of IK include pain, tearing, photophobia, and conjunctival injection. The IK associated with Cogan syndrome typically responds to topical corticosteroid therapy.

Clinically, PUK is typically manifested as pain, though not always. Peripheral corneal infiltrates may develop. Epithelial breakdown of the cornea occurs, followed by corneal ulceration and stromal thinning, which may progress circumferentially and then centrally (Fig. 34.10).⁹⁸⁻¹⁰⁰ If left untreated, the lesion progresses and results in corneal perforation and loss of vision. Bacterial corneal infection must be excluded first, particularly in patients with compromised corneal epithelia (e.g., KCS secondary to Sjögren syndrome). PUK typically occurs in RA and often involves the lower half of the cornea in a furrowing of the corneal periphery (Fig. 34.11). The development of PUK in patients with RA has been linked to immunologically mediated small-vessel vasculitis of the pericorneal vessels and is associated with advanced RA, elevated rheumatoid factor titers, and increased risk for mortality.⁵⁴ PUK has also been reported to occur in patients with other connective tissue disorders such as ANCA-associated granulomatous vasculitis, relapsing polychondritis, SLE, and progressive systemic sclerosis.³⁴

Treatment of PUK is aimed at the underlying disease. Local therapy such as the use of cyanoacrylate adhesive glue and corneal or scleral patch grafts is often needed to prevent perforation and to maintain tectonic support of the globe.^{99,101-103} However, these measures will eventually fail if the

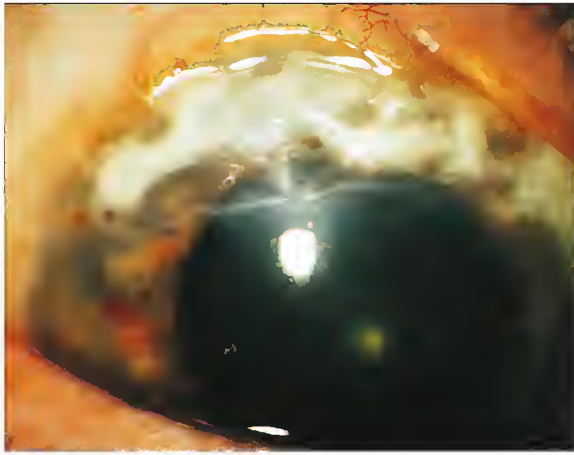


Fig. 34.11 Marginal ulceration of the cornea.

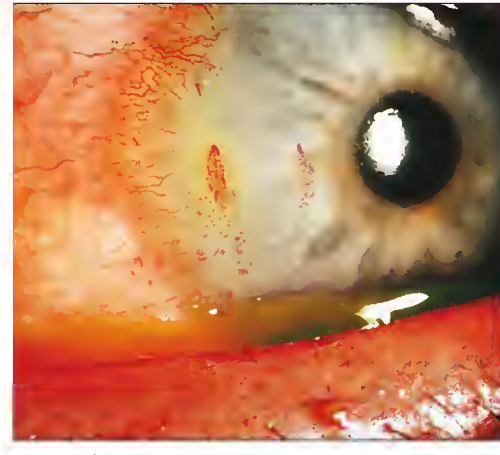


Fig. 34.12 Keratoconjunctivitis sicca.

underlying inflammation is not controlled. Very small central corneal perforations (<1.5 mm in diameter) may be sealed with a tissue adhesive such as cyanoacrylate glue. Larger perforations usually require emergency keratoplasty if any useful vision is to be salvaged. Topical corticosteroids are generally ineffective in the treatment of PUK and may accelerate the corneal thinning and increase the risk for corneal perforation.^{99,100}

KERATOCONJUNCTIVITIS SICCA

A common ocular complication of rheumatologic disease is KCS, or dry eye syndrome. Symptoms of KCS include dryness, ocular irritation, foreign body sensation, photophobia, and rarely pain. Sometimes patients complain of excessive tearing, which may merely describe a sensation or may be real and occur as a result of tear spillover. Clinically, the eyes may appear minimally affected with loss of surface luster, mild conjunctival redness, and perhaps some accumulation of mucus at the medial canthus (Fig. 34.12). Conjunctival and corneal punctate erosions occur secondary to failure of aqueous tear secretion and chronic damage to the oil-secreting glands of the palpebral conjunctiva, which induces more rapid evaporation of tears from the ocular surface. In severe cases, discrete corneal filaments may develop (filamentary keratitis), which represent tags of exfoliated epithelium still attached at one end and intermixed with surface mucin. Patients with KCS are more vulnerable to bouts of recurrent infectious conjunctivitis, perhaps as a result of reduced antibacterial tear lysozyme and lactoferrin. Thus, corneal ulcer and perforation are more likely to develop in these patients.

The diagnosis of KCS is made by a Schirmer test showing decreased tear production (typically <5 mm of wetting at 5 minutes in an anesthetized eye) and by demonstrating damage to the ocular surface with rose Bengal staining. The presence of KCS in association with evidence of salivary gland dysfunction, such as a positive minor salivary gland biopsy result or abnormal salivary flow study, as well as the presence of a defined connective tissue disease such as rheumatoid arthritis, SLE, or scleroderma, constitutes Sjögren syndrome (see Chapter 138).¹⁰⁴ Secondary Sjögren syndrome is diagnosed when a defined connective tissue disease is present and primary Sjögren syndrome when no definable connective tissue disease is present. Sjögren syndrome affects approximately 11% to 13% of patients with RA and approximately 20% of patients with SLE.¹ The cause of the dry eyes and dry mouth in patients with Sjögren syndrome is glandular destruction and dysfunction as a result of a chronic lymphocytic and mononuclear inflammatory infiltrate of the lacrimal and salivary glands.¹⁰⁴⁻¹⁰⁶ Immunohistologic studies have suggested that most cells in this infiltrate are CD4+ T cells, with lesser numbers of CD8+ T cells and B cells.¹⁰⁶

Treatment of KCS includes tear replacement therapy with artificial tears, punctal occlusion, effective treatment of secondary lid disease such as blepharitis, and the use of topical cyclosporine eye drops. Topical cyclosporine appears to benefit patients with severe dry eye secondary to Sjögren syndrome by improving tear film break-up times and decreasing rose Bengal staining of the corneal surface.^{107,108} It has been suggested that the mode of action for topical cyclosporine may be decreased inflammation of the lacrimal gland leading to improved lacrimal gland function and an increase in tear production.¹⁰⁷

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35

The heart in rheumatic disease

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- Cardiac complications are prevalent in rheumatic diseases; although any cardiac disease may occur, screening programs should focus on the most common associations.
- The presentation of cardiac disorders in rheumatic diseases is often atypical, and a high index of suspicion is required.
- A high prevalence of coronary disease is present in most patients with inflammatory rheumatologic conditions.
- Optimal management of atherosclerotic risk factors requires a proactive approach in rheumatology services.

OVERVIEW

Like all organs, the heart has abundant connective tissue; hence rheumatologic conditions can lead to abnormalities in all parts of the heart. Indeed, to summarize the cardiac pathologic conditions associated with connective tissue diseases (CTD) is to provide an overview of virtually all cardiac disorders. CTD may result in coronary artery disease, hypertension, cardiac failure, pericarditis, myocarditis, valvular heart disease, arrhythmias, and right-sided heart abnormalities either directly or secondary to pulmonary hypertension.

To begin, Table 35.1 shows the typical associations of various rheumatologic conditions with common cardiac disorders. This table is not intended to be exhaustive but rather to give a sample of the types of conditions one might consider in a given CTD population. Thus, for example, Behçet syndrome has been associated with pericarditis, myocarditis, endocarditis, intracardiac thrombosis, venous thrombosis, aortic and coronary aneurysms, and the more typical pulmonary artery aneurysms.

Patients with specific rheumatologic diagnoses should be monitored with particular cardiac complications in mind. Thus patients with rheumatoid arthritis (RA) are significantly more likely to develop coronary disease.¹ This statement is supported not merely by an excess of events but also by a threefold excess of coronary artery calcification.² In most patients symptoms of coronary atheroma are noted because of progressive exercise limitation. Given the confounding factors that limit mobility in RA, it is unsurprising that coronary disease often presents atypically in this population; hence the rheumatologist needs to be especially vigilant if such cases are to be identified before serious complications occur.

Systemic hypertension is common in the general population and has been reported as even more common in RA,³ although not all studies support this conclusion.⁴ However, recent studies confirm an increased prevalence of the typical complications of hypertension in RA patients, namely stroke and atrial fibrillation⁵; thus identification and treatment should be part of routine practice in the rheumatologic practice. Less clinically obvious associations include an increased incidence of heart failure, which may or may not relate to the fact that up to 30% of RA patients are found have cardiac amyloid in some postmortem studies.⁶ Finally, although it is rare, some patients develop hydroxychloroquine cardiomyopathy, a form of lysosomal storage disorder that may present with heart failure but is diagnosable only on cardiac biopsy.⁷

Libman-Sacks endocarditis as seen in lupus is by now rather rare except as an echocardiographic abnormality.⁸ Pericarditis, by contrast, occurs frequently but only uncommonly as part of the index event, and even then it is part of a multisystem presentation⁹; thus the cardiologist rarely has to

consider lupus as part of the differential when assessing the typical patient with viral pericarditis. The association of lupus with ischemic heart disease (IHD) is not well recognized outside rheumatology circles. As with RA the association is driven by promotion of atheroma, because coronary calcification is much more common at a given age in the systemic lupus erythematosus (SLE) population.¹⁰ In young women who experience coronary events, SLE is the most likely driver after diabetes and familial hypercholesterolemia.¹¹ Other associations, such as congenital complete heart block, are sufficiently understood that specific advice can be given to patients who possess the appropriate antibodies.¹² On the other hand, pulmonary arterial hypertension (PAH) is somewhat less common than the literature would suggest and is rather remarkable for showing an excellent response to immunosuppressive therapy and available pulmonary vasodilators.¹³

Systemic sclerosis (SSc) is now recognized as the third most common cause of PAH after idiopathic and congenital heart disease.¹⁴ Pulmonary hypertension related to lung disease and heart failure is also prevalent in SSc patients.¹⁵ Midwall fibrosis in a noncoronary distribution on cardiac magnetic resonance imaging (CMR) has been labeled as *scleroderma cardiomyopathy*¹⁶; however, such abnormalities are now understood to be nondiagnostic (they are present in cardiomyopathy of other causes) and are among the less common CMR abnormalities associated with scleroderma.¹⁷ The cardiac manifestations are thus protean: troponin-positive cardiomyopathy associated with myositis overlap, troponin-negative progressive dilated cardiomyopathy, and diastolic dysfunction associated with hypertension or replacement fibrosis, as well as a high prevalence of conduction tissue disease.¹⁸

The medium-vessel vasculitides form a spectrum of disorders, ranging from coronary artery aneurysms (polyarteritis nodosa), to intramyocardial vasculopathy presenting as dilated cardiomyopathy, to eosinophil-associated endomyocardial fibrosis.¹⁹

Dermatomyositis and polymyositis and scleroderma with myositis overlap, leading to troponin-positive myocarditis that, unchecked, results in dilated cardiomyopathy associated with midwall fibrosis on CMR.²⁰ Of note, steroids that may ease the skeletal myositis may be insufficient to prevent the progression of the cardiac element; this may require more robust immunosuppression.²¹ Less recognized is the fact that in common with other inflammatory CTDs these conditions are associated with atherosclerosis.²²

The classic large-vessel vasculitides are typically associated with stenosis and aneurysms of the aorta and its major branches in the case of Takayasu arteritis, and the coronary arteries in Kawasaki disease. All may involve the coronary arteries—in particular, the coronary ostia may be involved in Takayasu arteritis, whereas coronary artery aneurysms may occur in Behçet syndrome.²³

Sarcoid is feared as a cause of sudden death related to myocarditis and midwall fibrosis²⁴ but should perhaps be recognized as an important cause of pulmonary hypertension,²⁵ associated primarily with lung disease but also secondary to cardiac failure—primarily diastolic or, at the extreme end, a restrictive pattern—and occasionally related to pulmonary arterial involvement.

With this overview as a backdrop, various cardiac pathologic conditions and the role of associated rheumatologic disorders are now considered.

CORONARY ARTERY DISEASE

The prevalence rate of diagnosed IHD in 60-year-old men is 11%, whereas in 60-year-old women it is 3.5%.²⁶ Thus, although inflammatory conditions such as RA are associated with a 50% increase in risk, the low prevalence of CTDs means that 99.5% of all coronary artery disease (CAD) is not causally related to CTD. Hence, looking for the contribution of CTD to CAD in

TABLE 35.1
Typical associations of various rheumatologic conditions with common cardiac disorders

Rheumatologic diagnosis	Most prevalent	Others
Rheumatoid arthritis	IHD (+50%) Hypertension (+40%)	Cardiac amyloid, hydroxychloroquine cardiomyopathy
Lupus	Pericarditis: (30%) Premature IHD (×50)	Congenital complete heart block, PAH, valve lesions
Systemic sclerosis (SSc)	PAH, SSc cardiomyopathy	Pericardial effusion, conduction abnormalities
Polyarteritis nodosa, Churg-Strauss syndrome, Wegener granulomatosis	Cardiac failure (microvasculopathy)	Endomyocardial fibrosis (Churg-Strauss syndrome)
Dermatomyositis/polymyositis	IHD (×2)	Myocarditis
Takayasu arteritis, Behçet syndrome, Kawasaki disease	Vascular aneurysms or stenoses	Hypertension, bruits (Takayasu arteritis), pulmonary artery aneurysm (Behçet syndrome)
Giant cell arteritis, polymyalgia rheumatica	Medium-vessel vasculitis	Aortic aneurysm/dissection, stenoses
Sarcoid	Sudden cardiac death, pulmonary hypertension	Subclinical myocarditis

IHD, ischemic heart disease; PAH, pulmonary arterial hypertension.

BOX 35.1 CONTRIBUTION OF RHEUMATOID ARTHRITIS TO CORONARY ARTERY DISEASE

Prevalence of CAD = 3.5%; prevalence of RA = 1%; prevalence of CAD + RA = (3.5% of 1% × 3/2) = 0.0525%.

Excess CAD related to RA = 0.0175% = 1/200 of all CAD.

CAD, coronary artery disease; RA, rheumatoid arthritis.

the cardiology setting is futile. By contrast, the impact within a rheumatology cohort may be dramatic. Box 35.1 shows how the figures are derived.

The excess of coronary disease in inflammatory arthropathies is well documented. In a meta-analysis of 24 studies in RA populations conducted before 2005, Avina-Zubieta and colleagues¹ found a relative risk of 1.5 (95% confidence interval, 1.4 to 1.6) for cardiac death, 1.59 for diagnosed IHD, and 1.52 for cardiovascular disease in 117,000 patients. These were mainly noninception studies, however, with no analysis of risk factor prevalence. In an inception study, Crownson and associates²⁷ followed 525 patients over 8 years and observed that the standard Framingham risk score underestimated the cardiac event rate in the RA population by half for those younger than 65 years and by two thirds for those older than 75 years, which demonstrates that the relationship is not fully explained by standard risk factors. In a study of coronary calcification, a risk ratio of 3.4 was observed in RA patients compared with control subjects.²

In lupus a similar pattern of excess of coronary calcification after correction for age and sex has been identified.¹⁰ The relative risk of coronary events is much higher than anticipated even allowing for this, especially in young women, which suggests a much more direct causative relationship between the inflammatory and prothrombotic disorders.¹¹ Excess coronary events have also been identified in dermatomyositis, polymyositis, and the seronegative arthropathies.²² By contrast, no excess is seen in patients with scleroderma, which suggests that there is merit in fully understanding the dominant drivers for atherosclerosis and thrombosis in different rheumatologic conditions.²⁸

Better understanding of the relevant factors inducing inflammation and their correlation with coronary calcification could lead to improved insights into atherosclerosis, and greater understanding of the prothrombotic drivers may help unravel the relative importance of platelet activation compared with aspects of the clotting cascade.

Prevention of coronary events in rheumatologic conditions

Very large, long-term, placebo-controlled studies in the general population have shown that statin therapy is effective in secondary and primary prevention. Likewise, huge carefully constructed observational studies have provided a solid base for advising smoking cessation in the prevention of

coronary disease. Although the role of diet remains pivotal, evidence supporting effective intervention remains largely observational.

Intuitively, when one is deciding whether or not to treat to reduce conventional risk factors, one would recommend avoiding cyclooxygenase-2 inhibitors and steroids, and instead advocate widespread use of disease-modifying antirheumatic drugs and risk modification to reduce Framingham risk score given the known excess of coronary disease in certain rheumatologic conditions.

The only randomized, double-blind trial of statin therapy in RA was the Trial of Atorvastatin in Rheumatoid Arthritis (TARA), a 6-month trial involving 110 subjects. This study demonstrated that atorvastatin was safe and reduced cholesterol levels; secondary observations included a reduction of disease activity as well as interleukin-6 (IL-6) and C-reactive protein (CRP) levels.²⁹ A large randomized, controlled trial in which 4000 patients with active RA were to receive either atorvastatin 40 mg or placebo (Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis [TRACE RA]) was terminated prematurely after having recruited 3000 patients; the decision to terminate was due to the low rate of cardiac events in the placebo group.³⁰

A randomized, placebo-controlled trial with 2-year follow-up examined treatment with atorvastatin 40 mg daily in 200 SLE patients. At baseline 43% of patients had coronary artery calcification; there was no significant difference between the atorvastatin-treated and placebo-treated groups in progression of coronary artery calcification, carotid intima media thickness, or carotid plaque.¹⁰ An assessment of the feasibility of a prevention trial at a lupus clinic showed that fewer than 6% of the population would enter a primary prevention study, with over half receiving disqualifying medicines, one in three not in clinically stable condition or perceiving themselves as already taking too many tablets, and one in five refusing to participate in clinical trials.³¹

Despite such obstacles there is a clear clinical need. An assessment for the predictors of coronary events in a population of RA patients showed that traditional risk factors (diabetes, hypertension, and high triglycerides) and evidence of disease activity (elevated erythrocyte sedimentation rate and CRP level after 6 months of therapy) independently predict events.³² The Framingham risk score does predict coronary events, although it underestimates the event rate by more than half.²⁷ This suggests that to reduce coronary events in RA one should screen for traditional risk factors and consider therapy at much lower levels of calculated risk, similar to the way one assesses diabetic patients. In addition one may deduce that excellent control of disease activity may be beneficial not just in preventing complications but also in reducing coronary events.

The lack of evidence to support such deductions probably explains the poor compliance with guidance advice. In their assessment of coronary risk factor management at a lupus clinic Demas and colleagues³³ found that fewer than 3% of patients had had all five coronary risk factors assessed within the preceding year, and only a quarter had had four of five recommended assessments performed.

Antiphospholipid syndrome is rather different from the other inflammatory autoimmune diseases in that it is associated with arterial and venous thrombosis. Several studies have shown that thrombotic CAD can lead to

myocardial infarction, although this is less common than venous thrombosis (3% of 1000 patients with antiphospholipid syndrome experienced myocardial infarction, whereas 32% of patients had deep vein thrombosis).³⁴

In the systemic vasculitides, especially antineutrophil cytoplasmic antibody-associated diseases such as granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis, there is an excess of deaths due to cardiovascular causes, but data from the large prospective treatment trials that recorded cause of death have not yet been published.

Many attempts have been made to treat inflammation directly; none has been successful, but these attempts have led to a better understanding of the drivers of inflammation in atherosclerosis. Increased CRP and IL-6 levels, although strongly associated with inflammation and predictive of event rates, are probably not the drivers of atherosclerosis. By contrast, myeloperoxidase levels directly promote atherogenesis in animal models and have a strong claim on relevance based on human studies.

ATYPICAL CORONARY DISEASE IN CONNECTIVE TISSUE DISEASE

The classic CTD associated with specific coronary lesions is Kawasaki disease or mucocutaneous lymphadenopathy.³⁵ This condition classically affects male children younger than 5 years of age but recently has been reported in adults without the classical dermatologic lesions.³⁶ Administration of intravenous immunoglobulin IVIG while the disease is active reduced the prevalence of coronary aneurysms from 20% to 5%.³⁵ The aneurysms typically involve the proximal coronary arteries with substantial surrounding inflammatory tissue during the acute phase and can usually be identified on echocardiography.³⁵ Later, thin-walled aneurysms and secondary stenotic lesions predominate, and a significant body of experience now indicates that stenting of these lesions is safe and practical.³⁷

Behçet syndrome, although causing primarily dilation of pulmonary vessels, possibly through inflammation of the vasa vasorum (Fig. 35.1), also is associated with coronary aneurysms, which again develop in association with obvious disease activity and are improved by immunosuppressive therapy.³⁸ Although Takayasu arteritis generally spares vessels as small as the coronaries, involvement of the coronary ostia in aortic disease is well documented and causes angina and heart failure.¹⁹

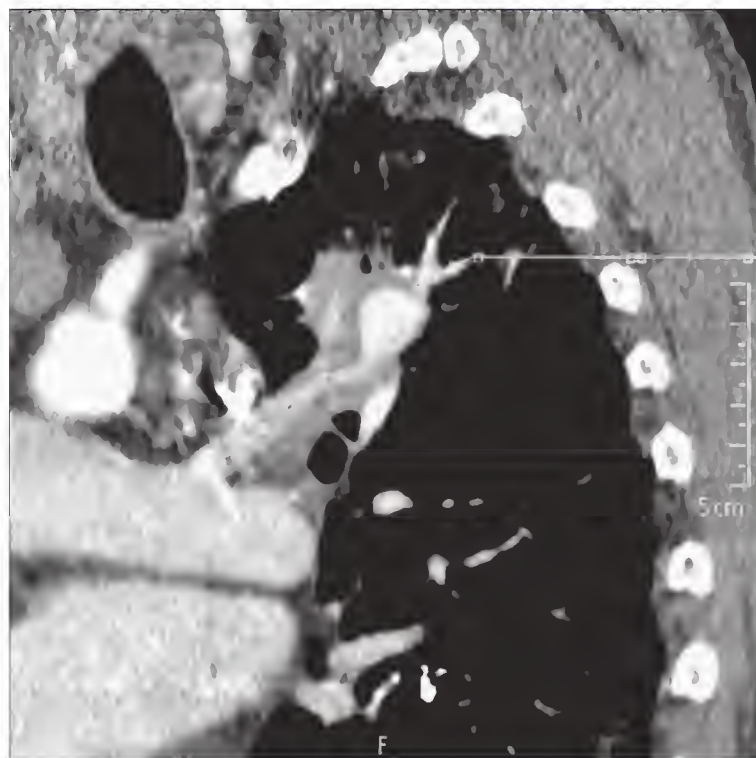


Fig. 35.1 Pulmonary artery aneurysm shown on computed tomographic pulmonary angiogram in a patient with Behçet syndrome and pulmonary hypertension.

Although coronary artery aneurysms are rare, atherosclerotic and congenital aneurysms are much more prevalent than CTD-associated aneurysms.³⁹

CORONARY ARTERITIS

Intramyocardial coronary arteritis occurs in conditions such as Churg-Strauss syndrome, granulomatosis with polyangiitis, and polyarteritis nodosa,¹⁹ although the latter can also cause coronary artery aneurysms.³⁹ Involvement of the coronary vessels causes no immediate symptoms and generally emerges as a clinical problem only when cardiac failure ensues.¹⁹ The natural history is not resolved because the disorder is subclinical, but the prevalence of heart failure (the end result) appears to decrease with good control of disease activity.⁴⁰

FUNCTIONAL CORONARY ARTERY DISORDERS

SSc is thought to impair intramyocardial vascular tone, leading to ischemia-reperfusion injury, and the classical histologic lesions of contraction band necrosis and replacement fibrosis are typical of reperfusion injury.¹⁸ Difficulty arises in determining the role of such observations in clinical disease, which is much less common than the histologic findings might suggest, and comparative histologic studies indicate that such lesions are only modestly more common in SSc patients than in the normal population.¹⁸

HYPERTENSION

Inflammation is thought to play a key role in the pathogenesis of hypertension. In prospective studies higher CRP levels are predictive of subsequent development of hypertension. After correction for confounders, however, a causative association seems highly unlikely.⁴¹ Early work shows many other associations, for example, between levels of fibrinogen, α_1 -antitrypsin, haptoglobin, ceruloplasmin, and orosomucoid and future hypertension,⁴² as well as between serum levels of soluble tumor necrosis factor receptors, IL-6, and IL-1 receptor antagonist and end-organ damage in the form of left ventricular (LV) hypertrophy.⁴³ Although by no means conclusive, such observations support findings in many animal models of hypertension. Idiopathic hypertension has to date defied a unifying theory of causation. Among the front runners presently is the theory of intrarenal microvascular endothelial dysfunction leading to transient microtubular ischemia.⁴⁴ In susceptible individuals secondary inflammation leads to persistent ischemia and thus chronic renin-angiotensin system activation.⁴⁴

Endothelial dysfunction is a hallmark of CTD, as is a heightened inflammatory response; thus a milieu is created in which an increased prevalence of systemic hypertension may well be expected. This is in addition to specific disorders such as direct renal involvement in SSc¹⁵ and lupus renal involvement, salt retention and hypertension induced by nonsteroidal anti-inflammatory drugs (NSAIDs)⁴⁵ or steroid therapy, and of course aortic and renal vascular stenosis in the large-vessel vasculitides.¹⁹

Antiphospholipid syndrome is associated with both renal thrombotic microangiopathy and stenotic lesions of the renal arteries, likely due to intimal hyperplasia, resulting in labile hypertension.⁴⁶

Among rheumatologic conditions, gout and hyperuricemia have the strongest association with hypertension.⁴⁷ In *in vitro* studies uric acid is a powerful pro-oxidant in the intracellular environment,⁴⁸ causing endothelial dysfunction⁴⁹ and inflammation. In humans, intervention to reduce uric acid levels appears to ameliorate hypertension.⁵⁰ Although the role of uric acid in hypertension remains a matter of controversy, there is a strong evidence base indicating that such a role is real and can contribute to our understanding of the nature of hypertension.

The association between psoriasis and multiple risk factors for cardiovascular disease, including hypertension, hyperlipidemia, diabetes, and metabolic syndrome, is well established. Increased levels of IL-6 and proinflammatory cytokines⁵¹ provides one possible explanation, and confounding factors such as treatment effects (e.g., cyclosporine) have not been excluded.

One would anticipate that hypertension is demonstrably more common in RA; however, a meta-analysis of available case-control studies showed no such excess in 2956 patients and 3713 controls,⁴ although results of individual studies are suggestive of an excess, particularly in those with significant long-term steroid exposure.³ More intriguingly, the typical consequences of hypertension, atrial fibrillation and stroke, have been found to be significantly more common in RA.⁵ This study included over 4 million adults older than age of 18 plus over 18,000 patients with RA followed for more than

13 years, and demonstrated a 40% excess of atrial fibrillation at all ages and a 30% excess of stroke that increased with age.

In other conditions such as lupus and scleroderma, renal involvement and low prevalence add considerably to the complexity of demonstrating a link between the underlying inflammatory drivers and hypertension.

HEART FAILURE AND DIRECT MYOCARDIAL INVOLVEMENT

Heart failure as a syndrome resulting from coronary disease, hypertension, myocardial disease, and valvular disease is expected as a consequence of rheumatologic diseases. In heart failure clinics atherosclerotic coronary disease dominates, so one might anticipate that conditions such as RA would lead to infarction-related heart failure—yet this is uncommon. With rarer diseases such as lupus, heart failure due to direct cardiac or valve involvement is classically described. Yet sarcoid is probably the dominant reason why cardiologists become involved in treatment of rheumatologic conditions.

RA is associated with a greater relative risk of heart failure (2:1), mainly diastolic. Proposed causes include amyloidosis, NSAID use, glucocorticoid therapy, IHD, and direct myocardial involvement.⁶ The presentation of heart failure is subtle (preserved systolic function), and heart failure is associated with a worse prognosis in the 6 months following acute exacerbations.⁵²

From the rheumatologic perspective, the salient points are that echocardiography is relatively insensitive as a tool for diagnosing RA-associated heart failure (assessment of diastolic dysfunction lacks specificity), and angiotensin-converting enzyme inhibition and β -blockade are not beneficial. Diagnosis requires a high index of suspicion, and measurement of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) should be considered when heart failure is suspected. On echocardiography, an enlarged left atrium may be the only feature (and this can also be caused by prolonged atrial fibrillation). CMR may well prove useful in the future, but presently data are limited.

Cardiac failure should be very common in scleroderma—up to 70% of patients have histologic evidence of cardiac involvement on postmortem examination¹⁸ and a similar percentage exhibit abnormalities on CMR.¹⁷ However, clinically systolic LV dysfunction is rather uncommon,¹⁶ and diastolic heart failure is encountered in only a minority. Although systolic heart failure is seen occasionally in the context of renal crisis or in association with myocarditis,⁵³ most commonly cardiac involvement remains subclinical unless there is an associated cardiac stress. Right-sided heart failure secondary to pulmonary hypertension is the most common reason that scleroderma patients have symptoms and signs of heart failure. Whether the subclinical cardiomyopathy contributes to the frequency of right-sided heart failure in scleroderma remains a matter of speculation. It is clear that the right side of the heart fails despite facing lower pulmonary pressures than in idiopathic PAH.⁵⁴

Cardiologists are sensitized to the possibility of sarcoid cardiac involvement—not so much because of the occurrence of heart failure, but because of the association with sudden death and heart block. Nevertheless, a byproduct of this is an awareness of the possibility of sarcoid as an underlying diagnosis when a patient has myocarditis or restrictive cardiomyopathy. The prevalence of cardiac involvement in sarcoid depends on the series chosen. Postmortem series, which are inevitably biased toward overestimation, suggest that 30% of patients have granulomas in the heart and that premortem diagnosis is uncommon.⁵⁵ Clinical prevalence lies between 5%⁵⁶ and 40%.⁵⁷ The clinical relevance of abnormalities identified in screened populations varies from benign⁵⁸ to more than a 50% rate of death or need for device implantation in less than 2 years.²⁴

In sarcoid, steroid therapy appears effective in reducing the cardiac contribution to death.⁵⁷ CMR is thought to be particularly sensitive in identifying sarcoid cardiac disease, and estimates of prevalence are likely to change as this technique is used more frequently.⁵⁸

Heart failure may present as part of an active inflammatory myocarditis, with persistent troponin leakage and evidence of diffuse myocardial edema and midwall fibrosis on CMR. Steroids and occasionally more aggressive immunosuppression (such as mycophenolate) is the mainstay of therapy. Therapy should be initiated early to avoid reduction of the ejection fraction to less than 40%, and given the association with ventricular arrhythmias, consideration should be given to use of a life vest or implantation of a defibrillator to deal with unpredictable arrhythmias during the initial phase of therapy.^{57,24} Alternatively, patients may have heart failure of more insidious onset, often associated with very large atria and features of restriction. This is a difficult form of heart failure to treat; only diuretics appear to have any role in management.

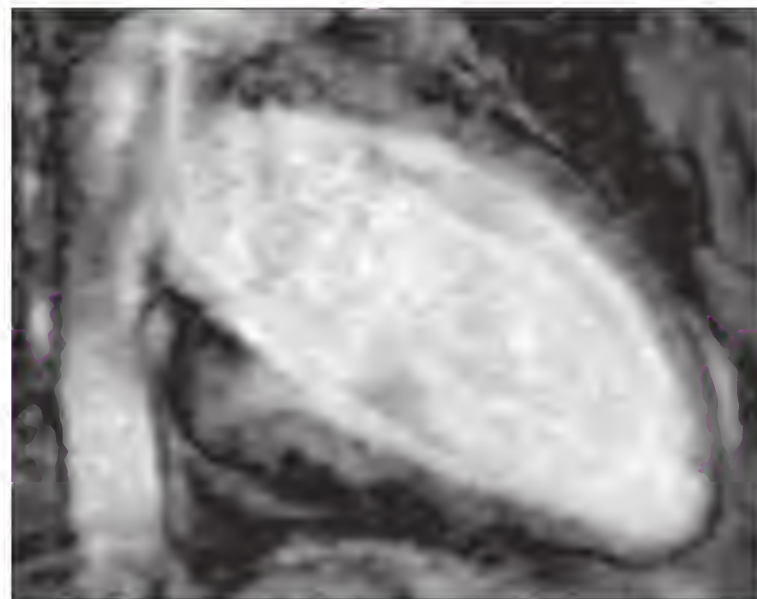


Fig. 35.2 Extensive diffuse myocardial edema in a patient with sarcoid-associated acute myocarditis. Cardiac magnetic resonance image showing late gadolinium enhancement (mottled gray appearance of left ventricular myocardium).

Eosinophilic endomyocardial fibrosis is almost never found in patients with Churg-Strauss syndrome and cardiac symptoms. Rather, a more common presentation in these patients is dilated cardiomyopathy thought to be due to microvascular ischemia, a process that is not necessarily controlled with standard immunosuppressive therapy for the systemic condition. An alternate possible explanation is suggested by recent data from a registry of 49 patients with Churg-Strauss syndrome. Nearly half of these patients had evidence of cardiac involvement, and in over a quarter¹³ this took the form of endomyocarditis on biopsy; these patients had the worst outcome.⁵⁹ Once heart failure is present, standard therapy is appropriate; however, prevention theoretically should now be possible by monitoring troponin levels when treating patients with these conditions if there are any concerns about cardiac involvement.

Current teaching is that heart failure in SLE is most likely the result of standard dilated cardiomyopathy or coronary disease rather than direct lupus or antimalarial drug toxicity.⁶⁰ Certainly, given the increased frequency of coronary disease, computed tomographic angiography seems a sensible first investigation in patients with systolic heart failure.¹⁰ CMR often shows evidence of myocardial edema and late gadolinium enhancement (Fig. 35.2), but whether this differentiates myocarditis from hydroxychloroquine toxicity has not been established, and myocardial biopsy with electron microscopic evaluation for myeloid bodies⁷ should be considered if other clinical features of disease activity are absent.

Heart failure is thought to be rare in inflammatory myopathies; however, the paucity of adequate registry data makes this uncertain. The finding of subclinical myocardial involvement in autopsy studies, backed by suggestions of a high cardiac mortality, indicate that cardiac failure may be underdiagnosed. Available data suggest that a process of lymphocytic infiltration similar to that observed in the skeletal muscle may affect the heart and that cardiac lesions may progress despite steroid therapy.²⁰ With more widespread use of troponin and NT-proBNP testing as well as CMR, the picture should clarify in the coming decade.

VALVULAR HEART DISEASE

Ask cardiologists about rheumatologic conditions that cause valvular heart disease, and they will recall Libman-Sacks endocarditis as a matter of historical interest and offer ankylosing spondylitis as a contributor to aortic valve disease. Such impressions are in part testament to the efficacy of current management of CTDs and in part reflection of cardiologic disinterest in subclinical valvular lesions.

Although clinically overt valve disease is now rare in SLE, echocardiographic studies suggest that involvement remains common, with 40% of patients exhibiting minor abnormalities on transthoracic echocardiographic and 70% on transesophageal echocardiographic studies, including vegetations in over 30%.⁸ Valvulitic lesions identified on transesophageal

echocardiography have been reported to exhibit activity in terms of progression and regression. Although a causative relation has not been demonstrated, a correlation between valvular lesions and stroke has been found, with microembolization proposed as a mechanism.⁶¹ It is increasingly recognized that the presence of antiphospholipid antibodies in SLE patients is more likely to be associated with cardiac valve disease than with Libman-Sacks endocarditis.⁶²

In ankylosing spondylitis, aortitis is thought to occur late in the disease process and may be quite common. Generally only thickening of the aortic wall is evident; however, this may lead to aneurysm formation, thickening and retraction of the aortic or mitral valve leaflets causing regurgitation, and/or fibrosis of the upper septum leading to conduction abnormalities. As with all largely subclinical processes, more detailed investigations lead to higher reported prevalence rates, and with transesophageal echocardiographic evaluation, root and valve abnormalities are found to be more than threefold more common in patients with ankylosing spondylitis than in control populations.⁶³

Scleroderma is not currently considered a major cause of valvular heart disease, but modest thickening of the leaflets with shortening of the chordae tendineae is common in echocardiographic studies, as is mild regurgitation. In the authors' experience most patients who require intervention for valve lesions have aortic stenosis, although at this time it is not evident that the prevalence exceeds that in the normal population.

PERICARDITIS

The rheumatologic condition classically associated with typical symptomatic pericarditis is lupus, with up to one fourth of patients having a syndrome of positional chest pain, fever, tachycardia, and/or pericardial rub, usually associated with an effusion.⁶⁴ Chest pain is common in lupus flares, and pericardial effusions are more common than true pericarditis. Pericarditis is rarely the dominant clinical syndrome in an index event; thus most patients seek treatment from rheumatologists rather than from a general medical or cardiac clinic. All types of pericardial involvement have been described, most commonly fibrinous pericarditis, and the pathologic basis appears to inflammatory depositions (immunoglobulin, C1q, C3) in the walls of pericardial vessels.⁹ Treatment is adequate control of lupus activity, with direct intervention rarely being required. It is remarkable how quickly even large pericardial effusions improve with corticosteroid therapy.

Pericardial effusions are also common in scleroderma, although clinical pericarditis is uncommon. Autopsy studies reveal frequent and diverse pathologic features, including fibrinous and fibrous pericarditis, adhesions, and effusions.⁶⁵ Clinically effusions are most relevant when they are associated with pulmonary hypertension, in which they provide evidence of right ventricular (RV) decompensation, and when they are associated with an active myocarditis,³³ which requires treatment in its own right.

In the setting of pulmonary hypertension, pericardial drainage should be avoided; it does not improve hemodynamics and can result in worsening of right-sided heart failure due to sudden reduction in free wall support; the apparent compression of the left ventricle that has been reported is caused by RV dominance rather than tamponade.

Clinical pericarditis is rare in RA; however, older echocardiographic and autopsy studies suggest that pericardial involvement was common before treatment with disease-modifying antirheumatic drugs was widely used. Pericardial effusions also are not uncommon in sarcoid, but clinical pericarditis is rare. Effusions tend to be inflammatory and may be regarded as an index of disease activity, often responding to steroid therapy.

Pericarditis is relatively common in Churg-Strauss syndrome (it was found in 9 of 49 patients in a recent survey)³⁹; in addition, multiple case reports highlight the association with polyarteritis nodosa, and occasional reports have indicated associations with the other large- and small-vessel vasculitides.

ARRHYTHMIAS

The arrhythmias classically associated with rheumatologic conditions are congenital heart block in lupus and heart block in sarcoid. The associations with conduction defects in scleroderma and myositis are less recognized. Atrial fibrillation, although clearly associated with RA, is underrecognized, and the prevalence of ventricular arrhythmias associated with myocarditis, impaired systolic function, and myocardial fibrosis has not been adequately delineated.

The presence of circulating autoantibodies targeting ribonuclear proteins (anti-Ro/SSA and anti-La/SSB) is associated with congenital heart block.¹²

The high mortality associated with this condition, which often requires external pacing, makes it a feared though uncommon disorder. Only around 5% of mothers with circulating antibodies will have an affected child, and although the prevalence in subsequent pregnancies is higher after a first affected child, it remains well lower than 50%.⁶⁶ In mothers at high risk of having a child with cardiac neonatal lupus, the use of hydroxychloroquine may protect against recurrence of disease in a subsequent pregnancy.⁶⁷

Lupus myocarditis has been associated with ventricular and atrial arrhythmias,⁶⁸ although no systematic study of the incidence has been undertaken given the apparent rarity of this condition; valvular heart disease, in particular mitral regurgitation, may lead to atrial fibrillation.

Granulomatous involvement and fibrosis of the atria, conducting tissue, and ventricular myocardium may lead to delayed conduction as well as atrial or ventricular arrhythmias in sarcoid.⁵⁹ Ventricular arrhythmias are thought to underlie the excess of sudden death,^{24,56} although there is a suggestion that this may be prevented with disease control using steroids.⁵⁶ When suggestive symptoms or electrocardiographic (ECG) abnormalities are present, echocardiography and troponin testing can identify patients with evidence of direct myocardial involvement who require immunosuppression and/or direct intervention for arrhythmias. The role of Holter or implantable monitoring is not firmly established but is recommended when high-grade block or ventricular arrhythmia is suspected.^{24,57}

Multiple ECG abnormalities have been reported in SSc, with equal frequency in the diffuse and limited forms. Abnormalities including septal Q waves, intraventricular conduction defects, prolongation of the PR interval, and bundle branch block are reported in over one quarter of SSc patients.¹⁸ Cases of heart block requiring pacing are thought to occur with increased frequency, and an association of SSc with myositis and sudden death,⁵³ added to evidence of myocardial fibrosis,¹⁷ leads to concerns that SSc patients may be at increased risk of ventricular tachyarrhythmias.

The association between RA and atrial fibrillation has been firmly established in the recent Danish population study,⁵ in which the incidence of atrial fibrillation was 40% higher in individuals with RA than in the general population. The incidence of stroke was 30% greater in the RA patients than in the general population. Among the proposed causes is the higher prevalence of heart failure in RA, which is strongly associated with atrial fibrillation; in addition, arterial stiffness, which is well described in RA, is also known to increase the risk of both heart failure and atrial fibrillation.

Inflammatory myopathies are associated with similar pathologic processes in the myocardium, so it is no surprise that ECG abnormalities, including various degrees of conduction delay, are commonly reported.²⁰ Pacemakers are only rarely required, and a clear association with ventricular arrhythmias, although expected (given the association with progressive ventricular impairment and sudden death), is not proven. Spondyloarthritis, in particular ankylosing spondylitis, has been clearly shown to cause heart block resulting from extension of fibrosis into the septum, but the frequency with which this occurs appears to be low, and high-grade block is rare.⁶⁹

PULMONARY HYPERTENSION

PAH is remarkably common in association with CTD. In scleroderma the estimated prevalence is approximately 10% in catheter-based studies; estimates are similar or higher in mixed CTD. In SLE the likely prevalence is under 1%, and cases are described in polymyositis and myositis.⁷⁰ An increased prevalence is suspected in sarcoid,²⁵ whereas the prevalence in rheumatoid is likely similar to background levels,⁷⁰ and in the rarer conditions there are insufficient data.

Much higher prevalences have been estimated in echocardiographic studies—due in part to the inaccuracy of echocardiographic estimations of pulmonary pressure⁷¹ and in part to the frequency of diastolic dysfunction and lung disease,^{6,15,25} which lead to elevated pulmonary pressures.

There is high prevalence of PAH in scleroderma. The DETECT study demonstrated the feasibility of screening for PAH,⁷² but only using a combination of clinical, serologic, and simple investigations, and further showed that PAH can be diagnosed much earlier in the course of the disease than previously thought possible within enriched subsets.

The second striking feature of CTD-associated PAH is the lower pulmonary vascular resistance and pulmonary pressures at the time of diagnosis compared with idiopathic PAH; this is true not just for scleroderma, but also for mixed CTD, dermatomyositis and polymyositis, sarcoid, and to a lesser extent lupus.^{25,70} It is still unclear whether this is due to greater ventriculo-arterial mismatch,⁷³ poor tolerance of rapidly escalating pressures by older patients, or the intrinsic myocardial dysfunction prevalent in CTD; the opportunity presented by early detection should help resolve this quandary. Autopsy and CMR studies suggest that myocardial involvement in SSc is

very common; and Meune and associates⁷⁴ demonstrated that although systolic dysfunction is rare—a trend toward minor diastolic abnormalities is the norm in SSc, but RV abnormalities are not particularly prevalent. Ventricular interdependence may be a way of squaring this particular circle. The left ventricle contributes to 40% of RV workload, and increasing LV contractility in isolation increases RV tolerance of afterload. It is thus possible that LV involvement in CTD is responsible for the failure of the right ventricle to tolerate higher workloads. This would explain the absence of more extensive fibrosis in the right ventricles of SSc patients than in patients with idiopathic PAH on CMR; it may also explain why the right ventricle takes a bigger hit when postcapillary pulmonary hypertension is present. If this is true, one should expect that evaluation of LV contractility in SSc-associated PAH compared with idiopathic PAH would provide insights into the lower RV tolerance of afterload.

Despite the more modest hemodynamic perturbation at diagnosis, the prognosis is worse in CTD PAH than in idiopathic PAH, except in SLE-associated PAH.⁷⁰

As a systemic condition, CTD-associated PAH requires much greater diligence in establishing the diagnosis, including being prepared to undertake left-sided heart catheterization when any doubts exist about the wedge pressure and performing a detailed assessment of coexistent lung disease. It is presently suggested that a wedge pressure of 12 mm Hg or above in an

adequately hydrated patient does not exclude postcapillary pulmonary hypertension.⁷⁵

In PAH associated with all CTDs as exemplified by SSc-related PAH, unlike in idiopathic PAH, significantly reduced gas transfer is the rule.^{70,72} This may relate to the presence of more diffuse pulmonary vascular lesions extending into the pulmonary veins.⁷⁶ It may also explain the worse prognosis associated with CTD-related PAH, because such patients tend to develop pulmonary edema on treatment with pulmonary vasodilators.⁷⁶ However, this issue is not settled. The authors' data suggest that fewer than 10% of SSc patients meet the criteria for a diagnosis of pulmonary veno-occlusive disease, and in none of the pivotal trials, or their follow-up, has an excess pulmonary edema event rate been reported in SSc patients. There is little doubt, however, that severely reduced gas transfer is indicative of a more diffuse abnormality of the gas-exchanging vasculature and a worse prognosis.⁷⁷

It may be concluded, therefore, that CTDs affect all aspects of cardiac function both directly and indirectly and that greater collaboration between cardiologists and rheumatologists would significantly improve patient care and our understanding of the cardiac contribution to adverse outcomes in these populations. The relatively low visibility of CTD in general cardiology cohorts reflects a poor signal-to-noise ratio that can be overcome with only dedicated cardiology/rheumatology clinics.

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36

The lung in rheumatic disease

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- All components of the respiratory system can be involved in the lung manifestations of rheumatologic disease.
- Lung disease may precede overt musculoskeletal features by several years.
- Pneumonitis caused by drugs or opportunistic infection related to immunosuppression can complicate diagnosis of lung manifestations of rheumatologic disease.
- High-resolution computed tomography with or without bronchoalveolar lavage can be helpful in differentiation of lung manifestations. Surgical biopsy may be required where there is residual doubt.
- Treatment approaches depend on the dominant pattern of disease.
- Outcome tends to be better than in the idiopathic interstitial pneumonias that share common pathologic patterns.
- Rarely, more explosive diffuse lung disease mimicking acute respiratory distress syndrome can occur. The outcome of this manifestation is often poor.
- On rare occasions, the majority if not all manifestations of an underlying autoimmune disease may be evident in the lung; this is referred to as *lung-dominant connective tissue disease*.

INTRODUCTION

Pulmonary manifestations of rheumatic diseases are among the most significant challenges for the practicing rheumatologist. Specifically, interstitial lung disease (ILD) is one of the most worrisome and challenging complications due to the progressive nature of the disease and variable response to therapy and prognosis. This chapter highlights major areas of lung involvement in specific rheumatic diseases including airway, pleural, vascular, and interstitial lung disease, the latter of which is the main focus of this chapter given its importance in rheumatologic practice.

Interstitial lung disease or parenchymal lung disease

ILD represents a significant challenge in the management of patients with rheumatic diseases. Prognosis is variable and strongly depends on the histopathologic pattern noted. Some studies suggest that ILD associated with rheumatic diseases has a better prognosis than idiopathic pulmonary fibrosis (IPF), whereas other studies suggest that prognosis is similar.¹⁻³ ILD associated with rheumatic disease occurs most commonly in scleroderma (systemic sclerosis form, or SSc), followed by polymyositis/dermatomyositis, mixed connective tissue disease, rheumatoid arthritis (RA), and less frequently Sjögren syndrome and systemic lupus erythematosus (SLE). ILD may precede the development of a specific rheumatic syndrome or present as part of a poorly defined or undifferentiated rheumatic syndrome that the rheumatologist may be asked to evaluate in the setting of active ILD.

Pathologic features in interstitial lung disease

An understanding of the histopathologic classification of ILD is important because different histologic subtypes portend different prognoses. The two

most common types of ILD associated with rheumatic diseases are nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), followed by lymphocytic interstitial pneumonia (LIP), cryptogenic organizing pneumonia (COP), and less frequently diffuse alveolar damage (DAD).

UIP is associated with a patchy heterogeneous process with fibrotic areas interposed with normal or near-normal lung. The distribution is predominantly subpleural and associated with honeycombing on chest computed tomography (CT) (Figs. 36.1 and 36.2). Pathologic specimens are notable for characteristic fibroblastic foci (Fig. 36.3). Although UIP is the classic pathologic lesion observed in IPF patients, it can also be seen in patients with RA, SSc, and other rheumatic syndromes. The presence of UIP in RA portends a worse prognosis than other histopathologic patterns.³

NSIP is characterized by a more uniform, homogeneous pattern, with variable degrees of inflammation (cellular NSIP) or fibrosis (fibrotic NSIP) and a noted paucity of fibroblastic foci on pathologic examination (Fig. 36.4). Typically, ground-glass opacities are noted and are often associated with a reticular pattern and traction bronchiectasis but a lack of honeycombing on chest CT scan (Fig. 36.5). NSIP is the histopathologic lung pattern seen more frequently in patients affected with rheumatic diseases and appears to have a better overall prognosis than UIP.⁴

COP, formerly known as *bronchiolitis obliterans organizing pneumonia*, is an inflammatory disease that predominately involves the distal airways (acini and respiratory bronchioles) and is characterized by its responsiveness to steroids. It is associated with many rheumatic diseases including SLE, RA, and polymyositis/dermatomyositis.

LIP is characterized by extensive lymphocytic infiltration associated with peribronchial lymphoid follicles; it is most often seen in Sjögren syndrome and RA and may be a feature of ILD in undifferentiated forms of autoimmune disease as well.

DAD is notable for the development of hyaline membranes. It can develop in a variety of rheumatic syndromes including SLE and polymyositis/dermatomyositis. DAD can occur *de novo* or in patients with preexisting lung disease. The presence of DAD is usually associated with severe respiratory failure and overall poor prognosis.

It is important to note that it is more difficult to predict progression in ILD associated with rheumatic syndromes than in IPF with its more predictable steady decline.

EVALUATION OF PATIENTS WITH LUNG INVOLVEMENT IN THE RHEUMATIC DISEASES

Radiographic studies

Chest radiography is not particularly sensitive in detecting mild forms of ILD; however, it may be useful in excluding other conditions such as congestive heart failure, pleural disease, and pneumonia. Chest CT with high-resolution imaging (HRCT) is the test of choice in detecting ILD, and detection of characteristic findings on CT may predate the onset of clinical symptoms.⁵ The most common finding in ILD is the presence of ground-glass opacities, which are characteristic of inflammatory disease and most often associated with NSIP. Another important finding is the presence of honeycombing (cystic spaces within clearly definable walls), which typically is found in a subpleural distribution and is pathognomonic for UIP. There is reasonable correlation of the radiographic appearance on chest CT with histopathologic changes in UIP and NSIP.⁶ Computer-aided quantitative scoring of CT scans is emerging as a method to detect and quantify the extent and severity of fibrosis.

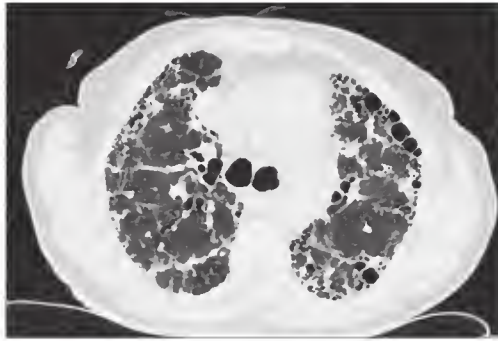


Fig. 36.1 Computed tomographic scan of the chest shows the pattern associated with usual interstitial pneumonia (UIP). Note the peripheral coarse honeycomb pattern that is the hallmark of UIP.



Fig. 36.2 High-resolution computed tomographic scan of the chest shows fibrotic changes in a subpleural distribution with honeycombing consistent with usual interstitial pneumonia.

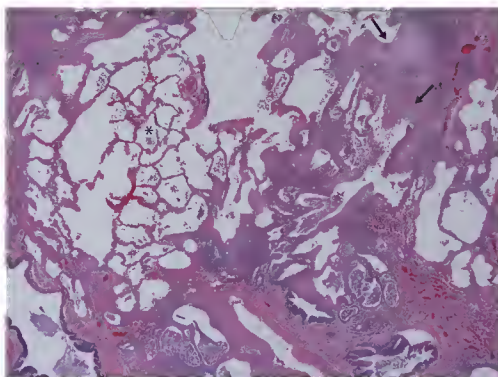


Fig. 36.3 This 40x view shows characteristic features of usual interstitial pneumonia (UIP) with the presence of normal lung (indicated by asterisk) next to fibrotic lung, which illustrates the temporal heterogeneity of UIP. Fibroblastic foci, commonly seen in UIP, are indicated by the arrows.

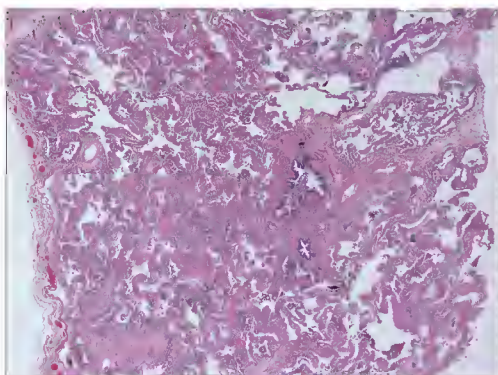


Fig. 36.4 This 40x view shows homogeneous inflammation and fibrosis of the interstitium of the lung characteristic of nonspecific interstitial pneumonia. (Courtesy Lynette Sholl, MD, Brigham and Women's Hospital.)



Fig. 36.5 High-resolution computed tomographic scan of the chest shows bilateral ground-glass opacities without honeycombing in a patient with dermatomyositis, which is consistent with nonspecific interstitial pneumonia.

Pulmonary function testing

ILD is characterized by the presence of restriction on spirometry and plethysmography (reduced forced vital capacity [FVC], increased ratio of forced expiratory volume in 1 second to FVC, a low total lung capacity, and low carbon monoxide diffusion capacity). The 6-minute walk test is a useful and simple test that can suggest early interstitial or pulmonary vascular disease when oxygen saturation drops below 95%; however, the use of the 6-minute walk test in clinical practice for this purpose has yet to be validated.⁷

Bronchoalveolar lavage

The main role of bronchoscopy, bronchoalveolar lavage, and transbronchial biopsy in ILD is to determine if there is concomitant infection. In rare instances an alternative diagnosis is established, such as granulomatous disease. Assessment of cell differentials and specific cell type predominance, such as a predominance of neutrophils, does not serve as an independent predictor of disease progression or response to treatment, as noted in the Scleroderma Lung Study.⁸

Lung biopsy

In many cases, when the disease pattern on HRCT clearly favors one diagnosis and the clinical features are straightforward, lung biopsy may not be necessary or advisable. However, when the clinical presentation is atypical or poorly differentiated or when other diagnoses such as COP or infection are being entertained, lung biopsy may offer important information that can influence treatment decisions.

Systemic sclerosis

Pulmonary disease is the leading cause of mortality and morbidity in SSc. Although ILD is the most common pulmonary manifestation, other complications such as aspiration pneumonia and pulmonary hypertension can occur separately or concomitantly with ILD.

The prevalence of disease varies from 25% to 90% depending on the subtype and definition of scleroderma, although clinically significant ILD in scleroderma occurs in about 40% to 50% of patients with diffuse disease and in about 30% of patients with limited disease.⁹ Most of the morbidity and progression of ILD in diffuse SSc occurs in the first 4 to 5 years, and severe ILD can occur in patients with limited disease and also in patients without cutaneous involvement of scleroderma, known as *sine scleroderma*.¹⁰ The predominant pathologic pattern seen is fibrotic NSIP followed by UIP; rarely COP and DAD may be seen.^{3,11} The pathogenesis of the fibrosis is not fully understood, but transforming growth factor- β , platelet-derived growth factor, and endothelin-1 among other cytokines, chemokines, and mediators play an important role in disease progression.¹²

Two prospective clinical trials using cyclophosphamide showed very modest benefit in terms of survival or clinically significant improvement in pulmonary function based on HRCT or pulmonary function tests (PFTs). In the Scleroderma Lung Study, oral cyclophosphamide was administered for a duration of 1 year, and a small improvement in FVC was noted after 1 year, although this benefit was not maintained by the end of year 2.¹³ In another prospective trial, a trend toward improvement in FVC was noted in patients given intravenous cyclophosphamide 600 mg/m² monthly for

6 months with prednisone 20 mg administered on alternate days followed by azathioprine for an additional 6 months.¹⁴ On balance, although the benefits of cyclophosphamide in scleroderma are modest and the benefits must be weighed against the risk of significant toxicity, cyclophosphamide may be useful in patients with ILD and is recommended as a treatment option by the European League against Rheumatism. Novel approaches for the treatment of ILD associated with scleroderma include tyrosine kinase inhibitors, mycophenolate mofetil, endothelin antagonists, and a host of emerging molecules that affect fibroblast proliferation.¹⁵

Aspiration related to esophageal dysmotility is seen commonly in SSc and may play a role in either the pathogenesis or exacerbation of ILD in SSc.¹⁶ Although no prospective trials have measured progression of lung function in response to control of reflux, it may be beneficial to minimize the risk of reflux by using high-dose proton pump inhibitors or to consider antireflux surgery in patients with evident ILD.

In some patients, severe pulmonary hypertension and ILD can occur concurrently, which is among the most challenging scenarios in terms of prognosis and therapy. Early recognition is important given the now numerous therapeutic options available to treat pulmonary hypertension, which may enhance survival and quality of life.

In summary, the initial pulmonary assessment of all patients with scleroderma involves baseline pulmonary function testing, HRCT, and echocardiography. Assessment using an algorithm combining findings on pulmonary function tests and HRCT can aid in prognostication and decisions regarding treatment.¹⁷ If significant ILD is present that appears to be progressive, then a trial of cytotoxic or other immune-modulating therapy with or without steroids may be considered, although data supporting their benefit is limited based on clinical trials in scleroderma patients. Finally, there are several ongoing trials assessing the use of stem cell transplantation in patients with aggressive disease, and patients with rapidly progressive lung disease may be considered for lung transplantation in selected centers.

Rheumatoid arthritis

Pulmonary disease is relatively common in RA. Although morbidity is more readily apparent in the articular system, increased mortality, observed in the first decade, can be attributed mostly to extraarticular organ involvement, in particular involvement of the cardiopulmonary system.^{3,18} A history of smoking (past or present) is a strong predictor of extraarticular organ involvement.¹⁹

The most significant pulmonary complication is RA-associated interstitial lung disease (RA-ILD), which occurs in nearly 10% of the RA population based on national data.²⁰ The histopathologic patterns most commonly seen are UIP and NSIP. Most interstitial pneumonias associated with collagen vascular disease have a slower rate of progression and better prognosis than idiopathic interstitial pneumonias (i.e., IPF) independent of histopathologic classification; however, RA-ILD with a UIP pattern has a worse prognosis than that with an NSIP pattern.^{3,21} Interestingly, histologic findings of UIP in lung biopsy specimens of patients with RA-ILD may be more frequent in smokers than in nonsmokers.²² The significance of anti-cyclic citrullinated peptide antibodies and citrullination in patients with RA-associated ILD and in patients with ILD without clinically evident RA is uncertain.²³

The incidence of RA-ILD has a bimodal distribution with a majority of patients developing ILD a decade after the onset of articular manifestations and a minority of patients developing clinically apparent disease shortly after the development of articular disease.²⁴ In a small subset of patients lung involvement is the first disease manifestation of RA. In general, RA-ILD with this atypical presentation is similar in clinical course, response to treatment, and prognosis to other RA-ILD.²⁵ These diverse clinical phenotypes suggest that genetic factors and environmental determinants (e.g., smoking) are potential disease modifiers that influence outcomes.

Preclinical ILD is relatively common in RA, and studies in which open lung biopsy or chest CT was performed demonstrate lung involvement in more than 40% of the study population.^{26,27} In one study, 33% of RA patients without dyspnea or cough had ILD as identified by chest CT scans; preclinical ILD like RA-ILD was associated with a history of smoking (past or present). Importantly, disease progression has been observed in this type of patient, which suggests that clinically significant pulmonary fibrosis is likely to develop in a subset of patients affected with preclinical RA-ILD.²⁴

Bronchiectasis or bronchiolectasis is observed in up to 30% of patients with RA studied with chest CT.²⁸ Similarly, obliterative bronchiolitis is more common in RA than in other rheumatologic diseases. Although the prevalence of obliterative bronchiolitis is low, the prognosis is poor due to the lack of effective treatments, and lung transplantation may be required to prolong survival and improve quality of life. Other forms of bronchiolar involvement may show an obstructive clinical picture and mosaicism on CT

scan similar to that seen in obliterative bronchiolitis but have a better overall prognosis and may be amenable to immunomodulating therapy.

Pulmonary nodules are usually an incidental finding on chest CT or, less frequently, open lung biopsy.²⁹ Nodule cavitation may result in hemoptysis or pneumothorax through the rupture of subpleural nodules. Caplan syndrome consists of nodules associated with coal miner's pneumoconiosis. Pleural disease is common in RA, and pleuritic pain occurs at some time in at least 20% of patients.

Dermatomyositis/polymyositis

The idiopathic inflammatory myopathies are a group of disorders characterized primarily by immune-mediated destruction and dysfunction of muscle; however, the disease frequently involves the skin, joints, cardiopulmonary system and lung, in the latter instance manifesting most notably as ILD. In some cases, rapidly progressive ILD may develop in patients with amyopathic dermatomyositis, and prognosis may correlate with the presence of anti-CADM-140/MDA5 antibody.³⁰ The most common variant of connective tissue disease-associated ILD is antisynthetase syndrome in which antibodies directed against Jo-1 (histidyl-transfer RNA [tRNA] synthetase) and other amino-acyl tRNA synthetases such as PL-12, PL-7, and others are associated with a clinical syndrome characterized by myositis, fever, Raynaud phenomenon, mechanic's hands, arthritis, and ILD.³¹

Although estimates of the overall incidence of ILD associated with inflammatory myopathy range from 5% to 45%, lung involvement is clearly more prevalent among patients possessing antisynthetase antibodies.³² Case series which included pathologic analysis have shown that ILD associated with antisynthetase syndrome encompasses a variety of histopathologic subtypes, including NSIP, COP, UIP, and DAD.^{33,34} As expected, response to therapy and overall prognosis largely reflect the underlying lung histologic characteristics. The predominance of NSIP in the majority of myositis-associated ILD case series may explain increased survival rates compared with more common idiopathic interstitial pneumonias like IPF.^{31,35}

Contrary to these data, recent evidence suggests that there is a subset of anti-Jo-1 antibody-positive individuals who have a rapidly progressive form of ILD that is reminiscent of the acute disease exacerbations observed in IPF patients.³⁶ Antiinflammatory and immunosuppressive therapy is likely to fail in these patients because of rapid disease progression, and therefore patients who are otherwise eligible should be referred early for lung transplant evaluation.

Systemic lupus erythematosus

Chest wall pain, costochondral pain, and pleurisy are common in SLE and often are part of the initial presenting symptoms, and clinically it may be difficult to distinguish between musculoskeletal and pleuritic pain. Pleurisy occurs in up to 50% of patients with SLE, but only a small percentage actually develop effusions, which typically are exudative with modestly low glucose concentration and complement levels.³⁷ Treatment is administered to symptomatic patients only and includes nonsteroidal antiinflammatory drugs (NSAIDs) in mild cases and corticosteroids in more severe cases.

Acute pneumonitis is a rare, poorly understood, but feared complication of SLE. It is characterized by fever, cough, dyspnea, and progressive hypoxemia. Sometimes, hemoptysis may be noted and chest radiographs show diffuse infiltrates and pleural effusions. Chest CT scans may show ground-glass opacities and consolidation. Biopsy specimens may show DAD with or without alveolar hemorrhage and capillaritis. The mortality associated with this syndrome is high, reported as 50% in one study of 12 patients.³⁸ Treatment includes high-dose steroids and consideration of additional immunosuppressive agents such as cyclophosphamide, although no controlled trials exist to guide therapy. In rare cases a more chronic ILD may develop in SLE, which may or may not occur following an acute pulmonary condition, and treatment considerations are similar to those noted earlier for ILD related to scleroderma.

Diffuse alveolar hemorrhage can occur in up to 4% of patients with SLE. It typically is found in a patient with known SLE who has dyspnea, cough, and often hemoptysis, although some patients have anemia and bilateral infiltrates without hemoptysis. In patients known to have SLE, one must consider underlying infection, pulmonary embolism, and capillaritis. Biopsy specimens may reveal bland hemorrhage, immune complex deposition, or capillaritis. Distinguishing this syndrome from acute pneumonitis can be difficult. Mortality can be high, and treatment involves the use of steroids, cyclophosphamide, and in some cases plasmapheresis.³⁹

Acute reversible hypoxemia can occur in patients with SLE who have unexplained hypoxemia and normal chest radiographs. Treatment with corticosteroids and aspirin can be effective.⁴⁰ Shrinking lung syndrome has

been noted in SLE and is characterized by dyspnea, pleuritic pain, and progressive decrease in lung volume. The syndrome should be considered in those patients with SLE who have dyspnea, clear chest radiographs, and elevated diaphragms. Pulmonary function tests may show an abnormal diffusion capacity that corrects for alveolar volume, and esophageal manometry may be useful to identify an abnormality in lung compliance. Corticosteroids, theophylline, and other immunosuppressive agents as well as pain control may be beneficial, although generally the disorder is self-limiting.⁴¹

Pulmonary hypertension occurs in a small but significant portion of patients with SLE. Mild to moderate disease may occur in up to 40% of patients.⁴² Recurrent thromboemboli also can result in pulmonary hypertension, especially in those with antiphospholipid antibody syndrome. Treatment of pulmonary hypertension in SLE is similar to that described for pulmonary hypertension in scleroderma. In some cases pulmonary hypertension in SLE may be due to pulmonary vasculitis as opposed to a plexogenic vasculopathy, and cyclophosphamide and rituximab may be useful therapeutic interventions.^{43,44}

Sjögren syndrome

Sjögren syndrome may have a variety of pulmonary manifestations, including bronchial and airway narrowing, ILD, cystic changes, and lymphoproliferative disease including, in rare cases, lymphoma.

Patients with Sjögren syndrome frequently complain of a dry cough and show evidence of hyperactive airways secondary to inflammatory infiltration of bronchial submucosa. ILD includes NSIP, UIP, COP, and LIP, with NSIP noted most frequently.⁴⁵ In certain cases, the distribution of lymphocytic infiltration is more localized to the bronchial tree, a condition known as *follicular bronchiolitis*.

Nodular lymphoid hyperplasia (pseudolymphoma) also may occur in Sjögren syndrome and is characterized by pulmonary nodules or infiltrates containing reactive lymphoid cells. On CT such lesions may be difficult to distinguish from B-cell lymphoma of the extranodal marginal zone B-cell type or more aggressive forms of non-Hodgkin lymphoma, and thus biopsy may be required.⁴⁶ Treatment options for ILD in Sjögren syndrome are similar to those for other forms of ILD and may also include B cell–deleting agents.

Drug-induced lung injury

A host of medications used in rheumatologic practice have been implicated in lung injury, most notably methotrexate (MTX). MTX lung toxicity usually presents within the first 1 to 2 years of treatment with the drug, and clinical manifestations can range from a cough to fulminant presentations with fever, progressive dyspnea, and life-threatening respiratory failure. Radiographs and CT scans may show diffuse or focal infiltrates, and pathologic findings include prominent lymphocytic infiltration, acute interstitial pneumonia, and sometimes COP. Although a chronic fibrotic lung reaction to MTX has been implicated, there is no clear evidence to support this interpretation, and many cases labeled as chronic MTX fibrotic disease probably represent progression of underlying ILD in patients with RA. Risk factors for MTX lung disease include older age, diabetes, hypoalbuminemia, and perhaps previous lung disease.⁴⁷ In patients with minimal underlying lung disease it is reasonable to consider using MTX, although with careful observation and monitoring.

Pneumonitis may occur in up to 1% of patients receiving leflunomide, and it may be more common in patients previously treated with methotrexate.⁴⁸ Other agents used in rheumatologic practice that may result in pulmonary toxicity include azathioprine, sulfasalazine, minocycline, NSAIDs, D-penicillamine, gold, and cyclophosphamide, rituximab, and adalimumab. In all cases of suspected drug-induced lung toxicity, treatment involves cessation of therapy in mild cases, consideration of underlying infection using bronchoscopy, bronchoalveolar lavage if needed, and use of corticosteroids in more severe cases.

The use of tumor necrosis factor (TNF)–modulating agents in patients with RA who have ILD is a matter of significant controversy. A number of case reports have noted progression of underlying ILD in patients given TNF inhibitors (mostly infliximab), and there have also been contrary reports

that ILD has either remained stable or actually improved in patients given TNF inhibitors, but comparison of a large cohort of RA-ILD patients receiving anti-TNF therapy with those receiving traditional disease-modifying antirheumatic drugs shows no difference in mortality.^{49–51} RA patients also may have a higher risk of bronchiectasis and in more severe cases are at higher risk of infectious complications. Therefore in RA patients with significant ILD or bronchiectasis, caution should be exercised in the use of TNF inhibitors.

Lung and vasculitic syndromes

Diffuse alveolar hemorrhage as a result of capillaritis is an important feature of various vasculitic syndromes, including antineutrophil cytoplasmic antibody (ANCA)–associated granulomatous vasculitis, microscopic polyangiitis, Goodpasture syndrome, SLE, and, in RA, rarely cryoglobulinemia and antiphospholipid antibody syndrome.⁵² Capillaritis may manifest clinically with hemoptysis, although there may be no clinical evidence of bleeding even on bronchoscopy. Capillaritis should be suspected in patients with respiratory symptoms, falling hematocrit, radiographic abnormalities including diffuse lung infiltrates and ground-glass opacities, and elevated diffusion capacity as the main clues to active bleeding in the lung. Lung biopsy may be helpful to distinguish pauci-immune disease associated with ANCA from immune complex– and complement-mediated diseases seen in SLE or anti-glomerular basement membrane disease seen in Goodpasture syndrome, although tissue is often more accessible from the kidney or other sources with less morbidity. Fibrosis and airflow obstruction as a result of chronic inflammation have been noted in ANCA-associated lung disease.^{53,54} Treatment involves administration of high-dose corticosteroids, cyclophosphamide, rituximab, or other immunomodulating agents and consideration in severe cases of plasmapheresis, especially in Goodpasture syndrome, although its usefulness in ANCA-associated pulmonary hemorrhage syndromes is uncertain.

TREATMENT OF INTERSTITIAL LUNG DISEASE ASSOCIATED WITH THE RHEUMATIC DISEASES

Except for ILD in scleroderma, there are no prospective, randomized trials examining the treatment of ILD in the rheumatic diseases. Therapeutic choices for ILD associated with the rheumatic diseases have therefore been extrapolated from the scleroderma experience, which may not be appropriate given the varied histopathologic patterns and natural history of lung disease in the different rheumatic disorders. In patients with active clinical symptoms and evidence of inflammatory disease or a mix of inflammatory and fibrotic disease on CT scans and/or cellular NSIP on lung biopsy specimens, a trial of antiinflammatory therapy with high-dose steroids and a second agent such as cyclophosphamide, mycophenolate mofetil, azathioprine, or a calcineurin inhibitor is a reasonable option. In severe disease, a 6- to 12-month course of cyclophosphamide followed by transition to a second agent such as mycophenolate mofetil or azathioprine is a reasonable clinical approach. In patients with predominantly fibrotic ILD, no clear therapeutic regimen can be recommended, although agents such as mycophenolate mofetil, pirfenidone, N-acetylcysteine, or other emerging agents that may have antifibrotic effects may prove beneficial.^{15,55–57} Emerging T and B cell–based and anticytokine therapies (e.g., those used in RA) may have a beneficial effect on coexisting lung disease. In patients who are treated, prophylaxis for *Pneumocystis jiroveci* pneumonia should be strongly considered, and immunization against influenza and pneumococcal pneumonia is strongly recommended. Finally, early referral for lung transplant evaluation should be considered in patients with progressive disease or poor response to therapy and good performance status.

In summary, great challenges still exist in our understanding of the natural history and treatment of ILD and other pulmonary manifestations in the rheumatic diseases. Expertise in capillary microscopy, elicitation of subtle clues on clinical examination, and interpretation of sophisticated immunologic testing are of great importance in establishing the appropriate diagnosis and tailoring treatment. Working in close collaboration with pulmonologists, radiologists, and pathologists, rheumatologists have much to offer to this most challenging group of patients.

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37

Gastrointestinal tract and rheumatic disease

■ MATILDA HAGAN ■ RAYMOND CROSS

- Joint disease is a common complication of gastrointestinal diseases. The exact pathogenesis of these disorders is unclear.
- The arthritides associated with gastrointestinal disorders can be highly variable, including axial, peripheral, pauciarticular, or polyarticular arthritis.
- Inflammatory bowel diseases, particularly Crohn disease and ulcerative colitis, are often complicated by the development of peripheral or axial arthritis.
- Arthritides associated with gastrointestinal infections are often self-limited and rarely result in chronic symptoms.
- Treatment of the underlying gastrointestinal disorder often results in resolution of the associated arthritis.

INTRODUCTION

Gastrointestinal illnesses are associated with extraintestinal manifestations of disease. It is not known why extraintestinal complications of disease occur; however, since many of these complications are seen in patients with active gastrointestinal inflammation, it has been postulated that increased intestinal permeability resulting from the underlying inflammatory process allows luminal antigens to be presented to the systemic immune system. Alternatively, because many inflammatory gastrointestinal illnesses cause a systemic inflammatory response, it is possible that the joint and other sites are innocent bystanders in the inflammatory process. Recent evidence has linked adhesion molecules, vascular adhesion protein-1, and T cells bearing β_7 integrin to joint synovial fluid,¹ which provides a direct link between intestinal and joint inflammation. Gastrointestinal diseases that have been linked to inflammatory arthritis include but are not limited to inflammatory bowel disease (comprised of ulcerative colitis and Crohn disease), celiac disease, bacterial enteritis, Whipple disease, vasculitides affecting the gastrointestinal tract such as polyarteritis nodosa, Henoch-Schönlein purpura, Behçet syndrome, and microscopic colitis.

INFLAMMATORY BOWEL DISEASE: CROHN DISEASE AND ULCERATIVE COLITIS

Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn disease (CD), is a chronic inflammatory condition of the intestines typically affecting young adults. The cause of IBD is unknown. However, a combination of a genetic predisposition, dysregulated immune system, and environmental antigens play a role in the development of IBD. CD and UC are usually easily distinguished from each other by clinical symptoms, endoscopic findings, and histologic characteristics. However, in approximately 15% of cases, differentiation between CD and UC is difficult. These patients are classified as having IBD type undetermined or indeterminate colitis. The extraintestinal manifestations, treatment options, and prognoses differ by disease.

UC usually presents with bloody diarrhea. UC is seen more often in nonsmokers and former smokers than in active smokers. The onset of bloody diarrhea after a patient has quit smoking is consistent with the diagnosis of UC until proven otherwise. The extent of colonic involvement determines the UC patient phenotype. UC phenotype is typically broken down into three groups: inflammation limited to the rectum (ulcerative proctitis), inflammation limited to the left colon (left-sided colitis), and

inflammation proximal to the splenic flexure (extensive colitis or pancolitis). The amount of colonic involvement is important, because patients with pancolitis are more likely to be treated with steroids, become hospitalized for UC, undergo colectomy, and develop colorectal cancer.^{2,3} Patients with UC have disease limited to the colon only; endoscopic examination reveals inflammation beginning at the anal verge and extending proximally in a continuous fashion. The inflammatory process tends to be more superficial in UC than in CD. Decreased anatomic markings, friability, and erosions are endoscopic hallmarks of the disease (Fig. 37.1). Patients with severe disease can have large or confluent ulcerations that make differentiation from CD difficult. Small bowel involvement does not occur except in patients with pancolitis who have “backwash ileitis” (inflammation in the distal 5 cm of terminal ileum). Skip lesions should not be seen; however, once patients undergo medical therapy, the inflammation can appear patchy. Biopsy specimens typically reveal both acute and chronic inflammation; active colitis is defined by the presence of neutrophils in the crypts (cryptitis and crypt abscess), whereas chronicity is established by expansion of the basal surface with plasma cells and lymphocytes, with distortion of the architecture (Fig. 37.2).

CD can affect any location in the gastrointestinal tract from the mouth to the anus. The terminal ileum is the most commonly affected site. CD is distinguished from UC by the presence of small bowel involvement, development of strictures and/or fistulas, endoscopic appearance, and histopathologic findings (Table 37.1). Symptoms of CD are heterogeneous and depend on the patient's phenotype.⁴ Patients with *inflammatory* CD usually have nonbloody diarrhea and crampy lower abdominal pain. Systemic symptoms may or may not be present. Patients with *obstructing* CD usually have intermittent abdominal pain, bloating, borborygmi, and obstipation. The symptoms are usually exacerbated by eating. Nausea and emesis can be seen as the strictures become more severe. The diarrhea associated with obstructive CD usually occurs after an episode of pain and is associated with relief of symptoms (post-obstructive diarrhea). Patients with *penetrating* CD have fistulas from a segment of bowel to adjacent organs or to another loop of intestine. Sinus tracts or severe transmural inflammation can result in intraabdominal abscess formation. Some 20% to 40% of patients develop perianal fistulas with or without abscess.⁵⁻⁷ This complication results in perianal pain and drainage from the fistula sites. Fistulas coupled with abscess are often associated with severe pain and systemic symptoms. The endoscopic appearance of the bowel in CD usually allows it to be easily distinguished from UC. Rectal involvement is less common, and patients typically have skip lesions with areas of normal intervening mucosa. The ulcerations seen in CD are typically large and deep and can be serpiginous (Fig. 37.3). The earliest lesions in CD are aphthous ulcers similar to those seen in the oral mucosa. On histopathologic examination, an acute and chronic inflammatory process is seen as in patients with UC; however, surgical specimens can reveal transmural inflammation and transmural lymphoid aggregates. Mucosal biopsy samples reveal pathognomonic noncaseating granulomas in 30% to 50% of patients (Fig. 37.4).⁸ Small bowel imaging can demonstrate ulcerations, stricture, or fistula in the small bowel.

Extraintestinal manifestations of inflammatory bowel disease

Extraintestinal manifestations associated with CD and UC are common, occurring in 20% to 30% of patients.^{7,9} Although joint manifestations are the most frequent,¹⁰ the oral cavity, eyes, skin, bone, kidneys, and biliary tract can also be involved. The incidence of extraintestinal manifestations differs for CD and UC, and the presentation of extraintestinal symptoms varies depending on onset, site, and activity of the bowel disease. With regard to extent of the disease, widespread bowel involvement is associated

with greater odds of developing extraintestinal manifestations than more limited bowel disease. Patients with extensive UC experience extraintestinal manifestations 22% of the time, whereas patients with left-sided colitis and proctitis have extraintestinal symptoms 12% and 5% of the time, respectively.¹¹ Likewise, patients with ileocolonic CD have extraintestinal manifestations 37% of the time compared with 25% of the time in patients with isolated ileal disease.¹² Some extraintestinal manifestations such as large joint monoarticular arthritis tend to occur when the bowel disease is active, whereas others such as small joint symmetrical arthritis occur before diagnosis or when the disease is quiescent. Some trends in gender differences and age at presentation are seen for certain extraintestinal manifestations. Women are more likely to have erythema nodosum and ocular manifestations, whereas men are more likely to have primary sclerosing cholangitis and ankylosing spondylitis¹³ (Table 37.2).



Fig. 37.1 Endoscopic view of a section of colon in a patient with ulcerative colitis. The entire visualized mucosa is affected in a continuous fashion with loss of the normal vascular markings and light reflex. The mucosa is erythematous, friable, and ulcerated.

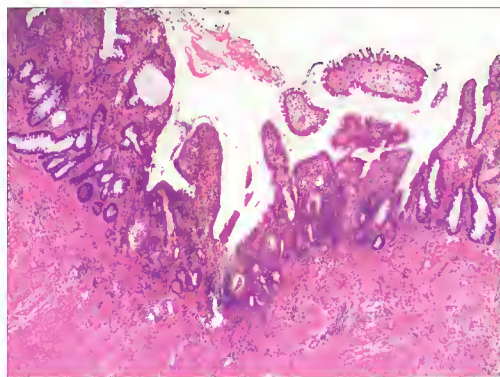


Fig. 37.2 Section of colon showing classic features of active chronic disease, including marked architectural distortion (crypt branching, crypt atrophy, crypt dropout) as well as expansion of the lamina propria by lymphoplasmacytic infiltrate and focal crypt abscesses (40x). (Courtesy Harris Yfantis, MD.)

Peripheral arthritis associated with inflammatory bowel disease

Peripheral arthritis, both polyarticular and pauciarticular, is estimated to occur in 10% to 20% of patients with IBD, with a higher prevalence of peripheral arthritis in CD than in UC.^{16,17} Recent studies have suggested several causes of IBD-associated peripheral arthritis. HLA-DR103 and HLA-B*27 have been associated with pauciarticular arthritis and HLA-B44 has been associated with polyarticular arthritis. Increased gut permeability to bacterial antigens may result in the induction of articular symptoms, primarily pauciarticular arthritis.¹⁷ IBD-related peripheral arthritis is diagnosed clinically, since radiographic findings often are normal and show no signs of joint erosion or deformity. Pauciarticular arthritis is more common than polyarticular arthritis in IBD.¹⁷ Men and women are affected equally. Pauciarticular arthritis, also known as *type I arthropathy*, involves four or fewer joints and tends to be acute and self-limited, commonly affecting large joints such as the knees, wrists, and ankles. Its presentation coincides with active disease, and it often emerges upon relapses of IBD. The duration



Fig. 37.3 Endoscopic view of the ileum in a patient with Crohn disease. Deep linear and serpiginous ulcers with intervening edematous mucosa are present (cobblestoning).

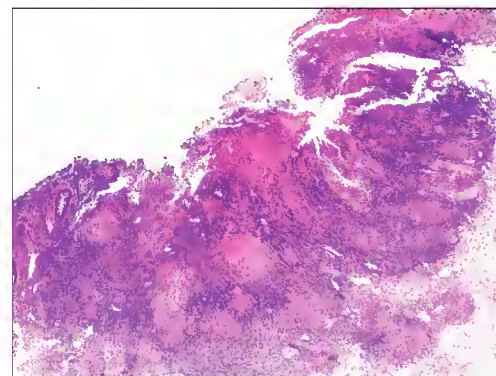


Fig. 37.4 Section of colon showing multiple epithelioid granulomas with surrounding chronic inflammation (40x). (Courtesy Harris Yfantis, MD.)

TABLE 37.1

Crohn disease and ulcerative colitis

	Symptoms/characteristics	Gastrointestinal involvement	Endoscopic findings	Pathologic features
Crohn disease	Abdominal pain, nonbloody diarrhea, perianal and internal fistulas Active smoking influences disease	Can involve intestine from mouth to anus	Skip lesions, serpiginous or deep ulcerations, strictures, fistulas, small bowel involvement	Transmural inflammation, noncaseating granulomas, skip lesions
Ulcerative colitis	Bloody diarrhea, tenesmus More common in nonsmokers and former smokers	Involves colon only	Superficial erosions or smaller ulcerations, continuous involvement from rectum to proximal colon	Continuous histologic inflammation from rectum to proximal colon

TABLE 37.2

Extraintestinal manifestations of disease in patients with inflammatory bowel disease

Manifestation	Description	Epidemiology	Correlation with active bowel disease	Treatment
Erythema nodosum	Painful, tender, raised, red nodules, often found on the anterior lower legs	1%-9% UC 6%-15% CD 5:1 female-male	90% associated with active bowel disease	Resolves with treatment of active bowel disease
Pyoderma gangrenosum	Ulcers on lower limbs, trunk, and adjacent to surgical stomas	0.5%-2% IBD	Not associated with active bowel disease ⁸	Immunosuppressive therapy; occasionally shows spontaneous resolution
Aphthous ulcers	Oral ulcerations in buccal mucosa	20%-30% CD	Associated with active bowel disease Associated with ocular and articular symptoms	Resolve with treatment of active bowel disease ¹²
Uveitis	Eye pain, redness, loss of visual acuity, floaters	3:1 female-male ¹⁵	Anterior uveitis: 30% associated with erythema nodosum Posterior uveitis: 90% associated with arthritis, particularly ankylosing spondylitis ¹⁵	Topical corticosteroids; systemic immune suppressants for severe cases
Episcleritis	Eye redness, irritation, and watering	5%-8% IBD 3:1 female-male	Associated with active bowel disease	Resolves with treatment of active bowel disease or topical corticosteroid therapy
Primary sclerosing cholangitis	Recurrent biliary sepsis, abdominal pain, pruritus, complications of portal hypertension and end-stage liver disease	3%-5% UC ¹³ Male preponderance	Not associated with active bowel symptoms; associated with colorectal cancer	Supportive therapy, management of complications of disease

CD, Crohn disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.
Additional data from Reference 14.

of arthritis can be up to 10 weeks, with a mean of 5 weeks; however, 10% to 20% of patients with pauciarticular arthritis will develop persistent joint symptoms. Pauciarticular arthritis is associated with an increased risk of other extraintestinal manifestations such as erythema nodosum and uveitis (see Table 37.1).

Polyarticular arthritis, also known as *type II arthropathy*, involves five or more joints and commonly affects the small joints in the hand, particularly the metacarpophalangeal joints.¹⁷ Its presentation is independent from the activity of the disease.¹⁸ In fact, polyarticular arthritis can occur before the diagnosis of IBD. The presentation can be insidious with symptoms lasting for years, with a mean duration of 3 years. Polyarticular arthritis is associated with uveitis (see Table 37.1).

Axial arthritis associated with inflammatory bowel disease

Sacroiliitis occurs in 4% to 32% of patients with IBD.^{16,19} The varying incidences can be explained by differences in whether the diagnosis is made based on clinical symptoms, plain radiographs, or cross-sectional CT images (Fig. 37.5). Patients typically have stiffness and/or pain in the buttocks that is worse in the morning or after rest. The symptoms commonly improve with exercise. Initial plain radiographs show unilateral or bilateral iliac erosion, followed by fusion of the sacroiliac joint from chronic inflammation. Sacroiliitis occurs more commonly in patients with CD than in patients with UC.²⁰ Patients with CD-related sacroiliitis are more likely to develop peripheral arthritis.²¹

IBD-associated ankylosing spondylitis manifests identically to idiopathic ankylosing spondylitis and is estimated to occur in 4% to 10% of IBD patients.^{22,23} A higher prevalence of 6% is seen in patients with CD compared with 2.6% in patients with UC.²⁴ However, it has been theorized that this number would be larger if all patients with ankylosing spondylitis were assessed for IBD.²⁵ One study found a 55% prevalence rate of any IBD-associated serologic marker, such as perinuclear antineutrophil cytoplasmic antibody (p-ANCA), antibodies to the cell wall mannan of *Saccharomyces cerevisiae* (ASCA), or antibodies to porin protein C of *Escherichia coli* (OmpC), in patients with ankylosing spondylitis who had no clinical signs or symptoms of IBD. It has been suggested that detection of p-ANCA in patients with ankylosing spondylitis should be an indicator for further evaluation given the high frequency of p-ANCA in patients with ankylosing spondylitis who also have UC.²⁶ Males and females are equally affected.

IBD-related ankylosing spondylitis has a strong genetic component, with a high correlation with the HLA-B27 antigen. More recently, CD and ankylosing spondylitis have been associated with interleukin 23 receptor variants

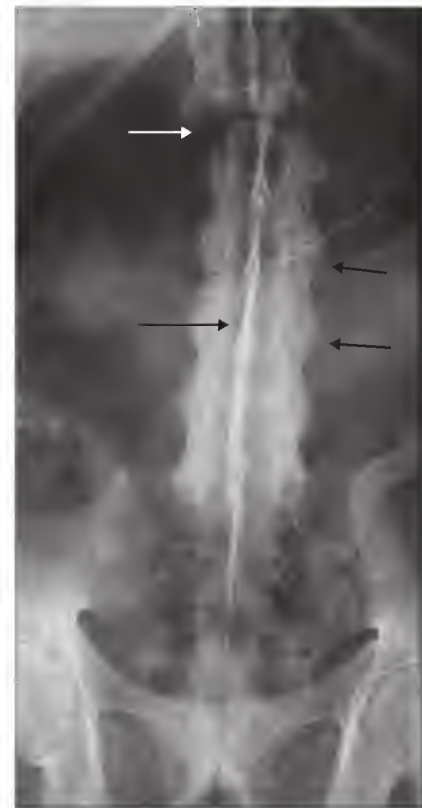


Fig. 37.5 Frontal radiograph of the lumbar spine shows fine bridging bone (syndesmophytes) across the intervertebral disk space (short black arrows) as well as ossification of the posterior interspinous ligaments (long black arrow). This results in a bamboo spine, which predisposes to spinal fractures (white arrow). The sacroiliac joints are fused. (Courtesy Jade Wong, MD.)

and the major histocompatibility complex.²⁷⁻²⁹ Symptoms of ankylosing spondylitis may include thoracic or lumbar pain, alternating buttock pain or chest pain, and morning stiffness of the spine and thorax. The spinal vertebrae of the lumbar, thoracic, and cervical regions may fuse, forming a so-called bamboo spine that limits mobility, causes changes in posture, and

TABLE 37.3

Organisms associated with reactive arthritis

<i>Campylobacter jejuni</i>	<i>Clostridium difficile</i>
<i>Yersinia enterocolitica</i>	<i>Chlamydia trachomatis</i>
<i>Yersinia pseudotuberculosis</i>	<i>Salmonella typhimurium</i>
<i>Shigella flexneri</i>	<i>Salmonella enteritidis</i>
<i>Shigella dysenteriae</i>	

leads to a loss of flexibility. The spine can easily fracture in response to minor trauma (see Fig. 37.5). Radiographically, formation of characteristic syndesmophytes between the vertebral bodies is seen, as the annulus fibrosis gradually ossifies. Axial arthritic symptoms manifest several years before active IBD is detected, and the arthritic disorder is considered independent in its disease course from the underlying bowel disease.

Arthralgias without frank arthritis occur in 14% of CD patients compared with 5% of UC patients.¹⁵ Polyarticular involvement is more prevalent than monoarticular or oligoarticular involvement.²⁷ Arthralgias can affect any joint, and their presentation coincides with active disease and emerges upon relapses of IBD. The only exception is in the case of arthralgias associated with steroid withdrawal (pseudorheumatism or steroid withdrawal syndrome). In this clinical situation, joint pain coincides with steroid withdrawal, requiring escalation of the corticosteroid dosage.

BACTERIAL ENTERITIS

Bacterial enteritis refers to infection and inflammation of the intestines caused by infection with a variety of bacterial pathogens, including *Campylobacter jejuni*, *Clostridium difficile*, *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Shigella*, and *Salmonella* (Table 37.3). Symptoms related to bacterial enteritides usually present acutely and include nonbloody or bloody diarrhea, abdominal cramping, and systemic symptoms. Patient history is important in determining the causative bacteria. Benefits of empiric antibiotic treatment are dubious in healthy adults; further, antibacterial treatment can precipitate hemolytic-uremic syndrome in patients with enterohemorrhagic *E. coli* infection.

Approximately a quarter to a third of patients with bacterial enteritis develop reactive arthritis,³⁰ usually within a few days to a few weeks after infection.³¹ In the majority of patients, the arthritis involves multiple large joints and is migratory. The arthritis tends to be asymmetric and usually affects the lower extremities more than the upper extremities. In addition, patients can develop an enthesitis or sacroiliitis. The arthritis is usually self-limiting, lasting a week to several months³²; however a chronic, relapsing arthritis occurs in a minority of patients.³³ The presence of HLA-B27 is associated with an increased likelihood of developing reactive arthritis, an increase in its severity, and likelihood of chronicity.²⁶ Additionally, a *Y. pseudotuberculosis* O:3 infection is associated with increased risk of arthritis.^{34,35} Treatment of the underlying bacterial enteritis with antibiotics does not hasten resolution of the joint symptoms.^{36,37}

CELIAC DISEASE

Celiac disease is a chronic inflammatory condition of the proximal small intestine resulting from exposure to gluten in a genetically predisposed host. It is perhaps the only autoimmune disease in which the environmental precipitant is known.³⁸ Celiac disease occurs primarily in whites of Northern European descent, with a prevalence in North America of 1 in every 133 people.³⁹ However, the prevalence may be underestimated, because a significant proportion of patients are either undiagnosed or asymptomatic. Two times more adult women than men are affected, but the difference diminishes after age 65.⁴⁰ The disease is associated with HLA class II alleles DQA1*0501 and DQB1*0201.⁴¹ Ingestion of gluten, a storage protein in wheat, and similar proteins in barley and rye leads to an inappropriate T cell–mediated inflammatory response through activation of both the innate and adaptive immune systems, causing damage to the small intestine and eventual destruction of the intestinal villi. Destruction of the villi results in a malabsorption syndrome. Symptoms of celiac disease include chronic nonbloody diarrhea, weight loss, abdominal bloating and distention, and overall failure to thrive.⁴² In adults, the presentation can be more protean. The most common clinical presentation in adults is iron-deficiency anemia.⁴³

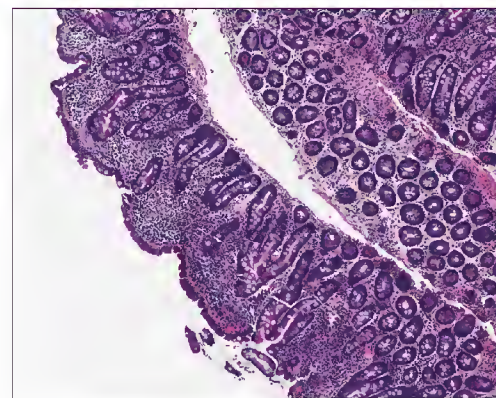


Fig. 37.6 Duodenal mucosa showing marked villous blunting and crypt elongation. There is intraepithelial lymphocytosis, and the lamina propria is expanded by increased numbers of lymphocytes and plasma cells (4×). (Courtesy William Twaddell, MD.)

Celiac disease is diagnosed by biopsy of the small intestine, which reveals increased lymphocytes, crypt hyperplasia, and varying degrees of villous atrophy (Fig. 37.6). The treatment for celiac disease is a gluten-free diet, which almost always leads to resolution of symptoms. Celiac disease is associated with a variety of extraintestinal manifestations, including aphthous ulcers, dermatitis herpetiformis, and development of reactive arthritides.⁴⁴

Celiac disease–associated arthritis can be peripheral, axial, or both⁴⁵ and commonly affects the lumbar spine, hips, and knees.⁴⁶ The joint symptoms often precede the diagnosis of celiac disease. Treatment with a gluten-free diet not only improves the intestinal symptoms and anemia but has been shown to decrease the duration of joint symptoms resulting in resolution of the arthritis within 6 months.⁴⁶

WHIPPLE DISEASE

Whipple disease is a rare, chronic systemic infection caused by the actinomycete *Tropheryma whippelii*. Approximately 12 new cases are diagnosed annually around the world,⁴⁷ occurring predominantly in white males between 40 and 60 years of age.⁴⁸ *T. whippelii* is thought to cause chronic infection by evading the immune system. Similarly, there may be a correlation between Whipple disease and defective ability of the host to clear the bacteria.^{48,49} Patients with Whipple disease typically have diarrhea secondary to fat malabsorption (steatorrhea), weight loss, fever of unknown origin, and arthritis. Neurologic symptoms are present in a minority of cases. Whipple disease is diagnosed by biopsy of the small intestinal mucosa, which reveals lymphatic dilation with macrophages that stain positive with periodic acid–Schiff stain and contain gram-positive, non-acid-fast bacilli in the lamina propria. Whipple disease is treated successfully with long-term administration of antibiotics, such as an initial 2-week course of an intravenous antibiotic like ceftriaxone or meropenem followed by at least a 1-year course of an oral antibiotic such as trimethoprim/sulfamethoxazole.⁵⁰ Relapses are common.

Arthritis is estimated to occur in 65% to 90% of cases of Whipple disease, with approximately 25% of patients showing axial involvement, either sacroiliitis or spondylitis.⁵¹ Large joints are more commonly affected than small joints. The arthritis is migratory, and the same joint is not always affected multiple times. Joint destruction does not occur. Joint involvement tends to occur several years before development of other clinical signs of the disease, and the duration of involvement is transient, spanning from hours to days.⁵² Treatment of Whipple disease with antibiotics also results in resolution of joint symptoms.

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is a necrotizing vasculitis that affects predominantly medium-sized but also small arteries (Fig. 37.7) (see Chapter 155). There is no known cause of this vasculitis, although numerous infectious agents have been implicated in the pathogenesis. For example, PAN develops within the first 6 months of a hepatitis B virus infection as a result of immune complex formation.⁵³ PAN has also been associated with hepatitis C virus infection.⁵⁴ PAN causes transmural inflammation of blood vessels



Fig. 37.7 Frontal view obtained during mesenteric arteriography in a patient with polyarteritis nodosa who experienced a gastrointestinal bleed from a gastroduodenal artery aneurysm, which was embolized. There are microaneurysms in the branches of the superior mesenteric artery (large arrows) and areas of saccular vessel dilatation (small arrows). (Courtesy Jade Wong, MD.)

leading to fibrinoid necrosis and formation of cutaneous nodules along superficial arteries. PAN can manifest systemically with involvement of multiple organs, including the gastrointestinal tract, kidneys, joints, brain, skin, and heart. Patients often have systemic constitutional symptoms such as fever, fatigue, weight loss, arthralgias, and myalgias. The diagnosis is made clinically, with biopsy of an accessible lesion performed for confirmation. In most patients with PAN, results of ANCA serologic testing usually are negative.⁵⁵ Gastrointestinal symptoms usually affect the small intestine, manifesting in approximately 50% of patients with PAN.⁵⁶ The symptoms are highly variable, from postprandial periumbilical pain to nausea and vomiting secondary to bowel infarction and perforation. PAN is treated with systemic steroids and immunosuppressive drugs.

Joint disease can also result from PAN, with joint involvement more extensive the longer PAN is present. It is estimated that 30% of patients with PAN have arthralgias or arthritis at presentation.⁵³ Males tend to experience articular symptoms almost twice as frequently as women. The systemic manifestations of PAN, including joint symptoms, often resolve with treatment of PAN.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is an immunoglobulin A-mediated small vessel necrotizing vasculitis that is also characterized by fibrinoid destruction of blood vessels (see Chapter 161). HSP is the most common vasculitis of childhood, seen predominantly in children between the ages of 3 and 10 years following a streptococcal upper respiratory tract infection.⁵⁷ However, the disease occasionally manifests in adults, and the course is often more severe than the course in children. Males are nearly twice as likely to be affected as females.⁵⁸ HSP often presents with a tetrad of symptoms including nonthrombocytopenic palpable purpura around the buttocks and lower extremities, arthritis or arthralgias, abdominal pain, and renal disease, most commonly hematuria with or without proteinuria.⁵⁸ Any of the four major symptom complexes can be the initial presenting feature. Moreover, the classic tetrad of symptoms is not seen in each case. Diagnosis is usually based on clinical symptoms, but if there is any doubt, a skin biopsy can be performed to confirm the diagnosis. Since HSP is self-limiting in 50% of patients, some argue that supportive care is the only indicated therapy, whereas others contend that medical treatment with corticosteroids and immunosuppressants improves renal outcomes in patients with HSP.^{59,60}

The joint symptoms are the second most common manifestation of HSP, occurring in approximately 70% of patients,⁶¹ with a higher frequency in adult-onset HSP.⁶² In 25% of patients, the arthritis precedes the purpura by approximately 1 week.⁶³ The symptoms are transient and nondeforming, and vary from mild arthralgias to debilitating arthritis; however, inflammatory arthritis is more commonly seen than arthralgias alone. Larger joints

TABLE 37.4

Common medications associated with microscopic colitis

Nonsteroidal antiinflammatory drugs ^{67-72,85}	Esomeprazole ⁸⁰
Simvastatin ^{72,75}	Ticlopidine ^{78,86}
Lansoprazole ⁸¹	Flutamide ⁷⁸
Omeprazole ^{75,80}	Sertraline ⁷⁸
Ranitidine ⁷⁸	Acarbose ⁷⁸

such as the ankles, knees, and wrists are more frequently affected. In one series, there was uniform involvement of the lower extremity joints, knees, ankles, and feet in all participants.⁵⁷ Retrospective studies have shown that HSP-associated arthritis is effectively relieved with corticosteroids.⁶³

BEHÇET SYNDROME

Behçet syndrome is a rare, chronic, multisystemic vasculitis involving small, medium, and large vessels of both the arterial and venous circulations, with a particular predilection for blood vessels in the oral and genital mucosa (see Chapter 159). Behçet syndrome is most frequently seen in the Middle East, Far East, and Mediterranean in patients 25 to 35 years of age. In a U.S. population-based study the estimated incidence was 0.38 per 100,000 population.⁶⁴ There is no known cause of this syndrome, but hypotheses include autoimmune effects, immune circulating complexes, and chemical agents.⁶⁵ Behçet syndrome has been associated with the HLA-B51/B5 risk allele.⁶⁶ A meta-analysis showed that carriage of the HLA-B51/B5 allele was associated with a 7% to 13% increase in the prevalence of genital, skin, and ocular involvement and a 30% relative risk reduction of gastrointestinal involvement.⁶⁷ Behçet syndrome is characterized by recurring and remitting symptoms that include oral aphthous ulcers, genital ulcers, and uveitis, as well as associated skin, joint, gastrointestinal, cardiac, and neurologic manifestations. Surgical resection of an aneurysm resulting from Behçet syndrome-mediated destruction is necessary in 10% of patients. Currently, there is not a specific diagnostic test for Behçet syndrome; diagnosis is based on clinical findings and recurrence of the disease over time. Treatments are customized to each patient's clinical symptoms and may include glucocorticoids, colchicine, 5-aminosalicylates, thalidomide, azathioprine, cyclophosphamide, and infliximab.^{68,69}

Joint manifestations occur in approximately 57% to 75% of patients with Behçet syndrome and are the presenting symptoms in 11% to 18% of cases.^{68,70} Large joints such as the knees and ankles are most commonly affected. Polyarthritis involving large and small joints occurs in 17% of cases, whereas monoarthritis and oligoarthritis occur in 11% and 16% of cases, respectively. The arthritis is self-limiting after a few weeks and does not cause permanent damage.

MICROSCOPIC COLITIS

Microscopic colitis, comprising collagenous colitis (CC) and lymphocytic colitis (LC), is characterized by chronic watery diarrhea. CC primarily affects older women at around 65 years of age; women are seven times more likely to be affected than men.⁷¹ LC affects middle-aged women, but the female-male ratio is lower, 2-3:1. In recent years the incidence of microscopic colitis appears to be increasing. Although the exact reason for the increase is unknown, current theories include increased clinical recognition of the disease through routine performance of random colonic biopsies in patients with chronic diarrhea and likely higher use of medications associated with microscopic colitis.⁷²⁻⁸¹ See Table 37.4 for a list of common medications associated with microscopic colitis.

The cause of microscopic colitis is unknown and is thought to be multifactorial, with the disease occurring in individuals who are susceptible to certain noxious luminal agents that result in microscopic mucosal inflammation. Clinically, CC and LC are indistinguishable from each other, causing chronic nonbloody, watery diarrhea that may be associated with diffuse abdominal pain and significant weight loss. Approximately 40% of patients with microscopic colitis have another associated autoimmune condition, most commonly a thyroid disorder, celiac disease, diabetes mellitus, or rheumatoid arthritis.⁷¹ Microscopic colitis is differentiated based on colonic mucosal biopsy of the colon and rectum; the endoscopic findings in both CC and LC are normal.⁸² CC manifests as excess subepithelial collagen

deposition with chronic mononuclear inflammation in the lamina propria, whereas LC causes increased intraepithelial lymphocytes but the collagen layer is normal. There are no known long-term complications of the disease or increased risk of colorectal cancer. Microscopic colitis is treated with antidiarrheals, bismuth subsalicylate, 5-aminosalicylates, budesonide, or corticosteroids with varying successes. Surgery rarely is indicated.

Articular symptoms accompany CC in rare cases, occurring in up to 7% of patients.⁸³ The arthritis is transient, nonerosive, and oligoarticular. Peripheral joints, including the metacarpophalangeal, proximal interphalangeal and wrist joints, are most commonly affected. The arthritis resolves upon treatment of the CC.⁸⁴

CONCLUSION

Extraintestinal involvement, particularly of the joints, is relatively common in patients with gastrointestinal disease. The cause of joint involvement is

not known but may relate to increased antigen presentation to the immune system secondary to increased gut permeability or the action of systemic cytokines on the joints. The list of gastrointestinal illnesses that affect the joints is extensive. The presentation of arthritis is highly variable, and arthritis (1) may affect the peripheral or axial joints; (2) may involve one, few, or many joints; and (3) may or may not be correlated with specific features of the underlying gastrointestinal symptoms. Most of the arthritides do not result in progressive joint destruction; improvement in the joint symptoms often coincides with treatment of the underlying disorder. The prognosis for many of these forms of arthritis is excellent. Internists, gastroenterologists, and rheumatologists need to be aware of the relationship between joint symptoms and gastrointestinal disease to improve accuracy of diagnosis and enhance clinical outcomes.

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38

The kidney and rheumatic disease

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- Because kidney disease is frequently asymptomatic, routine testing is imperative.
- Many drugs used in rheumatology are potentially nephrotoxic.
- Patients with kidney disease experience distinctive joint and soft tissue complications.

INTRODUCTION

The kidneys are involved in many homeostatic functions, including maintenance of acid-base balance, electrolyte concentrations, and osmolarity; excretion of toxins and metabolic wastes; and elaboration of certain hormones, including erythropoietin, 1,25-dihydroxycalciferol, and renin. Unlike rheumatologic diseases, the signs and symptoms of kidney disease tend to not be obvious physical findings until late in the course of disease, so routine screening for renal manifestations is essential for preservation of renal function. [Table 38.1](#) presents a list of the renal syndromes that occur in persons with rheumatic diseases.

The functional unit of the kidney is the nephron, which consists of a glomerulus followed by a long network of tubules. The glomerulus has a somewhat unusual anatomy in that its capillary bed is sandwiched between two arteries. This explains why glomerulonephritis (GN) is a frequent manifestation of systemic vasculitides such as systemic lupus erythematosus (SLE), Henoch-Schönlein purpura, Churg-Strauss syndrome, microscopic polyangiitis, antineutrophilic cytoplasmic antibody (ANCA)-associated granulomatous vasculitis, and cryoglobulinemic vasculitis.

Manifestations of renal disease**Proteinuria**

Proteinuria usually reflects an increase in the permeability of the glomerular barrier to normally nonfiltered molecules, such as albumin. When proteinuria is severe, it is usually manifested as diffuse peripheral edema. However, if the proteinuria is of a lesser degree, it may not be associated with any symptoms or signs and is often detected only on urinalysis.

Heavy proteinuria is highly suggestive of a “hole” in the filter of the kidney (i.e., a glomerular lesion) and is classified as nephrotic syndrome. This syndrome is characterized by (1) nephrotic-range proteinuria, defined as 3.5 g/day/1.73 m² or greater; (2) hypoalbuminemia; (3) hypercholesterolemia; (4) edema; and (5) lipiduria. Nephrotic-range proteinuria is almost always due to a glomerular pathologic process inasmuch as tubulointerstitial kidney disease will result in a more modest degree of protein spillage.

Nephrotic syndrome is associated with a hypercoagulable state, which may be manifested clinically as stroke, deep venous thrombosis, or renal vein thrombosis. In patients with nephrotic syndrome, one must maintain a high index of suspicion for renal vein thrombosis because it is infrequently manifested as the classic triad of flank pain, overt hematuria, and worsening kidney function. Patients with SLE and nephrotic syndrome who have experienced previous episodes of thrombophlebitis are particularly at risk for renal vein thrombosis.

Hematuria

Hematuria is usually asymptomatic and not visible to the naked eye (i.e., microscopic hematuria). Therefore, it often goes unnoticed until a urinalysis is performed. Macroscopic or “gross” hematuria is suspected when the urine is red, brown, or tea colored. As with microscopic hematuria, macroscopic hematuria tends to be asymptomatic. Both microscopic and macroscopic

hematuria is seen in rheumatologic disorders as a feature of renal vasculitis or acute GN. However, hematuria is more frequently due to nephrolithiasis, urinary tract infection, trauma, prostatitis, genitourinary cancer, or benign prostatic hypertrophy ([Box 38.1](#)). Because the most common manifestation of genitourinary cancer is hematuria, its presence in an adult obligates an assessment for an underlying carcinoma.

Renal dysfunction

Renal failure is arbitrarily divided into acute, subacute, and chronic based on the time course. Acute kidney injury (AKI), previously termed acute renal failure, is evidenced by an elevation in the serum creatinine concentration that develops over days to weeks, whereas chronic kidney disease (CKD) extends over a period of months to years. With CKD, the symptoms of uremia tend to occur insidiously. Such symptoms include easy fatigability, daytime somnolence, nighttime sleep disturbances, nausea, anorexia, pruritus, easy bruising, mucosal bleeding, and dysgeusia. Because these symptoms are nonspecific, they are frequently attributed to other disorders, such as depression or hypothyroidism. They may not be attributed to AKI or CKD until some estimate of kidney function is obtained. Fluid retention or edema and a reduction in urine volume are not frequent features of CKD until an advanced stage of CKD is reached. As with CKD, the symptoms of AKI tend to be relatively nonspecific and depend on the underlying disease process. The constellation of worsening or new-onset hypertension, hematuria, and AKI suggests acute GN, vasculitis, or both.

Approach to patients with rheumatologic disease and suspected renal involvement

The approach to a patient with suspected renal disease requires a careful physical examination and a directed laboratory assessment. Individuals with kidney disease tend to be asymptomatic, and therefore one is particularly dependent on laboratory tests for detecting kidney involvement in systemic disease. By integration of laboratory and clinical findings, one can classify the kidney involvement into one of the renal syndromes listed in [Table 38.1](#).

Physical examination findings

Hypertension is a common consequence of kidney disease, including the glomerular damage seen with autoimmune disorders. Renovascular disease accounts for 10% to 45% of cases of acute, severe, or refractory hypertension, but for less than 1% of mild hypertension. Aggressive control of blood pressure is of paramount importance in all individuals with hypertension, particularly in those with underlying kidney disease. Treatment with an effective antihypertensive regimen that includes either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker may prevent the progression of kidney disease.

Although dysfunction of several organs can be manifested as edema, this finding should trigger evaluation for proteinuria. With nephrotic syndrome, the distribution of edema tends to be generalized, unlike the distribution seen with congestive heart failure or cirrhosis. Despite massive proteinuria, edema does not develop in some patients as commonly seen with secondary focal segmental glomerulosclerosis (FSGS).

TESTING FOR KIDNEY DISEASE**Proteinuria**

Ordinarily, a normal healthy adult excretes 84 ± 24 mg of protein per day. The small amount of protein that appears in normal urine consists of albumin, immunoglobulins, products of hormone metabolism, and Tamm-Horsfall proteins.

TABLE 38.1

Renal syndromes in patients with rheumatic diseases*

Renal syndrome	Clinical features	Laboratory features	Course
Asymptomatic urinary abnormalities or "subacute"	None	Proteinuria and/or microscopic hematuria	Persistent; may evolve to nephrotic
Nephrotic syndrome	Edema ± ascites, effusions	Proteinuria >3.5 g/day, low serum albumin and elevated cholesterol levels	Persistent or remitting and relapsing
Acute nephritic syndrome	Reduced urine output, ± discolored urine, ± fluid retention	Elevated plasma creatinine, microscopic hematuria, red cell casts	Poststreptococcal form resolves; acute episodes in lupus may recur
Rapidly progressive glomerulonephritis	Progressive oliguria, discolored urine, systemic symptoms	Rapidly rising plasma creatinine level, falling GFR, hematuria, red cell casts	Progresses to renal failure in weeks or months
Persistent "subacute" glomerulonephritis (mixed nephrotic/nephritic)	± Edema, ± discolored urine, ± hypertension	Proteinuria, ± low serum albumin, microscopic hematuria	Persistent; may progress to renal failure (in years)
Renal vasculitis	± Discolored urine, ± visible hematuria, ± hypertension	Elevated plasma creatinine, proteinuria, hematuria, ± red cell casts	Variable with treatment; may mimic RPGN
Tubulointerstitial nephritis	± Discolored urine	Elevated plasma creatinine, sterile pyuria (white blood cells), microscopic hematuria	Acute (resolves in months) or chronic (persistent)
Chronic renal failure (mild to moderate)	Few or none, ± hypertension	Elevated plasma creatinine, reduced GFR, ± urinary abnormalities	Persistent; renal failure usually worsens
Chronic renal failure (severe)	Subclinical to severe uremic symptoms, ± hypertension	Plasma creatinine >6 mg/dL, GFR <10 mL/min, ± urinary abnormalities	Imminent need for dialysis or renal transplantation

*Same of the principal syndromes of renal involvement are shown. For each syndrome, typical clinical signs and symptoms are listed, together with the distinguishing findings on routine laboratory screening. Some degree of proteinuria is present in the vast majority of all these syndromes and is mentioned in the table only when it is a constant and defining feature of the syndrome. The typical course of evolution of each syndrome over time is also shown because it helps characterize the syndromes and is integral to the definition of some of them (e.g., RPGN). This information cannot be used as a basis for prognosis in individual cases, which varies widely. The laboratory features listed here are those obtainable only from tests used routinely for renal surveillance (blood chemistry, urinalysis, and urine microscopy), plus the results of 24-hour urine chemistry (timed protein quantitation and creatinine clearance to estimate GFR). The latter should be obtained at the initial evaluation of patients at risk for renal involvement, whenever new elevations in proteinuria or plasma creatinine are detected, or periodically in nephrotic and renal failure patients. Laboratory studies beyond those listed are appropriate for full diagnosis in all cases and may include additional chemical and serologic tests, imaging studies, and histologic evaluation of renal biopsy material. GFR, glomerular filtration rate (measured by creatinine clearance or other methods); RPGN, rapidly progressive glomerulonephritis.

Glomerular proteinuria

Glomerular proteinuria is typically in the nephrotic range, with associated hypoalbuminemia and lowered intravascular oncotic force, which often results in the development of edema. However, whether edema develops depends on other factors, including nutritional status and the type of underlying nephropathology.

The degree of proteinuria, together with the degree of tubulointerstitial damage, is the most powerful predictor of progression of CKD, regardless of the underlying disease process. Therefore, every effort must be made to minimize or extinguish proteinuria. ACE inhibitors or angiotensin receptor blockers (or both) should be considered first-line agents in the treatment of all cases of proteinuria.

Tubular proteinuria

Tubular proteinuria occurs in settings in which glomerular protein sieving is normal but tubular reabsorption of normally filtered low-molecular-weight proteins is impaired. As opposed to glomerular diseases, the range of proteinuria is much lower, usually in the range of 1 to 2 g/day. Tubular proteinuria can be associated with tubulointerstitial disease resulting from uric acid nephropathy, Sjögren syndrome, essential hypertension, and drugs such as aminoglycoside antibiotics.

Measurement of proteinuria

After protein spillage has been detected, the absolute amount of protein excreted should be quantified because this will help distinguish between glomerular and tubulointerstitial disease. Quantification is accomplished either by a timed (usually 24-hour) urine collection or by analysis of a spot urine sample. The 24-hour urine collection had been the "gold standard" method for quantification but has been replaced by the protein-to-creatinine ratio on a "spot" urine sample. A protein-to-creatinine ratio of 0.2 correlates with a protein excretion rate of approximately 200 mg/day, a ratio of 2.0 with 2000 mg/day, and a ratio of 3.5 with 3500 mg/day (i.e., nephrotic-range proteinuria). Detection of microalbuminuria has become extremely important in view of the appreciation of its clinical correlation with cardiovascular and kidney disease. The normal range of the urine albumin excretion rate is less than 20 mg/min on an overnight timed urine collection or 30 mg/day on a 24-hour collection. The abnormal microalbuminuria range is 20 to 200 mg/min (30 to 300 mg/day). Values higher than 300 mg/day suggest

"overt" proteinuria. First studied in diabetic patients, microalbuminuria has now been found to be a harbinger of renal involvement in many other diseases (see later). Microalbuminuria is present in the majority of patients with SLE, even in those with apparently normal urine and kidney function¹; biopsy may reveal histologic changes, and overt nephritis subsequently develops in some of these patients.

Hematuria

Hematuria, unlike proteinuria, may arise from anywhere in the urinary tract (see Box 38.1). Hematuria can be divided into upper tract bleeding (i.e., glomerular or tubulointerstitial) and lower tract bleeding (i.e., extrarenal). Diagnostic clues such as red blood cell (RBC) casts, significant proteinuria, or abnormal kidney function suggest upper tract bleeding. In subjects with rheumatic disease, microscopic hematuria will often be accompanied by proteinuria, which suggests upper tract bleeding.

Red blood cells

RBC morphology offers a clue to the site of origin of the hematuria. Non-glomerular hematuria will typically have less than 1% dysmorphic erythrocytes. However, glomerular hematuria usually contains a high proportion of abnormally shaped RBCs with vesicle-shaped protrusions (acanthocytes) and considerable anisocytosis (Fig. 38.1).

Other urine microscopy findings

Pyuria, or the presence of white blood cells (WBCs), suggests an infection within the genitourinary tract and mandates urine culture. Sterile pyuria has classically suggested renal tuberculosis but also can be seen with tubulointerstitial nephritis, such as occurs with allergic interstitial drug reactions, Sjögren syndrome, and lupus interstitial nephritis. As an indicator of acute interstitial nephritis, eosinophiluria has limited sensitivity.

Urinary casts are formed in the renal tubules from an aggregation of proteins, primarily Tamm-Horsfall proteins. Not all casts are pathologic; for example, hyaline casts can be seen in normal urinary sediment. When intact cells or cellular debris become trapped within the protein matrix, various "cylindrical casts" result: "muddy brown" granular casts with or without renal tubule epithelial casts are associated with acute tubular necrosis; WBC casts are classically associated with pyelonephritis or interstitial nephritis; and RBC casts are pathognomonic of intraparenchymal bleeding, such as

BOX 38.1 CAUSES OF HEMATURIA

Glomerulonephritis and other glomerular diseases
 IgA nephropathy
 Membranoproliferative (mesangiocapillary) glomerulonephritis
 Mesangial proliferative glomerulonephritis
 Lupus glomerulonephritis
 Glomerulonephritis with other rheumatic diseases:
 ■ Rheumatoid arthritis
 ■ Polymyositis/dermatomyositis, etc.
 Crescentic glomerulonephritis
 Glomerulonephritis with renal vasculitis:
 ■ ANCA-associated granulomatous vasculitis
 ■ Microscopic polyangiitis, etc.
 Alport syndrome
 Thin basement membrane nephropathy
 Fabry disease
 Renal vascular diseases
 Renal vasculitis (polyarteritis nodosa, etc.)
 Renal thromboembolism or infarction
 Hypertension
 Familial telangiectasia
 Arteriovenous malformations
 Renal vein thrombosis
 Renal vein occlusion
 Interstitial and medullary diseases
 Tubulointerstitial nephritis
 Polycystic kidney diseases
 Papillary necrosis from
 ■ Analgesic nephropathy
 ■ Sickle cell disease
 ■ Diabetes mellitus
 Medullary sponge kidney
 Disorders of coagulation
 Anticoagulants
 Bleeding disorders (hemophilia, etc.)
 Renal and urinary tract tumors
 Wilms tumor
 Renal cell carcinoma
 Transitional cell carcinoma
 Prostatic carcinoma
 Urethral carcinoma
 Infections
 Acute pyelonephritis
 Acute cystitis
 Prostatitis
 Urethritis
 Renal tuberculosis
 Schistosomiasis
 Bacterial endocarditis
 Stones and crystals
 Stones anywhere in the urinary tract
 Urate crystalluria
 Calcium oxalate crystalluria
 Hypercalciuria
 Miscellaneous
 Trauma
 Release of obstruction
 Loin pain–hematuria syndrome
 Endometriosis
 Chemical cystitis (e.g., with cyclophosphamide)
 Meatal ulcers
 Urethral caruncle
 Foreign body
 Factitious (added blood)

ANCA, antineutrophilic cytoplasmic antibody.

from GN or vasculitis. Broad and waxy casts, which are both acellular, strongly suggest CKD.

With nephrotic-range proteinuria, one may see lipid droplets. If present within renal tubule epithelial cells, they are called oval fat bodies. These fat bodies, when viewed under polarized light, have a characteristic “Maltese cross” appearance.

Kidney function testing

Kidney function is a nonspecific term usually applied to the principal function of the kidney: filtration of wastes by the glomerulus (i.e., the glomerular filtration rate [GFR]). The GFR is generally considered to be the best index of overall kidney function because an impairment in GFR correlates with the severity of structural abnormalities observed on biopsy specimens. A normal GFR is approximately 130 mL/min in men and 120 mL/min in women, but it also depends on age, sex, and body size. The GFR is not an all-inclusive index of function, and many kidney diseases do not alter the GFR.

Plasma creatinine measurement

The plasma creatinine concentration (P_{CR}) is a simple and useful correlate of GFR. Plasma creatinine is an inexpensive and widely used test of kidney function; when it is repeated serially in an individual, it may give significant insight into changes in kidney function.

Despite its appeal, significant problems arise when using P_{CR} as a sole marker of GFR. Specifically, in the lower range, small increases in P_{CR} reflect major reductions in the GFR (Fig. 38.2). Thus, in some cases up to half of renal function can be lost before P_{CR} exceeds the upper limits of normal. Also, when the GFR changes abruptly, output no longer equals input, and it may take several days before the system achieves a new steady state. Because 10% to 20% of creatinine is excreted by tubular secretion, in some cases elevations in P_{CR} are unrelated to changes in the GFR. Drugs that block tubular secretion, such as trimethoprim and cimetidine, are associated with such elevations in P_{CR} despite not affecting glomerular function. Other drugs such as cefoxitin and flucytosine may cause false elevations in creatinine measurements by interfering with the laboratory chemical assays for creatinine. Finally, some disease states are associated with hyperexcretion of creatinine by the proximal tubule, as is the case with sickle cell disease.

Another concern about the use of P_{CR} as the sole marker of kidney function is that although the GFR decreases markedly with age, P_{CR} barely rises (Fig. 38.3). This is due to a decrease in creatinine production as muscle mass decreases with age. This problem also affects other states in which muscle mass is lost, such as anorexia nervosa, amputations, and chronic illnesses.

Stages of chronic kidney disease

The National Kidney Foundation has established stages of CKD, as listed in Table 38.2.²

Tests for renal tubular dysfunction

The renal tubular disorders most likely to be encountered in patients with rheumatic disease are renal tubular acidosis (RTA) and either hypokalemia or hyperkalemia. These disorders are seen in several autoimmune diseases, including the interstitial nephritis of SLE and Sjögren syndrome. These problems develop in about 10% of patients with SLE, although subclinical defects in the handling of potassium, sodium, or hydrogen ions can be demonstrated in up to 60% of cases.³ RTA is manifested as a hyperchloremic, non-anion gap acidosis with a low plasma bicarbonate concentration. With distal, type 1 RTA, ammonium ion secretion into urine is reduced. The RTA seen in lupus is usually due to proton secretion defects in the distal tubules.³

Persistent hyperkalemia is invariably associated with renal tubular dysfunction, which results in impaired urinary potassium excretion. This occurs with advanced kidney failure, with any cause of hypoaldosteronism, or with marked volume depletion.

Hypocomplementemia and kidney disease

Measurements of C3 and C4 are often used to narrow the differential diagnosis of kidney diseases. The list of GNs associated with hypocomplementemia includes lupus nephritis, membranoproliferative GN (MPGN), mixed cryoglobulinemia, postinfectious GN, membranous nephropathy secondary to hepatitis B infection, and serum sickness. Complement levels tend to be normal in ANCA-associated granulomatous vasculitis, microscopic polyangiitis, Goodpasture syndrome, and Henoch-Schönlein purpura.

Renal imaging**Kidney ultrasonography**

Ultrasonography is the most commonly used technique to image the kidneys because it is noninvasive and does not depend on kidney function. It allows

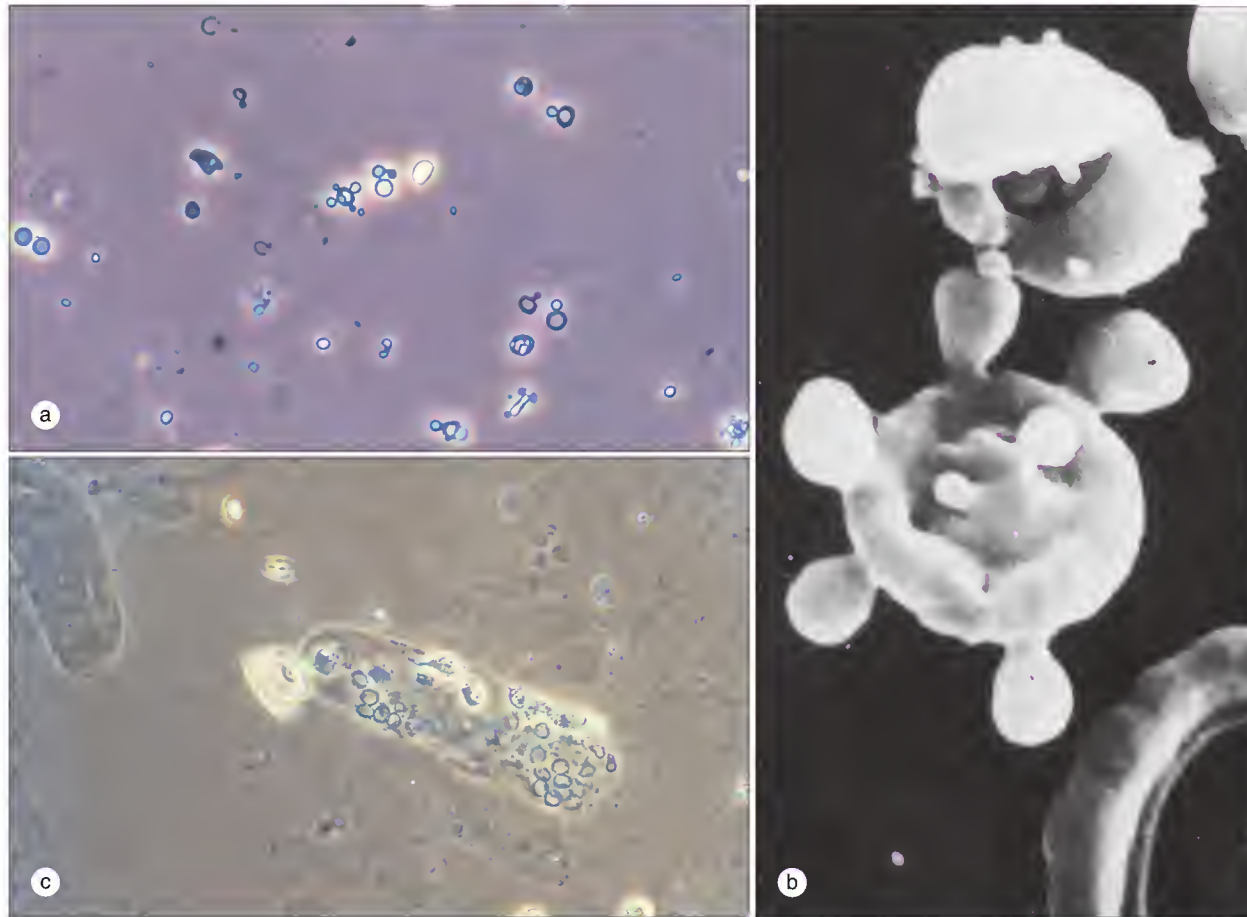


Fig. 38.1 Microscopy of urine. (a) Acanthocytes are seen through the microscope, which indicates a renal (probably glomerular) origin of the hematuria (phase contrast, original magnification $\times 640$). (b) Acanthocytes seen on scanning electron microscopy. Details of the “knobs” and protrusions can be seen. (c) A tubular cast containing red cells, which usually indicates a glomerular origin of concomitant hematuria and, in general, an active proliferative/infiltrative glomerular disease (phase contrast, original magnification $\times 400$). (a and c, Courtesy Dr. G.B. Fogazzi; b, reproduced with permission of Blackwell Science from Fasset RG, Owen JE, Fairley J, et al. Urinary red-cell morphology during exercise. *BMJ* 1982;285:1455-7.)

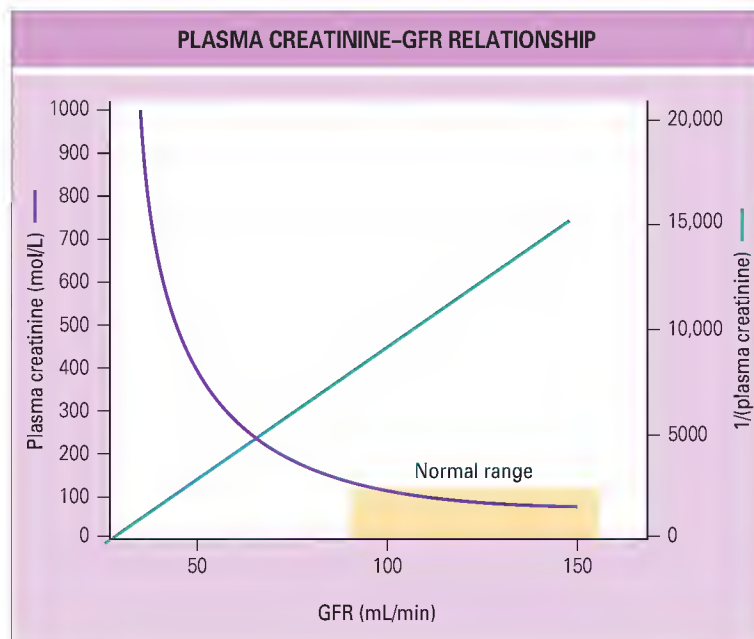


Fig. 38.2 As the glomerular filtration rate (GFR) decreases, plasma creatinine rises, but in a hyperbolic fashion, so plasma creatinine levels become abnormal (normal range shaded) only after considerable loss of renal function. One way of compensating for this hidden information is to use the reciprocal of plasma creatinine, which is approximately linear.

determination of kidney size, the degree of echogenicity, anatomic abnormalities, and obstruction.

Assessment of the renal vasculature

To assess for renal vasculitis, the best imaging studies include angiography, magnetic resonance angiography (MRA), and computed tomography (CT). For assessment of the renal vasculature in patients with rheumatic disease, duplex Doppler ultrasonography is better at detecting stenosis of the major branches of the renal arteries than at demonstrating vasculitis or aneurysms. Renal vein thrombosis may be diagnosed by Doppler ultrasonography, but its sensitivity and specificity are suboptimal; spiral CT and MRA are better, but the gold standard remains selective venography.

Kidney biopsy

Indications

Percutaneous kidney biopsy is an essential tool for determining the diagnosis, prognosis, and treatment options for patients with kidney disease. One of the strongest indications for performing kidney biopsy is in the setting of rapidly progressive GN (RPGN). The syndrome is defined clinically as a rapid decline in kidney function associated with active urinary sediment, typically with RBC casts. Delays in diagnosis and subsequent initiation of treatment may result in irreversible loss of kidney function. Common rheumatologic causes of RPGN include lupus, ANCA-related vasculitis, and Henoch-Schönlein purpura. Other indications for performing biopsy in patients with rheumatic disease include unexplained AKI, acute nephritic syndrome, persistent proteinuria, persistent hematuria, and nephrotic syndrome.

Renal Histopathology

An adequate kidney biopsy will result in two or three cores of kidney tissue, which are examined by light microscopy (LM), immunofluorescence (IF) microscopy, and electron microscopy (EM).

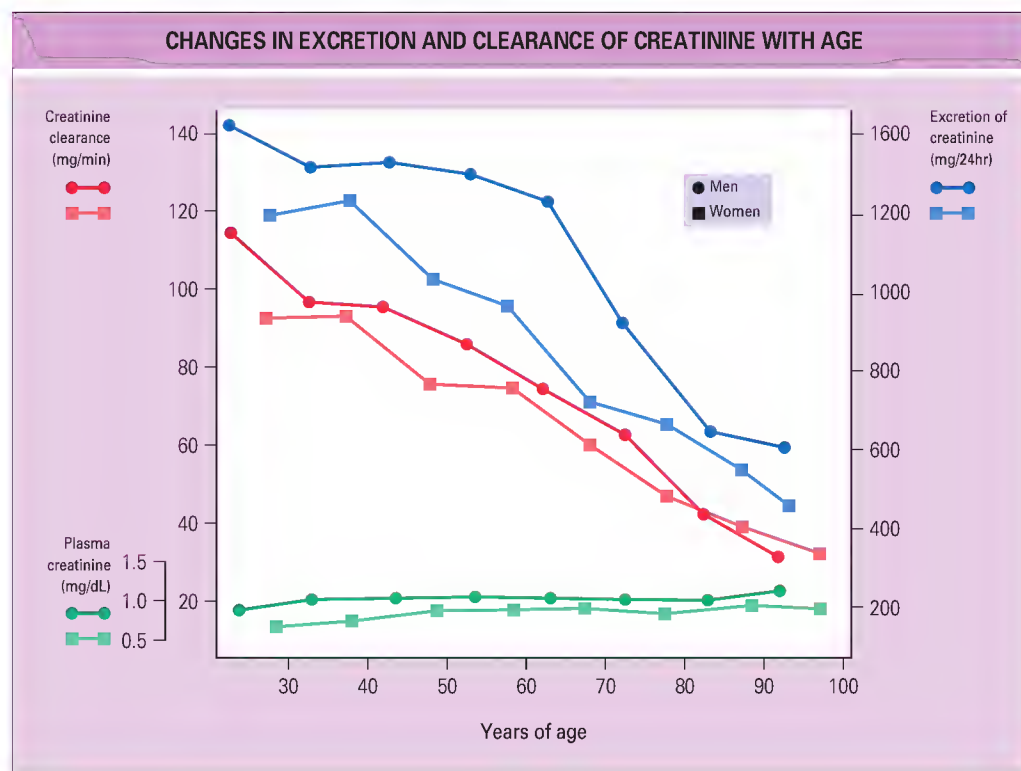


Fig. 38.3 The “hidden” reduction in renal function with age. Although normal creatinine clearance decreases dramatically with age to a mean of just 40 mL/min in the very elderly, the plasma creatinine value remains constant up to 100 years of age because of a concomitant reduction in excretion (and, by inference, production) of creatinine as a result of a reduction in muscle mass. (Data from Kampmann JM, Siersbaek-Nielsen K, Kristensen M, Hansen JM. Rapid evaluation of creatinine clearance. *Acta Med Scand* 1974;196:517-20.)

TABLE 38.2

Chronic kidney disease: a clinical action plan

Stage	Description	GFR (mL/min/1.73 m ²)	Action*
1	At increased risk	≥90 (with CKD risk factors)	Screening CKD risk reduction
	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mildly ↓ GFR	60-89	Estimating progression
3	Moderately ↓ GFR	30-59	Evaluation and treating complications
4	Severely ↓ GFR	15-29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Stages 1 through 5 identify patients who have CKD; the first row designates individuals who are at increased risk for the development of CKD. CKD is defined as either kidney damage or GFR lower than 60 mL/min/1.73 m² for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

*Includes actions from preceding stages.

CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate.

Patterns seen on immunofluorescence microscopy

Three patterns are seen on IF microscopy: linear, granular, and pauci-immune. The primary cause of a linear pattern is antibodies directed against the glomerular basement membrane (GBM), as is the case with anti-GBM disease. When associated with pulmonary hemorrhage, this constellation of findings is known as Goodpasture syndrome. In contrast to a linear deposition, diseases associated with immune complex deposition will have a granular, “lumpy-bumpy” appearance. This occurs with SLE and postinfectious GN. The term *pauci-immune* implies that no or minimal immunoglobulins are found on IF microscopy, and it is seen with ANCA-associated granulomatous vasculitis, microscopic polyangiitis, and other ANCA-related vasculitides.⁴

Transmission EM allows significant enhanced resolution in comparison to LM and can delineate the precise location and size of electron-dense deposits. Deposits can be divided into (1) subepithelial, in which accumulation of material occurs on the external aspect of the GBM, between the basement membrane and the visceral epithelial cell; (2) subendothelial, in which accumulation occurs between the GBM and the fenestrated endothelial cell; and (3) transmembranous or intramembranous, in which the deposits are within the GBM. Identification of subendothelial deposits correlates with the wire loop seen on LM in patients with SLE-related nephritis. EM can also reveal other ultrastructural features of diagnostic importance,

such as tubuloreticular structures, or so-called viruslike particles, in the glomerular endothelial cells of patients with SLE-associated nephritis.

Interpretation

The renal cortical parenchyma contains three different domains: the glomeruli, the tubules and interstitium, and the vasculature. Small- and medium-vessel vasculitis can be distinguished from changes caused by atherosclerosis, hypertension, diabetes mellitus, or systemic sclerosis. Tubulointerstitial changes can range from acute inflammation with edema to chronic fibrosis with scarring or may include granuloma formation, as seen with renal sarcoidosis.

Terminology

Specific terms have been assigned to describe the pattern of involvement in one glomerulus (segmental or global), and other terms have been assigned to describe the proportion of glomeruli involved in a pathologic process (focal or diffuse). The term *focal* is applied when less than 50% of all glomeruli are involved, and the term *diffuse* is used when more than 50% of all glomeruli are involved. The term *segmental* is applied to a lesion that involves a portion of one particular glomerulus, and the term *global* is applied to a lesion that involves the whole glomerulus. For example, if a total of 20 glomeruli are examined under LM and only 5 of them have pathologic changes, this would be referred to as a focal lesion. If these five

TABLE 38.3
Morphologic terminology in nephropathology

		All glomeruli	
		Focal (<50%)	Diffuse (>50%)
One glomerulus	Segmental (<50%)	Focal-segmental	Diffuse-segmental
	Global (≥50%)	Focal-global	Diffuse-global

glomeruli have only partial involvement, the process is further defined as segmental (Table 38.3).

Glomerular pathology is divided into primary, or idiopathic, lesions and secondary lesions. Five histologic patterns of primary glomerular lesions are recognized:

1. Minimal change disease: as its name implies, minimal change disease has minimal to no pathologic changes visible on LM or IF. In rheumatology practice it may be seen as a complication of the use of nonsteroidal antiinflammatory drugs (NSAID) (see later).
2. FSGS: This condition initially affects only a portion of each glomerulus and tends to involve some but not all the glomeruli. FSGS can be manifested as either nephritic or nephrotic syndrome or as a progressive decline in the GFR. Secondary causes of FSGS include human immunodeficiency virus (HIV) infection, reflux nephropathy, and obesity.
3. Membranous GN: On LM, the characteristic finding of membranous GN is thickening of the capillary walls because of subepithelial deposits. Membranous GN tends to be manifested as massive proteinuria (nephrotic syndrome) and edema. Secondary causes of membranous GN include SLE (class V nephritis), mixed connective tissue disease (MCTD), gold therapy, solid tumors, and hepatitis B infection.
4. Mesangial proliferative GN: On LM, the mesangium is expanded with increased cellularity and matrix. IF microscopy may demonstrate mesangial deposition of IgA, IgM, or IgG, with or without C3. When the predominant finding on IF is IgA deposits, the lesion is referred to as IgA nephropathy or Berger disease. The clinical findings of mesangial proliferative GN are variable. Important secondary causes include lupus nephritis, Henoch-Schönlein purpura (systemic Berger disease), rheumatoid arthritis, and ankylosing spondylitis.
5. MPGN: This lesion has also been called mesangiocapillary GN and is divided into type 1, type 2 (dense deposit disease), and type 3 based on findings on microscopy. They can all be manifested as RPGN, as macroscopic hematuria, less commonly as nephrotic syndrome, or as isolated proteinuria or microscopic hematuria (or both). Typical LM findings include capillary wall thickening because of the presence of deposits, which frequently take the form of a duplicated or split basement membrane (double contours or “tram tracking”). Secondary causes of MPGN include lupus (class III and IV) and a rare form associated with hypocomplementemic partial lipodystrophy.

Another significant abnormal finding is the presence of cells, fibrin, or collagen in the urinary space of the glomeruli. When this process involves more than 50% of the circumference of the glomerular tuft, it is termed a *crescent* (fibrous, fibrocellular, or cellular crescent, depending on the predominant finding). The presence of crescents is a marker for severe kidney injury and is usually the pathologic equivalent of the clinical syndrome of RPGN. Crescentic GN may be associated with other forms of primary GN, such as MPGN or IgA nephropathy, or with secondary forms of GN, such as SLE and ANCA-associated granulomatous vasculitis.

RHEUMATOLOGIC DISEASES AFFECTING THE KIDNEYS (Table 38.4)

Systemic lupus erythematosus

Kidney involvement is common in SLE, with approximately a third of patients initially seen by a nephrologist rather than a rheumatologist. The incidence of lupus nephritis probably exceeds 90% because some kidney involvement may be silent.⁵ Subgroups of patients with SLE at increased risk for the development of nephritis include men younger than 33 years at the time of diagnosis of SLE and non-European Americans.⁶ The presence of anticardiolipin antibody activity correlates with a worse kidney prognosis.⁷

The principal different renal lesions are summarized in Table 38.4. The World Health Organization's classification of lupus nephritis has been modified⁸ (Table 38.5). The primary advantage of the revised classification system is that it provides a clearer description of the lupus nephritis classes.

Treatment and prognosis are different for each type of nephritis.⁹ Additionally, transitions between the different classes of GN occur frequently but do not take place in a stepwise fashion. Most renal abnormalities emerge soon after diagnosis. In one study of 1000 patients seen in rheumatologic practice, kidney involvement was initially present in 16% and increased to 50% during follow-up.¹⁰ However, even if a subject does not have overt nephropathy, urinalysis and determination of the GFR (see earlier) should be performed routinely. Acute nephritis exacerbations require immediate evaluation and usually a kidney biopsy. Unfortunately, renal vasculitis and thrombotic microangiopathy are rarely demonstrable on biopsy specimens. Renal vein thrombosis in patients with lupus nephritis may similarly be clinically inapparent.

Overt distal RTA and hyperkalemia develop in about 10% of patients with lupus nephritis, although subclinical defects are present in a large number of individuals. The hyperkalemia may be exacerbated by the use of potassium-sparing diuretics or agents that interfere with blockade of the renin-angiotensin system, such as ACE inhibitors and angiotensin receptor blockers. Strategies to decrease hyperkalemia include limiting dietary potassium intake, use of fludrocortisone, and use of loop diuretics.

Mixed connective tissue disease

Though originally described as a syndrome without renal involvement, MCTD is now recognized as having kidney involvement in 25% to 50% of cases.¹¹ The most common lesion is membranous GN,¹¹ which is manifested similar to that seen in SLE. Individuals with more systemic manifestations from MCTD appear to be at higher risk for kidney involvement than those without systemic involvement. Hypertensive crises similar to those seen with “scleroderma kidney” may also develop in patients with MCTD.

Rheumatoid arthritis

The existence of a glomerulopathy associated with untreated rheumatoid arthritis is now generally accepted,¹² in addition to renal disease secondary to medications used to treat the underlying disorder. The most common kidney lesion is mesangial proliferative GN, but other renal lesions include membranous GN, focal proliferative GN, and secondary amyloidosis.¹² Rheumatoid arthritis may also be manifested as RPGN with either crescentic¹³ or necrotizing GN¹⁴ or as pauci-immune GN.¹⁵ Nephrotic syndrome in patients with rheumatoid arthritis most often reflects either membranous GN from gold or penicillamine toxicity or the development of systemic amyloidosis with glomerular involvement¹² (see later).

Sjögren syndrome

Sjögren syndrome typically does not result in glomerular pathology but more frequently produces an interstitial nephritis and defects in tubular function. The presence of interstitial nephritis in association with eye findings should raise the specter of the syndrome of tubulointerstitial nephritis associated with uveitis (TINU). This tubular pathology associated with Sjögren syndrome can be manifested clinically as a reduction in the GFR, distal RTA, or hypokalemia or as mild nephrogenic diabetes insipidus.¹⁶ MPGN and membranous GN have been diagnosed in patients with Sjögren syndrome.¹⁷

Relapsing polychondritis

Kidney disease is a variable feature of relapsing polychondritis and may be manifested as proteinuria, hematuria, or a decline in kidney function. Lesions accompanied by relapsing polychondritis may be associated with coexisting disease such as SLE. Renal pathology has included mesangial proliferative GN, crescentic necrotizing GN, and tubulointerstitial nephritis.¹⁸

Behçet disease

Kidney involvement in Behçet disease appears to be less frequent than in other types of vasculitis. However, there is an association with focal or diffuse proliferative and membranous GN.¹⁹ Amyloidosis is a more common renal complication of Behçet disease and may be manifested as nephrotic syndrome. Intrarenal microaneurysms have also been described in association with Behçet disease. In one study, urinary abnormalities (proteinuria,

■ TABLE 38.4

Principal types of renal pathology in the rheumatic diseases

	Glomerular diseases	Renal vascular diseases	Tubulointerstitial diseases
Systemic lupus erythematosus	Mesangial glomerulonephritis (WHO class II) Focal proliferative glomerulonephritis (WHO class III) Diffuse proliferative glomerulonephritis (WHO class IV), including membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis) and crescentic and necrotizing glomerulonephritis (WHO class V)	Vasculitis of the kidney Thrombotic microangiopathy (with thrombotic thrombocytopenic purpura or anticardiolipin syndrome) “Lupus vasculopathy” (see text) Renal vein thrombosis	Lupus tubulointerstitial nephritis Drug induced (NSAIDs, cyclosporine, etc.) Membranous glomerulonephritis
Mixed connective tissue disease	Membranous glomerulonephritis Mesangial glomerulonephritis	“Scleroderma kidney” (see later)	
Rheumatoid arthritis	Focal proliferative glomerulonephritis Crescentic necrotizing glomerulonephritis (with vasculitis) Membranous glomerulonephritis (gold, penicillamine) Renal amyloidosis (see later)	Vasculitis (rheumatoid) of the kidney Other drug induced (NSAIDs, methotrexate, cyclosporine, etc.)	Analgesic nephropathy (NSAIDs)
Sjögren syndrome	Membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis) (with cryoglobulinemia)		Lymphocytic tubulointerstitial nephritis (with hypokalemic renal tubular acidosis)
Relapsing polychondritis	Mild mesangial glomerulonephritis Focal sclerosing glomerulonephritis		Tubulointerstitial nephritis
Behçet disease	Crescentic glomerulonephritis or milder proliferative glomerulonephritis Renal amyloidosis (see later)	Renal artery aneurysms and intrarenal microaneurysms	
Polyarteritis nodosa (classic)	Ischemic sclerosis of glomeruli	Arteritis and aneurysms of medium-sized vessels	
Microscopic polyarteritis (polyangiitis)	Focal necrotizing and crescentic glomerulonephritis (pauci-immune)	Vasculitis of small vessels (arterioles, capillaries, and venules)	
ANCA-associated granulomatous vasculitis	Focal necrotizing and crescentic glomerulonephritis (pauci-immune)	Vasculitis of small vessels (arterioles, capillaries, and venules)	Granulomas, lymphocytic infiltrates (periglomerular)
Churg-Strauss syndrome	Focal glomerulonephritis Focal necrotizing and crescentic glomerulonephritis	Vasculitis	Granulomas, eosinophil infiltrates
Essential mixed cryoglobulinemia	Cryoglobulinemic glomerulonephritis Membranoproliferative glomerulonephritis	Small-vessel vasculitis	Tubulointerstitial nephritis (mesangiocapillary glomerulonephritis)
Henoch-Schönlein purpura	Diffuse proliferative glomerulonephritis with mesangial IgA deposits		
Ankylosing spondylitis	Focal proliferative glomerulonephritis with mesangial IgA deposits (mesangial IgA nephropathy) Renal amyloidosis (see later)		
Reactive arthritis	Focal proliferative glomerulonephritis with mesangial IgA deposits (mesangial IgA nephropathy)		
Progressive systemic sclerosis (“scleroderma”)	Ischemic glomeruli	Concentric layered thickening of the arterial walls with narrowed lumens	
Amyloidosis	Mesangial expansion because of the accumulation of amyloid fibrils		Peritubular amyloid deposits
Gout (chronic urate nephropathy)			Chronic interstitial inflammation and fibrosis

ANCA, antineutrophilic cytoplasmic antibody; NSAID, nonsteroidal antiinflammatory drug; WHO, World Health Organization.

hematuria, or both) were present in about 10% of patients, but serious kidney lesions developed in less than 1%.²⁰

Classic polyarteritis nodosa

The kidneys are the organs most commonly involved in patients with polyarteritis nodosa, which leads to hypertension and a variable decline in the GFR. Patchy cortical infarctions may be present, and renal artery aneurysms may rupture. GN is not a feature of polyarteritis nodosa because it tends to not be a small-vessel disease.

ANCA-associated vasculitides

ANCA-associated granulomatous vasculitis, microscopic polyangiitis, and idiopathic pauci-immune GN probably represent the spectrum of disease manifestations of the ANCA-associated vasculitides. Classic ANCA-associated granulomatous vasculitis involves the upper and lower respiratory tracts and the kidney. When the vasculitis has more limited systemic involvement but still affects the kidney, it is termed *microscopic polyangiitis*. When only the kidneys are affected by the vasculitis, the condition is termed *idiopathic pauci-immune GN*. The view that these three entities

TABLE 38.5

World Health Organization classification of lupus nephritis

Class	Description
Class I	Mesangial immune deposits without mesangial hypercellularity
Class II	Mesangial immune deposits with mesangial hypercellularity
Class III Subdivisions for active and sclerotic lesions	Focal glomerulonephritis (involving <50% of the total number of glomeruli)
Class IV Subdivisions for active and sclerotic lesions	Diffuse glomerulonephritis (involving ≥50% of the total number of glomeruli)
Class IV-S Subdivisions for active and sclerotic lesions	Segmental involvement
Class IV-G Subdivisions for active and sclerotic lesions	Global involvement
Class V	Membranous
Class VI	Advanced sclerosing lesions

Data from Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004;65:521-30.

represent a spectrum of forms of a unified disease is supported by several facts:

1. A positive test for ANCA is typically present in all three conditions.
2. The glomerular pathology is indistinguishable.
3. Typical pulmonary lesions consistent with ANCA-associated granulomatous vasculitis may develop later in patients in whom idiopathic pauci-immune GN or microscopic polyangiitis is diagnosed.
4. Systemic manifestations, including kidney involvement, may develop later in patients with “limited” ANCA-associated granulomatous vasculitis in which the clinical findings are isolated to the pulmonary system.

The renal lesion in these conditions is typically manifested as RPGN. Renal vessels other than glomerular capillaries can also be involved by the necrotizing vasculitis.

Allergic granulomatosis and angiitis, better known as Churg-Strauss syndrome, is typified by allergic rhinitis, asthma, eosinophilia, and small-vessel vasculitis. As in ANCA-associated granulomatous vasculitis and microscopic polyangiitis, patients tend to be ANCA positive. Although the most common organ involved is the lung, kidney involvement occurs more frequently than previously thought, with a prevalence as high as 84%.²¹ Unlike ANCA-associated granulomatous vasculitis, renal failure is rare. The predominant glomerular pathology is FSGN, and it may be associated with necrotizing features and crescents.²¹ Granulomas and eosinophilic infiltrates in the kidney are infrequent.

Essential mixed cryoglobulinemia

Essential mixed cryoglobulinemia (formerly known as Meltzer syndrome) is often an epiphenomenon of a chronic viral infection, such as hepatitis C or HIV infection. Cryoglobulins are immunoglobulins that precipitate in the cold with deposition of antigen-antibody complexes in small and medium-sized arteries. Such deposition results in hypocomplementemia, palpable purpura, arthralgias, hepatosplenomegaly, and peripheral neuropathy. Kidney involvement occurs in upward of 60% of cases of mixed cryoglobulinemia.²² It can be manifested as asymptomatic hematuria and proteinuria but may progress to nephrotic-range proteinuria or deterioration of kidney function. Histologic examination of the kidney reveals MPGN with some unique features.²³ The majority of cryoglobulin deposits have a characteristic substructure containing curved annular-tubular structures that measure approximately 30 nm in diameter and look like a “fingerprint” (Fig. 38.4).

Henoch-Schönlein purpura

Henoch-Schönlein purpura is a small-vessel vasculitis characterized by deposition of IgA-containing immune complexes in tissue. It more

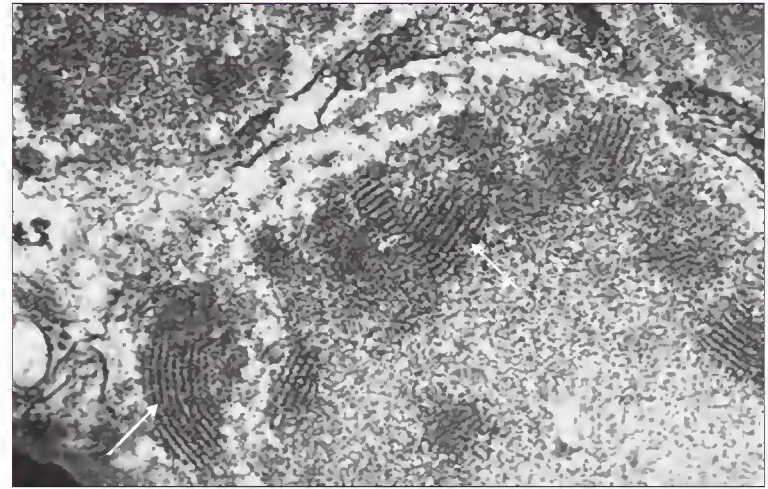


Fig. 38.4 Electron micrograph of a subject with cryoglobulinemia demonstrating electron-dense deposits of tubular fibrils in a “fingerprint” appearance (arrows).

frequently affects children than adults and has a classic tetrad of rash (palpable petechiae or purpura), arthralgias, abdominal pain, and kidney disease. The clinical severity of kidney disease varies from mild proteinuria and hematuria to the development of nephrotic syndrome or RPGN. The most common glomerular lesion seen in patients with Henoch-Schönlein purpura is mesangial proliferative GN, which has the characteristic finding of moderate to intense diffuse deposits of IgA in the mesangium. Less commonly, it can be manifested as crescentic GN. Henoch-Schönlein purpura-associated nephritis is an important cause of end-stage renal disease (ESRD) in children. In a retrospective, single-center study that examined kidney sequelae in adult patients with Henoch-Schönlein purpura and biopsy-proven cutaneous vasculitis, renal sequelae more commonly developed in patients with hematuria at disease onset or in those with renal involvement during the course of the disease.²⁴

The “seronegative spondyloarthritis” (ankylosing spondylitis, reactive arthritis)

The spondyloarthritis ankylosing spondylitis and reactive arthritis are infrequently associated with IgA nephropathy.²⁵ Clinically, this can be manifested as microscopic hematuria with or without a progressive decline in the GFR. Ankylosing spondylitis may also be complicated by the development of secondary amyloidosis.²⁶ These patients tend to initially be seen with nephrotic syndrome, which can progress to ESRD.

Progressive systemic sclerosis (scleroderma)

Scleroderma causes progressive mucoid thickening of the walls and narrowing of the vascular lumen of arteries, which results in severe hypertension and ischemic kidney disease. Diminished kidney blood flow is an early manifestation of scleroderma and appears before the development of hypertension, urinary abnormalities, or renal failure. “Scleroderma renal crisis” is characterized by acute renal failure associated with marked hypertension in the setting of relatively bland urinary sediment. There appears to be a significant association between antecedent high-dose corticosteroid therapy and the development of scleroderma renal crisis.²⁷ Kidney biopsy specimens have arterial changes that resemble thrombotic microangiopathy with edematous arteriolar intimal thickening and fibrinoid necrosis. Another classic finding seen on histology is “onionskin” concentric hypertrophy in the interlobular arteries. Because the hypertension is primarily due to ischemic activation of the renin-angiotensin system, ACE inhibitors are the mainstays of treatment.²⁸ Renal crisis will develop in 10% to 15% of patients with scleroderma, but a much larger percentage will have some kidney involvement.²⁹

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis can mimic systemic sclerosis or scleromyxedema (see Chapter 142).³⁰ It is seen only in individuals with significant CKD and is characterized by thickening and hardening of the skin and marked expansion and fibrosis of the dermis. Originally called nephrogenic fibrosing dermopathy, the name was changed because the pathologic

findings are not limited to the skin.³¹ Although the cause of nephrogenic systemic fibrosis remains unclear, there appears to be a high association with gadolinium, which is used as a contrast agent in magnetic resonance imaging and MRA. It is hypothesized that individuals with marked azotemia cannot eliminate the free gadolinium, which is highly toxic and results in tissue damage.³² Clinically, nephrogenic systemic fibrosis is characterized by skin involvement with or without systemic involvement.

Amyloidosis

Secondary amyloidosis, caused by the deposition of amyloid A (AA), tends to occur in concert with inflammatory rheumatologic conditions,²⁷ including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and familial Mediterranean fever (see Chapter 168). It is almost unknown in patients with SLE, in which only a handful of cases have been reported. This probably arises from the fact that patients with lupus have no increase in serum AA proteins during inflammatory episodes.

Clinically, renal amyloidosis is manifested as nephrotic syndrome and progressive renal failure. On imaging, the kidneys tend to be larger than expected because of amyloid deposition. On LM, amyloid fibrils are seen deposited within the mesangial regions and demonstrate dichroic birefringence under polarized light in tissue stained with Congo red. Amyloid can also infiltrate the tubulointerstitial compartment and lead to renal tubular defects.

In familial Mediterranean fever there is evidence that colchicine therapy may prevent the appearance of proteinuria and renal damage.³³

Gout

In the majority of cases, gout results from diminished kidney tubular secretion of uric acid. A number of pharmacologic agents can alter tubular function and result in hyperuricemia, such as cyclosporine, diuretics, and low-dose salicylates. Chronic hyperuricemia may involve the kidney in two distinct forms: chronic urate nephropathy and uric acid nephrolithiasis.

Before effective antihyperuricemic treatment, the prevalence of uric acid nephrolithiasis in patients with gout was about 20%.³⁴ Chronic urate nephropathy is secondary to urate deposition in the renal interstitium, which results in a chronic inflammatory reaction and varying degrees of fibrosis (tubulointerstitial disease). Clinically, this can be manifested as mild proteinuria, concentrating deficits, and potentially CKD. As opposed to chronic urate nephropathy, which occurs in patients with gout, acute uric acid nephropathy tends to occur in patients with bulky cancers in whom tumor lysis syndrome develops. It is characterized by oliguric AKI secondary to precipitation of uric acid crystals within the tubules. Classic measures used to prevent tumor lysis syndrome have included the use of allopurinol, alkalization of urine, and aggressive volume expansion. Newer medications, such as uricase (Rasburicase), catalyze uric acid into allantoin, which is more readily excreted by the kidney and may thereby decrease the incidence of tumor lysis syndrome.

The presence of gout in concert with CKD warrants consideration of the following potential underlying disorders:

- Familial juvenile hyperuricemia
- Chronic lead intoxication
- Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT)

Familial juvenile hyperuricemia is an autosomal dominant disorder localized to chromosome 16³⁵ and is characterized by severe underexcretion of filtered urate and renal failure. The renal failure results from tubulointerstitial disease, but this does not appear to be due to urate deposition. Early treatment with allopurinol may improve the kidney prognosis.³⁶

Chronic lead intoxication leads to tubulointerstitial damage with resultant impairment of tubular function. It can be manifested clinically as saturnine gout as a result of decreased urate secretion,³⁷ renal glucosuria, or aminoaciduria. Continued lead exposure produces progressive tubular atrophy and fibrosis, hypertension, and a decline in kidney function. Therefore, occult chronic lead exposure should be suspected when the constellation of hypertension, gout, and CKD is uncovered.

HPRT deficiency is an X-linked disorder. Deficiencies of HPRT lead to an inability to recycle hypoxanthine and guanine and result in the overproduction of uric acid. Clinically, its most severe form is known as Lesch-Nyhan syndrome, which is characterized by mental retardation, choreoathetosis, and self-mutilating behavior with signs of gouty arthritis and uric acid stone disease. Less severe forms of HPRT deficiency may appear as early-onset gout and sometimes have a positive family history.

Renal lesions with other rheumatic diseases

Poststreptococcal GN rarely develops in individuals who contract acute rheumatic fever because the nephritogenic and rheumatogenic strains of β -hemolytic streptococci are different. However, cases of mesangial proliferative GN have been described.³⁸

Persistent mesangial proliferative GN, manifested clinically as non-nephrotic-range proteinuria associated with microscopic hematuria, sometimes develops in patients with polymyositis and dermatomyositis.

A variety of renal abnormalities have been described in patients with psoriatic arthritis, including secondary amyloid and membranous GN.³⁹

Common renal manifestations of sarcoidosis include hypercalcemia-associated nephrolithiasis and interstitial nephritis with granuloma formation.⁴⁰ Infrequently, sarcoidosis may be manifested as obstructive uropathy secondary to retroperitoneal lymph node involvement. TINU syndrome is relatively uncommon and is characterized by eye pain associated with renal failure in young women.⁴¹ The differential diagnosis for interstitial nephritis associated with ocular findings should also include a number of rheumatologic disorders: sarcoidosis, ANCA-associated granulomatous vasculitis, SLE, Sjögren syndrome, and Behçet disease.

RENAL COMPLICATIONS OF DRUGS USED IN RHEUMATOLOGY

Rheumatologists are well aware of the potential nephrotoxicity of the medications that they prescribe. In addition, many over-the-counter nonprescription drugs have significant potential for adversely affecting kidney function. It is estimated that on any given day, one in five adults uses an analgesic medication. Use of such drugs is even more prevalent in patients with rheumatologic disorders, and many use them without informing their doctor. Therefore, periodic assessment of kidney function is warranted.

Nonsteroidal antiinflammatory drugs

Traditional NSAIDs inhibit both isoforms of the cyclooxygenase (COX) enzyme (COX-1 and COX-2), thereby impairing the production of prostaglandins (PGE₂), prostacyclin (PGI₂), and thromboxanes.

By focusing on inhibition of COX-2 to maintain antiinflammatory efficiency but avoiding inhibition of COX-1, there was also the consideration that these drugs might be more sparing of the kidneys. However, clinical models have demonstrated that COX-2 is probably the key sodium-regulating enzyme within the salt-handling parts of the kidney. A meta-analysis examining 19 randomized trials using COX-2 inhibitors demonstrated that they increased systolic blood pressure when compared with placebo and traditional NSAIDs.⁴² Additionally, selective COX-2 inhibitors induce reversible reductions in the GFR similar to that seen with traditional NSAIDs. As with nonselective NSAIDs, these effects are rarely of clinical significance unless they occur in a patient with compromised kidney function. Based on these data, one can assume that all NSAIDs, whether traditional or COX-2 selective, have a dose-dependent effect on blood pressure.

Functional effects

Reduction in glomerular filtration rate

The most common renal side effect of NSAIDs is a functional reduction in the GFR. Clinically, this is manifested as a clinical spectrum of mild azotemia to frank oliguric AKI. Typically, the azotemia is reversible once use of the NSAID is discontinued. Unfortunately, the functional azotemia may progress to acute tubular necrosis, which may take weeks to resolve or, on rare occasion, can result in permanent kidney failure. The risk for AKI from NSAIDs is dose dependent and most often manifested within the first few weeks.⁴³

The major risk for the development of functional azotemia with NSAID use is preexisting kidney disease or use in combination with other nephrotoxic agents. Additionally, NSAIDs are relatively contraindicated in settings of preexisting renal hypoperfusion that occur with effective intravascular volume depletion, either absolute or relative, such as nephrotic syndrome, congestive heart failure, cirrhosis, and protein-wasting enteropathies. Finally, because of progressive CKD with aging, one should prescribe NSAIDs judiciously in the elderly. Renal function should be monitored closely in high-risk patients treated with NSAIDs.

Hyperkalemia

Under normal conditions, PGI₂ stimulates renin-angiotensin-aldosterone secretion. Inhibition of PGI₂ may result in severe hyperkalemia, especially in patients with underlying CKD.

Peripheral edema

Inhibition of PGE₂ results in increased sodium reabsorption, which is manifested as edema. Edema typically occurs within the first week of therapy and is associated with a 1- to 2-kg gain in weight.

Interstitial nephritis and nephrotic syndrome

Less frequent than their functional effects, NSAIDs can produce overt histologic lesions of the kidneys, specifically, allergic interstitial nephritis, minimal change disease, and probably membranous nephropathy.⁴⁴

Allergic interstitial nephritis

Allergic interstitial nephritis occurs as an idiosyncratic reaction to NSAIDs and was commonly associated with fenoprofen use. Clinically, patients have AKI associated with mild proteinuria, usually less than 1 g/day. Rash, eosinophilia, and other systemic features are generally absent.

Nephrotic syndrome

NSAID-induced minimal change disease is typically manifested as anasarca and nephrotic-range proteinuria associated with tubulointerstitial nephritis.⁴⁵ Membranous nephritis is also manifested as massive proteinuria.⁴⁴ Kidney biopsy is needed to distinguish between these two histologic lesions because both are associated with nephrotic syndrome.

Analgesic nephropathy and papillary necrosis

Analgesic nephropathy is characterized by renal papillary necrosis and chronic interstitial nephritis caused by prolonged and excessive consumption of combination analgesics, typically those containing phenacetin. Analgesic nephropathy is manifested as patchy interstitial ischemia and fibrosis in the renal medulla.

Chronic use of NSAIDs is generally safe. However, daily NSAID use for more than 1 year may be associated with an increased risk for CKD, perhaps secondary to papillary necrosis. In the setting of AKI, NSAID therapy should be discontinued immediately. The hemodynamically mediated alterations typically improve relatively quickly, but NSAID-related glomerulopathy and CKD may persist after discontinuation of the offending agent.

Calcineurin inhibitors: cyclosporine and tacrolimus**Acute kidney injury**

Cyclosporine is associated with both acute and chronic renal toxicity.⁴⁶ The other major calcineurin inhibitor, tacrolimus (FK506), has the same potential for nephrotoxicity as cyclosporine does.⁴⁷ Both agents cause dose-dependent renal afferent artery vasoconstriction with subsequent acute decreases in the GFR.

Hypertension

Both calcineurin inhibitors can induce hypertension through a variety of mechanisms, including acting as powerful vasoconstrictors of the preglomerular vasculature and enhancing vascular responsiveness to vasopressin and angiotensin, as well as other mechanisms of action.

Chronic kidney disease

The long-term nephrotoxicity of calcineurin inhibitors appears to be dependent on both time and dose, results from interstitial fibrosis, and tends to be irreversible. This chronic nephrotoxicity is well documented in patients with rheumatoid arthritis.⁴⁷

Hemolytic-uremic syndrome

Though an infrequent complication, both calcineurin inhibitors have been implicated in causing hemolytic-uremic syndrome or a microangiopathic syndrome.

Hyperuricemia

Cyclosporine causes hyperuricemia and may lead to gout in individuals both with and without an organ transplant.⁴⁸ The afferent artery constriction from cyclosporine results in increased proximal tubular uric acid absorption and hyperuricemia. Calcium channel blockers such as amlodipine significantly reduce the hyperuricemia associated with cyclosporine use. Uricosuric agents or allopurinol may be beneficial.

RHEUMATOLOGIC COMPLICATIONS OF KIDNEY DISEASE

Most disorders of the soft tissues, joints, and bones that are referable to kidney disease occur in the setting of a diminished GFR, that is, with

CKD or in the post-kidney transplant setting. The cause of most can be traced to the biochemical imbalances classically associated with kidney failure, including disturbances in calcium and phosphorus homeostasis as a result of alterations in the vitamin D and parathyroid hormone (PTH) axes and retention of uremic toxins, such as β_2 -microglobulin. An exception to this rule is the syndrome of hereditary hypophosphatemic rickets, in which the GFR is normal but there is excessive renal tubular wasting of phosphorus.

Rheumatologic complications in patients with ESRD are very common, with more than 70% having joint pain. Additionally, a temporal relationship is seen between the duration of kidney disease and the prevalence of rheumatologic conditions.

Etiologic factors specific to kidney failure and their associated rheumatic syndromes **β_2 -Microglobulin amyloidosis**

β_2 -Microglobulin is an 11.8-kDa protein that is a component of the major histocompatibility complex type I antigen. It is normally filtered by the glomerulus and reabsorbed and catabolized by renal tubular cells. In ESRD, production exceeds excretion, which can result in a 60-fold increase in plasma β_2 -microglobulin concentration. The β_2 -microglobulin protein then appears to be modified by 3-deoxyglucose to form a glycosylated protein, which resists further catabolism and is found in amyloid deposits.⁴⁹

β_2 -Microglobulin has a high affinity for collagen, which may explain its predilection for deposition in bones, joints, and synovium. An autopsy study demonstrated a direct correlation of amyloid deposition with the number of years of dialysis.⁵⁰

Clinical features of β_2 -microglobulin amyloidosis include carpal tunnel syndrome, a destructive spondyloarthritis, bone cysts and fractures as a result of β_2 -microglobulin amyloid, and shoulder pain secondary to periarticular deposits of β_2 -microglobulin in the joint capsule, along with joint tenderness and loss of mobility (see Chapter 168). Similarly, adhesions caused by deposition of β_2 -microglobulin in the flexor tendons of the hand can result in contractures and thickening. Joint effusions are common with periarticular deposition of β_2 -microglobulin, especially in the shoulders and knees. See Chapter 168 for more details on this syndrome.

Calcium, phosphorus, and parathyroid hormone derangements

As the GFR declines, the filtered load of phosphate decreases, thereby leading to a positive phosphate balance. This can be seen in as early as stage 2 CKD (see Table 38.2). Phosphate retention increases as the GFR declines. Prolonged hyperphosphatemia can lead to soft tissue and vascular calcifications related to an increase in the calcium-phosphate product.⁵¹ An elevated calcium-phosphorus product is associated with increased morbidity and mortality.

Patients with CKD also often suffer from hypocalcemia. The etiology of the hypocalcemia is multifactorial and related to decreased production of 1,25-dihydroxyvitamin D, as well as to diffuse deposition of calcium (see later) as a result of increased calcium-phosphate product. The combination of hypocalcemia, reduced synthesis of 1,25-dihydroxyvitamin D, and hyperphosphatemia results in parathyroid gland proliferation with subsequent secondary hyperparathyroidism.

Strategies aimed at reducing hyperphosphatemia may ameliorate the development of secondary hyperparathyroidism. The serum phosphorus concentration should be maintained between 2.7 and 4.6 mg/dL, primarily through restriction of dietary phosphorus to between 800 and 1000 mg/day. However, because dietary phosphorus restrictions are often not sufficient, oral phosphate binders are needed. In the past, aluminum-based phosphate binders were used commonly, but this led to significant toxicity, including aluminum-related bone disease. Now, the most commonly used phosphate binders are calcium-based phosphate binders (calcium acetate) and phosphate-binding resin (sevelamer).

Oxalate deposition

Urinary excretion of oxalate is markedly impaired once the GFR is reduced below 20 mL/min (stage 4 CKD). Secondary oxalosis caused by CKD shares many features with the primary genetic form of hyperoxaluria, including increased vascular and osteoarticular calcification secondary to deposition of the poorly soluble calcium-oxalate complex. Avoiding carrots, spinach, cocoa, peanut butter, nuts, chocolate, megadose vitamin C, and tea will reduce dietary oxalate. Oral phosphate binders will also bind to oxalate and decrease its serum level.

Crystal arthropathies

Gout

With CKD, gout is paradoxically uncommon, in part because the fractional excretion of urate rises steadily as the GFR falls. Nevertheless, hyperuricemia is the rule in advanced CKD, which suggests that the uremic milieu suppresses the acute inflammatory response to urate crystals. An acute gout attack in patients with CKD should be treated with either intraarticular or systemic corticosteroids, depending on the number of joints involved. Colchicine is relatively contraindicated in patients in the later stages of CKD. Additionally, the use of NSAIDs may precipitate either hemodynamically mediated or tubulointerstitial AKI and should therefore be avoided in patients with CKD.

Long-term management of chronic gout with allopurinol requires dose adjustment for the diminished GFR in patients with CKD, but the dose of allopurinol should be sufficient to lower the uric acid level. The uricosuric agents sulfinpyrazone and probenecid are ineffective when the GFR is lower than 30 mL/min.

Calcium pyrophosphate dihydrate deposition disease

In patients with CKD, calcium pyrophosphate dihydrate deposition disease is more common than gout. Treatment of the acute arthritis is best accomplished with intraarticular injections; NSAIDs are relatively contraindicated.

Hydroxyapatite arthropathy

Acute episodes of joint pain, particularly in the shoulders, can punctuate the more chronic course of periartropathy because of calcium hydroxyapatite deposits. Seen in patients with ESRD, it is strongly correlated with prolonged hyperphosphatemia and an elevated calcium-phosphorus product. Crystals are usually absent on synovial fluid examination. Periarticular deposits may become large complex masses, called tumoral calcinosis.

The aims of therapy are threefold: (1) reduction of acute inflammation with intraarticular injections and cautious use of antiinflammatory drugs, (2) joint rest, and (3) reduction in calcium-phosphorus product by increasing phosphate binders and stopping vitamin D analogue administration.

Oxalate arthropathy

Arthritis associated with articular and periarticular deposits of calcium oxalate occurs secondary to CKD. Oxalate crystals are deposited in the renal parenchyma, skin, bone, and blood vessels and in and around joints. There they cause chondrocalcinosis, synovial calcification, and chronic or acute arthropathy.

Clinical features of renal bone disease

Renal osteodystrophy

Renal osteodystrophy is a term used to describe the skeletal complications of ESRD caused by a complex amalgam of various pathologic processes (see Chapter 205). The four principal types are osteitis fibrosa (formally known as osteitis fibrosa cystica), osteomalacia, adynamic bone disease, and mixed disease. Mixed osteodystrophy is an amalgam of osteitis fibrosa and osteomalacia (see later).

The classic histologic form of renal osteodystrophy is osteitis fibrosa, a lesion directly attributable to the secondary hyperparathyroidism seen with CKD. The hallmark lesion is peritrabecular fibrosis in the setting of accelerated bone resorption and formation. Clinically, it can be manifested as bone tenderness and proximal muscle weakness. Radiographic findings include subperiosteal bone resorption, best observed in the middle phalanges, and osteosclerosis.

Osteomalacia, as opposed to osteitis fibrosa, is characterized by a reduced rate of bone turnover associated with increased osteoid volume and defective mineralization. Because osteomalacia is associated with aluminum intoxication, its incidence is decreasing. Clinically, osteomalacia tends to cause more severe bone pain than osteitis fibrosa does and is also associated with pathologic fractures. Osteomalacia tends to have minimal radiographic

findings but may be associated with pseudofractures, which are radiolucent bands that run perpendicular to the long axis of bones.

Adynamic bone disease, also known as aplastic bone disease, is now the most common type of renal osteodystrophy. The pathogenesis of this condition is poorly understood, but a key factor appears to be excessive suppression of PTH. Bone turnover is markedly decreased, but unlike osteomalacia, osteoid formation is not increased. Clinically, adynamic bone disease may be asymptomatic or be manifested as hypercalcemia or an increased risk for hip fractures.⁵²

Management is based on the type of renal osteodystrophy. Although tests of PTH and serum aluminum levels may suggest the underlying pathologic process, the diagnostic gold standard is dual-labeled bone biopsy. General management should include normalization of serum phosphorus levels; correction of acidemia; avoidance of prolonged use of aluminum-containing phosphate binders, including sucralate; and control of hyperparathyroidism with the judicious use of vitamin D analogues. Despite effective therapy, intractable hyperparathyroidism may require parathyroidectomy.

"Brown tumors"

Severe hyperparathyroidism may lead to the development of osteoclastomas, also known as "brown tumors." They typically occur at the medial end of the clavicle but can form anywhere in the calvaria, long bones, sternum, or spine.

Other arthropathies in dialysis patients

Typical erosive osteoarthritis, mainly of the interphalangeal joints, is common in individuals maintained on dialysis. The clinical and radiologic features are indistinguishable from those of individuals without CKD. As in the general population, there is a female preponderance and an increased incidence with age. However, erosive osteoarthritis appears to be more common in patients with ESRD.⁵³ This increased incidence may be related to a higher incidence of hyperparathyroidism or iron overload (or both).

Tendinitis occurs frequently in patients undergoing hemodialysis; hyperparathyroidism appears to be the predisposing factor. Tendon rupture is common, principally of the quadriceps tendon but also the patellar, Achilles, triceps, or finger extensor tendons. The differential diagnosis of generalized muscle weakness in a patient maintained on dialysis is extensive and includes life-threatening processes such as severe hyperkalemia, severe hypophosphatemia, and bacteremia. More chronic or progressive weakness, if not neuropathic in origin, suggests a possible myopathy⁵⁴ that may be due to vitamin D deficiency, possible aluminum toxicity (see earlier), progressive malnourishment, or hyperparathyroidism.

Lupus tends to become more quiescent with the development of ESRD, although symptoms may continue.⁵⁵ Additionally, patients with rheumatoid arthritis may continue to have arthritis while undergoing hemodialysis. Individuals on dialysis who have previously received extended courses of corticosteroids for lupus or similar rheumatic conditions are at particular risk for hip osteonecrosis.

Arthropathies in renal transplant patients

Gout

Gout is just one of several arthropathies that are prevalent in kidney transplant recipients. The incidence of gout is increased in individuals who have received a kidney transplant and are treated with cyclosporine.

Osteopenia after transplantation

Before kidney transplantation, patients with CKD often have low bone mineral density because of renal osteodystrophy. After renal transplantation there is a rapid decline in bone mineral density. This rapid decline is due primarily to the use of glucocorticoids and persistent hyperparathyroidism. Clinically, the incidence of fractures is increased within the first 6 months after transplantation.⁵⁶ Bone loss may be reduced by the use of corticosteroid-free or ultralow-dose corticosteroid regimens. Additionally, the use of calcium, vitamin D, and bisphosphonates should be considered in all recipients of kidney transplants.

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39

The nervous system in rheumatic disease

■ JULIUS BIRNBAUM

- A wide spectrum of central nervous system and peripheral nervous system syndromes is associated with different systemic rheumatic diseases.
- An appropriate diagnostic framework can help the clinician distinguish whether neurologic syndromes are attributable to a rheumatic disease or to an alternative cause.
- Distinguishing whether neurologic syndromes stem from rheumatic diseases versus noninflammatory etiologies can help in the decision whether to implement symptomatic or immunosuppressive strategies.
- Although the American College of Rheumatology nomenclature and case definitions for neuropsychiatric systemic lupus erythematosus (SLE) are a useful tool, recent studies regarding the frequency of individual neurologic syndromes in SLE patients suggest that these case definitions may need to be modified.
- Demyelinating syndromes that occur in patients with SLE or Sjögren syndrome can be distinguished from multiple sclerosis or another idiopathic demyelinating syndrome.

INTRODUCTION

The interface between neurology and rheumatology includes a fascinating spectrum of syndromes that can affect any region in the central nervous system (CNS) and the peripheral nervous system (PNS). Syndromes may be seen ubiquitously across rheumatic diseases (e.g., a mononeuritis multiplex) or may be associated with only a single disease. Some neurologic disorders may reflect ominously escalating disease activity and require quick institution of immunosuppressive therapy. However, other neurologic syndromes may stem entirely from causes other than rheumatic diseases for which immunosuppressive therapy is contraindicated. Therefore the clinician needs to consider carefully other vascular, infectious, traumatic, metabolic, and neoplastic causes of neurologic syndromes.

On one level, this chapter is devoted to the neurologic complications of rheumatic diseases, with a focus on the spectrum of neurologic syndromes seen in individual rheumatic disorders as well as across many rheumatic diseases. However, this chapter also introduces the paradigm of using phenotypes of neurologic disease as a tool for identifying immunopathogenic mechanisms, and to better understanding when to apply immunosuppressive versus symptomatic therapies.¹ The reader is referred to other chapters in this book for a discussion of neurologic manifestations of antiphospholipid syndrome (Chapter 139), inflammatory myopathies (Chapter 149), and CNS vasculitis (Chapter 164). The neurologic complications of the remaining rheumatic diseases are addressed in this chapter.

EVALUATION OF THE PERIPHERAL NEUROPATHIES IN SYSTEMIC RHEUMATIC DISEASES

Classification and initial diagnostic approach to peripheral neuropathies

The classification, spectrum, clinical features, and initial diagnostic evaluation of neuropathies in rheumatic diseases are considered in [Figure 39.1](#). The most common neuropathies reported across the spectrum of rheumatic diseases are axonal sensory/sensorimotor polyneuropathies. Such symmetric

polyneuropathies occur mainly in the distal feet, are associated with lower rheumatic disease activity, are indolently progressive, and rarely require the use of immunosuppressive strategies. The evaluation of potential neuropathies should include electrodiagnostic studies, which can distinguish between axonal and demyelinating neuropathies and can help uncover asymmetric features that might suggest either a radiculopathy or a mononeuritis multiplex (see later in this chapter).

In contrast, there is a subset of painful sensory neuropathies may cause burning pain but may be associated with normal electrodiagnostic studies. Such neuropathies are designated as “small-fiber” neuropathies, target thinly myelinated A-delta and unmyelinated C-fiber nerves, and can be associated with selective deficits to “small-fiber” modalities (i.e., pinprick and temperature). Given that the integrity of such unmyelinated nerves cannot be assessed by electrodiagnostic studies, other diagnostic approaches such as skin biopsy or quantitative sensory testing are required.

Nerve and muscle biopsy is primarily reserved for patients in whom there is clinical or electrophysiologic suspicion of mononeuritis multiplex (see later in this chapter). Neuropathies can occur due to competing comorbidities rather than rheumatic diseases, and a strategy for memorizing most of the differential diagnoses is shown in [Box 39.1](#). The diagnostic approach to vasculitic neuropathies now represents a suitable starting point to focus on the specific PNS manifestations of rheumatic diseases.

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS OF VASCULITIS

Presentations of vasculitic neuropathies

Mononeuritis multiplex

Mononeuritis multiplex (also termed *multiple mononeuropathy*) has been described as one of the most dramatic disorders in clinical medicine because the presentation and evolution of this neuropathy can be stark and fulminant.^{1,2} When it occurs with such an explosive tempo, multiple named nerves are affected and can be remembered using the following three As: Acuity, Asymmetry, and Asynchrony. However, mononeuritis multiplex can also develop more gradually in a stepwise pattern that manifests over weeks or even over months.

Mononeuritis multiplex is necessarily a sensory neuropathy, which is usually painful. The absence of pain is a clinical red flag that argues against the diagnosis of mononeuritis multiplex. Sparing of sensory nerves on nerve conduction study is diagnostically incompatible with mononeuritis multiplex.

Mononeuritis multiplex is usually a length-dependent neuropathy. The longest nerves in the lower extremities are affected, including the peroneal nerve and sural nerve (more than 80% of cases), followed by the tibial nerve (38% to 50%), and then nerves in the upper extremity, including the ulnar nerve (35%), median nerve (35%), and radial nerves (25% to 40%).²

Other clinical presentations of a vasculitic neuropathy

Symmetric sensory or sensorimotor polyneuropathies may occur in some vasculitides at a frequency similar to that of mononeuritis multiplex. Small-fiber neuropathies are infrequently described but likely underdiagnosed.

Diagnosis

Electrodiagnostic studies

Nerve-conduction studies (NCS) are an essential part of the diagnostic workup of potential mononeuritis multiplex. First, such studies can confirm

peripheral neuropathies are increased compared with giant cell arteritis, Behçet syndrome, and other vasculitides. The frequency of vasculitic neuropathies is higher in Churg-Strauss syndrome than in other ANCA-associated vasculitides, which may reflect the fact that peripheral nerve injury in Churg-Strauss syndrome occurs due to eosinophilic infiltration as well as ischemic disease.

The wide range of prevalences of neuropathies reported in specific vasculitides reflects differences in how neuropathies were ascertained (clinically, electrophysiologically, and/or through tissue biopsies) and whether cohorts were composed of unselected patients or highly select patients studied at tertiary care neuromuscular centers.

Importance of evaluating for infection in patients with granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) and Churg-Strauss syndrome

Cranial neuropathies may reflect regional granulomatous disease in the retro-orbital region (e.g., an orbital pseudotumor syndrome), in the cavernous sinus, at the base of the meninges (e.g., basilar meningitis), or in the arachnoid and pial meningeal layers (e.g., leptomeningitis).⁴ But in all systemic vasculitides and rheumatic diseases, such syndromes can also represent skull-based, meningeal, and/or parenchymal extension of opportunistic infections. Therefore rapid evolution of ophthalmoparesis, facial numbness, or lower cranial nerve deficits (which may suggest a basilar meningitis) should prompt emergent neuroimaging, ideally by magnetic resonance imaging (MRI); a spinal tap if there is suspicion of a meningeal process; and consultation with a neurologist.

Other cranial neuropathies can occur due to vasculitic mechanisms as opposed to space-occupying disease. Such neuropathies include trigeminal neuropathies and facial neuropathies (unilateral more than bilateral). Hearing loss in a patient can be conductive (e.g., due to granulomatous disease causing bony or cartilaginous destruction), sensorineural, or mixed.

Treatment of vasculitic neuropathies

Treatment of mononeuritis multiplex should reflect the disease-specific strategies used when other vital end organs are jeopardized (e.g., a pulmonary-renal syndrome). See Chapters 155 and 157 on polyarteritis nodosa and ANCA-associated vasculitis for a discussion of protocols used for induction and maintenance of remission. In general, treatment of mononeuritis multiplex invariably uses regimens that induce remission in other vital organs. Studies have suggested that rituximab may have equivalent efficacy to cyclophosphamide in inducing disease remission in the ANCA-associated vasculitides.⁷ Oral or intravenous regimens of cyclophosphamide can be used in other systemic vasculitides. There is also ongoing interest in evaluating the efficacy of rituximab for the treatment of vasculitic neuropathies in cryoglobulinemias and Sjögren syndrome, which may be mediated by direct antibody damage, immune-complex deposition, and exuberant B-cell hyperreactivity.

Although immunosuppressive therapy is uniformly required in patients with the asymmetric presentation of mononeuritis multiplex, symmetric polyneuropathies may be more indolently progressive, can be clinically restricted to distal regions, and may cause primarily sensory as opposed to motor deficits. The decision about initiating immunosuppressive therapy may be guided by whether there is background disease activity or concomitant involvement of other end organs. However, such symmetric polyneuropathies may be caused by corticosteroid-induced diabetes or by other mechanisms associated with cumulative disease damage. In such cases, symptomatic as opposed to immunosuppressive therapy may be warranted.

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS OF SJÖGREN SYNDROME

Patients with Sjögren syndrome (see also Chapter 138) can be affected by a wide spectrum of most of the neuropathies which are noted in Figure 39.1. This includes axonal neuropathies (e.g., symmetric axonal sensory/sensorimotor polyneuropathies as well as vasculitic neuropathies), small-fiber neuropathies, other sensory neuropathies such as neuronopathies, autonomic neuropathies, and sensory and motor cranial neuropathies.¹

It may initially be difficult to approach the classification of such neuropathies in a systematic fashion, to understand whether a given neuropathy is typical or unusual in an individual patient with Sjögren syndrome, to assess the relationship of neuropathies to different etiopathogenic pathways, and finally to use an understanding about frequency, classification, and

etiopathogenesis to devise an effective therapeutic plan. These issues are therefore described in what follows.

Classification of peripheral neuropathies in Sjögren syndrome

Axonal neuropathies

Axonal polyneuropathies are reported in 1% to 10% of patients with Sjögren syndrome.^{1,8} These neuropathies are usually symmetric, are sensory or sensorimotor, typically manifest with length-dependent sensory symptoms, have minimal to absent weakness, are insidiously progressive, and rarely require immunosuppressive therapy.

The presentation of asymmetric mononeuritis multiplex is decidedly less common, seen in fewer than 1% of Sjögren syndrome patients, but it can lead to severe weakness that requires immunosuppressive therapy. The presentation, diagnosis, and evaluation of mononeuritis multiplex in Sjögren syndrome is similar to that described in the previous discussion of vasculitic neuropathies.

Mononeuritis multiplex can be associated with stigmata of cutaneous vasculitis, clinical and serologic indicators of higher disease activity, including cryoglobulinemia and C4 hypocomplementemia.

Sensory neuronopathies

Although occurring in fewer than 1% of Sjögren syndrome patients, the sensory neuronopathies (also called ganglionopathies) are devastating sensory neuropathies. There is loss of position sense that can affect larger joints. Such functional “deafferentation” of limbs potentially robs patients of the ability to ambulate, even when strength is preserved.⁹ Nerve-conduction studies reveal loss of multiple sensory nerve action potentials with minimal involvement of motor nerves.

Small-fiber neuropathies

Small-fiber neuropathies have been extensively reported in Sjögren syndrome patients but have not been well characterized in unselected cohorts.^{9a} Therefore, although the prevalence of such small-fiber neuropathies is difficult to ascertain, clinicians will readily appreciate that Sjögren syndrome patients frequently report burning pain and other somatosensory features described in small-fiber neuropathies. Altogether, such small-fiber neuropathies may be more prevalent than axonal neuropathies.⁸ The future characterization of small-fiber neuropathies by skin biopsy findings and other diagnostic biomarkers will clarify the frequency and mechanisms of small-fiber neuropathy in Sjögren syndrome.

Other neuropathies

Cranial neuropathies can affect sensory nerves (especially the trigeminal nerve) more than motor nerves. Unilateral or bilateral trigeminal neuropathies are the most frequent cranial neuropathy, followed by seventh nerve palsies. Sjögren syndrome patients frequently have symptoms suggestive of dysautonomia, manifesting as orthostatic symptoms, complaints of hypohidrosis or hyperhidrosis, decreased or increased gastric motility, and difficulty urinating. Formal diagnostic evaluation for autonomic neuropathies is limited to specialized centers, and therapy is mainly supportive, as has been described.¹ Plexopathies and demyelinating neuropathies are uncommon and occur in fewer than 1% of Sjögren syndrome patients.

Diagnostic evaluation, etiopathogenic relationship, and therapeutic options

The diagnostic evaluation should proceed as illustrated in Figure 39.1, using electrodiagnostic studies to help exclude a radiculopathy and to further characterize axonal neuropathies as a result of axonal and/or demyelinating disease, and skin biopsy to evaluate for potential small-fiber neuropathies. In general, mononeuritis multiplex may reflect mechanisms of immune-complex deposition, is associated with high disease activity, and requires immunosuppressive therapy. The distal axonal polyneuropathies are associated with lower disease activity and are usually managed symptomatically. The relationship of small-fiber neuropathy to disease activity requires further evaluation. Intravenous immunoglobulin has been reported to be efficacious in case series of patients with small-fiber neuropathy who have severe pain refractory to other immunosuppressive strategies¹⁰ and has been reported to halt further proprioceptive impairment in patients with sensory neuronopathies.¹

Irrespective of the use of immunosuppressive therapies, most neuropathies are painful and require separate treatment for neuropathic pain. The tricyclic antidepressants are avoided given their anticholinergic adverse effects, which can exacerbate sicca manifestations. Other therapies include

antiepileptic agents and the serotonin-norepinephrine reuptake inhibitors, which can also be effective in patients with fibromyalgia-type pain. However, Sjögren syndrome patients are more likely to develop adverse effects such as fatigue and cognitive slowing. Strategies may include slower titration toward therapeutic doses, combination of agents to induce therapeutic synergy, and a low threshold for referral to a neurologist or other pain specialist.

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS OF RHEUMATOID ARTHRITIS

As with other extraarticular complications of rheumatoid arthritis (RA), earlier and more aggressive treatment of RA has resulted in a decreased prevalence of neurologic complications that may be a result of disease activity (see Fig. 39.1). For example, mononeuritis multiplex is among the least frequent neuropathies encountered in RA patients, is associated with high disease activity, and requires immunosuppressive therapy. In contrast, distal axonal sensory or sensorimotor polyneuropathies have been reported more frequently (up to 10% of RA patients), are associated with lower disease activity, have an excellent prognosis, and can be managed symptomatically.

Compressive neuropathies are the most common neuropathies, described in 20% to 70% of patients.¹¹ Carpal tunnel syndrome (affecting the median nerve) and tarsal tunnel syndrome (affecting the posterior tibial nerve) are the most common compressive neuropathies, respectively presenting as numbness in the first three digits of the hands and feet. Compression neuropathies may result from synovial or bursa inflammation or can occur due to joint deformities or posttraumatic fibrosis not stemming from active disease. Conservative strategies, including splinting and tendon sheath injections, are tried before surgical release.

In contrast to compressive neuropathies, inflammatory demyelinating neuropathies have been temporally associated with the use of tumor necrosis factor (TNF) inhibitors.^{11a} Despite the rarity of these inflammatory demyelinating neuropathies (described in fewer than 100 RA patients treated with TNF inhibitors), such demyelinating neuropathies are otherwise not seen in RA patients, and therefore an etiopathogenic relationship is suggested. Although some patients show improvement or stabilization when the offending TNF inhibitors are withdrawn, other patients require treatment with intravenous immunoglobulin or other therapies used in the treatment of primary demyelinating neuropathies.

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS OF OTHER RHEUMATIC DISEASES

The most frequent neuropathies in patients with scleroderma and mixed connective tissue disease are entrapment neuropathies (usually at the wrist), followed by trigeminal neuropathies, which can be bilateral and occur in up to 5% of patients.¹² Axonal neuropathies have been infrequently described only in isolated case series or case reports, and require only symptomatic therapies. Gastrointestinal dysmotility may in part reflect an autonomic neuropathy.

NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Spectrum and attribution of neurologic syndromes: challenges and limitations

The neuropsychiatric manifestations of systemic lupus erythematosus (NPSLE) (see also Chapter 135) represent a logical and opportune disease to bridge the discussion between the PNS and CNS manifestations of rheumatic diseases. There are similar themes that are shared between PNS and CNS syndromes seen in SLE.

First, more so than patients with any other rheumatic syndrome, SLE patients show a unique predilection for developing either CNS or PNS neurologic disease attributable to causes other than primary rheumatic diseases. For example, between 40% and 50% of neurologic syndromes occurring in SLE patients may be attributable to non-SLE causes.^{13,14} Unlike patients with Sjögren syndrome, SLE patients are more likely to be taking corticosteroids and immunosuppressive therapies and are more prone to develop CNS manifestations due to infections. *Given that infections can mimic any CNS neurologic syndrome that may otherwise be mistakenly*

attributed to SLE, infections need to be included at the top of any differential diagnosis and evaluated with an appropriate level of vigilance.

Second, the current understanding of the spectrum of NPSLE has shifted dramatically over the past 10 to 15 years. This point is illustrated in Figure 39.2. Figure 39.2a shows the individual CNS and PNS syndromes that were included in the 1999 American College of Rheumatology (ACR) nomenclature and case definitions for NPSLE.¹⁵ These ACR NPSLE case definitions include 12 CNS and 7 PNS disorders. However, since publication of these ACR NPSLE case definitions, the frequency of individual neurologic syndromes has been evaluated in several cohort studies. As discussed later, several NPSLE syndromes included in the case definitions were nonspecifically seen with similar frequency in normal control subjects. Furthermore, new insights into disease classification and etiopathogenesis have been derived from other neurologic diseases and applied to NPSLE, which suggests that the ACR NPSLE case definitions need to be revised.

Altogether, these findings suggest that although the 1999 ACR NPSLE case definitions represented a valuable starting point in establishing a uniform nomenclature, such case definitions are not entirely representative of the spectrum of NPSLE disease. Therefore Figure 39.2 includes a proposed revision to the ACR case definitions. In Figure 39.2a, the neurologic syndromes initially included in the 1999 ACR case definitions that are not included in the proposed revision are indicated in shaded boxes. In Figure 39.2b, the neurologic syndromes not included in the 1999 ACR case definitions but that are included in the proposed revision are italicized. Such proposed revisions can also be useful in the evaluation of patients with suspected NPSLE, and is further discussed later in this chapter.

Peripheral nervous system manifestations of systemic lupus erythematosus

Syndromes that are currently included in the ACR NPSLE case definitions but potentially are not part of the spectrum of NPSLE

PNS syndromes that are currently included in the ACR NPSLE case definitions but potentially do not constitute part of the spectrum of PNS NPSLE are demyelinating syndromes (including Guillain-Barré syndrome) myasthenia gravis, and plexopathies, which all have been described in fewer than 1% of patients.¹⁶ These disorders may therefore be considered as the manifestation of a secondary inflammatory syndrome and therefore potentially diagnosed and treated in the same way as in non-SLE patients.

Syndromes that are not currently included in the ACR NPSLE case definitions but are part of the spectrum of NPSLE

Syndromes that are not currently included in the ACR NPSLE case definitions but constitute part of the spectrum of PNS NPSLE include the small-fiber neuropathies.^{17,18} Neuropathies have been described in up to 14% of SLE patients. Up to 40% of SLE neuropathies are attributable to non-SLE comorbidities (see Box 39.1). However, small-fiber neuropathies have been well described in SLE patients who are part of highly select neuromuscular cohorts.

Syndromes that are currently included in the ACR NPSLE case definitions and are part of the spectrum of NPSLE

Neuropathies have been described in up to 14% of SLE patients,¹⁴ but 40% of neuropathies are attributable to associated non-SLE comorbidities (see the VITAMINS mnemonic in Box 39.1). Studies that reported a higher frequency of SLE neuropathies were published in an era in which SLE disease was not aggressively treated, were evaluated in comparatively smaller numbers of patients, or systematically screened for SLE neuropathies even in the absence of neuropathic symptoms.

As in Sjögren syndrome patients, the most common neuropathies in SLE patients are axonal sensory or sensorimotor polyneuropathies, which as indicated in Figure 39.1 may occur in 5% to 10% of patients. Cranial neuropathies and mononeuritis multiplex are seen less frequently, with both neuropathies occurring at a frequency of less than 1%. Mononeuritis multiplex is associated with highly active SLE and requires immunosuppressive therapy. Yet except in the vasculitic neuropathies, there are no SLE-specific features that are found in SLE patients with particular subtypes of neuropathies but not in SLE patients without neuropathies. Therefore, with the exception of vasculitic neuropathies, the treatment of neuropathies is guided by treatment of the underlying SLE disease. Symptomatic therapies may be appropriate for patients with distal axonal polyneuropathies if such polyneuropathies are not progressing to cause significant weakness, if the intensity and distribution of neuropathic pain is unchanged, and if such neuropathies are not associated with increasing SLE activity.

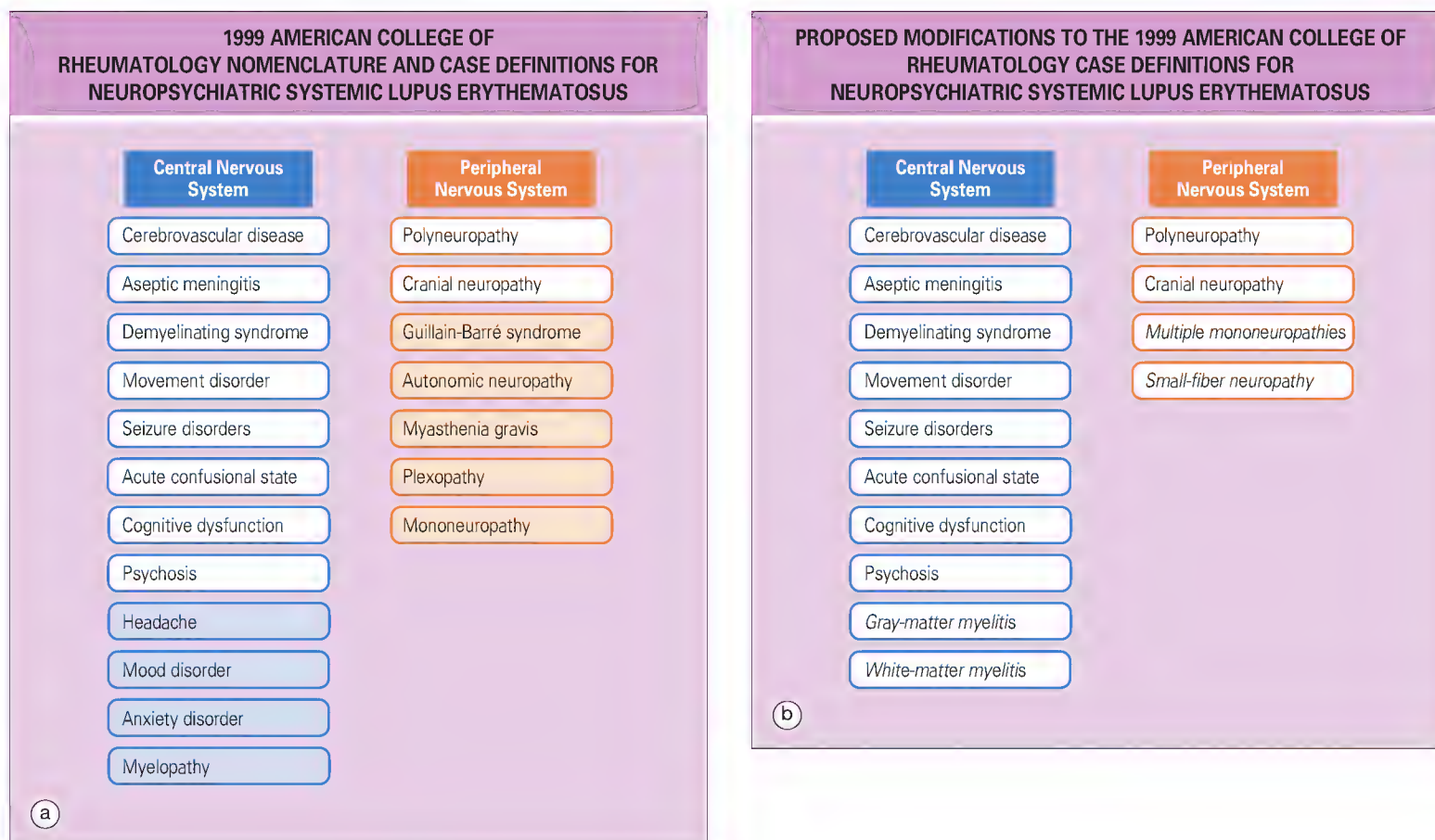


Fig. 39.2 (a) The 19 case definitions included in the 1999 American College of Rheumatology (ACR) nomenclature and case definitions for neuropsychiatric systemic lupus erythematosus (NPSLE). (b) The proposed revision to the ACR NPSLE case definitions no longer includes central nervous system syndromes that occur with similar frequency in non-SLE controls, (i.e., headache, mood disorders, and anxiety disorders) and no longer includes peripheral nervous system syndromes described in less than 1 percent of SLE patients (e.g., Guillain-Barré syndrome, autonomic neuropathies, myasthenia gravis, and plexopathies). Recent studies that have characterized subtypes of myelitis, including gray-matter and white-matter myelitis, and small-fiber neuropathies in SLE patients, are included in this proposed revision.

Central nervous system manifestations of systemic lupus erythematosus

Differential diagnosis

As with the PNS manifestations of NPSLE, up to 40% of CNS syndromes in SLE patients can be attributed to non-SLE causes.¹³ The initial approach therefore requires the development of a differential diagnosis to consider such non-SLE causes. Although such a differential diagnosis can seem challenging, it can be simplified by using the VITAMINS mnemonic in Box 39.2.

Syndromes that are included in the ACR NPSLE case definitions but may not be part of the spectrum of NPSLE

Figure 39.2 indicates those CNS syndromes that are seen in SLE patients at a frequency similar to RA patients and even in healthy controls, and may not constitute part of the spectrum of CNS NPSLE.¹⁹ Such syndromes include headaches, anxiety, and depression.

However, the ultimate decision about disease attribution requires clinical judgment. For example, there may be the infrequent SLE patient who develops a headache that shows unusual severity or intractability, may be a departure from a prior headache pattern, or manifests in the context of highly active SLE with no other non-SLE cause identified. In such exceptional cases, the headache may be considered to be attributable to SLE (i.e., a “lupus headache”), even though most SLE patients have headaches that can be managed similarly to those in non-SLE patients.

Syndromes that are not included in the ACR NPSLE criteria but likely are part of the spectrum of NPSLE

Not included in the ACR criteria but probably part of the spectrum of NPSLE are the different phenotypes of demyelinating syndromes, including gray-matter myelitis, white-matter myelitis, and neuromyelitis optica.²⁰ The approach to the demyelinating manifestations of SLE and other rheumatic diseases is considered in the final section of this chapter.

BOX 39.2 DIFFERENTIAL DIAGNOSIS OF CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS—THE MNEMONIC “VITAMINS”

Vascular

- Strokes (thrombotic and embolic)
- Strokes (hemorrhagic): subarachnoid (including aneurysm from septic emboli), subdural, or epidural
- Bland (e.g., conventional risk factors for atherosclerosis)
- Infectious (e.g., septic emboli, septic thrombophlebitis)

Infectious

- Classification as to cause (bacterial, fungal, malignancy related)
- Classification as to anatomic region
 - Parenchymal (e.g., abscess, parameningeal extension of meningitis)
 - Meningeal: meningitis
 - Vascular: septic emboli, septic thrombophlebitis

Traumatic: as in the general population (e.g., traumatic epidural hematoma)

Autoimmune: other primary autoimmune or inflammatory syndromes (e.g., sarcoidosis, demyelinating syndromes)

Metabolic: uncommon, but includes hyperhomocysteinemia (vascular), vitamin B₁₂ deficiency

Iatrogenic: steroids or glucose intolerance, infections (see above), use of nonsteroidal antiinflammatory drugs (aseptic meningitis)

Neoplastic: structural/metastatic (intraparenchymal, leptomeningeal)

Structural: as in disorders seen in the general population

Prevalence, spectrum, disease attribution, and immunologic features of CNS syndromes included in the ACR NPSLE criteria

For all of the CNS syndromes considered in the following sections, the reader is urged to use the VITAMINS mnemonic (see Box 39.2) to help discriminate between SLE and non-SLE causes.

Strokes. Cerebrovascular episodes have been described in 5% to 15% of SLE patients. Small-vessel disease causing lacunar infarcts is more common than larger-vessel arterial or venous occlusive disease, embolism, and hemorrhages (subarachnoid or intraparenchymal). SLE patients with antiphospholipid syndrome require anticoagulation therapy. Libman-Sacks endocarditis can cause embolic disease, either associated with or occurring independently of antiphospholipid antibodies.

It is crucial to emphasize that, although radiologists almost always list CNS vasculitis as a potential cause of strokes in neuroimaging reports, *CNS vasculitis is an extraordinarily rare cause of SLE cerebrovascular disease.*²¹ Most cases of cerebrovascular disease are caused by a bland vasculopathy and may be mediated by risk factors for atherosclerosis also seen in the non-SLE population. Therefore the isolated presence of strokes is not an indication for immunosuppressive therapy. However, the implication of atherosclerotic disease is different in an SLE patient than in a non-SLE patient, given that atherosclerosis in SLE patients is associated with different inflammatory biomarkers, is increased 5-fold to 10-fold compared with the general population,²² and doubtlessly represents a convergence of different facets of disease activity and damage.

Seizures. Seizures have been described in 6% to 51% of different cohorts, but in unselected cohorts the reported frequency is between 5% and 20% of patients.²² Seizures that occur within the first years of SLE diagnosis can be attributed to SLE in more than 80% of cases, may be associated with high disease activity, are more frequent in blacks, can be associated with cumulative organ damage, and have not been uniformly associated with the presence of antiphospholipid antibodies.²³ Therefore treatment of background SLE activity may lead to decreased risk of recurrent seizures and antiepileptic therapy may not be required. Nevertheless, an SLE patient with new-onset seizures needs to be evaluated for non-SLE causes, including CNS infections, metabolic disorders (including uremia), and malignancies. The decision about whether ongoing antiepileptic therapy is warranted may depend on the presence of structural injury and the severity of electroencephalographic changes.

Cognitive impairment. Cognitive impairment can affect up to 80% of SLE patient within 10 years of initial diagnosis, is present at time of initial SLE diagnosis in 60% of patients, is not associated with disease activity, and does not have a progressive course.²⁴ Mild degrees of cognitive impairment (defined by the ACR NPSLE criteria as impairment in fewer than three of eight cognitive domains) is also seen in control subjects with other diseases and may not reflect unique SLE mechanisms.¹⁹ Treatment is specifically directed at detecting other causes of cognitive impairment, including small-vessel ischemia, metabolic abnormalities (including uremia), and endocrine disorders (including hypothyroidism).

Psychosis and depression. Psychosis may occur in up to 5% of SLE patients.²⁵ The clinician should consider vascular, infectious, traumatic, neoplastic, and structural causes. However, once alternative causes have been excluded, a diagnostic challenge is whether psychosis in a patient with high SLE activity stems from SLE or is confounded by and occurring due to the high-dose corticosteroids used to treat active SLE. If SLE activity has been adequately controlled, making this distinction may require empirically lowering the dose of corticosteroids and seeing whether there is clearing of the sensorium.

Other CNS manifestations. Aseptic meningitis and movement disorders are described in fewer than 1% of cases¹⁶ but are also infrequent in nondiseased control subjects and may therefore represent the CNS spectrum of NPSLE. Nevertheless, infections and other non-SLE causes need to be pursued. Aseptic meningitis due to use of nonsteroidal antiinflammatory drugs is rare but should be considered.

Diagnostic evaluation

As has been repeatedly emphasized, the first task is to use the VITAMINS mnemonic (see Box 39.2) to help distinguish whether a CNS syndrome is attributable to SLE or to a non-SLE cause. The possibility of an infection must always be relentlessly pursued. The initial evaluation also seeks to identify clinical or laboratory stigmata of active SLE disease, with the

recognition that activity in the CNS compartment may not be mirrored by findings on serologic studies. Laboratory evaluation is also important to uncover metabolic derangements associated with specific CNS syndromes; for example, uremia leading to seizures. In most cases, more severe CNS manifestations will require neuroimaging approaches. A computed axial tomographic scan can rapidly exclude most hemorrhagic events. However, different sequences on magnetic resonance neuroimaging are required for identification of a particular CNS process (e.g., strokes as can be identified on diffusion-weighted imaging), to more precisely localize clinical deficits, and to also help elucidate surrogate features indicative of CNS pathologic processes (e.g., T2 hyperintensities that may reflect edema or microvascular disease).²² Lumbar puncture studies constitute an important part of the diagnostic process and are used to help exclude opportunistic infections as a cause of a specific CNS syndrome. Electroencephalography can be used to capture seizures or abnormal interictal phenomenon. Other neuroimaging approaches, such as diffusion tensor imaging and positron emission tomography, currently are used primarily for research purposes.

Diagnostic and mechanistic implications of the association of antibodies with CNS syndromes

Antiphospholipid antibodies. Currently, the only association between antibodies and CNS disorders that has diagnostic and therapeutic implications is the detection of antiphospholipid antibodies in patients experiencing CNS thrombotic episodes. The occurrence of such thrombotic strokes in SLE patients who satisfy the laboratory criteria for antiphospholipid syndrome justifies treatment with anticoagulants.²⁶ Cross-sectional studies have reported conflicting evidence about whether antiphospholipid antibodies are associated with nonthrombotic CNS manifestations such as seizures.²⁷ Anticoagulation is not warranted in these situations.

Anti-ribosomal P protein and anti-N-methyl-D-aspartate antibodies. *In vitro* and animal model studies suggested a potential pathogenic role of antibodies directed against the NR2 portion of N-methyl-D-aspartate (NMDA) glutamate receptors in the development of cognitive impairment.²⁸ However, an association between anti-NR2 glutamate receptor antibodies and cognitive impairment has not been consistently demonstrated in SLE patients. Similarly, the results of studies reporting an association between anti-ribosomal P protein antibodies and psychosis have not been consistently replicated. Therefore anti-ribosomal P antibodies and anti-NMDA antibodies do not currently have a diagnostic role in clinical practice.

Nevertheless, the association between anti-NR2 glutamate receptor antibodies and cognitive impairment is especially compelling given that NMDA receptors are enriched in the forebrain and hippocampus and have a role in learning and memory. Therefore the following discussion considers why there may still be an etiopathogenic role for such antibodies, despite the lack of an association with phenotypes in observational studies.

Mechanisms of CNS NPSLE

In many rheumatic syndromes, demonstrating a statistically significant association between the presence of a given antibody and an observed phenotype is often considered as a prerequisite step in showing that such an antibody is pathogenic. However, when it comes to highly complex CNS neuroinflammatory syndromes, it may be conceptually unrealistic to expect that any antibody—no matter how potentially pathogenic—might be associated with a phenotype solely on a statistical basis.

There are many stochastic steps that may need to occur for even a pathogenic antibody to be associated with a particular phenotype. For example, a peripherally generated antibody in the serum may need access to the CNS compartment and require other triggers to breach the blood-brain barrier. Interestingly, disruption of the blood-brain barrier was required before anti-NR2 antibodies were associated with cognitive impairment in the murine animal model.²⁸ Once an antibody is within the CNS compartment, its pathogenicity may be further amplified or mitigated by cytokines, which may alter the inflammatory microenvironment. Therefore epidemiologic studies may need to be integrated with *in vitro* and animal model studies to consider pathogenicity using a conceptual as well as a statistical framework.

In addition to antibodies, the two other mechanisms of NPSLE include a vasculopathy that is bland and affects the microangiopathic circulation, as well as cytokines and other immunologic signatures.²² These mechanisms may interact either to precipitate or to sustain a given phenotype; for example, triggers of a microangiopathy may afford access of an antibody to the CNS compartment.

Therapeutic strategies in the treatment of neuropsychiatric systemic lupus erythematosus

Treatment of NPSLE depends on the specific neurologic manifestation but generally requires distinguishing between SLE or non-SLE causes, noting the presence of background SLE activity, and considering whether SLE causes are related to active lupus disease or noninflammatory mechanisms. In general, mild cognitive impairment, depression, and headache can be managed symptomatically as in the non-SLE population.²⁹ As in Sjögren syndrome and RA, the only axonal neuropathies that require immunosuppressive therapy are vasculitic neuropathies. In patients with seizures, eradication of SLE activity may not require ongoing immunosuppressive or antiepileptic therapy. As noted previously, strokes are almost never associated with vasculitis, do not require immunosuppressive therapy if not associated with active SLE disease, and warrant anticoagulation when associated with antiphospholipid syndrome.²⁶ For the uncommon SLE patient who may require immunosuppressive therapy strictly because of CNS disease, regimens targeting the induction and maintenance of remission that are used in other end-organ disease (e.g., cyclophosphamide for SLE renal disease) may be considered.

The most salient point, however, is that in the majority of SLE patients, the isolated manifestation of CNS disease does not require such immunosuppressive therapy.

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF SJÖGREN SYNDROME

Among all of the CNS and PNS manifestations associated with rheumatic disorders, the CNS complications of Sjögren syndrome may have led to the greatest quandaries, disagreement, and subsequent consternation, even regarding such basic issues as disease prevalence³⁰—to say nothing of conflicting accounts as to whether certain neurologic disorders even exist in Sjögren syndrome. This has engendered great uncertainty about core issues including diagnostic workup and therapeutic strategies.

Uniform criteria have not been developed for the CNS manifestations of Sjögren syndrome, and unlike the heterogeneous PNS counterparts, the CNS manifestations remain poorly parsed and explicated. Therefore it is first relevant to consider how to define CNS Sjögren syndrome. As in SLE patients, the spectrum of Sjögren CNS manifestations is more clearly demarcated by considering disease specificity (i.e., whether specific CNS manifestations are more common in patients with Sjögren syndrome than in other cohorts) and also by considering mechanistic specificity (i.e., whether CNS manifestations may reflect etiopathogenic mechanisms that are unique to Sjögren syndrome patients).

Diffuse central nervous system syndromes *Frequently occurring diffuse CNS syndromes that are not specific to Sjögren syndrome compared with the general population*

Just as it was found that some CNS neurologic syndromes included in the ACR NPSLE nomenclature are seen with similar frequency in nondiseased cohorts,³¹ many diffuse CNS syndromes that occur in Sjögren syndrome patients likely occur with similar frequency in the general population. Such CNS syndromes include mild cognitive impairment, depression, and anxiety. The therapeutic implications are that such diffuse CNS syndromes can be managed symptomatically, with the caveat that Sjögren syndrome patients may be more vulnerable to anticholinergic adverse effects of medications.

Infrequently occurring diffuse CNS syndromes that may be more specific to Sjögren syndrome

Although aseptic meningitis and meningoencephalitis are infrequent manifestations of Sjögren syndrome (less than 1% prevalence), these CNS syndromes have been richly described across different Sjögren cohorts,^{30,32,33} are seen with even greater rarity in the general population, and can therefore be conceptualized as part of the spectrum of CNS Sjögren syndrome. The diagnostic workup should seek to rule out non-Sjögren causes as detailed in the section on NPSLE.

Cognitive impairment in Sjögren syndrome: uncertain aspects of disease specificity

More than one third of Sjögren syndrome patients describe cognitive symptoms using the metaphor of “brain fog.”³² This vivid metaphor suggests involvement of *subcortical* brain regions, with Sjögren syndrome patients frequently experiencing poor concentration, difficulty multitasking, and

shortened attention spans. However, specific *cortical* domains that are conventionally assessed in the Mini-Mental State Examination—which includes the “a” domains such as acalculia, aphasia, agraphia, and alexia—are characteristically spared.

Neuropsychologic testing frequently uncovers impairment of subcortical domains and should therefore be considered for Sjögren syndrome patients who have distressing cognitive symptoms. All Sjögren syndrome patients with cognitive impairment should be screened for depression, fatigue, endocrine abnormalities (particularly hypothyroidism), and fibromyalgia, especially given that Sjögren syndrome patients reporting cognitive symptoms have an increased frequency of fibromyalgia and depression.³² Further studies are warranted to understand whether pain and fatigue are modifiable risk factors for cognitive impairment. Unlike in SLE, there are no known or novel antibody specificities associated with cognitive impairment. Immunomodulatory approaches are not warranted.

Focal CNS syndromes that are not associated with disease-specific mechanisms and may not be part of the spectrum of CNS Sjögren syndrome

Strokes and seizures have been described in select cohorts enriched with patients with neurologic disease but are infrequent in unselected Sjögren syndrome patients. Unlike SLE patients, Sjögren syndrome patients have not been consistently demonstrated to have an underlying CNS vasculopathy³³ and generally do not have a higher frequency of antiphospholipid antibodies than the general population. Therefore it is not surprising that such focal syndromes are uncommon in Sjögren syndrome patients, and future studies are warranted to see whether the frequency of strokes and seizures is even increased in these patients compared with healthy controls.

CNS vasculitis is frequently mentioned as an unsettling possibility in the radiographic differential diagnosis for a Sjögren syndrome patient with non-specific white-matter lesions on brain MRI. As in SLE, it should be emphasized that CNS vasculitis is among the rarest of CNS manifestations and almost never occurs in Sjögren syndrome, regardless of whether Sjögren syndrome patients present with diffuse or focal syndromes. Therefore, for most CNS manifestations, immunosuppressive therapy is seldom warranted. The exception is the demyelinating syndromes, which are covered at the end of this chapter.

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Spinal misalignment in RA patients can cause myelopathies or frank cord compression due to C1-C2 atlantoaxial subluxation.¹¹ Although weakness of the arms and legs may be the latest findings, clinicians should be vigilant for earlier symptoms and neurologic findings in RA patients, including new onset of neck pain, occipital neuralgia, isolated lower extremity weakness, hyperreflexia, and urinary frequency due to a spastic bladder. Evidence of C1-C2 subluxation is sought by plain radiography (using anteroposterior, flexion, lateral, open mouth, and extension views) with more than a 9-mm separation between C2 odontoid and axis (anterior subluxation) associated with increased risk of cord compression. MRI is ideal for visualizing the spinal or brain stem compression but may underestimate the extent of C1-C2 subluxation as seen on plain radiographs.

Subaxial subluxation is a rare manifestation occurring due to rostral migration of the odontoid peg through the foramen magnum. Symptoms and examination findings can include new onset of vertigo, difficulty swallowing, change in voice, and diplopia. *Brain stem compression* is life-threatening and needs to be evaluated by imaging studies, including plain radiography and MRI.

Patients with subluxation often have increased disease activity or duration, seropositive disease, high levels of inflammatory markers, and bony erosions in peripheral joints. An RA patient with evidence of subluxation should be referred to an experienced orthopedic surgeon or neurosurgeon. Other CNS manifestations include pachymeningitis and nodules occurring in different anatomic regions (e.g., in the choroid plexus or extradurally in the brain or spinal cord¹¹) and have been described in case reports or small case series to respond to biologic agents.

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF SCLERODERMA

CNS manifestations directly attributable to scleroderma are uncommon, and most syndromes should therefore prompt a search for alternative diagnostic

explanations. Posterior reversible encephalopathy syndrome has been described in scleroderma renal crisis and can cause encephalopathy, seizures, and cortical blindness. Parry-Romberg syndrome has been described as a rare CNS complication in patients with coup de sabre lesions and associated osteocartilaginous atrophy.³⁴ Hemispheric involvement ipsilateral to these lesions can cause focal syndromes, encephalopathies, and seizures, which can secondarily generalize. An inflammatory cause is suggested by the improvement of encephalopathy and seizures in response to immunosuppressive therapies.

DEMYELINATING SYNDROMES IN RHEUMATIC DISEASES: DISTINCTION FROM MULTIPLE SCLEROSIS

Distinguishing between demyelinating syndromes in rheumatic diseases such as SLE and primary demyelinating syndromes (e.g., multiple sclerosis [MS] and idiopathic transverse myelitis) is frequently regarded as challenging. However, most rheumatic patients affected by demyelinating syndromes have clinical phenotypes, antibody findings, and neuroimaging findings that are highly unusual and atypical for MS.

For example, literature stemming from the 1970s referred to SLE patients with demyelinating syndromes as having “lupoid sclerosis”³⁵ based on the premise that demyelinating disease in SLE and MS have overlapping clinical and mechanistic features. Such vernacular is embedded in the ACR NPSLE case definitions, which define demyelinating syndromes using older MS definitions and consider demyelinating syndromes such as SLE myelitis to be single diagnostic entities. However, it was recently identified that SLE myelitis encompasses two distinct syndromes—gray-matter myelitis and white-matter myelitis—with both syndromes easily distinguished from MS on initial evaluation.³⁶

SLE patients with gray-matter myelitis have clinical findings suggestive of gray-matter necrosis (e.g., flaccidity and paraplegia), with hyperacute evolution to irreversible paraplegia highly suggestive of spinal cord infarction. Furthermore, it was noted that all patients with gray-matter myelitis invariably had urinary retention occurring hours to days before irreversible

paraplegia and were fully ambulatory without any motor deficits at the time of urinary retention.

Therefore all SLE patients with unexplained urinary retention (especially those with high SLE activity) should potentially be regarded as being at high risk of cataclysmic cord infarction and should strongly be considered for pulse corticosteroid therapy.

In contrast, SLE patients with white-matter myelitis can have features overlapping those seen in neuromyelitis optica (NMO; also known as *Devic disease*). Such patients with white-matter myelitis and features of NMO have attacks of optic neuritis and myelitis that are usually more severe than those in MS, have spinal cord lesions that span more than three vertebral segments, and may have antibodies directed against aquaporin-4 (i.e., the NMO-immunoglobulin G antibody³⁶).

Similarly, Sjögren syndrome patients are more likely to have demyelinating syndromes that are consistent with NMO than with MS. Furthermore, both SLE and Sjögren syndrome patients with demyelinating syndromes usually have brain lesions that are not characteristic of MS.

In summary, by focusing on clinical phenotypes of demyelinating syndromes in rheumatic diseases, diagnostic distinction from MS can be achieved. The relationship between NMO and rheumatic syndromes requires further study.

CONCLUSION

This chapter has emphasized a paradigm whereby meticulous classification of neurologic phenotypes can be a rewarding step in the evaluation of rheumatology patients with neurologic disease. When such an approach is used, diagnostic strategies are more clearly articulated, attribution of neurologic disorders to rheumatic disease versus comorbidities is more clearly understood, and the decision about whether to institute symptomatic or immunosuppressive strategies is made more rationally. At the heart of elucidating such phenotypes is the power and beauty of integrating symptoms with a neurologic examination. With such an approach, the interface between the nervous system and rheumatic syndromes can be illuminated by future biomarker studies, which can lead to exciting insights that can improve diagnosis and suggest novel therapeutic strategies.

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EVALUATION: IMAGING TECHNIQUES

40

Conventional radiography and computed tomography

■ STACY E. SMITH

- Conventional radiography has a major role in, and remains the mainstay of, initial evaluation and follow-up of rheumatologic disease.
- Although the majority of joints may be adequately assessed using orthogonal radiographic plain film views, specialized views may be required for some joints (e.g., Norgaard views for the hand and a modified anteroposterior Ferguson view for the sacrum).
- Multidetector computed tomography (MDCT) provides excellent contrast and delineation of cortical and trabecular bone and is established as a superb diagnostic tool for visualization of subtle cortical or intraosseous lesions not visible on standard radiography due to projectional superimposition. In particular, CT evaluation of osteoarthritis and rheumatoid arthritis before and after treatment has proven more reliable than evaluation via digital radiography.
- Dual-energy CT has proven useful in evaluating gout and monitoring its treatment.
- CT-guided facet, joint, or bursal injections or aspirations are often used in the diagnosis and treatment of rheumatologic disease.
- CT angiography is useful for diagnosis and evaluation of the large-vessel vasculitides, particularly giant cell arteritis and Takayasu arteritis, with some studies reporting utility in monitoring treatment response.

CONVENTIONAL RADIOGRAPHY

Conventional radiography is the most common and least expensive modality for imaging and evaluating patients with rheumatologic disorders. In particular, it is the mainstay of initial evaluation of the hands, wrists, feet, and sacroiliac (SI) joints.

Uses

The radiographic assessment of bones and joints includes evaluation of all the following: presence or absence of bone loss or bone production; joint space narrowing (an indirect sign of articular cartilage thinning) or widening; presence or absence of calcification/chondrocalcinosis, ankylosis, subluxation, or dislocation; changes in bone mineral density; and gross soft tissue abnormalities (Fig. 40.1). Interpretation of the radiographs requires a sound knowledge of radiographic anatomy; the patient's clinical presentation, symptoms, and laboratory information; and disease pathologic processes to provide the most correct diagnosis and/or differential diagnosis. The comparison of bilateral joints can further enhance the detection of subtle abnormalities, allowing for assessment of bilateral involvement and symmetry (Fig. 40.2). Serial radiographs can be used for staging, monitoring, and assessing treatment efficacy. Validated methods for scoring

radiologic damage in joints have been developed by several authors and used extensively in clinical trials, particularly those examining osteoarthritis and rheumatoid arthritis (see Chapters 45 and 178).^{1,2}

Conventional radiography does have limitations, however, including a wide variation in image quality, an inability to evaluate the very early stages of inflammatory disease in bone and soft tissue (e.g., synovitis), and the projectional superimposition of structures due to the two-dimensional (2D) representation of three-dimensional (3D) structures in a single plane. Wide variations in image quality (differences in projection and penetration) make it vital to ensure proper exposure and accurate positioning of serial shots to obtain accurate results and to provide a true comparison with prior studies.

The inability to evaluate the very early stages of inflammatory disease (early erosions, articular cartilage abnormalities, and synovitis) is due to the insensitivity of radiographs to both the trabecular bone loss and the intramedullary component of early bone erosions as well as the lack of soft tissue detail. Magnetic resonance imaging (MRI) and ultrasonography have both been reported to be more sensitive than conventional radiography in detecting these early changes, particularly articular cartilage abnormalities and early erosions.³ Radiography has been found to be more suitable for detecting cortical bone loss, which is a later phenomenon. As a result, radiography has proven useful as the mainstay for confirming established disease and for following the known disease process, with MRI being more sensitive in predicting which patients will not experience progression of disease in clinical trials and in detecting which will be predisposed to disease (early soft tissue changes).⁴ The use of radiography as the first line of defense in early diagnosis of bisphosphonate-related femoral fractures has been crucial recently in avoiding potential complete femoral shaft fracture and its ensuing complications. Imaging characteristics in such cases include a “beaklike” lateral cortical subtrochanteric femoral fracture deformity (Fig. 40.3). This entity is seen more commonly in female patients who have been treated with bisphosphonates (e.g., alendronate) for longer than 5 years.

Projection views

The projectional nature of radiography can lead to superimposition of overlapping structures. In rheumatoid arthritis this can obscure *en-face* erosions. For this reason articular disorders and disorders affecting the axial skeleton should be evaluated in at least two orthogonal planes (sometimes three, depending on the specific joint or anatomy) to increase the diagnostic sensitivity and allow full evaluation of the extent of the disease process. In the majority of patients imaging is therefore performed using two orthogonal views: a routine anteroposterior (AP) or posteroanterior (PA) view and an accompanying 90-degree lateral view (Fig. 40.4). Specialized views and techniques have also been developed that have been invaluable in allowing assessment of specific disease processes in certain joints. Such specialized views include the Norgaard view for the hand and wrist (see Fig. 40.4) and the modified AP Ferguson view for the SI joints (Fig. 40.5). Suggested routine radiographic techniques as well as some of the more specialized techniques and projections are listed in Box 40.1.⁵



Fig. 40.1 Radiographic assessment for disease-related criteria. (a) Anteroposterior (AP) view of the metacarpophalangeal (MCP) joints in a disease- and trauma-free patient showing normal joint spaces, soft tissues, and cortical/intramedullary integrity. (b) AP view of the MCP joints with narrowing and subluxation of the joints, periarticular osteopenia, and subtle marginal cortical erosions in a patient with rheumatoid arthritis. Lupus can present as similar subluxation but without cortical erosion. (c) AP view of an MCP joint with soft tissue swelling, cortical erosions, and destruction of both sides of the joint in a patient with chronic joint infection. (d) AP view of the MCP joints with osteopenia and multiple soft tissue calcifications about the joints in a pediatric patient with rheumatoid factor–positive mixed connective tissue disease.

Hand and wrist

Although the PA view of the hand and wrist is the best conventional view for assessment of malalignment, joint space narrowing, soft tissue abnormalities, and mineralization, it is of limited use for assessment of erosive changes. The Norgaard view (sometimes referred to as the *ball catcher's view*; see Fig. 40.4) is an AP oblique view of the hand and wrist that profiles both the radial aspect of the base of the proximal phalanges in the hand and the triquetral pisiform joint, two areas where the earliest erosive changes of any inflammatory arthropathy occur. Because the fingers are not rigidly positioned by the radiographer in this view, the reducible subluxations of inflammatory arthropathies and systemic lupus arthropathy also may be easily seen.

Sacroiliac joints

The modified AP Ferguson view (see Fig. 40.5) allows the best visualization of the anteroinferior-most portion of the SI joints. This is important histologically because the lower half to two thirds of the SI joint is a true synovial joint and is the area most frequently affected by rheumatologic disorders. To obtain the Ferguson view, the patient is placed supine with knees and hips flexed. The x-ray tube is centered at L5-S1 and angled 25 to 30 degrees toward the head to best profile the SI joint. It is essentially a centrally



Fig. 40.2 Rheumatoid arthritis. Bilateral posteroanterior hand radiographs demonstrate multiple erosions involving predominantly the proximal interphalangeal and metacarpophalangeal joints. Assessment of bilateral involvement and symmetry is helpful in narrowing the differential diagnosis.



Fig. 40.3 Anteroposterior view of the right femur depicting "beaklike" focal lateral cortical thickening of the subtrochanteric femoral diaphysis characteristic of a bisphosphonate-related fracture.

coned-down modification of a pelvic outlet view directed perpendicular to the sacral inclination to allow *en-face* visualization of the entire sacrum.

Knees

Another modification of radiographic technique involves the imaging assessment of the knees. AP or PA semiflexed views of the knees are best performed with the patient in the standing (weight-bearing position) rather than the supine position so as to best assess for cartilage loss. Medial and lateral femoral tibial joints may appear symmetric and normal in a supinely

Fig. 40.4 Standard orthogonal views and specialized radiographic views. Anteroposterior (a) and lateral (b) views of a normal hand depict three-dimensional anatomic structures in two-dimensional projection correcting for possible overlap of structures if imaged in only one plane. Bilateral Norgaard view (ball catcher's view) (c) of normal hands and wrists allows better visualization of the pisotriquetral joint, first and second carpometacarpal joints, and lateral cortical margins of the second to fifth proximal phalangeal bases. Early erosive changes are best seen at these locations.



positioned patient, whereas the standing images can reveal true early joint space loss. Joint space width of less than 4 mm has been reported to be consistent with cartilage loss.

Choice of joints

For patients with suspected polyarticular disorders, some authors suggest that survey radiographs of the hand and forefoot typically can provide the highest yield with the least amount of radiation exposure. Survey radiographs may be obtained for initial evaluation and at various intervals during subsequent examinations. The anatomic regions included in the survey depend on the specific disorder suspected clinically, its distribution, and laboratory findings and must reveal enough information to delineate the type and extent of the disorder without representing an overuse of the patient's, technician's, and physician's time or excessive radiation exposure and expense. Sartorius and Resnick suggest a minimum detailed high-yield radiographic survey for such investigations (see Box 40.1).⁶ Modifications to the survey are expected depending on the clinical and laboratory situation, and follow-up radiographs are not as extensive as the initial survey because they are tailored to the regions of specific interest.

Techniques and physics

X-rays are produced when highly energetic electrons interact with matter and convert their kinetic energy into electromagnetic radiation. The combination of an x-ray tube, x-ray tube housing (for shielding), x-ray field, and generator (the energy source that supplies the voltage to accelerate the

electrons and also controls voltage, current, and exposure time contributing to x-ray output) creates an x-ray beam of well-defined intensity for penetrability and spatial distribution (Fig. 40.6). Projection imaging (acquisition of a 2D image of the patient's 3D anatomy, i.e., radiography) compresses anatomic structures, concentrating the entire thickness of the patient's body into one single image known as the *radiograph*. This type of radiographic system uses the film-screen combination, consisting of a cassette, one or two intensifying screens (which decrease the radiation dose to the patient but can cause loss of spatial resolution), and a sheet of film (single or double photosensitive emulsion). Double-screen, double-emulsion film-screen systems are most commonly used for routine clinical radiography, whereas high-efficiency single-screen, single-emulsion film-screen combinations or single-emulsion film without screens is preferred for high-quality, high-resolution radiography, particularly in assessing therapeutic response to treatment of disease.

Magnification radiography

The quality of the radiographic image is important for accurate and detailed assessment of subtle skeletal abnormalities. High-resolution magnification radiography and fine-detail radiographs were developed to maximize diagnostic information. These are particularly useful in assessment of the hands, fingers, and feet. Magnification radiography is a highly specialized, not commonly available radiographic technique that results in higher resolution (sharpness), better contrast, and lower quantum noise than conventional radiography and is used primarily for research purposes.⁷ Image magnification up to 10 times that seen in conventional radiographs can be obtained. It is more sensitive than conventional radiography in detecting erosions,

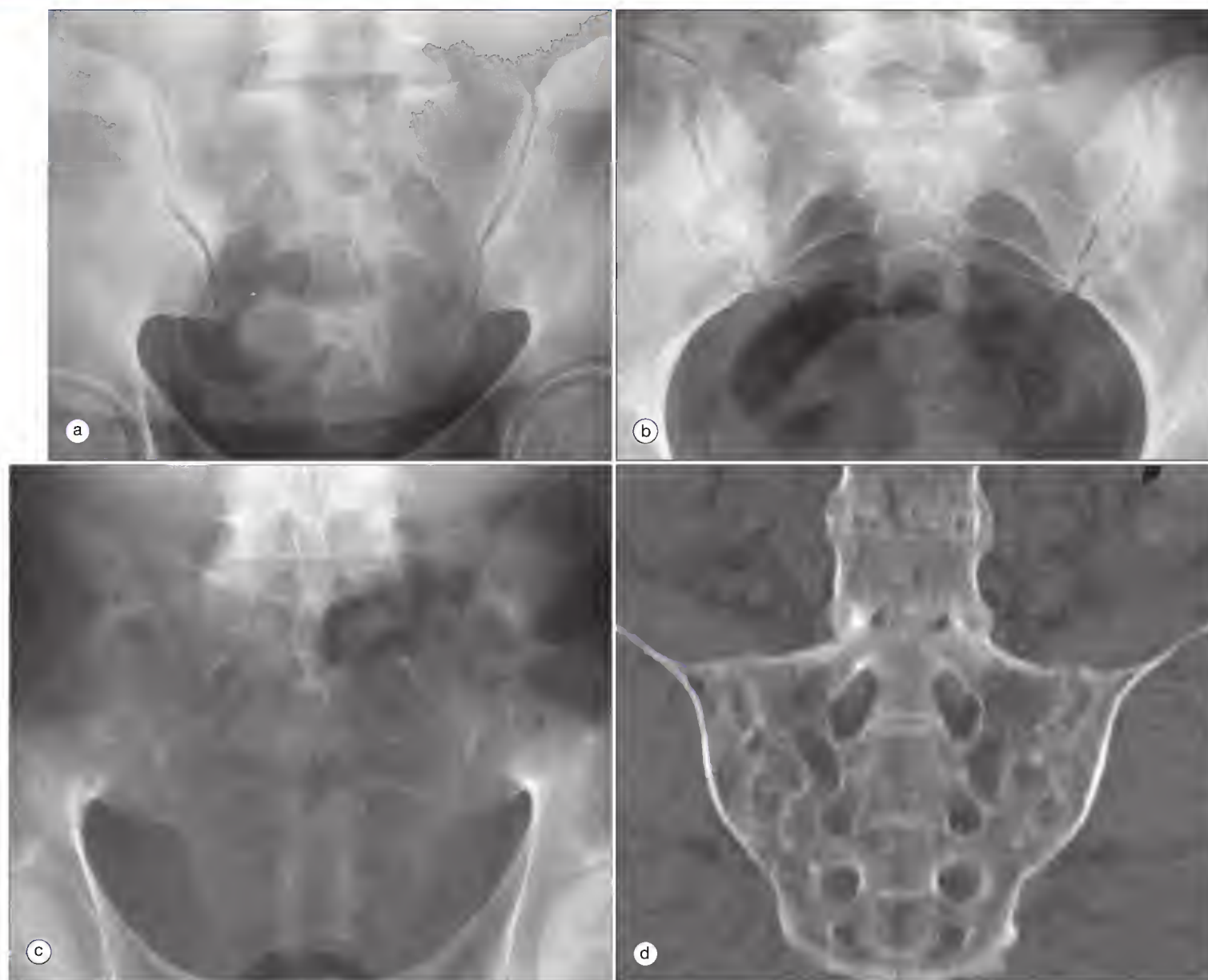


Fig. 40.5 Ferguson view of the sacrum and sacroiliac (SI) joint evaluation. Better visualization of the anteroinferior SI joints is noted in the specialized Ferguson view (a) than in the standard AP view (b) of the sacrum in a normal patient. Ferguson view in a patient with ankylosing spondylitis (c) shows apparent complete fusion of bilateral SI joints. Coronal multiplanar reconstructed computed tomographic image of the SI joints in the same patient (d) better depicts near-complete fusion of the SI joints.

patterns of bone resorption, early bone proliferation, chondrocalcinosis (i.e., crystal deposition disease [calcium pyrophosphate dihydrate deposition disease, or CPPD]), and the presence of soft tissue swelling and is useful when conventional radiography yields negative or equivocal findings. Fine-detail radiography is more sensitive in detecting the subtle early subperiosteal resorption, cortical striation, or tunneling seen in hyperparathyroidism.⁶ It may also be helpful in monitoring the course of this disease and its response to therapy.

Two forms of magnification radiography have been used:

1. *Optical magnification of fine-grain films.* The exposure obtained with conventional radiographic equipment and fine-grain industrial films is viewed with optical enlargement. Although increased radiation dose is noted with this technique, it has been used in the investigation of both metabolic and arthritic disorders by Genant⁸ and others, with good reproducibility.
2. *Direct radiographic magnification for skeletal radiography.* A small focal spot (100 to 150 μm) is used in this technique, which has received less attention than optical magnification, with only a few reports of its use in the literature.^{9,10} It is associated with fourfold increase in skin dose (exposure per surface area), but the use of a rare earth screen-film system and single-emulsion, single-screen systems as well as a decreased field of view can significantly counteract and reduce the total-body irradiation of this technique.

Digital radiography

Digital radiography has grown in popularity to become the mainstay of radiography given the current “filmless” digital age in radiology departments. This technique is more expensive because it requires high luminance and high-resolution monitors to view the digital image, generates large data sets that require large amounts of space on digital storage media, and depends on a high network bandwidth for picture archiving and communication systems (PACS).

The four main systems currently available for acquisition of digital radiographs are the following:

1. Computed radiography using photostimulable phosphor detector systems in which images are stored and viewed on PACS yet can be printed directly via a laser printer
2. Charge-coupled devices used in fluoroscopy
3. Direct detection flat-panel systems
4. Indirect detection flat-panel systems

Direct detection systems use a photoconductor material (usually selenium) applied on top of a thin film transistor array, whereas indirect systems use an x-ray–intensifying screen that converts x-rays to light, which is then detected by the flat-panel detector. The principal advantage of direct detection over indirect detection flat-panel systems is a decrease in blurring; direct detection systems have a higher spatial resolution than

BOX 40.1 STANDARD AND SPECIALIZED RADIOGRAPHIC PROJECTIONS

Adequate radiographic evaluation requires at least two orthogonal projections.

Standard radiographs**Finger:**

- PA projection
- Lateral projection

Hand:

- PA projection
 - Oblique projection (45-degree semipronated or semisupinated)
 - Lateral projection
- Magnification views are more sensitive for evaluating erosive disease, if available.

Wrist:

- PA projection (arm abducted 90 degrees from trunk and forearm flexed at 90 degrees to the arm)
- Oblique projections
- AP oblique view (Norgaard or ball catcher's view)
- Lateral projection

Foot:

- AP, oblique, and lateral views

Shoulder:

- AP views (in true external and internal rotation)

Knee:

- AP (standing semiflexed position to allow accurate evaluation of cartilage loss)
- Flexed lateral (nonstanding to allow patellofemoral evaluation) ± sunrise or Merchant patellar view and ± tunnel views

Hip:

- AP (best for femoral neck evaluation)
- Frog-leg lateral projection (best for femoral head evaluation and investigation of avascular necrosis)

Sacroiliac joints:

- Modified AP Ferguson view

Spine:

- AP and lateral views

Survey radiographs***Hands:**

- PA projection
- Semipronated oblique view

Wrists:

- PA projection
- Lateral projection
- Obliques (semipronated and semisupinated)

Shoulders:

- AP 40-degree posterior oblique view

Feet:

- Medial oblique view

Ankles:

- Lateral view including heel

Knees:

- AP projection
- Lateral projection

Pelvis:

- AP projection

Cervical spine:

- Lateral with neck flexion

*The survey requires modification depending on specific diagnosis and clinical questions (e.g., suspected ankylosing spondylitis) or emphasis on axial skeleton including sacroiliac joints (e.g., suspected calcium pyrophosphate dihydrate deposition disease), symphysis pubis, PA wrist, and AP knees.

AP, anteroposterior; PA, posteroanterior.

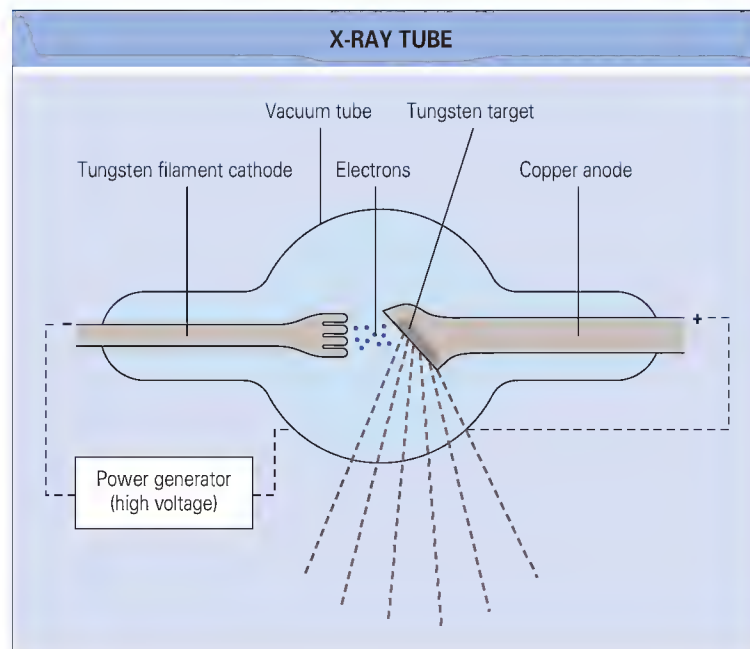


Fig. 40.6 The x-ray tube consists of a cathode tube filament producing electrons, a tungsten target in a copper anode, and a vacuum tube.

Computerized x-ray image analysis methods (computer-aided analysis)

Computer-aided analysis or computer-aided detection of radiographic data was developed to fill the need for quantitative surrogate outcome measures in clinical research. Large numbers of radiographs could be digitally imaged and stored by the computer software system for evaluation and training. These methods were initially used in mammographic and chest imaging. The computer algorithm was developed to be able to detect nodules and lesions and classify them as benign or malignant. Their utility in arthritis research is increasing.¹² Most of the work in developing computerized digital radiograph-based techniques in rheumatology has focused on the evaluation of osteoarthritis of the knee; more recent studies have involved the hip and hand, with the latter focusing on analyses of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis.^{13,14}

The general goal of such systems is to quantify arthritis progression by measuring the radiographic minimum joint space width by way of a computer software algorithm that can delineate the opposing margins of a joint on a digital radiographic image (Fig. 40.8). Although computerized techniques are objective and fast, they are prone to occasional error, and as a result, a quality assurance step is necessary that allows for correction. Overall, however, these systems are reproducible, providing a more objective measurement with improved interreader and intrareader reproducibility, and are more efficient and cost effective than manual scoring systems.¹²

Interventional techniques

There is an increasing use of interventional conventional radiography in rheumatology, of which fluoroscopically guided injection of joints for diagnosis or therapeutic intervention is the most important. Although advanced imaging (MRI or computed tomography [CT]) is more commonly used for assessment of synovial thickening, ligament degeneration or tear, or osteochondral bodies, fluoroscopically guided arthrography can be used in those patients who are claustrophobic or who are not candidates for MRI. Indeed, this latter technique can be useful, for example, in demonstrating some reliable indicators of synovial inflammation, such as corrugated irregularity of injected intraarticular contrast material within the wrist or glenohumeral joint, enlargement of the joint, and opacification of lymphatic vessels.¹⁵ Degeneration of the triangular fibrocartilage complex with eventual tear can be documented under fluoroscopy after injection of the radiocarpal joint as visualized leakage of contrast agent into the distal radial ulnar joint (Fig. 40.9). Osteochondral bodies can be seen as filling defects within the joints on arthrography of the shoulder, which help in diagnosis of osteochondromatosis.

Therapeutic injections include corticosteroid or analgesic injections into the joints, most commonly the shoulder, SI joints, or hips. Other substances that have been injected under fluoroscopy include cartilage-stimulating or

either computed radiography or indirect systems, require a lower radiation dose than conventional plain film radiography, and have improved tolerance for overexposure or underexposure (too bright or too dark images) because of a wider dynamic range (Fig. 40.7). The anatomic detail, contrast, and spatial resolution of these digital techniques have been found to be sufficient for the evaluation of arthritis.¹¹

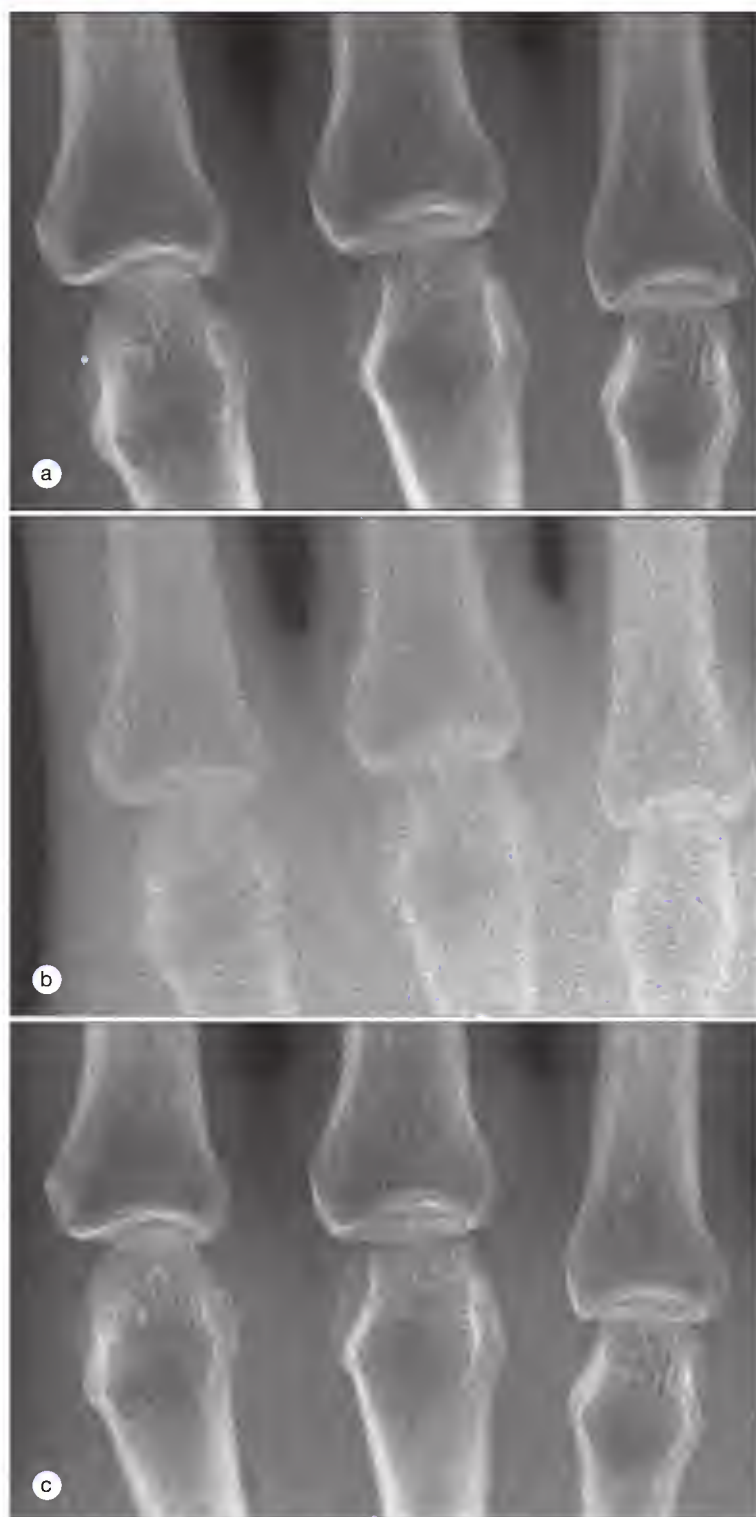


Fig. 40.7 Comparison of 100-speed conventional film-screen combination (a and b) and direct detection flat-panel system using selenium detectors (c). The voltage is 50 kV with exposure cut from 4.0 mAs in (a) to 0.56 mAs in (b and c). The conventional film-screen combination provides no diagnostic information (bone and articular structures) with a 50-kV 0.56-mAs exposure; however, the direct detection flat-panel system (c) provides images of diagnostic quality because of its greater dynamic range.

cartilage-replacement substances in patients with little or no cartilage remaining in the knees or hips. Injection of the joint of interest under fluoroscopic guidance may be used before MRI or CT for assessment of cartilage, joint space, ligament, and soft tissue integrity in arthritic patients; for evaluation for other causes of joint pain; and for presurgical assessment (Fig. 40.10)

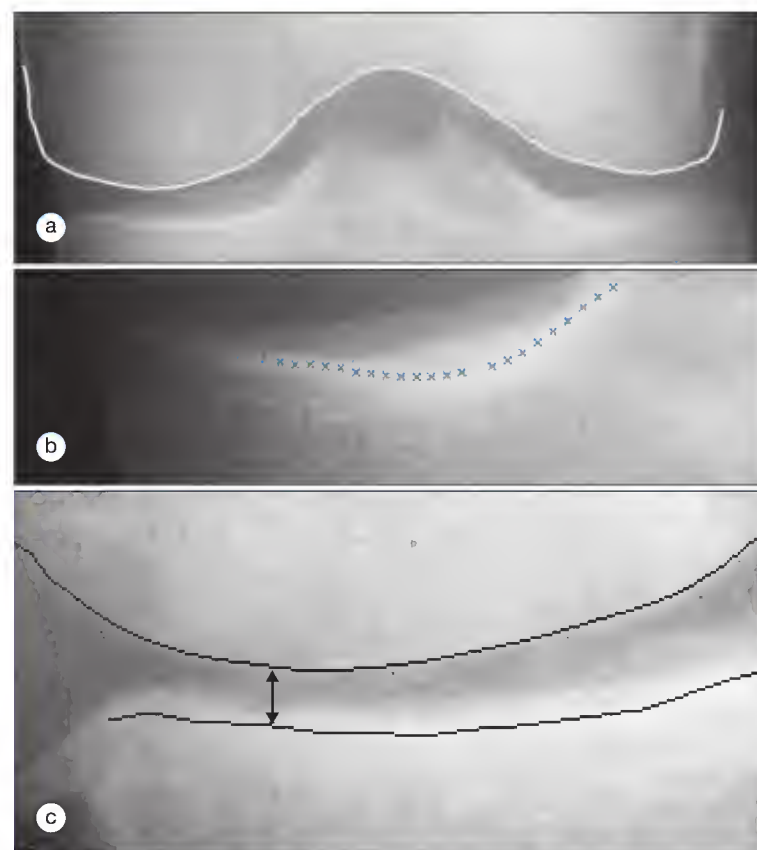


Fig. 40.8 Computerized x-ray image analysis for joint space narrowing. (a) Computer-delineated femoral condyle shown as the white line overlaid on the knee radiograph. (b) Computer-determined joints along the bright band corresponding to the base of the tibial plateau. (c) Computerized determination of minimum joint space width. The points on the tibial plateau have been connected. The shortest distance between the femoral condyle and the tibial plateau is automatically detected.

COMPUTED TOMOGRAPHY

Multidetector computed tomography

Multidetector computed tomography (MDCT), also referred to as *multislice*, *multidetector-row*, or *multisection CT*, is the latest, most widely used version of CT and is now a true 3D imaging modality. Gains over the transaxial cross-sectional technique include reduced scan time, section collimation, and increased scan length with high spatial resolution. Multislice CT allows extended anatomic coverage with thinner slices (0.5-mm slice width). This makes it possible to acquire isovolumetric data (arbitrary imaging planes). Thus techniques such as multiplanar reconstruction and 3D rendering (volume rendering, shaded-surface display, and maximum-intensity projections) become an integral part of the examination (Fig. 40.11).¹⁶ The multidetector scanners obviate the need for scanning patients in multiple positions to achieve true 2D sagittal, coronal, axial, or oblique images. Multiplanar reformatted images (i.e., not only sagittal and coronal but also oblique or 3D images) can be reconstructed in any plane from the original axial data set acquired during the initial scan.

MDCT began with 4-, 10-, then 64-detector array scanners, but 128-detector array scanners are now becoming the mainstay of radiology departments. Arrays with higher numbers of detectors result in less possibility of movement artifact, which not only is of benefit in the imaging of children, ill patients, and claustrophobic individuals but is especially important in the imaging of small joints so as not to lose data or critical information during the study. Scanners with 164 and 320 detectors have now been introduced in some institutions.

One of the issues in MDCT is that image noise is increased with sectional collimation reduction (thin slices), which requires either an increase in the radiation dose or thickening of image sections to decrease the noise. This problem is diminishing with the use of scanners with higher numbers of detectors. Also, thinner slice widths are more commonly used in imaging



Fig. 40.9 Fluoroscopy. (a) Anteroposterior view of a wrist arthrogram obtained under fluoroscopy demonstrates injection of the midcarpal joint without abnormal extravasation with needle now repositioned within the radiosaphoid joint. (b) Contrast injected within the proximal radiocarpal joint shows abnormal flow into the distal radioulnar joint consistent with triangular fibrocartilage ligament tear.



Fig. 40.10 Computed tomographic (CT) arthrogram of the knee obtained for presurgical assessment. Following fluoroscopically guided intraarticular contrast injection of the knee, sagittal CT images show (a) normal cartilage thickness of the lateral femoral and tibial surfaces (black arrows) paralleling subchondral bone and (b) full-thickness cartilage loss (white arrows indicate increased density of contrast filling the defect) involving posterior medial femoral and tibial cartilage in keeping with severe osteoarthritis.

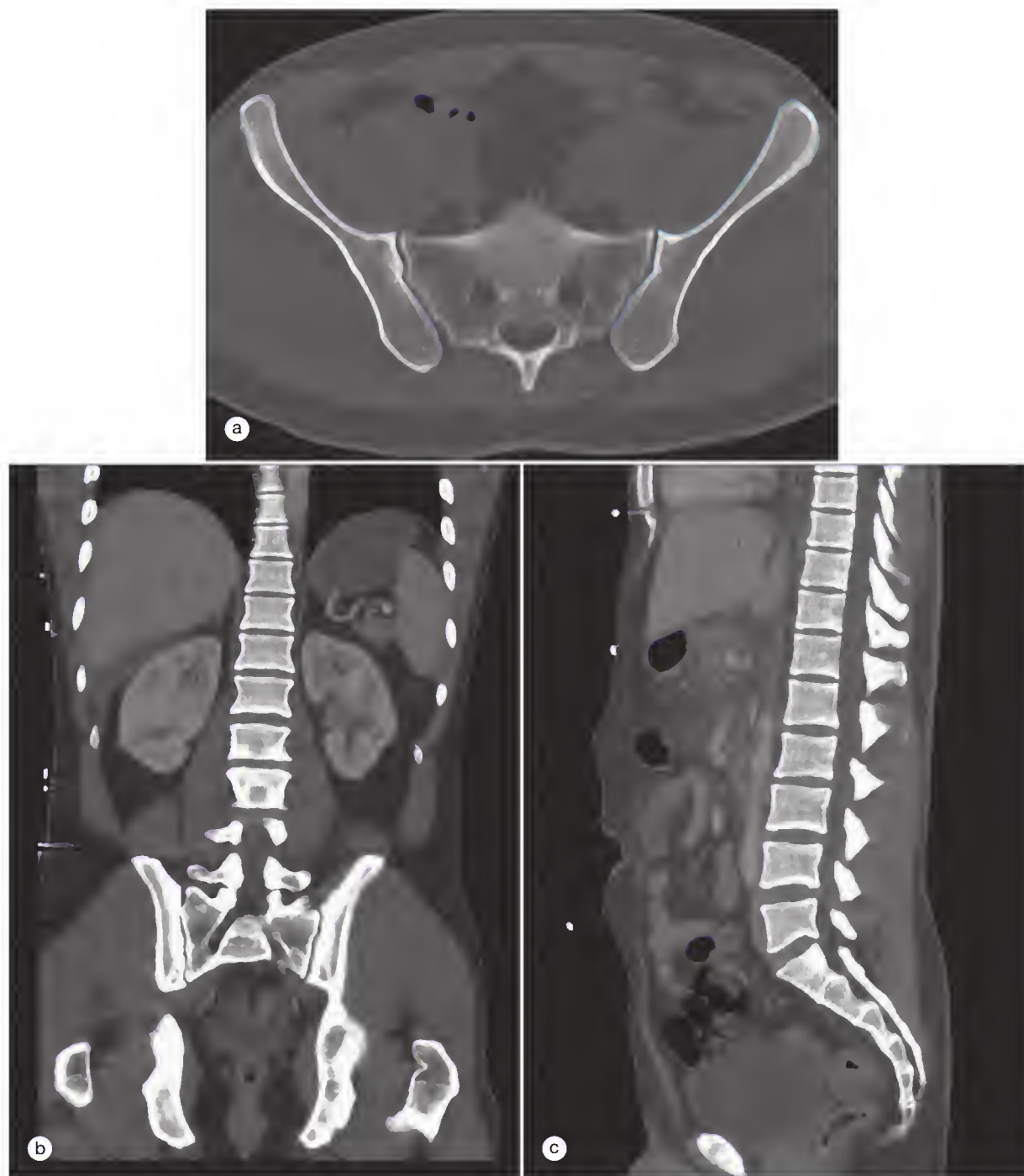


Fig. 40.11 Multidetector computed tomography (MDCT): two-dimensional (2D) and three-dimensional (3D) applications. (a) Axial MDCT image of the pelvis, just one of many thin slices in the original study database for this patient. (b and c) Coronal and sagittal multiplanar reconstruction CT images of the spine and pelvis, respectively, created from original data.

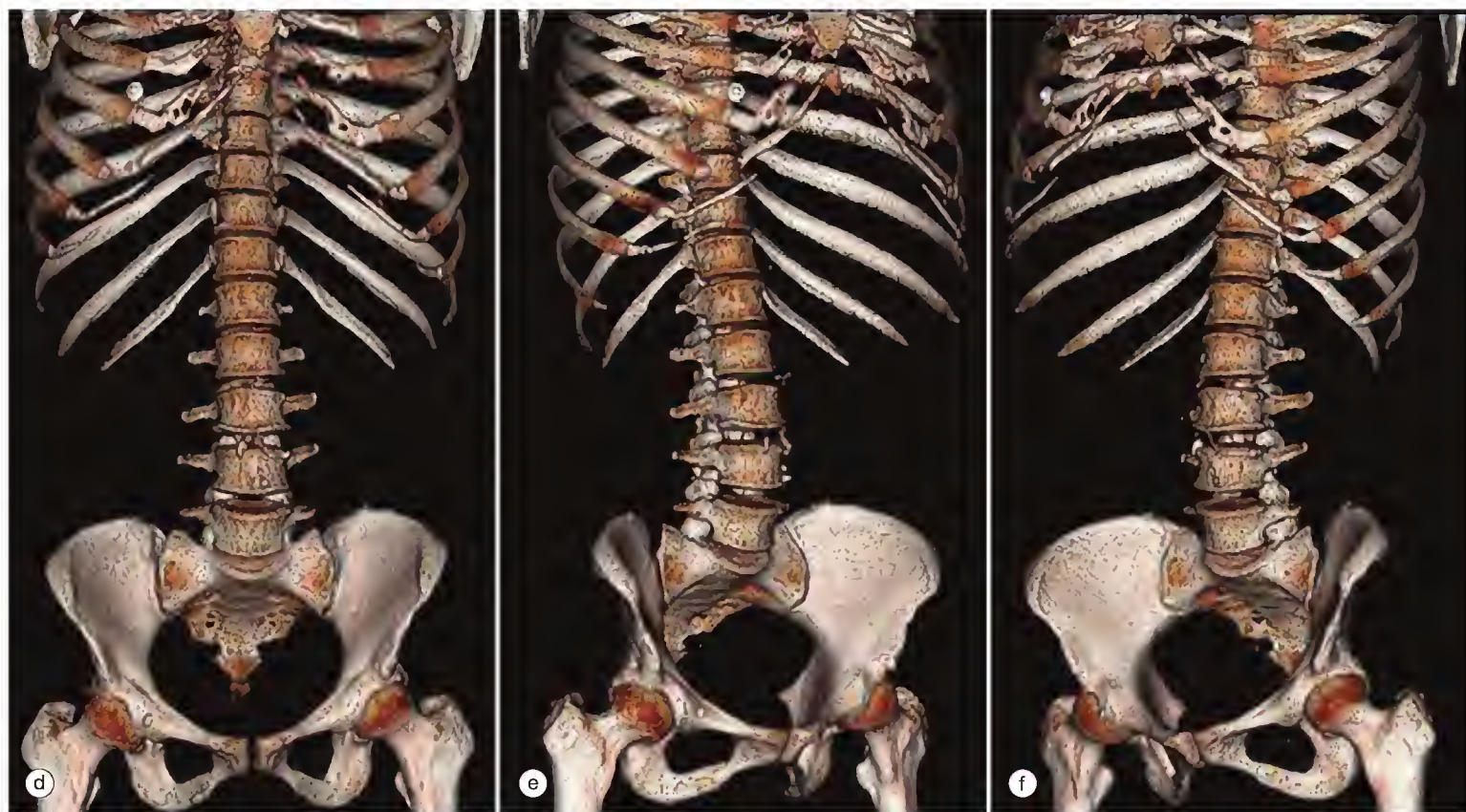


Fig. 40.11, cont'd 3D MDCT images of the spine using a volume-rendering technique in anteroposterior (d), right (e), and left (f) anterior oblique projections. *Continued*

the extremities, which do not contain radiosensitive tissue, so that radiation dose is less of an issue in these cases (Fig. 40.12).¹⁵

Applications in rheumatology

Bone

MDCT provides excellent contrast and delineation of cortical and trabecular bone and is established as a superb diagnostic tool for the visualization of subtle cortical or intraosseous lesions not visible on radiographs due to projectional superimposition (see Fig. 40.11). MDCT also allows for better detection of ossific and joint features in metabolic bone disorders and spondyloarthritis (Fig. 40.13). Although MRI and ultrasonography in experienced hands have been found to be superior to CT in detection of erosion, one study found that the scoring of erosions in the rheumatoid hand was higher with MDCT than with MRI at the metacarpal bases owing to the ability of MDCT to clearly delineate cortical bony margins and areas of sclerosis.¹⁷ MDCT provides validation of the bone damage or destruction suspected on MRI or ultrasonography and may be useful in treatment follow-up because sclerosis may be indicative of reparative changes (see Fig. 40.12).¹⁸ In a recent study comparing CT and digital radiography in the evaluation of first carpometacarpal (CMC) and scaphotrapeziotrapezoidal (STT) joint osteoarthritis, CT had a higher interreader reliability and detection rate than radiography for both first CMC and STT osteoarthritis. Because surgical treatment selection of thumb base osteoarthritis depends on the presence of pathologic changes in the first CMC and STT joints, the use of CT was thought to improve treatment selection and surgical planning.¹⁹

CT is less expensive than MRI and has a shorter scanning time, which may benefit some patients, although CT involves exposure to ionizing radiation. Because of its ability to assess both cortical and trabecular bone, CT can be used to assess for osteopenia or osteoporosis. This assessment can be made subjectively using a CT study performed for other purposes. Quantitative CT of the spine is one objective method for volumetric evaluation of bone mineral density, but it is generally reserved for research purposes. Bone mineral density evaluation and its methods are discussed in detail elsewhere (see Chapter 44).

Peripheral and axial joints

Joints that are difficult to visualize with the usual imaging techniques (apophyseal, costovertebral, sternoclavicular, and temporomandibular joints) may be better evaluated with MDCT and the use of reformatted images, maximum-intensity projections, or multiplanar reconstructions for visualization and evaluation of ligaments and bone, spinal cord compression, erosions of the odontoid process, subluxation, and presence of calcification (Fig. 40.14). The 3D analysis of standard joints such as the glenohumeral or hip joint with suspected osteoarthritis, rheumatoid arthritis, CPPD, or ischemic necrosis can be useful in assessment of subtle bone or joint changes as well as detection of any periarticular soft tissue masses or synovial cysts. The use of MDCT after intraarticular injection of a contrast agent has proved to be useful in these latter situations because even articular cartilage abnormalities can be visualized as a result of increased spatial resolution and increased delineation of bone versus cartilage (Fig. 40.15).²⁰

The CT findings of sacroiliitis are similar to those seen on conventional radiographs, including erosions, sclerosis, and eventual ankylosis if the disease progresses (see Figs. 40.5 and 40.13). Several studies indicate that CT is more sensitive than radiography in identifying sacroiliitis, leading to an earlier diagnosis of sacroiliitis and earlier implementation of treatment.²¹ CT is also useful in septic arthritis because irregular bone destruction and intraarticular or periarticular fluid is well seen, particularly after intravenous administration of a contrast agent, with the infected fluid collection demonstrating a characteristic peripheral rim enhancement pattern.²⁰

CT-guided facet, joint, or bursal injections are often used in the diagnosis and treatment of rheumatologic disease. CT fluoroscopy combines the careful delineation of anatomy with the real-time cineradiography of fluoroscopy, allowing finer visualization of placement and orientation of the procedural needle for appropriate injection or aspiration as required.

Soft tissues and vessels

CT is generally used for the evaluation of bone, but the soft tissue system can also be evaluated, although typically MRI may be a more appropriate



Fig. 40.11, cont'd (g and h) Volume-rendered 3D CT images of the pelvis and spine in coronal and sagittal projections, respectively, using bone windows. (i and j) Maximum-intensity projection images of the pelvis and hips in coronal and sagittal projections, respectively, clearly delineating the joint space and cortical integrity of the hips.



Fig. 40.12 Thin-slice 128-detector-array coronal multiplanar reconstruction computed tomographic image demonstrating healing erosions with sclerotic margins involving the second and third metacarpophalangeal joints and the first metacarpal head (arrows) in a patient with rheumatoid arthritis treated with methotrexate.

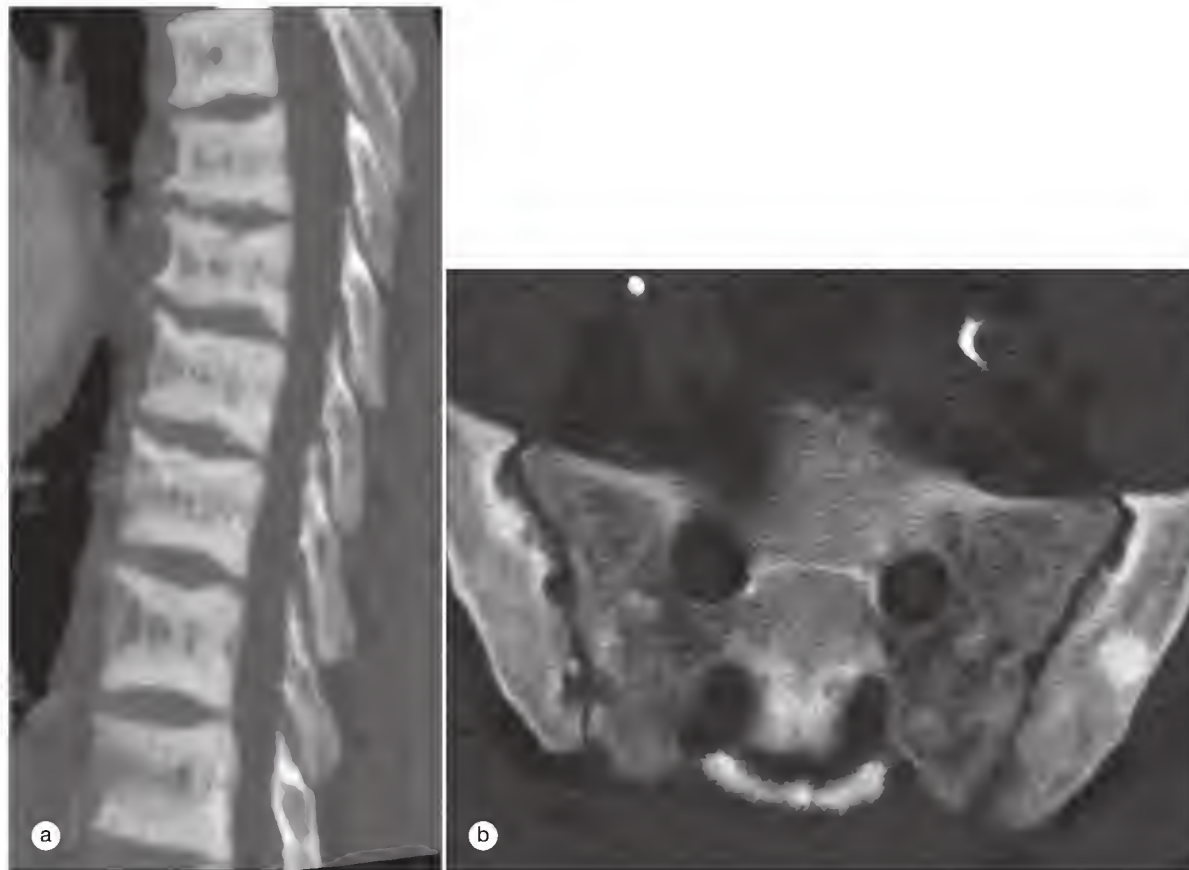


Fig. 40.13 (a) "Rugger jersey" appearance of the spine clearly depicted on sagittal multiplanar reconstruction computed tomographic (CT) image. (b) Associated axial CT image demonstrating prominent sacroiliac joint erosions, mixed sclerosis, and loss of bone density. Findings are in keeping with the patient's history of renal osteodystrophy and hyperparathyroidism.



Fig. 40.14 Rheumatoid arthritis of the odontoid. Lateral cervical spine radiograph (a) shows narrowing of the preodontoid space, osteopenia, and midcervical disk space narrowing. Multidetector computed tomographic sagittal (b), axial soft tissue (c), and bone window (d) images better demonstrate soft tissue pannus and erosions of the odontoid.

modality for imaging of these tissues. One of the more common soft tissue indications for CT in rheumatology is the evaluation of the large-vessel vasculitides using CT angiography.²² These disorders, particularly giant cell arteritis or Takayasu arteritis, can be detected, visualized, analyzed, and, according to some studies, even monitored using CT angiography, because it can evaluate both the vessel wall and the lumen and may show vessel wall alterations even when the lumen appears unaffected on standard angiography.²³ CT has a role in diagnosing both early and advanced Takayasu arteritis. In early Takayasu arteritis, CT may show arterial wall thickening with mural enhancement and low-attenuation ring on delayed images, whereas in advanced Takayasu arteritis, CT shows the typical late-stage complications, including vessel stenosis, occlusion, and aneurysm.²⁴ Aortic wall enhancement was shown to resolve after immunosuppressive therapy in 7 of 13 patients with Takayasu arteritis in one study.²⁵ CT angiography cannot visualize relatively small vessels, however, and therefore its use is limited to deep large-vessel evaluation.²⁶

Dual-energy computed tomography

Dual-energy computed tomography (DECT) has proven highly accurate for identifying uric acid calculi and differentiating it from other types of calculi (in particular, calcium) both *in vitro* and *in vivo* using specific attenuation characteristics that can identify or exclude gout.^{27,28} This technology has recently been applied to the evaluation, diagnosis, and management of gout in the musculoskeletal system.²⁹⁻³¹

DECT uses two x-ray tubes with different peak kilovoltages (80 and 140 kVp) that are used to acquire two CT image sets of a specific anatomic region simultaneously, which eliminates misregistration artifact or errors that can occur due to patient movement if the imaging is done sequentially. The chemical compositions of the scanned tissues can be differentiated by comparing the material-specific differences in attenuation using special software.³⁰ Color-coded cross-sectional images are created from postprocessing of the DECT data and can be used to create 3D surface-rendered models that are useful for visualization of tophus burden and location (Fig. 40.16). These

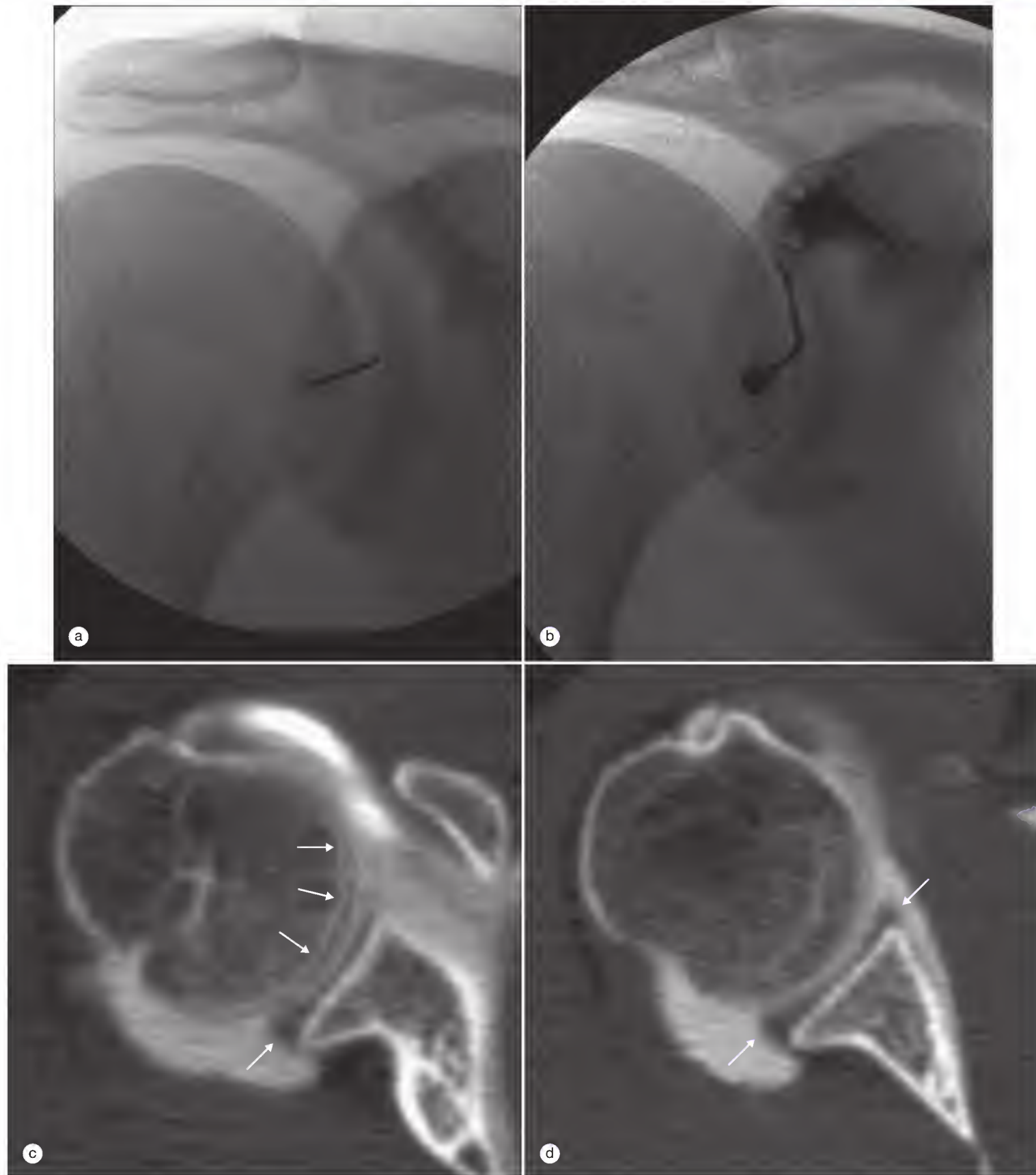


Fig. 40.15 Computed tomographic (CT) arthrography of the shoulder. (a) Anteroposterior fluoroscopic image of the right shoulder shows needle placement in the mid-distal third of the glenohumeral joint. (b) Contrast material subsequently injected into the glenohumeral joint is seen flowing along the curvilinear contour. (c) Axial multidetector CT scan acquired through the right shoulder joint after intraarticular injection of dilute radiographic contrast agent demonstrates the articular cartilage of the humeral head as a low-density structure (triple arrows) clearly outlined by the high-contrast material. The posterior labrum is well visualized (single arrow). (d) A more distal slice demonstrates the anterior and posterior portion of the glenoid labrum (arrows).



Fig. 40.16 Dual-energy computed tomographic (CT) images of a 72-year-old woman with history of painful left first metatarsophalangeal joint and a history of gout. Pain was thought to be due to a small spur and potential tophi seen medial to this joint on standing left foot radiograph (a). This is better depicted on CT (b) and color-coded composition (c) images obtained with postprocessing techniques showing uric acid deposits (green) within tophus distinct from the ossific calcium-containing structures (blue). Surface-rendered three-dimensional CT image (d) again clearly shows focal tophi (green) distinct from bone (purple and white). (Courtesy Dr. Mark J. Kransdorf, Mayo Clinic.)

volumetric renderings can be used in clinical trials or for routine treatment evaluation because they provide reproducible sensitive and specific volumetric quantification of tophi without significant user variability.³⁰

DECT has shown utility in the diagnosis of gout in patients with atypical manifestations, evaluation of response to treatment in patients with known gout (using serial volumetric quantification of subclinical tophi), differentiation of gout from entities that mimic gout (CPPD, rheumatoid arthritis,

progressive osteoarthritis, infection), and, in particular, evaluation of asymptomatic patients by detection of subclinical urate crystal deposits, which allows for earlier recognition and treatment before irreversible joint damage can occur. DECT can be useful regardless of the patient's serum urate levels (i.e., it can detect gout when serum urate level is normal or exclude it when it is elevated) and may help obviate the need for invasive diagnostic procedures in the acute disease setting in the future.²⁸

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41

Functional magnetic resonance imaging

■ LAUREN M. SHAPIRO ■ STEPHEN J. MATZAT ■ GARRY E. GOLD

- Magnetic resonance imaging (MRI), with its versatility and high sensitivity, allows for a comprehensive assessment of the anatomy and pathology of the musculoskeletal system.
- Three-dimensional imaging sequences have been developed and can be used to obtain isotropic resolution allowing for image reformation in oblique planes.
- Measurement of cartilage thickness and mapping can be used to track the progress of osteoarthritis.
- T2 relaxation time measurements can help characterize the state of fibrocartilage tissues such as the menisci and ligaments by detecting changes in the cartilage matrix.
- T1rho imaging can help visualize some of the earliest biomarkers of osteoarthritis through changes in macromolecular content such as proteoglycan depletion.
- Sodium imaging is sensitive to fairly small changes in proteoglycan depletion and provides a strong method with which to study early-stage osteoarthritis.

INTRODUCTION

Magnetic resonance imaging (MRI) is an extremely versatile and highly sensitive imaging modality used to evaluate the musculoskeletal system.¹ The wide range of contrast mechanisms available for MRI and the continuing development of new software and hardware have resulted in improvements in resolution and sensitivity. Unlike radiography and computed tomography (CT), MRI does not use ionizing radiation and therefore involves no significant patient risk when used within the U.S. Food and Drug Administration guidelines. The drawbacks to MRI include the high costs of equipment and scanning, long imaging times, and potential for motion and other artifacts that may decrease image quality. Despite these limitations, the overall soft tissue contrast and flexibility have helped to establish MRI as the modality of choice for assessment of the musculoskeletal system.

OVERVIEW OF BASIC PRINCIPLES

The fundamental basis of MRI and the physical property that makes it possible is known as the *magnetic resonance (MR) phenomenon*. Atoms that possess a net nuclear spin as a result of having an odd number of protons and/or neutrons exhibit this property. Although a number of different nuclei exhibit the MR phenomenon, almost all clinical MRI is done with protium (¹H) because of its natural abundance.

MRI requires the application of a strong external magnetic field (B_0) within which protons behave like bar magnets with magnetic moments or “spins.” The magnetic moment of a single proton is not detectable, but the additive effects of many protons can be measured (Fig. 41.1). In the absence of the external magnetic field, proton magnetic moments are oriented randomly and present a net zero moment when summed together. With an applied B_0 field, however, the spins align either parallel (with the magnetic field) or antiparallel (against the magnetic field). Because a slightly greater number of protons align with rather than against the field, a small net magnetization results in the direction of B_0 .

The spins aligned with the external B_0 field precess at a known angular frequency ω given by the Larmor equation, according to which $\omega = \gamma \cdot B_0$, where γ is a constant known as the gyromagnetic ratio. An external radio-frequency (RF) field is applied at the resonant frequency that tips the spins into the transverse plane perpendicular to the main B_0 field. After the RF pulse, the spins relax back toward the z-axis aligned with the B_0 field. This relaxation results in the emission of the MRI signal and is characterized by two exponential decay constants, T1 and T2. These relaxation rates depend on the tissue properties of the sample, and it is these differences in intrinsic T1 and T2 relaxation times that are often exploited to generate MRI contrast. Free induction decay, the process of the relaxation of the spins in the transverse plane, is illustrated in Figure 41.2.

T2 relaxation

The process of free induction decay is characterized by the exponential time constant T2. The B_1 RF pulse tips the longitudinally oriented spins into the transverse plane. The angle of the tip away from the z-axis is known as the *flip angle*. When tipped into the transverse plane, the spins are coherent and aligned in one direction. Over a period of time, the spins lose phase coherence in the transverse plane and the net magnetization in the x-y plane becomes zero. This is referred to as *spin-spin relaxation*, and the exponential time constant that governs this loss of phase coherence is the T2 relaxation time. The elapsed time between the peak signal and 37% of the peak signal is the T2 decay constant (Fig. 41.3). Different tissues in the musculoskeletal system have different T2 relaxation times, which greatly impacts their appearance on MR images. T2* relaxation is another important component that contributes to the generation of image contrast. T2* is the observed time constant for the free induction decay as a result of the loss of phase coherence. T2* decay, which is present on gradient-echo MR images, is shorter than T2 decay.

T1 relaxation

Loss of transverse magnetization occurs relatively quickly, whereas recovery of the longitudinal magnetization to equilibrium takes longer. This occurs along the z-axis and is referred to as *T1 relaxation*. As this occurs, individual spins must release their energy to the local tissue by way of a process that is called *spin-lattice relaxation*. The T1 relaxation time constant is the time needed to recover 63% of the longitudinal magnetization after a 90-degree B_1 pulse tips the spins into the x-y plane. Just as different tissues have different T2 relaxation times, they have different T1 relaxation times that impact their appearance on MR images. Measured T2 and T1 relaxation times for common musculoskeletal tissues are available.²

Magnetic resonance imaging contrast

In most MRI experiments, image contrast is determined by a combination of intrinsic proton density of the tissues and the T1, T2, and T2* relaxation times. The operator of the scanner can influence the appearance of the images by changing the timing of the signal acquisition after excitation (known as *echo time [TE]*) or the time between the excitations (known as *repetition time [TR]*). Images are typically acquired using different parameters that take advantage of the different relaxation types. For example, images with a relatively short TE and TR emphasize T1 relaxation time differences and are referred to as *T1-weighted images*. Images with a long TR and long TE emphasize T2 relaxation time differences and are termed *T2-weighted images*. Images with a long TR and short TE are proton density weighted because contrast in these images is generated as a result of tissue proton-density differences.

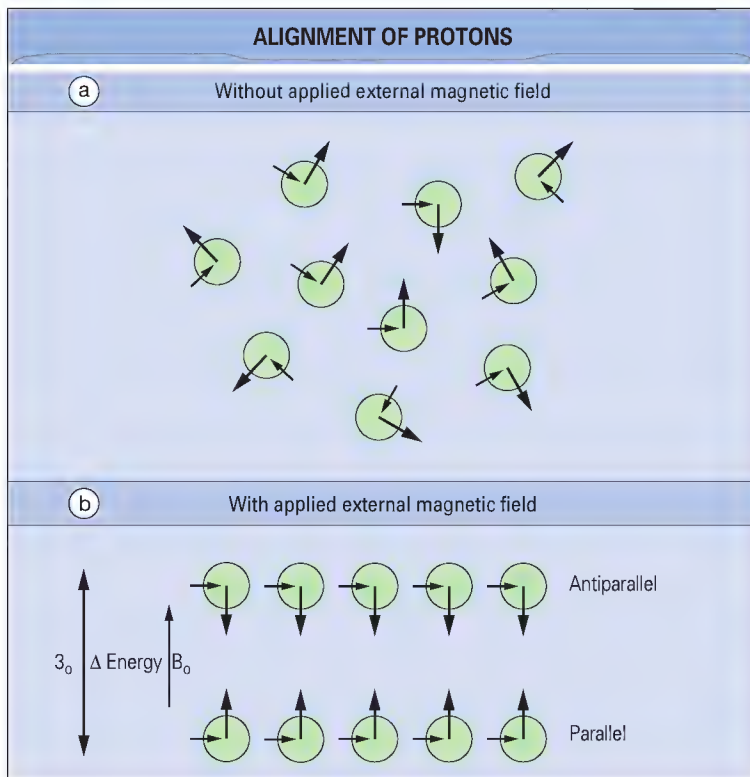


Fig. 41.1 Diagram of the alignment of protons without the applied B_0 field (a) and with the applied B_0 field (b). Slightly more protons align parallel with the B_0 field than antiparallel, which results in a net magnetization.

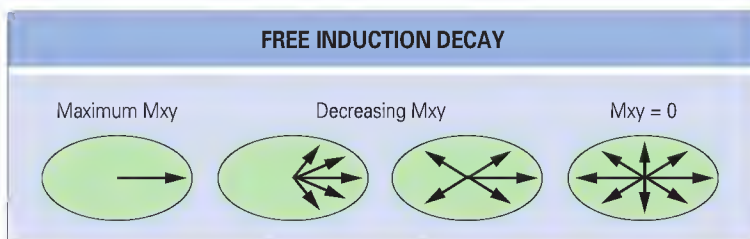


Fig. 41.2 Diagram of free induction decay in magnetic resonance imaging. Immediately after excitation, the magnetization in the x-y plane (M_{xy}) is a coherent vector, which results in the maximum magnetization. As the decay proceeds, the spins lose coherence and eventually are ordered in random directions, giving a net M_{xy} of zero.

IMAGE QUALITY

An essential aspect of MRI is the ability to evaluate and compare images obtained using different techniques. A variety of strategies are available with which to assess image quality; however, the three most valuable means of comparison are contrast sensitivity, spatial resolution, and signal-to-noise ratio (SNR). Contrast sensitivity is one of the primary reasons why MRI is so useful, and it can be altered to the parameters necessary for viewing the desired anatomy or pathologic process by changing the T1 and T2 relaxation times, flow-velocity properties, and spin densities. Spatial resolution is the ability of an imaging system to distinguish between two objects as they decrease in size and move closer together. Spatial resolution depends on matrix size, field of view, and slice thickness. SNR is used to measure the amount of the desired signal in relation to the amount of background noise (or "random" signal). There are several more robust and precise methods of calculating SNR, but the most commonly used method is to divide the standard deviation of background noise from a region of interest into the mean signal from another region of interest in the same image. SNR depends on many different variables, including but not limited to field of view, coil type, slice thickness, and magnetic field strength.

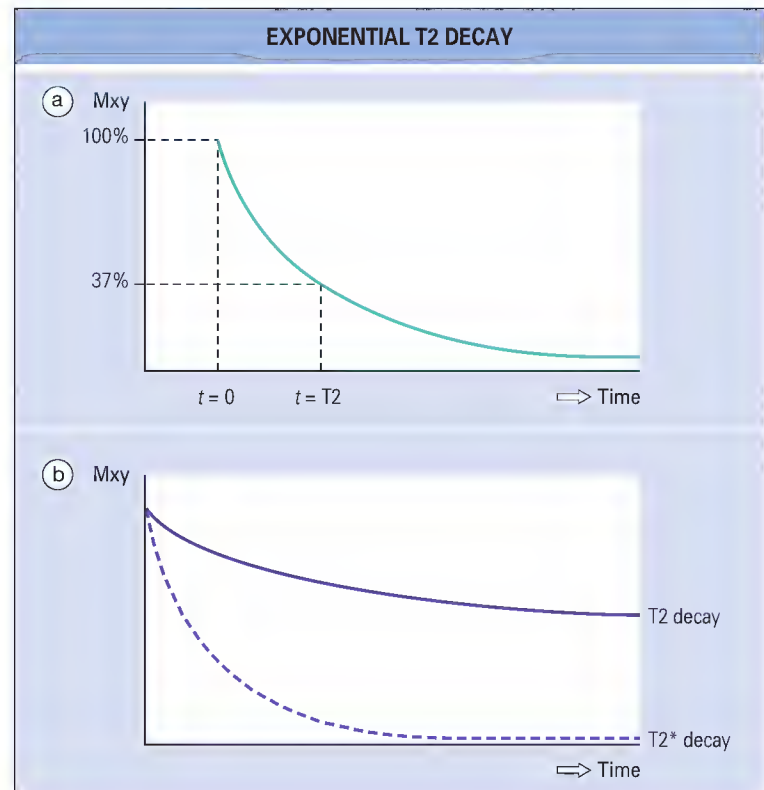


Fig. 41.3 Diagram of exponential spin-spin (T2) decay. (a) After one exponential time constant T_2 , the magnetization in the x-y plane (M_{xy}) has decayed to 37%. (b) Gradient-echo methods demonstrate T_2^* decay, which is faster than T_2 decay. Spin-echo methods in magnetic resonance imaging refocus the T_2^* decay, which results in T_2 decay.

CONVENTIONAL MAGNETIC RESONANCE IMAGING METHODS

MRI has emerged as the leading modality for imaging of soft tissue structures around joints.^{3,4} One of the major advantages of MRI is the ability to manipulate contrast to highlight different tissue types. Common contrast mechanisms include two-dimensional (2D) multislice T1-weighted, proton-density-weighted, and T2-weighted imaging, all of which can be derived with or without fat suppression. Imaging hardware and software have developed considerably in recent years; improved gradients and RF coils, fast or turbo spin-echo imaging, and techniques such as water-only excitation provide significant advancements in the field of MRI.

Although tissue relaxation times and imaging parameters are the major determinants of contrast differences between different tissue types, lipid suppression increases contrast between nonlipid and lipid-containing tissues and affects how the MR scanner sets the overall dynamic range of the image. Fat saturation, in which fat spins are excited and then dephased before imaging, is the most common type of lipid suppression. Another type of lipid suppression that can selectively excite water-only spins is known as *spectral-spatial excitation*.⁵ Finally, in areas of magnetic field inhomogeneity, a technique called *inversion recovery* provides a way to suppress lipids that comes at the expense of SNR and contrast-to-noise ratios.

The type of contrast is critical for SNR and the visibility of pathologic processes. Although T2-weighted imaging creates contrast between short T2 tissues and synovial fluid, it does so at the expense of the MRI signal. High signal from fluid is useful to highlight defects such as fissuring or tears, yet variation in internal short T2 signal is poorly depicted. Also, T2-weighted scans are often 2D, leaving small slice gaps that may contain areas of tissue damage.

Another technique, three-dimensional spoiled gradient-recalled echo imaging with fat suppression (3D-SPGR), destroys or spoils the transverse magnetization between successive TRs. This method produces high cartilage signal but low signal from adjacent joint fluid. 3D-SPGR is the standard for quantitative morphologic imaging of cartilage.⁶ This technique is useful for cartilage volume and thickness measurements but does not adequately highlight surface defects with fluid and does not allow thorough evaluation of other joint structures such as ligaments or menisci.

MRI of joints requires close attention to spatial resolution. For example, to see early morphologic degenerative changes in cartilage, imaging with a resolution on the order of 0.2 to 0.4 mm is required.⁷ The ultimate resolution achievable is governed by the SNR possible within a given imaging time and system. Use of high field strength and dedicated phased-array or surface coils usually results in the best possible resolution *in vivo*. A high-resolution technique that provides both morphologic and physiologic data would be ideal in the evaluation of joints. Given current techniques, it is likely that a combination of a high-resolution morphologic imaging sequence with a sequence for evaluation of tissue physiology will be the most useful.

Two-dimensional fast spin-echo imaging

Conventional MRI of the musculoskeletal system is commonly performed with turbo or fast spin-echo (FSE) methods and is often limited to 2D multislice acquisitions obtained in multiple planes. These methods provide excellent SNR and contrast between tissues of interest but produce anisotropic voxels and slice gaps, which results in the inability to reformat the images into multiple oblique planes. For example, a typical sagittal image may have 0.3- to 0.6-mm in-plane resolution but a slice thickness of 2 to 5 mm. These methods provide excellent depiction of structures in the imaging plane, but evaluation of oblique or small structures across multiple slices can be challenging. For these reasons, 3D acquisitions with thin slices are more appealing.

Two-dimensional FSE methods are the primary clinical sequences used to image internal derangements of joints and show great ability to detect cartilage lesions (Fig. 41.4).⁸ They can also detect bone marrow edema,⁹ effusions, synovium,³ and ligament and meniscal tears.⁴ Several scoring systems for osteoarthritis, including Whole-Organ Magnetic Resonance Imaging Score (WORMS), Boston-Leeds Osteoarthritis Knee Scoring (BLOKS), and Knee Osteoarthritis Scoring System (KOSS),^{10,11} have been developed based on this acquisition method.

Bone marrow edema that corresponds to inflammation, seen in the early pathogenesis of inflammatory processes such as rheumatoid arthritis and ankylosing spondylitis, is best appreciated with MRI, especially fluid-sensitive T2-weighted FSE imaging. CT imaging, in comparison, is better for visualization of structural changes seen in later-stage pathologic processes.^{12,13}

Three-dimensional gradient-echo techniques

Three-dimensional MRI sequences are extremely valuable because they produce images with isotropic voxels that do not contain slice gaps. These characteristics allow the images to be reformatted into various oblique planes, which improves the visualization of the anatomy while shortening examination time. Traditional 3D gradient-recalled echo (3D-GRE) methods have the potential to acquire data with isotropic voxel sizes but suffer from a lack of contrast, especially compared with 2D spin-echo approaches. 3D-SPGR has demonstrated high accuracy for imaging cartilage lesions^{1,14,15}; however, it has two main disadvantages: (1) a lack of reliable contrast between tissue and fluid, and (2) long imaging times that may require up to 8 minutes. Due to the lack of reliable fluid sensitivity, 3D-GRE methods are less useful for diagnosis of ligament or meniscal tears than spin-echo techniques. Despite its limitations, 3D-SPGR is considered the standard for morphologic imaging of cartilage.⁶

The SPGR and GRE techniques can be combined with water-fat separation methods such as iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) to produce excellent-quality water and fat images with high resolution (up to $0.3 \times 0.3 \times 1.0$ mm). The SPGR method suppresses signal from joint fluid, whereas the GRE method accentuates it (Fig. 41.5). Compared with balanced steady-state free precession (see later), these methods are less SNR efficient but also less sensitive to magnetic field inhomogeneity. Therefore, an ideal 3D cartilage imaging sequence that provides an optimal combination of resolution, SNR efficiency, and minimal artifacts has yet to be established. For this reason,

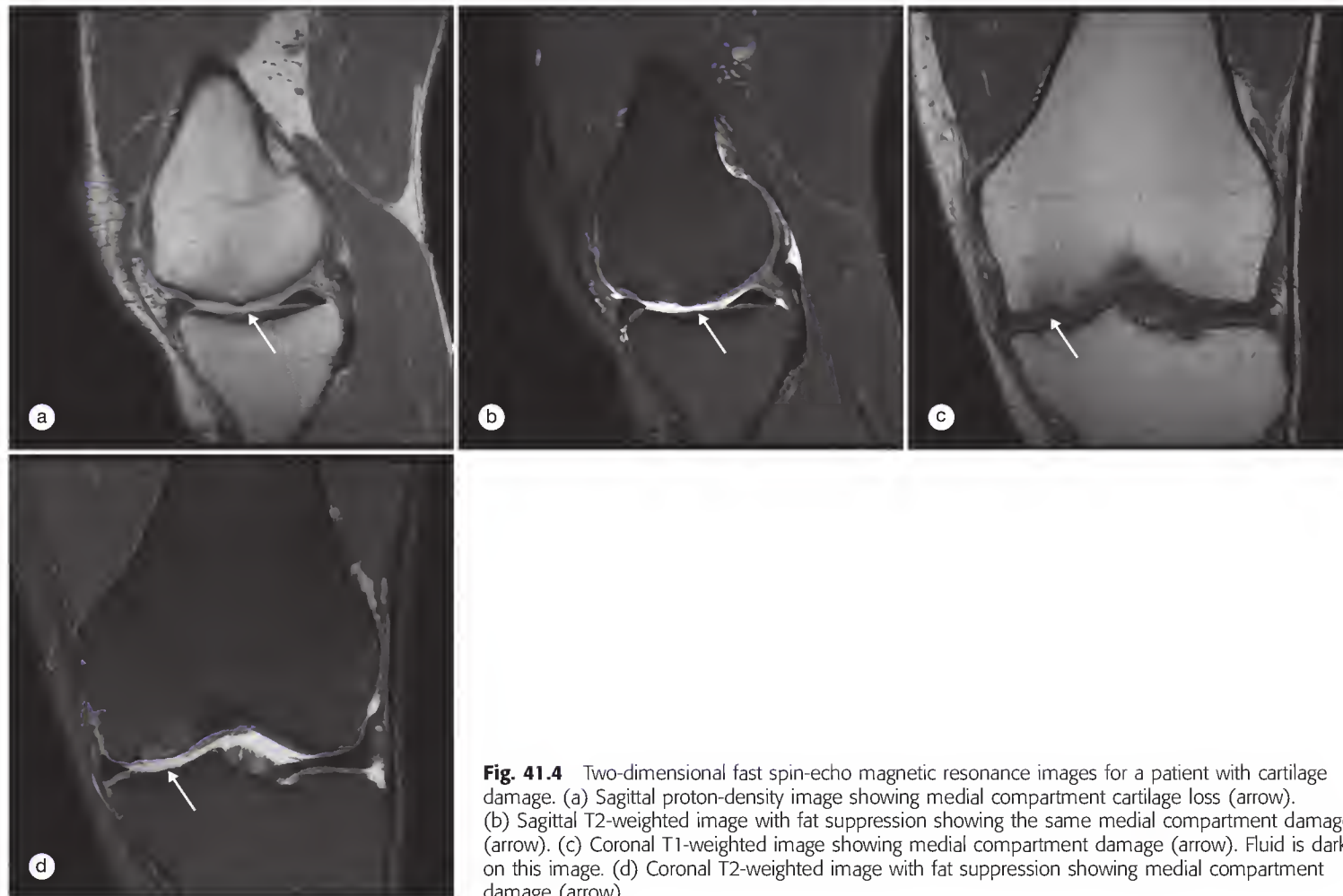


Fig. 41.4 Two-dimensional fast spin-echo magnetic resonance images for a patient with cartilage damage. (a) Sagittal proton-density image showing medial compartment cartilage loss (arrow). (b) Sagittal T2-weighted image with fat suppression showing the same medial compartment damage (arrow). (c) Coronal T1-weighted image showing medial compartment damage (arrow). Fluid is dark on this image. (d) Coronal T2-weighted image with fat suppression showing medial compartment damage (arrow).

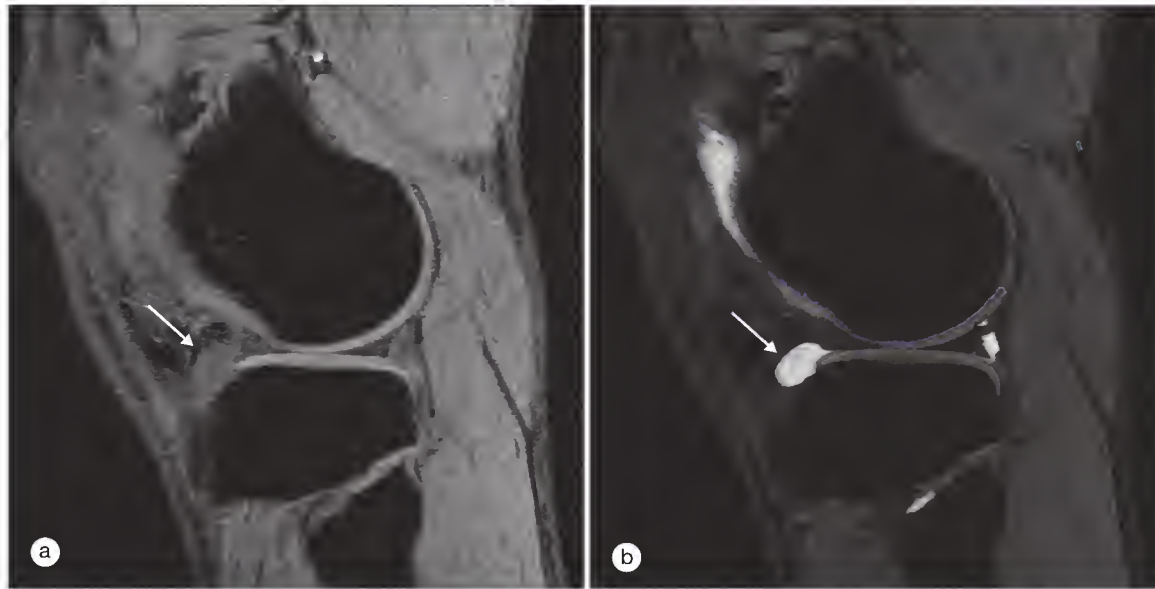


Fig. 41.5 Three-dimensional gradient-echo images for a healthy volunteer. (a) Sagittal spoiled gradient-recalled echo image showing bright cartilage but intermediate to dark fluid (arrow). (b) Sagittal gradient-recalled echo showing bright cartilage and brighter fluid (arrow).

a number of newer techniques have been developed to improve cartilage imaging.

ADVANCED MAGNETIC RESONANCE IMAGING TECHNIQUES

Dual-echo steady-state imaging

Dual-echo steady-state (DESS) imaging has proved useful for evaluation of cartilage morphology, for both volumetric and degradation assessment, because of its ability to maximize contrast between cartilage and synovial fluid.¹⁵ DESS acquires two or more gradient echoes separated by a refocusing pulse and then combines both echoes into the image. This results in an image with higher T2* weighting, which has bright signal from both cartilage and synovial fluid. This is currently the imaging method of choice for cartilage evaluation in the Osteoarthritis Initiative.¹⁴

Driven equilibrium Fourier transform imaging

Driven equilibrium Fourier transform (DEFT) imaging has been used in the past as a method of signal enhancement in spectroscopy.¹ DEFT imaging uses a 90-degree pulse to return magnetization to the z-axis, which increases signal from tissues with long T1 relaxation times such as synovial fluid. Unlike in conventional T1- or T2-weighted MRI, the contrast in DEFT imaging depends on the ratio of the T1 and T2 of a given tissue. For musculoskeletal imaging, the DEFT method produces contrast by enhancing the signal from synovial fluid, rather than attenuating the signal from cartilage as in T2-weighted sequences. This results in bright synovial fluid at short TR. At short TR, DEFT imaging shows much greater cartilage-fluid contrast than SPGR, proton-density FSE imaging, or T2-weighted FSE imaging.¹⁶ DEFT imaging has been combined with a 3D echoplanar readout to make it an efficient 3D cartilage imaging technique. Unlike in T2-weighted FSE, cartilage signal is preserved owing to the short TE. A high-resolution 3D data set of the entire knee using a 512×192 matrix, 14-cm field of view, and 3-mm slices can be acquired in about 6 minutes. Initial studies of cartilage morphology have been done using DEFT imaging,¹⁵ but this technique has not been conclusively proven to be superior to 2D approaches. A similar sequence, referred to as *DRIVE*, is FSE with driven equilibrium pulses and has also been used in musculoskeletal imaging.^{1,16}

Balanced steady-state free precession imaging

Balanced steady-state free precession (bSSFP) MRI is an efficient, high-signal method for obtaining 3D MR images.¹ Depending on the manufacturer of the MRI scanner, this method is also called *True-FISP* (Siemens, Malvern, Pa.), *Fiesta* (General Electric, Milwaukee), or *balanced FFE*

imaging (Phillips, Andover, Mass.).¹⁷ Advances in MR gradient hardware have made it possible to use bSSFP without experiencing the banding or off-resonance artifacts that were previously a problem. However, banding artifacts due to off-resonance are still an issue as TR increases or at 3.0 T. Hence, TR is usually kept below 10 ms, which limits the overall image resolution. Multiple-acquisition bSSFP can be used to achieve higher resolution at the cost of additional scan time.¹

Many methods have been proposed to provide fat suppression with bSSFP imaging. With a sufficiently short TR and homogenous magnetic field, conventional fat suppression or water-excitation pulses can be used.¹⁸ Linear combinations of bSSFP¹⁹ and fluctuating equilibrium MRI (FEMR)²⁰ use the frequency difference between fat and water and multiple acquisitions to separate fat and water. Intermittent fat suppression uses transient fat saturation pulses to suppress lipid signal.²¹ IDEAL uses multiple acquisitions to separate fat and water but does not depend on the fat-water frequency difference to constrain the TR.²² Rapid separation of water and fat can be achieved with phase detection.²³

Several studies have demonstrated the usefulness of bSSFP articular cartilage and musculoskeletal imaging.²⁴ Because of the bright synovial fluid and 3D nature of the acquisition, bSSFP is also effective for imaging internal derangements of ligaments and menisci, which makes it more generally useful than SPGR. Vastly interpolated projection reconstruction imaging (VIPR), a variant of bSSFP, has been shown to be useful in imaging the cartilage, ligaments, and menisci in a rapid manner with isotropic resolution (Fig. 41.6).²⁵

Three-dimensional fast spin-echo imaging

Two-dimensional FSE imaging is a powerful clinical tool but suffers from anisotropic voxels, slice gaps, and partial volume effects. 3D acquisitions with FSE were applied in brain imaging several years ago.²⁶ 3D FSE, with flip angle modulation to reduce blurring and parallel imaging to reduce imaging time, has made isotropic imaging with spin-echo contrast a clinical reality.^{26,27} Preliminary studies demonstrating the effectiveness of using 3D FSE with isotropic resolution in the knee,²⁶ ankle,²⁸ and wrist²⁹ have been promising; however, additional studies are warranted before these sequences replace 2D FSE. 3D FSE imaging shows isotropic resolution with the ability to obtain high-quality multiplanar reformatted images (Fig. 41.7).

High-field magnetic resonance imaging

Several centers currently have 7.0-T human MRI systems available for research purposes. Although these systems suffer from RF penetration and high-power deposition problems, they have a considerable SNR advantage over lower-field systems.³⁰ These systems are able to get to a higher resolution in a shorter period of time and may be useful for showing tissue ultrastructure. Figure 41.8 shows a representative 7.0-T data set.

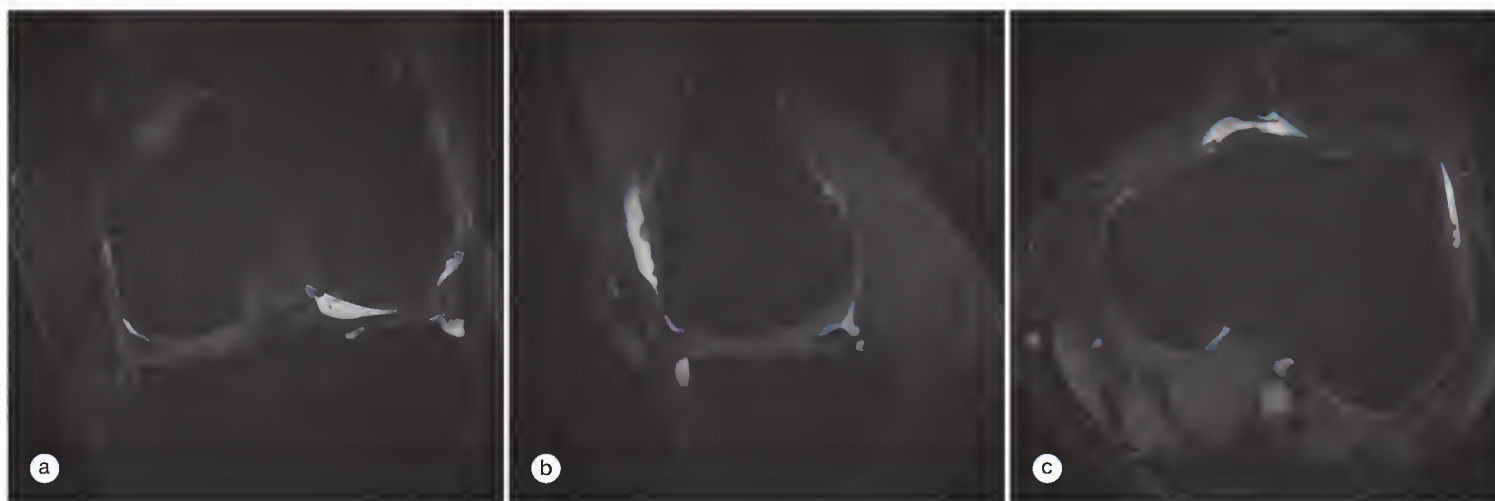


Fig. 41.6 Vastly interpolated projection reconstruction balanced steady-state free precession images of the knee at 3.0 T for a healthy volunteer. This technique produces isotropic 0.4-mm resolution across the knee, which allows reformatted images in any imaging plane. Scan time was only 5 minutes. (a) Coronal image, 2-mm section thickness. (b) Sagittal reformatted image, 2-mm section thickness. (c) Axial reformatted image, 2-mm section thickness. (Courtesy W. Block, University of Wisconsin, Madison.)

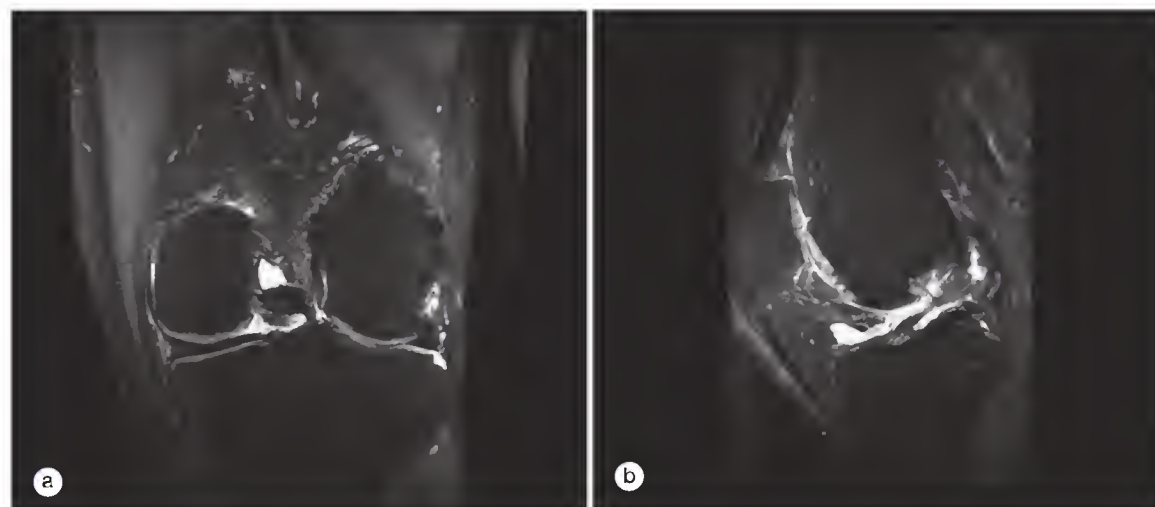


Fig. 41.7 Three-dimensional fast spin-echo imaging using flip angle modulation and parallel imaging. This acquisition was done at 3.0 T with an imaging time of 5 minutes and an isotropic 0.6-mm resolution. (a) Coronal image, 2-mm section thickness. (b) Sagittal reformatted image, 2-mm section thickness.



Fig. 41.8 Sagittal image for a healthy volunteer at 7.0 T using a three-dimensional spoiled gradient-echo method. Excellent signal-to-noise ratio was achieved with a resolution of $0.3 \times 0.3 \times 1.0$ mm in 3 minutes. (Courtesy R. Regatte, New York University.)

Cartilage thickness and volume mapping

Measurement of cartilage thickness and volume can be useful in tracking osteoarthritis. The Osteoarthritis Initiative uses high-resolution 3D imaging and manual or semi-automated segmentation of images to demonstrate that changes in cartilage thickness can be visualized in high-risk populations in as short a time as 1 year.³¹ Figure 41.9 shows a 3D reconstruction of knee cartilage from MRI data.

Magnetic resonance imaging to demonstrate physiologic activity

Contrast-enhanced imaging

Intravenous contrast agents used in MRI often contain gadolinium coupled to a large molecule to prevent toxicity. These agents reduce the T1 relaxation time of vascular tissue and areas of enhancement appear bright on T1-weighted images. These images are often acquired with fat suppression to improve the dynamic range and conspicuity of the enhancing tissues. This technique is especially useful in inflammatory arthritis because synovium and pannus are quite vascular and show considerable contrast enhancement (Fig. 41.10). This method can be used to track synovitis in osteoarthritis as well as the activity of drugs for inflammatory arthropathies.³²

T2 relaxation time mapping

The T2 relaxation time is a function of both the water content and collagen ultrastructure of the tissue. Measurement of the spatial distribution of the

T2 relaxation time may reveal areas of increased or decreased water content, correlating with tissue damage. To measure the T2 relaxation time with a high degree of accuracy, attention must be paid to the MR technique. Typically, a multiecho spin-echo technique is used, and signal levels are fitted to one or more decaying exponentials, depending on whether it is believed that there is more than one distribution of T2 within the sample.³³ However, for TEs used in conventional MRI, a single exponential fit is adequate. An image of the T2 relaxation time is then generated with either a color or a gray-scale map representing the relaxation time, as shown in Figure 41.11.

When the spatial distribution of T2 relaxation times within articular cartilage is investigated, aging appears to be associated with a T2 relaxation time increase in the transitional zone,³⁴ whereas relaxation times have been shown to be anisotropic with respect to orientation in the main magnetic field.³⁵ Focal increases in T2 relaxation times within cartilage have been associated with matrix damage, particularly loss of collagen integrity. Studies on T2 relaxation times documenting the effects of age,³⁴ gender,³⁶ and activity³⁷ have also been published. T2 relaxation time measurements also may be useful in characterizing the state of fibrocartilage tissues such as the menisci and ligaments.³⁸



Fig. 41.9 Three-dimensional volume rendering of knee cartilage from segmented high-resolution magnetic resonance imaging. Segmentation allows quantitative measurements of thickness and volume.

T1rho mapping

T1rho imaging, which involves the relaxation of spins under the influence of an RF field, is a promising technique for evaluating cartilage and other tissues.³⁹ T1rho imaging is useful because it may be sensitive to early proteoglycan depletion.^{39,40} In T1rho imaging the magnetization is tipped into the transverse plane and “spin locked” by a constant RF field. Recent advances in T1rho imaging have led to rapid cartesian acquisition strategies for use at 3.0 T.^{41,42} An example of a T1rho map for a healthy volunteer is shown in Figure 41.11. T1rho imaging has also been shown to be useful in detection of early meniscal and cartilage lesions.^{43,44}

Delayed contrast-enhanced imaging

Negatively charged Magnevist or Gd-DTPA2⁻ (Berlex, Richmond, Calif.), is a common MRI contrast agent. After intravenous injection, Gd-DTPA2⁻ penetrates into cartilage and concentrates where glycosaminoglycan (GAG) content is relatively low. Subsequent T1 imaging (which is reflective of Gd-DTPA2⁻ concentration) therefore yields an image depicting GAG distribution. This technique is referred to as *delayed gadolinium-enhanced MRI of cartilage* (dGEMRIC), with the “delay” referring to the time needed for Gd-DTPA2⁻ penetration and distribution.⁴⁵ A T1 map allows assessment of GAG content, with lower values corresponding to areas of GAG depletion.

Various clinical cross-sectional studies in specified populations have provided much insight. One study reported that individuals who regularly exercise have higher dGEMRIC indices than individuals who are sedentary. In a relatively large study of patients with hip dysplasia, measures of the severity of dysplasia (the radiographically determined lateral center edge angle) and pain both correlated with dGEMRIC indices but not with the standard radiologic parameter of joint space narrowing. In another study, lesions in patients with osteoarthritis were more apparent with the dGEMRIC technique than with standard MRI scans.⁴⁶ Additionally, dGEMRIC findings have been correlated with Kellgren and Lawrence radiographic grading of osteoarthritis.⁴⁷ Combining dGEMRIC methods with T2 mapping requires careful attention to technique.⁴⁷ It is important to note that, as a free ion, Gd-DTPA2⁻ can be toxic; however, Gd-DTPA2⁻ contrast agents approved by the U.S. Food and Drug Administration are chelated, which greatly reduces their toxicity. Patients with renal insufficiency or dysfunction should avoid imaging using this contrast agent.⁴⁸

Physiologic methods like dGEMRIC and T2 mapping can be time consuming and difficult to perform on a routine basis. dGEMRIC is often performed using a variable flip angle 3D-SPGR approach, as shown in Figure 41.12.^{47,49} SSFP methods also show promise in improving the speed and SNR of T1 and T2 relaxation time measurements.⁵⁰

Sodium magnetic resonance imaging

Because sodium-23 (²³Na) has an odd number of protons and/or neutrons it possesses a net nuclear spin and can exhibit the MR phenomenon. ²³Na



Fig. 41.10 Coronal magnetic resonance images of the wrist for a patient with rheumatoid arthritis. (a) T1-weighted image shows bone erosions as areas of signal loss in the marrow fat. (b) Contrast-enhanced image of the wrist shows brightly enhancing synovium and pannus.

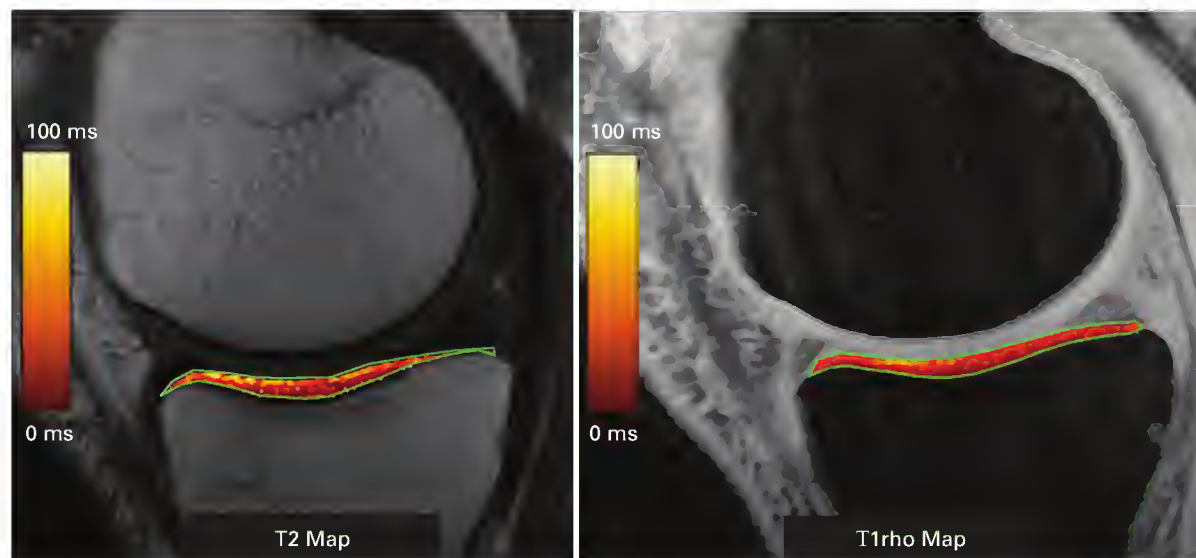


Fig. 41.11 Measurements of tissue physiology with magnetic resonance imaging T2 map (left) and T1rho map (right) of the tibial cartilage in a healthy volunteer. The color scale shows relative relaxation time values between 0 and 100 ms. Changes in T2 relaxation time are correlated with collagen matrix status; changes in T1rho are correlated with proteoglycan content.

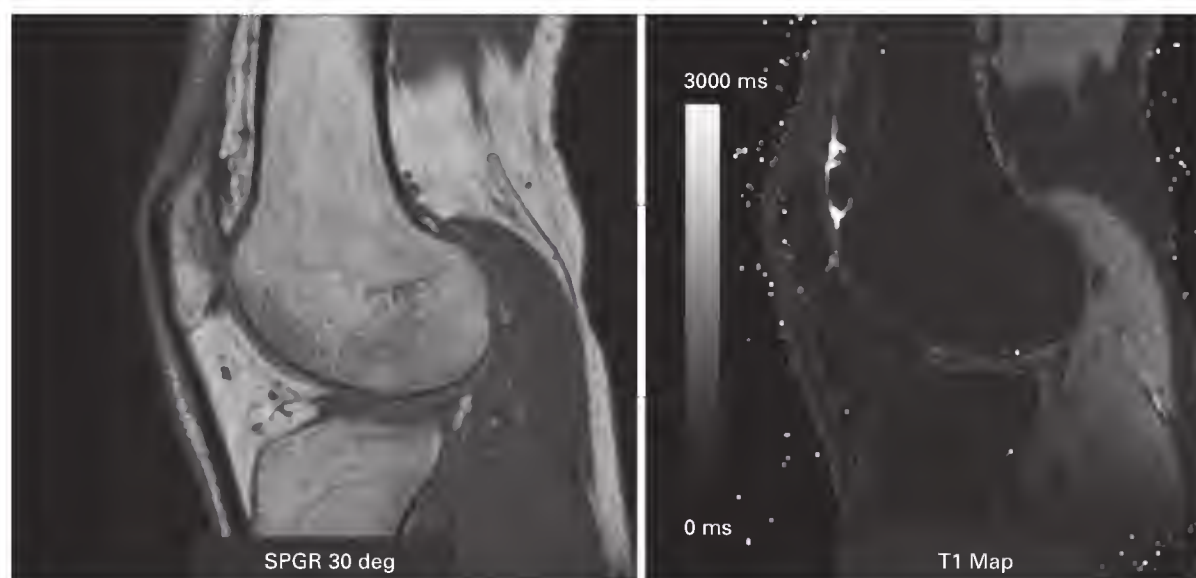


Fig. 41.12 Delayed gadolinium-enhanced magnetic resonance imaging of cartilage in a healthy volunteer. The left image is a spoiled gradient-echo image used to map the T1 relaxation times. The right image is a T1 relaxation time map with a gray scale from 0 to 3000 ms.

MRI has been shown to be useful in musculoskeletal imaging owing to the natural abundance of sodium in articular cartilage. As a result of the opposing charges associated with sodium and GAG, ^{23}Na MRI can be used to estimate the GAG content in cartilage. Although it is both accurate and noninvasive, ^{23}Na MRI requires high-field MRI systems (3.0 or 7.0 T). The concentration of ^{23}Na in normal human cartilage is about 320 μM , with T2 relaxation times between 2 and 10 ms.⁵¹ The combination of lower resonant frequency, lower concentration, and shorter T2 relaxation times compared with ^1H make *in vivo* imaging of ^{23}Na challenging. The use of ^{23}Na MRI is limited because special transmit and receive coils and relatively long imaging times are required to achieve adequate SNR.

^{23}Na MRI has shown promising results in the imaging of articular cartilage due to its ability to depict regions of proteoglycan depletion.⁵¹ The ^{23}Na atoms are associated with the high fixed-charge density present in proteoglycan sulfate and carboxylate groups. Some spatial variation in ^{23}Na concentration is present within normal cartilage.⁵¹ Because of the short T2 relaxation times of sodium, imaging is often done with a non-cartesian trajectory.⁵² Figure 41.13 shows proton and sodium images from a patient with a prior ligament injury. In cartilage samples, sodium imaging has also been shown to be sensitive to small changes in proteoglycan concentration.⁵³ It is sensitive to early decreases in proteoglycan concentration in osteoarthritis and can be even more sensitive to early changes when triple-quantum-filtered imaging is used.⁵⁴

CONCLUSION

MRI is a powerful tool for the imaging and understanding of musculoskeletal tissue. Improvements have been made in morphologic imaging of joints in terms of contrast, resolution, and acquisition time. This allows for the development of detailed tissue maps and provides the ability to quantify both thickness and volume. Much progress has been made in the imaging of joint physiology. Important areas include the detection of changes in proteoglycan content and collagen ultrastructure in cartilage and other tissues.

The choice of a particular MRI protocol for joint imaging is strongly dependent on patient factors. For many patients with internal derangement, imaging with standard FSE and/or 3D-SPGR sequences may suffice. For patients being considered for surgical or pharmacologic therapy, a more detailed evaluation may be required. For example, fast morphologic imaging along with evaluation of cartilage physiology may allow for noninvasive evaluation of cartilage implants at different time points.

Current musculoskeletal MRI protocols include multiple planes of 2D-FSE and 3D-GRE images. The new morphologic methods presented here such as VIPR, 3D-FSE, and bSSFP achieve isotropic resolution for an entire joint in a single acquisition, which decreases scan time. The isotropic data can then be reformatted into standard or oblique planes using slice averaging to improve SNR. Combining these methods with fat-water



Fig. 41.13 Proton and sodium magnetic resonance images of the knee of a patient 3 years after anterior cruciate ligament injury. The proton image (a) shows intact articular cartilage. The sodium concentration measured at 3.0 T is overlaid on the proton image as a heat scale (b). An area of decreased sodium is seen in the trochlea cartilage, which may represent an area of proteoglycan depletion.

separation methods, such as IDEAL, provides water, fat, and combined images, which has various advantages.

Additional studies are required to validate the sensitivity of these isotropic methods in detecting common joint disorders such as meniscal tears. Isotropic acquisitions could improve patient throughput or allow detailed studies of tissue physiology when used in combination with T2 mapping,

T1rho mapping, or sodium MR methods. The integration of fast, high-resolution morphologic imaging methods with newer physiologic techniques has the potential to expand the sensitivity of MRI to early cartilage degeneration. Ideally, the combination of these techniques will lead to an MRI examination that is brief, is well tolerated, and contains both morphologic and physiologic data.

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42

Musculoskeletal ultrasound

■ DAVID KANE

- Musculoskeletal ultrasound is an established tool in rheumatologic practice.
- Ultrasound performed in clinic provides immediate diagnosis and objective measures of rheumatologic disease.
- Ultrasound applications in rheumatology extend beyond the joint to many different tissues involved in rheumatologic disease (e.g., nerves, blood vessels, salivary glands).
- Ultrasound can guide interventions such as joint and soft tissue aspiration and injection, nerve blocks, and synovial biopsy.

INTRODUCTION

Musculoskeletal ultrasound imaging is now an established diagnostic technique for all clinicians who manage musculoskeletal disease. Over the past two decades, rheumatologists have pioneered the introduction of ultrasound directly into rheumatology clinics, thus exploiting the immediate diagnostic potential of this technique.¹ Aided by the development of high-frequency transducers, reduced equipment costs, and a better understanding of pathologic features as revealed by musculoskeletal ultrasound, there has been a rapid international adoption of this technology by rheumatologists. Ultrasound is now a compulsory part of specialist rheumatology training in some European countries, and training guidelines have been published by the European League Against Rheumatism (EULAR)² and the Pan-American League Against Rheumatism (PANLAR)³ with ultrasound courses now being run in most countries in which rheumatology is practiced.

The principal reason that ultrasound has become an increasingly useful tool in rheumatology is that it can be directly performed by the rheumatologist as an extension of the clinical examination^{4,5} (Fig. 42.1). This is in contrast to other imaging modalities such as magnetic resonance imaging (MRI), scintigraphy, and computed tomography (CT), which are performed remote to the clinical evaluation. Ultrasound is a high-definition imaging technique that can simultaneously image soft tissues and bone, producing multiplanar real-time dynamic images without exposing the patient to ionizing radiation. Although it is safe, inexpensive, and highly acceptable to patients, ultrasound should always be selected in the context of all imaging modalities available to the rheumatologist.⁵ Ultrasound has poor penetration of deep musculoskeletal tissue and cannot image the internal structures of bones; thus MRI and CT scanning are much more suitable for indications such as evaluation of internal and bony structures, deep-lying joints, and spinal structures.

MUSCULOSKELETAL ULTRASOUND IMAGING

Basic principles of ultrasound

Musculoskeletal ultrasound produces images of soft tissues through emission of high-frequency sound waves from an ultrasound transducer.⁶ For optimal musculoskeletal imaging, these frequencies range from 5 to 18 MHz and are inaudible to the human ear. Ultrasound waves travel through different soft tissues at different speeds based on the propagation speed of that tissue. The propagation speed depends on the density of the tissue but also on the number of internal reflective structures, for example, tendon fibers,

which absorb or reflect the sound wave energy. The transducer also acts as a receiver for the reflected sound waves. In brief, less dense structures such as fluid that lack tissue interfaces will appear as dark or hypoechoic, whereas more dense structures with multiple interfaces such as tendon will appear as brighter or hyperechoic. The tissue interfaces also produce typical features of a tissue, such as the regular parallel lines of a tendon or ligament, which aid in their identification.

Ultrasound can be used to determine tissue movement—such as blood flow—based on the Doppler principle.⁷ This principle dictates that sound waves increase in frequency when they reflect from objects that are moving toward the transducer and decrease in frequency when they reflect from objects moving away from the transducer. There are two main types of Doppler ultrasound: color flow Doppler (CFD) and power Doppler (PD). CFD represents an estimate of the mean Doppler frequency shift and relates to the velocity and direction of red blood cells. This allows CFD to determine direction of blood flow, with blood flow moving toward the transducer indicated as a red signal and blood flow moving away from the transducer indicated as a blue signal. CFD is best suited for evaluation of high-velocity flow in large vessels. PD measures the amplitude of the Doppler signal without directional information. Both PD and CFD produce color images of blood flow superimposed on the gray-scale ultrasound image. In assessing tissues for Doppler signal, it is critical first to obtain an adequate, well-orientated gray-scale image of the area of interest before evaluation with Doppler imaging. Otherwise, normal vascular structures around joints may be erroneously diagnosed as inflammatory tissue within the joint.

Because PD has increased sensitivity to low-volume, low-velocity blood flow, it has been particularly useful for measuring blood flow associated with soft tissue inflammation in joints and other musculoskeletal tissues. Additionally, the PD signal in a standard reference gray-scale image can be scored on a semiquantitative scale of 0 to 3 or a quantitative scale based on the number of colored pixels in a region of interest.⁸ This has a potential advantage when monitoring inflammatory changes in joints in response to therapy. Recent advances in CFD imaging technology have improved sensitivity for the detection of soft tissue inflammation, and PD and CFD now approach similar levels of sensitivity for detection of synovitis.

Ultrasound equipment

Inadequate ultrasound equipment leads to inadequate musculoskeletal ultrasound imaging. In selecting equipment, one can choose from a wide variety of available equipment ranging from larger, less mobile, high-definition systems to smaller, portable systems.⁹ In general, the price of ultrasound equipment is inversely proportional to the size of the equipment and directly proportional to the quality of the image. Portability is an attractive feature for those who require mobility at different clinics and at the bedside but increases the cost of the equipment. The minimum requirements are a linear-array high-frequency transducer capable of imaging larger, deeper joints (range of frequency is 5 to 10 MHz) but also capable of imaging small superficial structures such as tendons and nerves (range of frequency is 10 to 15 or even 20 MHz).

Color and power Doppler imaging options are an essential requirement for musculoskeletal ultrasound imaging. In combination with the high-frequency linear-array transducer, the ultrasound system should have a dedicated musculoskeletal software package. Additional software options such as an extended field of view, elastography, three-dimensional capabilities, and contrast capability are playing a growing role in musculoskeletal ultrasound but are not essential for routine practice.

Consideration should be given to how the ultrasound examination results will be archived, and additional software for picture archiving may



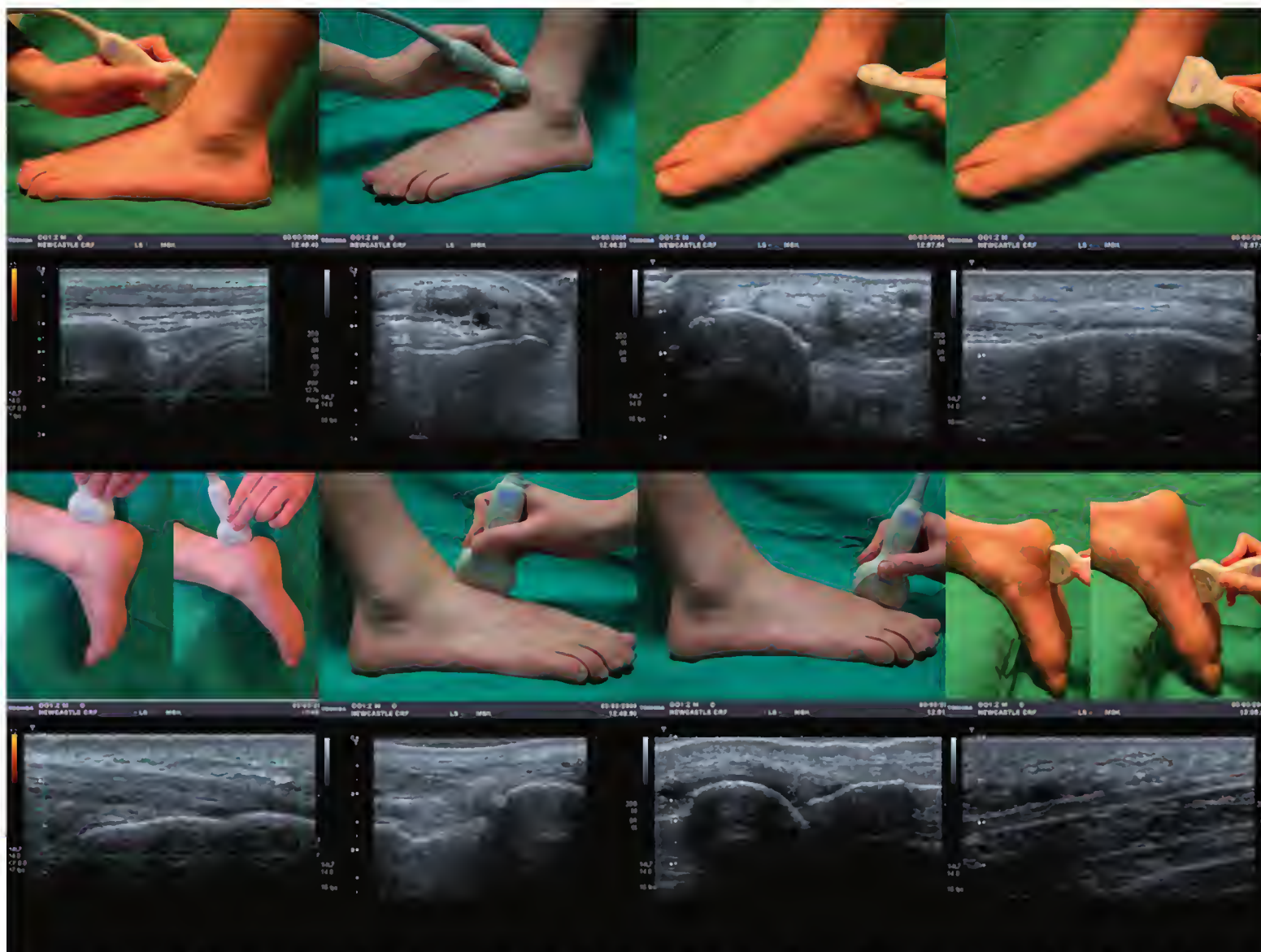


Fig. 42.1 Ultrasound of the foot and ankle in the rheumatology clinic. After history taking and physical examination the rheumatologist can immediately apply the ultrasound probe directly to the symptomatic anatomic area on the foot and ankle, which allows immediate confirmation of the clinical diagnosis and prescription of therapy. The panel of images shows multiple probe positions and corresponding ultrasound images demonstrating the flexibility of this technique.

be required. It is important to consider the environment in which the ultrasound examination will be performed and to ensure good ventilation or air conditioning and the availability of an adjustable-height examination couch and chair for the operator to optimize the ergonomics of the work environment of the ultrasonographer.

Education and training

Enthusiasm for ultrasound in rheumatology has been tempered by the realization that this is an operator-dependent technique which requires a significant period of technical skills training.¹⁰ Although there has been a considerable increase in the number of rheumatologists practicing musculoskeletal ultrasound, there still are barriers related principally to access to equipment and access to trainers and training. Most national and international ultrasound societies now provide short intensive ultrasound courses for rheumatologists. EULAR has been at the forefront of musculoskeletal ultrasound education and was the first to establish a system of basic, intermediate, and advanced ultrasound courses and to have published guidelines on standardized images, curriculum, and training.² The American College of Rheumatology⁵ and PANLAR³ have now also published guidelines and organized courses, and national societies in countries such as Germany and Italy have incorporated ultrasound into the training curriculum for rheumatologists.¹¹

All of these guidelines recognize that the trainee must undertake a significant period of scanning practice to acquire the appropriate technical skills. Formal short courses, textbooks, and Internet-based educational aids

are useful adjuncts to training but do not substitute for continuous interactive learning with an experienced mentor. There is no consensus yet on competency or competency assessment in musculoskeletal ultrasound. Although performing a quantity of ultrasound scans ranging from 250 to 500 is estimated to be equivalent to an adequate period of training by the various guidelines, evaluation of competency should include a practical qualitative assessment. It is recommended that all ultrasonographers keep a log book of ultrasound scans for validation of training. There is a need for an internationally recognized competency qualification in ultrasound in rheumatology both to consolidate and to develop this subspecialty interest.

Standard views and artifacts

Ultrasound imaging is a dynamic technique performed in multiple planes in real time. A number of standard imaging planes have been described for peripheral joints to orientate the examiner and also to provide ease of reference and comparison of ultrasound scans performed at different times.¹² All ultrasound scans are defined by two perpendicular views: transverse (short axis) and longitudinal (long axis). All pathologic processes should be confirmed and fully described in two perpendicular views. Most ultrasound systems now have predetermined settings for different-sized joints and soft tissues, although the operator may adjust other technical features such as contrast, brightness, and sharpness using image-processing software to optimize the image. It is important for the operator to have a technical knowledge of specific frequency, gain and software settings to optimize imaging

depending on the tissue examined. Each ultrasound system has different applications for this and further information should be provided by the system manufacturer.

Artifacts are ultrasound echoes that do not correspond to the real imaging target in either distance or direction.¹³ Although these can cause confusion in the interpretation of the image, a number of standard artifacts can be an invaluable aid in identifying soft tissue landmarks and pathologic processes.

Anisotropy



Anisotropy is the most common artifact observed in musculoskeletal tissues and is extremely valuable in identifying structures such as tendons (Fig. 42.2, Video 42.1). Anisotropy occurs when the angle of the ultrasound beam is not perpendicular to the tissue being scanned. This causes the sound waves to be scattered rather than reflected back to the transducer/receiver; this results in loss of signal, which is presented as a hypoechoic area in linear structures such as tendons. Although this can result in an inaccurate diagnosis of tendon lesions such as tendinosis or tendon tears, the operator

learns to change the angle of the ultrasound transducer to a perpendicular plane and thus eliminate the artifact. In deeper or dense tissues, this technique can also allow identification of small tendon structures through the ability to change them from hyperechoic to hypoechoic structures with slight angulation of the probes.

Refractile shadowing/edge artifact

When the ultrasound beam hits a structure at an oblique angle (e.g., edge of a tendon in transverse view), a hypoechoic area can occur at the edge of the hyperechoic structure. This can erroneously be interpreted as fluid or tendon sheath thickening (Fig. 42.3c).

Acoustic shadowing

Acoustic shadowing occurs when an ultrasound beam hits a highly reflective surface such as bone or calcified tissues and there is a failure of echo return from the tissues beneath the reflected surface with consequent loss of signal. The appearance is of a hyperechoic reflection with little or no signal distal to it (see Fig. 42.3b).

Fig. 42.2 Anisotropy. (a) The transducer is placed perpendicular to the flexor tendon in the anatomic hand model. (b) The corresponding ultrasound plane in a normal subject shows the tendon as hyperechoic and homogeneous. (c) The transducer is placed at an acute angle to the flexor tendon in the anatomic hand model. This angulation causes anisotropy when imaging the tendon. (d) The corresponding ultrasound plane in a normal subject shows the tendon as hypoechoic and heterogeneous.

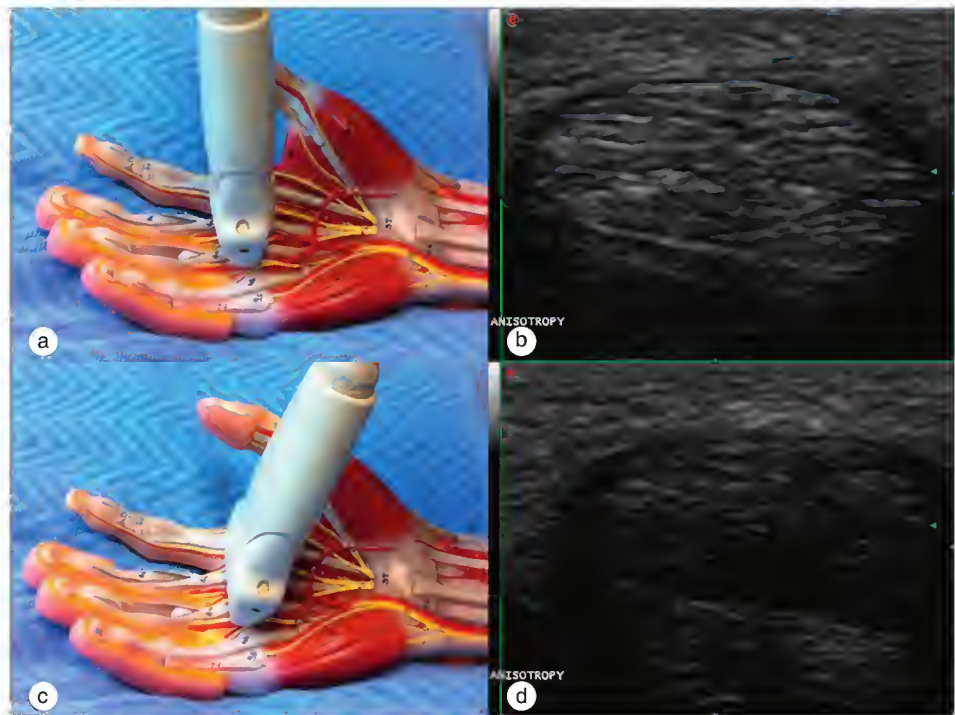
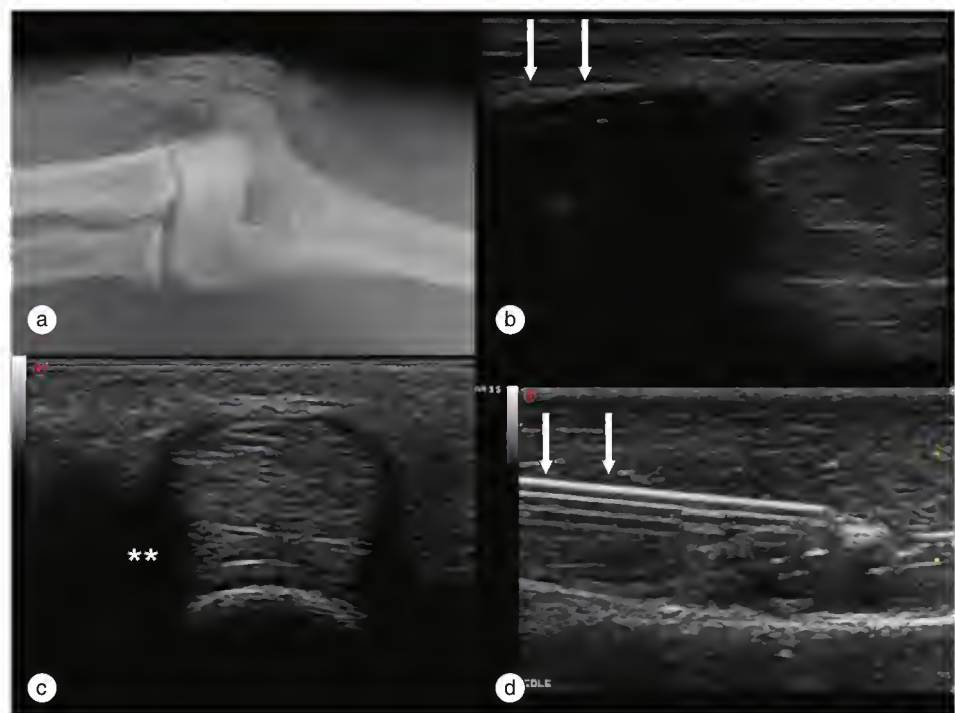


Fig. 42.3 Common ultrasound artifacts. (a) Plain radiograph for a patient with systemic lupus erythematosus showing subcutaneous calcification on the ulnar aspect of the elbow. (b) The corresponding ultrasound image shows the edge of the area of calcification with hyperechoic calcified tissue (arrows) with acoustic shadowing deep to the calcified tissue on the left and normal skin, subcutaneous tissue, and muscle on the right-hand side. (c) Beam edge artifact caused by refractile shadowing at the side of a flexor tendon gives a hypoechoic appearance and can be mistaken for tendon sheath thickening or fluid. (d) “Comet tail” appearance of a needle in muscle tissue is a reverberation artifact.



Acoustic enhancement

As the ultrasound beam travels through an increasing depth, the intensity of the echoes returned to the transducer decreases; however, should the beam encounter a fluid collection, there is enhanced transmission of sound waves through the fluid, which leads to a brighter signal in the tissues distal to the fluid collection. This can be mistaken for an integral change in the tissue structure.

Reverberation

Reverberation of image occurs when an ultrasound beam encounters highly reflective surfaces, which leads to multiple reflective echoes. The most typical example of this is the “comet tail” artifact, such as is produced by a needle (see Fig. 42.3d, Video 42.2). The presence of this artifact can be of use in interventional procedures in identifying the needle tip. Similar metal artifacts are observed with joint prostheses.

Power Doppler scanning technique artifacts

Before assessment for Doppler imaging, it is critically important that the operator obtain a reference gray-scale image with the tissue motionless. Then any Doppler signal detected can be attributed to a specific anatomic region being examined and is not due to transducer, operator, or tissue movement. An inexperienced operator can exert undue pressure on the soft tissues to obtain this fixed image, thus obliterating small-vessel blood flow and giving a false-negative PD signal.

Doppler imaging artifacts

An extensive description of the artifacts that occur with Doppler imaging has been presented by Torp-Pederson and Terslev.⁷ These include (1) random noise, which is caused by setting the color gain too high; (2) mirror artifact, in which Doppler flow can be seen beneath the bone surface as well as above; (3) aliasing, which occurs with CFD but not with PD; and (4) blooming, in which the pictorial representation of the vessel flow expands beyond the vessel wall, which is also caused by oversetting of the gain. In practice, it is advisable to adjust the pulse repetition frequency to the point at which there is no vessel signal below bony cortex and then to adjust the gain until random-noise Doppler artifacts disappear.

MUSCULOSKELETAL ULTRASOUND IN RHEUMATOLOGY

Synovial tissue and the synovial joint

The application of ultrasound in the diagnosis of rheumatoid arthritis (RA) not only has aided in more rapid diagnosis of disease but also has provided novel insights into the pathologic processes in RA.¹⁴ Ultrasound has consistently been proven to demonstrate synovial fluid effusion and synovial thickening with a greater sensitivity than clinical examination. This has been confirmed in both small and large joints, and the OMERACT/EULAR Ultrasound Task Force has published definitions of these pathologic findings that will aid in the standardization of ultrasound diagnosis and the development of ultrasound findings as an outcome measure in RA.¹⁵

Synovitis is a term used to refer to joint inflammation seen on ultrasound, which appears as joint effusion, synovial thickening, or a combination of both. Joint effusion is observed as an anechoic or hypoechoic area within the capsule of the joint that is compressible and displaceable but does not have a PD signal. Synovial thickening is diagnosed by the presence of abnormally thickened hypoechoic tissue within the joint capsule that is partially compressible but not displaceable and that may demonstrate PD signal. Ultrasound has demonstrated subclinical synovitis in both early disease and late disease, and in patients in remission.¹⁶ The relevance of subclinical synovitis seen on ultrasound remains controversial and challenges the concept of defining both diagnosis and prognosis based on the number of clinically inflamed joints. In one study, up to a third of cases of clinically diagnosed oligoarthritis were redefined by ultrasound assessment as polyarthritis, which has a potentially worse prognosis.¹⁷ In patients in remission, subclinical synovitis detected by ultrasound and MRI correlated with progressive radiologic damage, which confirms that it is a relevant finding.¹⁸

Doppler ultrasound examination is a standard part of the assessment for synovial joint inflammation. PD is most sensitive in small and superficial joint structures, with less PD signal demonstrated in deeper joints such as the hip and shoulder. PD shows blood flow within the synovial tissue, which is due to a combination of angiogenesis and vasodilatation. Both these processes are important components of the chronic inflammation of the synovial joints. PD can detect blood flow even within some normal joints, has

been demonstrated to have sensitivity and specificity comparable to those of MRI,⁸ and has been validated through correlation with the findings of synovial histopathologic analysis. PD semiquantitative scoring has been developed and shows good intraobserver and interobserver reproducibility. This allows for the quantification of PD signal in joints before and after therapy. A number of studies have also indicated that PD findings may have a predictive and prognostic value. Studies of patients in remission confirmed that persistent PD signal correlated with the development of joint damage.¹⁸ In another study of patients with established RA, time-integrated assessment of PD ultrasound results demonstrated a strong correlation with damage progression on plain radiographs. This assessment was demonstrated to be superior to clinical and laboratory parameters.¹⁹

A number of studies have examined whether it is necessary to study all joints or only a subset of synovial joints in RA to assess disease activity objectively by ultrasound.²⁰ Given the time required to image multiple joints, scanning of a more limited but representative subset of joints would provide a more practical means of evaluation. Backhaus and colleagues²⁰ have reported that a panel of seven areas assessed by ultrasound (US7 score) provided a highly reproducible score that correlated well with other clinical and laboratory parameters of disease activity. Naredo and colleagues^{20a} performed a study developing a 12-joint score for RA. Further studies are being undertaken to see whether a limited subset of ultrasound images in RA patients can provide a more objective evaluation of disease activity than current clinical and laboratory scores.

Ultrasound-determined synovitis has the same characteristic imaging appearance in RA and in seronegative arthritis and cannot reliably differentiate the two diseases. In osteoarthritis, ultrasound studies have shown synovial inflammation features—including effusion, synovial thickening, and increased PD signal—in almost half of osteoarthritic knee and interphalangeal joints.²¹ The degree of synovial inflammation is less than that seen in RA, and PD signal is less frequently observed, being present in only 10% of interphalangeal joints. Ultrasound-determined synovial inflammation in hand osteoarthritis did not correlate with hand symptoms or with symptomatic response to treatment with methylprednisolone (Fig. 42.4, Video 42.3).²²

Tendon and enthesis

Ultrasound imaging of the tendon in inflammatory disease demonstrates the early changes of tendonitis as hypoechoic thickening of the tendon with widening of the spacing of the regular fibrillar infrastructure.²³ Tenosynovitis is seen as hypoechoic synovial tendon sheath thickening, which may consist of both hypoechoic tissue and fluid. PD signal is not normally seen in tendons but is observed in association with tendon inflammation. Later stages of tendon disease may show the progression of more circumscribed, hypoechoic foci in the tendon with gradual degeneration of the tendon, potentially culminating in tears (Fig. 42.5).

In the rheumatoid hand, flexor and extensor tendon involvement has been observed on ultrasound in up to 90% of cases in early RA and 100% of cases in established RA. In the wrist, the flexor carpi ulnaris tendon is most commonly involved in the early stage of RA, but ultimately any of the flexor or extensor tendons can become affected by the disease. In comparative studies of rheumatoid hand disease, MRI has been shown to be superior to ultrasound in detection of joint synovitis and erosion, whereas ultrasound has a higher sensitivity for the detection of tendon abnormalities. Standardized definitions now exist for tendon pathologic processes, and a validated scoring system for tenosynovitis is in development.²³ The options are to present quantitative measurements of the tendons and tendon sheath at fixed bony points in joints or to rely on a semiquantitative scoring system using standard EULAR reference images of tendons overlying joints. Some literature has focused on the size of tendons as an aid to the diagnosis of tendon abnormalities. A key limitation of this approach is that the size of the tendon also depends on the size of the individual, and it is important always to compare with the tendon on the opposite side in the patient, particularly if the tendon is asymptomatic.

In spondyloarthritis, ultrasound has been consistently demonstrated to be superior to clinical examination in the detection of tendon and enthesis inflammation.²⁴ This is of important diagnostic usefulness, because the clinical detection of enthesitis is one of the key features in the diagnosis of spondyloarthritis (Fig. 42.6). Although enthesitis is a cardinal feature of spondyloarthritis, it may also be found in situations such as mechanical stress and diseases such as gout. Thus it is important for the ultrasonographer to limit his or her reports to anatomic detail of sites rather than making diagnostic inferences. An additional advantage of ultrasound is that the bony surface of the tendon insertion can also be examined; this allows the identification of erosions and vascular changes, which are more typical in

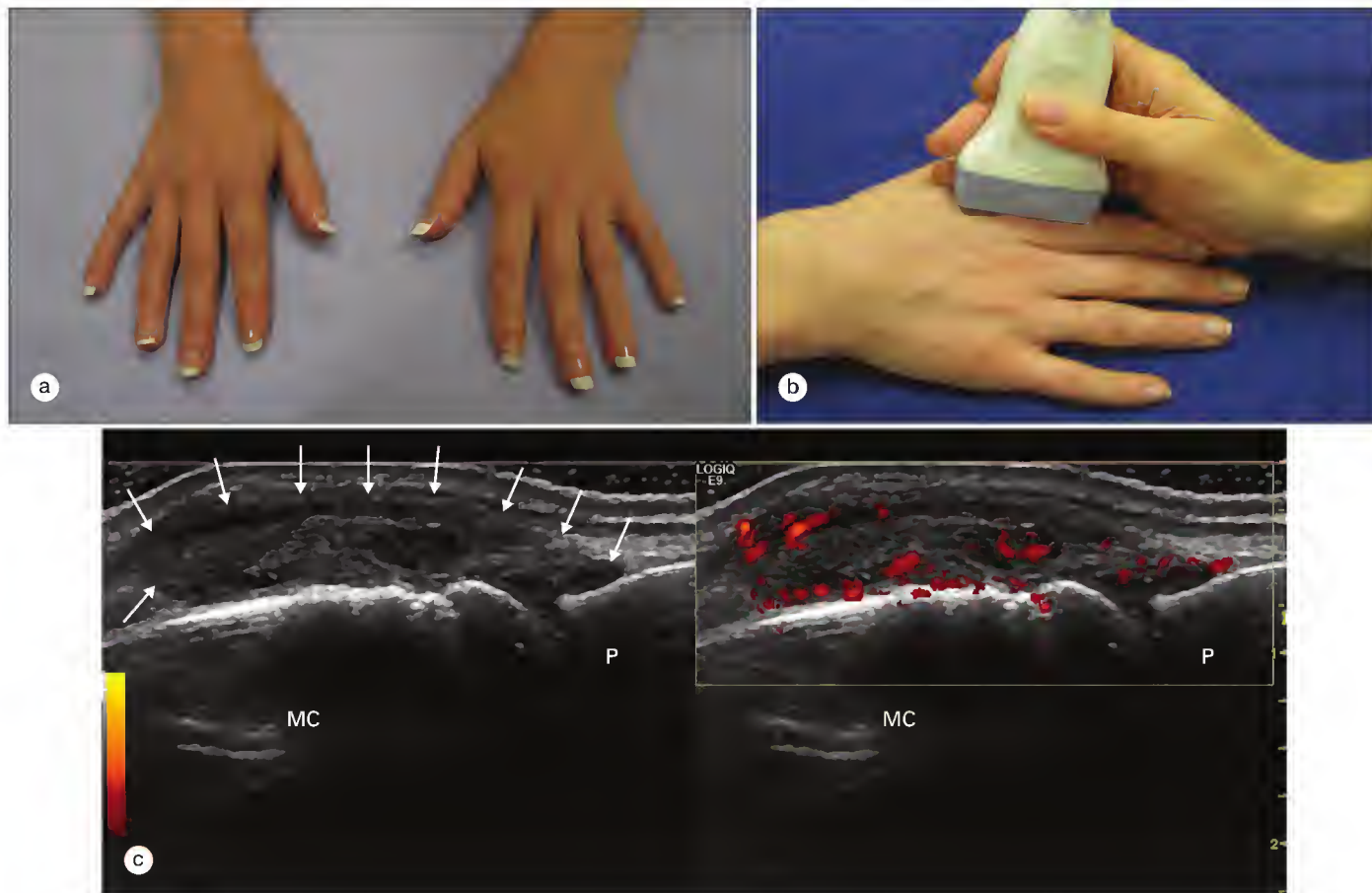


Fig. 42.4 (a) Patient with puffy fingers and arthralgia. (b) Technique of performing an ultrasound examination on a metacarpophalangeal joint. The dorsal longitudinal plane is shown. (c) Marked gray-scale synovitis is demonstrated (arrows) in longitudinal view. There are also marked Doppler signals within the synovium. MC, metacarpal head; P, phalanx.



Fig. 42.5 Achilles tendinopathy. (a) Panoramic longitudinal view of the Achilles tendon shows hypoechoic thickening of the tendon distal to the calcaneal insertion. (b) Power Doppler signal is increased in the Achilles tendon, which confirms hypervascularity. Histologic studies show very little inflammatory infiltrate in this condition.

inflammatory disease than in mechanical stress. Associated bursitis and underlying joint synovitis can also be assessed at the same examination, which highlights the usefulness of ultrasound in the clinic.

Ultrasound can be used to monitor tenosynovitis and enthesitis and provides an objective score for assessing the effects of therapy. The Glasgow

Ultrasound Enthesitis Scoring System (GUESS) produces a combined score for gray-scale ultrasound features at entheses commonly involved in spondyloarthritis.²⁴ A four-point semiquantitative score based on gray-scale and PD features of tenosynovitis in hand, wrist, and ankle tendons in RA has been described and has moderate interobserver reliability.²⁵

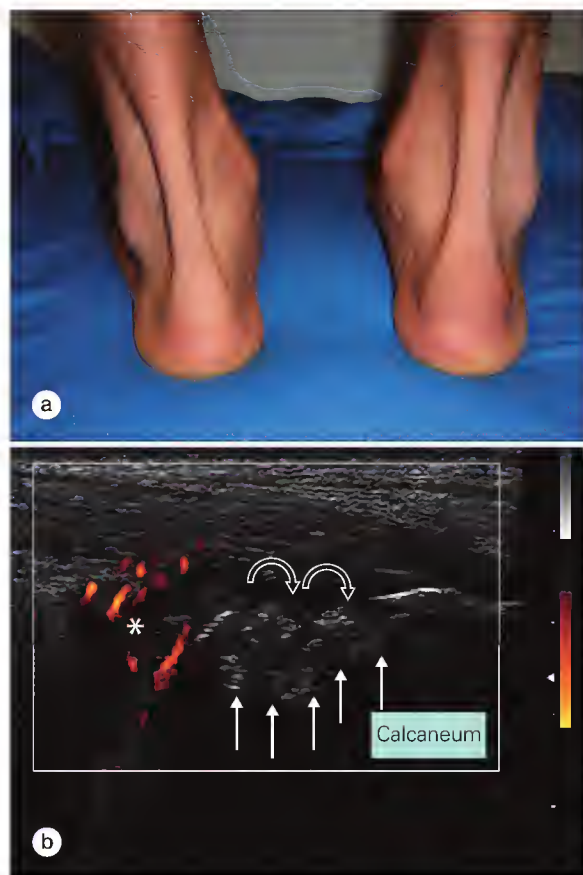


Fig. 42.6 Achilles enthesitis. (a) Acutely painful posterior heel on right in a young man with a 6-week history of diarrhea and weight loss secondary to underlying Crohn disease. (b) Longitudinal ultrasound section through the Achilles tendon. There is bony irregularity of the calcaneum (straight arrows), hypoechoogenicity, loss of fibrillar pattern of the tendon at the bony insertion (curved arrows), and increased power Doppler signal in the region of the retrocalcaneal bursa (asterisk).

Dactylitis

Dactylitis is a characteristic sausage-shaped swelling of the toes or fingers seen in spondyloarthritis and most typically in psoriatic arthritis. Ultrasound has confirmed that the principal components of dactylitis are flexor tenosynovitis and increased subcutaneous soft tissue swelling.²⁶ One study of dactylitis in more established disease has also highlighted the need to consider underlying joint involvement, which can be masked by the degree of soft tissue swelling.²⁷ An interesting feature of dactylitis is that an equivalent degree of flexor tenosynovitis seen on ultrasound in RA does not provoke the same degree of exuberant adjacent soft tissue swelling seen in spondyloarthritis.

Muscle

In myositis, ultrasound demonstrates initial hypoechoic edema in inflamed areas of muscle. With marked perimysial edema, the hypoechoic fluid surrounding the muscle fibers can by contrast make the fibers appear hyperechoic. Hypervascularity is also seen on Doppler studies of inflamed muscle. In later stages of disease, muscle fiber atrophy and hyperechoic fat infiltration are observed. MRI is generally preferred for diagnostic imaging of the muscle in myositis because it is more sensitive for muscle edema. Ultrasound findings correlate well with MRI findings in myositis, and ultrasound may be an alternative to MRI for the diagnosis of myositis; however, more standardization needs to be done on the ultrasound definition of myositis (Fig. 42.7).²⁸

Ultrasound can readily demonstrate hypoechoic grade 2 and 3 muscle fiber tears and associated fluid in partial or complete muscle rupture. The targeted nature of ultrasound examination and the possibility for muscles to be contracted and relaxed during examination improve the sensitivity of ultrasound in the detection of tears, but MRI is superior in the detection of grade 1 tears, in which there may be only subtle edema. On the other hand, large amounts of muscle edema on MRI can obscure other structural abnormalities in larger tears. Ultrasound is very sensitive to calcific changes in tissues such as occur with myositis ossificans.²⁹

Bone erosion and osteophyte

Because of its highly reflective nature, bone has generally been considered an obstacle to ultrasound imaging. One advantage of the highly reflective signals produced by bone cortex is that bone surface changes in rheumatologic disease can be readily identified.

An *erosion* is defined as a clear cortical break visualized in two perpendicular planes at a site not associated with a nutrient foramen. Studies have

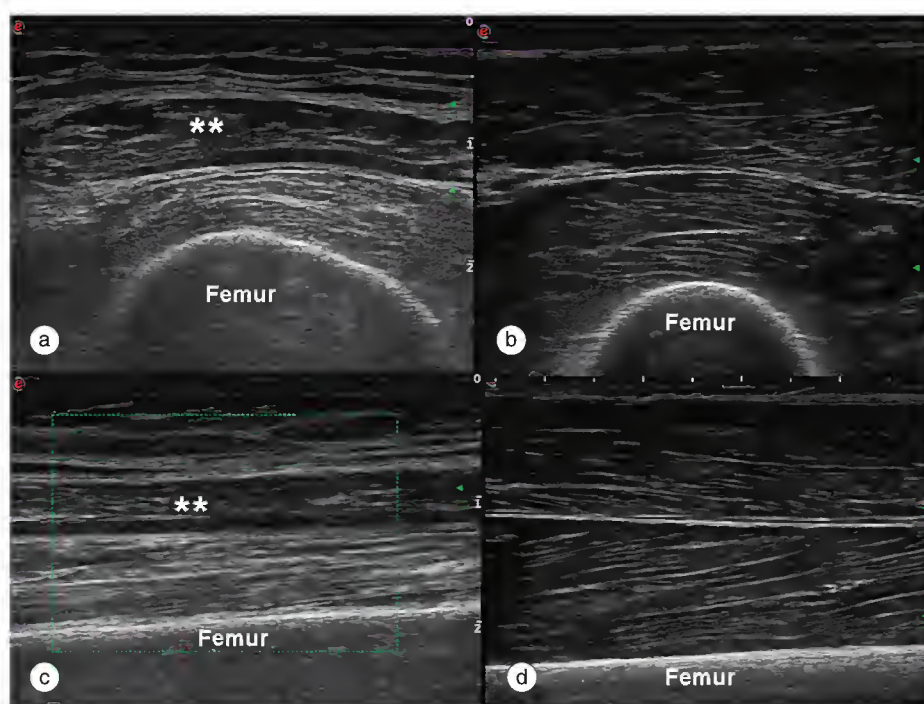


Fig. 42.7 Inclusion body myositis. (a) Transverse view of anterior mid-thigh shows hypoechoic atrophic quadriceps femoris (asterisks). (b) Transverse view in normal subject. (c) Longitudinal view of anterior mid-thigh shows hypoechoic and atrophic quadriceps femoris (asterisks). (d) Longitudinal view in normal subject.

compared ultrasound with conventional radiography, CT, and MRI in the diagnosis of joint erosions. Both ultrasound and MRI have been found consistently to be superior to plain radiography in detecting erosions, particularly in early RA.^{16,20} One particular advantage of MRI is that it has the ability to identify changes within the bone that may precede cortical breaks. Both MRI and ultrasound also can demonstrate synovial thickening and inflammation associated with the erosion; this gives rise to the concept of an “active erosion,” which cannot be distinguished on radiograph (Fig. 42.8, Video 42.4).



A limitation of ultrasound in the detection of bone erosion is that some joints such as the wrist carpal bones and the third and fourth metacarpophalangeal joints present only a limited part of their bony surfaces to an ultrasound probe, which reduces sensitivity in detecting erosions. Despite the increased sensitivity of ultrasound in the diagnosis of joint erosions, most rheumatologists continue to use plain radiographs to assess interval changes in joint damage. This is because radiographic scoring systems are well described and well validated. Scoring systems for bone erosions imaged by ultrasound have been described that either document the size and number of individual erosions or use a global score of the percentage of bone surface area affected by erosion. For ultrasound findings to be used as an outcome measure of bone erosion, studies of reproducibility and variability of such scores must be performed and the number of joints that need to be scored for erosion must be determined.

Osteophytes are also readily imaged using ultrasound, and recent imaging studies have noted the presence of both erosions and osteophytes in osteoarthritis of the hands.³⁰

Cartilage

Ultrasound can produce only limited views of cartilage in joints and was not originally considered useful for the diagnosis of cartilage disease, with MRI and arthroscopy being preferred. However, anatomic knowledge combined with optimal positioning of some joints (e.g., full flexion in the knee) can expose large areas of cartilage for direct examination, which is of diagnostic utility. Hyaline cartilage appears anechoic or hypoechoic and is located superficial to the hyperechoic bone cortex. Normal hyaline cartilage appears as a homogeneous, regular, hypoechoic layer, and the thickness of the cartilage can be measured at reference sites. Pathologic cartilage changes include the initial loss of regularity of the superficial surface, with the cartilage gradually thinning and initial focal cartilage defects becoming more generalized. It is not known if the more limited views of cartilage obtainable by ultrasound yield findings that correlate adequately with those obtained from the more extensive views provided by MRI and arthroscopy.

Fibrocartilage is more hyperechoic than hyaline cartilage but can also be visualized in sites such as the menisci of the knee and labrum of the hip and glenohumeral joints. Ultrasound can demonstrate inhomogeneity and irregularity of fibrocartilage and aid in the diagnosis of fibrocartilage tears

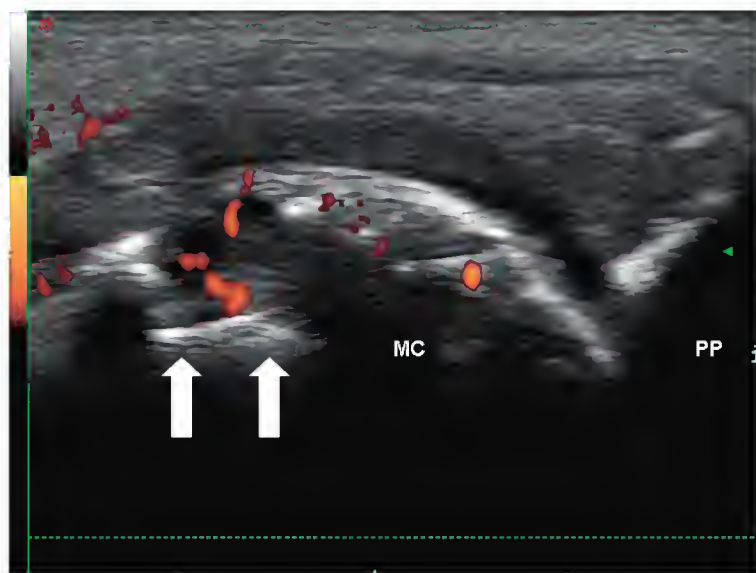


Fig. 42.8 Bone erosion in rheumatoid arthritis. Longitudinal view of second metacarpophalangeal joint shows generalized cortical irregularity in the metacarpal (MC) head with a large, well-demarcated cortical break (arrows) with associated hypoechoic synovial thickening and power Doppler signal within the erosion indicating synovitis. PP, proximal phalanx.

and cysts, although again MRI and arthroscopy can provide a more extensive view of the structures.

Soft tissue calcification and crystal-induced arthritis

Ultrasound is very sensitive for the detection of calcification in soft tissues because of the highly refractile nature of calcified tissues on ultrasound.³¹ Calcific deposits in calcific tendonitis of the shoulder can be diagnosed, localized, aspirated, and injected using ultrasound. Calcification within muscle hematoma or soft tissue calcification in connective tissue disease can also be readily identified. Calcification within hyaline and fibrocartilage occurs in chondrocalcinosis and calcium pyrophosphate crystal-induced arthritis. These calcifications can be identified within the cartilage substance on ultrasound. A common site is within the hyaline cartilage on the femoral condyle of the knee, where calcific deposits initially appear as hyperechoic intracartilaginous spots with subsequent formation of intracartilaginous linear deposits. Hyperechoic speckling can also be observed in the fibrocartilage of the menisci of the knee and calcific particles can be imaged within joint bursae or effusions.

Urate crystals aggregating in joints and soft tissues can be imaged as hyperechoic particles on ultrasound, although they are not usually as reflective as calcific deposits. Hyperechoic crystal aggregates can be observed within synovial fluid in acute gout, and tophi appear as circumscribed, heterogeneous, hyperechoic material in periarticular structures, tendons, and bursae. Ultrasound can be used to detect hyperechoic deposits of urate crystals lying on the surface of cartilage, which produce what is described as the “double contour” sign (Fig. 42.9, Video 42.5). Once a crystalline aggregate is detected, ultrasound has the additional advantage of being able to guide diagnostic aspiration.³²



Noninflammatory soft tissue disorders

Ultrasound provides better resolution of superficial soft tissue than does MRI. Because ultrasound involves real-time imaging, the operator can localize symptomatic structures in communication with the patient and perform dynamic assessments with either probe or finger pressure and movement to reproduce and localize painful symptoms. Therefore ultrasound is an excellent modality for examination of regional noninflammatory soft tissue disorders of peripheral joints and particularly those involving tendons and ligaments. These disorders are usually referred to as *tendinopathy* to differentiate the underlying noninflammatory cause, but the structural ultrasound features are often similar to those encountered in systemic inflammatory disease of tendons and ligaments. The most common sites of overuse tendinopathy encountered in rheumatology practice are the wrist (de Quervain tendonitis), elbow (epicondylitis), shoulder (rotator cuff tendonitis), hip (greater trochanter pain syndrome), knee (patellar tendinopathy), ankle (Achilles tendinopathy), and heel (plantar fasciitis).³³

The characteristic appearance of tendinopathy is hypoechoic enlargement of the tendon with widening of spaces between the tendon fibers due to increased ground substance. Neovascularization is observed as increased PD signal within the tendon, although histologic studies do not demonstrate an inflammatory infiltrate in the tissue as is observed in enthesitis or tenosynovitis of autoimmune inflammatory arthritis. Later stages of tendinopathy are characterized by partial or complete tendon rupture, which is characterized by hypoechoic loss of tendon substance. With complete tears there is also a lack of synchronous movements on dynamic scanning; this is also described as a *bell and clapper sign* in complete tears of both muscle and tendon.

Spine and sacroiliac joint

Ultrasound has a very limited role in spinal disease. MRI and CT are the optimal modalities for imaging of the sacroiliac joint, but one study has suggested that contrast-enhanced ultrasound may have a potential role in the diagnosis of sacroiliitis.³⁴ Ultrasound can also be used to guide spinal injection of the sacroiliac joints and pain medicine interventions in the spine such as rhizotomy.

Intervention

Ultrasound may be used to guide joint and soft tissue aspiration and therapeutic injection because the needle can be readily localized within musculoskeletal tissues as a hyperechoic reflective structure with typical acoustic reverberation artifact (Fig. 42.10, Box 42.1). Ultrasound-guided aspiration and injection are more accurate than injections using palpation guidance,

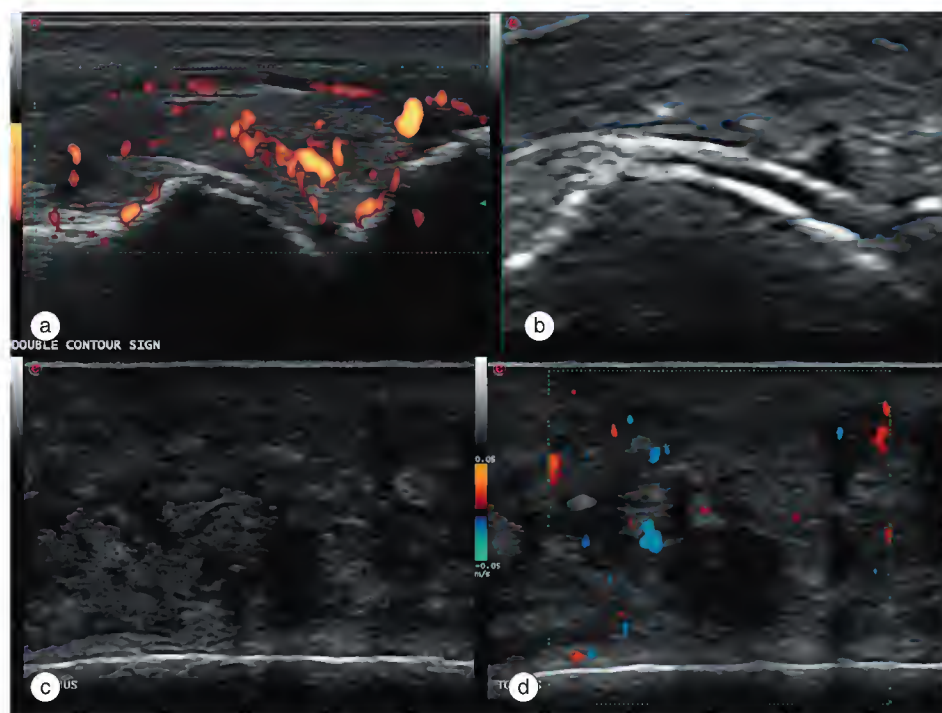


Fig. 42.9 Gout. (a) Acute gout of the first metatarsophalangeal (MTP) joint. Ultrasound shows acute inflammation with heterogeneous enlargement of the joint capsule and increased power Doppler signal due to tophaceous material and synovitis. (b) Double contour sign of gout is the appearance of a hyperechoic line superficial and parallel to the bone cortex caused by urate crystal deposition on the surface of cartilage. There are also focal hyperechoic speckles in the joint space caused by urate crystal aggregates. (c) Mixed hyperechoic and hypoechoic appearances of tophus adjacent to the first MTP joint. (d) Color Doppler ultrasound of tophus shows it to be hypervascular in this case of acute gout.

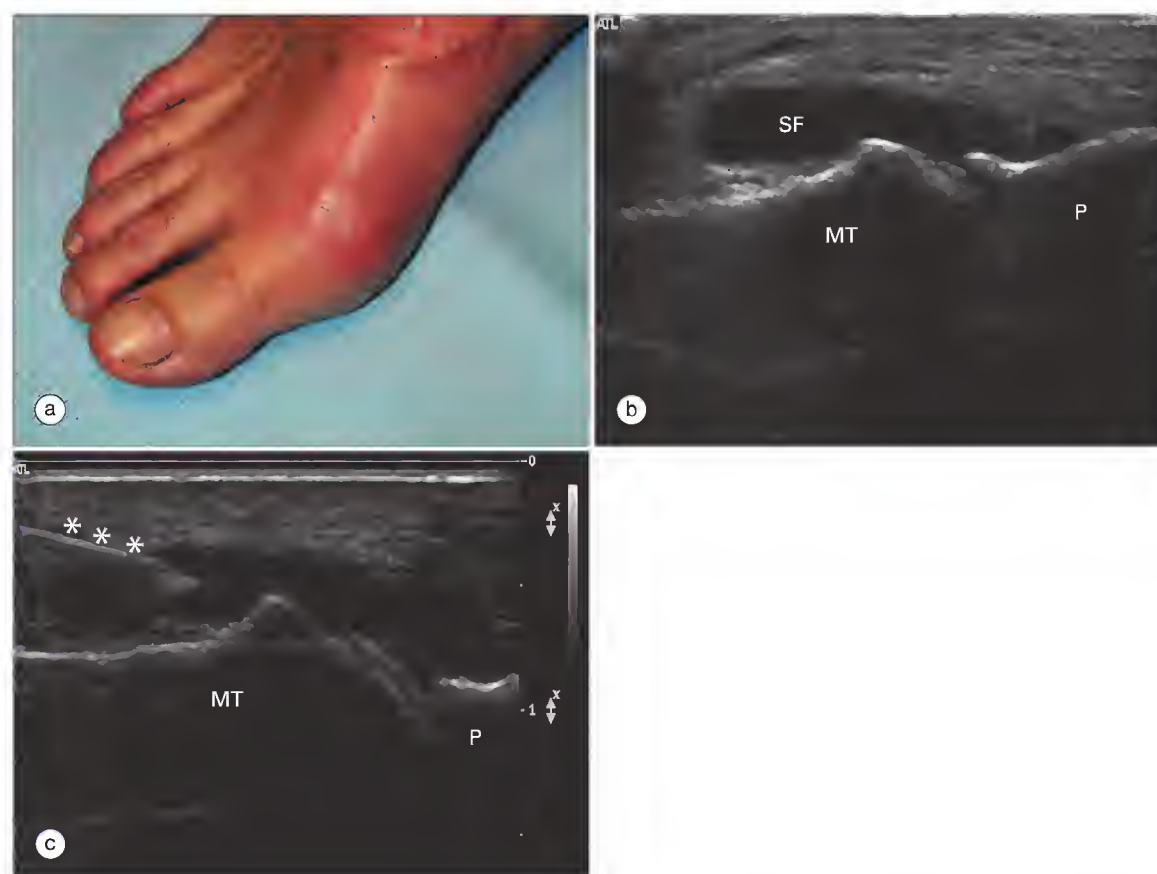


Fig. 42.10 Inflammation of the first metatarsophalangeal joint, presumed to be gout. (a) This patient had acute swelling of the big toe with pain and erythema. The diagnosis of gout was suspected, but the serum urate level was within normal limits. (b and c) These longitudinal images through the toe demonstrate a hypoechoic collection in the joint that was compressible and displaceable and consistent with an effusion. A needle (asterisks) was subsequently introduced into the joint under ultrasound guidance and withdrew a small amount of fluid. Analysis confirmed the presence of urate crystals. MT, metatarsal head; P, phalanx; SF, synovial fluid.

BOX 42.1 INDICATIONS FOR ULTRASOUND GUIDANCE OF INTERVENTION

1. Diagnostic fluid is required (ultrasound guidance improves success rate).
2. Palpation-guided injection has failed.
3. The target joint is deep lying (e.g., sacroiliac joint or hip).
4. The target joint is small (e.g., metacarpophalangeal, intercarpal joint).
5. The anatomy is distorted or difficult to ascertain due to deformity or obesity.
6. There are no bony landmarks (e.g., bursa or tendon sheath).
7. The target is adjacent to blood vessels or nerves (e.g., subtalar joint).
8. Injection of a nonsoluble substance (e.g., hyaluronic acid) is required.
9. Injection of a substance potentially toxic to nontarget soft tissues (e.g., radioactive synovectomy) is required.
10. A specialized procedure is necessary, such as synovial biopsy, muscle biopsy, soft tissue biopsy, nerve block, spinal facet joint injection, or rhizotomy.

and palpation-guided injections may be placed inaccurately in up to 50% of cases.³⁵ Ultrasound-guided injection has been regarded as a technically advanced skill, but a trainee was able to learn ultrasound-guided hip injection in a relatively short period with resultant high levels of accuracy.³⁶ In patients with inflammatory arthritis, a randomized controlled study confirmed that ultrasound guidance improved accuracy of corticosteroid joint injections but did not improve short-term outcome.³⁵ Other studies have noted that the application of ultrasound alters the site selected on clinical grounds to be injected and point out that this may be an important factor in improving outcome. Ultrasound-guided injection of the shoulder produced a better outcome than palpation-guided injection of the shoulder.³⁷ The techniques of ultrasound-guided injection are described more fully in Chapter 69.

NONMUSCULOSKELETAL TISSUE ULTRASOUND IN RHEUMATOLOGY

The application of ultrasound imaging in the rheumatology clinic for examination of musculoskeletal structures has been followed by its use to study a number of other nonmusculoskeletal conditions encountered in rheumatology.

Peripheral nerve

Peripheral nerves appear on ultrasound as hypoechoic structures bounded by a hyperechoic rim. For larger nerves the component nerve fibers can be visualized and have a similar appearance. Musculoskeletal ultrasound is ideal for assessing peripheral nerves, and most large and medium-sized peripheral nerves can be visualized with high-frequency ultrasound and a good anatomic knowledge of the nerve location. Ultrasound can be used both for diagnostic examination of peripheral nerves and for guidance of nerve block procedures.

The ultrasound features of the median nerve in carpal tunnel syndrome have been well described and have been correlated with the results of diagnostic electrophysiologic studies.³⁸ In entrapment neuropathy, the nerve develops a fusiform swelling thought to be caused by intraneural venous congestion and edema, and there may be increased Doppler signal within the nerve. The most consistent ultrasound diagnostic criterion in carpal tunnel syndrome is an enlarged cross-sectional area of the median nerve within the carpal tunnel, with a cutoff of more than 10 mm² being most commonly used. When small degrees of median nerve enlargement are assessed, it is important to confirm enlargement by evaluating the median nerve proximal to the carpal tunnel and to compare with the asymptomatic carpal tunnel. Causative pathologic processes such as anatomic anomalies, tenosynovitis, or a ganglion cyst can also be noted on ultrasound examination of the carpal tunnel. Nerve entrapment at other sites such as entrapment of the ulnar nerve in the cubital tunnel have also been described.

Vasculitis

Duplex ultrasound—gray-scale ultrasound and Doppler ultrasound—can readily visualize carotid, axillary, brachial, femoral, and temporal arteries, assessing both the lumen and the vessel wall.³⁹ Schmidt³⁹ described the temporal artery vessel wall inflammation and thickening in temporal arteritis as having a hypoechoic “halo” appearance in combination with luminal stenosis on ultrasound. These features on ultrasound have an overall sensitivity of 69% and a specificity of 82% compared with biopsy findings. Involvement of the proximal upper extremity arteries has also been described in large-vessel giant cell arteritis and Takayasu arteritis. Although very promising as a noninvasive first-line diagnostic technique, ultrasound has not replaced temporal artery biopsy in the diagnosis of temporal arteritis because of the absence of validated and standardized diagnostic criteria (Fig. 42.11, Video 42.6).

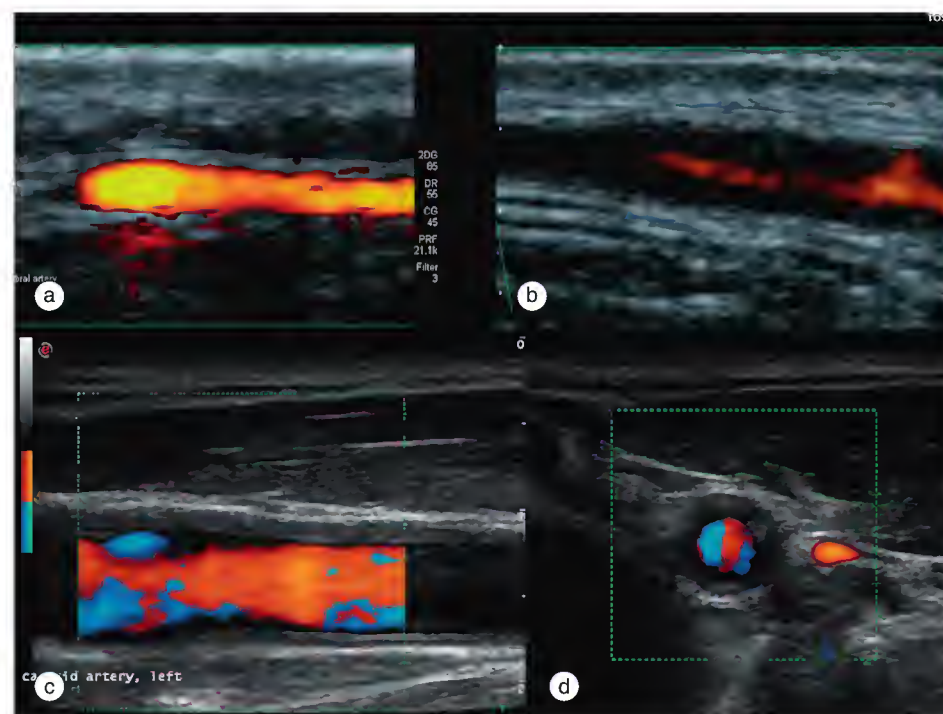


Fig. 42.11 Temporal arteritis and large-vessel giant cell arteritis. (a) Normal temporal artery following temporal artery biopsy. The artery lumen is patent with no stenosis and the vessel wall is hyperechoic and of normal thickness (confirmed on histologic analysis). (b) Temporal arteritis. The artery shows a narrowed lumen and thickened hypoechoic arterial wall. (c) Arteritis of the carotid artery. A skip lesion is seen on longitudinal view with hypoechoic arterial wall thickening. (d) Transverse view of the carotid artery showing the halo sign, a circumferential hypoechoic thickening of the arterial wall.

Parotid and salivary glands

Ultrasound can be used to assess the parotid, submandibular, and submental salivary glands and provides a noninvasive alternative to salivary gland biopsy in the diagnosis of Sjögren syndrome. Initially the salivary glands show diffuse enlargement with normal echogenicity; this gradually progresses to a heterogeneous ultrasound appearance with multiple round hypoechoic areas within the parenchyma. Increased PD signal may be observed in the glands. Advanced disease is characterized by large hypoechoic cystic change and atrophic changes in the residual gland tissue (Fig. 42.12). Ultrasound has been shown to have a good correlation with MRI and sialography in the diagnosis of Sjögren syndrome.⁴⁰

Skin

Because the skin is readily amenable to direct diagnostic inspection, the role of ultrasound is largely in the measurement of the thickness of skin involvement in psoriasis and scleroderma for purposes of disease monitoring. In psoriasis the plaque has both hyperechoic areas of hyperkeratosis and deeper hypoechoic subcutaneous skin inflammation, and this is associated with increased PD signal in the thickened hypoechoic tissue.⁴¹ Ultrasound measurement of dermal thickness in patients with systemic sclerosis has been described⁴² and allows differentiation of early hypoechoic edematous thickening and later hyperechoic fibrotic skin involvement. Ultrasound thickness of skin in scleroderma correlates with modified Rodman score.

CONCLUSION

Ultrasound imaging is now an integral part of clinical rheumatology practice because it provides immediate and objective diagnostic information and can be used to assist in a large number of interventional procedures. It has a developing role in the objective quantification of inflammatory musculoskeletal disease, but its application now extends beyond the joint to include many different tissues involved in rheumatologic disease (e.g., nerves, blood vessels, salivary glands). Future expansion of the use of ultrasound in rheumatology will require further standardization of diagnostic and quantitative

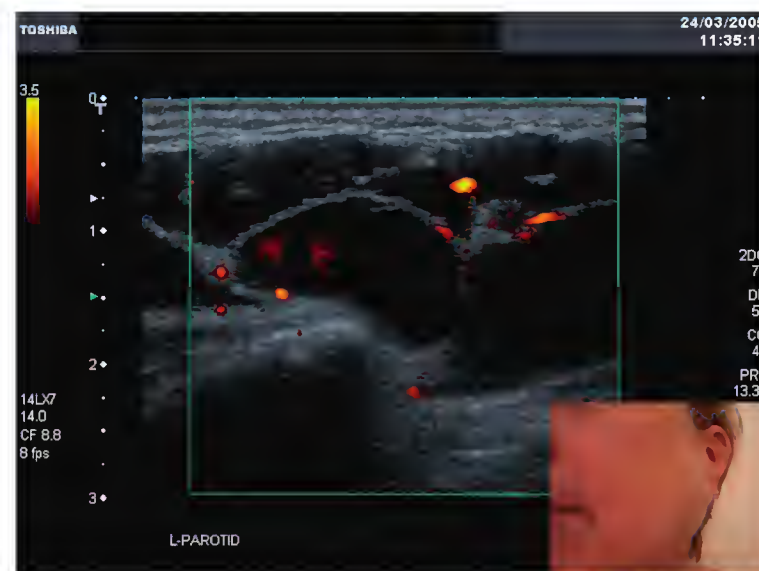


Fig. 42.12 Sjögren syndrome. Ultrasound image of swollen parotid gland shows hypoechoic change in the gland with almost complete loss of normal gland tissue and increased power Doppler signal in a patient with longstanding Sjögren syndrome.

techniques and international standardization and validation of ultrasound training.

Acknowledgment

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43

Bone scintigraphy and positron emission tomography

■ CLIO RIBBENS ■ GAUTHIER NAMUR

- Bone scintigraphy with technetium-labeled diphosphonates is a nuclear medicine technique widely used for the investigation of bone and joint diseases. It is highly sensitive for depicting foci of increased bone turnover and increased blood flow, but uptake is nonspecific and combination with other imaging modalities, or the use of hybrid devices (SPECT/CT), is necessary for differential diagnosis.
- Positron emission tomography (PET) is a technique using molecules labeled with isotopes that emit positrons from their nucleus, the most widely used being 2-deoxy-2-[^{18}F]fluoro-D-deoxyglucose (^{18}F -FDG). ^{18}F -FDG accumulates in foci of increased glucose consumption, such as inflammatory lesions, which allows for direct identification of increased metabolic activity.
- PET devices are combined with computed tomography (PET/CT), which allows for precise localization and frequently even a morphologic description of the lesions with increased metabolic activity.
- The clinical applications of ^{18}F -FDG-PET include the detection of inflammation in various rheumatic diseases such as vasculitis, arthritis, lupus, or sarcoidosis, as well as the workup of fever of unknown origin.

INTRODUCTION

Imaging in rheumatology has greatly evolved in the past two decades, which has led to major advances in the clinical management of patients. Concurrently with the improvement in imaging techniques, with ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) being added to conventional radiography, nuclear medicine techniques have made progress not only in the research area but also in the clinical world. They play a role in both diagnosis and follow-up of inflammatory diseases.^{1,2} The most common nuclear medicine technique used in rheumatology is bone scintigraphy, but more recently developed methods such as positron emission tomography have emerged that provide information regarding the metabolic status of tissues in addition to the morphologic information provided by the other imaging modalities.

BONE SCINTIGRAPHY

Principles

The high affinity of diphosphonates for bone led to their use in imaging with technetium-99m ($^{99\text{m}}\text{Tc}$) labelling for bone scintigraphy in the early 1970s. The energy of the photon emitted by the $^{99\text{m}}\text{Tc}$ nuclide (140 keV) is well adapted to the physical properties of the current gamma cameras. On decay, radionuclides emit a gamma ray at their characteristic energies in different directions. Some of these rays interact with the gamma camera, whereas others may scatter, lose direction, or never interact with the camera.³ Gamma cameras acquire data in a single plane. The resultant images are therefore a two-dimensional representation of a three-dimensional subject, referred to as *planar imaging*. $^{99\text{m}}\text{Tc}$ -methylene diphosphonate (MDP) and $^{99\text{m}}\text{Tc}$ -hydroxymethylene diphosphonate (HMDP) are the most commonly used radionuclides for bone scintigraphy. Diphosphonates are either taken up by bone or rapidly cleared through the kidneys. Approximately 50% of the dose is distributed in the skeleton within 3 hours after

intravenous injection, with the remainder excreted in the urine.⁴ In a normally hydrated subject, less than 5% of the dose remains in the blood 3 hours after injection.⁴

Single-photon emission computed tomography

The disadvantage of planar images obtained with scintigraphy can be overcome by single-photon emission computed tomography (SPECT), which acquires volumetric data by rotating the gamma camera detectors around the patient. It offers images in three planes and has better spatial resolution. The main current clinical applications focus on evaluation of the skull and spine. The development of gamma cameras with tomographic capabilities combined with a CT scanner (SPECT/CT) introduced the concept of blended imaging devices providing complementary information, that is, a fusion image with functional (SPECT) and anatomic (CT) correlation. These cameras allow the simultaneous acquisition of tomographic scintigraphy and x-ray CT images. Scintigraphy is sensitive for the detection of active osteoarticular lesions but lacks specificity and does not provide anatomic landmarks. CT shows the anatomic details of osteoarticular structures perfectly and is able to highlight structural changes that are often quite specific of a particular disease or group of diseases. Unfortunately, these structural changes are the result of earlier phenomena of bone formation and osteolysis and provide few details about the active or inactive nature of a lesion. With SPECT/CT, the sensitivity of scintigraphy in detecting active lesions and the specificity of CT in revealing the nature of those lesions are associated. Moreover, the images from the two examinations are fused, which allows for precise localization of the otherwise poorly anatomically detailed scintigraphic abnormalities, which cannot be obtained with separate acquisitions (Fig. 43.1). The combination of the two techniques therefore leads to a real synergy.

Uses

Because the uptake of $^{99\text{m}}\text{Tc}$ -diphosphonates in bone depends on the osteoblastic activity as well as on the regional blood flow, bone scintigraphy is highly sensitive for many disorders causing increased bone turnover (Fig. 43.2). It lacks specificity, however, and distinguishing metastatic disease from osteoarthritis, for example, requires the use of other imaging modalities, or a SPECT/CT acquisition.

Bone scintigraphy is particularly useful when the arthritis is difficult to detect clinically, such as in sacroiliitis. Sacroiliitis may be detected on the basis of increased uptake of $^{99\text{m}}\text{Tc}$ -diphosphonates in the sacroiliac joints. A high uptake in these joints is also found in normal individuals,⁵ however, and the ratio of the peak sacroiliac joint count to the peak sacrum count is generally used, although normal values of this ratio can vary significantly depending on age and gender. Even so, the specificity is low, and other imaging modalities such as MRI are of better value for diagnosis of sacroiliitis in spondyloarthritis.⁶ Increased uptake of $^{99\text{m}}\text{Tc}$ -diphosphonates in arthritis, whether septic or not, is linked to increased blood flow, expanded blood pool volume, and vascular permeability, and the hyperemia involves not only the synovial membrane but also the juxtaarticular bones.⁷ This technique therefore cannot discriminate accurately between actively inflamed joints and chronically damaged joints⁸ and does not allow correct evaluation of inflammatory arthritis.

Use of other tracers

Given the limitations of $^{99\text{m}}\text{Tc}$, other radiotracers have been investigated for the evaluation of arthritis (Box 43.1). These radiotracers are not widely used, however, due to lack of specificity or concerns about the hazards associated with manipulation of labeled cells. Bone scintigraphy with

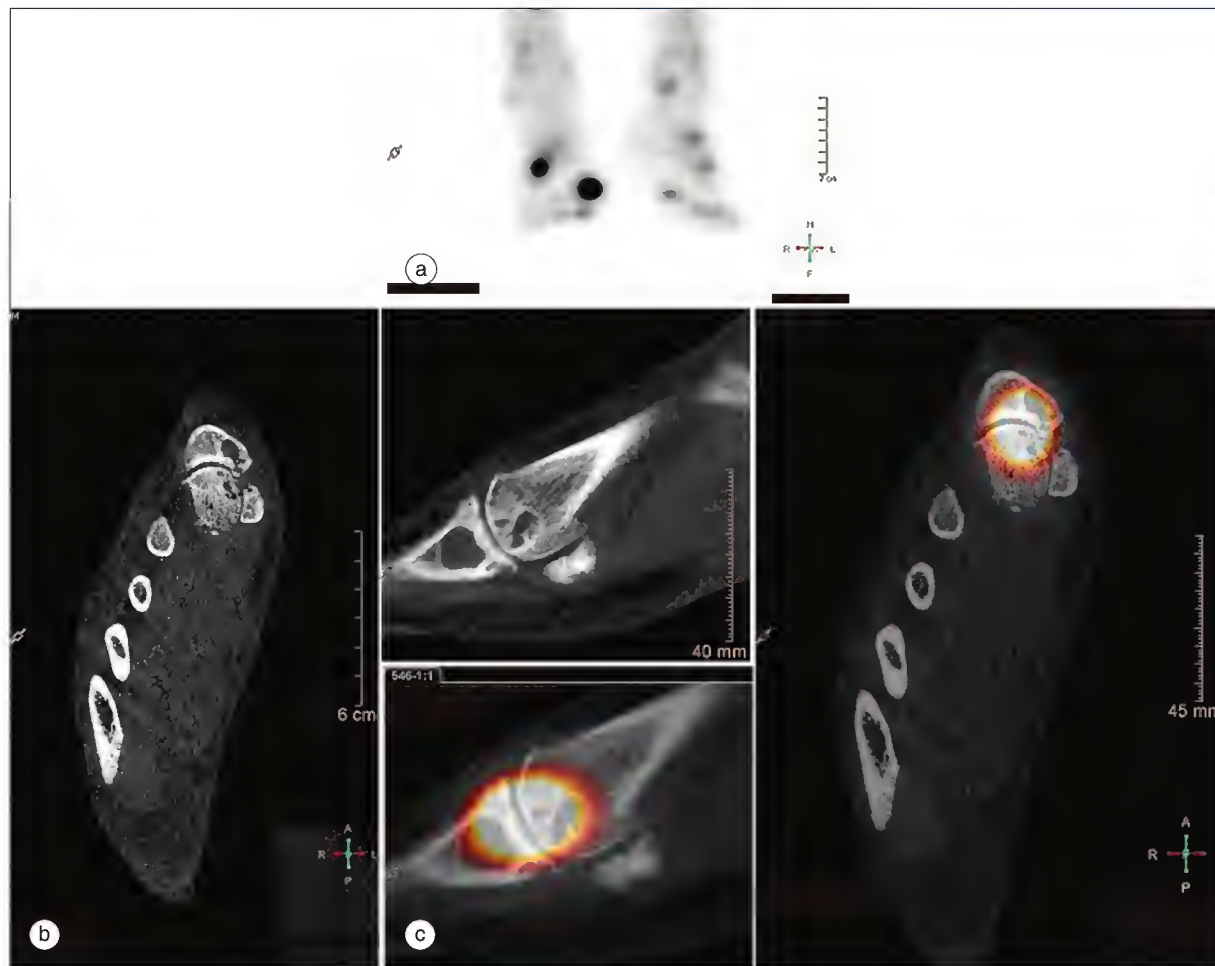


Fig. 43.1 Single-photon emission computed tomography (SPECT), computed tomography (CT), and SPECT/CT fusion images of right forefoot. (a) Maximal-intensity projection SPECT shows two foci of nonspecific disease located approximately in the right forefoot. (b) CT shows marginal erosions of several metatarsophalangeal and tarsometatarsal joints (first metatarsophalangeal is shown), as well as intraosseous para-articular lesions with soft tissue density compatible with tophi deposition. (c) Fusion SPECT/CT images clearly confirm the articular nature of the scintigraphic abnormalities and identify among the abnormal joints which ones are the site of active disease. A diagnosis of gouty arthritis is suggested.

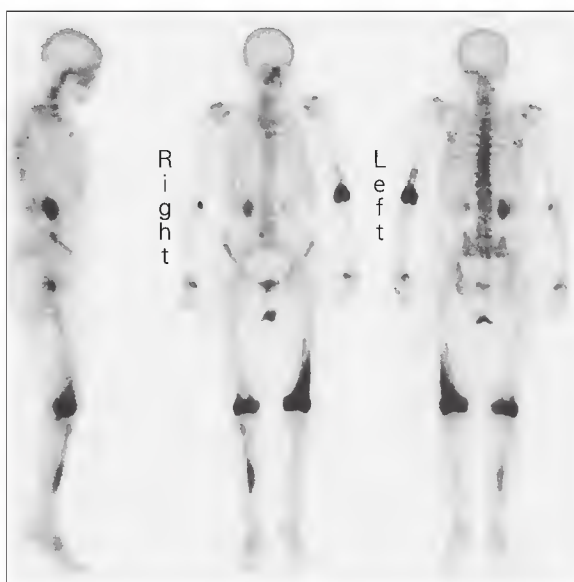


Fig. 43.2 Right lateral, anterior, and posterior whole-body bone scintiscans in a patient with Paget disease showing involvement of the distal parts of both femurs, distal part of the left humerus, and right tibial diaphysis.

BOX 43.1 RADIOTRACERS INVESTIGATED FOR THE EVALUATION OF ARTHRITIS⁷

Gallium-67 (^{67}Ga) citrate
 Indium-111 (^{111}In) chloride
 Technetium-99m ($^{99\text{m}}\text{Tc}$) hexamethylpropylene amine oxime-labeled leukocytes
 $^{99\text{m}}\text{Tc}$ -labeled liposomes
 $^{99\text{m}}\text{Tc}$ -labeled polyclonal human immunoglobulin G monoclonal antibodies to granulocytes
 $^{99\text{m}}\text{Tc}$ -labeled anti-CD4 monoclonal antibodies

$^{99\text{m}}\text{Tc}$ -labeled diphosphonates therefore remains the standard nuclear medicine technique for assessing joint involvement in a whole-body approach.

POSITRON EMISSION TOMOGRAPHY

Background

In contrast to scintigraphy or SPECT in which molecules are tagged with radioisotopes emitting gamma rays, positron emission tomography (PET) uses molecules labeled with isotopes that emit positrons from their nuclei. These relatively short-lived positron-emitting isotopes are created in a cyclotron, a device used to accelerate charged particles, and include ^{15}O (half-life of 2 minutes), ^{13}N (10 minutes), ^{11}C (20 minutes), and ^{18}F (110 minutes). The most commonly used radiolabeled molecule, referred to as a *probe* or *tracer*, is 2-deoxy-2- ^{18}F fluoro-D-deoxyglucose (^{18}F -fluorodeoxyglucose or ^{18}F -FDG) in which one of the hydrogen atoms has been replaced by the ^{18}F radioisotope. ^{18}F -FDG is an analogue of glucose, and following intravenous

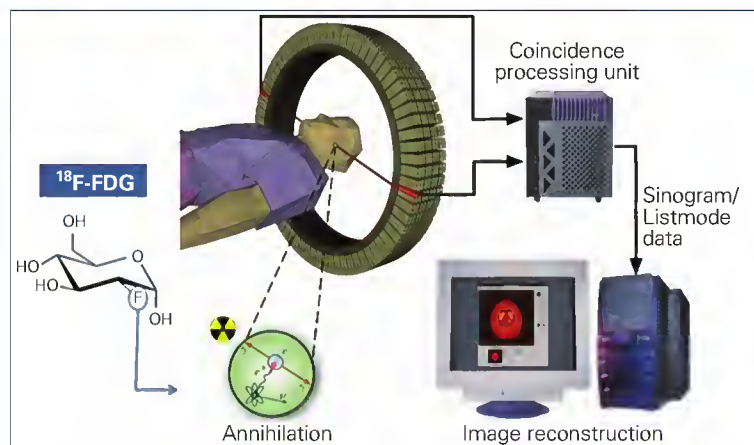


Fig. 43.3 Principles of positron emission tomography (PET). 2-Deoxy-2-[^{18}F] fluoro-D-deoxyglucose (^{18}F -fluorodeoxyglucose or ^{18}F -FDG) is a labeled glucose analogue in which the hydrogen atom in the 2 position is replaced by the ^{18}F radioisotope, a positron emitter. A positron is the antiparticle of an electron, with opposite charge. ^{18}F -FDG accumulates in cells proportionally to their glucose consumption. ^{18}F -FDG decays by emitting a positron from its nucleus. After traveling a short distance into the patient's body, this positron encounters an electron, which results in an annihilation process. This process involves the emission of two photons of 511 keV in diametrically opposite directions. These photons are registered by the PET "camera" as soon as they arrive at the detector ring. After the photon registration, the data are forwarded to a processing unit that decides if two registered events are selected as a so-called coincidence event. All coincidence events are forwarded to the image-processing unit where the final image data are produced via mathematical image reconstruction procedures.

injection it is taken up by cells according to their level of glucose metabolism. ^{18}F -FDG is transported through the cell membrane via glucose transporters into the cytosol and is phosphorylated by the enzyme hexokinase into ^{18}F -FDG-6-phosphate. In contrast to glucose, ^{18}F -FDG-6-phosphate cannot proceed further in the glycolytic pathway, and ^{18}F -FDG-6-phosphate is not further dephosphorylated and accumulates in the cell in proportion to the cell glucose consumption. ^{18}F decays by emitting a positron from its nucleus. This positron eventually collides with a nearby electron, which results in an annihilation event in which two 511-keV photons in the form of gamma rays are emitted approximately 180 degrees apart.³ These photons are detected by the PET "camera," a ring array of detectors (composed of scintillation crystals and photomultiplier tubes) around the patient. A single annihilation event results in the activation of detectors opposing one another, which is recorded as a "coincident event." Mathematical analysis of the coincident events yields the location of cell populations or tissues that have accumulated ^{18}F -FDG (Fig. 43.3). The spatial resolution of the most recent clinical PET scanners is approximately 4 to 6 mm.

Uses

The development of PET was closely linked to that of ^{18}F -FDG in the 1970s. PET was first used in cardiology and neurology, and the clinical application of PET was extended to oncology in view of the increased glucose metabolism in tumoral cells. The use of ^{18}F -FDG-PET for evaluating infection and inflammation arose from the occurrence of false-positive findings in patients undergoing evaluation for malignancy as well as from the demonstration of increased glucose metabolism in many inflammatory cell types and ^{18}F -FDG uptake by inflammatory tissues. Animal studies showed that ^{18}F -FDG uptake by tumors is due not only to the tumor cells themselves but also to the inflammatory cells (macrophages, neutrophils, fibroblasts, endothelial cells) appearing in association with growth or necrosis of the tumor.^{9,10} Therefore ^{18}F -FDG-PET is a fully tomographic technique, offering three-dimensional visualization of glucose metabolism. Compared with scintigraphy, it offers several advantages for the assessment of patients with inflammation. First, the ^{18}F -FDG uptake is directly related to the activity of metabolically active inflammatory cells, whereas bone scintigraphy detects the indirect hyperemia. Second, the spatial resolution and count rates of ^{18}F -FDG-PET are much improved compared with planar scintigraphy.¹¹ Finally, the uptake phase of ^{18}F -FDG is shorter than that of $^{99\text{m}}\text{Tc}$ -MDP, which allows a whole-body examination to be completed within an hour

and a half, whereas more than 4 hours (uptake plus acquisition) is needed for a bone scan. Furthermore, ^{18}F -FDG has a 110-minute half-life, which permits its use in centers distant from a cyclotron, and delivers a dose to the patient that is acceptable when compared with $^{99\text{m}}\text{Tc}$ -MDP.

Positron emission tomography/computed tomography

The advent of the combination of PET with CT in 2000 has allowed determination of the precise anatomic location (revealed by CT) of increased metabolic activity (provided by PET). The optimal methodology for performing and interpreting the PET/CT studies remains to be defined. To contribute fully to the diagnostic information, the CT scan should be acquired using the appropriate parameters in terms of beam collimation (which is related to slice thickness) and dose, possibly with the use of intravenous contrast agents. Whether such full diagnostic CT is really needed in addition to low-dose CT remains an unanswered question and probably depends on the justification for the examination. Still, there are no procedural guidelines for PET imaging of inflammation, whereas established procedural guidelines exist for tumor imaging with ^{18}F -FDG-PET^{12,13} that specify duration of patient fasting, activity of ^{18}F -FDG to be injected, and delay before image acquisition.

Finally, PET/MRI may become the blended-modality choice of the future,¹⁴ allowing for an even more precise anatomic localization of the increased metabolic activity with lower radiation exposure than PET/CT, which could be of particular relevance in pediatric patients. The development of targeted MRI contrast agents based on certain tissue metabolic properties leading to enhanced tissue contrast could further improve our knowledge of functional tissue properties and anatomic consequences of pathologic processes and hence of the cause and outcome of diseases.¹⁴

Applications of ^{18}F -fluorodeoxyglucose positron emission tomography in inflammatory diseases

PET can be used in the detection of inflammation in various rheumatic disorders with articular or extraarticular involvement, such as vasculitis, lupus, sarcoidosis, myositis, and arthritis, and can also be of help in the workup for fever of unknown origin.^{1,2}

Large-vessel vasculitis

The diagnosis of the large-vessel vasculitides giant cell arteritis and Takayasu arteritis relies on a spectrum of clinical, biologic, angiographic, and histopathologic features. It can be troublesome in some patients, and American College of Rheumatology criteria combining these various features have therefore been established. However, they do not have a specificity or sensitivity of 100% and were originally designed for classification and not diagnostic purposes. Histopathologic features cannot be obtained in Takayasu disease and can be missed in giant cell arteritis, in which biopsies should be performed bilaterally and in an extended manner. Imaging modalities such as Doppler ultrasonography, angiography and gadolinium-enhanced MRI can be useful in cases of suspected vasculitis but false-negative results can occur. Because glucose metabolism is increased in active vasculitis, ^{18}F -FDG-PET has been used in recent years in the evaluation of giant cell arteritis and Takayasu arteritis¹⁵⁻¹⁸ and could become a first-line investigative technique to allow a shorter and more successful diagnostic workup in the near future.¹⁷⁻¹⁹ Vascular uptake of ^{18}F -FDG is not specific for vasculitis and can also be found when atherosclerotic plaques are present. The two conditions can be differentiated, however, by taking into account the vascular distribution of the ^{18}F -FDG uptake pattern and the intensity of ^{18}F -FDG accumulation. A grading system has been developed by Meller and associates²⁰ and is based on comparison of the ^{18}F -FDG uptake by vessels and by the liver. Asymptomatic extracranial vessels can be affected in giant cell arteritis¹⁸ (Fig. 43.4). The common uptake pattern in great vessels in giant cell arteritis is linear and continuous and predominantly of grade II (i.e., vascular uptake similar to liver uptake); thoracic vessels are the most frequently affected, followed by abdominal vessels. ^{18}F -FDG-PET has been shown to identify significantly more affected regions than MRI. The whole-body evaluation procedure in ^{18}F -FDG-PET could therefore be of use in vascular screening and in identification of aortic uptake in these patients, who are known to develop aortic aneurysms more frequently. ^{18}F -FDG-PET can be used to evaluate the response to treatment (Fig. 43.5). However, it has not been shown to be useful for the prediction of relapses of giant cell arteritis.¹⁶ Furthermore, pathophysiologic features could be investigated because subclinical vasculitis has been highlighted by ^{18}F -FDG-PET in patients with polymyalgia rheumatica (Fig. 43.6), which is closely related to giant cell arteritis.

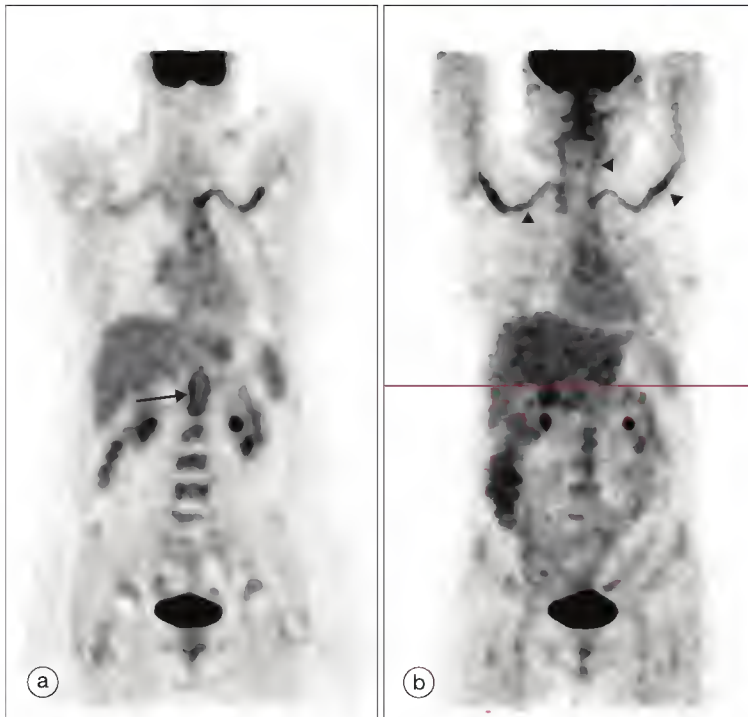


Fig. 43.4 ^{18}F -fluorodeoxyglucose positron emission tomographic images of a patient with giant cell arteritis. (a) The arrow in the coronal image points to an area of intense hypermetabolism of the abdominal aortic wall. (b) The arrowheads in the maximal-intensity projection image indicate hypermetabolism of the subclavian, axillary, and carotid arteries.

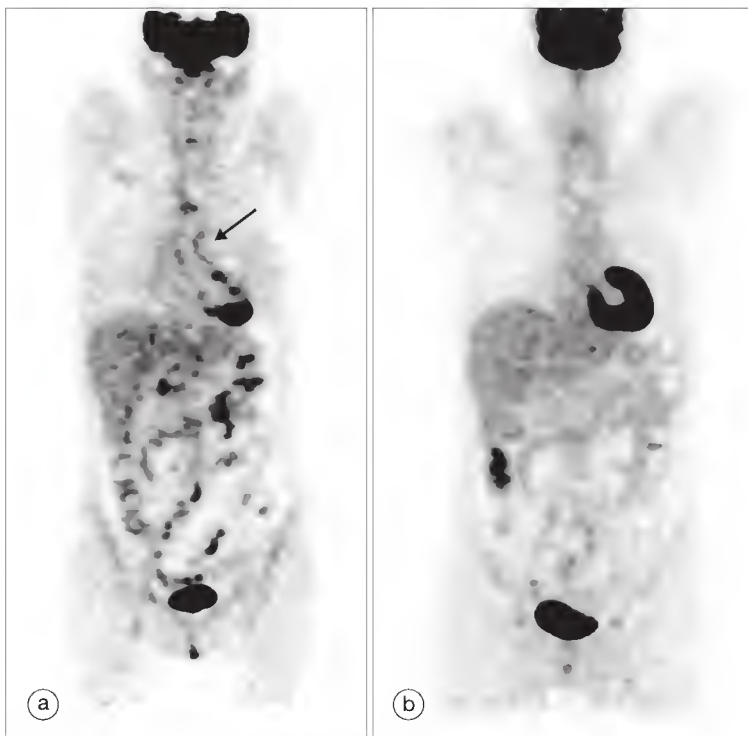


Fig. 43.5 Coronal ^{18}F -fluorodeoxyglucose positron emission tomographic images of a patient with vasculitis before (a) and after (b) treatment with corticosteroids. Note the disappearance of the aortic wall hypermetabolism on the posttherapeutic scan.

In Takayasu arteritis, the uptake pattern of ^{18}F -FDG is linear and continuous in the early phase (Fig. 43.7) but can become patchy in the late phase. In this disease, metabolic imaging with PET has been shown to be able to identify more vascular injured foci than does morphologic imaging with MRI. The latter, however, may provide information about changes in the wall structure or luminal blood flow. Hybrid PET/CT or PET/MRI imaging could therefore be of particular interest in large-vessel vasculitis.

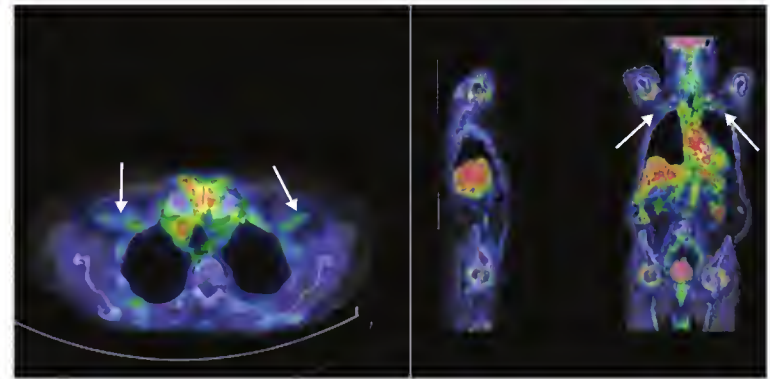


Fig. 43.6 ^{18}F -fluorodeoxyglucose positron emission tomographic/computed tomographic fusion images of a patient referred for fever of unknown origin. Bilateral shoulder and hip hypermetabolism is highlighted, consistent with a diagnosis of polymyalgia rheumatica. Note the hypermetabolism of the subclavian arteries (arrows).

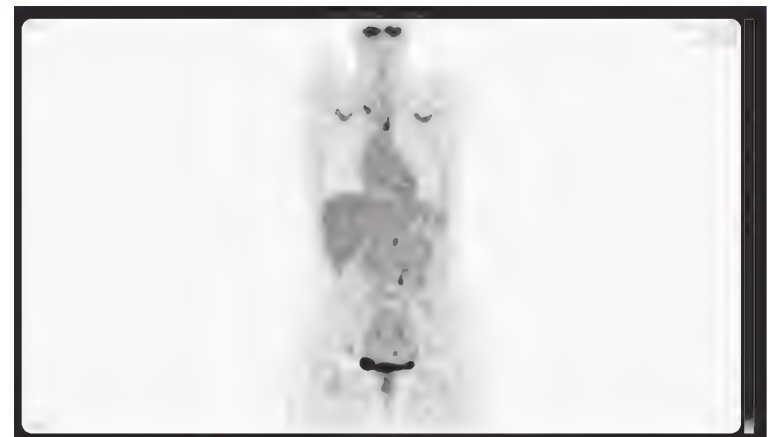


Fig. 43.7 Coronal ^{18}F -fluorodeoxyglucose positron emission tomographic image showing an intense hypermetabolism of the aortic arch and both subclavian arteries in a patient with Takayasu arteritis.

The combination of PET and CT has already been shown to be of value in Takayasu disease.²¹ The CT can increase the sensitivity of the PET modality in diseased vessels with weak ^{18}F -FDG uptake and can also help to localize accurately a mediastinal ^{18}F -FDG uptake coming from pulmonary arteries. On the other hand, ^{18}F -FDG accumulation can be found in arteries without vascular wall thickening on CT (i.e., areas of inflammation that have not yet progressed to vascular thickening).²¹ In summary, ^{18}F -FDG-PET is highly effective in evaluating in a single procedure the activity and extent of large-vessel vasculitis and may become a first-line imaging modality technique in patients suspected of having such vasculitis.

Systemic lupus erythematosus

^{18}F -FDG-PET is used in systemic lupus erythematosus (SLE) mainly to demonstrate central nervous system (CNS) involvement. Although MRI is the current gold standard for evaluating neuropsychiatric SLE, there are still problems with regard to sensitivity and specificity.²² The most common white matter hyperintensities can also be associated with hypertension and increase with age in the general population. Periventricular lesions associated with antiphospholipid syndrome can be impossible to differentiate from those of multiple sclerosis. Other neuroimaging techniques such as magnetic resonance spectroscopy, magnetization transfer imaging, SPECT, and PET have therefore been evaluated.²² PET can detect subtle brain changes in lupus patients. In a study of 22 lupus patients with severe or mild CNS symptoms, brain hypometabolism was detected by PET in all patients, most often affecting the parieto-occipital regions, whereas only half of the patients displayed abnormalities on MRI images.²³ The change in brain metabolism on follow-up PET scans correlated with the clinical outcome of cerebral symptoms.²³

Lymph node involvement can also be detected by PET in SLE,²⁴ as it can in amyloidosis secondary to SLE or to Sjögren syndrome²⁵ and in rheumatoid arthritis,²⁶ and must be differentiated from lymphoma. PET can also assess the distribution of activated lymphocytes and thus provide insight

into the pathophysiologic immune mechanisms of disease. Increased ^{18}F -FDG uptake has been found in the lymph nodes of patients with both active and inactive SLE, which suggests an enhanced metabolic and probably immunologic activity in lymphoid organs in SLE, even when the disease is clinically quiescent.²⁷ Furthermore, increased ^{18}F -FDG uptake was observed in the thymus of some SLE patients, even adults, but only in active SLE, which suggests a role for the thymus in SLE disease activity.²⁷

Sarcoidosis

The classical workup for patients with suspected sarcoidosis includes chest CT, which in patients with the disorder demonstrates bilateral hilar and mediastinal lymphadenopathy with or without lung parenchymal infiltrates or interstitial disease. However, the precise distribution of sarcoid disease cannot be determined by a single CT examination. Gallium-67 (^{67}Ga) scintigraphy has been widely used for the diagnosis of sarcoidosis, which shows the typical lambda sign attributable to mediastinal and hilar lymphadenopathy, as well as for management of the disease with detection of clinically silent sites and monitoring of therapeutic response.² PET can also provide a whole-body evaluation and detect unsuspected sites of involvement. It can reveal sarcoid lesions undetected by ^{67}Ga scintigraphy,²⁸ in particular in the abdomen. Both thoracic and extrathoracic sarcoid granulomas are detected with great sensitivity by PET/CT except for skin lesions, which can be identified visually.²⁹ Response to treatment can also be evaluated with PET.^{2,29} Thus ^{18}F -FDG-PET/CT is a valuable tool for the management of sarcoidosis, allowing for complete morphofunctional mapping of active inflammatory sites evaluation of treatment efficacy, especially in atypical, complex, and multisystemic forms of the disease²⁹ (Fig. 43.8).

Arthritis

The main application of ^{18}F -FDG-PET in arthritis concerns rheumatoid arthritis (RA). The first reports on the imaging of ^{18}F -FDG uptake in RA patients described incidental findings in patients undergoing PET for cancer screening or follow-up, who showed uptake in joints alone³⁰ or also in lung by rheumatoid nodules.³¹ The first specific studies involving rheumatoid joints go back to 1995, when Palmer and associates³² showed that PET could be used to quantify joint inflammation and that ^{18}F -FDG uptake in rheumatoid wrists was correlated with gadolinium uptake evaluated by MRI. Similarly, rheumatoid knees with ^{18}F -FDG uptake (Fig. 43.9) (i.e., PET-positive RA knees) exhibit higher ultrasonographically measured synovial thickness

and higher gadolinium-enhancement parameters on MRI than PET-negative knees.³³ Significant associations are found between the standardized ^{18}F -FDG uptake values (SUVs), which are correlated with ^{18}F -FDG tissue concentrations, and MRI parameters, synovial thickness measured by ultrasonography, serum level of C-reactive protein (CRP), and serum level of matrix metalloproteinase-3, a synovium-derived parameter reflecting joint inflammation.³³ These data clearly relate to animal studies showing that joint ^{18}F -FDG accumulation increases with the progression of arthritis and is correlated with the pannus rather than with the inflammatory cells around the joint; the main cell type responsible for FDG uptake is fibroblasts, and a dramatic increase in FDG uptake is induced by proinflammatory cytokines in fibroblasts and macrophages.³⁴ The main interest in the use of ^{18}F -FDG-PET in RA, however, grows out of the fact that it allows a whole-body evaluation of inflammation. Beckers and associates³⁵ studied RA synovitis in 21 patients with active RA and used the cumulative SUV (i.e., the sum of SUVs in PET-positive joints) as a measure of “metabolic” rheumatoid disease activity. This cumulative SUV was significantly correlated with clinical parameters (numbers of swollen and tender joints), biologic parameters (erythrocyte sedimentation rate and CRP levels), composite indices of disease activity (the 28-joint Disease Activity Score [DAS28] and Simplified Disease Activity Index), and ultrasonographic parameters (cumulative synovial thickness, number of Doppler-positive joints). Goerres and associates³⁶ also used ^{18}F -FDG-PET for global evaluation of RA, attempting to develop a simple score without using SUVs by adding the scores graded from 0 to 4 for each of the 28 joints included in the DAS28. The precise method for global evaluation of RA disease activity has not yet been standardized. The use of devices combining PET and CT will further improve the localization of metabolic activity and will be of great interest in evaluating small joints such as hands by making it possible to determine whether foci of increased activity are due to synovitis, inflammation of tendon sheaths (Fig. 43.10), or increased muscular uptake (Fig. 43.11b). Another potential future application of ^{18}F -FDG-PET could be the use of SUVs to

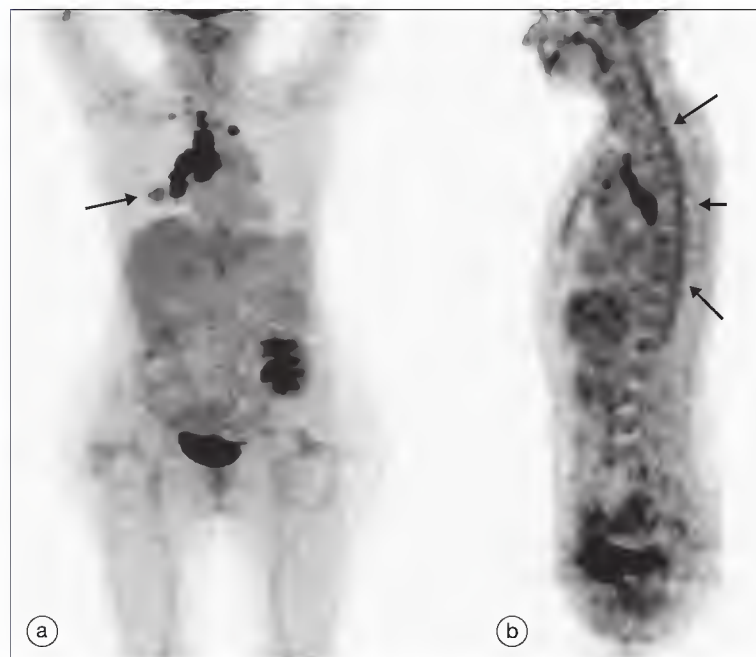


Fig. 43.8 ^{18}F -fluorodeoxyglucose positron emission tomographic image of a patient referred for fever of unknown origin associated with dyspnea and headache. (a) The coronal slice shows multiple intense hypermetabolic mediastinal and right hilar lymphadenopathies as well as a right pulmonary lesion (arrow). Transbronchial biopsy specimens showed nonnecrotizing granulomas. (b) The sagittal slice shows an unusual increased spinal cord uptake (arrows). The cerebrospinal fluid analysis highlighted a lymphocytic meningitis. The final diagnosis was pulmonary-mediastinal and neural sarcoidosis.

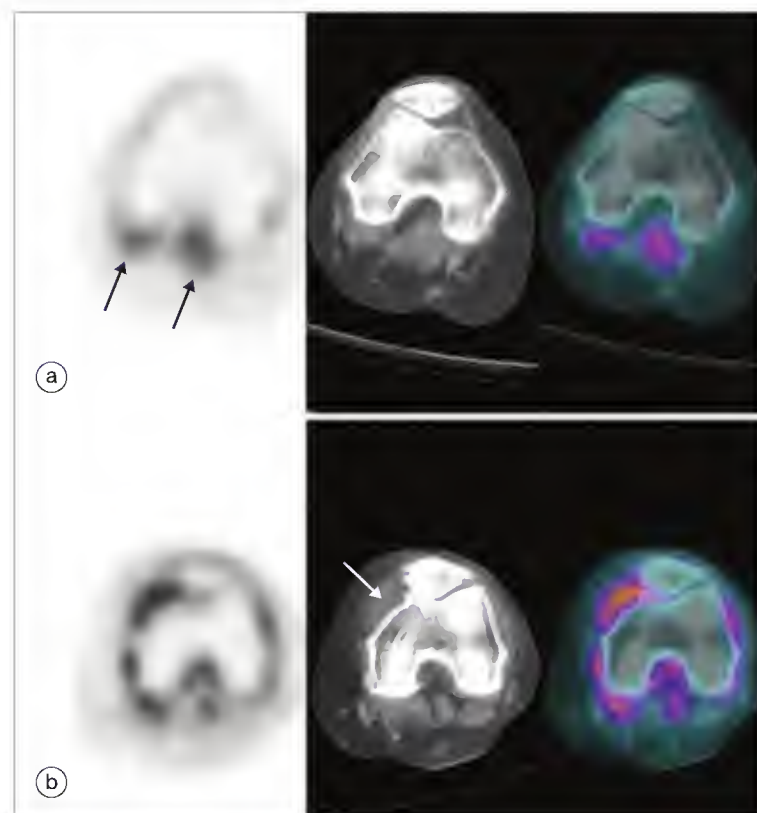


Fig. 43.9 (a) ^{18}F -fluorodeoxyglucose positron emission tomographic (^{18}F -FDG-PET), computed tomographic (CT), and fused PET/CT transverse sections of a normal knee. The CT helps to identify foci of relative hyperactivity seen on PET images posterior to the internal condyle and intercondylar notch (black arrows) as physiologic muscle uptake. (b) ^{18}F -FDG-PET, CT, and fused PET/CT transverse sections of the knee of a patient with rheumatoid arthritis. The PET (left) and fusion (right) images show a vast hypermetabolic ringlike lesion surrounding the condyles, consistent with a synovitis. Note the thickening of the synovium recognizable on the CT image (white arrow).

determine prognosis. In oncology, pretherapeutic SUVs have been shown to predict response to treatment and overall survival.^{37,38} The advent of effective but expensive biologic therapies in rheumatology has prompted an interest in methods that can detect changes in response to treatment with great sensitivity. The usefulness of PET in the assessment of therapeutic response has been shown for low-dose prednisone and methotrexate,³⁹ for intraarticular injections,⁴⁰ and recently for anti-tumor necrosis factor. In RA patients treated with anti-tumor necrosis factor, changes in ^{18}F -FDG uptake in knees were significantly correlated with changes in MRI parameters as well as with biologic parameters (CRP and matrix metalloproteinase-3 levels) after 4 weeks of treatment.³³ Global ^{18}F -FDG-PET joint score was decreased after three infusions of infliximab in patients showing a clinical response but not in those showing no clinical response.³⁶ Figure 43.11 illustrates the response to rituximab. Whether PET will be able to identify patients in need of biologic therapies or to detect an early response to these treatments remains to be shown.

^{18}F -FDG-PET can visualize joint inflammation in other inflammatory arthritides such as psoriatic arthritis⁴¹ and ankylosing spondylitis.⁴²

Accumulation of ^{18}F -FDG can also be found in various joints due to a local inflammatory reaction, even in degenerative disorders, such as bursitis or nonspecific synovitis in shoulder osteoarthritis (Fig. 43.12).⁴³ Uptake of ^{18}F -FDG by osteoarthritic joints has been found in shoulders,⁴³ hands,⁴⁴ and knees.⁴⁵ The favorability of the cost-benefit ratio of PET imaging in these diseases remains to be proven.

Fever of unknown origin

Many noninfectious inflammatory disorders treated by rheumatologists, such as arthritis and vasculitis (giant cell arteritis, Wegener granulomatosis, polyarteritis nodosa), can give rise to fever of unknown origin (see Figs. 43.6 and 43.8). Although ^{18}F -FDG-PET alone is sometimes unable to distinguish reliably between aseptic inflammatory disease and infectious disease or malignancy, it can localize active lesions and, in conjunction with other imaging modalities, identify the tissue or organ to be biopsied to establish a diagnosis.²

PRACTICAL ISSUES

As a rule, when ionizing radiation is being used in human studies, the level of exposure must be carefully taken into account. The effective dose resulting from a bone scan with $^{99\text{m}}\text{Tc}$ -labeled diphosphonates is 0.0057 mSv/MBq. The administered dose is typically 740 MBq, which gives an effective dose of approximately 4 mSv.⁴⁶ Doses in PET studies are within the same range (i.e., 5 mSv for 250 MBq of ^{18}F -FDG). The radiation exposure associated with the CT portion of a PET/CT study is highly dependent on the acquisition protocol. Low-dose studies such as those performed at the authors' institution and for which images are shown in Figures 43.7 and 43.9 through 43.12 result in an additional dose of 4.5 mSv.⁴⁷ Overall, the radiation burden may be considered minimal, and the theoretical risks are largely counterbalanced by the clinical benefits.

The cost of nuclear medicine techniques is linked to cost of the sophisticated machines themselves as well as to the cost of the isotopes used. The technetium-labeled isotopes used for scintigraphy are inexpensive, but their production is characterized by recurrent shortages. The isotopes used for PET are generated by a cyclotron, which needs to be within a few hours' reach of the user for practical purposes. Their cost can be highly variable but has tended to decrease due to greater availability.

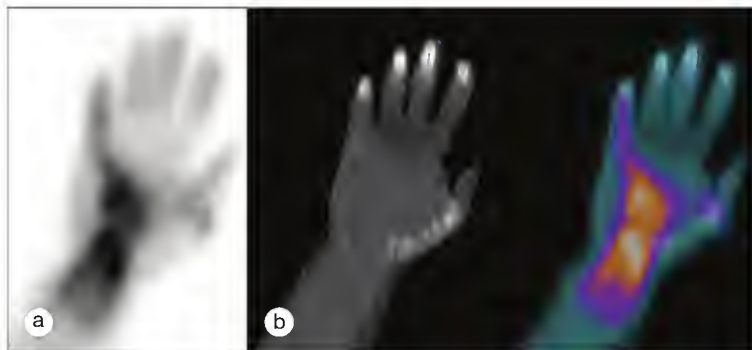


Fig. 43.10 (a) ^{18}F -fluorodeoxyglucose positron emission tomographic (^{18}F -FDG-PET), computed tomographic (CT), and fused PET/CT coronal slices of the distal part of the right upper extremity in a patient with rheumatoid arthritis. (b) The PET (left) and fusion (right) images are strongly suggestive of inflammation of the ulnar bursa, in continuity with the flexor sheath of the fifth digit.

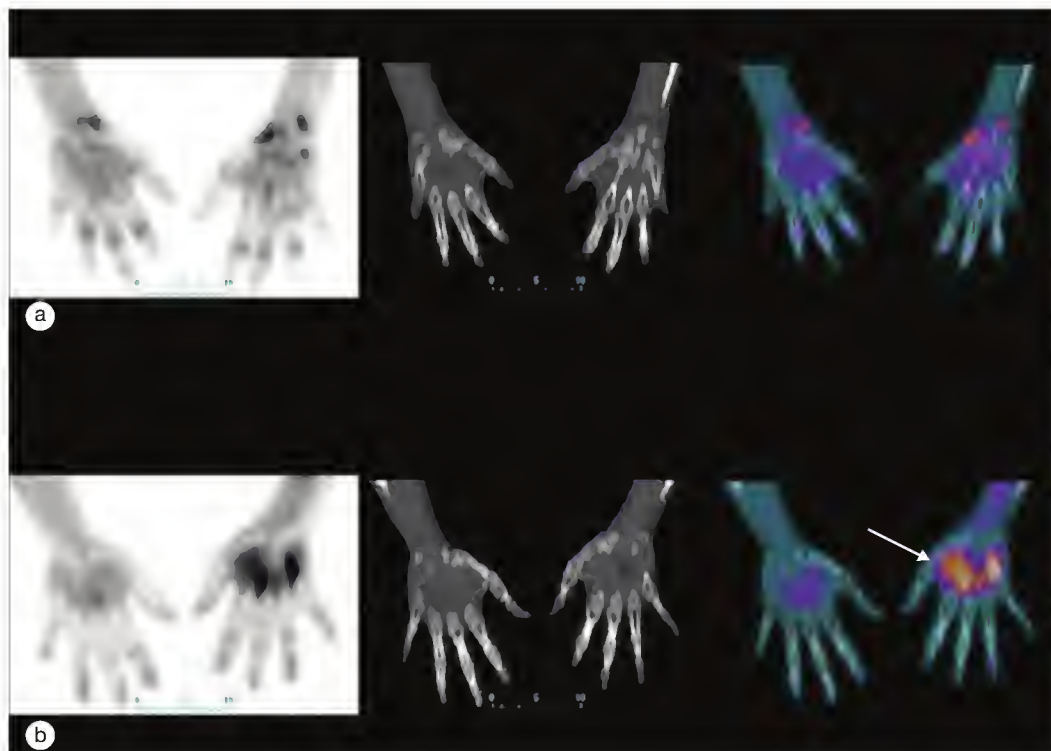


Fig. 43.11 ^{18}F -fluorodeoxyglucose positron emission tomographic (^{18}F -FDG-PET), computed tomographic (CT), and fused PET/CT coronal slices of the distal upper extremities in a patient with rheumatoid arthritis. (a) Inflammatory involvement of several proximal interphalangeal joints of both hands and multiple joints of both wrists. (b) Response to rituximab treatment. After 16 weeks, there is a complete metabolic response in the wrists and a partial response in the interphalangeal joints. Zones of relative hyperactivity in the left hand (arrow) correspond to physiologic muscle uptake.

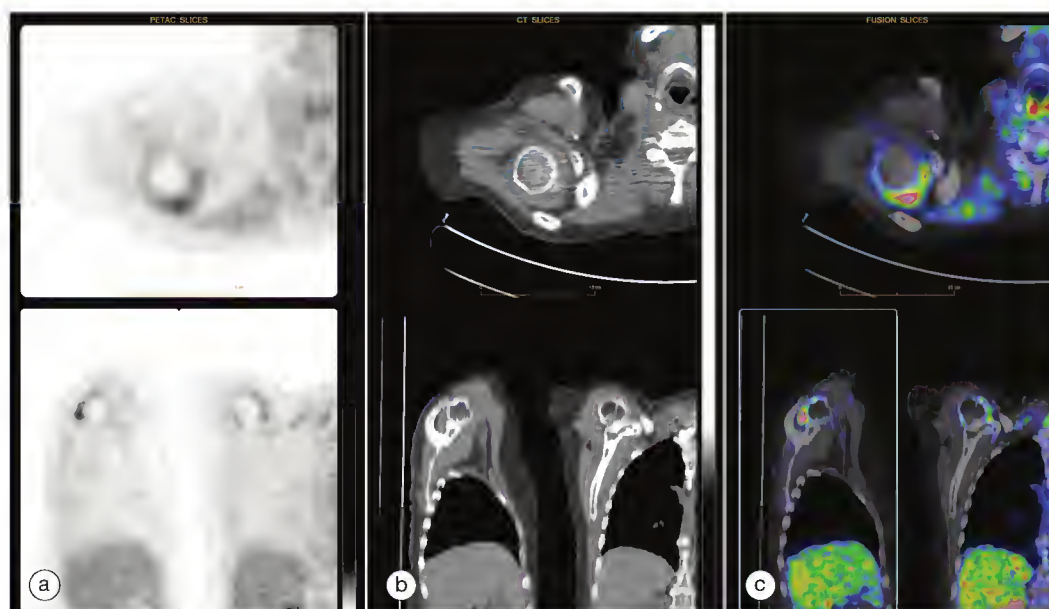


Fig. 43.12 ^{18}F -fluorodeoxyglucose positron emission tomographic (^{18}F -FDG-PET) images (a), computed tomographic (CT) images (b), and fused PET/CT images (c) of a patient referred for oncologic reasons. Uptake in the right shoulder is incidentally highlighted.

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44

Dual x-ray absorptiometry and measurement of bone

■ SYDNEY L. BONNICK

- Clinical guidelines for determining bone density are based on dual-energy x-ray absorptiometry (DXA) measurements of the posteroanterior lumbar spine and proximal end of the femur, with other skeletal sites and techniques being reduced to a lesser role.
- The World Health Organization (WHO) criteria remain the standard for diagnosing osteoporosis on the basis of bone mineral density (BMD).
- FRAX, the WHO's 10-year absolute fracture risk prediction algorithm, has refined prediction of the risk for fracture.
- Understanding precision and the least significant change is critical to interpretation of serial BMD measurements.
- New imaging applications for lateral spine DXA have extended the utility of DXA beyond the measurement of BMD.

INTRODUCTION

Dual-energy x-ray absorptiometry (DXA) was approved by the Food and Drug Administration (FDA) for clinical use in 1988. Because of its versatility and relative ease of use, DXA has become the dominant technology used to quantify bone density in clinical practice. Other technologies have had their utility diminish in the face of societal guidelines that rely on measures derived with DXA. Such guidelines also tend to focus on DXA measures of the posteroanterior (PA) lumbar spine and proximal femur, thereby diminishing the clinical utility of non-PA lumbar spine and proximal femoral sites.

The origins of bone densitometry can be traced to the field of dentistry in the late 1890s, but the birth of clinical densitometry did not occur until almost a century later with the approval of DXA for clinical use in 1988.¹ In DXA, photon energy is generated by an x-ray tube. Two distinct energy peaks are produced, either by filtering the photon energy or by pulsing the power to the x-ray tube. These two distinct peaks allow separation of bone from soft tissue. The magnitude of attenuation of photon energy through bone is compared with standards created from dried, defatted, ashed bone.

Initially viewed as a quantitative technique only, the current imaging capabilities of modern DXA devices have resulted in FDA approval for structural diagnosis in the spine and detection of abdominal aortic calcification. Bone mineral density (BMD) can be quantified in virtually every region of the skeleton, as well as in the skeleton as a whole. Analysis of body composition can also be accomplished with DXA and is considered by some to have replaced the previous "gold standard" of underwater weighing for this purpose. The primary applications of DXA, however, remain quantitative diagnosis of osteoporosis and prediction of fracture risk.

DIAGNOSIS OF OSTEOPOROSIS

Before the advent of quantitative definitions of osteoporosis based on measurement of bone density, osteoporosis was largely defined by the presence of a low-trauma fracture. In the late 1980s and early 1990s, a bone density that was 2 or more standard deviations (SD) below the young adult mean bone density had become the *de facto* working definition of osteoporosis. In 1994, the World Health Organization (WHO) redefined osteoporosis as a bone density that was 2.5 SD or greater below the young adult mean.² The WHO created other diagnostic categories based on measurement of bone density as well, as shown in Table 44.1. The threshold of 2.5 SD or greater below the young adult mean seemed reasonable because it created a prevalence of osteoporosis that was similar to previously observed lifetime risks for fracture. In creating four diagnostic categories, the WHO maintained the

recognized gradient of risk for fracture with declining bone density and the additional effect of prevalent fracture.

The original WHO criteria for diagnosis of osteoporosis based on measurement of bone density were described in terms of the number of standard deviations below the young adult mean bone density. Because this is the definition of the T-score used in bone densitometry, the WHO criteria are now generally characterized as T-score cut points, which are also shown in Table 44.1.

Although the WHO intended these criteria to be used for determining the prevalence of osteoporosis in world populations, they recognized the likelihood that the criteria would be applied to individuals as well. The WHO cautioned that different diagnoses could result depending on the skeletal site measured, the technique applied, and the reference database used. This was because the WHO criteria were derived from single-photon absorptiometry (SPA), dual-photon absorptiometry (DPA), and DXA bone density studies of the spine, proximal femur, and radius in white women.

A detailed discussion of controversies regarding the use of different methods for determination of bone density is presented in the online supplement.

Several authors have attempted to define T-score cut points for nonspine, non-proximal femoral measurements of bone density that would identify individuals with WHO-defined osteopenia or osteoporosis of the PA lumbar spine, proximal femur, or both.⁹ The results of such efforts identified T-score cut points that ranged from -1.9 to +1.06, depending on the site, technique, and objective of the cut point. It is thus clear that use of the WHO criteria at sites other than the spine or proximal femur and with techniques other than DXA can be inappropriate and misleading. This does not reflect a lack of accuracy or precision of measurements at these sites or with non-DXA devices. It simply reflects the effects of attempting to apply criteria developed by wholly different means. The unfortunate but predictable result of reliance on the WHO criteria for the diagnosis of osteoporosis is a dramatic reduction in the clinical utility of these non-DXA techniques and nonspine, non-proximal femoral skeletal sites. Although non-DXA technologies and nonspine, non-proximal femoral skeletal sites can be used for case finding for DXA studies of the spine and proximal femur, the bone density measured at such sites or with non-DXA devices should not be used as the sole determinant of the presence or absence of osteoporosis in the spine or proximal femur. The threshold for case finding also depends on the peripheral site and technology used for the initial measurement and should not be based on inappropriate application of the WHO criteria to bone density at the peripheral site.

The ISCD currently recommends that a gender-specific reference database be used when applying the WHO criteria to men older than 50 years. However, the IOF recommends the use of a white female reference database in conjunction with the WHO criteria for the diagnosis of osteoporosis in men.⁸ This recommendation stems largely from recognition that the difference in fracture rates between women and men is primarily due to non-bone density factors, not to differences in bone density. At a given level of bone density, the risk for fracture imparted by that level of bone density appears to be the same in both genders. Therefore, if the purpose of diagnosing osteoporosis based on some level of bone density is to imply a certain level of fracture risk imparted by that bone density, use of the white female reference database in men would be appropriate.¹⁰ This concept is gaining acceptance, although it is not the current standard in the United States.

PREDICTION OF FRACTURE RISK

Prediction of fracture risk with DXA bone density measurements is a separate entity from the diagnosis of osteoporosis. Although the four diagnostic



Even when the WHO criteria were applied to bone density measurements of the proximal femur in white women only, it became clear that there was enough variation in the proximal femoral reference databases between manufacturers to result in different diagnoses. This issue was addressed by Faulkner and colleagues,³ who demonstrated that substitution of a common proximal femoral reference database, the 1997 Third National Health and Nutrition Examination Survey (NHANES III) database, largely eliminated the differences in assignment of diagnostic categories. Since that time, the NHANES III proximal femoral database has become the standard proximal femoral database for white men and women. No other common reference database currently exists for any other skeletal site that could be used by manufacturers. Differences in assignment of diagnostic categories based on measurements of PA lumbar spine BMD among manufacturers are minimal, however, when compared with pre-NHANES III assessments of BMD at the proximal femur.

Applicability of the WHO criteria to men of any ethnicity and to non-white women is still controversial given that the original thresholds were chosen on the basis of reconciling fracture risk and prevalence established in white women. Similarly, because the original data came from DPA and DXA studies of the PA lumbar spine and proximal femur and from SPA studies of the radius, application of the WHO criteria to bone density studies at other skeletal sites with any technique or to the spine, proximal femur, and radius with other techniques remains controversial.

When other techniques and other skeletal sites are used, a given T-score may reflect only the variability in bone density in the population rather than

some level of fracture risk. In 1999, Faulkner and coworkers⁴ compared the T-score regression with age in women with the use of quantitative ultrasound (QUS) of the heel, quantitative computed tomography (QCT) of the spine, and DXA of the proximal femur, PA and lateral lumbar spine, and forearm based on the reference database provided by the manufacturer of the specific device. The expected T-score for an average 60-year-old woman ranged from -0.7 at the heel with QUS to -2.5 at the spine with QCT. In other words, the WHO diagnostic category could be normal to osteoporotic in the same woman, depending on the site and technique used. A study published in 2002 in men revealed similar findings.⁵ This dilemma resulted in part from different populations being used to create the reference databases for the various devices and skeletal sites, as well as from differences in the nature of the measurement with QUS, QCT, and DXA and in expected rates of bone loss in the various skeletal sites. It also reflected the effect of extending the WHO criteria beyond its original reach.

Findings such as these have led to recommendations from various organizations that use of the WHO criteria be restricted to specific skeletal sites measured with DXA. The International Society for Clinical Densitometry (ISCD) recommended that the WHO criteria be used only in conjunction with measurements of the PA lumbar spine, total hip, or femoral neck and that the lowest of the three be used.⁶ The WHO itself suggested that the criteria be applied only to measurements of the proximal femur with an emphasis on the femoral neck region of interest,⁷ whereas the International Osteoporosis Foundation (IOF) has stated a preference for the total hip region of interest.⁸

categories created by the WHO attempted to retain the concept of a gradient of increasing fracture risk with declining BMD, the four categories contain ranges of BMD that are too wide to use a category for accurately characterizing fracture risk in a given individual.

The ability to predict fracture risk with a single bone density measurement was considered controversial until 1993, when two published studies clearly demonstrated a statistically significant increase in the relative risk (RR) for fracture per SD decline in BMD for different types of fractures, as well as for specific fracture types when BMD was measured at different skeletal sites.^{11,12} RR was the appropriate statistical metric in these studies because it is the strongest indicator of the strength of the relationship between a risk factor, such as low bone density, and disease outcome, such as fracture. The utility of RR data in clinical practice is extremely limited, however, because its meaning is diminished when applied to the individual. Use of RR in clinical densitometry is no longer considered appropriate because there is now sufficient data to assess absolute risk. In 2008 the WHO introduced FRAX, a 10-year absolute fracture risk prediction algorithm for the prediction of risk for hip fracture and any major osteoporotic fractures, the latter including hip, clinical spine, humerus, and wrist fractures.¹³

FRAX is unique in predicting absolute fracture risk based on validated clinical risk factors, as well as BMD. Selection of the clinical risk factors included in the FRAX model was based on reviews of the medical literature to establish the magnitude of the relationship between the risk factor and fracture risk.¹⁴⁻²⁰ Ultimately, the data used to create FRAX came from 9 different study cohorts around the world and were validated in 11 other cohorts in similar geographic locations.²¹ The specific risk factors that were ultimately chosen came to be known as the WHO 8: age, body mass index, prior fracture, parental hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, and excessive alcohol consumption.

FRAX is available at no cost as an Internet-based application (www.shef.ac.uk/FRAX). A FRAX application for various devices and

desktop use is available for purchase. FRAX has also been incorporated into recent versions of DXA software. FRAX algorithms are available for different countries and, in some cases, for different ethnicities within a country. The FRAX data entry algorithm page from the website for U.S. white individuals is shown in Figure 44.1. The algorithm can provide an assessment of absolute fracture risk in the absence of BMD measurement; however, risk assessment is improved by inputting femoral neck BMD. The user should select the type of DXA machine from the drop-down box and then enter the femoral neck BMD. After clicking on “calculate,” 10-year absolute fracture risks are presented for hip fracture specifically and for any major osteoporotic fracture.

Clinical risk factors have been reduced to dichotomous variables requiring a “yes” or “no” response. The risk factor “prior fracture” refers to a low-trauma fracture occurring as an adult. The subjectivity of this assessment is unavoidable. Captured in this assessment are previous morphometric spine, clinical spine, nonspine, and hip fractures. The number, location, and type of preexisting fracture or fractures are not captured. If multiple fractures have occurred, the algorithm may underestimate the 10-year probability of fracture. When the risk factors are reduced to dichotomous variables, the inability to convey the effects of a “dose-response relationship” is inevitable. This limitation also applies to the risks associated with smoking, use of glucocorticoids, and alcohol consumption. Rheumatoid arthritis is considered separately from other causes of secondary osteoporosis because it imparts a risk for fracture that is independent of BMD.¹⁶ Therefore, if “yes” is selected for rheumatoid arthritis, this will contribute to calculation of the 10-year fracture probability regardless of whether a femoral neck BMD is entered. Selection of “yes” or “no” for other secondary causes of osteoporosis has no effect in this circumstance on the fracture probability calculation. If BMD is not entered and “no” is selected for rheumatoid arthritis and “yes” for other secondary causes of osteoporosis, the 10-year fracture probability calculation is affected by the selection of “yes” for other secondary causes of osteoporosis. If BMD is entered, there is no effect of the “yes” response to other secondary causes of osteoporosis on the 10-year fracture probability. When BMD is inputted, the contribution to fracture risk from secondary osteoporosis is captured in the BMD.

Some caveats are associated with the use of FRAX. First, the actual femoral neck BMD in g/cm² should be used rather than the T-score because the T-score used in FRAX calculations is based on the 1998 NHANES III proximal femoral database for white women, regardless of the gender or ethnicity of the patient. This should also be done even if the patient is a white woman because many DXA devices use the 1997 NHANES database rather than the 1998 database used by FRAX. When the BMD in g/cm² is entered, the FRAX program will calculate the requisite T-score from the 1998 NHANES III database.

The FRAX algorithm was never intended for use in patients receiving therapy. The algorithm does not account for the effect that pharmacologic therapy might have on reduction of fracture risk. It must then be assumed that FRAX risk predictions in individuals undergoing therapy will be overestimations of risk. Leslie and associates suggested that the 10-year major

TABLE 44.1
1994 World Health Organization criteria for diagnosis of osteoporosis based on measurement of bone density and T-score equivalent

Diagnostic category	Standard deviation (SD) below the young adult mean	T-score
Normal	≤1 SD	Equal to or better than -1
Osteopenia (low bone mass)	Between 1 and 2.5 SD	Between -1 and -2.5
Osteoporosis	≥2.5 SD	Equal to or poorer than -2.5
Severe (established) osteoporosis	≥2.5 SD + a fragility fracture	Equal to or poorer than -2.5 + a fragility fracture

The screenshot displays the FRAX WHO Fracture Risk Assessment Tool. The 'Calculation Tool' section is active, showing a questionnaire for a 69-year-old female with a weight of 60.69 kg and height of 166.88 cm. Clinical risk factors include previous fracture (No), parent fractured hip (No), current smoking (No), glucocorticoids (No), and rheumatoid arthritis (No). The femoral neck BMD is 0.761 g/cm², resulting in a T-score of -2.0. The 10-year probability of fracture is 21.3%. The results section shows a 17% probability for major osteoporotic fracture and a 3.3% probability for hip fracture. The tool also includes weight and height conversion options and a footer indicating it is for individuals assessed since June 1st, 2011.

Fig. 44.1 FRAX is a 10-year absolute fracture risk prediction algorithm developed by the World Health Organization that incorporates clinical risk factors for fracture and femoral neck bone mineral density (BMD). These data are for the patient whose bone density studies are presented in Figure 44.4a and b. (Image used with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. FRAX is registered to Professor J. A. Kanis, University of Sheffield, UK.)

osteoporotic fracture risk might still be used in such individuals after retroactively calculating FRAX probabilities in more than 35,000 women older than 50 years from the Manitoba Bone Density Program and noting whether they had received pharmacologic intervention and their level of adherence.²² They found that only women highly adherent to at least 5 years of bisphosphonate therapy had an observed hip fracture risk lower than that predicted by FRAX. The FRAX major osteoporotic fracture risk was similar to the risk observed in all groups. This suggests that the FRAX 10-year major osteoporotic fracture risk can still be assessed in patients undergoing therapy but that the 10-year hip fracture risk may be overestimated in highly adherent patients after at least 5 years of bisphosphonate therapy.

Because of the inability to reflect a dose-response relationship for some of the clinical risk factors as noted previously, FRAX may also underestimate fracture risk in some circumstances. The ISCD and IOF jointly issued guidelines to address this problem in 2010.²³ These guidelines are available at www.iscd.org.

FRAX uses femoral neck BMD in its calculations. In circumstances in which the lumbar spine T-score is poorer than the femoral neck T-score, concern arose that FRAX would underestimate such a patient's fracture risk. Leslie and associates,²⁴ again using the Manitoba BMD database, suggested that the FRAX-calculated major osteoporotic fracture risk be rounded up or down as appropriate by 10% for each rounded T-score difference between the lumbar spine and femoral neck.

Importantly, FRAX does not indicate the necessity for treatment. Separate guidelines that incorporate FRAX risk predictions have been developed to help clinicians identify individuals who would benefit from pharmacologic interventions to reduce fracture risk.²⁵ Ultimately, FRAX should never substitute for clinical judgment in assessing fracture risk and the need for pharmacologic intervention.

Monitoring changes in bone density

Changes in bone density, whether attributable to disease or therapeutic intervention, can be quantified with DXA. Such changes cannot be interpreted properly without applying the concepts of precision and least significant change (LSC). Changes in bone density must also be measured at a clinically relevant skeletal site, with relevance being determined by the condition, disease, or drug that may cause the change in bone density.

In densitometry, precision refers to the ability to reproduce a quantitative measurement when the measurements have been performed under identical conditions in the setting of no real biologic change. When an individual has several bone density studies performed within minutes of each other, the results of each test are not expected to be identical because of variability in the measurement even when performed consistently perfectly, although the variability is expected to be small. Nevertheless, because there is variability, it must be quantified for the physician to know when the variability of the test has been sufficiently exceeded to conclude that a real biologic change has occurred. The variability of the test is its precision. Because variability is undesirable, this variability is also called the precision error of the test. Variability is most reasonably quantified by performing a short-term precision study.

To perform a short-term precision study, individuals undergo repeated bone density testing over a 7- to 14-day period, with studies on any one individual preferably not being performed on the same day.²⁶ The number of individuals and bone density studies per individual is based on narrowing the resulting confidence interval for the calculated precision value as much as reasonably possible. In general, the number of individuals and studies per individual is chosen to achieve 30 degrees of freedom.²⁷ Combinations such as 15 individuals studied three times each or 10 individuals studied four times each are often chosen to avoid learned positioning or excessive radiation exposure on the part of the subject undergoing many studies and the logistic issue of recruiting many subjects for the precision study. The individuals participating in the precision study should be representative of the patient population in which the resulting precision value will be applied.

Details on how precision is calculated are presented online.



IMAGING THE SPINE WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY

Technologic improvements in image resolution with DXA have led to imaging applications for assessing vertebral deformities (vertebral fracture assessment [VFA]) and abdominal aortic calcification (AAC). With some DXA devices the spine can be imaged from T4 to L5 in seconds to minutes, depending on the scan mode, but always at a fraction of the radiation

exposure that occurs with conventional spine radiographs. Lateral spine DXA also largely avoids the problem created by parallax in plain radiography of the spine. Because movement of the scan arm allows the DXA beam to pass parallel to the vertebral endplates throughout the entire length of the spine, the vertebral dimensions are not distorted by the angle of the beam. If the patient has severe scoliosis, however, some parallax effect may be unavoidable.

Assessment for vertebral fractures

With VFA imaging, T4 to T6 may be poorly visualized. This does not generally present a problem because the majority of osteoporotic fractures occur below these levels. Assessment for previously undiagnosed vertebral fracture is imperative for accurate diagnosis, evaluation of fracture risk, and informed decision-making regarding the need for therapeutic intervention. The finding of a previously undiagnosed vertebral fracture may change the WHO diagnostic category and will change assessment of the patient's future fracture risk. Either or both may result in a different therapeutic decision. Studies in the medical literature have documented that the majority of morphometric vertebral fractures are undiagnosed. This seems to be true even in patients who have had radiographs taken in which the spine was visualized.^{29,30} Thus the ability to image the spine for diagnosis of vertebral fracture in conjunction with a bone density measurement is highly desirable in clinical practice. Of considerable importance is the finding that a significant percentage of women with nonosteoporotic bone densities have been found to have vertebral fractures. In a study by Schousboe and colleagues³¹ in which 342 women underwent lateral spine imaging with DXA, 27.4% of the patients 60 years and older with osteopenic bone densities according to the WHO criteria were found to have vertebral deformities consistent with a diagnosis of fracture. Forty-two percent of the patients 60 years and older with osteoporotic bone densities were found to have vertebral deformities as well. In 2007 the ISCD published extensive guidelines on patient selection for VFA.³² The guidelines assume that plain films of the spine have not previously been obtained and that knowledge of a vertebral fracture would change patient management. These guidelines are available at www.iscd.org. The ISCD also noted that the Genant visual semiquantitative method was the preferred method for VFA. In the Genant semiquantitative method the vertebrae are characterized as normal or deformed based on their appearance rather than their measured dimensions, as illustrated in the lower right-hand portion of Figure 44.2.³³ The VFA study in Figure 44.2 is from a 66-year-old man. No vertebral deformities are seen in this study. Because of the superb image resolution, small anterior osteophytes can be seen at T8. Some DXA VFA software now provides an automated Genant semiquantitative assessment of deformed vertebrae.

Assessment for abdominal aortic calcification

AAC can also be visualized during lateral spine imaging with DXA. Although several studies have suggested a relationship between aortic calcification and low bone density, a more important prognostic attribute of aortic calcification is its relationship to risk for myocardial infarction and stroke. A significant increase in the hazard ratio for myocardial infarction and in the RR for stroke with increasing aortic calcification was found in the Rotterdam study, a prospective population-based cohort study of almost 8000 men and women 55 years and older.^{34,35} The risk for congestive heart failure or coronary heart disease was also shown to be significantly related to the degree of aortic calcification in the Framingham Heart Study.^{36,37} Using the 24-point grading system for AAC seen on plain radiographs that was developed by Kauppila and coworkers,³⁸ an AAC-24 score of 5 or higher was associated with a significant increase in the risk for congestive heart failure or coronary artery disease.^{36,37}

Although the AAC-24 scoring system can be used with DXA VFA images, Schousboe and colleagues³⁹ proposed an 8-point grading system to improve its ease of use. The AAC-8 scoring system is shown in Table 44.2. Application of the AAC-8 scoring system to a VFA image is shown in Figure 44.3. Schousboe and colleagues⁴⁰ studied 174 postmenopausal women 55 years and older to compare performance of the AAC-24 and AAC-8 scoring systems on plain radiographs and lateral spine DXA imaging. The sensitivity of a lateral DXA AAC-8 score of 3 or higher for identification of women with an AAC-24 score of 5 or higher on plain radiographs was 62% with a specificity of 96%. The positive and negative predictive values associated with a lateral DXA AAC-8 score of 3 or higher were 82% and 89%, respectively. An AAC-24 score of 5 or higher on lateral DXA imaging had a sensitivity and specificity of 59% and 97%, respectively, for identification of women with an AAC-24 score of 5 or higher on plain radiographs. The positive and negative predictive values for a lateral DXA AAC-24 score of 5

Precision is calculated as the root-mean-square standard deviation (RMS-SD) rather than the arithmetic mean SD because use of the latter would result in underestimation of the gaussian error. RMS-SD is calculated by using the following equation:

$$SD_{RMS} = \frac{\sqrt{\sum_{j=1}^m (SD^2)}}{m} \quad (1)$$

where m is the number of patients in the precision study and SD is the SD for the scans on each patient. RMS-SD is expressed in units of measurement, which for DXA is g/cm². The RMS-SD precision value is used to calculate the LSC. LSC is the value that must be equaled or exceeded before a real biologic change can be said to have occurred.

The magnitude of the LSC is determined not only by the precision but also by the level of statistical confidence that is required and the number of measurements made at baseline and at follow-up. The formula for calculating LSC is shown in equation 2:

$$LSC = Z'(Pr) \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \quad (2)$$

where Z' (pronounced z-prime) is chosen from a z-distribution table found in many statistical texts based on the desired level of statistical confidence, Pr is the precision expressed as the RMS-SD, n_1 is the number of measurements performed at baseline, and n_2 is the number of measurements performed at follow-up. The ISCD recommends that the LSC be calculated at a 95% confidence level using a two-sided approach.²⁸ The Z' value for such a calculation is 1.96. Because common clinical practice is to perform one measurement at both baseline and follow-up, the value under the square root sign becomes 2. The formula for calculation of the LSC at a 95% confidence level with one measurement at baseline and one at follow-up then becomes

$$LSC = 1.96(Pr)1.414 = 2.77(Pr) \quad (3)$$

The LSC will also have the same units as those for precision.

Interpretation of the LSC is straightforward. If the LSC has been equaled or exceeded, a statistically significant change in BMD is said to have occurred, at whatever level of statistical confidence the LSC was calculated. If the LSC was not equaled or exceeded, no significant change in BMD is said to have occurred. When the LSC is calculated via a two-sided approach, as recommended by the ISCD, an increase or a decrease in BMD that equals or exceeds the LSC would be considered a significant increase or decrease. If the LSC is not known, serial measurements of bone density cannot be interpreted. It is simply not possible to know whether the variability in measurement has been sufficiently exceeded to conclude that a change has occurred in the patient.

The inherent precision of DXA is superb. Few, if any quantitative tests used in clinical medicine provide superior precision. Nevertheless, a short-term precision study must be done at the bone density facility to establish the precision of the test, from which the LSC can then be calculated. The precision at every skeletal region of interest that might be used to monitor bone density must be established. The same study population can be used for this, but precision must not be assumed to be the same at every skeletal site. Precision tends to be the best at the total hip and proximal forearm sites. The lumbar spine, trochanteric region, and femoral neck follow, generally in this order.

Better precision results in a smaller LSC. This generally means that less time is required between measurements to detect a statistically significant change in bone density. However, the anticipated rate of change in bone density at a particular site profoundly affects the time required to see a significant change. For example, precision is superb at the proximal forearm, but the rate of change at that site from commonly used bone-active agents is too slow for that site to have clinical utility in monitoring the effects of these agents on bone. In contrast, although precision at the lumbar spine or trochanteric region is not generally as good as that at the proximal forearm, the rate of change at these highly trabecular sites tends to be greater, thereby resulting in a shorter and more clinically useful interval to detect a statistically significant change in bone density.

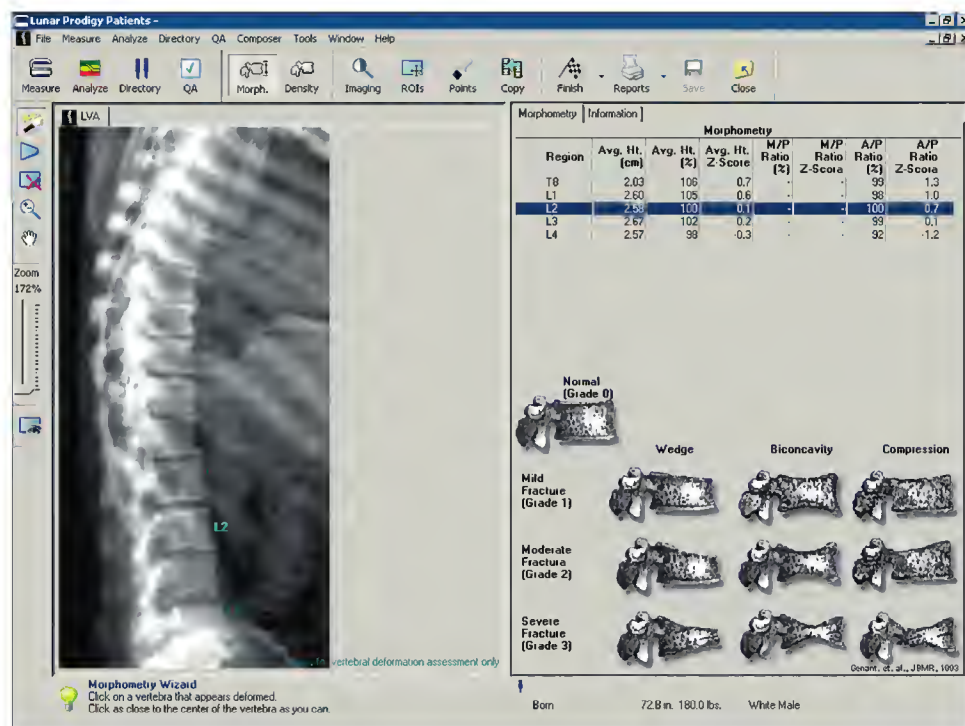


Fig. 44.2 Lateral spine dual-energy x-ray absorptiometry (DXA) for assessment of vertebral fractures in a 66-year-old man. This study was performed with a GE Lunar Prodigy DXA device. No vertebral deformities are seen. The AAC-8 score is 0. Small osteophytes are visible anteriorly at the T8-T9 level. The Genant semiquantitative grading system is shown in the lower right portion of the image.

TABLE 44.2
AAC-8 scoring system

Abdominal aortic calcification (AAC) length relative to lumbar vertebral height	Score
None	0
1 vertebra	1
>1 but ≤2 vertebrae	2
>2 but ≤3 vertebrae	3
>3 vertebrae	4

A point score is awarded for the anterior abdominal aortic wall and the posterior abdominal aortic wall based on the number of vertebrae spanned by the length of the aortic calcification. The worst possible score for both walls combined is 8.

or higher on plain radiographs was 85% and 88%, respectively. Importantly, an AAC score of 0 on either the 8-point or the 24-point scale on lateral spine DXA images had a negative predictive value of 94% for an AAC-24 score of 5 or higher on plain lateral spine radiographs.

Identification of aortic calcification alone is not considered sufficient justification for performing lateral spine imaging with DXA. Nevertheless, the opportunity to assess this important risk factor for heart disease and stroke presents itself every time that VFA is performed.

APPLICATION OF BONE DENSITOMETRY IN CLINICAL PRACTICE

Different devices, different data?

Although the appearance of screen images and computer printouts from the various manufacturers of DXA equipment may vary, the information provided is actually similar. Figures 44.4 to 44.6 are screen images of PA lumbar spine and proximal femoral bone density studies from GE Lunar, Norland, and Hologic DXA devices. Careful review of the images will reveal that although the initial appearance is quite different among the three devices, the nature of the information provided is the same.

On the left of the GE Lunar DXA PA lumbar spine and left proximal femoral studies (shown in Figure 44.4), the skeletal images are depicted. On the lower right are the bone density results and standard score comparisons (T- and Z-scores) for various regions of interest. On the upper right is the age-regression graph. Above the graph is the notation that indicates from which region of interest the plotted data came. The colorful graph does not



Fig. 44.3 Lateral spine dual-energy x-ray absorptiometry performed for assessment for vertebral fractures in which abdominal aortic calcification is seen. The AAC-8 score was 6. (Case provided courtesy Hologic, Inc., Bedford, Mass.)

provide any additional information beyond the numbers seen on the lower right. On the bottom portion of the screen, relevant biographic data are presented. On the Norland PA lumbar spine and left proximal femoral DXA studies seen in Figure 44.5, the layout is similar but not identical. An obvious difference is that images of the spine and proximal femur are in color, although they can be changed to gray-scale images if desired. The age-regression graph is seen on the upper right of the image and numerical data across the bottom of the image.

Fig. 44.4 (a) Posteroanterior lumbar spine study performed with a GE Lunar Prodigy DXA device on a 69-year-old woman. Bone mineral density (BMD) and standard scores are given for each vertebra, as well as for every possible combination of contiguous vertebrae. L1-L4 BMD is plotted on the age-regression graph. (b) Left proximal femoral study performed with a GE Lunar Prodigy device on the same patient.

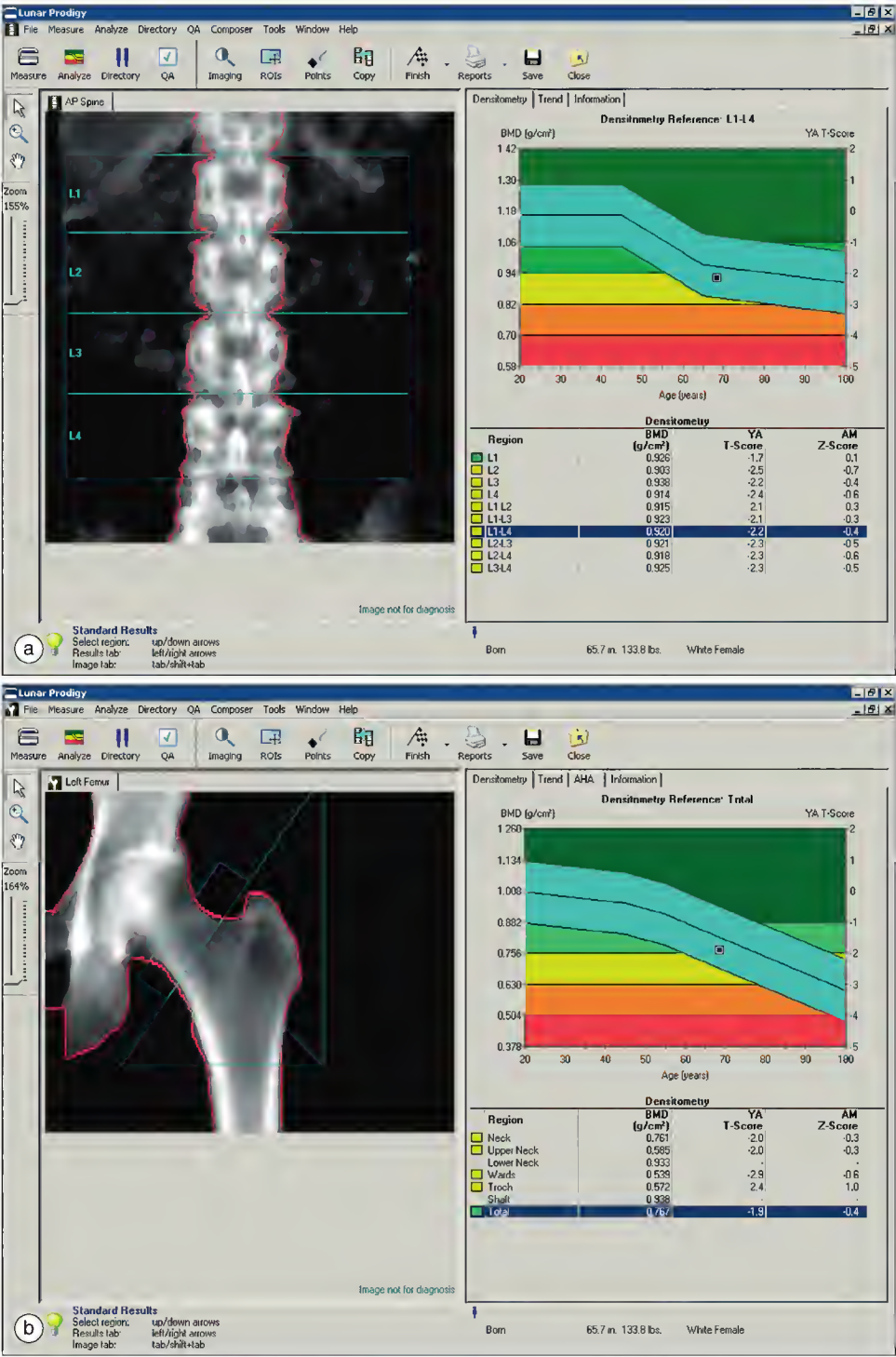


Figure 44.6 shows PA lumbar spine and left proximal femoral studies obtained with a Hologic DXA device. The age-regression graph is not seen on this particular screen image; however, it is provided on the computer printout. Patient biographic data are clearly seen on the upper right, and once again, numerical data are provided on the lower right.

In the GE Lunar spine study in Figure 44.4a, a BMD value is given for each of the four lumbar vertebrae and for every possible combination of contiguous lumbar vertebrae. This is not the case with the Norland DXA spine study seen in Figure 44.5a. Note that in the Hologic PA spine study in Figure 44.6a, L1-L4 BMD is referred to as the “total” rather than L1-L4, as it is in the GE Lunar and Norland studies. In the proximal femoral studies shown here, all the manufacturers provide results for the total hip, femoral neck, and trochanteric regions of interest. In the GE Lunar and Norland but not the Hologic proximal femoral studies, values are provided for Ward’s area. This difference is of little consequence because Ward’s area, though of historical interest, has little, if any, clinical utility in the individual.

The age-regression graphs are simply plots of BMD from the selected region of interest versus the patient’s age. The center regression line

indicates the expected BMD for age. The upper and lower boundaries of the center regression line are ± 1 SD or ± 2 SD, depending on the manufacturer. This is a visual representation of the comparison to the patient’s age and gender-matched peers. The numerical comparison is found in the standard scores. In the case of the Norland graph, the background color scheme of green, yellow, and red also corresponds to the WHO T-score diagnostic category cut points. Fracture risk characterizations are made within these different colored zones. Note, however, that these colored zones span the entire age range shown on the graph and thus must be interpreted with extreme caution.

All the manufacturers provide standard score comparisons for BMDs from the various regions of interest. The standard score comparisons indicate the number of standard deviations above or below the average value in which the patient’s value lies. The T-score is a comparison to the average for a young adult and the Z-score is a comparison to the average for the patient’s age-matched peers. The T-score is used with the WHO diagnostic criteria as shown in Table 44.1. A Z-score poorer than -2 suggests the need to evaluate a patient for secondary causes of bone loss. However, a Z-score

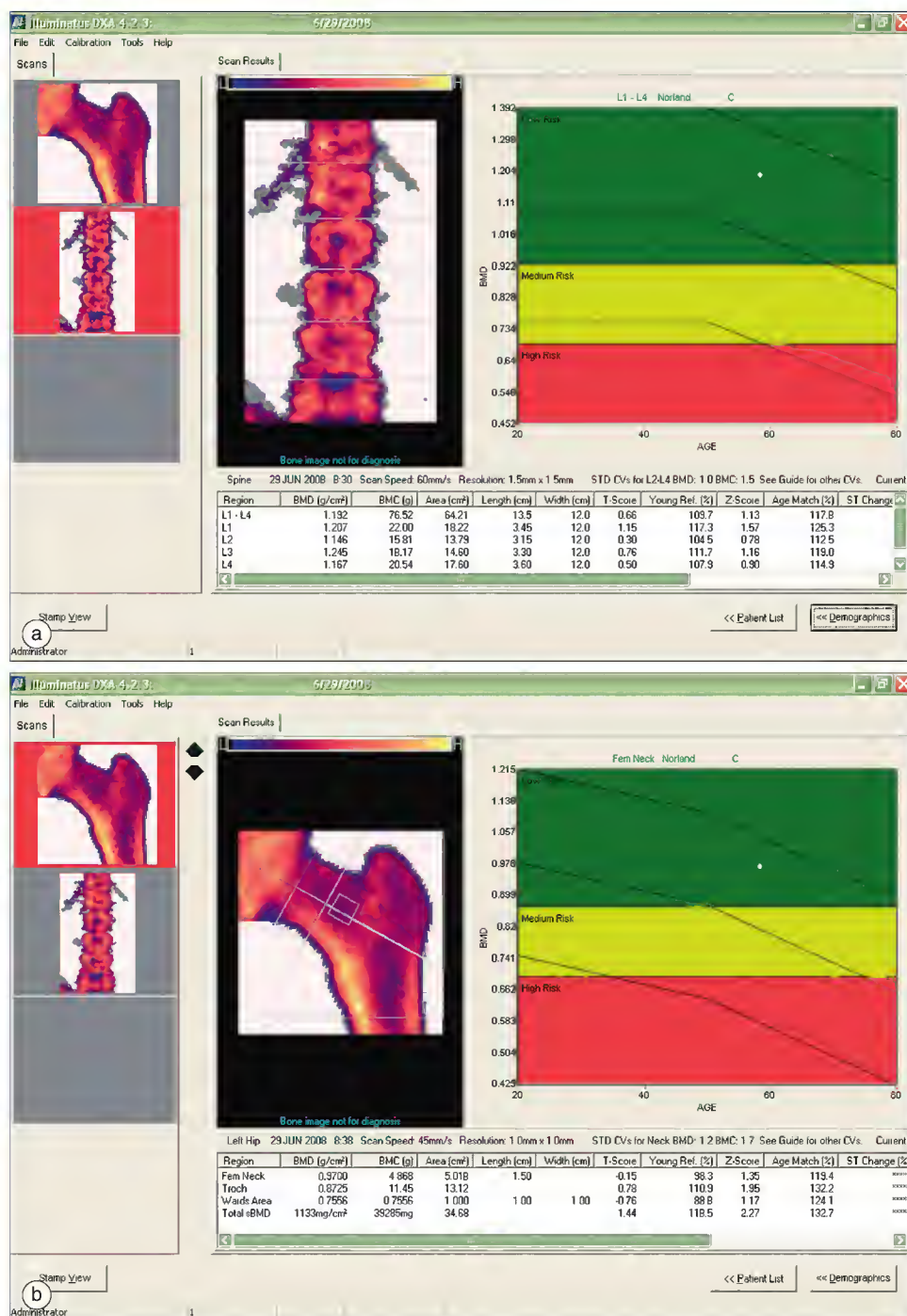


Fig. 44.5 (a) Posteroanterior lumbar spine study performed with a Norland DXA device. (b) Left proximal femoral study on the same patient. Note the density-modulated color images of the skeleton. The chosen region of interest is plotted on the age-regression graph. The boundaries of the graph are twice as wide as those seen on the GE Lunar studies. (Case provided courtesy Cooper-Surgical Norland, Trumbull, Conn.)

of -2 or better does not negate this possibility, and evaluation for secondary causes of bone loss should always be considered in an individual with low bone density.

The image of the skeleton should be reviewed to confirm proper patient positioning, correct labeling of the regions of interest, and identification of any potential artifacts or structural changes that would affect the accuracy of the bone density measurement. It may be necessary to review the image on the computer itself rather than the printout because resolution of the image will be superior on the computer screen. Unlike VFA images, bone density images have not been approved by the FDA for structural diagnosis, but the nearly radiographic quality of these images makes such a structural review appropriate. Once the image has been reviewed and the physician is satisfied with the technical quality of the study, only then should the all-important numerical data be addressed.

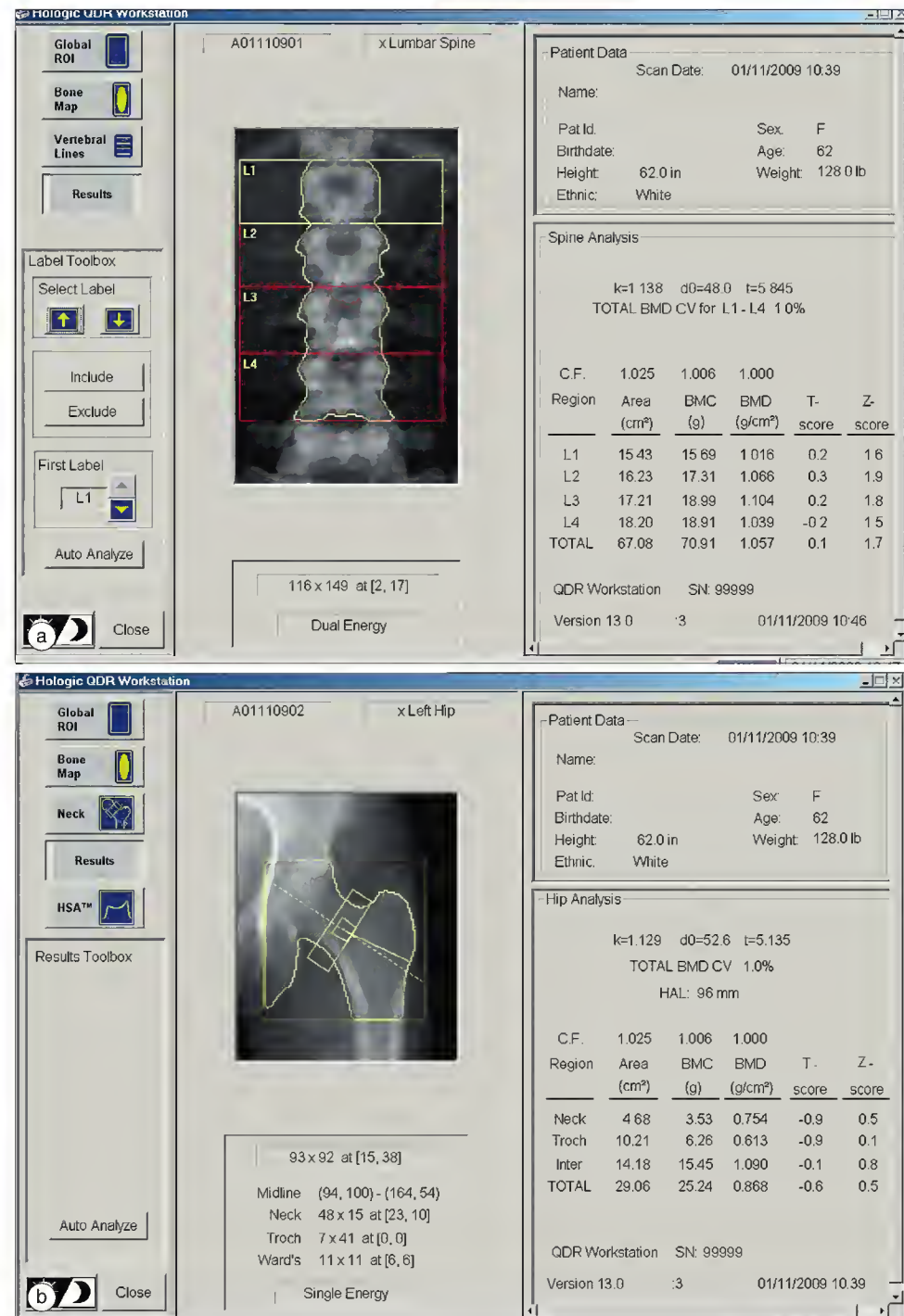
On the PA lumbar spine study, the L2-L4 or L1-L4 BMD value is preferred over BMD values from a single vertebra or from only two contiguous vertebrae. This preference is for reasons of accuracy and precision. All major manufacturers of DXA equipment provide the L1-L4 BMD, although as noted earlier, on Hologic studies this is called the "total." At the proximal femur Ward's area is the least accurate of all the proximal femoral measures as a result of its very small size. Because of the localization routines used

in these devices, Ward's area should be expected to have the lowest BMD. Ward's area is also placed slightly differently from manufacturer to manufacturer. This is true for the femoral neck as well. The most similar region of interest among the manufacturers in the proximal femur is the total femoral region of interest. Even so, the actual measured BMD at a given skeletal site should never be directly compared among the manufacturers because of differences in machine calibration. At the proximal femur, a rough comparison of total hip T-scores can be attempted only if the T-scores are derived from the same NHANES III database.

A CASE STUDY

A 69-year-old postmenopausal white woman was referred for a DXA PA lumbar spine and proximal femoral study after a wrist fracture, which she suffered in a fall from a standing height on a wet surface. Her baseline studies are the GE Lunar studies previously seen in Figure 44.4. A review of the spine image indicated good positioning and no apparent degenerative changes, artifacts, or vertebral deformities that would affect the accuracy of the study. The vertebral labeling also appeared to be correct. A review of the left proximal femoral study also indicated good positioning and no artifacts

Fig. 44.6 (a) Posteroanterior lumbar spine study performed with a Hologic DXA device. Note that L1-L4 bone mineral density (BMD) is called the total BMD. BMD values and standard scores are provided for each vertebra as well. (b) Left proximal femoral study on the same patient. (Case provided courtesy Hologic, Inc., Bedford, Mass.)



that would affect the accuracy of the study. Applying the WHO criteria for diagnosis and the ISCD guidelines for application of the WHO criteria, the L1-L4 T-score of -2.2 should be used for diagnosis. Thus this patient has osteopenia. Her 10-year absolute risks for hip fracture and major osteoporotic fracture calculated with FRAX are shown in Figure 44.1. The NOF recommends consideration of pharmacologic intervention in postmenopausal women with osteopenia and a FRAX 10-year absolute hip fracture risk of 3% or greater or a 10-year major osteoporotic fracture risk of 20% or greater.²⁵ Applying these guidelines, treatment with an antiresorptive agent was subsequently begun.

To assess therapeutic efficacy, the patient underwent bone density testing after 2 years of therapy. Her BMD at this time was 0.971 g/cm^2 at L1-L4, 0.797 g/cm^2 at the femoral neck, and 0.796 g/cm^2 at the total hip site. BMD in the three regions appeared to have increased. Before the physician can conclude that this has indeed happened, several things must be considered.

First, was the same type of machine used for both the baseline and follow-up studies? The answer here is yes. Not only was the same type of machine used, but exactly the same machine was used. This is extremely important. If a different manufacturer's machine had been used between

baseline and follow-up, the BMD values could not be compared. When two different machines from the same manufacturer are used, a comparison can be made but the LSC cannot be calculated directly and must be assumed to be greater than it would otherwise be. In addition to the same machine being used, the same technologist performed both sets of studies, which was the best possible circumstance. Next, it is important to ensure that adequate quality control monitoring of the machine was performed during the period in question. The bone densitometry facility must perform quality control procedures at least as often as recommended by the manufacturer and track the results. Drifts and shifts in machine values can and do occur. If they are not recognized and corrected, comparisons of values even on the same machine are not valid. Another area of concern is any software changes in the interim that could potentially affect the values. If the software version is the same between the two scans, this concern is moot. Finally, were comparable regions of interest identified on the two sets of scans? In other words, is an "apples to apples" comparison being made? The images from both sets of studies should be compared to determine that similar regions of interest were identified and labeled. Once all these preliminary issues have been resolved, the final issue to undertake is to determine whether the change measured equals or exceeds the LSC. This means, of course, that

TABLE 44.3

A comparison of current guidelines from major medical organizations for the use of bone density testing in clinical practice

	Women ≥65 yr	Postmenopausal women ≤64 yr and at least 1 risk factor	Postmenopausal women with fractures	Men ≥70 yr	Technique for diagnosis	Site for diagnosis
NOF 2010	✓	✓	✓	✓	DXA	PA lumbar spine, total hip, or femoral neck, whichever is lowest
AACE 2010	✓	✓	✓*	—	DXA	Spine, proximal femur, proximal radius
NAMS 2010	✓	✓	✓	—	DXA	PA lumbar spine, total hip, or femoral neck, whichever is lowest
ISCD 2007	✓	✓	✓	✓	DXA	PA lumbar spine, total hip, or femoral neck, whichever is lowest

*Consideration was limited to low-trauma fractures.

AACE, American Association of Clinical Endocrinologists; DXA, dual-energy x-ray absorptiometry; ISCD, International Society for Clinical Densitometry; NAMS, North American Menopause Society; NOF, National Osteoporosis Foundation; PA, posteroanterior; —, no comment.

precision of testing at a given skeletal site must previously have been determined.

In this case, calculations from an earlier short-term precision study indicated that the RMS-SD was 0.012 g/cm² at L1-L4, 0.006 g/cm² at the total hip, and 0.011 g/cm² at the femoral neck. To calculate the LSC, as recommended by the ISCD, each of these values was multiplied by 2.77. The resulting LSCs were 0.033 g/cm² at L1-L4, 0.017 g/cm² at the total hip, and 0.031 g/cm² at the femoral neck. The changes measured at L1-L4, the total hip, and the femoral neck all exceed their respective LSCs. Based on these comparisons, it is appropriate to conclude that a statistically significant increase in BMD occurred in all three regions of interest and that based on the intermediate endpoint of BMD, the antiresorptive therapy was efficacious. If the changes measured in BMD had not equaled or exceeded the LSC at any region of interest, the appropriate conclusion would have been that no change in BMD had occurred at that region. No change in BMD would also suggest therapeutic efficacy. If, however, a decline in BMD had been observed that equaled or exceeded the LSC, a statistically significant loss of BMD can be said to have occurred, a circumstance that should prompt reevaluation of the patient.

LIMITATIONS OF BONE DENSITY TESTING WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY

The limitations of DXA bone density testing should not detract from the extraordinary clinical utility of the technology. DXA is a two-dimensional measurement. As a consequence, measurements of bone density are mixed measurements of trabecular and cortical bone, unlike three-dimensional QCT, in which the trabecular and cortical components can be separated. Because DXA is an x-ray-based technology, exposure to ionizing radiation is unavoidable. However, radiation exposure is extremely low and, from a practical clinical perspective, virtually negligible. The accuracy and precision of bone density measurements can unquestionably be affected by degenerative skeletal changes, which are common in the spine after 60 years of age. Thus, less reliance should be placed on PA lumbar spine BMD in individuals of this age and greater reliance placed on proximal femoral measurements. Surgical hardware or previous fractures will also render a measurement invalid at the site of the hardware or fracture.

Perhaps the most controversial limitation of DXA, which also applies to measurement of bone density with any other technique, is the recognition that measurement of bone density does not capture every determinant of fracture risk and, conversely, measurement of bone density does not capture every aspect of the therapeutic efficacy of bone-active agents in reducing fracture risk. Nevertheless, there is unquestionably a statistically significant and exponential relationship between declining BMD and increasing fracture risk. A single measurement of BMD is predictive of future fracture.^{11,12} Absolute fracture risk prediction algorithms such as FRAX go beyond the recognized limitations of measurement of BMD to refine the fracture risk prediction. BMD is considered an intermediate endpoint in assessing the therapeutic efficacy of a bone-active agent in reducing fracture risk. Because no agent reduces the risk to 0, the presence or absence of a fracture while receiving therapy cannot be used as a measure of efficacy. There is a statistically significant relationship between increases in BMD with therapy versus placebo and decreases in fracture risk.⁴¹⁻⁴³ It is only the magnitude of this relationship that remains controversial.⁴⁴ At present there is no better quantifiable measure of therapeutic efficacy than a measurement of BMD indicating stability or an increase in BMD.

INDICATIONS FOR BONE DENSITY TESTING

Several organizations have published thoughtful guidelines on patient selection for bone density testing. In general, most guidelines reflect the positions taken by the NOF, which issued its first guidelines for physicians on the use of bone densitometry in 1988. The NOF's most recent guidelines were issued in 2010.²³ Other organizations such as the ISCD, the American Association of Clinical Endocrinologists (AACE), the North American Menopause Society (NAMS), and the American College of Rheumatology (ACR) have issued guidelines as well.⁴⁵⁻⁴⁸ Guidelines from the AACE⁴⁶ and NAMS⁴⁷ are provided in the context of prevention and treatment of postmenopausal osteoporosis and are therefore understandably focused on postmenopausal women only, whereas guidelines from the NOF,²³ ISCD,⁴⁵ and ACR⁴⁸ address bone density testing in both men and women. In all the guidelines, however, bone density testing is recommended for women 65 years and older regardless of other risk factors. In guidelines from the NOF, ACR, and ISCD, bone density testing is recommended in men 70 years and older. A comparison of the guidelines is presented in Table 44.3.

Various organizations have also provided guidelines on the frequency of testing when monitoring changes in bone density. Most organizations do not recommend the use of an appendicular skeletal site for this purpose. Instead, bone density measurements at the lumbar spine or proximal femur are preferred. In its 2010 recommendations, the ACR advised that patients initiating glucocorticoid therapy at any dose with a planned duration of 3 or more months undergo baseline bone density testing. Serial measurements as part of monitoring were also suggested, but the ACR noted that the appropriate interval remains controversial.⁴⁹ If the patient was receiving therapy to prevent glucocorticoid-induced bone loss, annual follow-up measurements were recommended. The ISCD, though noting that 1 year after initiation or change in therapy was an appropriate monitoring interval, also stated that in conditions associated with rapid bone loss such as glucocorticoid therapy, more frequent testing was appropriate.⁴⁵ Both the AACE and NAMS, which focused on postmenopausal osteoporosis, provided different recommendations based on the treatment or bone density status of the woman. NAMS recommended a monitoring interval of 2 to 5 years in untreated women and a monitoring interval of 1 to 2 years in women receiving treatment.⁴⁷ AACE recommended a monitoring interval spanning 1 to 10 years in untreated postmenopausal women, depending on their initial BMD and anticipated rate of loss.⁴⁶ In women being treated for osteoporosis, measurements were recommended every 1 to 2 years until stability was demonstrated. Thereafter, a monitoring interval of 2 years was recommended but could be lengthened with demonstration of persistent stability. The guiding principle behind all these recommendations is reflected in the ISCD guidelines,⁴⁵ in which it is noted that "follow-up BMD testing should be done when the expected change in BMD equals or exceeds the LSC."

CONCLUSION

Clinical guidelines are based on DXA measurements of the PA lumbar spine and proximal femur, with other skeletal sites and techniques being reducing to a lesser role. The WHO criteria remain the standard for diagnosing osteoporosis based on BMD. The WHO's 10-year absolute fracture risk prediction algorithm FRAX has refined fracture risk prediction. Understanding precision and the LSC is critical to the interpretation of serial bone density measurements. Finally, new applications for DXA lateral spine imaging have extended the utility of DXA beyond the measurement of BMD to identification of spinal fractures and assessment of aortic calcification.

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45

Use of imaging as an outcome measure in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in clinical trials

■ DÉSIRÉE VAN DER HEIJDE

- The general methodology used for scoring and analyzing the results should be applied to imaging as part of clinical trials.
- In rheumatoid arthritis, radiographs of the hands and feet are the preferred imaging method for assessing structural damage in clinical trials.
- Magnetic resonance imaging (MRI) may be useful in early drug development for rheumatoid arthritis and psoriatic arthritis.
- In ankylosing spondylitis, MRI of the sacroiliac joints and spine gives important information on inflammation, whereas radiographs are still the standard for assessing structural damage.

INTRODUCTION

Imaging is an important way to assess the efficacy of treatment in clinical trials. Depending on the imaging technique, it can be used to assess inflammation, structural damage, or both. The focus of this chapter is predominantly on structural damage. It is this aspect that makes imaging an important outcome measure in clinical trials. To show that a drug has the capability of modifying disease, a reduction in the signs and symptoms (of inflammation), preservation of physical function, and inhibition of progression of structural damage must be demonstrated. Some general concepts about using imaging as an outcome measure are discussed first. Because assessment of structural damage on radiographs is well established for rheumatoid arthritis (RA), it will frequently be used to illustrate the concepts. This is followed by a discussion of specific issues by disease for RA, psoriatic arthritis (PsA), and ankylosing spondylitis (AS) and by imaging method (conventional radiography, magnetic resonance imaging [MRI], and ultrasonography).

GENERAL ASPECTS FOR CLINICAL TRIALS

With respect to clinical trials, some general aspects apply to all imaging methods and scoring in general, as well as handling of the data. These aspects are summarized as points to consider and include the following:

- Different phases of drug development
- Different phases of disease
- Readers
- Statistical aspects of reader agreement
- Grouping of films—reading sessions
- Blinding time sequence
- Statistical handling of missing data
- Statistical analyses
- Minimum duration of trials
- Placebo versus active comparator
- Presentation of data
- Repair

Different phases of drug development

The choice of imaging method depends on what feature will be assessed (inflammation vs. damage), duration of follow-up, and experience with various imaging techniques in centers, including patients. In the early phases of development the most important issue is proof of concept. This might apply to imaging of inflammation and structural damage. For the first, only MRI and ultrasonography are applicable; for damage, radiographs can also be used. MRI is more widely standardized and applied than ultrasonography in clinical drug development. Information on bone damage (edema and erosions) in RA can be obtained with MRI, whereas radiographs provide insight on the effect on bone (erosions) and indirectly on cartilage (joint space narrowing [JSN]). In later phases of drug development the data will be used for filing to drug agencies. At the moment radiographs are used for this purpose. Acceptance of MRI needs to be discussed at the outset.

Different phases of disease

In principle, the same imaging techniques can be used with early and advanced disease. Progression of structural damage on radiographs is most prominent in patients who already have structural damage. On theoretic grounds it might be especially useful to apply MRI in the early phases of the disease before structural damage can be visualized on radiographs.

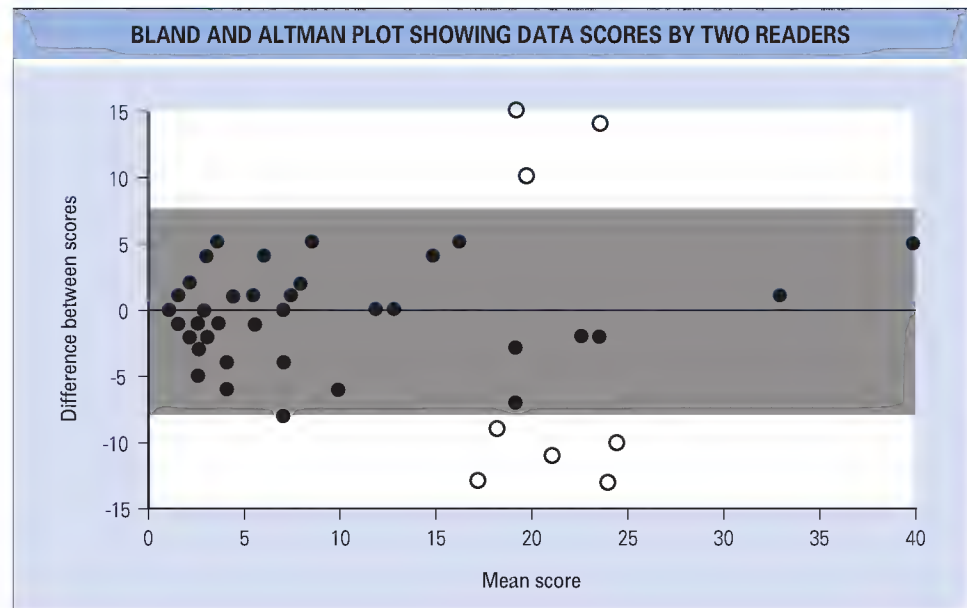
Readers

Because precision of reading is important, it is advised that two readers score all the images independently. The average data from the two readers will then be used for the primary analysis. Ideally, these same two readers score all images, but if not possible, three or four readers can score the images so that a set of two scores is available for each film. Preferably, the readers score a similar number of images and all possible reader combinations are made. Which reader should read which image should already be decided before commencement of the reading. Increasing the number of readers to three or more for all images would further improve the precision but at the cost of feasibility (including time and cost).¹ For pivotal clinical trials the optimal number of readers is two; however, for observational studies or early-phase development scores, one reader could be sufficient. It is also important to use experienced, well-trained readers because the consequent reduction in random error increases the power of a study over the use of untrained readers.

Statistical aspects of reader agreement

An important aspect is assessment of the agreement of the readers. Traditionally, this is done with the intraclass correlation coefficient (ICC), which can be defined as the proportion of all the variance explained by differences between subjects, that is, suggesting a small contribution from observer variation. The Pearson and Spearman correlation coefficients should be avoided because they give only a measure of association, not agreement. Nevertheless, the ICC also clearly has limitations because it is largely influenced by the data set: a data set with great variation in the data yields higher ICCs than does a data set with minor variation, although this is not a reflection of better agreement between the readers. This issue is especially

Fig. 45.1 The Bland and Altman plot can be applied to status scores and to change scores. On the x-axis the mean score of the two readers is depicted and plotted against the difference between the scores of reader 1 and reader 2 on the y-axis. If no variation is present, all data will be on the line $x = 0$ (which indicates that the difference between the readers is 0 for all values). If the mean difference is not equal to 0, one of the readers is systematically scoring higher than the other reader. It is important to check whether the variation between the readers is equal over the entire range of the scores. The limits of agreement do include 95% of the data, and this is a value for the random variation (the gray zone in the figure). This forms the basis for calculation of the smallest detectable difference and smallest detectable change.



pertinent when comparing the agreement of progression scores, which are typically small. Consequently, the ICC might suggest poor agreement whereas it is actually caused by lack of variation in the data. An additional analysis for checking agreement between readers is use of the Bland and Altman plots (in which the difference between the two readers is plotted against their mean), which assess real agreement in the units of the measurement scale.² An example is presented in Figure 45.1. Calculating the 95% limits of agreement provides a value that is also referred to as the smallest detectable difference (SDD), which can be used as a cutoff to determine whether a change beyond measurement error is present. The SDD reflects the situation for testing whether a change in patient A is different from a change in patient B. Mostly, we are interested in the question whether a change in patient A is a real change, in other words, whether there is a change beyond measurement error in this particular patient. For this purpose the smallest detectable change (SDC) should be used,³ which can be derived from the SDD by dividing by the square root of 2. The disadvantage of both the SDD and SDC is that they are frequently relatively high numbers and underestimate real progression because progression judged by clinicians as being clinically relevant (e.g., sufficient to change treatment) is usually below the SDD or SDC. So the best value of SDD and SDC lies in obtaining information for judging the level of agreement of reader pairs, but if used as a cutoff to determine progression, it will most likely underestimate the number of patients with progression.

Grouping of films—reading sessions

Typically, all the images from different time points that will be analyzed together are scored in the same reading session and are offered simultaneously to the reader. For example, a 1-year trial with images at weeks 0, 24, and 52 is offered at the same time to the reader. Although most scoring methods provide absolute scores, the option to compare images at various time points is an important aspect of scoring; in addition, by doing so, differences in imaging technique (e.g., overexposure or underexposure, rotation) can be taken into account. Moreover, change scores are the most important for analysis of treatment effect. A consequence of this is that if for the trial in the example the week 104 film becomes available, rescoring of the earlier time points is required. A rule is that all the data that will be used in one analysis or comparison need to be included in the same reading. It is of major importance to define at the outset which time periods need to be compared to select the correct images for follow-up reading sessions. Especially in the current trial environment with minor progression in many patients, the optimal reading circumstances are of major importance.

Blinding time sequence

The advantage of images is that they can easily be blinded for patient identity and treatment group and rescored at later points in time (e.g., when new images become available). An important aspect is blinding of the time sequence. The sets of images per patient can be offered to the reader with information on which image belongs to baseline and which to follow-up

dates. However, in most trials the dates of the images are also blinded. Scoring in chronologic order can be feasible, such as in observational cohorts in which new annual follow-up images become available. If scoring in a blinded time order, each new radiograph would mean a new scoring of all the images. In the case of scoring with a known time sequence, scoring of new images is performed with the baseline and two previous images presented at the same time as the scores of the previous scoring session.

In clinical trials, scoring with a blinded time sequence is preferred because it avoids bias, although errors such as nonexistent repair of erosions may result. Moreover, most statistical tests require that scoring errors be equally likely to occur in both directions (overscoring and underscoring), which is the case with blinded reading. This is also a prerequisite for the proposed assessment of possible repair in a trial arm. Finally, regulatory agencies in both the United States and Europe require that the order of images be blinded.

Presentation of data

For each trial, information on mean and median values (with appropriate assessment of variation) should be presented because both give additive information. Moreover, graphic representation of all the individual patient data in a so-called cumulative probability (or frequency) plot shows all the information in a comprehensive manner.⁴ In a probability plot the scores per group (usually the change scores over a defined period) are ordered from the lowest to the highest (Fig. 45.2). This provides an opportunity to appreciate the full range, the median, and the corresponding value for every percentile that one might be interested in. The plot can also be used to determine the percentage of patients showing progression above a certain limit. Preferred cutoffs can be applied. This methodology is much more powerful than simply representing patients as being above 0.5 (if the average of two readers is being used), above 0 (if one reader is used), or above the SDC. Moreover, the coherence of the data can be appreciated, and it illustrates the prevalence and influence of outliers well.

Statistical handling of missing data

Missing data are a significant issue in clinical trials, especially with long-term follow-up. This pertains to clinical as well as imaging data. However, how to deal with missing imaging data is fundamentally more challenging. Theoretically, clinical data on follow-up have three options: no change, improvement, or worsening. Structural damage, however, is largely irreversible; consequently, only two options are in fact available: no change or worsening. Moreover, in most trials there is preferential dropout in the comparator arm of the trial (either placebo or the frequently less effective standard treatment). In case of inefficacy, this is usually based on clinical data: a high level of disease activity. By applying the technique of last observation carried forward (LOCF), this high level of disease activity is captured in the analysis of clinical efficacy data. Also, the imputation of a nonresponder status in the clinical analysis provides the correct information that this patient did not respond well to treatment. However, application of the

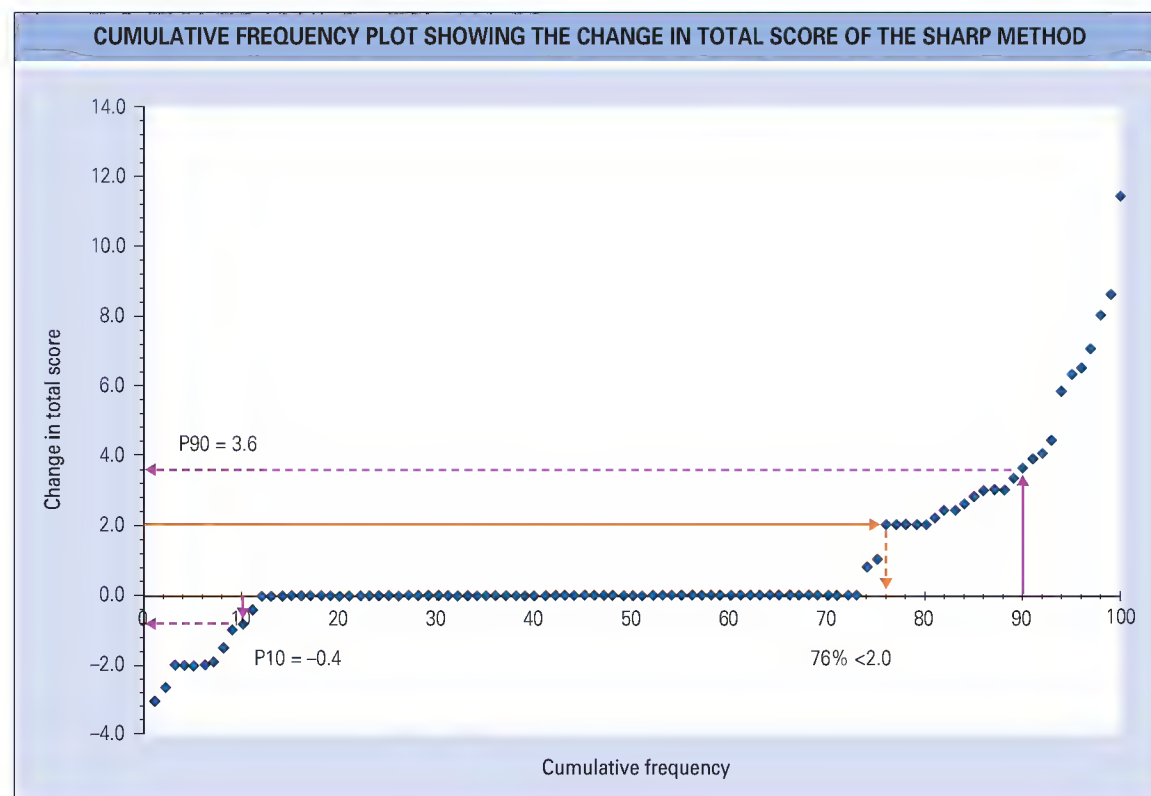


Fig. 45.2 On the y-axis the cumulative frequency plot shows the change in total score of the Sharp method, with the scores of all individual patients being depicted as diamonds. These scores are ordered from the lowest to the highest and are presented on the x-axis as cumulative frequency. If you want to read the 10th percentile, you draw a line starting at 10% cumulative frequency and connect it where it crosses the figure on the y-axis. The corresponding score on the y-axis (−0.4) can be read. Similarly, the 90th percentile corresponds to a change in score of 3.6, and the median is a change of 0. You can also start with a certain change in score (e.g., +2.0) and read the corresponding percentage on the x-axis: 76% of the patients show a change in score of 2.0 or less. The magenta lines indicate scores belonging to percentiles; the orange line indicates the percentage of patients belonging to a certain score.

LOCF technique to imaging data underestimates actual progression because it might be expected that it is more likely that these patients will show worsening than no change. Responder data are not frequently used for imaging, certainly not as a primary endpoint, because this greatly decreases the power of a trial. The most widely used “best approach” is linear extrapolation of the progression. To be able to apply this technique, at least a baseline film and one follow-up film need to be available. Although progression in individual patients is not always linear, it is on a group level and suffices for analysis of structural damage data. With the use of early-escape trial designs, the control group frequently has only a short follow-up before being switched to the open label of the treatment under investigation. With the primary endpoint for imaging being at 24 or 52 weeks and early escape between 12 and 16 weeks, linear extrapolation is an important aspect in analysis of the data. In trials with treatment that suppresses structural progression effectively, progression in the control arms determines the power of the study. Such progression can be detected only in the first 12 to 16 weeks until early escape for patients who choose this option, which might be a very high number as shown in recent trials. It has been demonstrated that radiographs are sufficiently sensitive to detect changes over a 12- to 16-week period. It should be stressed that it is crucial to obtain follow-up radiographs in all patients regardless of premature discontinuation and to limit data imputation as much as possible.

Missing data on individual joints need to be handled within the same joint group. For example, if data on metacarpophalangeal (MCP) joints are missing, these data will be substituted by data from the remaining MCP joints. The imputation is based on progression scores. Most frequently, missing up to 20% to 30% of the joints in a particular joint group is accepted before the entire time point is set as missing.

Statistical analysis

For the primary analysis, the average of two readers is used. The scores of single readers can be applied as sensitivity analyses. Because radiographic progression is typically not normally distributed, nonparametric testing should be applied. The primary endpoint is the change in progression (extrapolated if necessary) based on the average score of two readers. This can be done by several parametric and nonparametric methods, but an

analysis of covariance (ANCOVA) using the ranks of change with factors at baseline that are expected to influence structural progression is frequently performed. The baseline structural damage score is such a factor. Mixed-effect modeling is another way to analyze the data; it allows longitudinal interpretation (development in time) of the data because it uses all time points instead of only one predefined endpoint. Under certain conditions, mixed-effect models provide more statistical power. Both ANCOVA and mixed-effect models can be fit to raw scores, as well as be used after logarithmic transformation.

To confirm the robustness of the data an LOCF analysis can be performed, although it should be realized that statistical significance might be lost.

Minimum duration of trials

It has been demonstrated that effects can already be demonstrated after 6 months and even after 3 to 4 months. Thereafter, it is important that the gain obtained in the first 6 months be maintained over the second 6 months and ultimately over the second year. Currently, structural damage, as assessed on radiographs, is considered the “gold standard.” The challenge with the early-escape design is the length of duration of the control arm. It is being accepted more and more that if the difference obtained during the period with a control arm is sustained over the follow-up period, this is sufficient to fulfill the required longer follow-up period. In practice this means that a significant difference at week 24 (with or without extrapolated data), with maintenance of the difference between the originally randomized trial arms over the next half-year or over the next 18 months (or both), is sufficient for filing. However, this needs to be discussed with the agencies for each trial specifically.

Placebo versus active comparator

True placebo arms with a sufficiently long follow-up to assess structural damage are no longer accepted for ethical reasons. The closest to such assessment is the partial-responder trial design in which patients who still have active disease are randomized to continue receiving the same treatment with placebo added or with the treatment under investigation added. Also

in this situation, only short periods of follow-up are accepted to be ethical, and patients have the opportunity to opt for early escape at a fixed time of follow-up, usually between 12 and 16 weeks. Until now this was sufficient to detect change in the control arm. There is, however, a trend of including patients in trials with less active and less severe disease. Consequently, progression in the control arm is smaller, which necessitates larger trials to maintain the same power. It is thought that alternative trial designs are needed.

Repair

Although most emphasis is on detection of progression of structural damage, over the past decades it has become apparent that repair of damage is also possible. This could be observed in individual joints and patients but also in studies specifically designed to test the concept of repair, as well as on the group level in clinical trials. By definition, there is proof of repair on a group level if the mean change over time, including the 95% confidence interval, is below zero, which indicates that the group had statistically significant improvement. Determining definite repair in an individual joint or patient is more difficult. Based on data obtained in a trial,^{4a} there is circumstantial evidence that repair is a real phenomenon because it is almost exclusively observed in joints without swelling, can be reproduced in independent reading sessions, and is prevalent predominantly in patients treated with tumor necrosis factor blockers.

RHEUMATOID ARTHRITIS

Conventional radiography *Films of the hands and feet*

Structural damage, especially erosions, is frequently present in the joints of both the hands and feet. Moreover, these are the sites that structural damage can easily be detected because of the size of the joints. Importantly, these sites show the first erosions, and erosions are even more frequent in the feet than in the hands. The wrist is the joint most predisposed to early JSN. Therefore it is recommended that films of the hands and feet always be taken. By doing so a large number of joints are available for evaluation. It is not necessary to routinely take films of the large joints for assessment of the course of disease because it has been demonstrated that damage in the small joints is representative of damage in the large joints. Important in this respect is that patients with normal radiographic findings in the hands and feet do not have structural damage in any of the large joints.⁵

For scoring it is sufficient to take films of the hands in the posteroanterior view and the feet in the anteroposterior view. It is of utmost importance that positioning and technical aspects be standardized to ensure comparable images at follow-up. Additional views of the hands, such as the Nørgaard or Brewerton (ball catcher's) views, are not recommended because it is hard to standardize and obtain comparable images over time.

Scoring methods

Information from radiographs can be used as an outcome in clinical trials only if it is quantified. Several scoring methods discussed later in this chapter are available for this purpose. Selection of the most appropriate scoring method is largely dependent on the setting in which it will be applied. For example, in clinical practice and large cohort studies, feasibility is of major importance, whereas in clinical trials, sensitivity to change drives selection of a method.

The methods that have been used most frequently in recent research and clinical practice are described here. For a historical overview of all published scoring methods, readers are referred to the literature.⁶ Below, the methods of applying a global score, mainly based on the Larsen method, are presented first, followed by presentation of the more detailed scoring methods. An overview of the various characteristics of the scoring methods, such as the joints and features included, the range per joint, and the total score, is presented in Table 45.1.^{7,8}

Because erosions and JSN are reflections of different disease processes, it is advantageous to score these features independently, which is done in the detailed scoring methods. This opens the possibility of assessing a differential effect of specific treatment on bone versus cartilage.

Global assessment per joint

Larsen score

The Larsen score applies a grade from 0 to 5 to individual joints.⁹ This method is the only one that can be applied to both large and small joints,

and a reference atlas with grades for the various joints is available. The scoring is a combination of mainly erosions and JSN, and it results in a global grade. The original Larsen scoring method included soft tissue swelling and juxtaarticular osteoporosis in grade 1. Only from grade 2 onward are definite structural abnormalities such as erosions present. Grade 5 represents mutilating abnormality. Several modifications of the scoring system have been published by the authors, with the most important modification being that for use in longitudinal studies. Most studies include only the joints of the hands, wrists, and feet. The information in Table 45.1 is based on the original method applied to the hands, wrists, and feet. Originally, the wrist was evaluated as a single joint. In total, 32 joints are scored, which leads to a scoring range for the hands and feet of 0 to 160. The modification published by Larsen and associates in 1995 changed both the sites to be evaluated and the grading. Most striking is the deletion of soft tissue swelling and osteoporosis for grade 1.¹⁰ Now, erosions less than 1 mm and slight JSN are graded as 1. The number of areas in both the hands and feet has been changed. The interphalangeal (IP) and MCP joints of the thumb are no longer included, nor are the IP and metatarsophalangeal (MTP) joints of the big toe. In this modification the wrist is scored in quadrants. Therefore the number of joints assessed remains 32.

Scott modification of the Larsen method

The modification by Scott and coworkers is frequently used when the "Larsen" method is applied.¹¹ These researchers redefined the grading and applied it to the same 32 joints as in the original Larsen method. Moreover, the wrist is scored as a single joint but is weighted by a factor of 5 to obtain the total score. This brings the range for hands and feet from 0 to 200.

Ratingen score

In this modification of the Larsen score, grading is based entirely on the surface area of the joints destroyed by erosions.¹² This is graded from 0 to 5 (grade 1, <20%; grade 2, 21% to 40%; up to grade 5, >80% destroyed). In total, 38 joints of the hands are scored, which results in a range of 0 to 190.

Detailed scoring methods

Sharp method

The Sharp method is the first published method that described a detailed scoring system for erosions and JSN separately for joints in the hands and wrists. The Sharp method that is used at present is in fact the modification described in 1985.¹³ The number of joints scored was reduced from 27 originally for both erosions and JSN to 17 for erosions and 18 for JSN per hand.

Moreover, the method was developed and validated for scoring the joints of the hands, but at present the same methodology is also applied to the joints of the feet. Erosions are scored from 0 to 5 per joint and are counted when discrete, and surface erosions are scored according to the surface area involved. JSN is scored on a scale of 0 to 4: focal narrowing (score of 1), joint space loss of less than 50% (score of 2), joint space loss of greater than 50% (score of 3), and complete joint space loss or ankylosis (score of 4). Subluxation or luxation is not included in the score. The erosion score and the JSN score can be used separately but are usually summed to obtain a total score (range for hands: 0 to 314).

Genant modification of the Sharp method

A modification of the Sharp method was described by Genant in which the scale for progression was extended from a 6-point scale to an 8-point scale with 0.5-point increments from 0 to 3+ for erosions and from a 5-point scale to a 9-point scale with 0.5-point increments from 0 to 4 for JSN.¹⁴ This score is applied to 14 joints of each hand and wrist for erosions and to 13 joints for JSN. It results in a total score range of 0 to 202 for the hands. Frequently, this is normalized to a 200-point scale. If the feet are scored, this is applied to the five MTP joints and the IP joint of the first toe. The maximum score for the hands and feet is 292, frequently normalized to 290.

van der Heijde modification of the Sharp method

The main modification by van der Heijde was the addition of six joints per foot (five MTP joints and the IP joint of the first toe) to the scoring system. Moreover, two sites for erosions and two sites for JSN were deleted from the scoring areas outlined in the Sharp method in 1985, which leaves 16 sites for erosions and 15 for JSN per hand.¹⁵ Scoring of erosions in the hands remained the same, with a range of 0 to 5 per joint. However, for scoring of erosions in the feet the scoring range was expanded to 10 per joint, with a maximum of 5 for the metatarsal and phalangeal sites of the joint. Another major difference is that subluxation and luxation (malalignment) are integrated into the grading of JSN. JSN is scored on a scale of 0 to 4, with the same grading as described for the Sharp method, but in this modification a

TABLE 45.1
Comparison of radiographic scoring methods for rheumatoid arthritis

	Larsen method	Scott modification of Larsen method	Ratingen method	Sharp method	Genant modification of Sharp method	van der Heijde modification of Sharp method	Simple erosion narrowing score
Films							
Hands	X	X	X	X	X	X	X
Feet	X	X	—	—	X	X	X
Large joints	X*	—	—	—	—	—	—
Joints included							
PIP/IP	X	X	X	X	X	X	X
MCP	X	X	X	X	X	X	X
Wrist	X	X	X	X	X	X	X
MTP	X	X	—	—	X	X	X
IP1	X	X	—	—	X	X	X
Features scored							
Erosions	—	—	X	X	X	X	X
JSN	—	—	—	X	X	X	X
Malalignment	—	—	—	—	—	X	X
Global	X	X	—	—	—	—	—
No. of joints per hand/foot scored							
Erosions	—	—	19	17	14	22	22
JSN	—	—	—	18	13	21	21
Malalignment	—	—	—	—	—	†	†
Global	16	16	—	—	—	—	—
Range per joint							
Erosions	—	—	0-5	0-5	0-3.5 [‡]	0-5/0-10 [§]	0-1
JSN	—	—	—	0-4	0-4 [‡]	0-4	0-1
Malalignment	—	—	—	—	—	†	†
Global	0-5	0-5	—	—	—	—	—
Total	0-160	0-200	0-190	0-314	0-292	0-448	0-86

*Large joints are assessed separately; the remaining information in this table is based on the hands and feet.

†Combined with the JSN score.

‡Scored in 0.5-point increments.

§Erosions are scored 0 to 5 for hands and 0 to 10 for feet.

IP, interphalangeal; JSN, joint space narrowing; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

Reproduced with permission from van der Heijde D. Quantification of radiological damage in inflammatory arthritis: rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. *Best Pract Res Clin Rheumatol* 2004;18:847-60.

score of 3 can also be applied in the case of subluxation of a joint and a score of 4 in the case of complete luxation. These features are scored mostly in the MCP and MTP joints. The range for the total score is 0 to 448. An example of scoring the MCP joints is presented in Figure 45.3.

Figure 45.4 shows a comparison of the sites in the hands included in the Sharp method, the van der Heijde modification of the Sharp method, and the Genant modification of the Sharp method. The major differences are in sites in the wrist, both for erosions and for JSN. Table 45.2 shows weighting of the erosions and JSN scores in the three scoring methods. The Genant scores apply a normalization, and thereafter the weight for erosions and JSN is equal. The van der Heijde modification has the largest weight on erosions, whereas for the Sharp method the weight is intermediate.

Simple Erosion Narrowing Score

This method is based on the joints included in the van der Heijde modification of the Sharp method for the hands and feet. Instead of scoring the joints for erosions and JSN, the number of eroded joints and the number of narrowed joints are simply counted.¹⁶ A score of 1 is applied if a site is eroded and also per narrowed site. In total, 15 joints per hand are scored for erosions and 16 for JSN and 6 joints per foot for both erosions and JSN, which results in a scoring range of 0 to 86.

Magnetic resonance imaging and ultrasonography

Conventional radiography, despite being the most widely used imaging method for assessing structural damage in RA, has limitations. It does not



Fig. 45.3 Scores according to the van der Heijde modification of the Sharp method for grading erosions and joint space narrowing in the metacarpophalangeal and interproximal phalangeal joints of the left hand. The arrows indicate the location of an erosion; the number indicates the score of the erosion. The sum of the erosions per joint is depicted as "E." The score for joint space narrowing per joint is presented as "N." The interproximal joint is not scored for joint space narrowing.

Fig. 45.4 Sites in the hands included in the Sharp method (a), the van der Heijde modification of the Sharp method (b), and the Genant modification of the Sharp method (c). The green areas indicate sites for scoring joint space narrowing and the red areas indicate sites for scoring erosions.

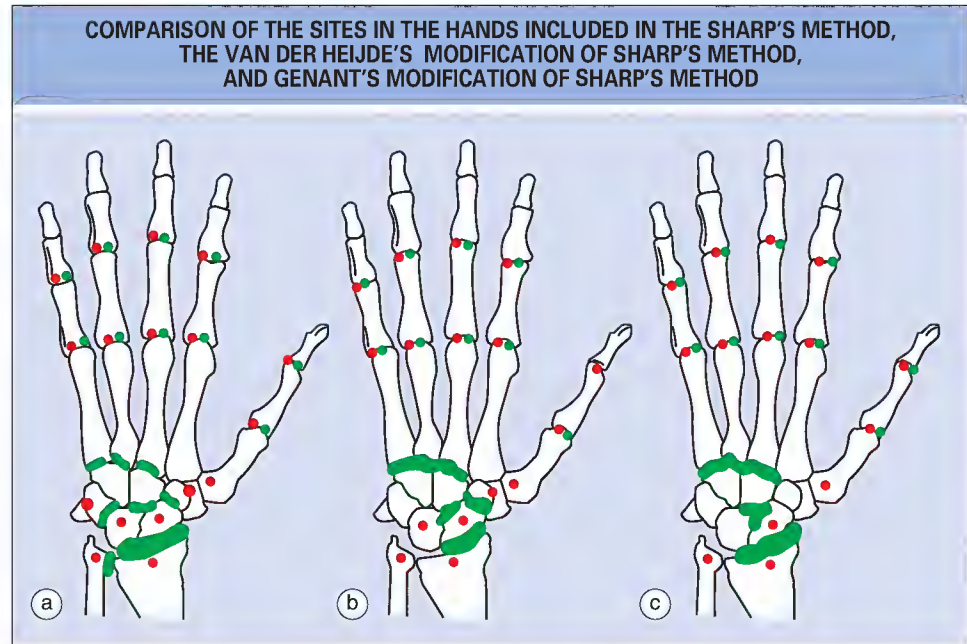


TABLE 45.2

Comparison of the weight of erosions and joint space narrowing in the Sharp method, van der Heijde modification of the Sharp method, and Genant modification of the Sharp method

	Hand erosions	Hand JSN	Hand total score	Hand and foot erosions	Hand and foot JSN	Hand and foot total score
Sharp method	170	144	314	230	192	422
van der Heijde modification	160	120	280	280	168	448
Genant modification	98→100*	104→100	200	140→145	152→145	290

*The scores with an arrow have been normalized to the indicated number.
JSN, joint space narrowing.

visualize the earliest stages of bone erosion. In contrast, MRI and ultrasonography allow direct visualization of the early destructive joint changes in RA. For ultrasonography, no widely accepted scoring methods are available for use in clinical trials, although validation of several methods is under way.¹⁷ For MRI, the RAMRIS (RA MRI scoring system) is the validated scoring method of choice. It is a semiquantitative assessment of synovitis, bone erosions, and bone edema in the hands and wrists.¹⁸ A minimum set of MRI sequences (Box 45.1), as well as a consensus MRI definition of important joint pathologic processes (Box 45.2), were also suggested. An atlas with reference images for scoring is available. The main features of the RAMRIS are presented in Box 45.3.

Magnetic resonance imaging sum scores

Sum scores for synovitis, erosion, and edema can be calculated by summation of the individual joint scores, as a total sum, or separately in the evaluated wrist and second to fifth MCP joints. For synovitis, the possible range of the sum scores of the unilateral second to fifth MCP joints, wrist joint, and both are 0 to 12, 0 to 9, and 0 to 21, respectively. Corresponding values for bone erosion are 0 to 80, 0 to 150, and 0 to 230, whereas for bone edema they are 0 to 24, 0 to 45, and 0 to 69.

PSORITIC ARTHRITIS

Conventional radiography

Typical lesions and site of lesions

Although PsA has similarities with RA, there are also major differences in the type and site of lesions, as well as in the joints involved. Whereas RA is characterized by mainly osteodestructive lesions, PsA has both osteodestructive and osteoproliferative manifestations that may even coexist not only in the same patient but even in the same joint. Characteristic radiographic features of PsA include joint erosions, JSN, and bony proliferation, including periarticular and shaft periostitis, osteolysis, ankylosis, spur

BOX 45.1 MINIMUM SET OF BASIC MAGNETIC RESONANCE IMAGING SEQUENCES

- Imaging in two planes* with T1-weighted images before and after intravenous administration of gadolinium[†]
- A T2-weighted fat-saturated sequence or, if this is not available, a short tau inversion recovery (STIR) sequence

*Imaging in two planes can be achieved by obtaining a two-dimensional sequence in two planes or a three-dimensional sequence with isometric voxels in one plane to allow reconstruction in other planes.

[†]Intravenous injection of gadolinium is probably not essential if destructive changes alone (bone erosions) are considered important.

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formation, and spondylitis. Abnormalities are seen in the phalangeal tufts and at sites of attachment of tendons and ligaments of the bone. Although the erosive changes in early PsA are marginal, as in RA, they become irregular and ill defined with progression of disease because of periosteal bone formation adjacent to the erosions. In severe cases, erosive changes may progress to the development of a “pencil-in-cup” deformity or gross osteolysis. These features are typical of arthritis mutilans.

Joint involvement in PsA is often asymmetric and may be oligoarticular. Asymmetric erosions may be visible radiographically in the carpus and in the MCP and proximal (PIP) and distal (DIP) IP joints of the hands, but the DIP joints are often the first to be affected. The hands tend to be involved much more frequently than the feet, with a ratio of nearly 2:1. Erosive changes and bone proliferation in the feet usually involve the IP and MTP joints; the IP joint of the first toe is most often affected. Radiographs of the

BOX 45.2 DEFINITIONS OF IMPORTANT RHEUMATOID ARTHRITIS JOINT PATHOLOGIC PROCESSES ON MAGNETIC RESONANCE IMAGING

Synovitis: An area in the synovial compartment that shows above normal gadolinium enhancement of a thickness greater than the width of normal synovium.

- Enhancement (increase in signal intensity) is judged by comparison of T1-weighted images obtained before and after the intravenous administration of gadolinium.

MRI bone erosion: A sharply margined bone lesion with correct juxtaarticular localization and typical signal characteristics that is visible in two planes with a cortical break seen in at least one plane.

- T1-weighted images show loss of the normal low signal intensity of cortical bone and loss of the normal high signal intensity of trabecular bone. Quick gadolinium enhancement suggests the presence of active, hypervascularized pannus tissue in the erosion.
- Other focal bone lesions, including metastases, must obviously be considered but are generally distinguishable by associated imaging and clinical findings.

MRI bone edema: A lesion within trabecular bone with ill-defined margins and signal characteristics consistent with increased water content.

- This may occur alone or surrounding an erosion or other bone abnormalities.
- Signal intensity is high on T2-weighted fat-saturated and STIR images and low on T1-weighted images.

MRI, magnetic resonance imaging; STIR, short tau inversion recovery.

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BOX 45.3 RAMRIS SCORING SYSTEM

- **Bone erosions:** Each bone (wrists: carpal bones, distal radius, distal ulna, metacarpal bases; MCP joints: metacarpal heads, phalangeal bases) is scored separately. The scale is 0 to 10 and is based on the proportion of eroded bone in comparison to "assessed bone volume" as judged on all available images: 0 = no erosion, 1 = 1% to 10% of bone eroded, 2 = 11% to 20%, etc. For long bones, "assessed bone volume" is from the articular surface (or its best estimated position if absent) to a depth of 1 cm, whereas in carpal bones it is the whole bone.
- **Bone edema:** Each bone is scored separately (as for erosions). The scale is 0 to 3 and is based on the proportion of bone with edema: 0 = no edema, 1 = 1% to 33% of bone edematous, 2 = 34% to 66%, and 3 = 67% to 100%.
- **Synovitis:** Synovitis is assessed in three wrist regions—(1) the distal radioulnar joint, (2) the radiocarpal joint, and (3) the intercarpal and carpometacarpal phalangeal joints—and in each MCP joint. The first carpometacarpal phalangeal joint and the first MCP joint are not scored. The scale is 0 to 3. A score of 0 is normal, whereas scores of 1 to 3 (mild, moderate, severe) designate thirds of the presumed maximum volume of enhancing tissue in the synovial compartment.

MCP, metacarpophalangeal.

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hand are most important in the follow-up of patients, but the addition of films of the feet makes the picture more complete.

Scoring methods

The development and validation of scoring methods for PsA are less well worked out than for RA. All the methods used presently find their basis in scoring methods for RA. There are two global scoring methods and two detailed scoring methods, which are summarized in Table 45.3 and described below.

Global assessment per joint

Modified Steinbrocker score

This method was developed in the PsA clinic at the University of Toronto.^{19,20} Each joint is scored on a scale of 0 to 4: 0 = normal; 1 = juxtaarticular

osteopenia or soft tissue swelling; 2 = erosion; 3 = erosion and JSN; and 4 = total joint destruction, either lysis or ankylosis. This score is applied to 14 joints in each hand and 6 joints in each foot. The range of the score is 0 to 160.

Psoriatic arthritis Ratingen score

This method includes 40 joints in the hands and feet.^{20,21} All joints are scored separately for destruction and proliferation. The destruction score is based on the amount of joint surface destruction on a scale of 0 to 5: 0 = normal, 1 = one or more definite erosions with an interruption of the cortical plate of greater than 1 mm but destruction of less than 10% of the total joint surface, 2 = destruction of 11% to 25%, 3 = destruction of 26% to 50%, 4 = destruction of 51% to 75%, and 5 = destruction of greater than 75% of the joint surface. The proliferation score considers any kind of bony proliferation typical of PsA on a scale of 0 to 4: 0 = normal; 1 = bony proliferation of 1 to 2 mm measured from the original bone surface or, if the margins of the proliferation cannot be distinguished from the original bone surface, clearly identifiable bone growth not exceeding 25% of the original diameter of the bone; 2 = bony proliferation of 2 to 3 mm or bone growth between 25% and 50%; 3 = bony proliferation greater than 3 mm or bone growth greater than 50%; and 4 = bony ankylosis. The destruction score with a range of 0 to 200 and the proliferation score with a range of 0 to 160 are summed to give the total score (range of 0 to 360).

Detailed scoring methods

Psoriatic arthritis scoring method based on the Sharp scoring method for rheumatoid arthritis

The erosion scale used for RA has a range of 5 per joint. Scores are applied as 0 = no erosion, 1 = one discrete erosion or involvement of less than 21% of the joint area by erosion, 2 = two discrete erosions or involvement of 21% to 40% of the joint, 3 = three discrete erosions or involvement of 41% to 60% of the joint, 4 = four discrete erosions or involvement of 61% to 80% of the joint, and 5 = extensive destruction involving more than 80%.^{20,22} The erosion scale was expanded with the scores 6 and 7 to accommodate the more extensive bone destruction seen in many cases of PsA, such as gross osteolysis or a "pencil-in-cup" lesion. However, scores of 6 and 7 are not added to obtain the total erosion score; instead, these features are kept separately. The erosion score is applied to 21 joints in each hand and to 6 joints in each foot, which results in a range of 0 to 210 for the hands and 0 to 60 for the feet. Scoring of JSN is on a scale of 0 to 4 as used for RA. The JSN scores are 0 = normal joint; 1 = asymmetric or minimal narrowing; 2 = definite narrowing with loss of up to 50% of the normal space; 3 = definite narrowing with loss of 51% to 99% of the normal space; and 4 = absence of a joint space, presumptive evidence of ankylosis. A score of 5 is added in the case of widening, which is automatically scored when gross osteolysis is present. Again, the score for widening is not included in the total narrowing score but is analyzed as a separate feature. The JSN score is applied to 20 joints in each hand and 5 joints in each foot, which results a range of 0 to 160 for the hands and 0 to 40 for the feet.

Sharp-van der Heijde modified scoring method for psoriatic arthritis

A similar scoring system as used for RA is applied to PsA.²⁰ The same joints are scored for erosions and JSN, with the addition of the eight DIP joints for erosions and the eight DIP joints and two IP joints of the thumb for JSN. Again, the maximum score for erosions is 5 in the joints of the hands and 10 in the joints of the feet. Scores for erosions are applied as follows: 0 = no erosion, 1 = discrete erosion, 2 = large erosion not passing the midline, and 3 = large erosion passing the midline; a combination of these scores may lead to the maximum of 5 per entire joint in the hands and 5 at each site of the joint (a maximum of 10 for the entire joint) in the feet. The so-called JSN score is based on the following features: 0 = normal; 1 = asymmetric or minimal narrowing up to a maximum of 25%; 2 = definite narrowing with loss of up to 50% of the normal space; 3 = definite narrowing with loss of 50% to 99% of the normal space or subluxation; and 4 = absence of a joint space, presumptive evidence of ankylosis or complete luxation. Gross osteolysis and "pencil-in-cup" lesions are scored separately. In the final summary score, joints with one of these abnormalities receive the maximum score assigned for both erosions and for JSN. The total maximum score for erosions is 200 for the hands and 120 for the feet; the total maximum score for JSN is 160 for the hands and 48 for the feet. The total maximum erosion score is 360, the total maximum JSN score is 168, and the total maximum score is 528.

Magnetic resonance imaging and ultrasonography

Both MRI and ultrasonography have not been widely applied in PsA, although similar advantages as described for RA and AS can be expected.

TABLE 45.3
Comparison of radiographic scoring methods for psoriatic arthritis

	Modified Steinbrocker method	Ratingen method	Sharp method	van der Heijde modification of Sharp method
Films				
Hands	X	X	X	X
Feet	—	X	X	X
Large joints	—	—	—	—
Joints included				
DIP	X	X	X	X
PIP/IP	X	X	X	X
MCP	X	X	X	X
Wrist	X	X	X	X
MTP	—	X	X	X
IP1	—	X	X	X
Features scored				
Erosions	—	X	X	X
JSN	—	—	X	X
Malalignment	—	—	—	X
Proliferation	—	X	—	—
Global	X	—	—	—
No. of joints per hand/foot scored				
Erosions	—	40	27	26
JSN	—	—	25	26
Malalignment	—	—	—	*
Proliferation	20	40	—	—
Global	—	—	—	—
Range				
Per joint for erosions	—	0-5	0-5	0-5/0-10 [†]
Per joint JSN	—	—	0-4	0-4
Per joint malalignment	—	—	—	*
Per joint proliferation	—	0-4	—	—
Per joint global	0-4	—	—	—
Total	0-160	0-360	0-470	0-528

*Combined with the JSN score.

[†]Erosions are scored 0 to 5 for hands and 0 to 10 for feet.

IP, interphalangeal; JSN, joint space narrowing; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

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No generally accepted or validated methods for assessment of PsA activity or damage exist. Recently, an OMERACT PsA scoring system (PsAMRIS) has been developed for use in hands with PsA, including discussions on appropriate MRI sequences and consensus definitions of important pathologic processes.²³ The scoring system needs further testing and validation in longitudinal studies.

ANKYLOSING SPONDYLITIS

Conventional radiography

Scoring methods

Three methods have specifically been designed for assessment of the structural damage in AS. An overview of the various characteristics of the scoring methods is presented in Table 45.4. All the methods are suitable to assess damage in the spine. In addition, scoring methods for the sacroiliac joints exist, as well as one specific method for assessment of the hips in AS.

Global assessment of the spine

Bath Ankylosing Spondylitis Radiological Index

The Bath Ankylosing Spondylitis Radiological Index for the spine (BASRI-spine) has three components: the lumbar spine, the cervical spine, and the

sacroiliac joints.²⁴ To assess the lumbar spine, lateral and anteroposterior views are used. The score for the lumbar spine, from the lower border of T12 to the upper border of S1, is a composite score of both views that takes all the affected levels into account in deriving the score. The cervical spine was defined as extending from the lower border of C1 to the upper border of C7. A global score ranging from 0 to 4 (normal, suspicious, mild, moderate, and severe) is applied to both the lumbar and cervical components. The grades are summarized in Table 45.5. Squaring, sclerosis, erosions, syndesmophytes, and fusion are the features included. Syndesmophytes and fusion are the most important features driving the scoring method. The sacroiliac joints are scored according to the four grades of the modified New York criteria. The BASRI-spine is the sum of the mean scores of the right and left sacroiliac joints (in one decimal) plus the score of the lumbar spine and the score of the cervical spine. The range for the BASRI-spine is 2 to 12 (because patients with AS have sacroiliitis by definition, the minimum score is 2). A similar grading system has been developed for the hips: the BASRI-hip. The sum of the BASRI-spine and BASRI-hip is called the BASRI-total, which has a range of 2 to 16.

Detailed assessment of the spine

Stoke Ankylosing Spondylitis Spine Score

The Stoke Ankylosing Spondylitis Spine Score (SASSS) is a detailed scoring system for the anterior and posterior sites of the lumbar spine and includes

TABLE 45.4
Comparison of radiographic scoring methods for ankylosing spondylitis

	BASRI	SASSS	Modified SASSS
Films			
Anteroposterior pelvis	X	—	—
Lateral cervical spine	X	—	X
Lateral lumbar spine	X	X	X
Anteroposterior lumbar spine	X	—	—
Joints/vertebrae included			
Sacroiliac	X	—	—
Hip	X	—	—
Cervical spine	X	—	X
Lumbar spine	X	X	X
Features scored			
Erosions	—	X*	X*
Squaring	—	X*	X*
Sclerosis	—	X*	X*
Syndesmophyte	—	X	X
Global	X	—	—
No. of sites per film scored			
Erosions	—	6* [†]	12* [†]
Squaring	—	6*	12*
Sclerosis	—	6*	12*
Syndesmophyte	—	6	12
Global	3-4 [§]	—	—
Range			
Per vertebra for erosions	—	0-1	0-1
Per vertebra squaring	—	0-1	0-1
Per vertebra for sclerosis	—	0-1	0-1
Per vertebra syndesmophyte	—	2-3	2-3
Per joint/vertebra global	0-4	—	—
Total	2-12/16	0-72	0-72

*The maximum score per corner is 1; either erosion, sclerosis, or squaring can be scored.

[†]Four corners of six vertebrae are scored.

[‡]The two anterior corners of 12 vertebrae are scored.

[§]Without the hips, three sites (cervical and lumbar spine and sacroiliac joints) are scored; with the hips, four sites are scored.

^{||}Without the hips the range is up to 12; with the hips the range is up to 16.

BASRI, Bath Ankylosing Spondylitis Radiological Index; SASSS, Stoke Ankylosing Spondylitis Spine Score.

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the lower border of the 12th thoracic vertebra, all five lumbar vertebrae, and the upper border of the sacrum on a lateral view.²⁵ All four corners of each vertebra are examined and scored 1 if one or more of erosion, sclerosis, or squaring is present; scored 2 for a syndesmophyte; and scored 3 for total bony bridging; the maximum possible score is 72.

Modified Stoke Ankylosing Spondylitis Spine Score

This method is a modification of the SASSS in which the anterior site of the lumbar and cervical spine is scored on a lateral view.²⁶ The anterior site of the same vertebrae of the lumbar spine as described for the SASSS is scored, and the anterior site of the cervical spine from the lower border of the second cervical vertebra up to the upper border of the first thoracic vertebra is scored. Scoring of features is identical to that for the SASSS. The range is also 0 to 72. The modified SASSS has been selected as the preferred method for assessing structural damage in the spine by the Assessment in SpondyloArthritis international Society (ASAS) and the Outcome Measures in Rheumatology (OMERACT) based on favorable reproducibility and sensitivity to change in comparison to the BASRI and SASSS.^{27,28} An example of scoring the cervical spine is presented in Figure 45.5.

TABLE 45.5
BASRI grading of the spine in patients with ankylosing spondylitis*

Score	Grade	Description
0	Normal	No change
1	Suspicious	No definitive change
2	Mild	Any number of erosions, squaring, or sclerosis with or without syndesmophytes in ≤ 2 vertebrae
3	Moderate	Syndesmophytes on ≥ 3 vertebrae, with or without fusion involving 2 vertebrae
4	Severe	Fusion involving ≥ 3 vertebrae

*The scores are applied to the lateral cervical spine and to the lateral and anteroposterior lumbar spine combined. The scores for the sacroiliac joints are added to obtain the BASRI total score (range, 2 to 12).

BASRI, Bath Ankylosing Spondylitis Radiological Index.



Fig. 45.5 Scores according to the modified Stoke Ankylosing Spondylitis Spine Score of the cervical spine. The numbers are related to each corner at the anterior site of each vertebral body starting at the lower border of C2 to the upper border of T1. The vertebral body of C7 is indicated.

Magnetic resonance imaging and ultrasonography

MRI is a very important imaging modality for AS because of its ability to visualize inflammatory changes in bone and soft tissue. It is the most sensitive modality for imaging changes in the spine and sacroiliac joint. AS may also involve peripheral arthritis and enthesitis, which can also be visualized with MRI. Typical AS lesions of the spine that can be visualized with MRI include spondylitis, spondylodiskitis, and arthritis of the apophyseal, costovertebral, and costotransverse joints. Findings indicating active disease in the sacroiliac joints (sacroiliitis) include juxtaarticular bone marrow edema, capsulitis, and enhancement of the joint space after the administration of contrast medium, whereas visible chronic changes include bone erosions, sclerosis, periarticular accumulation of fatty tissue, transarticular bone bridges, and ankylosis. Enthesitis is also common and may affect the inter-spinal and supraspinal ligaments of the vertebral spine and the interosseous ligaments in the retroarticular space of the sacroiliac joints.

The majority of MRI studies of the sacroiliac joint have used only one imaging plane (semicoronal, i.e., parallel to the axis of the sacral bone). To be maximally sensitive for changes in the ligamentous portion of the sacroiliac joints, imaging in two perpendicular planes is required. This is particularly important when MRI is used for diagnostic purposes and probably less so when used as an outcome measure in trials. Similarly, the majority of MRI studies of spines with AS involve only sagittal images, which are not

optimal for visualizing changes in the apophyseal and costovertebral joints. The importance of such changes remains to be determined.

It is generally agreed that adequate MRI of the spine in AS, as for the sacroiliac joints, must include at least a T1-weighted sequence without fat saturation and a short tau inversion recovery (STIR) sequence in one plane. To what extent further sequences, including contrast-enhanced sequences or more planes, are needed is debated and depends on the goal of the examination.

Ultrasonography is not used for determination of outcome in clinical trials of AS.

Scoring methods

Several scoring systems for assessment of disease activity in the sacroiliac joints and spine have been proposed. They have been tested against each other by the OMERACT-ASAS MRI in AS group. They are described next, followed by a description of the few systems available for assessment of chronic damage.

Activity—spine

Three different scoring systems have been developed and validated: the Ankylosing Spondylitis spine Magnetic Resonance Imaging—activity (ASSpMRI-a) score, in which activity is graded from 0 to 6 per vertebral unit in 23 units²⁹; the Berlin modification of the ASSpiMRI-a score, in which activity is graded 0 to 3 per vertebral unit in the same 23 units³⁰; and the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system, in which only the 6 vertebral units considered by the reader to be

the most abnormal are scored, with additional points given for “depth” and high “intensity” of the lesion (Table 45.6).²⁹⁻³² In an OMERACT-ASAS multireader exercise, the feasibility, reliability, sensitivity to change, and discriminatory capacity of all three scoring systems in patients with AS were evaluated. The SPARCC method had the highest sensitivity to change, as judged by the Guyatt effect size, and the highest reliability, as judged by the interreader ICC, but the Berlin modification had the highest reliability if judged by the SDC.³³ All these methods perform well, and none were selected as a preferred method.³⁴

Activity—sacroiliac joints

Three main scoring approaches based on either global scores per quadrant or individual scores in consecutive semicoronal images through the joint have been proposed (Table 45.7).³⁵⁻³⁷ The presence and extent of bone marrow edema in the cartilaginous portion of the joint are the primary MRI features that are scored, although one method also scores inflammation in the joint space and the ligamentous portion of the joint.³⁵⁻³⁷ In an OMERACT-ASAS multireader exercise, agreement between readers and sensitivity to change were compared and found to be somewhat better for the most detailed scoring method (the SPARCC method).³⁸

Damage—spine and sacroiliac joints

The only method proposed for scoring the spine in AS is the Ankylosing Spondylitis spine Magnetic Resonance Imaging—chronicity (ASSpMRI-c) score, which grades chronic changes (sclerosis, squaring, syndesmophytes, and fusion) from 0 to 6 per vertebral unit in 23 units (see Table 45.6).³²

TABLE 45.6
Magnetic resonance imaging scoring methods for assessment of the spine in ankylosing spondylitis

	Activity			Damage
	SPARCC ³¹	ASSpMRI-a ²⁹	Berlin ³⁰	ASSpMRI-c ³²
Images	Sag STIR	Sag post-Gd T1W FS + sag STIR	Sag post-Gd T1W FS + sag STIR	Sag T1W
Area	6 most affected DVUs	All 23 DVUs	All 23 DVUs	All 23 DVUs
Features	Bone marrow edema	Bone marrow edema/enhancement and bone erosion	Bone marrow edema/enhancement	Sclerosis, squaring, syndesmophytes, and bridging/fusion
Grades	0-1 per DVU quadrant + 1 for depth ≥ 1 cm and 1 for high intensity of lesion	0-6 per DVU	0-3 per DVU	0-6 per DVU
Total score range	0-108	0-138	0-69	0-138

ASSpMRI-a, Ankylosing Spondylitis spine Magnetic Resonance Imaging—activity; ASSpiMRI-c, Ankylosing Spondylitis spine Magnetic Resonance Imaging—chronicity. DVU, diskovertebral unit defined as the region between two virtual lines through the middle of each vertebra, including the intervertebral disk and the adjacent vertebral endplates; FS, fat saturated; Gd, intravenous injection of gadolinium-containing contrast agent; sag, sagittal; SPARCC, Spondyloarthritis Research Consortium of Canada; STIR, short tau inversion recovery; T1W, T1 weighted.

TABLE 45.7
Magnetic resonance imaging scoring methods for assessment of the sacroiliac joints in ankylosing spondylitis

	Activity			Damage	
	SPARCC ³⁵	Puhakka—activity ³⁶	Hermann—activity ³⁷	Puhakka—damage ³⁶	Hermann—damage ³⁷
Images	Semicoronal STIR	Pre- and post-Gd semicoronal and semiaxial T1W FS; semicoronal STIR	Semicoronal pre- and post-Gd T1W FS and STIR	Pre-Gd semicoronal and semiaxial T1W and T1W FS	Semicoronal pre- and post-Gd T1W and T1W FS
Area	SI joints, 6 consecutive semicoronal slices	SI joints in 2 planes	SI joints in semicoronal plane	SI joints in 2 planes	SI joints in semicoronal plane
Features	Bone marrow edema	Bone marrow edema, bone marrow enhancement, joint space enhancement	Bone marrow edema, bone marrow enhancement	Erosion, sclerosis, joint space width	Erosion, sclerosis, joint space width, bone bridging/ankylosis
Grades	In each slice: 0-1 per quadrant + 1 for depth ≥ 1 cm and 1 for high intensity	Marrow edema: 0-3 per quadrant; marrow enhancement: 0-3 per quadrant; joint space enhancement: 0-3 per joint	Global: 0-3 per quadrant	Erosion: 0-3 per quadrant; sclerosis: 0-3 per quadrant; joint space: 0-3 per joint	Global: 0-4 per joint
Total score range	0-108	0-60	0-24	0-60	0-8

FS, fat saturated; Gd, intravenous injection of gadolinium-containing contrast agent; sag, sagittal; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada; STIR, short tau inversion recovery; T1W, T1 weighted.

Two scoring methods for assessing chronic changes in the sacroiliac joints have been described but are not widely used. The first scores bone erosions and sclerosis at four osseous positions per joint (the iliac and sacral sides of the cartilaginous and ligamentous portions of the joints, respectively), as well as joint space width.^{35,37} The second method scores each

sacroiliac joint from 0 to 4 based on a global assessment of erosion, sclerosis, joint space width, and bone bridging/ankylosis (see Table 45.7). Validation of the methods for assessment of damage is limited, and their value has not yet been clarified.

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PRINCIPLES OF MANAGEMENT

46

Arthritis patient education, health promotion, and team approaches to management

■ MAURA D. IVERSEN ■ NANCY SHARBY

- Good communication between patients and providers leads to a more accurate diagnosis and prognosis, enhances adherence to treatment, increases satisfaction with care, and improves health outcomes.
- Patients' and providers' beliefs about medical care in general and arthritis care in particular have an impact on patients' perception of the quality of their care and their interest in adhering to medical interventions. Discrepancies between the health beliefs of the provider and the patient are a significant factor in health care outcomes and disparities and must be addressed when developing patient education.
- Adults approach learning with different perspectives and needs than children and teens do. They seek active engagement in learning, build on previous knowledge, and see the impact of learning on their lives.
- Health literacy is a significant component of patient understanding and adherence to medical therapy. Providers and educators need to acquire an array of skills to develop material that will address the needs of patients with low literacy levels.

Patient education is integral to the management of chronic diseases. In the broadest sense, education "is an activity undertaken or initiated by one or more agents that is designed to effect changes in the knowledge, skills and attitudes of individuals, groups or communities"¹ Patient education includes the provision of information; instruction in self-management skills, behavioral therapies, and motivation strategies; and techniques to enhance or develop social support for healthful behavior. Educational activities are essential to promote collaborative care. Patients have a right to receive information about their medical condition and the spectrum of treatment options available to them² and to actively engage in decision-making about their care.³ Patients who understand their condition and are knowledgeable about how and when to use their medications are more adherent to interventions and in the short term demonstrate improved health outcomes.^{3,4} Effective patient education programs are based on psychobehavioral theories and incorporate techniques designed to actively engage patients in their care and to enhance their problem-solving skills.⁵ They can be provided by one or more individuals involved in the patient's care and may occur in many settings (Table 46.1), beginning with the clinical encounter and expanding to public media. This chapter focuses on patient education and health promotion in various settings, evidence for the effectiveness of patient education, sample strategies, and the use of team approaches to the management of arthritis.

PATIENT EDUCATION DURING THE CLINICAL ENCOUNTER

Patient education begins the instant that the provider and patient encounter each other. The way that providers present themselves, including body language, tone of voice, word choice, and pattern of talk, influence the development of a trusting relationship⁶ and the manner in which information is received. Typically, the provider and patient enter the encounter with specific goals in mind, with a successful exchange being anticipated. The provider must establish rapport with the patient, formulate and convey a diagnosis and prognosis, explain the potential impact of the condition on the patient's life, listen to patient's ideas and concerns, and discuss treatment options. At the conclusion of the encounter, the patient and provider should have an established plan of care that is acceptable to both.

Good communication between patients and providers has many benefits. It leads to a more accurate diagnosis and prognosis, improves adherence to treatment,^{7,8} increases satisfaction with care,^{8,9} and improves health outcomes.⁸ Although physicians are not always comfortable counseling patients about their options and treatment choices, research demonstrates that these skills can be learned.¹⁰ Strategies such as sharing an assessment of the patient's understanding of the information, exploring patients' preferences and expectations of care, and actively listening to patients' concerns are essential for successful communication and education.¹¹⁻¹⁴

RESEARCH ON PROVIDER-PATIENT COMMUNICATION IN ARTHRITIS

Provider-patient communication studies focus on attributes of the participants, as well as on processes and outcomes of discussions. Patients' concerns extend beyond managing symptoms and medications to the social, emotional, and psychological effects of their disease. Physicians, however, may be unaware of the psychosocial and work issues affecting patients with arthritis and may fail to address these issues.¹⁴ Failure to elicit these issues increases the likelihood that the patient will raise concerns too late in the visit to be addressed.^{14,15} It is good practice to begin with simple open-ended questions such as "Tell me how things are going" or "Tell me about what you have been doing?" and then wait for a response before proceeding. Do not interrupt until the patient is finished. Although this technique might seem more time intensive, in fact it is not. Most patients provide 80% of the information that one needs to know in 2 to 3 minutes.¹⁵ This strategy provides an opportunity to address misconceptions, present information, identify barriers to adherence, and suggest strategies to overcome these barriers, including information on available resources (e.g., community exercise, self-management programs).

TABLE 46.1
Settings for arthritis patient education

Setting	Type of patient education
Medical office visit	Patient education delivered by physicians as part of the medical consultation
Surgical or hospital unit	Preoperative or perioperative education for patients with arthritis undergoing joint surgery (may be individual or small group) or with other serious conditions
Outpatient or community interdisciplinary health care team	Patient education delivered by an individual or a team approach involving allied health professionals; it often includes physical therapists, occupational therapists, nurses, pharmacists, and health educators. This occurs in many community settings, outpatient clinics, and hospital settings. It may be conducted in either individual or small-group settings or in single or multiple sessions
Media	Broad programs reaching a wide target audience and consisting of other forms of arthritis education, such as books, pamphlets, brochures, written self-instructional material, audiovisual material, computer-assisted learning, and Internet resources
Population-based resources	Dissemination of public education via mass media campaigns and activities and support group development and activities carried out by national arthritis foundations, societies, and the Centers for Disease Control and Prevention (Arthritis Action Plan, Physical Activity Campaign, etc.)

Patient expectations about clinical discussions along with treatment expectations have important effects.¹³⁻¹⁷ Unfortunately, provider and patient expectations of the medical encounter may differ. In a survey of rheumatology patients, Rao and associates¹² noted that 33% were not satisfied with their clinical visit. Nearly half reported unmet expectations with regard to general information and 31% with respect to information about new medications. Patients' expectations of the efficacy of treatment also influence outcomes. In one study, patients' preoperative expectations of function and pain relief after spinal surgery influenced their pain and function up to 6 months after surgery.¹⁷ Clinical discussions inform patients of the purpose of treatments, as well as how and when to take medications or engage in exercise. Unfortunately, patients often misunderstand this information. A study of first visits to an arthritis clinic found that 15% of patients failed to understand the purpose of their prescriptions. They were less likely to be adherent to medication after 4 months than were patients who understood the purpose of the medication.¹⁶ Information on how to take medications properly, their side effects and benefits, and whether a latency period exists before the drugs take effect is also necessary for understanding and adherence to therapy. Unfortunately, most patients forget about 50% of the medical instructions in a very short time.¹⁶ Fraenkel and colleagues³ showed that use of a decision tool for disease-modifying antirheumatic drug (DMARD) therapy successfully improved knowledge and the likelihood of making an informed choice. To enhance patients' understanding of medical advice and adherence, information should be provided in simple, nonthreatening language along with clear written instructions. Pharmacists can also be engaged in these conversations either by their presence at the location of the health encounter or as an asset that patients can be taught to access at their local pharmacy.

Studies of patients' preferences for medications have helped elucidate issues related to adherence to drug therapy.¹³ For example, perceptions about the need for medications and fear of medication overuse influence adherence more than medical demographic factors do. Data suggest that Latino patients may be reluctant to use medications and might prefer to use herbal therapies.¹⁸ Both patients' and providers' beliefs affect the quality and outcome of the clinical encounter. They affect how patients interpret information and perceive how they are treated during visits, how much information they recall, and what they do with the clinical advice.^{6,16} Providers' beliefs and attitudes toward treatments influence the content of discussions and the likelihood of receiving a prescription.¹⁹ Thus, each contact needs to be individualized to develop the best plan of care.

Patients' desire for participation in decision-making is not routinely recognized by providers and may vary depending on their circumstances.^{11,20} In a cross-sectional study of 420 arthritis patients who were taking DMARDs or a biologic agent, Lim and coauthors⁵ reported that only 64% were satisfied with their level of participation in the decision-making process. Communicating information about risks in understandable terms^{3,21} and clarifying patients' beliefs and attitudes toward treatments and preferences for participation in decision-making are crucial. Even patients who would rather be passive during clinical discussions are more satisfied with their providers when they participate more fully in negotiations about disease management.²⁰

DESIGNING PATIENT EDUCATION PROGRAMS

Patient education is well grounded in behavioral change theory, which is derived from a range of disciplines, including psychology and the principles of adult learning. Theory-based approaches, including cognitive-behavioral and self-management programs, hold the most promise for successful arthritis education.²² Social learning theory posits that health-enhancing behavior results from the interplay between physiologic, social, and physical factors, as well as individuals' cognition about their disease.²³ This approach integrates program components often applied in isolation, such as cognitive-behavioral change strategies and a self-management framework.²³ A key cognitive dimension is self-efficacy, or an individual's situation-specific confidence in performing a task. Perceptions of the possible consequences of performing or not performing a behavior are also key to adoption of suitable health behavior.²³ Improving self-efficacy frequently leads to increases in appropriate health behavior and health outcomes.²²⁻²⁴

Conducting a needs assessment is the first step in developing effective education and personalized care of patients with arthritis.²² A needs assessment is the process of defining patients' knowledge, skills, resources, motivation, and barriers to effective management that influence their response to their illness.⁴ Patients with a chronic condition such as arthritis seek something to blame their disease on and develop construct models of illness to explain their symptoms. They describe and conceptualize their disease and symptoms in terms of their lives, their understanding of how their bodies work, their social networks, and the mass media.

HEALTH EDUCATION AND THE ADULT LEARNER

Traditionally, adults have been taught by instructional methods and philosophies developed for youth. However, adults approach learning with different perspectives and needs that must be considered when developing instructional material. Knowles, Holton, and Swanson, in *The Adult Learner: The Definitive Classic in Adult Education and Human Resource Development*,¹ provide strategies for how this can be accomplished. In essence, as people age, they develop along different life trajectories, so a group of adult learners will have more differences than the same-sized group of adolescents. Values, beliefs, level of education, life experiences, readiness to learn, goals, motivation, and learning styles will vary widely. Adult learning is driven by a need to know and a priority for information that will be immediately useful. "Hands-on" or active learning activities are the most successful, especially when they match the learner's readiness to learn. An effective learning strategy is the "teach-back" method in which instructors ask learners to describe what they will do when they get home based on what was discussed.²⁵ To initiate this exchange, the provider might say, "We have talked about a lot of things today and I know it can be difficult to remember everything. Can you tell me what you learned from today's visit and how you will take your new medication?" Depending on the patient's response, the provider acknowledges that the information was conveyed correctly or offers clarification.

In patient education and self-management programs, skills are taught through practice, modeling, group problem solving, and interactive discussions. Peer leaders often role-model behavior. Small-group programs usually consist of 6 to 10 members to allow time for individual needs, as well as group processes. Groups composed of patients with similar conditions and needs allow discussion and cross-fertilization of ideas and skills.²⁶ Program length, learning objectives and goals, and selection of leaders are important considerations. Short-term self-management programs enhance knowledge and skills, although these skills may diminish with time.²⁶ Periodic reinforcement is suggested to maintain skills and appropriate behavior. A mix of caregiver-based individual counseling and small-group education is optimal.

TABLE 46.2
Arthritis patient education content

Content area	Examples of specific content
Knowledge	Anatomy, disease process, inflammation Symptoms and signs and changes in severity of disease Importance of disease monitoring Pharmacologic therapy: use, effects, side effects, alternative therapy, when to change dosages of medication Benefits of surgical intervention Podiatry Nutrition, diet, and hazardous diets; weight control Community resources, helping agencies, potential assistance from government agencies Role of exercise, rest, joint protection skills, transcutaneous electrical nerve stimulation, acupuncture
Skills and behavior	Home exercise and physical activity programs Specific goal setting Modification of daily routines, domestic and leisure task management Self-monitoring or adherence Pain management: use of hot/cold, relaxation, other pain management behavior Work and occupational simplification (when possible) Stress monitoring and management
Problem solving (linked to self-management skills)	Communicating with health care providers Assertiveness, ability to ask questions, and negotiation of a shared plan of care Strategies for reducing anxiety, increasing confidence (self-efficacy), and reducing feelings of helplessness and fear Coping with the impact of chronic illness and depression Eliciting support from family, friends, and community members

CONTENT OF ARTHRITIS EDUCATION PROGRAMS

The major components of patient education programs include knowledge transfer, behavioral change and skill development, and psychosocial counseling (Table 46.2). The goals are to help patients understand their diagnosis and prognosis, critically appraise new information, and seek resources. However, patient education alone does not result in cognitive or behavioral changes.²⁰ Therefore, most programs emphasize the development of self-management skills to promote and adapt behavior based on patients' symptoms and disease activity. Self-management skills may include the use of splints and adaptation of exercise in those with hot swollen joints. These skills are learned through observation, performance, and the practice and consequences of such behavior.^{22,23} For example, patients who exercise regularly report improved function and decreased joint pain and stiffness.

Psychosocial counseling seeks to help patients cope with their arthritis and to feel more confident about their ability to maintain an active social and functional lifestyle.²⁷ Recruitment and training of lay leaders with arthritis to conduct education programs has resulted in positive short-term psychological effects for participants and leaders.²⁸ On a psychosocial level, social support can play a significant role in generating positive feelings of physical and mental well-being.²⁷ Family members and significant others may also have a role in facilitating the understanding and recall of information.

Importance of health literacy and cultural considerations

Multiple forms of communication are used to educate patients. Unfortunately, low health literacy is common. More than a third of the U.S. population struggle to understand even basic health information; twice that number find it challenging to navigate the health care system.²⁹ Literacy is a crucial

aspect of the patient's profile inasmuch as poor literacy is correlated with poor health outcomes.³⁰ Health literacy can be defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."^{29,31} Thus, a patient may not understand how to read a prescription label, when to call a care provider for help, or how to follow through on a home activity program. In a study of literacy among patients with rheumatoid arthritis,³² one in six were illiterate and struggled to understand patient education material and prescription labels. These patients also had significantly more hospital visits. A second study³³ designed to assess the reading level of 80 patients with rheumatoid arthritis reported that 10% had difficulty reading patient material and 31% scored at or below the ninth-grade reading level. These results are consistent with research indicating poor health, poor understanding of treatment, greater use of health services, and low adherence to treatment regimens by patients with limited literacy.³⁴ Most patient education material is written at an 11th-grade or higher level, but the average reading level of the general public is below the 8th grade.³⁴ The following strategies are recommended to enhance patient education and improve adherence to treatment:

- Speak in simple language, avoid medical jargon, and repeat instructions.
- When possible, hire staff members who are bilingual.
- Provide easy-to-read material in plain English (fifth- to eighth-grade reading level) with illustrations.³¹
- Include significant others or family members in discussions (with patient consent). However, do not ask these family members or friends to act as translators.
- Motivate and enhance patient self-efficacy by discussing the pros and cons of treatment and incorporating information acquired from patients about their perspective.
- Engage patients in problem-solving strategies to address potential barriers to adherence and help develop contingency plans for dealing with treatment failure.

Designing culturally relevant educational material is especially important in groups with low literacy because interpretation of illustrations and behavioral modeling may be particularly sensitive to cultural context.^{29,31} Zhang and Verhoef³⁵ examined illness management strategies among Chinese immigrants with arthritis and found that management strategies fluctuate between Western and traditional Chinese medicine. Western medicine was believed to be less effective than traditional medicine for chronic conditions such as arthritis. The importance of health literacy goes beyond just comprehension of written or spoken material. Patients must also be able to synthesize the information to solve complex problems. Health literacy is fundamental to the ability to engage in healthy behavior that lowers the risk for secondary complications. When patients feel empowered to make their own choices about being healthy rather than just having a prescribed set of interventions to follow, they are more likely to make good choices.²⁹

Social and cultural factors

Social, cultural, and environmental factors influence the manner in which care is provided and perceived.³⁴ As diversity increases, we can no longer expect that everyone will "be on the same page" when it comes to the kind of health care and health communication that they desire. These preferences for care are not mere niceties but are strongly associated with health outcomes and health disparities.³⁶ Congruence between the way that care is delivered and the patient's cultural beliefs is termed *culturally competent care*. It means that during the delivery of interventions, patient-provider interactions and patient education material must conform to the social and cultural beliefs that each patient brings to the encounter.^{36,37}

Use of the Internet for patient education

Delivering patient education and self-management advice through the Internet has received less formal evaluation. Generational acceptance of technology and multimedia approaches to patient education exist and are even embraced by some. They can be explored to better understand cost-effective and efficacious delivery modes. In a study assessing the acceptability of an Internet-based self-management program for adolescents with juvenile idiopathic arthritis, 36 children of various ages, disease severity, and subtypes were recruited from four pediatric centers and participated in focus groups.³⁸ These adolescents stated that a Web-based intervention was a promising avenue to improve accessibility and availability of self-management techniques, such as gaining control over their disease, developing social support, and learning to communicate with providers. However, in a study of 71

older adults with arthritis, Tak and Hong³⁹ reported that just 39% of older adults used the Internet to obtain information on arthritis and only 28% had a home computer.

An important consideration when referring patients to Internet sites is the quality of the material. Ansani and colleagues⁴⁰ evaluated the quality of Internet-based information on arthritis with a standardized rubric and reported that the quality varied widely. The best sources of information were located on websites with URLs having suffixes of “.gov” and “.edu.” Kim and associates⁴¹ examined the impact of Web-based arthritis information on arthritis patients’ knowledge and medical practice. First, they reviewed and scored websites based on authorship, type of publication, contents, and financial interests. Next, 257 Korean adults with arthritis and rheumatologists were surveyed about use of the information from these sites. Twenty-eight percent of patients reported that they searched for arthritis information on the Internet. Significant correlates of the use of Web-based information were younger age, being employed, and having a higher income and higher education. Ratings of the accuracy of Web-based information on arthritis did not differ between physicians and patients. However, only 16.1% of physicians believed that patients understood the content, and physicians’ attitudes were less positive than those of patients.

Evidence for the effectiveness of arthritis education programs

Patient education programs range from provision of information to the use of cognitive-behavioral strategies, exercise prescriptions, and psychosocial support. Variability in content, target populations, and disease conditions, duration, and frequency complicates systemic evaluation of programs. Systematic reviews include a mix of study designs, patient education definitions, and health outcomes or include heterogeneous patient populations with respect to disease. Patients with osteoarthritis or rheumatoid arthritis are most often included in patient education trials. Comparisons of patient education programs by diagnosis indicate differences in outcomes that are not consistent across studies. Notably, patient education programs with behaviorally based interventions appear to be more effective than instructional programs alone.⁴

A review of 31 randomized controlled trials of arthritis patient education was recently performed.⁴ Patient education was defined as an intervention that includes formal structured instruction on arthritis and ways to manage the disease, such as psychobehavioral strategies, exercise, biofeedback, or psychosocial support. The results indicated modest improvements in functional disability, joint counts, global assessment, psychological status, and depression in the short term (up to 2 months), but no difference at follow-up (3 to 14 months). Improvements in functional disability translated into a 10% improvement on the Health Assessment Questionnaire. This review is unique in that separate analyses were performed, depending on the type of intervention. The data indicated that behavioral interventions resulted in greater improvement than no intervention did. However, the overall quality of the trials was not very high.⁴ These results are similar to data from Warsi and colleagues,²⁴ who evaluated the outcomes of 71 trials and found small to moderate effects. Mulligan and coworkers¹² pointed out that randomized controlled trial may not be the best design for examining self-management programs. Few studies have examined the impact of arthritis education programs on health care use and costs.⁴³

Structured patient education programs based on commonly accepted principles of education and psychology and applied consistently by trained personnel produce small improvements in knowledge, behavior, physiologic measures, and health outcomes beyond the effects of medications.^{4,42} Effects tend to be strongest when programs include behavioral strategies. Well-designed patient education programs are effective and integral to arthritis management. A randomized controlled study examining the outcomes of a small arthritis self-management group versus tailored-print education found slightly better results for the tailored-print program in the first year but that the results attenuated over time.⁴⁴ This study suggests that well-designed, tailored material increases patient education and allows greater dissemination of information.

MULTIDISCIPLINARY TEAM ROLES AND APPROACHES TO MANAGEMENT

Arthritis team care improves health care delivery and outcomes.⁴⁵ The multidisciplinary team care concept began more than 50 years ago, before new pharmacologic approaches were introduced. The team care philosophy is to rely on each professional’s knowledge and expertise to maximally address patients’ needs. Scandinavian countries were the first to initiate the team

care approach. Multidisciplinary team care may be provided in the hospital or on an outpatient basis in regular or day care facilities.⁸

The notion of team care varies across the globe. *Team care* is defined here as care involving the patient and a health care provider plus at least one other health care provider or family member that incorporates a team approach to information sharing, decision-making, and goal setting. The team may include a primary care physician, rheumatologist, nurse practitioner, physical therapist, occupational therapist, social worker, psychologist, podiatrist, vocational rehabilitator, the patient’s family, and the patient. Although team composition varies, the central team member is the patient. For a team to be effective, members need to understand and respect each other’s role (Box 46.1) and be cognizant of the information that they have imparted to prevent communication breakdown, prevent overlap and omission of services, and maximize patient care. In theory, team care allows different professionals to motivate and reinforce learning and provide care across a range of patient care settings. Team functioning is important and is becoming a stronger emphasis in health professional education and training.⁴⁶

Although team care is prevalent in Europe, such is not the case in North America, partly because of budgetary constraints, shortages of health care professionals, and reimbursement issues. Consequently, innovative team care models have emerged, such as the clinical nurse-specialist model⁴⁷ and the primary therapist model.⁴⁸ In these models, extensions of clinical practice are promoted.^{46,47} Study results suggest that patients referred to a primary therapist might have better outcomes than those referred to receive

BOX 46.1 STRATEGIES FOR DESIGNING EFFECTIVE PATIENT EDUCATION MATERIAL

Interview patients about their needs:

- What do you feel that you know the most about?
- What would you most like to know?
- How do you best like to learn? Listening, reading, watching, doing, using the Internet, watching video/movies?
- Do you like to learn in groups or alone?
- What are your biggest concerns?

Interview patients about their health beliefs and needs.

Obtain demographic information about clients:

- Chart reviews.
- Public data (Centers for Disease Control and Prevention, Census Bureau).
- Determine the patient’s health literacy level.

Write for your reader:

- Create messages that are culturally relevant.
- Consider language, health beliefs and practices, gender roles, etc.
- Match content to health literacy levels.
- Use plain language and simple short sentences.
- Do not use medical jargon.
- Use the simplest tense.
- Use “must” to convey requirements.
- Avoid abbreviations.
- Avoid calling the same thing by different names (e.g., medicine, drug, therapy).
- Use “you” and other pronouns.
- Repeat the most important information more than once.
- Use the active voice.
- Use the appropriate tone—what does this mean.
- Do not talk down to your audience.
- Write in positive not negative terms.
- Avoid ALL CAPS—appears as though you are yelling at the person (especially true for Web formats).
- Keep subjects and objects close to their verbs.
- Place conditional words after the main thought (e.g., “Take 3 aspirin if you have pain more than 5 hours and are not taking another NSAID”—NOT “If you have pain more than 5 hours and are not taking another NSAID, take 3 aspirin.”)
- Complex information may be better presented in tables.
- Simple pictures and diagrams can be helpful.

NSAID, nonsteroidal antiinflammatory drug.

Adapted from Rudd R, Anderson JE. The health literacy environment of hospitals and health centers. Harvard School of Public Health: Health Literacy Website; 2010. Available at www.hsph.harvard.edu/healthliteracy/files/healthliteracyenvironment.pdf. Accessed September 2, 2012.

traditional therapy.⁴⁸ Studies of the use of health care professionals in extended clinical roles are promising and warrant further investigation.

PUBLIC HEALTH APPROACHES TO EDUCATION OF PATIENTS WITH ARTHRITIS

Increasing recognition of health education and health promotion as primary prevention is evident by the growing emphasis on public health approaches to the management of arthritis by the Centers for Disease Control and Prevention and the Arthritis Foundation. Public health approaches provide population-based programs that enable access to individuals to reduce social inequalities and promote health. Approaches include health care professional and physician training (Table 46.3), community education programs, environmental modifications, health policies, and the use of mass media to provide low-intensity but widely disseminated messages on arthritis.

Public health approaches engage in three levels of health promotion. Primary prevention activities prevent the development of a health condition. This would not be appropriate for rheumatology practices because patients already have a health condition. Secondary prevention involves conditions that occur as a result of the primary health problem. For patients with arthritis this may include weakness, deconditioning, and joint stiffness or tightness. This is often the focus of patient education but may need to be explained in terms that are meaningful to the patient. For example, weakness may have an impact on someone's ability to play on the floor with grandchildren or to garden. Tertiary interventions are treatments intended to reverse or manage the disease process. They may also help the patient participate in activities that are important. Referral to various rehabilitation professionals or surgery may be useful here (see Table 46.3).

A main objective of a public health approach to arthritis is to reach all segments of the population, including socially disadvantaged groups, those whose first language is not English, and those who cannot access specialist medical care. To educate patients with arthritis, we need to develop programs and material for the less common but serious varieties of rheumatic disease. Health care providers and patients must advocate for policies and programs that reach the majority of individuals in a cost-efficient and cost-effective manner. *Healthy People 2020* includes a section devoted to arthritis, osteoporosis, and back care.⁴⁹ The Centers for Disease Control and Prevention has a dedicated arthritis initiative. The Arthritis Prevention, Control, and Cure Act is legislation designed to provide public access to arthritis education.

THE FUTURE OF ARTHRITIS PATIENT EDUCATION

In coming years we will experience an expansion in the application and dissemination of technology-based arthritis patient education. New devices are being implemented to dispense patient education and provide reinforcement opportunities through personal digital assistants, home cable boxes, or cell phones. These systems convey an auditory or text signal to engage and empower patients to be active in their care. Newer technologies are expanding to allow remote monitoring of patients while improving communication and maintaining a high level of personalized care.

We will develop, adapt, and evaluate patient education programs for specific populations such as minorities, those with limited literacy,³⁴ and individuals with rare forms of arthritis. With increasing health care

TABLE 46.3
Health professional roles in patient education and treatment

Professional	Role in patient education (examples)
Nurse	Has a primary care role in explaining and demonstrating medication use, action, interactions, side effects, and medication administration devices
Nutritionist	Explains the role of diet, helps plan a healthy diet and individualize it for the patient, discusses "alternative" diets and their potential risks, and provides weight control strategies
Occupational therapist	Provides training in relearning or adapting routine activities of daily living, recreation, and leisure pursuits; use of assistive devices and functional aids; and joint support to immobilize joints
Pharmacist	Provides patient education about the effects and side effects of drugs, how to read prescription bottles and take medications, and when and how to modify drug regimens; monitors for possible drug interactions
Physical therapist	Evaluates clients' restrictions in activity, functional limitations, and participation in society. Designs static and dynamic exercises and aerobic conditioning programs to improve mobility, prevent contractures or weakness, and improve cardiovascular pulmonary health. Suggests modifications of physical activity during the active phases of disease, instructs in pain management strategies, and provides modalities when needed to reduce pain (e.g., transcutaneous electrical nerve stimulation). Provides general information and strategies on health and well-being
Physician	Explains the disease and its physiology, natural history, and the range of therapies available; the need for disease monitoring; and the place of intraarticular injection, surgery, and other interventions. In some countries this is the role of community general practitioners, especially for uncomplicated and prevalent conditions (e.g., osteoarthritis, osteoporosis) and for providing adjunctive care for complicated or multisystem disease
Psychologist	Provides counseling for anxiety and depression and aids in dealing with denial or disease crises and coping with relationships, sexuality, and stress or management
Social workers	Helps with "patients' rights" to treatment, arranging time off work, enabling support from caregivers in the family and from the community and government, and possibly providing individual or family counseling

constraints and rheumatology workforce issues, we must explore innovative models of patient care delivery and education, assess their cost-effectiveness and health benefits, define outcomes that reflect the learning process, and capture the psychosocial dimensions and skill developments anticipated with education.

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Principles of rehabilitation:
physical and occupational therapy

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- Rehabilitation is the process of enabling persons with impairments, limitations in activity, or disabilities that cause suboptimal participation in various life situations (self-care, work, recreation and leisure, or community life) to regain or obtain the capacity necessary to participate at an optimal level. Rehabilitation therefore requires determining the optimal level of function, identifying the barriers that prevent the individual from obtaining that level of function, and providing interventions that facilitate attainment of that optimal level.
- Rehabilitation interventions can be classified as either remedial or adaptive processes.
- Remedial rehabilitation works to *restore* or *establish* capacity or ability. It focuses on improving impairments in muscular strength and endurance, joint motion, cardiorespiratory fitness, balance and coordination, and cognitive function (depression, anxiety, fear, self-efficacy) and may also refer to retraining in lost skill sets, such as self-care, dexterity, and work skills.
- Adaptive rehabilitation works to *compensate* for lost or absent capacity or ability. It focuses on providing alternative or supplementary methods to perform a task or activity so that performance can be optimized. Adaptive rehabilitation includes the use of equipment that substitutes for lost capacity, teaching new methods of performing tasks that incorporate existing capacity, altering the environment to facilitate performance, and changing the requirements of the task.
- Most rehabilitation therapists use a combination of remedial and adaptive rehabilitation methods to obtain optimal function.
- Because rehabilitation is a multifactorial process, it will often require a multidisciplinary team approach to optimize restoration of function in people with rheumatologic disorders.

DEFINITION OF REHABILITATION

The United Nations defines rehabilitation as “a goal-orientated, time-limited process aimed at enabling an impaired person to reach an optimum mental, physical, and/or social level.”¹ Rehabilitation is the process of enabling persons with impairments, limitations in activity, or disabilities that cause suboptimal participation in various life situations (e.g., self-care, work, recreation, leisure) to regain or obtain the capacity necessary to participate at an optimal level. Rehabilitation therefore requires determining the optimal level of function, identifying barriers that prevent the individual from obtaining that level of function, and providing interventions that facilitate attainment of that optimal level.

**PATIENT-CENTERED APPROACH
TO REHABILITATION**

Because each patient with arthritis has a unique set of impairments and functional deficits, rehabilitation therapists should use a patient-centered approach to determine an optimal level of function for every individual patient, depending on what that person *needs* and *wants* to be able to do.

Once the patient's optimal level of function has been targeted, the next step is to identify barriers that prevent the patient from achieving this optimal level. Both the rehabilitation therapist and patient work together via a thorough examination process to identify these barriers. Patient-reported measures of pain and function, as well as performance-based measures of function, should be used to identify the types of functional tasks that are problematic and to quantify the severity of these problems. Physical examination procedures are performed to identify the presence of physical impairments (i.e., muscle weakness, limited joint motion, joint stiffness, balance and coordination deficits) that may be associated with the functional problems. An assessment of the patient's living or work environments may be undertaken to identify environmental or social support factors that could be either potential barriers or potential assets in achieving optimal function. Assessment of biobehavioral characteristics (i.e., anxiety, fear, depression, self-efficacy) may also be helpful in determining whether any of these factors are influencing physical activity or responsiveness to rehabilitation interventions.

After specific barriers have been identified through the examination process, the rehabilitation therapist and patient design and implement a rehabilitation intervention program that addresses the specific barriers to optimal function. Rehabilitation interventions can be classified as either remedial or adaptive processes. Remedial rehabilitation works to *restore* or *establish* capacity or ability. It focuses on improving impairments in muscular strength and endurance, joint motion, cardiorespiratory fitness, balance and coordination, and cognitive function (depression, anxiety, fear, self-efficacy) and may also refer to retraining in lost skill sets, such as self-care, dexterity, or work skills. Adaptive rehabilitation works to *compensate* for lost or absent capacity or ability. It focuses on providing alternative or supplementary methods to perform a task or activity so that performance can be optimized. Adaptive rehabilitation includes the following methods:

- Providing equipment that substitutes for lost capacity
- Teaching new methods of performing tasks that incorporate existing capacity
- Altering the environment to facilitate performance
- Changing the requirements of the task

Most rehabilitation therapists use a combination of remedial and adaptive rehabilitation methods to achieve optimal function.

Rehabilitation is a multifactorial process that requires addressing a variety of features and issues to achieve the goal of obtaining optimal function and participation in life for patients with arthritis. Thus, it is logical that the rehabilitation process would require a multidisciplinary approach to achieve these goals. This chapter focuses its discussion mainly on the perspective of two rehabilitation disciplines, physical and occupational therapy. However, depending on the specific problems and needs of the individual patient, the services of other health care professionals, such as clinical psychologists, vocational rehabilitation counselors, rehabilitation engineers, or recreational therapists, should be used to provide the most comprehensive care for each patient. It should also be recognized that in many areas of the rehabilitation process, the roles and responsibilities of various disciplines overlap. For example, both physical and occupational therapists use methods to address a variety of impairments related to functional deficits. Both disciplines also use methods of functional retraining, education in joint protection techniques, and the use of assistive devices in their treatment programs. Because of the significant overlap in roles and responsibilities between disciplines, this chapter will not be discipline specific in the presentation of methods and issues related to the rehabilitation of people with arthritis.

REMEDIAL REHABILITATION APPROACHES

Pain control

Pain is a major cause of disability in people with arthritis. Physical modalities, including thermal agents and electrical stimulation, have been included in recommendations for the treatment of pain in people with arthritis.^{2,3} Thermal agents include hot or cold packs, paraffin, shortwave diathermy (SWD), ultrasound, and low-level laser modalities. Evidence for the use of these interventions to control pain is modest at present and supports selective rather than global use of these modalities. Low-level laser therapy has been shown to provide some relief of pain and stiffness in the foot, knee, and hand regions of patients with rheumatoid arthritis (RA) and also knee pain in patients with knee osteoarthritis (OA).^{4,5} Ultrasound used in water at 0.5 W/cm² demonstrated a small benefit in relief of hand pain in patients with RA but was not shown to be effective for relieving pain in patients with knee OA or in patients with back pain.⁵⁻⁷ Paraffin applied to the hand in combination with an exercise program seems to be helpful in reducing pain and stiffness and in improving range of motion in patients with RA and in those with scleroderma; however, the use of paraffin alone does not seem to be beneficial.^{8,9}

A recent randomized clinical trial compared the combined use of exercise with hot packs, hot packs and ultrasound, hot packs and SWD, or hot packs and transcutaneous electrical nerve stimulation (TENS) with exercise alone in women with knee OA.¹⁰ The researchers reported greater improvements in pain relief when exercise was combined with a thermal intervention than when the thermal agent was used alone. A recent systematic review of SWD for the management of knee OA also concluded that SWD can have an overall immediate effect on pain perception following completion of the last treatment session but that no long-term benefits are evident.¹¹ Additionally, the effects SWD are apparent only when it evokes at least some degree of thermal sensation.¹¹ Further studies (using comparable protocols and outcome measures) are needed to determine the possible long-term effects of thermal SWD in relieving pain in patients with arthritis.

TENS, the process of providing an electrical stimulus through the skin with surface electrodes for the purpose of reducing pain, has been shown to be effective in the treatment of pain. Use of TENS has been advocated as a stand-alone treatment of pain in published treatment guidelines for arthritis.^{2,3,5} There are many different applications of TENS that combine various stimulus parameters (pulse frequency, pulse duration, pulse amplitude) and various treatment durations. Low-frequency, high-amplitude TENS (sometimes referred to as acupuncture-like TENS) was shown to be effective in relieving hand and wrist pain in patients with RA, but higher-frequency TENS was not.¹² In patients with knee OA, high- and low-frequency TENS was deemed effective in increasing the pressure pain threshold after a single TENS treatment.¹³ However, patient-reported pain ratings at rest and during movement were similarly reduced by active TENS and placebo TENS, thus suggesting a strong placebo component of the effect of TENS.¹³ To this end, a recent systematic review of randomized or quasi-randomized controlled

trials could not confirm whether TENS is effective for pain relief in patients with knee OA.¹⁴

In summary, although thermal agents and TENS have a place in controlling pain in people with arthritis, their use should be limited to selective cases rather than global applications across all people with arthritis. When considering the rising cost of health care, many patients may be served better by instructing them in the home use of hot packs, warm baths, paraffin, or TENS for pain control rather than having them make frequent visits to a therapist to receive these treatments. An alternative to the use of physical agents for pain control is exercise and physical activity. A number of different types of exercise activity, including aerobics and strengthening exercises, may have a systemic effect on modulating pain. Studies have shown a reduction in pain thresholds in response to different types of pain stimuli at areas remote from the exercised limb segments, thus suggesting a centralized, systemic response.^{15,16} The use of various exercise applications for improving pain and function are addressed in subsequent sections of this chapter.

Range of motion

Loss of joint motion is a common impairment associated with arthritis. Limitations in joint motion or joint stiffness can increase the difficulty of performing activities of daily living (ADLs) and result in greater disability. It is also conceivable that with reduced joint motion, less joint surface area is available for distributing compression and shear loads across the joint surface. This could result in more concentrated loading in smaller areas of the joint surface and thereby lead to increased joint stress and potentially accelerate progression of the arthritis. Therefore, addressing limitations in joint motion is an important element of rehabilitation for people with arthritis. Published guidelines for the treatment of hip and knee OA recommend the use of treatments designed to maintain or improve joint mobility.² Such interventions may include stretching exercises (sometimes referred to as flexibility exercises), joint mobilization, and splinting to improve pain, function, and joint motion.

Stretching exercises are designed to increase the length of soft tissue structures that may be limiting joint motion, such as the joint capsule and musculotendinous units. Stretching exercises involve moving the joint to the end of the available range of motion and then applying some manual overpressure to increase passive tension in the target soft tissue structures. The stretch position should induce enough passive tension in the target structure to elicit a “slight stretch discomfort” but not to the extent that joint or soft tissue pain is elicited. This position is then held for a short period (Table 47.1).

In a study of 55 older adults with and without knee OA, three 60-second bouts of hamstring stretching with 60 seconds of rest between each bout resulted in immediate beneficial adaptations in terms of 4 to 5 degrees of increased knee extension range of motion.¹⁷ Similarly, in a small randomized trial of 19 female subjects between the ages of 65 and 89 years with limited ankle dorsiflexion, subjects who received an 8-week calf-stretching program

TABLE 47.1
Exercise prescription recommendations

Exercise	Intensity	Volume	Frequency
Flexibility	Stretch to the point of feeling tightness or slight discomfort	2-4 stretches/key muscle group; hold position for 10-30 sec A reasonable target is to perform 60 sec of total stretching time for each flexibility exercise	≥2-3 days/wk
Resistance			
Isometric	Low to moderate: 40%-60% MVC	1-10 submaximal contractions involving key muscle groups; hold the contraction for 1-6 sec	Daily
Isotonic	Low: 40% 1 RM	10-15 reps, 2-4 sets, 2- to 3-min rest intervals	2-3/wk
	Moderate: 40%-60% 1 RM	8-10 reps, 2-4 sets, 2- to 3-min rest intervals	
	High: >60% 1 RM	6-8 reps, 2-4 sets, 2- to 3-min rest intervals	
Aerobic	Low to moderate: 40%-60% of $\dot{V}O_2\text{max}$ /HRmax RPE: 12-14 = 60%-65% $\dot{V}O_2\text{max}$	Accumulation of 30-60 min/day Exercise may be performed in one (continuous) session per day or in multiple session lasting ≥10 min to accumulate the desired duration and volume of exercise per day	≥3 days/wk

MVC, maximal voluntary contraction (measurement of isometric strength); reps, repetitions; 1 RM, one rep maximum (measurement of isotonic or dynamic strength); RPE, rating of perceived exertion; HR max, age-predicted heart rate maximum; $\dot{V}O_2\text{max}$, maximal aerobic capacity (measurement of aerobic fitness).

Data from Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334-59; and American Geriatrics Society Panel on Exercise and Osteoarthritis. Exercise prescription for older adults with osteoarthritis pain: consensus practice recommendations. A supplement to the AGS Clinical Practice Guidelines on the management of chronic pain in older adults. *J Am Geriatr Soc* 2001;49:808-23.

consisting of 10 repetitions of a 15-second hold at the end of the available range of ankle dorsiflexion had improved ankle dorsiflexion, higher agility test scores, and faster walking speeds than did control subjects.¹⁸ Although the most effective dosage for stretching may vary from muscle to muscle, it appears from these studies that improvements in muscle length and joint motion may be obtained from moderate-intensity stretching exercise. Patients who can hold for longer durations may not need to do as many repetitions. Likewise, if they cannot tolerate holding for longer periods, benefit may still be obtained by performing more repetitions at shorter durations.

Joint mobilization techniques are frequently used to increase joint motion by improving the accessory joint motions (i.e., sliding or distractions between joint surfaces) that accompany normal joint motion. For example, during knee flexion, the tibia slides posteriorly on the femur during the flexion motion of the joint. If this posterior sliding is inadequate, limited knee flexion motion will be present. The therapist performs joint mobilization techniques designed to restore the normal posterior slide, which in turn improves knee flexion motion. Joint mobilization techniques vary, depending on the joint motions being targeted and the accessory motions that accompany the targeted motions. Higher-intensity mobilizations (oscillations of the accessory motions near the end of the available range) are used to improve joint motion; however, lower-intensity mobilizations (oscillations of the accessory motions in the middle of the available range) can be used to induce relaxation and perhaps pain modulation.

Only a few studies have examined the effects of joint mobilization in patients with arthritis. In a randomized clinical trial of patients with knee OA, the combined use of joint mobilization with a supervised stretching and strengthening exercise program for all impaired lower extremity joints and the spine resulted in greater improvements in self-reported and performance-based measures of function than when only a home exercise program without joint mobilization was used.¹⁹ Changes in knee motion were not reported in this study. Similarly, in a randomized trial of patients with hip OA, subjects receiving a distraction joint manipulation technique, combined with lower extremity stretching and strengthening, had greater improvements in pain, self-reported hip function, hip range of motion, and walking speed than did subjects randomized to exercise without hip manipulation.²⁰ In these studies, groups randomized to exercise only did not appear to receive exercise programs equivalent to those of the groups undergoing the joint mobilization/manipulation techniques. Therefore, the exact contribution of these techniques to the outcomes is not clear. At any rate, combined use of joint mobilization techniques with other exercises appears to be helpful.³ Recently published systematic reviews further support the notion that the addition of manual mobilization to exercise therapy appears to be more effective in reducing pain than does strength training or exercise therapy alone in patients with knee OA²¹ and that joint mobilization may be an effective treatment option for those with hip OA in the short and long term.²²

Muscle strength

Muscle strengthening is recognized as an important element of rehabilitation for people with arthritis.^{2,3,12} Muscle weakness is frequently associated with greater disability in patients with arthritis, and in some cases, such as knee OA, there is debate whether muscle weakness may be a precursor to arthritis. In addition, muscles can play a significant role in absorbing and dissipating loads across joints, which may help reduce pain and prevent damage to joint structures. Muscle-strengthening programs have resulted in reduced pain, increased muscle force output, and improvements in performance-based and self-reported functional measures for some people with various forms of arthritis.^{2,12,23}

Several alternative types of strengthening exercises can be used. Isometric exercises involve contracting the muscle against resistance without allowing joint motion to occur. These types of exercises are usually performed at multiple angles throughout the joint's range of motion. Isotonic exercise involves moving a constant amount of resistance through a joint's range of motion. Weightlifting exercises are a type of isotonic exercise. In some clinic settings, computerized dynamometers can be used with isokinetic exercises to allow resisted muscle contractions to be performed through a range of motion at constant velocity. Few studies have compared the effectiveness of isometric, isotonic, and isokinetic exercise, but evidence suggests that all three types can improve pain, walking speed, muscle strength, and self-reported disability.²⁴

Strengthening exercises can be designed to use concentric or eccentric contractions. During concentric contractions the limb is accelerated against external resistance (e.g., gravity, weights), which results in overall

shortening of muscle length during the movement. During eccentric contractions the limb is decelerated against an external resistance, which results in overall lengthening of the muscle.

Functional activities involve combinations of isometric, isotonic, concentric, and eccentric muscle contractions. Therefore, a well-rounded strengthening program should include activities that involve each of these types of muscle contractions. Recently, some investigators have explored the use of functional task-specific strengthening in elderly subjects.^{25,26} With this type of training the therapist and patient identify which functional tasks are most problematic. The therapist then breaks the task up into segments that can be used as strengthening exercises. In this manner, patients train their weak muscles exactly as they will need to use them to perform tasks. As the patient gets stronger, the therapist adjusts how the patient performs the task-specific exercise, with more effort demanded from the target muscles as they get stronger. Some evidence suggests that this approach may be more effective than standard exercise approaches in improving overall function.^{25,26}

No matter what type of exercise is used in the strengthening program, adequate training dosage is an important consideration to obtain beneficial effects (see Table 47.1). The approach must provide enough loading on the muscle to induce a strength-training effect without exacerbating pain and inflammation of the joints. Recent studies indicate that using a graded progression of exercise resistance and adjusting training volume to match the level of resistance allow people with either fibromyalgia or RA to train intensely enough to obtain improvements in pain, strength, muscle hypertrophy, and performance-based and self-reported measures of function without exacerbating symptoms at their joints.^{27,28}

In many forms of arthritis, such as RA, the hands are particularly affected, with significant decreases in strength and range of motion secondary to the development of deformities. Therapy often focuses on remediating hand function by providing a home program of hand-specific resistive exercises, such as Thera-Putty, and full-range passive or active range-of-motion exercises. In a small nonrandomized study, 6 weeks of hand training resulted in a significant improvement in hand force and hand function in patients with RA, and the improvement was even more pronounced after 12 weeks.²⁹ A recent randomized trial of exercise therapy aimed at improving hand strength in individuals with hand deformities secondary to RA resulted in significant improvements in handgrip and pinch strength, as well as functionality.³⁰ Given the recent evidence that significant gains in hand strength in individuals with RA are most likely due to neural adaptations without gains in muscle mass, hand rehabilitation program for patients with RA should be designed to maximize this particular physiologic mechanism of strength gain.³¹

Aerobic capacity

Aerobic exercises are typically moderate-intensity exercises involving larger muscle groups that are performed over extended periods to improve cardiovascular function. Examples of aerobic exercise include walking, cycling, and pool exercises. Regardless of what type of exercise is used in the aerobic exercise program, maintaining an adequate aerobic dose of 40% to 60% of maximal aerobic capacity (maximum heart rate or $\text{VO}_{2\text{max}}$) is necessary (see Table 47.1). Aerobic exercise has been recommended as part of the management of patients with a variety of rheumatologic disorders in a number of published treatment guidelines.^{2,3,32,33} Aerobic exercise programs have been shown to reduce pain, improve function and quality of life, increase aerobic capacity and endurance, and improve mental health.^{2,33-35}

Walking programs have generally been studied for effectiveness. The Ottawa Panel recently concluded that aerobic walking combined with stretching and strengthening exercises, education, or behavioral programs is recommended to improve pain relief, functional status, and the quality of life of adult individuals with OA.³² Cycling is another form of aerobic exercise that can be beneficial. Low-intensity cycling was shown to be as effective as high-intensity cycling in improving function and gait, decreasing pain, and increasing aerobic capacity in subjects with knee OA.³⁶ Cycling should be considered for those with arthritis who may have difficulty with a walking program because of joint pain.

Aquatic exercise programs are an alternative for people with rheumatologic conditions because the buoyancy of water helps reduce loading on joints and thus makes it easier for patients with arthritis or fibromyalgia to exercise. These programs can include a combination of limb movements against water resistance and walking or jogging in the pool. Several studies of aquatic programs have reported improvements in pain, muscle strength, aerobic capacity, self-report and performance-based measures of function, daytime fatigue, anxiety, and depression.^{34,35,37}

Balance and agility

In recent years, more attention has been directed to the importance of balance in patients with arthritis. Studies have indicated that people with knee OA have deficits in measures of balance when compared with age- and gender-matched controls and that these balance deficits may be associated with limitations in function and functional decline.³⁸ In some cases, balance may be altered even in the absence of deficits in muscular strength.³⁹ Therefore, rehabilitation programs may need to incorporate interventions specifically designed to challenge balance ability in people with arthritis.

A variety of activities can be used for balance training in people with arthritis. Some authors have described techniques that use a combination of balance board and roller board activities.⁴⁰ Single-leg standing and tandem standing activities, as well as agility-training techniques that focus on quick stops and starts, sudden changes in direction, and crossover stepping, have also been combined with balance board activities to challenge balance.⁴⁰ Tai chi activities are also being used more frequently in aging people and those with arthritis.⁴¹ Even though strengthening exercise can result in improved balance and function, some evidence indicates that balance- and agility-training techniques, when combined with strengthening exercises, can result in greater short-term improvements in functional measures than strengthening alone can.⁴²

Pain-related fear

Patients' perception that physical activity or exercise may harm their joints is sometimes referred to as "pain-related fear." Pain-related fear may be a barrier to optimal patient participation in an exercise or physical activity program. Pain-related fear has been shown to be associated with poorer physical function scores in people with arthritis.⁴³ One rehabilitation approach that may improve the outcome of rehabilitation in patients with pain-related fear is "graded *in vivo* exposure" (GivE).⁴⁴ In this approach the therapist and patient identify the types of physical activity or tasks that invoke a fear response and then rank-order the tasks with respect to the amount of fear. At the beginning of therapy, patients are educated in the concept of fear avoidance behavior and how this can limit an individual's ability to function. During therapy the therapist models task-specific modifications and proper body mechanics for the fear-inducing tasks or activities. The patient then practices these modifications and body mechanic techniques under supervision of the therapist. The gradual and systematic exposure to the fear-inducing activity is intended to disconfirm the patient's pain and fear-related expectations associated with the physical activity.

Although the GivE approach has not been formally evaluated in people with arthritis, it would seem that this type of approach could be helpful for patients with arthritis who have fear of performing certain physical tasks or activities. Clinicians should assess whether their patients with arthritis are experiencing pain- or activity-related fear and pursue approaches that will help diminish the fear so that functional capacity can be optimized.

ADAPTIVE REHABILITATION APPROACHES

Because many arthritic conditions are progressive in nature, teaching compensatory skills to promote independent, safe, and comfortable functioning is a key rehabilitation technique. Many people with arthritis experience limitations in their ability to perform ADLs because of limitations in range of motion, strength, and endurance. The phrase *activities of daily living* refers to a very large category of tasks and activities: those that involve taking care of oneself and one's immediate environment. They are often broken down into basic ADLs, or tasks related to self-maintenance, such as functional mobility (including transfers), personal hygiene and grooming, bathing, bowel and bladder management and hygiene, dressing, eating, and sexual activity, and instrumental ADLs, or tasks that involve interacting with the immediate environment, such as care of others, use of communication devices, community mobility, financial management, meal preparation, home care, response to emergencies, and shopping.⁴⁵ Strong associations have been made between ADL ability and impairments in strength, range of motion, and endurance, which suggests that remediating these impairments can improve performance of ADLs.⁴⁶ However, research also suggests that a person's level of impairment does not always predict ADL performance⁴⁷ because other factors, such as the environment or pain-related fear, can facilitate or prevent function. Providing compensatory techniques is one method to improve ADL ability and the most responsive to changes in ability as the disease progresses.

Assistive devices

One method to remediate ADLs is to provide an assistive device. "Assistive device" is a broad term defined as "any item, piece of equipment, or product system, whether acquired commercially off the shelf, modified or customized, that is used to increase, maintain, or improve functional capabilities of individuals with disabilities."⁴⁸ Even though prescription of assistive devices is common in therapy, only limited high-quality evidence is available to support their use. The research available suggests that assistive devices can improve performance in people with arthritis⁴⁹ and that they have been associated with improved psychological well-being.⁵⁰

Unfortunately, compliance with the use of assistive devices may be limited; estimations suggest that 36% of bathing equipment, 26% of dressing devices, and 19% of mobility devices are not used.⁵¹ Compliance depends on a variety of factors such as age, diagnosis, disease severity, and perception of the utility and attractiveness of the assistive device.⁵² The environment in which the device will be used affects compliance; for example, durable medical equipment, such as toilet seats, may be discarded if they do not fit the toilet, if the user cannot access the bathroom because of narrow doorways, or if they do not fit the person.⁵¹ One way to increase compliance is to ensure that assistive devices are prescribed by an experienced person and that patients are properly trained in their use.⁵¹

One type of assistive device that can be either remedial or compensatory is a hand orthotic device, or splint.³ Hand splints can be used for a variety of reasons—to provide support, align joints, immobilize joints, reduce pain, prevent or correct deformity, assist weak muscles, or position the hand for functional activities—and they are particularly useful for patients with RA and carpometacarpal (CMC) joint OA. Hand splints can be custom-made by an occupational therapist or be purchased prefabricated.

Although hand splints are frequently provided to patients with arthritis, few high-quality studies have been performed to assess their effectiveness. Systematic reviews of the effectiveness of splints for RA have reported that the evidence is unclear whether splints significantly improve work performance, although they may have a positive effect on pain.⁵³ A systematic review of the effectiveness of opponens-type splints (a splint that immobilizes the thumb) in the treatment of CMC joint OA reported that these splints are effective in both reducing pain and increasing function.⁵⁴ One study that examined the effectiveness of splinting on increasing range of motion of the proximal interphalangeal joints of individuals with RA reported that both static splints (i.e., splints that have no moving parts) and dynamic splints (i.e., splints that apply a graded or increasing force on a contracted joint) are effective in increasing range of motion, increasing hand strength, and improving function.⁵⁵ Although the evidence to support hand splints is somewhat equivocal, Egan and colleagues⁵⁶ suggested that since splints are relatively inexpensive and not harmful, current clinical practice should be to prescribe splints for patients on a case-by-case basis to see whether they help.

Lower extremity orthoses, such as knee braces and shoe inserts, can also be used as adjunctive interventions to reduce pain, relieve joint stress, or improve joint stability in people with arthritis. Knee orthoses have specially designed axes and straps to reduce compartmental loading of the knee. The most common type is a valgus brace, in which a valgus force is applied to the knee through the brace to unload the medial compartment. These types of braces can also be modified to apply a varus load to the knee for patients with lateral compartment involvement. Evidence of the effectiveness of these braces is limited, but it appears that they can help some individuals.⁵⁷ Biomechanical studies have shown that these braces can reduce joint compartmental loading,⁵⁸ and a recent study suggested that bracing may improve joint stability.⁵⁹ Currently, no specific guidelines are available to identify who will respond to this type of bracing. There is probably a cutoff point with regard to the degree of joint deformity beyond which the brace may no longer be effective, but this cutoff point has not yet been established. The willingness of a patient to wear the brace can also be a limiting factor inasmuch as some patients find the brace to be cumbersome. However, newer, lighter-weight designs may help address this problem. Valgus bracing may be a reasonable option for patients who are not good candidates for surgical realignment procedures.

Like knee braces, shoe inserts may also be used to reduce lower extremity pain or joint stress. A lateral wedge insert is believed to reduce medial compartment loading indirectly by enhancing foot and ankle pronation, which in turn should result in increased valgus load at the knee. Some biomechanical studies have indicated that these inserts can reduce varus moments at the knee.⁶⁰ The use of a "subtalar" strap, combined with a lateral wedge, seems to have a moderately better effect in reducing medial compartment loads, as well as in improving pain and function, than a lateral wedge alone does.^{61,62} The strapping may help by preventing excessive

pronation at the foot and ankle, which might otherwise dissipate the effect of the insert on the knee. Regardless of whether a subtalar strap is used, it appears that this intervention is most effective in patients with mild to moderate arthritis and may not be very effective in those with severe knee OA. Additionally, recent evidence suggests that laterally wedged insoles provide no long-term symptomatic or structural benefits for patients with knee OA.⁶³

Self-management instruction

One common trend in arthritis management is education in self-management techniques.^{2,3} These programs provide people with arthritis education about aspects of their disease, such as pain management, fitness and exercise, and healthy eating, and are often combined with training in effective coping, such as goal setting, action plans, and problem solving.^{64,65} Such programs can vary tremendously in content and can include disease information, methods of pain management, exercise, training in ADLs, social skills training, and relaxation techniques.⁶⁴ Although the quality of the research varies, studies have generally found that education programs have a small effect on pain and a moderate effect on function in the short term,⁵³ but carryover of these positive outcomes is less apparent.^{65,66} Self-management programs using a variety of session numbers,⁶⁴ group versus individual design,⁶⁷ and various delivery systems such as a mail delivery program⁶⁸ or the Internet⁶⁹ have been shown to be effective. One common educational program is joint protection (JP). JP techniques are taught primarily to those with RA, although patients with OA have also been trained in JP.⁷⁰ JP programs focus on teaching techniques thought to reduce stress on joints weakened by the disease, thereby reducing the tendency for deformities such as subluxation and ulnar drift. Several high-quality systematic reviews and clinical practice guidelines specifically support the effectiveness of JP techniques in improving function.^{3,53}

Fatigue

Chronic fatigue is a very common, yet frequently undertreated symptom of many types of arthritis. Chronic fatigue in those with arthritis has been described as being different from the normal tiredness experienced by healthy people. Chronic fatigue is characterized as a profound lack of energy that is not linked to specific overexertion but occurs almost randomly.⁷¹ Chronic fatigue is reported by patients with arthritis to significantly affect many aspects of their life, including basic ADLs, work and leisure, and family relationships. Fatigue is reported to limit social contact, and many workers cut their work back because of fatigue.^{72,73} Although fatigue is often identified to be as limiting as pain for many people with arthritis, they seldom discuss it with others.

Interventions to remediate fatigue can generally be divided into two types: aerobic exercise and behavioral interventions. Aerobic exercise has been shown to be an effective method of reducing fatigue, and research suggests that low-intensity aerobics (such as brisk walking) performed at least three times weekly for 15 to 30 minutes can reduce feelings of chronic fatigue.⁷¹ Behavioral programs that provide education in self-management techniques have been shown to be effective in reducing fatigue.⁷¹ One fatigue self-management program is energy conservation. Energy conservation provides persons with arthritis specific strategies to address issues related to fatigue, such as valuing rest, budgeting and banking energy, taking planned rest periods, breaking fatiguing tasks down into smaller components, using good body mechanics, and learning to communicate personal needs to others.⁷⁴

Work adaptations

Work is a valued activity, both for individuals and for society. Arthritis is the third leading cause of work disability: 8.2 million working U.S. adults (about 1 in 20) report work limitations as a result of arthritis.⁷⁵ Work disability refers to limitations in the ability to work because of impaired health and is manifested as premature work cessation (before the normal age of retirement) and, among employed persons, as reduced productivity.

People with RA have identified several job accommodation strategies that reduce work disability. One common accommodation was to make the job more flexible, including controlling work hours, taking rest breaks, or delegating tasks. However, Chorus and coauthors⁷⁶ reported that job modifications that resulted in loss of productivity, such as working fewer hours or delegating, were associated with a greater risk for eventual work disability. Modifications developed with the assistance of a health care provider, such as work-specific self-management programs and ergonomic assessments to modify the work environment or work task methods to better fit the needs

of workers with arthritis, have been reported to be effective ways to adapt the job.⁷⁷⁻⁷⁹ Workers who received work interventions by health care professionals were less likely to report work disability.⁷⁸

One method for obtaining work modifications is use of the Americans with Disability Act (ADA), Title I. The ADA was enacted in 1990 to prevent discrimination in the workplace against workers with disabilities. An important aspect of the ADA was to ensure that employers provide workers with any requested “reasonable accommodation,” or a modification or adjustment in a job or work environment that enables a qualified person with a disability to perform essential job tasks. Reasonable accommodations can include physical changes in the environment (e.g., raising or lowering work heights), adaptive equipment (e.g., special chairs, power-assisted lifting devices), and changes in work organization (e.g., telecommuting, altered hours, changes in nonessential job function). Although the ADA is available for people with arthritis, few use it to remain employed. A recent study reported that although 63% of workers with arthritis needed a job accommodation, only 10% had used the ADA. Factors that affected use of the ADA included not knowing that the ADA was available, the perception that they did not have a disability that could be addressed through the ADA, lack of skill in requesting reasonable accommodations, and no interaction with a health professional who suggested using the ADA.⁸⁰

Vocational rehabilitation is another method to prevent work disability. Vocational rehabilitation is a coordinated, multidisciplinary program that addresses work retention, prevention of loss of work, or return-to-work programs. Vocational rehabilitation assists people in reentering employment in the same or different jobs after a period of sick or disability leave. The actual interventions vary according to the needs of each patient and are developed on a case-by-case basis. The effectiveness of vocational rehabilitation for people with arthritis has been assessed, with conflicting results. A systematic review of six uncontrolled studies on vocational rehabilitation for people with arthritis reported some evidence of short-term improvement in employment.⁸¹ More recent controlled studies were equivocal: Allaire and coworkers⁸² reported that vocational rehabilitation had a positive effect on job loss, whereas de Buck and associates⁸³ reported no difference when compared with usual outpatient care.

Unfortunately, work disability is rarely addressed in those with arthritis. A recent qualitative study examining issues experienced by workers with arthritis suggested that work is rarely discussed with physicians or health care practitioners.⁷⁸ Studies on workers with arthritis find that they frequently implement coping strategies such as changing jobs, reducing hours, or reconfiguring their workstation, but they rarely have interventions by health care practitioners.⁷⁸ Those in these studies who report having had work interventions by health care professionals were more likely to report less work disability.

Although ergonomic assessment, work self-management, and vocational rehabilitation may be effective strategies to reduce work disability, most workers with arthritis do not obtain these interventions. They may not know that ergonomic assessments exist, they may not know whom to request or pay for an ergonomic assessment, and they may fear disclosing their condition to an employer.⁷⁸ Unwillingness to disclose their arthritis condition to an employer and coworkers is fairly common in workers with RA. Many workers with RA report that they fear adverse consequences, such as loss of work, discrimination in job promotions, being less valued as a worker, stigmatization, and dealing with negative coworker reactions.⁷⁸ In addition to the barriers to obtaining ergonomic assessment and intervention through work, many workers with RA do not discuss their problems at work with their rheumatologists, who are gatekeepers for these interventions.⁸⁴

SUMMARY

The purpose of rehabilitation is to assist patients with arthritis in restoring and maintaining an optimal level of function. The patient is the main stakeholder in this endeavor and therefore sets the bar in determining the optimal level of function. Rehabilitation therapists identify the barriers that may limit the ability of people with arthritis to achieve optimal function and then provide interventions to overcome these barriers. Because the barriers are often multifactorial, a successful rehabilitation process will require a multidisciplinary effort that involves not only physical and occupational therapists but also clinical psychologists, vocational rehabilitation counselors, rehabilitation engineers, and recreational therapists.

In this chapter both remedial and adaptive rehabilitation approaches were discussed (Table 47.2). Many patients with arthritis need a combination of both approaches. Remedial rehabilitation is directed at restoring or

TABLE 47.2

Summary of rehabilitation techniques

Intervention	Application	Comments
Remedial approaches		
Physical agents Thermal agents (e.g., heat, cold, ultrasound) Electrical stimulation (e.g., TENS)	Pain control	Most appropriately applied on a case-by-case basis
Stretching/range of motion	Improve joint motion Improve function	
Joint mobilization	Improve joint motion Pain control Improve function	Lower-intensity joint mobilization may be effective in controlling pain.
Strengthening exercise Isometric Isotonic Isokinetic "Task specific"	Increase muscle force output Pain control (when combined with physical agents) Improve balance Improve function	Patients need a combination of strengthening (isometric, concentric, etc.) to best improve functional ability.
Aerobic exercise	Improve aerobic capacity and endurance Pain control Reduce fatigue Improve function Improve mental health	Walking or cycling programs have been shown to be effective methods to improve aerobic fitness.
Balance training	Improve balance and agility Improve function	Tai chi programs are potentially effective methods to improve balance.
Adaptive approaches		
Assistive devices	Compensate for impairments Improve function Improve mental health	Compliance can be an issue if the devices are improperly prescribed or provided without training in their use.
Splinting	Pain control Improve joint motion Provide support Immobilize joints Correct deformity Assist weak muscles Improve function	Splints should be considered on a case-by-case basis.
Educational programs Self-management Joint protection Vocational rehabilitation	Pain control Improve function Reduce fatigue	

TENS, transcutaneous electrical nerve stimulation.

establishing physical capacity and ability, with a focus on addressing the impairments associated with arthritis.

Adaptive rehabilitation is directed at finding ways to compensate for lost or absent physical capacity or ability and focuses on developing alternative or supplementary methods to assist patients in improving their performance

of tasks. Because many people with arthritis are still of working age, ergonomic assessments and work task modifications for these patients are important. Physicians and therapists may need to take a more proactive role in making sure that the occupational needs of their patients with arthritis are being assessed and addressed.

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48A

Complementary and alternative medicine

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- The majority of rheumatology patients use some form of complementary and alternative medicine (CAM).
- Acupuncture, herbal medicine, nutraceuticals, and homeopathy are among the most commonly used CAM treatments.
- The majority of research on traditional Chinese medicine in the West has focused on acupuncture.
- Studies have shown acupuncture to be effective for specific types of pain reduction.
- Some herbal therapies may be as effective as analgesics and antiinflammatories for rheumatic and musculoskeletal conditions.
- Nutraceuticals, in particular glucosamine and chondroitin, may be effective in the treatment of osteoarthritis and in prevention of long-term joint damage.
- Homeopathy has not been definitively proven to work for treatment of rheumatologic conditions.
- Physicians should consider that CAM can be integrated into the conventional management of rheumatologic conditions in a thoughtful, professional, and cooperative manner.
- Rheumatologists need to consider the view of patients with rheumatic diseases and be prepared to have informed discussions with them about CAM.

OVERVIEW

Complementary, alternative, and integrative medicine are blanket terms that comprise a large variety of health treatments clustered together because they are generally considered to be outside the parameters of conventional treatment.¹ The terms *complementary, alternative, and integrative* refer not just to the particular modalities used but to the manner in which health care is obtained; in other words, people can obtain health care from a nonconventional practitioner in conjunction with conventional care (complementary) or instead of conventional care (alternative), or from a provider or group of providers that have blended conventional and nonconventional care in their practice (integrative).

It is commonly known that the traditional medical systems of Asia have been practiced for thousands of years, but the history of complementary and alternative medicine (CAM) in the West, although well documented,² is not always discussed. CAM use in the West is not a recent phenomenon; rather, many of the alternative systems of medicine being used today (e.g., herbalism, chiropractic, naturopathy, and homeopathy) have evolved alongside allopathic medicine. In addition, Asian systems of medicine were formally introduced to the West as early as 1683, when the first European text on acupuncture and arthritis was written,³ and the first journal articles on acupuncture appeared in the 1820s.^{4,5} Over time, as these medical systems developed and the needs of the population continuously changed, the popularity of CAM ebbed and flowed accordingly.⁶

WHO SEEKS COMPLEMENTARY AND ALTERNATIVE MEDICINE AND WHY

According to nationwide population-based surveys, a substantial proportion of U.S. adults use CAM,⁷ and the prevalence of CAM use has remained

consistently high in recent years.⁸ CAM use is more prevalent among women, the middle aged, and the well educated⁹ but is by no means restricted to these groups.^{10,11}

People who have chronic diseases in general and rheumatologic diseases in particular are more likely to use CAM. Reported prevalence rates for CAM use in rheumatology patients vary across surveys and diagnoses.¹¹⁻²⁰ CAM is also commonly used by rheumatology patients in non-Western cultures.²¹⁻²⁴ Variation in reported prevalence rates probably reflects differences in methodology and CAM definitions as well as differences in underlying rates of CAM use.

Rheumatology patients use CAM partly because they perceive a need for additional treatment. Health indicators that have been associated with CAM use in arthritis, lupus, and/or osteoporosis include more severe pain, poorer functional status, poorer self-rated health, longer disease duration, and worse lumbar spine T-score.^{11,15,18,19,23,25-27} Consistent with these findings, rheumatology patients commonly report using CAM to help them manage ongoing symptoms such as pain and fatigue.^{23,25,28} Having additional comorbidities may also increase the likelihood of CAM use.^{11,27,29} Personality factors have also been associated with CAM use.^{29,30}

CAM is often used alongside rather than instead of conventional medicine,^{13,22,27,31-33} and patients make decisions about individual CAM modalities in the context of other treatments that they are currently using.³⁴ When patients take an active role in choosing to try CAM treatments they also review their choices and cease using therapies that prove ineffective³⁵ or otherwise dissatisfying.³⁶ For some patients, CAM provides a means to actively avoid or delay more invasive conventional treatments such as surgery.³⁷ For others, CAM is simply another form of treatment that they will try if their doctor recommends it.³⁸

CAM use can be seen contextually as just one part of patients' attempts to cope with the challenges of illness on a day-to-day basis. From this perspective, the task for doctors is to support and guide patients in making safe, well-informed decisions about their personal use of CAM in relation to other forms of health care. Evidence strongly suggests that patients would value such support and guidance, particular with regard to potential drug interactions.¹⁶

WIDELY USED COMPLEMENTARY AND ALTERNATIVE MEDICINE SYSTEMS AND THEIR THERAPIES

Surveys indicate that chiropractic, copper bracelets, magnets, herbs, topical treatments, electrical stimulators, nutraceuticals, homeopathy, massage, acupuncture, diet therapies, relaxation, and spiritual healing are all therapies used by rheumatology patients.^{39,40} This section aims to give a brief introduction to the philosophy and practice of a few main, commonly used modalities. These examples have been chosen to illustrate the complexity of CAM systems as well as to introduce the reader to some of the major clinical, philosophical, and research issues that must be confronted if integration of these therapies into mainstream medical practice is to occur.

Traditional Chinese medicine and acupuncture
Philosophy and history

Traditional Chinese medicine (TCM) is the product of thousands of years of philosophical, political, spiritual, and scientific evolution. Although its exact origin remains controversial, it is generally accepted that the first true Chinese medical texts emerged around 200 BC.⁴¹ TCM is an intricate medical system based on ancient philosophies, symptom-based clinical practice, a complicated individualized diagnostic system, and a variety of treatment

modalities including various types of acupuncture, massage (*tui na*), and herbal medicines. Like many CAM systems, TCM is based on a belief in the existence of a life force or vital energy that runs through the body and affects its functioning. Imbalances are diagnosed into syndrome patterns according to a number of complex yet subtle theories that provide the basis for treatment. Central to this is the theory of yin and yang. The terms and concepts within TCM have no Western equivalents; at best, they are roughly translated and are therefore easily misinterpreted.

Treatment

The TCM system encompasses many different treatment modalities, each, according to traditional theories, used to shift the vital energy of the body. Many of these techniques stimulate specific points on the body to alter the flow of *qi* (a term frequently used to describe the life force or energy in the body); usually, these points are located on meridians (specific channels that carry *qi* though the body; Fig. 48A.1). Acupuncture involves the insertion of thin, stainless steel needles into these points. Internal remedies are a vital component of TCM. These herbal remedies are always given in combination and are chosen to complement and balance each other. Additionally, TCM incorporates a unique system of massage called *tui na* and uses meditative exercises such as *qi gong*.

The TCM approach to rheumatic disease is very different from that of conventional modern medicine. The concept of rheumatic disease as it is understood in the West does not exist in TCM. The TCM treatment of rheumatic disorders, as in many CAM disciplines, is individualized, and the majority of rheumatic disorders fall into the general classification of painful obstructions (*bi syndrome*). Consequently patients with the same conventional diagnosis may receive different TCM diagnoses and treatments.

Evidence

Although there have been many randomized controlled trials examining the use of acupuncture for treatment of rheumatic conditions, they have often been of questionable methodologic quality. As a result, systematic reviews are of limited value and difficult to interpret. For example, for the rheumatic conditions of fibromyalgia⁴²⁻⁴⁴ and rheumatoid arthritis,^{45,46} no firm conclusions about efficacy, or lack thereof, can be drawn from systematic reviews because the existing randomized controlled trials are scarce, underpowered, heterogeneous, and often methodologically unsound.

However, for musculoskeletal pain (i.e., back and neck pain) and osteoarthritis, there is a substantial database of adequately powered and methodologically sound randomized controlled trials, which provide a reliable evidence base for systematic reviews. Although there have been previous summary-data systematic reviews of the use of acupuncture for musculoskeletal pain and osteoarthritis, the most current and valid estimates of the effects of acupuncture for treatment of these two conditions comes from a 2012 meta-analysis of individual patient data.⁴⁷ The individual patient data for acupuncture included data for individual participants in 29 trials, totaling 17,922 patients. Each trial was reanalyzed using analysis of covariance, with the standardized mean difference (i.e., post-treatment scores divided by pooled standard deviations) as the dependent variable, and the covariates being the baseline scores and the variables used to stratify randomization. The standardized mean difference was the measure of effect size because the trials assessed the same pain outcome but measured pain in various ways. The meta-analysis found statistically significant differences between true acupuncture and a sham acupuncture control procedure, and also between true acupuncture and no acupuncture. After exclusion of a set of outlier

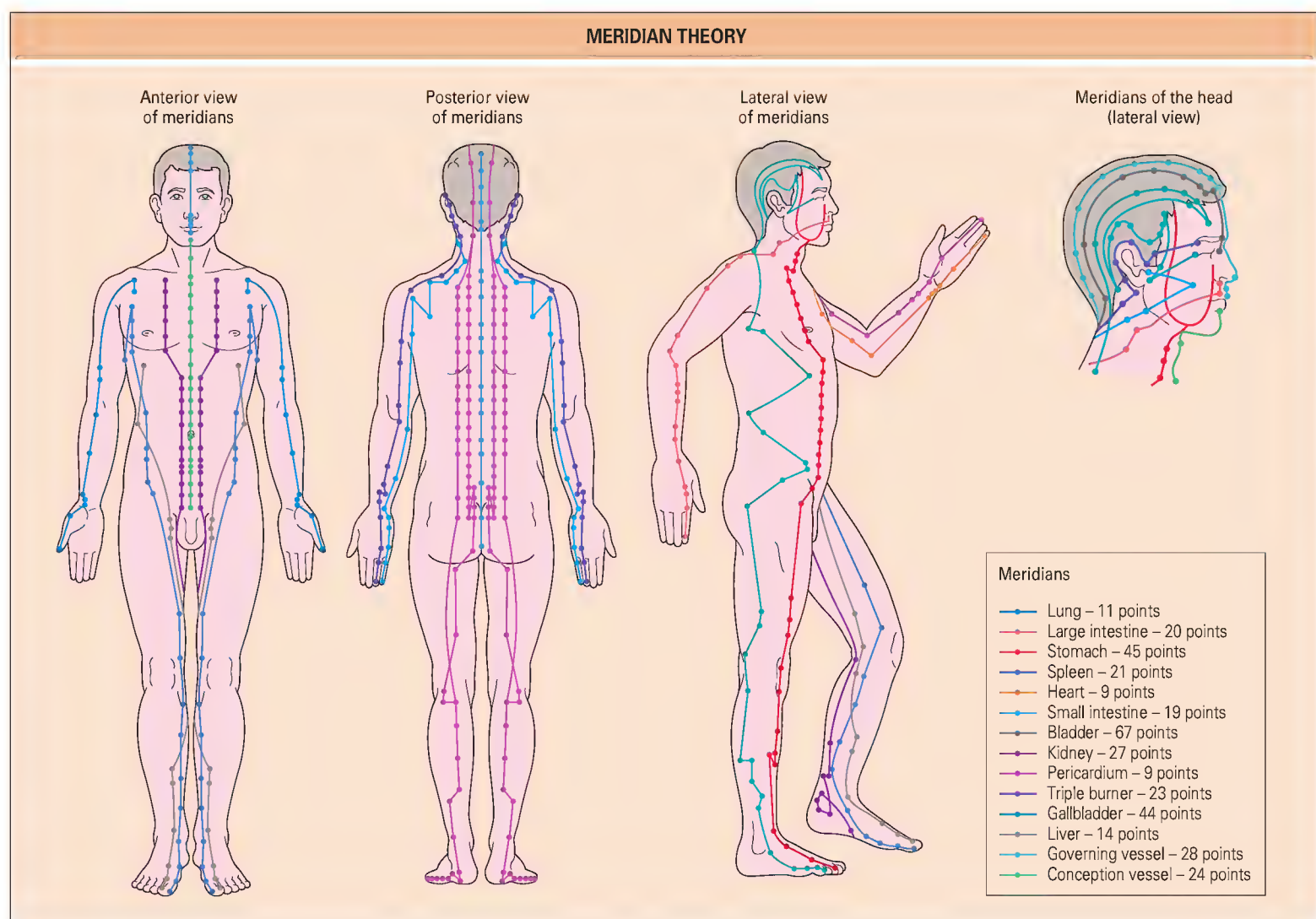


Fig. 48A.1 Qi is believed to run through the body in channels called *meridians*. Although most meridians are associated with a major organ of the body (e.g., kidney, spleen), they each govern a much broader range of emotional and physiologic functions. Although they flow inside the tissue and organs of the body, the meridians are accessible from the surface in some areas; thus the *qi* can be manipulated by needling acupuncture points on the meridians. However, *qi* flow is not restricted to specific channels; there are numerous acupuncture points that are not located on meridians.

trials that strongly favored acupuncture, the effect sizes were fairly similar for these two rheumatic conditions. Relative to a sham acupuncture control group, participants receiving true acupuncture had less pain, with effect sizes of 0.23 (95% confidence interval [CI], 0.13 to 0.33) and 0.16 (95% CI, 0.07 to 0.25) for musculoskeletal pain and osteoarthritis, respectively; the corresponding effect sizes were 0.55 (95% CI, 0.51 to 0.58) and 0.57 (95% CI, 0.50 to 0.64) relative to a no-acupuncture control group. The average effects of acupuncture relative to no acupuncture were thus of clear clinical relevance. The effects of acupuncture relative to sham acupuncture were smaller; however, there were nonetheless robust differences that could be clearly distinguished from bias.

The relatively modest effect sizes for acupuncture relative to a sham acupuncture procedure and the larger effects of acupuncture relative to a no-acupuncture control condition suggest that other factors besides the point-specific placement of the needles play an important role in the overall therapeutic effect of acupuncture. These factors include the nonspecific physiologic effects of needling as well as the psychological effects related to the participants' expectations and beliefs that acupuncture will be more effective than no acupuncture (i.e., the placebo effects). This individual patient data meta-analysis of acupuncture studies has provided the strongest evidence to date that acupuncture is a reasonable referral option for patients of rheumatologists.^{48,49}

In addition to the effectiveness of acupuncture, other important considerations in determining whether or not to include acupuncture as part of standard care for rheumatology patients include acupuncture's adverse effects and its benefits relative to its costs. Incidence rates for major adverse effects of acupuncture, which are extremely rare, are best estimated from large prospective surveys of practitioners. Four such surveys of acupuncture safety, two conducted in Germany^{48,49} and two in the United Kingdom,^{50,51} confirm that serious adverse events after acupuncture are very uncommon.

It is also important to study the benefits of acupuncture relative to its costs, using cost-effectiveness trials.^{48,52,53} Indeed, because acupuncture has a low risk of adverse events, and because rheumatology patients are accepting of acupuncture,⁵⁴ its benefit-cost ratio is probably the most important factor to consider in determining acupuncture's clinical usefulness. Five methodologically sound trials have evaluated the cost effectiveness of acupuncture for rheumatic conditions, including two trials in patients with low back pain,^{52,55} two in patients with osteoarthritis,^{33,56} and one in patients with neck pain.⁵⁷ The outcome measure used in all of these trials was the incremental cost incurred per quality-adjusted life-year gained. All of these trials found that acupuncture treatment was associated with significantly higher costs than usual care, with this increase in costs due mostly to the cost of the acupuncture treatments. However, these trials also all found that acupuncture provided a cost-effective use of health care resources. That is, in all five of these cost-effectiveness trials, the incremental cost-effectiveness ratio per quality-adjusted life-year gained met international threshold values for a cost-effective treatment.

Several systematically derived evidence-based clinical practice guidelines exist for both osteoarthritis and low back pain. Major clinical practice guidelines for osteoarthritis have not endorsed the use of acupuncture for this condition, primarily citing the fact that there is not sufficient conclusive evidence of clinical efficacy or cost effectiveness to allow a firm recommendation.⁵⁸⁻⁶¹ However, these guidelines are periodically updated, and their recommendations can change with changes in the evidence landscape. In contrast, major guidelines for treatment of low back pain⁶²⁻⁶⁵ generally recommend that clinicians consider acupuncture as one possible treatment option for patients with low back pain. Indeed, because the UK National Institute for Health and Clinical Excellence recommended acupuncture as a treatment option for patients with low back pain,⁶² the UK National Health Service now provides a maximum of 10 sessions of acupuncture over a period of 12 weeks for people with low back pain that has persisted for longer than 6 weeks.

Herbal medicine

Philosophy and history

Herbs are the most popular and ancient CAM modality⁷ and are commonly used in isolation with expectations that they will treat a particular disease or symptom. Traditionally, combinations of herbs are used in multiple organ systems and are applicable to many different conditions. Herbal treatment protocols are highly individualized, and indications for herbs may be very specific. The majority of herb users self-medicate without informing their doctors⁶⁶ or herbalist, and inappropriate selection or combinations of herbs can cause adverse events that may mimic, magnify, or oppose the effects of pharmaceuticals^{66,67} (Table 48A.1). Accordingly, inappropriate combinations or improper use of herbs can result in serious adverse effects. One such

example involves ephedra,⁶⁸ a powerful sympathetic nervous system stimulant that when used in excessive doses or inappropriate situations for weight loss and increased energy has resulted in serious adverse effects.

The pragmatic clinical practice of traditional herbalism is a plant-centered whole system and requires the use of whole plant material as it is found naturally. This ensures that all the possible complex and unidentified synergistic compounds within the plant are included along with the known active constituents.

Treatment

Herbs are usually prescribed in combination and treatment is individualized. Treatments are usually given orally but may be prescribed as external salves. The bulk of a typical herbal formula is composed of various different herbal actives, including antirheumatics and antiinflammatories such as sarsaparilla, black cohosh, celery, meadowsweet, nettle, turmeric, boswellia, wild yam, devil's claw, and ginger. Often, blends contain diuretics, immune stimulants, circulatory stimulants, and digestive tonics as well; only a small portion of the blend addresses symptoms through analgesic action.⁶⁹ Nutritional approaches are frequently combined with herbal approaches; ideally, herbs are woven into the daily diet as spices and foods.

Evidence

To date, systematic and meta-analytic reviews of the literature in rheumatology indicate that a number of herbs may be effective treatments for rheumatic and musculoskeletal conditions.⁷⁰⁻⁷³ These herbs have been evaluated as individual products, in contrast with their traditional use. Those for which there is the strongest clinical evidence to date are capsaicin, devil's claw, ginger, boswellia, and several herbal combination products (Phytodolor, SK1 306X).

Capsaicin

Capsaicin is an extract of chili peppers from the genus *Capsicum*, which includes the cayenne pepper commonly used in culinary applications. When used therapeutically for pain relief, capsaicin is usually applied topically as a gel with a capsaicin concentration ranging from 2.5% to 8%. The primary mechanism through which capsaicin is thought to reduce pain is depletion of substance P, a neuropeptide involved in the transmission of pain signals from nerve endings to the brain and the activation of inflammatory cytokines in joints. Many high-quality randomized, double-blind, placebo-controlled trials have found topical application of capsaicin gel to be an effective treatment for osteoarthritis pain. Four randomized controlled trials investigated topical capsaicin (cayenne) for the treatment of osteoarthritis.⁷⁴⁻⁷⁷ Collectively, meta-analysis of these data indicates that capsaicin is an effective therapy for pain, tenderness, and impaired range of motion.^{73,78} Pooled data in a meta-analysis conducted by Zhang and Li Wan Po⁷⁸ found that topical application of capsaicin in concentrations between 2.5% to 7.5% was four times as effective as placebo gel in reducing pain and tenderness of osteoarthritis. No serious adverse effects were noted in these trials, although minor burning following application of capsaicin gel at these concentrations is relatively common. Motivated by the relatively frequent sensation of minor burning experienced at these concentrations, a recent trial conducted by Kosuwon and colleagues⁷⁹ assessed topical application of capsaicin at a concentration of 1.25% in 100 patients with mild to moderate osteoarthritis of the knee. The authors determined that capsaicin at this lower concentration was effective in improving pain, stiffness, and function. Although a mild burning sensation was common, no participants dropped out of the study for this reason. Thus lower concentrations of topically applied capsaicin appear to be an effective treatment option for mild to moderate osteoarthritis.

Devil's claw

Devil's claw is an extract obtained from the root of the African plant *Harpagophytum procumbens*. Devil's claw has been found to have strong antiinflammatory and analgesic effects,⁸⁰ thought to be due largely to high concentrations of the iridoid glycosides, including harpagoside. Numerous observational studies and several high-quality randomized, placebo-controlled trials and systematic reviews have been conducted assessing the efficacy of devil's claw in osteoarthritis. Brien and associates⁸¹ reviewed 14 studies examining devil's claw as a treatment for osteoarthritis: 4 double-blind, placebo-controlled trials, 2 comparator trials, and 8 observational studies. The authors concluded that devil's claw appears to be effective in reducing the pain of osteoarthritis, although higher-quality trials are needed. Gagnier and colleagues⁸² reviewed six randomized trials and determined that devil's claw standardized to 60 mg harpagoside was a moderately effective treatment for osteoarthritis of the spine, hip, and knee. Although devil's claw appears to carry only a minor risk of adverse effects compared with

TABLE 48A.1
Reported potential herb-drug interactions relevant to rheumatology practice

Herb	Pharmaceutical	Effect	Mechanism/comment
Asian herbal mixtures: Sho-saiko-to	Prednisone	Decreased AUC	Contains <i>Glycyrrhiza glabra</i> , <i>Bupleurum falcatum</i> , <i>Pinellia ternate</i> , <i>Scutellaria abaicalensis</i> , <i>Zizyphus vulgaris</i> , <i>Panax ginseng</i> , <i>Zingiber officinale</i>
Saiboku-to		Increased AUC	Same as above, with addition of <i>Poria cocos</i> , <i>Magnolia officinalis</i> , and <i>Perillae frutescens</i>
Betel nut (<i>Areca catechu</i>)	Prednisone, albuterol (salbutamol)	Inadequate control of asthma	Arecoline challenge caused dose-related bronchoconstriction
Cayenne (<i>Capsicum</i> spp.)	ACE inhibitors Theophylline	Cough Increased absorption and bioavailability	Capsaicin depletes substance P
Devil's claw (<i>Harpagophytum procumbens</i>)	Warfarin	Purpura	
Dan shen (<i>Salvia miltiorrhiza</i>)	Warfarin Aspirin Warfarin Paracetamol and ergotamine/caffeine Thiazide diuretic	Increased INR, prolonged PT/PTT Spontaneous hyphema Intracerebral hemorrhage Bilateral subdural hematoma Hypertension	Decreased elimination of warfarin in rats Inhibition of platelet adhesion factor May be due to ginkgo alone Ginkgo alone is not associated with hypertension.
GLA-rich herbs (evening primrose, black currant, borage)	Drugs that lower seizure threshold	Increased adverse effects	Decreased seizure threshold
Licorice (<i>Glycyrrhiza glabra</i>)	Prednisone	Glycyrrhizin decreases plasma clearance, increases AUC, increases plasma concentrations of prednisolone	Glycyrrhizin and its metabolite, glycyrrhetic acid, are inhibitors of 5 α ,5 β -reductase and 11 β -dehydrogenase (converts endogenous cortisol to cortisone)
	Hydrocortisone	Glycyrrhetic acid potentiates cutaneous vasoconstrictor response	
	MAOIs Oral contraceptives	Increased adverse effects Hypertension, edema, hypokalemia	Glycyrrhizin is an MAOI Oral contraceptives may increase sensitivity to glycyrrhizin
Nettles (<i>Urtica dioica</i>)	NSAIDs	Increased therapeutic effect	Potential of antiinflammatory activity
<i>Panax ginseng</i>	Warfarin Phenelzine Corticosteroids Estrogen replacement	Decreased INR Headache and tremor, mania Increased adverse effects Postmenopausal bleeding or mastalgia	Similar adverse effects
Papaya (<i>Carica papaya</i>)	Warfarin	Increased INR	
St. John's wort (<i>Hypericum perforatum</i>)	Paroxetine Trazodone Sertraline Nefazodone Theophylline Digoxin	Lethargy, incontinence Mild serotonin syndrome Mild serotonin syndrome Mild serotonin syndrome Decreased theophylline concentrations Decreased AUC, decreased peak and trough concentrations	Can occur with St. John's wort alone Most studies indicate that St. John's wort inhibits cytochrome P450 isoenzymes.
	Phenprocoumon Cyclosporin Oral contraceptives	Decreased AUC Decreased concentrations in serum Breakthrough bleeding	
Tamarind (<i>Tamarindus indica</i>)	Aspirin	Increased bioavailability of aspirin	
Yohimbe (<i>Pausinystalla yohimbe</i>)	Tricyclic antidepressants	Hypertension	Yohimbe alone is associated with hypertension; combination with tricyclics lowers active yohimbe dose

It is impossible to summarize all drug-herb interactions. Clinical data are sparse, uncontrolled, and often unreliable; most data are in the form of case reports, and information on dosage, temporal relations, contamination, and concomitant drug-herb use are often unreported. Moreover, the majority of the herb-drug interactions described in the literature are theoretical and have not been shown to occur in clinical practice; thus only clinically reported interactions are summarized here. In addition, the effects may depend on mode of ingestion; for example, effects may be stronger if an extract is used (e.g., standardized oil) than when herbs are incorporated into the diet (e.g., garlic cloves in food).

ACE, angiotensin-converting enzyme; AUC, area under the curve; INR, international normalized ratio; GLA, γ -linolenic acid; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal antiinflammatory drug; PT, dilute prothrombin time; PTT, partial thromboplastin time.

Data from Fugh-Berman A. Herb-drug interactions. *Lancet* 2000;355:134-8; Deol CL, Schnitzer TJ, Lipstein E, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. *Clin Ther* 1991;13:383-95; Hordy M. Herb-drug interactions: an evidence-based table. *Altern Med Alert* 2000;June:64-9.

nonsteroidal antiinflammatory drugs (NSAIDs), there exists the potential for interaction with anticoagulant medications, and patients taking these drugs should be monitored.

Ginger

The root of the ginger plant (*Zingiber officinale*) has been consumed and used medicinally in Asian cultures for thousands of years. Among its many

medicinal properties, ginger has demonstrated potent antiinflammatory effects, which are due in part to its high concentration of gingerols and salicylates. Studies show that ginger root targets inflammation through several different pathways (including prostaglandin activity and inhibition of 5-lipoxygenase enzyme,^{83,84} which may contribute to its ability to reduce pain. Four randomized controlled trials⁸⁵⁻⁸⁸ have found that ginger was superior to placebo in reducing pain scores, usage of analgesic medications,

and disability related to osteoarthritis. The dosage typically used in clinical practice is 1000 mg daily over a treatment period of at least 4 weeks. Although mild gastrointestinal distress may occur at higher doses, ginger is highly tolerable and adverse effects are rare. Ginger may interact with anti-coagulant medications, so caution should be taken in this regard.

Boswellia serrata

Boswellia serrata, also known as *Indian frankincense*, is a plant extract that has been featured as an important component of Ayurvedic medicine for thousands of years. As with many herbs used in the treatment of osteoarthritis, Western medicine has corroborated traditional usage because *Boswellia serrata* elicits potent antiinflammatory activity through its inhibition of the 5-lipoxygenase enzyme. Several forms of *Boswellia serrata* have been studied and used clinically, including traditional 60% to 70% extracts of *Boswellia serrata* gum resin and the commercial preparations 5-Loxin and Aflapin. Five randomized controlled trials have been conducted assessing the effects of *Boswellia serrata* extracts on osteoarthritis of the knee.⁸⁹⁻⁹³ All of these trials found statistically and clinically significant reductions in pain and improvements in physical function. Improvement in symptoms was noticed as early as 5 days after treatment commenced, and in one trial, these benefits persisted for 1 month following conclusion of treatment. Daily dosages used in these studies were 100 mg of Aflapin, 250 mg of 5-Loxin, and 333 mg of 65% standardized *Boswellia serrata* extract. *Boswellia serrata* was well tolerated in all trials, and aside from minor gastrointestinal distress in some participants, very few adverse effects were noted.

Herbal combination products

Practicing herbalists generally prescribe herbs in combination, and for this reason a variety of herbal combination products are available commercially. Of these products, the two for which the clinical evidence is most promising are SKI 306X (*Clematis mandshurica*, *Prunella vulgaris*, and *Trichosanthes kirilowii*),⁹⁴⁻⁹⁶ and Phytodolor (aspen [*Populus tremula*], common ash bark [*Fraxinus excelsior*], and goldenrod herb [*Solidago vigaurea*]).⁹⁷ Six randomized controlled trials of the herbal mixture Phytodolor showed significantly decreased pain,^{72,98,99} increased function,⁹⁸ and decreased need for rescue medication^{100,101} in patients with mixed rheumatic disorders, including osteoarthritis. A recent meta-analysis of 11 randomized controlled trials found that Phytodolor was superior to placebo in reducing pain associated with musculoskeletal disorders. The efficacy of Phytodolor in reducing pain did not differ statistically from that of NSAIDs, but it caused no major adverse events and far fewer minor adverse events than NSAID therapy.⁹⁷ Because of the paucity of high-quality trials, many herbs traditionally used by professional herbalists have not been investigated adequately (if at all). Further research is clearly needed.

Nutraceuticals and dietary supplements

The term *nutraceuticals* is a general classification that refers to the wide array of biologically based products available to health practitioners and consumers; they include vitamins, minerals, neurotransmitters, hormones, animal products such as shark cartilage and glandular preparations, and other naturally occurring substances such as glucosamine and S-adenosylmethionine (SAM-e). The sheer number of these products can be overwhelming to practitioners and consumers alike; to date, the efficacy and safety of most of these therapies have not been thoroughly investigated. However, there are several nutraceuticals for which a substantial evidence base is beginning to emerge in the treatment of rheumatic and musculoskeletal diseases, most notably glucosamine and chondroitin, SAM-e, and essential fatty acids.

Glucosamine and chondroitin

Current research suggests that glucosamine and chondroitin may be chondroprotective agents.¹⁰² Both are constituents of connective tissue and are capable of increasing proteoglycan synthesis in articular cartilage.¹⁰³ In addition, glucosamine and chondroitin appear to regulate gene expression of nitric oxide and prostaglandins involved in osteoarthritis.¹⁰⁴ Moreover, despite controversy in this area, both substances appear to be absorbed intact in the digestive tract and have a minimal adverse effect profile.^{102,105,106} Numerous narrative and meta-analytic reviews indicate that glucosamine, either combined with chondroitin or alone, is an effective treatment for osteoarthritis.¹⁰⁷⁻¹⁰⁹ Towheed and colleagues¹⁰⁹ reviewed 16 randomized double-blind studies and found glucosamine to be significantly more effective than placebo and more effective than or equal to NSAIDs with minimal adverse effects. McAlindon and associates¹⁰⁸ reviewed randomized trials of both glucosamine and chondroitin and found moderate to large effect sizes; modest yet positive effective sizes were found when methodologically weak studies were excluded and results were recalculated for outcomes at

4 weeks. A randomized controlled trial (n = 212) published since the aforementioned reviews¹¹⁰ has shown that patients taking 1500 mg of oral glucosamine sulfate daily over 3 years experienced no significant joint space loss and minimum joint space narrowing compared with patients receiving placebo.

The large Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)¹¹¹ funded by the National Institutes of Health compared glucosamine alone, chondroitin sulfate alone, glucosamine/chondroitin sulfate, and celecoxib with placebo. Participants in the glucosamine/chondroitin group did not demonstrate a statistically significant improvement compared with the placebo group in primary outcome (20% improvement in WOMAC pain score) in the overall study sample of patients with osteoarthritis of the knee. Some 66.6% of the overall study sample in the glucosamine/chondroitin group experienced at least a 20% improvement in pain, and the lack of statistical significance was thought by the authors to be due to the surprisingly high improvement in the placebo group (60.1%).¹¹²

Although the findings of the more than 50 randomized controlled trials of the use of glucosamine/chondroitin in osteoarthritis have not been universally positive, consideration of the totality of the evidence suggests that glucosamine/chondroitin is a safe and at least moderately effective treatment for osteoarthritis. A daily dose of 1500 mg glucosamine and 1200 mg chondroitin has been studied most often and is the typical recommended dosage.

S-adenosylmethionine

SAM-e originally was used to treat depression,^{113,114} and the effects of SAM-e on joint pain were discovered serendipitously when they were observed as side effects in clinical trials. Produced from L-methionine and adenosine triphosphate, SAM-e is a methyl donor involved in a wide variety of metabolic processes throughout the body.¹¹⁵ Although the mechanism of action is not completely understood, SAM-e has been shown to have antiinflammatory and analgesic effects without gastrointestinal damage in animal models¹¹⁶; *in vitro*, SAM-e has exhibited chondroprotective effects via the stimulation of chondrocytes and the subsequent increase in new cartilage production.¹¹⁷

A meta-analysis of 13 trials investigating SAM-e in the treatment of osteoarthritis¹¹⁸ indicated that SAM-e is comparable to ibuprofen and superior to placebo. A large randomized controlled trial published after this review compared the efficacy of SAM-e with that of celecoxib in patients with osteoarthritis.¹⁰⁴ The study found that despite a slower onset of action, SAM-e was as effective as celecoxib in relieving pain and improving physical function after 16 weeks of treatment. SAM-e has no known adverse effects,¹¹⁴ but the long-term effects are unknown. Most clinical studies to date have used a daily dosage of between 400 and 1600 mg.

Essential fatty acids

Essential fatty acids, including ω -6 fatty acids—linolenic acid (LA) and γ -linolenic acid (GLA)—and ω -3 fatty acids— α -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)—are the first components of a physiologic cascade that results in prostaglandin, leukotriene, and thromboxane production.¹¹⁹ Specifically, the presence of ω -3 fatty acids can antagonize the cellular biosynthesis of prostaglandins E₂, interleukin-1 β , leukotriene B₄, and tumor necrosis factor^{120,121}; these compounds play an important role in the pathophysiology of rheumatoid arthritis.¹²² Moreover, ω -3 fatty acids may inhibit the platelet-activating factor synthesis pathway, the cyclooxygenase pathway, and the 5-lipoxygenase pathway.¹²³

The ω -3 fatty acids have been shown in numerous reviews to improve rheumatoid arthritis symptoms.^{121,124-126} In addition, multiple studies indicate that ω -3 supplementation can reduce dependence on NSAIDs and antirheumatic drugs¹²⁷⁻¹³⁰; however, additional studies are needed before definitive conclusions can be made.¹²¹ No significant toxicities have been associated with their use.¹³¹

The ω -3 fatty acids are found in fish oils (EPA, DHA), leafy green vegetables (ALA), and plant oils such as flaxseed, rapeseed, and walnut oils (ALA); although all forms are important, EPA and DHA are more easily utilized by the body,¹³² because conversion from ALA to EPA and DHA is poor. For this reason, the optimal forms of ω -3 fatty acids taken for therapeutic purposes in rheumatic conditions are EPA and DHA. To date, most studies have investigated the effects of fish oils; these studies show that a minimum daily dosage of 3 g of EPA and DHA is required for clinical efficacy, and benefits become apparent after a minimum of 12 weeks.¹²¹

In addition, there is evidence for the efficacy of certain ω -6 fatty acids¹¹⁹; these, however, are generally administered in the form of herbal extracts of evening primrose, borage, or black currant.^{78,133,134} In a systematic review Little and colleagues¹³⁵ examined herbal interventions using herbs rich in GLA to treat rheumatoid arthritis. Compared with placebo oils (olive oil,

sunflower oil, cottonseed oil, liquid paraffin, and soybean oil), the oils containing GLA significantly improved joint tenderness, swelling, stiffness, and functionality.

Avocado/soybean unsaponifiables

Avocado/soybean unsaponifiables (ASU) is a compound consisting of the unsaponifiable oils (remnants after hydrolysis that do not form soap) of avocado and soybean. ASU is composed of one third avocado and two thirds soybean unsaponifiable oils. An extensive body of literature supports ASU's antiinflammatory properties, including blocking the activation of cyclooxygenase-2 transcripts and the secretion of prostaglandin E₂ as well as inhibiting the inflammatory cytokines tumor necrosis factor- α and interleukin-1 β .¹³⁶ ASU has also demonstrated the ability to stimulate the synthesis of collagen in human joint chondrocyte cultures.¹³⁷ The efficacy of ASU in improving osteoarthritis of the knee and hip has been evaluated in four randomized controlled trials that were the subject of a meta-analysis.¹³⁸ Three of these trials found that ASU was significantly more effective than placebo in improving osteoarthritis symptoms, whereas the fourth found no significant improvement compared with placebo. Meta-analysis of data from these studies (n = 664) found that twice as many participants in the ASU groups as in the placebo groups reported improvement in symptoms (reduced pain and increased ability to perform activities of daily living). ASU was associated with very few adverse effects in these studies. The typical dosage was 300 mg/day.

Homeopathy

Homeopathy is probably one of the most widespread, and certainly one of the most controversial, whole-system approaches within CAM. It involves a long and involved consultation and a prescription of often very dilute, indeed in some cases ultramolecular, "medication." The first principle of homeopathy is the idea of similars: this principle states that patients who have particular signs and symptoms can be cured if they are given a homeopathic medication that produces the same signs and symptoms in a healthy individual. Homeopathy is designed around the concept of picture-matching the patient's symptoms with a drug picture produced by a homeopathic remedy, and the idea of "like cures like" is derived from this concept. The second principle, and probably the most confusing to orthodox physicians, is the serial dilutions and shaking of a medication, often until the medication contains no molecules of the original product. Homeopaths suggest

that the medication still retains its effects even though it is ultramolecular (diluted beyond the Avogadro number). Homeopathy therefore confronts conventional science at its core, and many believe that homeopathic medicines can have no more than a placebo effect. The reason for including homeopathy in this chapter is not to provide conclusive evidence that it "works" in arthritic conditions but to illustrate some of the problems and debates that are confronted within CAM research.¹³⁹

Evidence

Jonas and colleagues' systematic review¹⁴⁰ of the quality of homeopathic clinical trials encompassed 59 studies of various homeopathic treatments for conditions ranging from stroke, postoperative complications, arthritis, and fibromyalgia to influenza. The studies in rheumatology indicate an odds ratio that, overall, significantly favors homeopathy but clearly suggests that there is currently inadequate evidence to make specific claims about the use of homeopathy to treat any particular condition. The debate about the evidence for clinical effects of homeopathic medicines is amply illustrated by two other systematic reviews that analyzed much the same clinical trial data and came to entirely opposing conclusions.^{141,142} When this occurs, and minor changes in the methodology of a systematic review can have such a profound impact on its conclusions, we must step back and realize that we have too little data on the specific effects of the remedy to be definitive.

REFERRAL AND PROFESSIONAL PRACTICE

Above all, physicians need to initiate an open dialogue with their patients about CAM therapies; more than 70% of patients who use CAM do not inform their physician that they are doing so.¹⁴³ Many patients use both conventional and CAM modalities simultaneously to manage their chronic problems.¹⁴³ When discussing CAM use with patients, it is important to remain neutral, because negative attitudes or application of labels such as "unorthodox" may discourage patients from discussing CAM use¹⁴⁴ or even create polarization that causes them to abandon good-quality conventional care.¹⁴⁵ Moreover, issues of safety and efficacy (of both conventional and CAM options) should always be reviewed, and patient preferences and expectations should be discussed and documented. This will allow patients and physicians to make responsible decisions *together* about treatment options and jointly monitor progress with the CAM provider.

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48B

Placebos, caring, and healing in rheumatology

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- Chronic rheumatic diseases are complex and occur in different, and changing, social and cultural contexts. Linear cause-and-effect models may not be appropriate for their explanation or management.
- The placebo response has a powerful influence on symptoms such as pain and is responsible for the majority of the beneficial effects seen from symptomatic therapy.
- Nocebos have very powerful negative effects on symptoms. Health anxiety is a key mediator of the nocebo response.
- Prior expectations and conditioning are important mediators of both placebo and nocebo responses.
- Placebo and nocebo administration can cause release of neurotransmitters and other changes in brain function (detected by functional magnetic resonance imaging) that may explain their actions.
- Caring, compassion, empathy, and validation improve symptoms and can relieve pain.
- The polyvagal, nurturing (safety) response provides a neuroregulatory theory to help explain the value of caring and relationships in health care.
- Humans live in stories (narratives) and have to find ways of including illness within those narratives. Helping them achieve this can reduce distress.
- Some medical narratives (e.g., "You have medically unexplained symptoms") are incompatible with patients' need to reduce health anxiety and make meaning of their problems.
- Beneficial, profound transformational changes are sometimes observed in patients. This is called the *healing response*. Positive human interactions appear to be a critical way of facilitating a healing response.

INTRODUCTION

Whether medicine should be regarded as an art, a science, or both has been debated for centuries¹; perhaps it is an art nested within science. Current mainstream Western medicine is certainly dominated by the sciences, particularly biomedical science, as this and most other textbooks testify. This chapter is more about the art of being a rheumatologist than the science of rheumatology. But it also discusses some of the science that is helping us understand the central importance of context, caring, relationships, stories, and healing in medicine.

CONTEXT AND COMPLEXITY

Medicine, like everything else, takes place within a cultural context that shapes the beliefs and behaviors of its practitioners and patients. Over time, a plethora of different approaches and systems for health care have been developed. Currently, in the developed world, we have largely excluded all but one of these (biomedicine), and indoctrinated ourselves and the public into thinking that it is the only "reasonable" approach to health and illness.^{2,3}

Our biomedical view of the world is based in positivist, reductionist philosophy.⁴ It is generally thought that if we can break the body down into its constituent parts and understand how each bit works at a molecular level, we will then be able to find answers to problems that arise with our bodies.

We believe that this approach can "fix" things. We take a linear view of causality, believing that one thing will predictably cause another.

This reductionist biomedical approach has served us well in dealing with infectious disease and many of the acute medical problems that affect our species. But it does not work well for chronic disease. Complexity science teaches us that linear cause-and-effect models are not good at predicting outcomes in complex systems and that any attempt to induce change in such systems is likely to have unpredictable outcomes and result in strange "emergent properties."⁵ Chronic diseases are certainly complex. Chronic ill health is generally related to a multifactorial mix of cultural influences, social problems, and psychological issues affecting an individual trying to function within a complex social system, sometimes complicated by the presence of an organic disease; and yet we continue to use single interventions to affect the disease element alone, in the hope that this will result in predictable improvements in health status. Quantum theory has made many theoretical physicists move away from the reductionist model, and it may be time that medical science do the same thing and consider alternative paradigms such as realism.⁶

CLINICAL TRIALS AND THE PLACEBO AND NOCEBO RESPONSES

One of the main methods used in our reductionist biomedical approach to health care, and in evidence-based medicine, is the randomized controlled trial (RCT).⁷ Since the 1950s RCTs have been seen as the best way of testing whether a drug is effective and, importantly, more effective than dummy pills (placebos), which might make people imagine that they were getting better in the absence of an active ingredient.⁸ However, trialists soon found that people given dummy pills often got better and that this "placebo response" was not confined to unintelligent, gullible people, as had previously been assumed.⁹ Such a finding was not helpful to investigators looking at the effect of a specific intervention, and the placebo response became something to adjust for in the analysis of trial outcomes.⁸ As drugs and science have improved, it has been considered unethical to include no-treatment groups in trials. Consequently, there often is no true comparator for the effects that result when people are given a placebo treatment. This has allowed some to deny the very existence of the placebo response.¹⁰ However, many recent studies have confirmed the symptomatic value of placebos in different contexts.^{11,12}

A systematic review of trials of interventions for pain in osteoarthritis in which a no-treatment control group was included was published in 2008.¹³ This review illustrated the power of placebo, because the effect size on pain in such three-arm trials (active drug, placebo, and no treatment) was between 0.5 and 0.7, considerably larger than the effect sizes of around 0.2 to 0.3 that is achieved with most active treatments. Others have obtained similar results from the analysis of trials of antidepressant drugs.¹⁴ So, the placebo response accounts for the majority of the benefit that patients gain from analgesic or antidepressant therapies.

A placebo, by definition, has no active ingredient that can have any specific effect on the target problem—it cannot *do* anything.¹⁵ It is the context in which treatments are given that is responsible for placebo effects. It is a response dictated by the expectations and beliefs that the patient brings, the environment in which the treatment is administered, and the behaviors and rituals of the health professionals who administer it.¹⁶ An RCT is a highly artificial experiment in which investigators try to "control" for many of these factors, so it may underestimate the power of context. Paterson and Dieppe¹⁷ hypothesize that this is particularly likely for interventions in which there is an interaction between the behaviors of the health professional and the intervention itself, such as physiotherapy and most

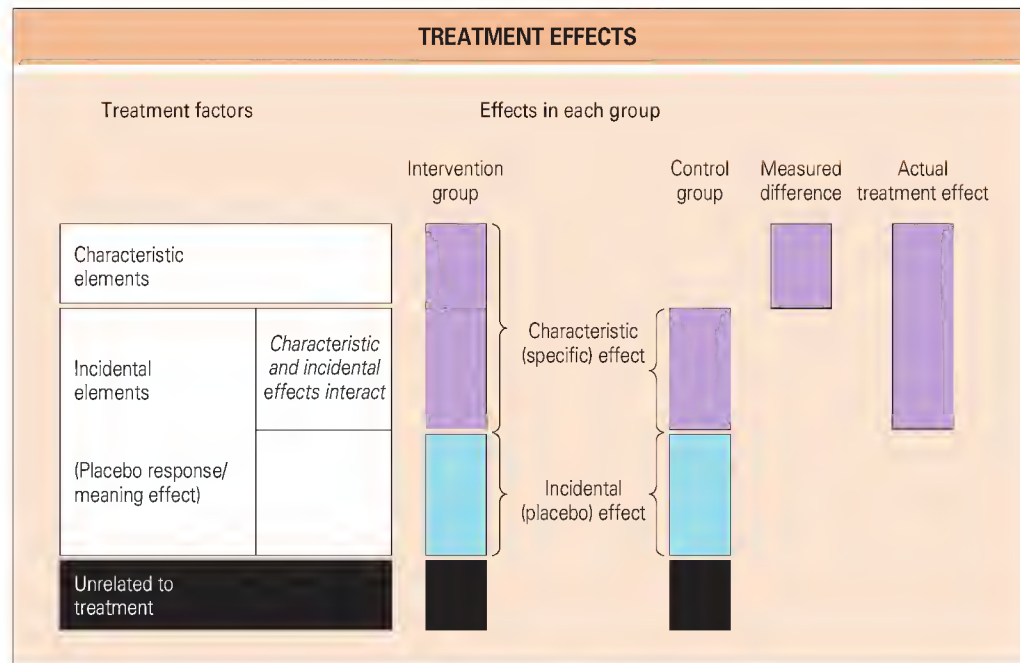


Fig. 48B.1 Treatment effects can be divided into characteristic effects (the specific effect of the intervention on the target disorder) and incidental effects (also called *placebo effects*, *context effects*, or *meaning effects*). The incidental effects are a complex combination of all factors that affect the outcome other than the characteristic effects of the intervention and include interactions between therapist and patient and a wide variety of other contextual and environmental factors. For symptoms such as pain and depression the size of the incidental effect is often larger than that of the characteristic effect. In many complex interventions, such as physiotherapy, there is an interaction between the characteristic element (e.g., muscle strengthening) and incidental elements (e.g., the ability of the physiotherapist to motivate the patient to do the exercises). This can lead to underestimation of the effect of an intervention if a classical randomized controlled trial design is used, because such trials measure only the difference between the effects of characteristic and incidental elements. (Adapted from Doherty M, Dieppe P. The “placebo” response in osteoarthritis and its implications for clinical practice. *Osteoarthritis Cartilage* 2009;17:1255-62; and Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ* 2005; 330:1202-5.)

complementary and alternative (CAM) therapies (Fig. 48B.1). If Paterson and Dieppe are right, it suggests that we should not be using the simple RCT model to investigate such interventions because it will systematically underestimate their effects (and facilitate the sceptics’ dismissal of all CAM as useless nonsense).

Nocebo effects and the importance of anxiety

The *nocebo* response has been described as the “evil twin” of the placebo response¹⁸ and can be very powerful, as voodoo deaths indicate.¹⁹ Nocebo has been the subject of much less research than placebo, but it is clear that just as positive expectations and suggestions can help induce beneficial responses to an intervention in the absence of any active ingredient, so negative expectations and suggestions can make things worse.¹⁸ As with placebos, the whole context matters, including the environment—but especially what is said.²⁰ Anxiety appears to be one of the key mediators of a powerful *nocebo* effect.²¹ Negative emotions, particularly health anxieties, induced by a health care encounter can exacerbate symptoms and block the effects of drugs such as analgesics.²²

The science of the placebo and *nocebo* responses

There are two main psychological theories about placebo: conditioning and expectations.²³ A *conditioned response* occurs when the brain gets used to the pairing of stimuli; in the classical pavlovian conditioning experiments, dogs came to associate the ringing of a bell with the provision of food and would then salivate immediately when the bell was rung. In more recent experiments it has been shown that volunteers can be conditioned to induce immunosuppression in response to a novel green drink if it has previously been paired with the administration of cyclosporine A.²⁴ Such work raises the exciting possibility of achieving immunosuppression without high doses of drugs.^{25,26} Conditioning may also explain phenomena seen in rheumatology, such as a patient’s experiencing the same adverse effects to every drug that the patient tries: the patient has been conditioned to have that adverse effect to tablets.

Cognitive expectations have been researched extensively. For example, people will respond to coffee with a psychological and physiologic response characteristic of a caffeine shot if they think the coffee is caffeinated, even if it is not.²⁷ Similarly, one can observe a graded response to a placebo

analgesic cream applied to the skin with a progressively stronger assurance that the cream will block the pain induced by an algometer.²⁸

There is also compelling *biochemical evidence* that placebo administration (and the rituals surrounding it) can lead to the release of neurochemicals such as dopamine and endogenous opioids that have a direct effect on the brain resulting in suppression of disease-related symptoms.^{18,23} Functional magnetic resonance imaging studies are also helping to describe neurologic mechanisms that underlie this intriguing phenomenon.²⁹ Finally, as outlined later, the social sciences are contributing to our understanding of the placebo response.

CARING AND RELATIONSHIPS

In 1927 Francis Peabody’s landmark article “The Care of the Patient” was published.³⁰ Peabody expressed concern that science within medicine might be marginalizing the central importance of caring; he famously concluded that “the secret of the care of the patient is in caring for the patient.”

Peabody was writing well before the scientific revolution in medicine, and more recently many other authors have expressed concern that science is marginalizing caring, that physicians have turned into body “mechanics” rather than carers, and that physicians have forgotten their core values.^{31,32} However, core values and caring have continued to be major concerns in nursing literature, where many theories of caring, such as Watson’s “*carative*” factors,³³ have been developed.

In medicine more emphasis has been given to concepts such as relationship-centered care,³⁴ caring in the community, and the role of carers.³⁵ Although caring may not have been at the forefront of biomedical thinking in recent years, no one would deny its central importance to health care. Each of us has experienced the value of being cared for by another during times of distress.

The science of caring

Compassion, empathy, and validation

There has been a lot of research on the importance of compassion and empathy in health care encounters.^{36,37} *Physician empathy* has been defined as the understanding of the patient as well as verbal and nonverbal communications that result in changes in patient behavior³⁷; this definition

views it as the creation of a relationship that facilitates appropriate use of treatments. However, the creation of a good relationship can go further than that. It can facilitate healing, as discussed later in this chapter. The neurobiology of empathy has also been the subject of a good deal of research, much of it concerned with mirror neurons (the system that facilitates imitation of the gestures of others).³⁸ It appears that not only are embodied actions created by the mirroring representation systems in the brain, but we work cognitively to achieve empathy; we take the perspective of others and imagine their problems and feelings.

Validation (and its opposite—invalidation) goes further than empathy. Validation of another is more about communicating your understanding to the other, rather than just being compassionate or empathetic. It emphasizes the position of the recipient—his or her interpretation of and feelings about the interaction that has taken place.³⁹ The sense of being validated or understood has been shown to affect symptoms such as pain. For example, one study found that participants experiencing chronic back pain who received invalidating feedback during a semistructured interview reported higher levels of negative affect, higher pain intensity, more frustration, and lower levels of patient satisfaction than participants in the group receiving validating feedback.⁴⁰

The nurturing response

The fight-or-flight response is a reaction to perceived threats; it activates the sympathetic part of the autonomic nervous system, the release of adrenaline, and profound physiologic and emotional changes. Porges⁴¹ has described the neurophysiology of its opposite, the “nurturing response.” This response is activated by perceived safety and results in parasympathetic activation, calmed emotions, and relaxation. It is this nurturing response that helps people to care for their young (witness the response of anyone seeing a young baby smile) and work together in effective groups in a collaborative way.⁴² The muscles of facial expression and voice production are linked into this polyvagal system: when the threat response is activated people’s faces become less expressive and their voices flat, whereas when the nurturing (safe) response is active they express their emotions through their faces, have more expressive voices, and are better able to interpret the emotional state of someone they are interacting with.^{41,42} Therefore whether the individual is feeling safe or threatened during a health care consultation has a huge effect on the interactions and outcome. It is sobering to consider how often our patients are likely to be in the threat mode while in our consulting rooms, and how often the doctors and nurses themselves feel threatened. No wonder communications often fail and caring for and nurturing another person can be absent from a clinical encounter.

Clearly, we need to be able to make sure that we as clinicians, as well as our patients, are in a safe place during a consultation (Fig. 48B.2).

HEALTH, SUFFERING, HEALTH BELIEF, STORIES, AND MEANING

The World Health Organization defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.” But, as Petr Skrabenek pointed out, such a state is rarely achievable—it is “the sort of feeling ordinary people may achieve fleetingly during orgasm, or when high on drugs.”³¹ Life is a process with its ups and downs, and symptoms such as aches and pains are a part of it. Distress, grief, and suffering are also things that we all experience from time to time. The idea of health as “complete” and static is untenable.

How much we worry about our everyday symptoms, such as aches and pains, and whether we take them to a doctor or not, is dictated by a mixture of social, cultural, and psychological factors. Our health beliefs and the stories we live in affect the response we have to arthritis and the drugs prescribed for it.⁴³ For example, a study of people who reported symptoms of severe lower limb arthritis but had not sought medical help found that many regarded their arthritis as part of their identity or as an inevitable result of the ways in which they had led their lives.⁴⁴ Emerging methods such as narrative-based medicine take a particular approach to eliciting and understanding the stories patients live in and the way in which those stories shape their response to disease.⁴⁵

Moerman has coined the phrase *meaning response* to extend this idea of stories, combining the placebo response with narrative-based medicine and the human need for meaning in life.^{46,47} He cites a number of examples to illustrate the ways in which the meaning that a certain intervention has to an individual shapes the individual’s response to it. One striking example is the response to dummy (placebo) pills that are either red or blue. If told that one color is a sedative and the other excitatory, most people will get sleepy when given the blue one and excited when given the red one. In Italy,

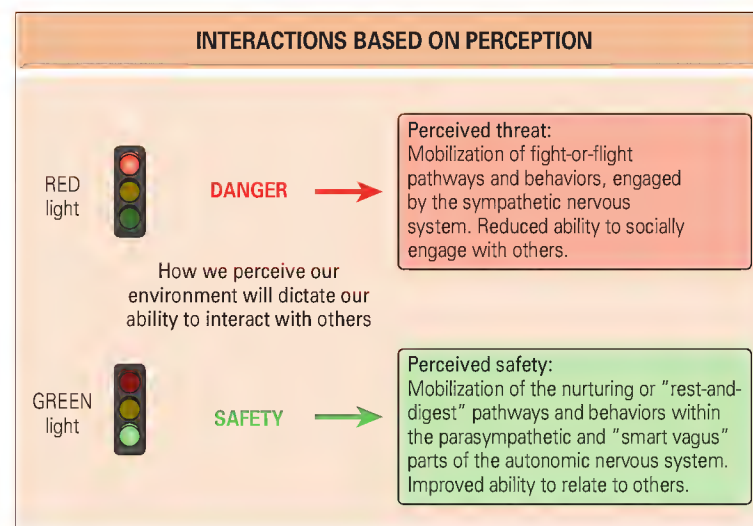


Fig. 48B.2 We are constantly monitoring our environment to see if any threats are present. If we feel threatened, then the fight-or-flight response is activated, which results not only in physiologic changes to the cardiovascular system, but also to changes in the ability to communicate effectively with others. In contrast, if we feel safe, the nurturing response is activated. We then feel calmer and more relaxed, we are more receptive to information and advice from another, and our feelings are expressed more fully through facial expression and tone of voice. Good clinical interactions, therefore, are facilitated when both the clinician and the patient feel safe. Unfortunately, hospitals and physicians are often threatening. (Adapted from Porges SW. *Social engagement and attachment: a phylogenetic perspective*. *Ann N Y Acad Sci* 2003;1008:31-47; and Porges SW. *The polyvagal theory: neurophysiological foundations of emotions, attachment, communication and self-regulation*. New York: WW Norton; 2011.)

however, it is the other way around, and Moerman speculates that this may be because the national football team plays in blue uniforms.⁴⁷

We have to find meaning to our existence; it is not surprising, then, that we fit abnormal symptoms or changes in our bodies into our stories.^{45,48} Physicians take a different approach—they try to fit the experiences described into a diagnostic category so that they can label the patient as having a disease.⁴⁹ If the physician cannot make biomedical sense of the patient’s dilemma and “box” it into a diagnosis, she or he is likely to label it “medically unexplained physical symptoms,” a negative term implying that biomedicine does not yet understand the patient’s problem but that some further tests or a different physician might be able to find the cause. This approach seems designed to engender anxiety and “doctor shopping.” It leaves the patient in a difficult place—and, of course, all symptoms in all conditions are medically unexplained from the patient’s perspective.

The designation of conditions such as fibromyalgia as “medically unexplained” illustrates another issue for modern biomedicine: its difficulty with the cartesian split between mind and body. Patients have the same difficulty. If a patient with chronic widespread pain is encouraged to see a psychiatrist, the patient may respond angrily, “So you think it’s all in the mind, then, do you?” which indicates that the patient views mental and physical problems as different things. Physicians often fall into the same philosophical trap.

Recent research comparing conditions for which medicine can find an organic explanation with those for which it cannot has shown that there is very little difference in their effect on quality of life or utilization of services, but that it is the number of symptoms experienced by the patient and the patient’s levels of anxiety that predict health status.⁵⁰ The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* reclassifies medically unexplained physical symptoms as somatic symptom disorders,⁵¹ which may help both physicians and patients deal with the stigmatization that can result from the label “medically unexplained symptoms.”

TRANSFORMATIONAL CHANGE AND THE HEALING RESPONSE

Physicians often witness extraordinary, unexpected, transformational changes in a patient. Someone who seems to have an incurable or untreatable disease problem changes for the better for no apparent reason, a change that can occur relatively quickly or over a period of weeks, months, or years. We call this the *healing response*, the activation of the natural ability of the

body, mind, and soul of a person to regain balance and congruence after a period of disturbance or disruption. Just as we are all hard-wired for nurturing and caring for others, we all have the intrinsic ability to self-heal from many conditions, to regain the homeostasis that all living organisms seek.⁵²

Healing has been defined in many different ways. In the medical literature it is used largely to describe bodily healing alone (the healing of wounds or the repair of a fracture), but in the CAM, lay, and healing literature it has a much wider meaning and is used to describe wholeness and the integration of body, mind, and spirit (Box 48B.1).⁵³⁻⁵⁷

The science of healing

The preceding sections have emphasized that there is plenty of hard science to support the notions of placebo and nocebo responses, and the value of caring. Is there any science to support the concept of healing?

There are systematic reviews which report a beneficial effect in trials.⁵⁸ Furthermore, much of what is considered healing might be a part of the placebo response, related to rituals and embodied experiences, facilitated by validation, or enhanced by induction of the polyvagal safety response, described earlier. But perhaps there is more to it than that. All societies and cultures have had their healers and healing rituals,⁵⁷ and most emphasize something more than just bodily healing, something more spiritual or metaphysical. The healing community emphasizes the concept of energy flow,⁵⁹ a concept that also has some scientific evidence behind it,⁶⁰ and one that is important to other medical systems such as Chinese traditional medicine or Indian ayurveda.⁵⁷ In their scientific examination of what might be termed *anomalous healing experiences* Krippner and Achterberg cite a 1958 joint British Medical Association and Anglican archbishop's commission looking into unusual healing which concluded that "we cannot afford ... to disregard any means at our disposal which may lead to the restoration of ... health."⁶¹ Perhaps, as Hamlet said to Horatio, "there are more things in heaven and earth than are dreamt of in [our biomedical] philosophy."

CONCLUSION

Symptoms and their meaning are what matter to patients, and the more symptoms they have and the more anxious they are about them, the more likely it is that their health will be compromised. Rheumatologists need to listen to symptoms, ask about symptoms that have nothing to do with the musculoskeletal system, ask patients what they think are the causes of these symptoms, and ask how serious patients believe them to be and how much they worry about them. We need to listen to the answers, so that patients feel heard and validated, and help patients to make sense and meaning of what is going on. And above all else, we must try to make patients feel safe; reduce health-related anxieties rather than increasing them with investigations and treatments of borderline value; and thus avoid the nocebo effect and make way for the beneficial placebo and healing responses.⁶²

BOX 48B.1 THE HEALING RESPONSE

Healing is a slippery concept that is difficult to define or recognize because it is an intensely personal experience that gets to the core of one's identity and spirit. It is a process that comes from within a person rather than being dependent on a specific intervention. This box notes what some of the different descriptors are in the literature and what some authors who have studied healing consider to be the keys to facilitating healing in the context of a modern health care encounter.

Some descriptions of healing

Various authors

- A process of restoration of the whole person
- Reachieving balance and homeostasis
- Bringing together of body, mind, and spirit

Egnew (2005)⁵³

- A reconciliation of the meaning an individual ascribes to distressing events with his or her perception of wholeness as a person
- The personal experience of the transcending of suffering

Csardas (2002)⁶³

- The transformation of a person, a self that is a bodily being

Kirmayer (2004)⁵⁶

- From feeling ill to wellness, from afflicted to healed

Some facilitators of healing

Various authors

- Total attention with good intention—or the intentional beneficial influence of one person upon another without the use of a specific intervention

Scott et al (2008)⁵⁵

- Creating a nonjudgmental emotional bond
- Consciously managing clinician power to the benefit of the patient
- Displaying a commitment to caring over time

Churchill and Schenck (2008)⁵⁴

- Doing the little things
- Taking time
- Being open and listening
- Finding something to like, to love
- Removing barriers
- Letting the patient explain
- Sharing authority
- Being committed

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Drug development

■ LACHY McLEAN

- Drug development is the process of bringing a new therapeutic molecule from preclinical studies through to regulatory approval and availability to the patient and prescriber.
- Before human clinical studies are begun, extensive preclinical research is performed on new drug candidates to validate the target, optimize the molecule, understand potential toxicities, predict key properties in humans, and devise translational biomarkers.
- Clinical development is divided into phase 1 (single and multiple rising dose studies, drug interaction studies), phase 2 (proof of concept, dose-ranging studies), and phase 3 (confirmation of efficacy and safety). Clinical trial duration, size, and cost increase progressively.
- Phase 1 studies typically are done in healthy volunteers for small molecules and in patients for biologics.
- Drug development is lengthy and expensive, and the risk of failure is high.

INTRODUCTION

Drug development is the process of bringing a new drug molecule into clinical practice. In its broadest definition this encompasses all steps from the basic research process of finding a suitable molecular target to supporting the commercial launch of the drug. In a narrower sense, *development* refers only to the clinical parts of this process, with *discovery* used to describe the nonclinical research components; this topic is rich in jargon that is used in different ways by different companies and individuals.

This chapter focuses on key aspects that rheumatologists are likely to encounter as investigators in clinical research trials and as expert advisors to industry. More details of the pharmaceutical research and development process can be found in standard texts and in the many guidance documents produced by regulatory authorities and other professional bodies.¹

PRECLINICAL RESEARCH

Target validation

The discovery and clinical development of a new drug may be broken down into several parts (Fig. 49.1). Preclinical research generally begins with the identification of a drug *target*, a molecule thought to play a crucial part in the pathogenesis of a disease of interest. The target may be truly novel (the product of the company's own basic research) or may have entered the public domain through scientific publications or a patent. Many factors must be considered in the choice of a "good" target (Box 49.1).

The early steps in preclinical research focus on *target validation*: characterizing the target and its putative role in disease and in normal physiology. Key components of validation for a new rheumatology target may include analysis of its place in molecular pathways known to be involved in inflammation or immune cell signaling; an exhaustive review of published scientific and patent literature; demonstration of the target in relevant tissues (e.g., increased expression in rheumatoid synovial tissue); study of the effects of an inhibitor on patients' peripheral blood or synovial cells *in vitro*; and use of animal models of arthritis. A targeted genetic deletion (knockout) of the prospective drug target or a knockdown using RNA interference may

help establish the role of the target both in normal physiology and in disease models.

Clinical precedents

A further element of validation may come from prior clinical experience with earlier drugs affecting the target itself or other parts of the molecular pathway. For example, the efficacy of anti-interleukin-17 in managing inflammatory disorders supports exploration of small-molecule drug approaches against retinoic acid receptor-related orphan nuclear receptor (ROR γ t), a transcription factor crucial for type 17 helper T lymphocytes.

Early knowledge of potential toxicities can permit early termination of research efforts on a target. Many companies shy away from targets that may affect prostanoid pathways or peroxisome proliferator-activated receptor- γ because of prior associations with major adverse cardiovascular events.

Drug discovery

The starting point for creating a small-molecule drug for a new target may be a high-throughput screen. Robotic samplers and microwell plates are used to test a large library of *drug-like small molecules* (approximately 500 Da) for binding to a known target or for activity in a biologic system. Medicinal chemists then use the most promising molecules identified in this way ("hits") as the starting point for designing a drug molecule suitable for further *in vitro* and animal testing. The resulting drug-like candidates are sometimes referred to as *leads*, and the next layer of improvements as *lead optimization*. Advances in x-ray crystallographic techniques have led to *structure-based* and *fragment-based drug design*, in which assembly of the new molecule is steered by the three-dimensional structure of the target.

A drug that binds its target with a tighter fit and higher affinity will require lower concentrations to inhibit the target and is less likely have undesirable activity against related targets. Desired affinities for new small-molecule drugs are usually in the low nanomolar range. Drug molecules are also tested for the ability to impair the function of the target (e.g., the enzymatic activity of a kinase) using *in vitro* cell-based systems.

Druggable targets

Small-molecule drugs can affect a target only if they get access to a specific part of the molecule—ideally a small cleft or pocket at a site critical to the molecule's function—and bind strongly enough to affect its behavior. Around 10% of the human genome represents such "druggable" targets, but only 5% of these targets are both druggable and relevant to human disease.² Past success with related targets, for example *protein kinases* (see Chapter 64) and *G protein-coupled receptors*, goes some way toward predicting future success. Certain structural features may also help predict the ability to optimize the fit of a small-molecule drug to a new target.³ These concepts are likely to change as new techniques are developed.

Drug optimization

A good small-molecule drug must also be absorbed well from the gastrointestinal tract, distributed to parts of the body where it is needed, and remain at the site of action long enough.⁴ Common issues are poor oral absorption, rapid elimination by hepatic metabolism, and failure of the drug to penetrate cells or its quick removal by efflux pumps. The key pharmacokinetic (PK) properties of *absorption*, *distribution*, *metabolism*, and *excretion* are assessed in preclinical species, and the equivalent parameters in human are estimated by *allometric scaling*.

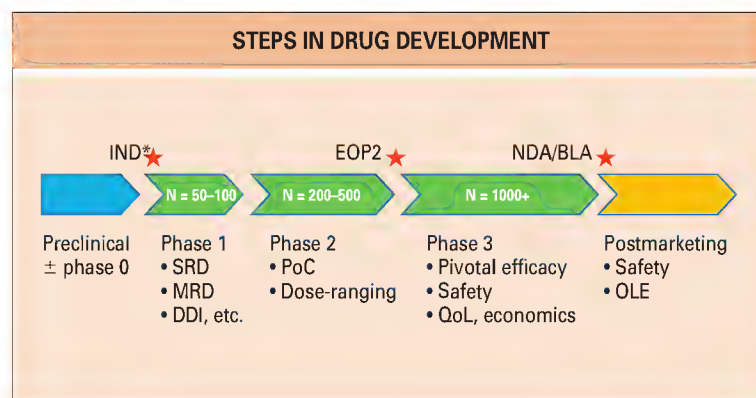


Fig. 49.1 Progression of a new drug through clinical development is divided into three main phases. Phase 0 work (e.g., biomarker development) may be done in parallel with preclinical testing. Phase 1 studies other than single rising dose (SRD) and multiple rising dose (MRD) studies are usually done in parallel with phase 2 or 3. Clinical trial duration and the number of subjects in each phase (N) varies according to the indication and any specific issues with the drug. Red stars indicate key regulatory steps. *Or equivalent outside the United States. BLA, biologic license application; DDI, drug-drug interactions; EOP2, end of phase 2 (agency meeting); IND, investigational new drug; NDA, new drug application; OLE, open-label extension; PoC, proof of concept; QoL, quality of life.

BOX 49.1 FACTORS CONSIDERED IN CHOOSING A DRUG TARGET AND INDICATION

Target characteristics

Target validation/role in disease
Role in physiology
Phenotype of knockout/knockdown
Preclinical disease model
Structurally enabled (crystallography)
Precedent for inhibiting pathway
Novelty of mechanism
Target polymorphisms
Pharmacodynamic biomarker

Availability of good study sites

Companion diagnostic
Validated endpoints

Regulatory pathway

Perceptions of disease severity and impact
Approval precedents
Guidance document(s)

Commercial attractiveness

Number of eligible patients
Unmet medical need
Competitive landscape (existing and pipeline)
Patent loss-of-exclusivity timeline
Pricing potential

Clinical development pathway

Patient definition (accepted criteria)
Disease heterogeneity
Standard-of-care therapy
Disease-proximal biomarkers
Availability of clinical trial patients

Biologics

The protein therapeutic agents used in rheumatology are generally either monoclonal antibodies or fusion constructs comprising a “decoy” cytokine receptor coupled to the Fc portion of an IgG molecule. Coupling to Fc increases the half-life and can help with disposal of the target. Another approach is coupling to polyethylene glycol (pegylation), for example, certolizumab pegol used in rheumatoid arthritis (RA) and pegloticase used in treatment-resistant gout.

The starting point for a new therapeutic antibody is either immunization with the target or screening of an antibody library for affinity with the target. The resulting antibody is then engineered to improve its properties, including (1) increasing the affinity of the antibody for its target, (2) replacing animal portions of the antibody with human equivalents to decrease immunogenicity (the generation of antibodies aimed against the therapeutic molecule itself—*antitherapeutic antibodies*—because the patient’s immune system sees these as “foreign”), and (3) enhancing effector functions.

As with small-molecule drugs, the biologic is tested in several activity assays and animal efficacy models, PK properties are assessed, and toxicity potential is studied (see later). Attention is given to developing the stable cell lines that will be used to produce the biologic; scaling up to increasingly large culture systems; establishing processes for purification, quality-testing, and storage; and filling sterile vials or other packaging ready for storage and use in humans.

BOX 49.2 PRECLINICAL CHARACTERIZATION OF A NEW DRUG CANDIDATE

Affinity for target
Activity in enzyme- and cell-based assays
Tissue distribution
Metabolic route, active metabolites*
Predictions of human pharmacokinetics
Identification of pharmacodynamic markers
Kinase (and other off-target) screens*
QT interval liability (effect on hERG, Purkinje system, ECG telemetry)*
Development of translational biomarkers
Efficacy in animal arthritis models
Whole-animal toxicology studies
Genotoxicity screening, carcinogenicity
Phototoxicity
Safety pharmacology
Injection tolerability (subcutaneous biologics)
Stability testing

*For small molecules.

Biologic versus small-molecule drugs

Intracellular molecules are not an easy target for protein biologics because they require specialized delivery systems to move across lipid bilayers. On the other hand, protein-protein interactions over a large surface area are difficult to disrupt with a small-molecule drug and favor a biologic approach.

Although small molecules offer the convenience of oral dosing, in recent years both rheumatologists and patients have gained comfort with biologics. Most patients find injectable drugs an acceptable alternative, particularly if the injection is convenient (e.g., subcutaneous, self-administered, and performed using an “automatic” prefilled injection device), dosing is relatively infrequent, and severe injection-site reactions do not occur.

In addition, because of the high specificity of antibody-antigen interactions, therapeutic antibodies are much less likely than small molecules to have off-target activity, and biologics have more predictable PK properties.

Preclinical safety testing

During *toxicology* studies the drug is given to animals in progressively higher doses to establish the exposures associated with damage to key organs, to determine whether the effects are reversible, and to establish a *no observed adverse effect level* that will guide *first into human* doses and dose escalation schedules in phase 1 clinical trials. In general these studies are done in two species (often rat and dog) for small molecules, and are of sufficient duration to at least match the intended duration of the initial human studies. Because the high specificity of biologics limits their cross-species reactivity, toxicology studies may be done in primates such as the cynomolgus monkey. Innovations such as “lab-on-a-chip” methods may eventually replace some *in vivo* testing.⁵

The final preclinical studies done before the new drug is tested in human subjects (sometimes called *regulatory* or *IND-enabling* studies, where *IND* stands for “investigational new drug”) are performed using *good laboratory practice* standards and drug material prepared according to *good manufacturing practice* (a set of principles to ensure quality practices).

Safety pharmacology studies focus on potential adverse effects on the cardiovascular, respiratory, and central nervous systems. Other preclinical studies are summarized in Box 49.2.

Efficacy models

Preclinical studies include assessment of efficacy in animal models and the exposures needed to produce beneficial effects. Preclinical models of autoimmune disease are notoriously poor at predicting efficacy in the corresponding human disease. Autoimmune diseases in such models are of acute onset, artificially induced rather than spontaneous, occur in animals with a homogenous genetic background and environment, and have a cytokine and cellular pathogenesis that only partly reproduces that seen in the human disease. Nevertheless, such models are valuable for studying the relationship between PK markers and pharmacodynamic (PD) markers (measures of the drug’s activity on downstream pathways) and for devising translational biomarkers.

CLINICAL DEVELOPMENT

Study design

All studies involving human subjects must comply to ethical standards (see Chapter 27). Key aspects include the principle that the patients entering a clinical trial should have tried established standard-of-care therapies with either inadequate response or unacceptable tolerability/safety outcomes or, depending on how inadequate the response was, should continue standard-of-care treatment as stable *background therapy*.

The protocol should also include “escape routes,” so that a patient who does not show adequate response within a defined period of time has access to alternatives, preferably without having to exit the study completely.

The clinical trial protocol describes the study’s scientific rationale, known properties of the drug, objectives and endpoints, inclusion and exclusion criteria, limitations on concomitant use of other medications, study procedures, safety information, clinical trial materials, ethical aspects, and plans for data analysis, including statistical methods. Efficacy endpoints vary according to the indication. In early development, objectives involving PK, PD, and biologic markers feature strongly. In phase 3 trials, key aspects of study design are confirmed in advance with regulatory authorities.

Once the trial has started, any modifications need careful consideration to avoid undermining the credibility of the study’s findings. Investigators should deviate from the protocol only when it is essential for patient safety. Any changes in a protocol are made with a formal *protocol amendment*, which requires review by the institutional review board or ethics committee.

The approach to analyzing the key data—the *statistical analysis plan*—is finalized in advance of unlocking the study database. The methods for handling *missing data* (e.g., when a patient leaves the study early because of drug-related adverse events or lack of efficacy) and *multiple endpoints* should be specified in advance to avoid biases.^{6,7}

The strategic goal(s) of a study from the sponsoring company’s perspective may differ from the stated objectives as described in the protocol. Typically there is a focus on gathering enough key information for decision-making regarding the continued development of the compound according to *go/no-go criteria* that were agreed upon in advance of the study.

Reduction of confounders

Comorbid medical conditions and use of other medications may cloud the interpretation of adverse effects. As much as possible, concomitant medications are kept constant for the duration of the study. For example, changes in background therapy, including prednisone and methotrexate (MTX) dose, usually are very restricted during a clinical trial of a new biologic drug for RA. An exception is that certain study designs have protocol-specified dose reductions, for example a lupus trial aiming to test the steroid-sparing ability of the new drug.

The negative consequence of the desire for a “clean” study is that the populations studied in clinical trials are not representative of the population that is eventually given the drug in clinical practice—they are often healthier, take fewer medications, and are more homogenous.

Patient enrichment

Enrichment is the use of certain patient characteristics to increase recruitment of patients most likely to show a treatment effect or, conversely, to exclude patients who are less likely to show an effect. Enrichment may rely on various characteristics, including patient phenotype, history, treatment responses, serologic parameters, other “routine” laboratory criteria, or radiologic findings, or it may involve a specialized biomarker.

There may be a specific scientific rationale for enrichment (e.g., seropositivity in the case of a B-cell mechanism) or simply the desire to make the population as homogenous as possible (less variability equals a smaller sample size equals a faster, cheaper study). Enrichment is useful in phase 1 and 2 trials to address particular scientific questions, but additional studies would be needed to evaluate the drug’s efficacy and safety profile in the “general” patient population. Enrichment strategies also make patient recruitment more difficult, a challenge not enjoyed by study sites.

Companion diagnostics

A biomarker or genetic test that has sufficient sensitivity, specificity, and prognostic power for predicting which patients will and will not respond well to the drug and that is technically robust for use in a routine clinical diagnostic laboratory may play a useful role in clinical decision-making. When designed to be used in the prescribing decision the test may be

referred to as a *companion diagnostic*. For drugs with a high cost, high toxicity, slow onset, or slow reversibility, such a predictive marker has clear advantages. Under other circumstances the traditional “try it and see” approach may remain perfectly adequate.

Despite extensive research no practical companion diagnostic has emerged for any rheumatology drug, even for the “low-hanging fruit” of highly targeted biologics with a well-understood mechanism of action. Many reported biomarker associations have not been confirmed by larger studies.⁸ Part of the problem is that in chronic inflammatory diseases like RA, the response to a given therapy is seldom a clear-cut yes or no; shades of gray are typical. The more promising personalized medicine approaches in rheumatology have largely been limited to helping avoid uncommon serious toxicities (e.g., thiopurine methyltransferase activity for azathioprine, presence of HLA-B*5801 for allopurinol).

A further obstacle is timely availability. To be of most commercial benefit to a sponsor, the companion diagnostic should be available when the drug is launched. To enable this, the company needs to start development of the companion diagnostic during the late preclinical stages or (at the very latest) in early clinical development.

Good clinical practice

Drug development is highly regulated. Guidelines exist for general aspects of study design, conduct, and interpretation. A large body of guidance documents is available covering preclinical requirements, efficacy, safety, and statistical topics (e.g., www.ich.org, www.fda.gov).

Good clinical practice (GCP) standards provide an internationally agreed upon framework to ensure that the rights and well-being of study participants are protected and to safeguard future patients by ensuring that the data collected during the study are valid. This is done by maintaining an audit trail for all data and using quality control and quality assurance measures to ensure that all data are factual and accurate.

The sponsoring pharmaceutical company will check the *case report forms* at each study site to ensure that the documentation is complete, that any alterations are accounted for, and that important clinical findings can be verified against source material at the site. This *site monitoring* may be done by the company itself or by a *contract research organization*. The site monitors are often referred to as *clinical research associates*. The clinical research associates and the company’s data managers work with the study sites to address any queries before locking the study database.

These procedures reduce, but do not eliminate, the possibility of sloppy or fraudulent activities by clinical researchers. Site monitoring uncovers a variety of problems, including protocol violations, noncompliance with informed consent procedures, poor drug accountability, poor adverse event reporting, documentation problems (missing signatures, missing or incorrect dates), and—fortunately in only a small minority of cases—the deliberate falsification of data.

The sponsor provides a physician with experience in clinical trials—the *medical monitor*—to act as an liaison with investigators and provide additional information about the drug being tested and study procedures, particularly if safety issues arise.

Operational aspects

Steps involved in a clinical trial are summarized in [Box 49.3](#). There is seldom such a thing as a “quick” development study; a protocol with 12 weeks of drug treatment may actually take 15 to 18 months overall (longer for some indications, depending on recruitment kinetics). Times increase further if more study sites are needed and more countries are involved.

Phase 1

Phase 1 studies include *single rising dose* (SRD; also referred to as *single ascending dose*), *multiple rising dose* (MRD, also referred to as *multiple ascending dose*), PK studies including the effects of food and of drug-drug interactions (DDI), studies to exclude an effect on the electrocardiographic QT interval (an effect of small-molecule drugs that interact with certain cardiac ion channels, which carries a risk of the malignant ventricular arrhythmia *torsades de pointes*), and studies in special populations including elderly, renally impaired, and hepatically impaired patients. First-in-human SRD studies of small-molecule drugs for rheumatologic indications are usually done in healthy volunteers. Certain phase 1 studies (e.g., those addressing DDI) often can be deferred and done in parallel with phase 2 and 3 studies.

Ensuring safety is of paramount importance when a new drug is first given to a human subject. Despite extensive preclinical testing there are many uncertainties. Phase 1 studies of a novel small-molecule drug are generally done in a *clinical pharmacology unit* (CPU). The subjects are

BOX 49.3 OPERATIONAL STEPS IN A CLINICAL TRIAL*

Concept for study/clinical development plan	Site initiation
Consultation with external expert advisors	Patient screening
Study synopsis	Initiation of recruitment (first patient in)
Site feasibility survey	Treatment period
Company management approval (multiple layers)	Planned (and <i>ad hoc</i>) safety reviews
Study protocol	Safety follow-up
Institutional review board/ethics committee	Last patient out
Regulatory submission	Monitoring and addressing of data queries
Central laboratory, laboratory kits	Database lock
Biomarker procedures/processing	Unblinding
Investigator meeting	Primary data “flash” analysis
Drug supply, randomization procedures	Decision on drug’s progression
Site paperwork (e.g., review of staff qualifications)	Exploratory analyses
	Clinical study report preparation
	Regulatory submissions
	Preparation of scientific abstracts, publications

*Steps not necessarily in this sequence; activities are conducted in parallel as much as possible to tighten overall timelines. Terminology and processes vary among companies.

resident in the CPU during the study to allow close clinical monitoring, standardization of diet, and the frequent venipuncture needed for safety, PK, and PD assessments.

SRD and MRD protocols have defined decision points for dose escalation and the declaration of the *maximum tolerated dose* (MTD). Various dose-escalation schedules are possible; a common practice is to escalate in approximately half-log₁₀ intervals, for example, 0.1 mg, 0.3 mg, 1 mg, 3 mg, and so on.

Phase 1 studies of biologics are typically performed in patients, often in academic medical centers. The duration of action of a protein drug is long enough that a clinical or biomarker effect can often be anticipated. The term *proof of mechanism* is sometimes used for an efficacy-related signal—for example, a reduction in levels of key cytokines measured in serum, alteration of a messenger RNA expression profile, or perhaps a trend toward improvement in a clinical endpoint for which the sample size does not provide adequate statistical power. Because of the variability inherent in data from small samples, there is the possibility that the new drug may, by chance, look better (or worse!) than it really is; it is common for promising early-phase efficacy data to become less appealing in subsequent better-powered studies.⁹

The size of the SRD and MRD cohorts varies according to the molecule, the indication, the resources of the sponsor, and any particular safety issues or PK-PD questions highlighted in the preclinical program. For an SRD study there might be between 4 and 8 subjects per dose cohort; for an MRDs study, 6 to 12. Typically, a quarter to a third of the subjects receive placebo.

Depending on the number of dose levels, a typical phase 1 MRD and SRD program will include in the vicinity of 50 to 100 subjects. MRD studies for small-molecule drugs are generally of 1 to 2 weeks’ duration, and those for biologics, 1 to 3 months. It is also common to seek preliminary information on food and drug-drug interaction effects during a small-molecule MRD study. In addition to the drug’s having suitable safety, tolerability, and PK properties, progression to phase 2 is usually contingent on its showing an effect on a PD biomarker which confirms that the drug is having a relevant effect *in vivo*.

Phase 2

Phase 2 study goals generally include establishment of *proof of concept* (PoC) for the drug in treatment of the indication being studied and *dose ranging*. Phase 2 studies are performed in patients. It is now common to combine the phase 2a/PoC and the phase 2/dose-ranging components into a single protocol to accelerate progression through clinical development. This reduces overall phase 2 time and hence speeds the availability of a successful drug to prescribers and patients. It is also in the company’s interests, because a combined protocol lowers overall study costs, and faster progression also increases the time between launch of the drug and expiration of the drug’s patent.

PoC requires a robust effect on a clinical endpoint that leaves no doubt as to the drug’s efficacy. PoC may use the same “regulatory” endpoint(s) as a phase 3 trial, subscales of a recognized instrument (e.g., joint counts), or a novel measure. In a phase 2a study, PoC may be tested using a single

“high” dose of the drug (one or two steps below the MTD) in comparison with placebo. Preclinical data, PK data, and PD data from phase 1 predict the doses to administer in phase 2 using *modeling and simulation* approaches.

Standard-of-care (SoC) medication for RA—for example, analgesics, MTX, folic acid, and prednisone (or equivalent, ≤10 mg daily)—may continue as stable background therapy to first assess the new drug as an “add-on” treatment before testing its ability to replace a SoC component. Initial studies generally enroll patients who have experienced an inadequate response to multiple standard-of-care options. For RA, the patient population showing inadequate response to MTX and the population showing inadequate response to a biologic agent differ in ease of recruitment, likelihood of response, applicability for the new drug when launched, and commercial attractiveness.

Dose ranging

For a dose-ranging phase 2b study, it is usual to examine three or four dose levels. It may also be necessary to compare different dose regimens (e.g., once vs. twice a day for a small-molecule drug, every 2 weeks vs. every 4 weeks for a biologic, necessity for a *loading dose*). Broader ranging may be needed if the agent has a novel mechanism of action or if the relationship between drug exposure and clinical response (the PK-PD-*efficacy* triad) is not well understood.

Typical designs for RA trials have 50 or so patients per study arm (depending on statistical power estimations for the desired effect size) and a 12-week treatment period, with a shorter period possible for PoC (e.g., 4 weeks) with some mechanisms of action.

The ideal outcome of a dose-ranging study is to bracket the desired clinical dose by showing that the next dose down has less efficacy and that the next dose above has no added efficacy and perhaps is associated with poor tolerability or high rates of adverse events. Because phase 3 studies involve larger numbers of subjects and longer study periods (with much greater costs for each dose studied), it is preferred to take fewer regimens into phase 3.

Risk may be reduced by *adaptive study designs* in which expansion to a full dose-ranging protocol is gated on seeing a positive efficacy signal and acceptable safety findings in an initial smaller cohort. Adaptive designs may also be used to fine-tune the number of dose levels and numbers of patients taking each dose, although care must be taken to avoid compromising the integrity of the study (e.g., by unmasking treatment assignments).

Additional studies to better understand the mechanism of action of the drug and to help *differentiate* the drug from competitors are often done during phase 2, either as substudies or as separate clinical trials. Rheumatology examples include synovial biopsy and magnetic resonance imaging studies. Studies involving other immunologic indications (e.g., psoriasis, multiple sclerosis, Crohn disease) may also be initiated in parallel with phase 2 as the start of *life-cycle management* for the drug.

In RA phase 2 or 3 studies, it has also become common to include comparison with an established competitor drug, for example one of the biologic tumor necrosis- α antagonists. In phase 2 these comparisons are generally not double blinded (a complex task if the new drug is an oral small-molecule agent and the comparator an injected biologic) and do not include enough patients for formal statistical testing of the new drug’s possible superiority.

Phase 3

Phase 3 clinical trials are done to confirm the efficacy and safety of the drug for treatment of the desired indication. They are much more costly—in the case of emerging rheumatology drugs, \$50 million to \$100 million or more per study.

If the studies during the earlier phases were done well, the phase 3 program should not yield any unpleasant surprises on the efficacy side. A *phase 3 failure* for the drug (inadequate efficacy, unacceptable safety findings) or for the study (major design or conduct flaws) is a huge waste of resources and may represent the inappropriate exposure of many patients to avoidable risk.

In most instances regulatory authorities require two separate, robust phase 3 trials, both showing efficacy of the drug to a rigorous statistical level, to approve the drug. The two pivotal studies might have nearly identical designs but, for example, be done in different regions of the world or with different background SoC. Two studies are needed in case one single trial has a false-positive outcome. Phase 3 studies are sometimes referred to as *pivotal* or *registration* trials.

Patients completing the main part of a phase 3 study (and some phase 2 studies) may be offered entry into an *open-label extension*, which gives them ongoing access to the drug and allows the collection of long-term safety and maintenance of efficacy data.

The size of the phase 3 program is dictated by (1) the efficacy signal expected (for any given statistical power and *P* value, the larger the effect

the smaller the sample needed), and (2) the size of the safety database required. The guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use specify minimum requirements (a total of 1500 patients treated for certain time periods), but the chronicity of rheumatic disease treatments and the likely widespread use of a successful new drug require larger samples. Additional phase 3 studies may be done; for example, a study in which a new RA drug is given on a background of several possible disease-modifying antirheumatic drugs and/or with more liberal (“real-world”) entry criteria.

Additional studies conducted after the submission of the new drug to the regulatory authority (*new drug application* for a small-molecule agent; *biologic license application* for a biologic; *marketing authorization application* in Europe) but before the approval of the drug are usually referred to as *phase 3b* studies.

Postmarketing studies

Postmarketing, or *phase 4*, studies are performed after approval of the drug. These are often done as a condition of approval by the regulatory authority, termed a *postmarketing commitment*. These studies are most often performed to obtain additional safety information; for example, a cardiovascular outcomes study may be required if the possibility of an increase in stroke or myocardial infarction was noted during clinical trials or is suggested by the mechanism of action.

Drug safety

Drugs may elicit adverse effects through many mechanisms. Some are implicit in the mechanism of action; for example, any drug that works by modulating the immune response (except via an autoantigen-specific mechanism) may have an impact on host defense against infection and malignancy. This is central to most emerging drugs targeting RA, systemic lupus erythematosus, and spondyloarthritis.

Whether a host defense defect has significant clinical consequences depends on the magnitude of the impact, the part of the immune system affected, and the presence of redundant mechanisms for coping with the pertinent microbes. For predicting whether issues will arise in humans the preclinical host defense models are even worse than the preclinical arthritis models. Close vigilance is needed during clinical development and the postmarketing period.

Adverse events occurring in clinical trials are graded according to severity by agreed-upon criteria (e.g., Common Terminology Criteria for Adverse Events, with Grade 1 being mild and Grade 5 meaning a fatal outcome). When the adverse events are summarized in study reports they can be classified according to the part of the body involved, usually according to system-organ-class categories. Raw data on the incidence of a particular adverse event can also be translated into plain language. The Council for International Organizations of Medical Sciences has defined events occurring in 1 in 10 subjects or more as “very common”; in between 1 in 10 and 1 in 100 subjects as “common” or “frequent”; in between 1 in 100 and 1 in 1000 as “uncommon” or “infrequent”; in between 1 in 1000 and 1 in 10,000 as “rare”; and in 1 in 10,000 or fewer as “very rare.”

An adverse event occurring during a clinical trial is considered serious (SAE) when certain criteria are met: death results, hospitalization (or prolongation of hospitalization) is required, the effect is life-threatening, permanent disability or damage results (or medical intervention was required to prevent these outcomes), or the effect is medically important in some other way (a potential gray zone). All SAEs must be reported quickly, regardless of whether the investigator and/or the company believes they are related to the drug.

An approximate sense of safety during various stages of drug development comes from the *rule of threes*: a study in which 300 patients receive the active drug should catch an adverse event occurring at least once in 100 subjects exposed to the drug; a study of 3000 patients would be needed to largely rule out events occurring at an underlying incidence of 1 in 1000; and so on. Uncovering the uncommon but serious events relies on *postmarketing surveillance*.

Particular concerns over safety aspects may be managed by an independent *data monitoring committee* or *data safety and monitoring board* (DSMB). DSMBs have access to unblinded data during the trial and so can better assess whether a poor risk-benefit balance is emerging. The DSMB may recommend altering or stopping the trial.

Regulatory aspects

Regulatory agencies are government bodies that safeguard patients’ interests by ensuring that a new drug molecule has suitable efficacy and safety in

treating the proposed indication. This role is performed in the United States by the Food and Drug Administration (FDA) and in the European Union by the Committee for Medicinal Products for Human Use of the European Medicines Agency; there are equivalent agencies in other countries.

Submission for regulatory review is a major landmark in the drug development process and requires months of preparation. Similarly, the regulatory agency needs many months to thoroughly review the data. The expected date for a regulatory decision in the United States is often referred to as the *PDUFA date*, a term derived from the Prescription Drug User Fee Act, which dictates the fees the company must pay for review (just under \$2 million in 2013) in return for having a reasonable expectation of timely review.

Special provisions are available for areas of high unmet need. Designation as an *orphan drug* provides certain financial advantages to the sponsoring pharmaceutical company to encourage companies to target uncommon diseases for which the development of drugs might otherwise be unprofitable or seen as too “difficult.” In general this status is more likely to be granted for disorders that have a tightly defined clinical phenotype or specific diagnostic test. The *breakthrough drug* designation is a relatively new pathway designated by the FDA for highly novel approaches.

When a drug is approved, the regulatory agency and the company agree on specific language (the drug’s *label*, *prescribing information*, *package insert*) that describes the indication(s), dosing and administration, and potential safety issues of which the patient and prescriber need to be aware. Major safety issues—for example, a description of serious infection or malignancy risks with a new RA drug—may be described in a *black box* portion of the package insert and advertising material.

Commercial aspects

The time between starting target validation and beginning the first human studies is 4 to 5 years if all preclinical parts of the process go well (and often they do not), and the clinical steps from phase 1 trials through approval take 7 to 8 years. Committing the resources required needs careful evaluation. Major ingredients include knowledge of the number of patients likely to benefit, the efficacy and safety profile that the drug is likely to deliver, the competitive landscape of existing standard of care and emerging competitors (hence, the likely market share), the price the drug is likely to sell for, and the number of years between the launch of the drug and the expiration of the drug’s patent, which will allow entry of a cheaper *generic* version to the market.

A key tool is the *target product profile* (TPP; [Box 49.4](#)). *Market research* is done to explore the weighting that patients, prescribers, and payers place on the various attributes desired of the new drug. The TPP dictates what the clinical trials need to deliver in terms of safety and efficacy requirements. Typically this is some middle ground between what the company’s commercial functions would ideally want in the drug label and what the research, clinical, operations, and regulatory functions think are realistic expectations. The TPP may define attributes that require the new drug to be either the *first in class* (for a novel mechanism) or *best in class* (where one or more competitors with the same mechanism are ahead, e.g., by offering a more convenient dosing regimen).

Company conduct

As publically traded commercial entities, pharmaceutical companies have the standard fiduciary obligation to maximize the returns to their shareholders; in plain terms, *to make as much money as possible*. Fortunately, the interests of shareholders and patients overlap: good drugs can make the company a lot of money, mediocre drugs do not, and bad drugs or unethical corporate conduct invite large financial losses through lawsuits, fines, and wasted development and commercialization costs.

The many historical sins of the pharmaceutical industry have been documented extensively.¹⁰⁻¹² These include off-label promotion; excessive payments (beyond legitimate fee-for-service honoraria) to *key opinion leaders* in a position to influence prescribing; *post-hoc* changes in study design to produce outcomes favorable to the company; and ghost writing of reviews favorable to the company’s drug. A further issue is failure to disclose clinical trial data that might cast doubt on the efficacy and/or safety of the drug, although a recent analysis found that RA studies did not show any evidence of bias from selective publication of “favorable” data.¹³

The consequences of some of these behaviors are not lost on the industry, including large fines (up to \$3 billion in recent years) for illegal promotional activities and the adverse impact on a company’s reputation. The bright sunlight of full disclosure of any potential conflict of interest (ideally through a centralized disclosures database) may prove a good deterrent against excessive financial payments to prescribers and key opinion leaders.¹⁴

BOX 49.4 TARGET PRODUCT PROFILE***Indication**

For the treatment of moderate to severe rheumatoid arthritis in patients who have shown an inadequate response to one or more disease-modifying antirheumatic drugs

Efficacy

ACR50 40% above placebo rate after 12 weeks of therapy
Clinical improvement apparent within 2 weeks of starting dosing
Inhibition of radiographic progression by $\geq 75\%$
HAQ improvement by >0.5 over placebo, significant quality-of-life improvement

Safety

Well tolerated alongside standard-of-care medications
Safe for long-term use
Monitoring requirements not greater than those for methotrexate
Infections not exceeding background rates by $>2\%$
No serious atypical or opportunistic infections greater than background levels

Dosage and administration†

Once-a-day dosing
Flat dosing (same dose irrespective of body weight)
No dose adjustment for age or for mild-moderate renal or hepatic impairment
No dose adjustment for concomitant administration of commonly used drugs

*An optimistic profile for a fictitious new drug intended for treatment of rheumatoid arthritis. Competitive hurdles are lower for diseases that are less well served by current treatment (e.g., systemic lupus erythematosus). Target product profiles (TPPs) may have variations such as *optimistic*, *base case*, and *minimum* requirements, an alternative version if the quest for a predictive *companion diagnostic* is successful, or include explicit comparisons with known competitors. Early in development the TPP is a generic wish list and will be tempered by reality as data emerge and as the competitive landscape evolves.

†Small-molecule example. The TPP for a new protein biologic might instead specify desired attributes such as subcutaneous dosing, injection site reactions in $<5\%$ of patients and not exceeding grade 2, dosing once a month, patient self-administration, and availability of an autoinjection device at launch.

ACR50, American College of Rheumatology 50% improvement criteria; HAQ, Health Assessment Questionnaire.

Economics of drug development

Even for biologics the cost of manufacturing the drug is usually a small proportion of the high marketed price of a new drug; the majority rests on research and development (R&D) costs. Contemporary estimates cover a wide range, with sums between \$1 billion and \$2 billion at today's prices commonly quoted.¹⁵⁻¹⁷ Analysis of R&D expenditures compared with new drug approvals over a 15-year period showed that the 12 largest pharmaceutical companies had spent between \$3.7 billion and \$11.8 billion to produce each new approved drug.¹⁸ These huge sums are driven not so much by the cost of producing the few successful drugs, but rather by the cost of the many more drugs that fail. Failure at later phases is particularly damaging, because phase 3 expenditures account for up to 90% of overall drug development costs.

Although it is clear that drug development costs are high and growing, and that the pharmaceutical industry's productivity is low and shrinking, the solutions are not so apparent. Suggestions include a focus on maximizing the scientific information obtained in early phases of development to reduce the uncertainties of the more expensive later phases.^{16,19,20}

For the clinical development of new rheumatology drugs, this translates into a bigger emphasis on getting efficacy-oriented readouts in the early steps of drug development. Investigators may expect to see an increasing emphasis on biomarker endpoints, early-phase trials conducted in patients rather than in healthy volunteers, patient enrichment strategies, and adaptive and combination designs that minimize costs and the time to complete studies.

CONCLUSIONS

Patients with rheumatic diseases have benefited from several recently approved drugs. Drug development, the process of bringing a new drug from an initial research idea through to the clinic to help address the unmet medical needs of patients, is a long and expensive process with a high rate of failure at each step. New developments in clinical trial design aim to improve the success of the process.

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Nonpharmacologic pain management

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- Pain is determined by a combination of biologic, psychological, and social factors.
- Sixty percent of rheumatology patients report severe pain and irritation.
- Nonpharmacologic interventions include cognitive-behavioral therapy, relaxation therapy, patient education, self-management, and social support interventions.
- These types of interventions aim to change behavior, cognitions, and emotions by targeting the psychosocial processes that are implicated in the perceptions of and response to pain.
- There is good evidence that these interventions can be effective in changing pain, particularly in relation to the cognitions surrounding pain; however, this is predominantly in the short term.
- More research is needed to identify who may benefit from nonpharmacologic interventions.

INTRODUCTION

The traditional biomedical model suggests that pain is a direct result of a confirmed organic dysfunction. Treatments are therefore aimed at alleviating or curing this damage and/or blocking these impulses. It is now widely accepted, however, that associations between physical impairment and pain reporting and disability are modest at best. Purely physiologic explanations have been unable to explain why patients sometimes report pain in the absence of physical damage or why identical conditions can lead to pain that varies greatly in severity, intensity, or quality. In response to the shortcomings of the physiologic model, the gate-control theory of pain¹ and a recent extension, the neuromatrix theory of pain, were developed. These theories incorporate both psychological and physiologic factors and offer a biologic basis for the role of psychological factors in pain. The biopsychosocial model of pain recognizes the role of biology and psychology but also the role of social determinants of pain regardless of what the source of the pain is or whether it is associated with psychopathology. It proposes that environmental factors such as the responses of significant others, cognitive factors such as beliefs about pain, and coping behaviors all influence the experience.

PREVALENCE OF PAIN IN RHEUMATOLOGIC CONDITIONS

Pain is the main symptom for most people with arthritis.² In a study of more than 11,000 individuals with a rheumatic condition, over 60% reported severe pain and irritation. Of these, 45% said the pain limited daily activities, 37% felt that the ability to lead a normal life was affected, and 22% were always in pain.³ A comparison of people with osteoarthritis (OA), rheumatoid arthritis (RA), and fibromyalgia found no difference in reported pain severity between individuals with OA and those with RA, but individuals with fibromyalgia reported significantly greater pain severity.⁴ The impact of pain goes beyond the sensation; it is associated with frequent use of medication and health services,⁵ as well as time off work.⁶ Besides the sensation of pain itself, its widespread influence results in a significant impact on quality of life.

MEASUREMENT OF PAIN

Pain is a personal experience; it is not amenable to direct clinical measurement and therefore must be inferred from subjective pain reports. There are various aspects of pain to measure and many ways to perform this measurement. Pain intensity is most commonly measured via rating scales, many of which are considered to be reliable, valid, and appropriate to clinical practice. Some measures, however, may be best suited to individuals experiencing constant daily pain. There are also composite pain scales that are well validated, including the Arthritis Impact Measurement Scale (AIMS). In addition to measures of intensity there are instruments that assess the impact of pain (e.g., Multidimensional Pain Inventory) and the different ways in which people respond to pain.

The experience and qualities of pain have been captured in the McGill questionnaire, which has shown similarities and differences between individuals with different rheumatic conditions. Those with RA and fibromyalgia both use the description *aching and exhausting* to describe their pain. They differ in that RA patients use the words *stiff* and *moving* most frequently, whereas fibromyalgia patients use the words *nagging* and *hurting*.⁷ Pain quality can also be dependent on the activity in which an individual is engaged because pain at rest tends to be described differently from pain in movement.⁸

PSYCHOLOGICAL FACTORS AND PAIN

It is understandable that chronic pain that persists for months and years influences all aspects of a person's functioning. In longitudinal studies, pain has been found to be predictive of physical⁹ and psychosocial¹⁰ health-related quality of life.

Coping with pain

Coping is the cognitive, behavioral, and emotional strategies people use on a day-to-day basis to help them manage the consequences of their disease and has been found to mediate the relationship between pain and physical disability in RA.¹¹ A review of the psychological aspects of persistent pain by Keefe and colleagues¹² suggests that the psychological and behavioral factors associated with more severe pain include catastrophizing (the tendency to focus on pain and negatively evaluate one's ability to deal with and control it), pain-related fear, helplessness, and avoidant coping. In contrast, lower levels of pain are linked to higher levels of self-efficacy (belief that one has the capacity and confidence to deal with one's pain), a greater perception of control, active coping, readiness to change, and acceptance. In fact there is growing evidence that increasing levels of self-efficacy through psychosocial interventions is related to improved outcomes.¹³ Positive relationships have been found between catastrophizing and severity of pain, tenderness, pain-related disability, and disease activity.¹⁴ Similarly, feelings of helplessness have been positively related to levels of pain¹⁵ and may explain why some patients view pain as inevitable and discontinue treatment as a result of failed coping attempts.

Problems for patients can sometimes arise through excessive attempts to control or avoid pain, and there is a growing recognition of the important role of acceptance in management of pain. Acceptance does not involve trying to control or avoid the pain but being willing to perform valued activities regardless of the pain.

Emotions and pain

A number of factors contribute to the coexistence of depression in a large proportion of patients with rheumatic diseases. First, the prevalence of

rheumatic diseases is higher in women, as are levels of depression.¹⁶ There is also a vast amount of literature demonstrating that the presence of pain not only is associated with depression¹⁷ but appears to predict future depression in people with RA¹⁸ and OA.¹⁹

Feelings of anxiety—in particular, fear of completing tasks that may exacerbate pain—can lead to avoidance of activities and situations that involve movement. Studies suggest that fear of movement and reinjury better predict functional limitations than biologic factors or even pain severity and duration.²⁰

Social support and pain

A considerable amount of research has linked lower perceived social support to poorer health outcomes, including higher mortality.²¹ The stress-buffering hypothesis²² proposes that social support helps to mitigate the adverse effects of a stressor such as a chronic disease by enhancing a person's perceived ability to cope with the demands of the disease and by reducing maladaptive emotional or behavioral responses. Social support has been found to have an indirect effect on pain through the use of specific coping strategies and the effectiveness with which these coping strategies are employed.²³ Social support can have detrimental as well as beneficial effects, however; overly protective or overly critical social support has been linked to increased pain.²⁴

PSYCHOSOCIAL INTERVENTIONS FOR PAIN

Many people with pain do not gain adequate relief from medication,²⁵ and there is increasing recognition of the need to include psychosocial approaches in pain management.

Psychosocial interventions to address pain aim to change behavior, cognitions, and emotions by targeting the psychosocial processes that are implicated in the perceptions of and response to pain. These interventions are often offered after traditional biomedical therapies have failed and increasingly alongside traditional pain interventions. A number of general reviews have been undertaken which reveal that psychosocial interventions for people with rheumatologic conditions can significantly reduce pain and increase self-efficacy in comparison with control conditions, although the overall effect size is often small.^{26,27} Psychosocial interventions have a variety of components, often related to each other and customarily presented in combination. A description of the main types and the underlying principles of these interventions is presented before the evidence is examined.

Cognitive-behavioral therapy

The most widely applied and dominant intervention, cognitive-behavioral therapy (CBT), is based on the premise that cognitive and affective factors influence behavior and aims to alter maladaptive cognitive and behavioral responses to pain. CBT aims to assist patients in understanding that they can manage their pain effectively and then provide them with the skills to do so. There are five primary assumptions that underlie all CBT interventions (Box 50.1).

The four essential components of CBT are education, skills acquisition, cognitive-behavioral rehearsal, and generalization plus maintenance. Education aims to provide a credible rationale for the intervention by engaging the patients and encouraging them to believe that they are able to learn the skills necessary to cope better with their pain. Skills acquisition allows patients to learn these new behaviors and cognitions and practice them in the real world. Patients are encouraged to formulate a problem, define an

achievable goal, and identify strategies to achieve that goal, and are rewarded for successful completion. To ensure generalization and maintenance after the completion of the sessions patients are encouraged to anticipate and plan for future events concerning their pain, recognizing that setbacks will occur and that they now have the techniques that will allow them to overcome these problems.

Acceptance-based interventions

Acceptance-based techniques involve developing an awareness of one's pain without judgment, rather than attempting to control or fight it. Mindfulness-based therapies attempt to teach participants how to be aware of the present moment and disidentify with everyday thoughts through formal meditation exercises. Acceptance and commitment therapy targets ineffective coping strategies by helping patients distance and let go of unhelpful thoughts, beliefs, and memories, and accept pain and fully engage with the here and now.

Relaxation therapy

Relaxation is a widely used component of many psychosocial interventions to address pain and aims to reduce the psychophysiologic arousal frequently associated with pain. It involves breathing steadily and deeply and passively ignoring everyday thoughts and is encouraged as a distraction technique for coping when pain is particularly severe. The various forms of relaxation therapy include progressive muscle relaxation (PMR), biofeedback, meditation, autogenic training, and guided imagery.

Patient education

Patient education refers to a set of planned educational activities designed to reduce pain and its consequences. Pain education activities include topics such as information about the condition, encouragement of feasible activities that promote quality of life, the pacing of activities, coping advice, and information about sources of support. The underlying assumption is that patients who are better informed about their condition, treatment options, and prognosis will be better able to manage their disease and therefore achieve better health.

Self-management

Self-management is in part a combination of CBT and patient education, incorporating the idea of patient empowerment. According to Barlow and colleagues,²⁸ “self management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent in living with a chronic condition.” There is a range of possible components to a self-management intervention, and education is one of these. Other widely adopted techniques include self-monitoring, skills training, challenging of unhelpful behaviors, management of emotions, enhancement of communication skills, social support, promotion of readiness to change, enhancement of self-efficacy, problem solving, and goal setting. Fundamental to self-management is skills training to assist patients in managing their condition. Information is seen as a necessary but not sufficient component.

Self-management interventions can help patients understand how their thoughts can influence their behavior and mood and can allow people to explore different ways of viewing situations. Many different psychological theories have been used to develop self-management interventions (Table 50.1). These models all identify concepts that need to be modified to produce a desired change in behavior. By encouraging the routine use of self-management techniques for a particular aspect of a person's disease, such as pain, the hope is that the individual will translate these techniques to address other aspects of the disease. Despite the evidence base for these theories, a number of intervention studies that claim to use self-management techniques are not explicitly based on any theory.

Social support interventions

Social isolation has been found to impact health; therefore, some interventions have aimed to alter levels of social support. The premise is that having others around giving support can encourage appropriate behaviors, provide emotional support and information, and offer alternative ways of dealing with the condition. This can be achieved by creating new social networks relevant to the needs of the patient, such as self-help or support groups. An alternative is to focus on those people already in the patient's life and develop their skills to provide additional and appropriate support.

BOX 50.1 ASSUMPTIONS OF COGNITIVE-BEHAVIORAL THERAPY

1. An individual's behavior is influenced by his or her belief about the expectations and consequences of the behavior.
2. An individual's thoughts may alter his or her behavior by interacting with emotions and physiologic responses, and, in turn, these thoughts may also be influenced by emotional and physiologic responses.
3. The interactions between an individual's behavior and environmental reactions are reciprocal.
4. Interventions should address the emotional, cognitive, and behavioral dimensions of the problem.
5. Individuals must become active participants in learning adaptive methods of responding to their problems.

TABLE 50.1
Models of behavior change

Self-regulation or common sense model ⁵⁶	- Describes how a patient will come to understand his or her illness and how to develop the coping strategies necessary to manage the patient's disease. - Relies on an individual's ability to monitor his or her own actions and reflect on them and their associated consequences.
Social cognition model based on social cognition theory ^{57,58}	- Implies that changing illness perceptions may lead to changes in relevant self-management behaviors. - Suggests that behavior is directly influenced by goals and self-efficacy expectations and indirectly by self-efficacy, outcome expectations, and sociostructural factors. A majority of the empirical applications of this theory focus on self-efficacy.
Theory of planned behavior ⁵⁹	Suggests that behavior is determined by the strength of a person's intention to perform that behavior and the amount of actual control the person has over performing it.
Stages of change or transtheoretical model ⁶⁰	- Assumes that behavior change involves movement through a sequence of discrete stages. - Holds that different factors influence the different stage transitions and that interventions should be matched to the person's current stage.

EVIDENCE BASE

When the evidence base for these interventions is assembled, a number of limitations need to be acknowledged. Descriptions of the interventions often are not detailed enough to be entirely clear with regard to content. The labeling of interventions can also be confusing; for instance, one intervention might be called CBT and another, patient education or self-management when, in fact, they involve similar components. In addition, interventions may have similar content but may differ significantly in duration and in the way in which they were delivered. These problems are common in attempting to integrate findings from complex interventions and make it difficult not only to group interventions by type and compare them but also to draw distinct conclusions about what makes them effective. An additional important caveat is that some interventions are not aimed primarily at managing pain but measure pain as one of many secondary outcomes.

Nonpharmacologic interventions are delivered over a discrete period and are assessed at various times after intervention. The follow-up to determine efficacy has characteristically occurred immediately after or relatively soon after the intervention has ceased. Whether there are enduring effects of nonpharmacologic interventions has only infrequently been evaluated. For example, a review by Dixon and associates²⁶ found that only 10% of studies assessed the impact of the intervention beyond the immediate posttreatment period. An additional complication is the way in which pain is measured. Because different measures of pain cover different concepts and have different psychometric properties, the measure used, rather than the intervention per se, may influence the final conclusions. Finally, a number of studies have compared an intervention with "standard care." Any conclusion about an intervention's effectiveness requires an explanation of "standard care," because standard care differs vastly in different environments and therefore cannot be considered a constant.

Cognitive-behavioral therapy

In a recent review of psychological interventions for pain management in arthritis, 80% were labeled as CBT,²⁶ and of these only two showed significant effects. General reviews have offered contradictory results regarding CBT and pain. A narrative review by Bradley and colleagues²⁹ concluded that CBT is a well-established treatment for RA pain and is probably efficacious for patients with knee OA. However, the authors of a recent Cochrane review, who applied more restrictive selection criteria for studies, examined the effectiveness of psychological therapies for nonmalignant chronic pain, including a number of rheumatic conditions, and concluded that CBT has

weak effects in improving pain.³⁰ When compared with usual care, CBT had a small but significant effect on pain after treatment, but this effect was not maintained at the 6- or 12-month follow-up.

Key to understanding the impact of CBT is to establish for whom the intervention works and what techniques are related to success. Keefe and Van Horn³¹ attribute the variability in the success of CBT interventions to differences in psychological variables such as self-efficacy, pain coping strategies, and feelings of control, as previously discussed. Similarly, when the mediating and moderating factors that predict therapeutic change in CBT were examined, pretest to posttest treatment changes in pain beliefs, catastrophizing, and self-efficacy for managing pain were found to mediate the effects of CBT.³² Other studies have demonstrated that those who adhere to a CBT program are more likely to show gains—an important point, but often taken for granted.

Although some studies fail to find differences in self-reported pain, changes in other associated pain measures have been reported. When Parker and colleagues³³ compared CBT with an educational intervention and standard care in patients with RA, they found no significant difference in self-reported pain but significant changes in pain-related coping strategies, such as control, at 6 months and 12 months after intervention. In addition, when occupational therapy and a standard-care control condition were compared with CBT, Kraaimaat and colleagues³⁴ found that, for people with RA, CBT resulted in a significant increase in the use of distraction after treatment but no change in other pain-related measures.

The long-term effectiveness of CBT has been extensively debated. When compared with standard care, patient education, and symptom monitoring CBT has been found to significantly improve various aspects of pain; however, these significant changes are not always maintained in the long term. These studies suggest that CBT can have a small effect on pain. However, these interventions result in greater improvements in the cognitive and behavioral aspects of pain, such as pain behavior and pain self-efficacy, than in self-reported measures of intensity. These benefits tend to be found immediately after interventions, and there are mixed findings as to whether they are maintained at long-term follow-up. Overall, the need to examine individual differences to identify in whom these interventions are effective and to determine which variables influence outcome is vital.

Acceptance-based interventions

The ability to be mindful and accepting of pain has been found to be predictive of lower levels of catastrophizing.³⁵ When Zautra and colleagues³⁶ compared a mindfulness-based therapy with conventional CBT and an education-only placebo control condition in people with RA, they did not find any differences between the groups in daily pain scores. However, participants in both intervention groups reported greater increases over time in pain coping self-efficacy compared with the control group. Perceived pain control improved more in the CBT and placebo control groups than in the mindfulness-based therapy group.

A systematic review and meta-analysis of studies using acceptance-based interventions for the treatment of chronic pain found a small but significant effect on pain intensity.³⁷ However, the review included only two studies rated as high quality; therefore, the findings must be treated with caution. Although the reported effect size was similar to that of CBT,³⁰ traditional CBT has been tested more widely. Veehof and colleagues³⁷ concluded that mindfulness-based programs are not superior to CBT but may be a suitable alternative, and they recommended further research to identify characteristics that could be important in deciding whether to refer patients to either CBT or a mindfulness-based program.

Relaxation training

A number of systematic reviews have been published looking at the efficacy of specific relaxation techniques in managing chronic pain. Carroll and Seers³⁸ examined nine randomized controlled trials that reported the use of only a relaxation strategy as an active treatment compared with at least one other active or control treatment in individuals with a variety of conditions. The most common form of relaxation was PMR with audiotapes and regular home practice. There was little evidence, however, to support the effectiveness of relaxation in the relief of chronic pain. The two studies in individuals with rheumatologic conditions reported contradictory results. One in RA found a significant benefit in favor of relaxation in at least one pain outcome, whereas hydrogalvanic baths were found to be more beneficial than relaxation therapy in fibromyalgia patients.

In a more recent systematic review, Kwekkeboom and Gretarsdottir³⁹ included studies in which relaxation training had been used in combination with other interventions, such as guided imagery or CBT. They concluded

that, when results were considered across conditions, a majority of studies showed a significant effect of relaxation on pain as measured before and after intervention. PMR, autogenic training, jaw relaxation, and systematic relaxation, in particular, showed benefit. However, when PMR was compared with exercise therapy and hypnosis, no significant effects on pain were found.

These interventions reveal a somewhat mixed picture in terms of the efficacy of relaxation training for pain management. Those studies that used relaxation techniques in combination with other psychological interventions appeared to show more success than those that used relaxation alone, which suggests that it may be other components of the programs that resulted in significant changes in pain.

Self-management and educational interventions

Self-management interventions have received much attention over the past two decades. The most well-established self-management intervention is the Arthritis Self-Management Program. This 6-week program is open to all people with rheumatic conditions and involves peer-led sessions that include information about arthritis, an overview of self-management principles, exercise, cognitive symptom management, ways of dealing with depression, nutrition, communication with family and health professionals, and contracting. Weekly goal setting is encouraged as a means of practicing the skills taught in class and as a way of increasing self-efficacy. There have been numerous studies looking at the efficacy of this training program in various populations, but results with regard to pain have been variable. For example, an evaluation in the United States that recruited participants through public service announcements reported a significant effect on pain at the 4-month follow-up,⁴⁰ but this finding was not replicated in a U.S. primary care setting.⁴¹ A United Kingdom evaluation of this intervention in people with any type of arthritis found no difference in pain scores between the intervention and control groups; however, the intervention group reported a greater improvement in pain control self-efficacy.⁴² Similar results were found when the intervention was evaluated in a United Kingdom primary care setting in a population with OA of the hip or knee.⁴³

A number of systematic reviews have been undertaken to summarize the effectiveness of both patient education and self-management interventions. The findings are somewhat mixed but in general indicate a small effect of self-management interventions on pain, which is not maintained in the long term.

A systematic review of patient education for adults with RA identified 50 studies from 1966 to 2002 and found only a trend toward significance for the effects of patient education on pain scores at first follow-up and no significant effects at final follow-up.⁴⁴ Sensitivity analysis, however, found that there was much variation in the way in which pain was assessed; moreover, the time frame patients were asked to consider in reporting pain (e.g., over the past day, week, or month) varied significantly. A significant effect for the intervention was found at first follow-up when a visual analogue scale was used to measure pain, but no effect was found when validated measures such as the AIMS were used. No long-term effects were found regardless of the type of measure used, nor were there any significant differences when the results for information provision, counseling, and behavioral treatments were examined separately. A more recent meta-analysis of trials published up to March 2010 found that self-management interventions had a moderate significant effect in reducing pain intensity at 4, 6, and 12 months after intervention.⁴⁵ However, only three studies were included in the meta-analyses for 6-month and 12-month follow-up.

A recent systematic review⁴⁶ sought to assess the efficacy of individual behavior change techniques. The review examined whether self-management interventions that included five behavior change techniques—goal setting, planning, self-monitoring, feedback, and relapse prevention—demonstrated greater efficacy than other psychological interventions. The rationale was that these techniques would be expected to facilitate more effective self-management. Cumulative effect sizes of all studies included in the review showed a significant effect on pain immediately after treatment and at follow-up (ranging from 2 to 14 months). Interventions that used more behavior change techniques did not have a greater effect on pain than other interventions; however, they did have a greater effect on depressive symptoms and anxiety.

In a systematic review to determine the long-term benefits of self-management and identify intervention or participant characteristics that are associated with a beneficial outcome Iverson and colleagues⁴⁷ examined 30 articles. Only 14 studies had follow-ups of 12 months or longer, of which 4 demonstrated a significant effect on pain. Booster sessions had been included in eight studies, of which four had follow-ups of 12 months or longer. Only one of these studies found a positive effect on pain, and this

benefit was maintained at the 12-month follow-up. The authors of the review recommended that studies with demonstrated benefits at 6 to 12 months should seek to extend that follow-up period and include evaluation of cost effectiveness. The characteristics of programs that were beneficial (for any outcome, not necessarily pain) were a duration of at least 6 weeks; use of social cognitive or cognitive-behavioral approaches; inclusion of exercise; use of individualized weekly action plans with review; protocolization with participant handbooks; and use leaders trained in grouped facilitation.

In summary, the short-term effects of these interventions seem to be fairly well established, even though many are not specifically designed to target pain. It should also be noted that in a majority of cases these interventions are provided in addition to standard care; therefore, the effects are always supplementary to the benefits of standard practice. There is much less evidence, however, to suggest that these benefits remain in the long-term. Future research needs to establish how short-term benefits can be maintained.

Social support interventions

A small number of interventions have included components that aim to influence health outcomes in musculoskeletal conditions by manipulating social support. These have often involved adapting cognitive-behavioral interventions, and although they have had limited success in changing levels of pain, beneficial effects have been found in pain and coping self-efficacy. Spouse-assisted coping skills training has been assessed in individuals with OA and chronic back pain. In one study spouse-assisted coping skills training was compared with conventional coping skills training and with spouse-assisted education; patients in the spouse-assisted coping skills training group reported significantly higher levels of self-efficacy for pain compared with those in the educational group, but not compared with patients in the conventional coping skills training group. These results suggest that it was the coping skills training, rather than the addition of spousal support, that had an impact on self-efficacy.¹³ In more recent trials patients with OA and those with chronic lower back pain were found to benefit from the addition of spouse assistance in coping skills training, showing higher posttreatment pain-coping attempts and less rumination about pain at the 12-month follow-up.^{48,49} Alternative approaches include providing social skills training to participants; however, although improvements have been found with regard to fatigue, depression, and perceived support, no effect was found for pain.⁵⁰

To date, there does not appear to be strong evidence for a beneficial effect of social support interventions on pain management. Although the relationship between social support and health outcomes is well documented, direct evidence is still lacking for the psychological mechanisms that might help to explain this link, and this hinders the development of well-informed interventions.

USE OF TELEHEALTH IN PAIN MANAGEMENT

Attending an intervention program that lasts several weeks may not be desirable or practical for many people. In fact, a trial to evaluate the efficacy of the Arthritis Self-Management Program in Australia had to be terminated because of lack of sufficient enrollment. Reasons given included work and family commitments, difficulty in getting to courses, and poor health.⁵¹

Recent developments in telehealth may offer a way to make such programs more accessible. Electronically delivered programs may also have the potential to include more intensive booster sessions than is usually feasible and thus help to enhance maintenance of beneficial effects that currently are seen mainly in the short term. Telehealth may also offer more flexibility in tailoring programs to the needs of the individual. Promising attempts have been made to adapt face-to-face self-management interventions for use in patients with fibromyalgia and RA that suggest significantly greater improvement in pain compared with standard care⁵² and high levels of acceptability.⁵³ Although this field is growing rapidly, reviews have reported on few randomized controlled trials assessing efficacy, and therefore a more extensive evaluation is required.^{54,55}

CONCLUSION

Overall there is evidence that psychologically based interventions can be effective in changing pain, particularly in relation to pain cognitions. The findings tend to be clearer for the short term, and the evidence is less persuasive that these results persist in the longer term. To maintain

improvements after the interventions, special attention needs to be paid to the generalization and maintenance of what has been learned and to the integration of these techniques into everyday life.

There is a lack of research investigating which individuals benefit from different types of interventions and the mechanisms through which these

interventions work. In chronic rheumatic pain, attention needs to be directed to the crucial beliefs and coping strategies that have the capacity to explain the effect of psychological interventions. A valuable approach would be to identify these important psychological factors so that future interventions can be tailored appropriately.

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Pharmacogenomics in rheumatology

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- Pharmacogenomics is the application of genomics to optimize drug design and selection and the course of therapy based on individual patients' genetic profiles, whereas pharmacogenetics refers specifically to elucidation of the roles of individual genetic variations in determining drug response.
- Single nucleotide polymorphisms (SNPs) are single nucleotide variations in the DNA sequence occurring in at least 1% of the population and present in the human genome at a density of 1 per 1000 base pairs or greater. SNPs may be tested individually for direct association with a phenotype or be used as part of a set of markers to identify genomic regions associated with a phenotype and are thus a powerful tool in the field of pharmacogenetics.
- Association studies are population-based studies that test for statistically significant relationships between particular genotypes and phenotypes. Association studies have been used widely in efforts to identify putative genetic risk factors for poor or toxic responses to commonly administered therapies for rheumatologic diseases.
- The impact of pharmacogenetics on clinical medicine is likely to be substantially enhanced in the near future by convergence of the availability of larger, better-characterized patient populations, continued improvements in the speed and cost-effectiveness of high-throughput genotyping technologies, optimization of marker selection for more complete and efficient coverage of the genome, and improved understanding of both target disease etiologies and the mechanisms of action of drugs.

PHARMACOGENOMICS

The rapidly growing field of pharmacogenomics focuses on the application of genomics to optimize drug design and selection and the course of therapy based on individual patients' genetic profiles. Pharmacogenetics, a branch of pharmacogenomics, refers specifically to elucidation of the roles of individual genetic variations in determining drug response. Although the long-term impact of these fields on clinical medicine is uncertain, the principle of particular allelic variants affecting the incidence of lack of efficacy or adverse response to drug therapy has been established for decades.¹⁻³ This chapter provides a brief introduction to pharmacogenetics with a focus on practical considerations for researchers in the design and interpretation of pharmacogenetic studies, as well as a review of the current literature on pharmacogenetics research relevant to rheumatology.

In recent years the availability of detailed sequence data in the wake of the Human Genome Project and the rapid evolution of high-throughput genotyping systems have provided tools that substantially enhance the capabilities of researchers in performing genomics research. Of particular utility in identifying genetic markers for directing therapy has been a rapidly increasing number of single nucleotide polymorphisms (SNPs) identified throughout the genome at a reported frequency of roughly 1 per every 1000 base pairs of DNA or higher. Such information is of value for biomedical research on a number of levels. First, identification of an SNP within a gene of known relevance to a phenotype of interest provides the basis for asking whether an allele of that SNP is associated with the phenotype. This could occur directly, such as through alteration of a gene's regulatory properties (e.g., promoter region, splice site, mRNA stability), or by encoding a change

in an amino acid that affects the structure or function (or both) of the protein. Alternatively, a phenotypic association with an SNP allele could result if the allele is in linkage disequilibrium with (i.e., segregates with) an allele of a second SNP or another genetic variation that confers such an effect. Thus, a single SNP may by itself provide a sufficient basis for uncovering a genotype/phenotype association.

SNPs have also become increasingly useful as genetic markers for use in mapping and genome-wide association studies (GWASs). In such cases the SNP is not being used on an individual basis but rather as one of a set of SNPs distributed across the genome such that alleles of particular SNPs within the set that associate with a phenotype of interest serve to identify the region or regions of the genome in which the gene or genes responsible for the phenotype lie. Within what gene, if any, an SNP is located is not of direct importance when it is used for this purpose but rather the extent to which the SNP set adequately covers the genome. In general, the smaller the average distance between SNP markers across the set, the greater the likelihood that at least one marker will be in sufficient linkage disequilibrium with each contributing allele for the tract to be mapped. An important caveat to this rule is that varying degrees of linkage disequilibrium exist across the genome, which results in "blocks" of sequence and, with them, SNPs that segregate together. Such strings of contiguous SNP genotypes are referred to as haplotypes, and a large-scale effort has been completed in which a human genome "HapMap" has been established to identify the location and size of these blocks of sequence to potentially ease the performance of association studies by reducing the number of markers that need to be genotyped to cover the genome.^{4,5} Still, SNP density remains a critical factor in determining the success of such mapping projects, and as the density of known SNPs across different populations continues to increase, so does researchers' ability to interrogate the genetic components of pharmacogenetic (and other) phenotypes.

Experimental approaches and considerations regarding study design and data interpretation

Drug response presents unique challenges as a phenotype (see later) and often limits the experimental approaches that an investigator may apply to elucidate its genetic basis, but many of the design considerations critical to the success of genetic association studies in general apply to pharmacogenetic studies as well. Briefly, in both cases one must address issues such as the heritability of the phenotype (i.e., fraction of the response phenotype attributable to genetic rather than nongenetic factors), the size and make-up of the sample population, the choice of markers, the accuracy of the genotyping methods used, the accuracy of phenotypic classifications, and the statistical methods applied for data analysis.⁶ These and other factors have an impact on the statistical power achieved in the analysis, which is central to the success of any genetic association study.

The most common approach to testing for an SNP association with a drug response phenotype is through clinic-based association studies in which one asks whether the allele frequency of an SNP of interest is significantly different in a group of patients exhibiting a particular response phenotype relative to a control group that does not or, conversely, whether patients with a particular genotype for an SNP or SNPs have a significantly different incidence of a response phenotype relative to those without it. Such studies are most commonly performed retrospectively such that the chart records of patients given a drug are used to categorize them for a response phenotype, after which allele frequency data for SNPs of interest are determined and appropriate statistical analyses are performed to identify associations. This approach, though pragmatic with regard to time and expense, has a number of weaknesses based in part on the fact that because the objectives of the study were not known at the time of drug treatment, the amount

TABLE 51.1
Tests for association of *MTHFR* SNP alleles and response to MTX

Polymorphism	Reported associations	Lack of associations	Reference
C677T	Increased risk for discontinuing MTX therapy because of adverse events Increased rate of toxicity	Efficacy or toxicity Toxicity Efficacy	Van Ede et al. ¹² Urano ¹³ Kumagai ¹⁷ Berkun ¹⁴ Van Ede ¹²
A1298C	Reduced likelihood of MTX-related side effects Lower dose Toxicity	Efficacy or toxicity Disease activity	Berkun ¹⁴ Urano ¹³ Kumagai ¹⁷ Berkun ¹⁴ Hughes ¹⁵

MTHFR, methylenetetrahydrofolate reductase; *MTX*, methotrexate; *SNP*, single nucleotide polymorphism.

lower doses than did those without them. Kumagai and coworkers¹⁷ reported associations of homozygosity for two alleles of thymidylate synthase with higher MTX dosage and 50% or greater improvement in serum C-reactive protein levels, respectively. Neither Berkun and coworkers¹⁴ nor Kumagai and colleagues¹⁷ found associations between either the *MTHFR* 677 or 1298 genotype and efficacy. Wessels and associates¹⁶ reported that the 1298AA genotype was associated with improved efficacy of MTX. Furthermore, a multigene pharmacogenetic model was developed by Wessels and coworkers¹⁹ that included genes for MTX metabolism and purine and pyrimidine synthesis.

In the case of both MTX efficacy and toxicity there has been an apparent lack of consistency in the identification of associations across studies, particularly with regard to *MTHFR* genotype (Table 51.1). To address these inconsistencies, which may relate to cohort size and statistical power, Fisher and Cronstein²⁰ conducted a meta-analysis of published studies on *MTHFR* SNPs and risk for toxicity. In the meta-analysis the C677T SNP was associated with increased risk for toxicity (odds ratio, 1.71; 95% confidence interval, 1.32 to 2.21). As discussed earlier, a number of factors may contribute to variability, and in this instance, relatively small patient populations and inconsistent phenotyping criteria may be at least partially responsible.

Azathioprine

A number of studies have been conducted on the pharmacogenetic properties of azathioprine, with a primary focus on the role of SNPs in the gene for thiopurine methyltransferase (*TPMT*) in determining susceptibility to toxicity, and the literature in this area has been reviewed elsewhere.^{21,22} Among the studies based on data from rheumatologic use, Black and associates²² reported that 5 of 6 individuals who incurred toxicity out of a cohort of 67 patients receiving azathioprine for rheumatologic disease were heterozygous for mutant *TPMT* alleles. In another study, among a group of patients with RA treated with azathioprine, those experiencing adverse effects showed a significantly decreased level of *TPMT* activity relative to those who did not, and toxicity developed in 7 of 8 patients with “intermediate” *TPMT* activity.²³ Combined with evidence from the many studies on patients with nonrheumatic diseases, these data strongly support the notion that the *TPMT* genotype is a useful predictor of azathioprine-associated toxicity.

Sulfasalazine

It has long been established that the pharmacokinetic properties, efficacy, and toxicity conferred by sulfasalazine therapy are influenced by acetylator phenotype,²⁴ and more recently, the relationships of alleles of the *N*-acetyltransferase 2 (*NAT2*) gene with these phenotypes have become increasingly understood.²⁵ Kumagai and associates²⁶ reported that the *NAT2* genotype is associated with both the pharmacokinetics (sulfapyridine/*N*-acetylsulfapyridine) and efficacy of sulfasalazine treatment in a cohort of patients with RA. Tanaka and colleagues²⁷ found in a group of patients with RA that slow acetylators who lacked the *NAT2**4 allele experienced adverse effects from therapy more often than did fast acetylators who had at least

one *NAT2**4 haplotype. Kita and coworkers²⁸ showed that the differences between *NAT2* genotype groups in the pharmacokinetic profiles of sulfasalazine are enhanced after multiple dosing relative to single dosing. These are among the studies demonstrating the importance of variants of the *NAT2* gene on sulfasalazine outcomes.

Biologic disease-modifying antirheumatic drugs

The vast majority of pharmacogenetic studies of biologic agents have focused on tumor necrosis factor (TNF) antagonists for the treatment of RA. Early studies reported associations in relatively small cohorts. Martinez and colleagues²⁹ reported associations within the major histocompatibility complex with response to infliximab after 3 months of therapy in a cohort of 78 patients with RA. Mugnier and associates³⁰ found that among a group of 59 patients with RA treated with infliximab, those with the TNF- α -308 G/G genotype had better response than did those with the A/A or A/G genotypes. In a study based on a population of 123 patients with RA, the combination of -308 TNF1/TNF1 and -1087 G/G was associated with response to etanercept, whereas a combination of SNPs within the interleukin-1 receptor antagonist and transforming growth factor- β 1 gene was associated with nonresponse.³¹ More recently, larger population studies of TNF pharmacogenetics in patients with RA have been published. Criswell and colleagues³² reported that the combination of two HLA-DRB1 shared-epitope alleles, as well as two extended haplotypes that included the HLA-DRB1 shared-epitope alleles and six SNPs in the lymphotoxin- α (LTA)/TNF region, are associated with response to etanercept. The significance of any of these findings remains unclear in light of the common clinical observation that individuals who do not respond to one anti-TNF biologic agent may respond to a different one. One of the largest cohort studies was reported by Maxwell and colleagues.³³ They examined eight SNPs in the region containing the TNF gene in 1050 patients with RA, including 455 prescribed etanercept and 450 prescribed infliximab. An association between the TNF-308 genotype and change in the 28-Item Disease Activity Score (DAS28) was observed, thus replicating the TNF-308 findings of other investigators. However, a subsequent systematic review and meta-analysis, the largest meta-analysis published to date and involving more than 2800 patients, concluded that the TNF-308 variant is not a predictor of response.³⁴ Studies examining RA risk alleles have identified the *PTPRC* gene, which encodes protein tyrosine phosphatase, receptor type C (also known as CD45), as a predictor of response, which has been replicated.^{35,36} However, a subsequent meta-analysis failed to confirm *PTPRC* as a predictor of response to anti-TNF biologics.³⁷

Finally, recent studies have approached the question by using the unbiased GWAS design to identify genetic predictors of response. A pilot GWAS published by Liu and colleagues³⁸ on a small cohort of patients identified a number of promising candidate SNPs. However, these SNPs failed to be replicated as predictors of response in an independent Spanish RA cohort.³⁹ More recently, a larger GWAS was performed to identify additional candidate SNPs, and replication studies will also be required.⁴⁰

CONCLUSION

The work discussed in this chapter provides some evidence for the notion that the pharmacogenetic properties of antirheumatic drugs are likely to play an important role in the future of rheumatology. Because the majority of this work consists of studies focusing on single-allele associations, these data may, in fact, represent only the beginning of what such studies will ultimately yield. As is the case in complex disease genetics, it is likely that the genetic components of drug response will be found to be conferred by multiple genes. Among the challenges for researchers is the difficulty obtaining patient cohorts of sufficient size so that the number of patients in each genotypic category can provide adequate statistical power for analysis. Resolving these issues will require the implementation of large-scale, prospective association studies. Ultimately, the promise of pharmacogenetics will be fully realized when genetic biomarkers can predict who will be more likely to respond to an individual drug and who may incur a drug-related toxicity (Fig. 51.2).⁴¹

The value of pharmacogenetics research to the field of rheumatology, though promising thus far, is likely to continue to grow as the tools and knowledge available to investigators continue to evolve. As the genotyping and analysis tools, as well as the patient cohort data, required for large-scale, genome-wide studies capable of teasing out alleles with increasingly small effect sizes continue to improve, so will investigators' understanding of the target diseases, as well as the mechanisms of action of drug therapies and their toxicities. The convergence of these data is certain to enhance the

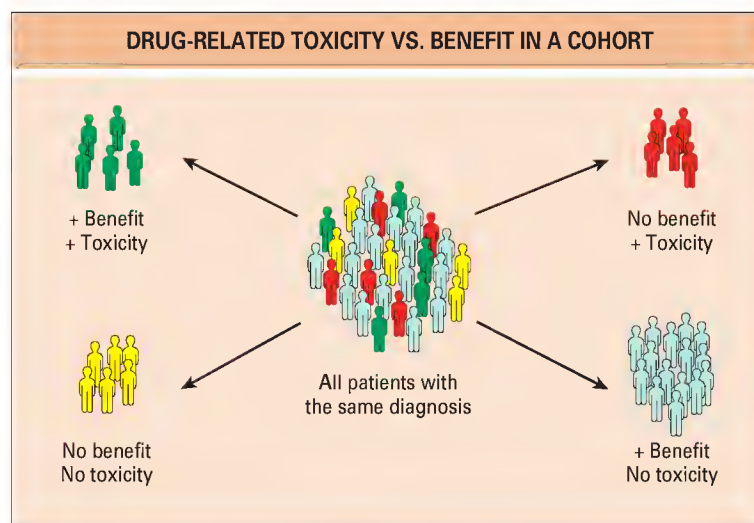


Fig. 51.2 Pharmacogenetics has the potential to identify which patients will benefit from a drug with a robust clinical response and which patients will incur drug-related toxicity. (Adapted with permission from Marsh S, McLeod HL. Pharmacogenetics: from bedside to clinical practice. *Hum Mol Genet* 2006;15:R89-93.)

power of pharmacogenetics research and thus the promise of rationally individualizing therapy with the use of genetics in the future of clinical medicine.

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Principles of opioid treatment of chronic musculoskeletal pain

■ BILL MCCARBERG ■ CHELSEA J. HODGKISS-HARLOW

- Musculoskeletal pain decreases quality of life and productivity across all ages, but the impact may be underestimated in older patients.
- The use of opioid therapy for chronic pain is controversial, but strategies can be implemented to decrease risk to patients and prescribing physicians while continuing to provide compassionate care for suffering.
- Prescription of short- or long-acting opioids can be individualized to the patient based on dose-response and adverse effects. No single opioid is preferred. Cross-tolerance among opioids varies in individuals and should be taken into account when changing opioids.
- Adverse effects can often be managed effectively. Prophylactic management of constipation is recommended on initiation of long-term opioid therapy.
- Aberrant behavior exists along a continuum. The four A's for monitoring patient outcomes should be evaluated during prescription follow up visits. Various strategies can be implemented to distinguish between and manage aberrant behavior.

PRINCIPLES OF PRESCRIBING

Introduction

Although it is difficult to determine the prevalence of pain, according to the 2010 Institute of Medicine Report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, more than 100 million Americans are burdened with chronic pain.¹ Because pain is a common reason to seek medical attention, prescription analgesics are among the 20 most frequently prescribed therapeutic classes and together account for more than 10% of prescriptions.² In a recent survey, less than half of those with pain reported “a lot” of control over their pain despite receiving medical help, and only one third had complete or a great deal of pain relief.³

Pain has an impact on multiple domains of life, with 40% of pain patients reporting that pain interferes with their enjoyment of life, mood, sleep, and activities.³ In addition to affecting quality of life, pain also interferes with the ability to work. American productivity reported in a 2003 study showed that pain conditions cost employers \$61.2 billion each year.⁴ During the study period the U.S. workforce experienced a mean of 4.6 hours of decreased work productivity because of pain, the most common cause being headache, followed by back pain, arthritis pain, and other musculoskeletal pain.⁴

Nearly 20% of the more than 46,000 individuals surveyed in 15 European countries reported pain levels of at least 5 of 10 on a numeric rating scale (NRS); two thirds had moderate pain (5 to 7 on an NRS), and one third had severe pain (8 to 10).⁵ Over-the-counter medications were used by half: 55% used nonsteroidal antiinflammatory drugs (NSAIDs), and 43% used acetaminophen. The most common prescription analgesics were NSAIDs (44%), and only 5% reported taking strong opioids. Rheumatoid arthritis and osteoarthritis (OA) were found in 42% of the respondents, and just 1% reported that their pain was due to cancer. Primary care physicians treated 70% of the patients; 27% were treated by an orthopedist, 9% by a rheumatologist, and 10% by a neurologist or neurosurgeon.

Pain is even more problematic as patients grow older. With diminished sight and hearing, frequent incontinence, and failing memory, all of which impair function and quality of life, a persistent pain problem can be devastating. Epidemiologic studies of long-term care observed that 45% to 80%

of residents have substantial pain of musculoskeletal origin.⁶ A study of 97 elderly patients in extended care found the most frequently reported sources of pain to be lower back pain (40%), arthritis (24%), previous fractures (14%), and neuropathies (11%).⁷ In 325 patients randomly selected from 10 Los Angeles area nursing homes, arthritis accounted for 70% of the pain complaints.⁸ Musculoskeletal pain includes conditions affecting connective tissue, joints, and related structures and is characterized by tissue inflammation, degradation, or metabolic derangement. OA is the most common rheumatic disease seen in older individuals. More than 80% of people older than 75 years have clinical OA, and more than 80% older than 50 have radiologic evidence of OA.⁹ The pain resulting from rheumatic diseases is often unrecognized and untreated, with the undertreatment rate reported to be as high as 85% in long-term care facilities.¹⁰ Inadequate care results from patient fears and insufficient provider education. Falls are common in this population, and concerns about increasing this risk, diminished cognition, addiction, and other side effects, especially constipation, lead to dismissing pain complaints. Elderly patients can contribute to this problem by fearing to report pain. In one study, more than half of all health symptoms were found to be regularly underreported in our aging population.¹¹

Pain mechanisms

Pain arising from rheumatic diseases often starts as acute, inflammatory pain resulting from tissue injury. A variety of inflammatory chemicals and neurotransmitters are involved in this noxious stimulus. Frequently, the pain is proportional to the severity of tissue injury; when repair occurs, the pain subsides. In chronic rheumatologic conditions, however, tissue injury may be of a very low level, yet pain can be persistent. A poor relationship is often found between structural abnormalities and symptoms. Up to 40% of individuals with grade 3 to 4 OA of the knee have no symptoms, and 10% of patients with severe pain have normal radiographic findings.¹² Psychological factors are often implicated but explain very little of this variance between symptoms and anatomy.¹³ Disorders such as rheumatoid arthritis, OA, degenerative disc disease, and chronic gout are associated with persistent pain and may be characterized by intermittent acute exacerbations related to flares of the underlying pathology or be due to patient activity, changes in barometric pressure, anxiety, or other factors.

It is widely believed that older patients do not experience the same intensity of pain as younger populations do.¹¹ Aging is associated with widespread changes in the nervous system designed to sense pain. Although differences exist, the threshold for pain is more likely to be increased in older people.¹⁴ This decreased pain acuity may place older people at greater risk for injury. However, aging does not appear to be associated with substantive functional changes over much of the pain stimulus-response curve.¹⁵ Increases in pain reported with age may occur when stimuli are intense or persist for longer periods. The presence of sensitized pain fibers is a biologic benefit in the presence of injured tissues. However, peripherally sensitized pain fibers are slower to resolve in older people, thus leading to prolonged pain states not seen in younger populations. The commonly held belief that older people are marginally insensitive to pain is not borne out in the literature. Under circumstances in which pain is likely to persist, older people are especially vulnerable to the negative impact of pain.

Opioid therapy for chronic musculoskeletal pain

Opioid therapy for chronic pain has become increasingly contentious and controversial after more than 20 years of escalating use of these powerful drugs. Prescribing opioids to manage chronic pain has been accompanied by alarming increases in misuse and abuse, fatal overdoses, and diversion.¹⁶ There has been a call for action by the federal government, including



voluntary education recommendations on the use of long-acting opioids as part of a risk evaluation and mitigation strategy. Debate about long-term opioid therapy has resulted in a dispute between commitment to compassionate care of suffering patients with chronic pain and adequate response to an epidemic of opioid misuse and abuse.

Strong evidence supporting the use of long-term opioid therapy for patients with chronic pain is lacking. Controlled trials lasting up to 6 months show only modest pain relief versus placebo; whether this efficacy is maintained is unknown.^{17,18} The American Pain Society and the American Academy of Pain Medicine reviewed the literature in 2009 and rated 21 of their 25 recommendations as being based on “low-quality evidence.”¹⁸ Yet it is clear to many practicing providers that in some patients, opioids provide improvement in pain with substantial functional enhancements over alternative therapies.

Given the knowledge gaps and escalating concerns about misuse, abuse, and opioid-related deaths, greater caution and selectivity are needed when prescribing long-term opioid therapy. Until stronger evidence becomes available, clinicians should prescribe cautiously and limit long-term therapy to patients who receive significant benefits. The 1996 consensus statement by the American Pain Society and the American Academy of Pain Medicine¹⁹ on chronic opioid therapy failed to predict the current epidemic of misuse and abuse.¹⁶ The rate of prescription opioid abuse in clinical practice varies from 4% to 26%,²⁰ but misuse is not rare. Rates as high as 26% were found for purposeful oversedation, 39% for unilaterally increasing doses, 20% for coadministering alcohol to relieve pain, and 18% for purposes other than pain.²⁰ As many as 13,000 yearly overdose deaths involve prescription opioids, thus exceeding motor vehicle accidents as the leading cause of death from injury in persons 35 to 54 years of age.²¹

Opioid risks are not limited to addiction and overdose deaths. Side effects, most commonly constipation, can be problematic, especially in an older population. Neuroendocrine dysfunction can result in hypogonadism with infertility, erectile dysfunction, decreased libido, osteoporosis, and mood disturbances.²² Central and obstructive sleep apnea, cardiac rhythm disturbances, immunosuppression, and tooth decay are among the many distressing side effects. Opioid-induced hyperalgesia heightens nociceptive perception paradoxically by making pain sensations worse, not better, and leads to escalating doses, especially when the provider is not aware of this effect.²³

Despite the lack of long-term evidence and risks to the patient and society, patient comfort and quality of life must be taken into account. Lacking adequate alternatives for reducing pain and increasing function, opioid therapy should be considered and in selected patients may be the best option. Even though risk is increased in older patients, the lack of adequate alternatives has led the American Geriatrics Society to recommend that all patients with moderate to severe pain be considered for opioid therapy.²⁴ The medical risks associated with long-term opioid therapy have clearly not been studied adequately, which has led others to conclude that the risk may outweigh the benefits despite the lack of safe alternatives.²⁵

Patient selection for long-term opioid therapy

Selecting patients for long-term opioid analgesic therapy requires careful assessment of the pain, including the medical history and physical examination, as well as the characteristics of the patient and disease. When opioid treatment is warranted, a treatment plan should state objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function, as well as whether other treatments are planned to improve outcomes.²⁶ Such treatments may include nonopioid analgesics such as NSAIDs or adjuvant therapies, including duloxetine, which may allow a lower opioid dose.²⁷ Nonpharmacologic modalities such as psychological and physical strategies, when appropriate and available, should also be considered as additional treatment options.²⁸ Most state medical boards have adopted wholly or in part the recommendations for prescribing opioids outlined by the policy from the Federation of State Medical Boards. This policy includes the following:

- Patient evaluation—includes the history and physical examination to arrive at a diagnosis, psychological evaluation, and risk for addiction.
- Treatment plan—includes alternatives to opioids and expected functional outcomes.
- Informed consent and treatment agreement—informed consent may differ from the treatment agreement; however, both may be included in one form. Informed consent and treatment agreements may be written, signed documents or verbal agreements, but it must be documented in the medical record that the patient understands the risks, benefits, and alternatives to opioid therapy and appreciates what is

expected during treatment (i.e., one pharmacy, refill interval, urine drug testing, and other requirements).

- Periodic review—varies by state.
- Referral—some states require consultation (e.g., Washington when more than 120 mg of morphine equivalent is used), whereas other states suggest referral when appropriate.
- Documentation—inadequate documentation is the most frequent area in which providers are found deficient.
- Compliance with relevant law—for example, prescribing methadone or Suboxone for addiction without the appropriate license.

Assessing pain

Assessment of pain should include the type and quality of pain, source, intensity, location, duration and time course, pain affect, and effects on lifestyle and functional status. Pain intensity can be measured with tools such as an NRS, verbal rating scale, visual analog scale, and the faces of pain scale.²⁹

Assessing risk

Long-term opioid management requires assessment of risk for misuse and abuse. Several tools have been validated, including the Opioid Risk Tool (ORT) and the Screener and Opioid Assessment for Patients with Pain (SOAPP). The five-question ORT predicts which patients may be at risk for opioid-related aberrant behavior once treatment is initiated (Table 52.1).³⁰ The SOAPP is another brief, self-administered screening instrument used to assess the suitability of patients for long-term opioid analgesic therapy.³¹ Tools such as the ORT or SOAPP should be used by clinicians when considering initiating opioid analgesic therapy for a chronic pain problem or for a patient being treated with opioids for an acute pain problem that is becoming chronic and long-term opioid therapy is an option.

Informed consent

Patients must understand the risks and benefits of the long-term use of opioid therapy. The physician can consider the use of a written agreement outlining the treatment plan, expectations, and responsibilities of the patient and physician; this is particularly important if the patient is at high risk for medication abuse. A written and signed form may be required in some states. The procedures or actions that will be taken should problems arise must be explained.³² A sample informed consent is available at http://www.painknowledge.org/physiciantools/Opioid_Informed/Opioid%20Informed%20Consent%20Formatted_1_23_2008.pdf.

Opioid selection

Selecting an opioid requires knowledge of the patient's pain intensity, age, medical comorbid conditions, previous experience with opioids,

■ TABLE 52.1

The opioid risk tool

Mark each box that applies		
	Female	Male
Family history of substance abuse		
Alcohol	☐ 1	☐ 3
Illegal drugs	☐ 2	☐ 3
Prescription drugs	☐ 4	☐ 4
Personal history of substance abuse		
Alcohol	☐ 3	☐ 3
Illegal drugs	☐ 4	☐ 4
Prescription drugs	☐ 5	☐ 5
Age (mark the box if between 16 and 45 yr)	☐ 1	☐ 1
History of preadolescent sexual abuse	☐ 3	☐ 0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1
Scoring totals		

0 to 3 points: low risk (unlikely to abuse opioids); 4 to 7 points: moderate risk (just as likely to abuse or not abuse opioids); 8 or more points: high risk (likely to abuse opioids).

ADD, attention deficit disorder; OCD, obsessive-compulsive disorder.

From Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med* 2005;6:432-42.

drug-specific differences (interpatient variability and drug-drug interactions), and available formulations and cost. Intermittent pain that is related to activity may be better treated with short-acting schedule 3 opioids combined with acetaminophen or ibuprofen taken as needed. No single opioid is preferred. In recent years, recognition of the large individual variation in response to different opioids warrants searching for the best opioid for individual patients. Therapeutic failure with one drug may be followed by remarkable success with another.

For persistent pain, a long-acting agent is recommended to control baseline pain, supplemented by a short-acting agent for breakthrough pain. Since all opioids have similar efficacy, personal experience, the patient's previous exposure to pain medication and experience (including efficacy and adverse effects), and cost should guide therapy. Most short-acting opioids require a dosing interval of 4 to 6 hours, whereas long-acting agents are effective for 8 to 72 hours.

When initiating an opioid trial in an opioid-naïve patient, short-acting agents are preferred with the dose individualized to the patient. Start at the lowest dose likely to be effective and increase gradually until the desired pain relief and functional improvements have been achieved with tolerable side effects.³³ Dose increases of 30% to 50% are safe and usually large enough to observe a meaningful change in effect.³⁴ If the pain is severe and the patient is not predisposed to opioid toxicity, a higher increment—up to 100% of the existing dose—may be safe and effective.³⁴

Another method for increasing doses is to calculate the amount of breakthrough medication used in a 24-hour period and convert this amount to the fixed daily dose schedule. Single-entity opioids (e.g., oxycodone) can be titrated without a ceiling dose, whereas opioid combinations are limited by the amount of acetaminophen or ibuprofen that they contain. Side effects may limit dose titration and thus prompt rotation to another opioid that may not have the same adverse effects. After a stable dose is achieved with a short-acting opioid, it may be converted to a long-acting opioid if a simplified regimen is desired or to optimize adherence.

Methadone has a long half-life and therefore requires care during titration. Because of availability and cost, methadone is a popular long-acting analgesic. Its elimination half-life can be quite variable among individuals and ranges from about 12 hours to almost a week. Methadone may also prolong the QT interval, particularly at higher doses.³⁵ In addition, methadone has been responsible for a disproportionate number of unintentional deaths because of provider inexperience and too rapid dose adjustments. Always wait 3 to 5 days before titrating the dose of methadone if pain control is inadequate.

Pharmaceutically long-acting opioids include sustained-release (SR) preparations of short-acting or immediate-release opioids (e.g., morphine, oxycodone, fentanyl, hydromorphone, oxymorphone). Some of the SR opioids can also be initiated in opioid-naïve patients, although not all have been systematically evaluated as an initial agent. For the oral SR opioid formulations, patients should be advised to swallow the tablet whole and not to break, crush, or chew the tablet because this can result in rapid release of high doses of the opioid and overdose.

Managing side effects

Side effects are common, with constipation being the most frequent adverse effect reported. Sedation, nausea and vomiting, pruritus, sweating, dry mouth, and weakness also frequently occur. All these adverse effects, however, may be missed unless the patient is specifically questioned.

Constipation may contribute to abdominal pain, distention, nausea, and anorexia and may progress to bowel obstruction. Constipation should be anticipated and treated prophylactically. Numerous types of laxatives are available, including bulk-forming agents, lubricants, osmotic agents, surfactants, contact cathartics, prokinetic drugs, a chloride channel activator, and opioid antagonists.³⁶ The conventional first-line approach is a combination of docusate, a stool softener (surfactant), and a cathartic agent (either senna or bisacodyl). Most patients respond to this therapy. For patients who do not, a trial of an osmotic agent, such as lactulose, or a lavage agent, polyethylene glycol, might be considered.

When traditional laxatives are not effective, methylnaltrexone administered subcutaneously can also be considered.³⁷ Patients with refractory constipation may be considered for a trial of a prokinetic drug (metoclopramide). Lubiprostone, a unique chloride channel activator, may also be tried for refractory constipation.

Individualize therapy

Because of variability in efficacy, side effects, and tolerance profiles,²⁰⁻²³ some patients may respond better to one opioid than to another with enhanced analgesia and side effects.³⁸ Itching, for example, may occur with one opioid (common with morphine) and not another. Opioid requirements may vary

TABLE 52.2
Dosing and conversion chart for opioid analgesics

Drug	Route	Equianalgesic dose (mg)	Duration (hr)	Plasma half-life (hr)
Morphine	IM	10	4	2-3.5
	PO	30	4	4
Codeine	IM	130	4	3
	PO	300	4	
Oxycodone	IM	—		
	PO	30	3-4	4
Hydromorphone	IM	1.5	4	2-3
	PO	7.5	4	
Meperidine	IM	75	3-4	2
	PO	300	3-4	Normeperidine
Methadone	IM	10*	6-8†	12-24
	PO	20*	6-8†	20-200
Fentanyl	IV	0.1		
Hydrocodone	IM	—		
	PO	30	3-4	4

*The equianalgesic dose of methadone with respect to other opioids is extremely variable with chronic dosing. The conversion factor from oral morphine to oral methadone may range from 4:1 to 14:1.

†Central nervous system depression is a risk with repeated use, and accumulation may occur in the elderly or persons with impaired renal function with regular dosing. Monitor for patient variability in the duration of efficacy.

IM, intramuscularly; IV, intravenously; PO, orally.

Adapted from Foley KM. The treatment of cancer pain. *N Engl J Med* 1985;313:84-95.

because of differences in μ -opioid receptors and necessitate higher or lower doses. Opioid switching is common since it is not currently possible to predict which individual will respond to any one opioid.³⁹ The availability of a wide variety of opioids allows clinicians to better match a drug to the patient.

Incomplete cross-tolerance

When switching from one opioid to another, conversion tables are frequently used (Table 52.2). However, the new opioid may be less efficacious and result in less analgesia, increased pain, and occasionally withdrawal symptoms. In others the effect is exaggerated, with patients being overly sedated and rarely leading to respiratory depression and death. It is assumed that if a patient is tolerant of one opioid, that patient will be tolerant of another opioid, but the principle of incomplete cross-tolerance illustrates that μ -receptor variability makes tolerance difficult to predict.⁴⁰

Clinicians have long used the principle of incomplete cross-tolerance among analgesics whereby highly tolerant patients are rotated to treatment with a different drug to regain analgesic sensitivity. When switching opioids in an opioid-tolerant patient, it is recommended that calculation of the equianalgesic dose be based on the predicted equivalent dose in conversion tables and then the calculated dose lowered by 25% to 50% to account for incomplete cross-tolerance. Safety is maintained with this method, but at the expense of efficacy. Breakthrough medication must often be used until adequate analgesia is achieved.

Drug-drug interactions

Since most drugs are metabolized through the liver via the hepatic cytochrome P-450 system, care must be taken when using opioids.³⁴ The isoenzyme 2D6 converts codeine and hydrocodone to the active drugs morphine and hydromorphone, respectively. Methadone, oxycodone, and tramadol are also metabolized through 2D6. Fentanyl and buprenorphine are metabolized by 3A4. Concomitant treatment with drugs that inhibit or induce CYP450 enzymes can affect the level of these opioids and their metabolites, thus changing their analgesic efficacy or side effect profile and causing possible opioid overdose or acute withdrawal.^{41,42} Many potential interactions can produce clinically relevant effects (Table 52.3).

The importance of hepatic metabolism is shown in the conversion of prodrugs such as codeine or hydrocodone. Up to 10% of the population lack the enzyme pathway needed for converting these compounds to their active agent and have a poor analgesic response.⁴²

Morphine, hydromorphone, and oxymorphone are metabolized chiefly through conjugation reactions with uridine diphosphate glucuronyl transferase enzymes (glucuronidation). Since they do not use hepatic pathways,

TABLE 52.3

Common inhibitors and inducers of CYP450 enzymes

Enzyme	Opioid substrate	Inhibitor	Inducer
CYP2D6	Codeine, hydrocodone, methadone, oxycodone, tramadol	Citalopram (weak), desipramine, fluoxetine, olanzapine (weak), paroxetine, sertraline, venlafaxine (weak), quinidine	Carbamazepine, phenobarbital, phenytoin
CYP3A4	Fentanyl, meperidine, buprenorphine	Dextromethorphan, fluoxetine (weak), paroxetine (weak), sertraline, venlafaxine, azole antifungals, macrolide antibiotics, nefazodone	Carbamazepine, dexamethasone, erythromycin, modafinil, phenobarbital, phenytoin, rifampin

From Armstrong SC, Cozzo KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, part II. *Psychosomatics* 2003;44:515-20.

inhibition/induction or genetic polymorphisms should have little effect on activation or clearance of these drugs.

Periodic review

Follow-up for patients taking opioids long-term depends on the stability of the medical condition and the patient. Required follow-up intervals may be mandated by state medical board pain acts and vary across the United States. Regular monitoring should assess *analgesic* response, *activity* level or functional outcomes, *adverse* effects of the opioid treatment, and *aberrant* behavior observed during the follow-up period.⁴³ Box 52.1 lists these four A's to remind clinicians that a successful outcome in pain therapy involves more than a pain score. Stabilization or improvement of psychosocial functioning and sleep, tolerable side effects, optimization of physical functioning, and absence of aberrant behavior should also be considered.⁴⁴

Referral to an expert in pain management may be mandated by state pain acts to ensure adequate evaluation and management of chronic pain patients, especially when troublesome behavior surfaces with opioid therapy. A pain specialist or pain center should be involved whenever clinicians have exceeded their expertise in any specific area of opioid-related pain management. This may include the dose of opioids prescribed, the patient's ability to adhere to the prescribed regimen, an inability to achieve adequate pain control despite increasing the dose of opioids or switching to different opioids, unresolved troublesome side effects, or unresolved issues of substance misuse or abuse.⁴⁵ Special attention should be given to patients identified during risk assessment to be at high risk for medication misuse and abuse.

Differentiating aberrant drug-related behavior

Aberrant behavior exists in a continuum, with no type being absolutely predictive of addiction (Box 52.2).⁴⁶ The differential diagnosis of aberrant drug-related behavior includes addiction, undertreatment of pain, and psychological distress, but criminal intent and diversion should also be considered. It is important that clinicians distinguish between addiction with physical dependence, tolerance, and pseudoaddiction. The four A's include evaluation of aberrant behavior since monitoring and prescribing of the opioid should change when this behavior surfaces. More frequent follow-up, smaller amounts of medication, urine drug testing, access to a prescription-monitoring program (PMP), and referral to addiction specialists are among the changes to be considered when aberrant behavior is noted.

Psychological factors that may lead to aberrant behavior include anxiety, depression, bipolar disorder, personality disorder, or changes in cognitive state because of the treatment regimen.⁴⁷

Addiction is a primary chronic neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behavior that includes one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Physical dependence is a state of adaptation that is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution in one or more of the drug's effects over time.

Finally, pseudoaddiction is a drug-seeking behavior resulting from inadequate opioid dosing. Patients may seek alternative sources or increased doses.⁴⁸

Urine drug testing

Urine drug testing has become commonplace in pain practices and is recommended by state medical boards. Whom to test and how often to screen

BOX 52.1 THE FOUR A'S OF OPIOID MONITORING

Analgesia
Activities of daily living
Adverse effects
Aberrant drug-related behavior

From Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther* 2004;26:552-61.

BOX 52.2 EXAMPLES OF ABERRANT DRUG-RELATED BEHAVIOR

Less indicative of aberrance

Drug hoarding during periods of reduced symptoms
 Acquisition of similar drugs from other medical sources
 Aggressive complaining about the need for higher doses
 Unapproved use of the drug to treat another symptom
 Unsanctioned dose escalation one or two times
 Reporting psychic effects not intended by the clinician
 Requesting specific drugs

More indicative of aberrance

Prescription forgery
 Concurrent abuse of related illicit drugs
 Recurrent loss of prescriptions
 Selling prescription drugs
 Multiple unsanctioned dose escalations
 Stealing or borrowing another patient's drugs
 Obtaining prescription drugs from nonmedical sources

From Reference 46.

vary by providers and patient risk factors. Higher-risk patients as identified by the ORT or SOAPP or patients demonstrating aberrant behavior or deviation from the opioid agreement should be screened more often. Some pain practices screen patients at the first visit and at random intervals throughout their care. The point-of-care urine test done in the office uses an immunoassay and has known false negatives and false positives. Gas chromatography/mass spectrometry (GC/MS) done at reference laboratories can identify multiple drugs and specific drug types and has far fewer inaccurate results. GC/MS provides higher specificity for compounds, but none of the current testing can identify the quantity of the opioid taken, especially when opioids are used chronically.

A positive urine drug test is defined as follows:

- Absence of a prescribed drug
- Presence of an unprescribed scheduled drug or an illicit substance

Cross-reactivity, false positives, and false negatives can confound the results of the urine screen and skew the results; for example,⁴⁹

- Several quinolone antibiotics can potentially produce false-positive results for opioids by immunoassay but are correctly identified by GC/MS.
- Codeine and heroin are metabolized to morphine. Patients taking codeine should have morphine identified in their urine.
- Hydrocodone metabolizes to hydromorphone, and both compounds should show up in the urine.

- Cannabinoids may show up in the urine of patients taking NSAIDs, Marinol, and pantoprazole. Bystander exposure to marijuana will not result in a positive test for cannabinoids.
- Opioids may be present in the urine of patients ingesting poppy seeds, chlorpromazine, and dextromethorphan.
- Amphetamines may be identified in patients taking ephedrine, trazedone, bupropion, and Vicks Vapor Spray.

When interpreting the results of urine drug tests, consider the possibility of errors and patient variability, and therefore repeat the testing if indicated.

Prescription-monitoring programs

Most states have PMPs that allow providers access to all pharmacies within a state giving an identified patient scheduled medication (Fig. e52.1). Similar to urine drug testing, PMPs can be useful when questions arise about patient's aberrant behavior. Many pain practices check the state PMP at the first referral and at each visit.



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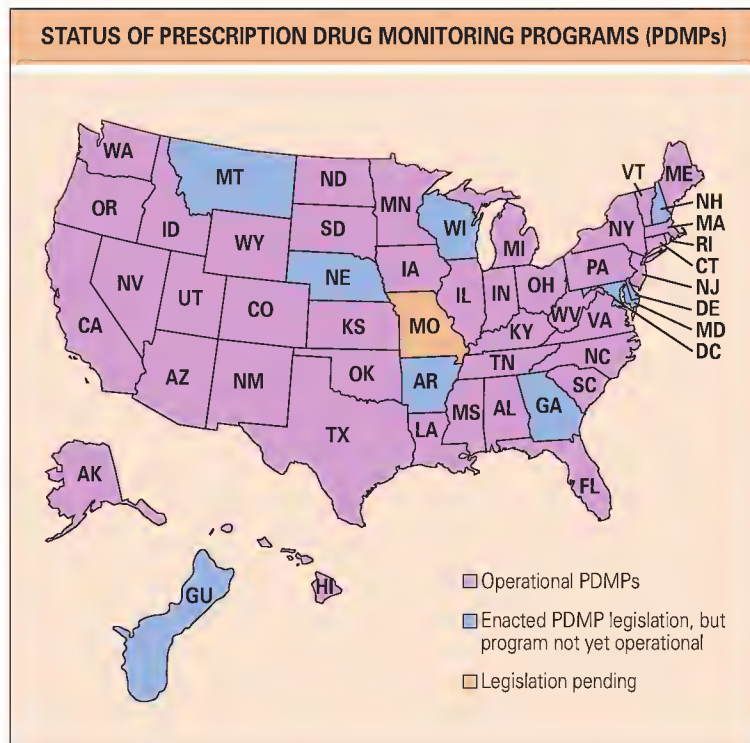


Fig. e52.1 Operational or legislated PDMPs in 49 states and 1 territory in 2012. (Adapted from Alliance of States with Prescription Monitoring Programs. Available at www.pmpalliance.org/pdf/pmpstatusmap2012.pdf.)

53

Nonsteroidal antiinflammatory drugs

■ CARLO PATRONO

- Nonsteroidal antiinflammatory drugs (NSAIDs) continue to provide “background” antiinflammatory therapy for rheumatic diseases.
- Variability in response to NSAIDs is seen in terms of both antiinflammatory activity and adverse events.
- Newer NSAIDs with selective inhibition of cyclooxygenase-2 (COX-2) are associated with a lower incidence of gastrointestinal adverse events.
- The vast majority of COX-2 inhibitors, regardless of selectivity, are associated with increased risk for myocardial infarction.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) constitute a chemically heterogeneous group of compounds that provide symptomatic relief of pain and inflammation associated with a variety of human disorders, including the rheumatic diseases. Their shared therapeutic actions (i.e., analgesic, antiinflammatory, and antipyretic) are usually accompanied by mechanism-based adverse effects that can, at least in part, be attenuated as a function of their individual pharmacokinetic or pharmacodynamic properties, or both.¹ The main chemical classes of NSAIDs are detailed in Table 53.1.

MECHANISM OF ACTION

The best characterized mechanism of action of NSAIDs is inhibition of the cyclooxygenase (COX) activity of prostaglandin (PG) H synthase 1 and 2 (PGHS-1 and PGHS-2, also referred to as COX-1 and COX-2) (Fig. 53.1). Given the role that prostanoids such as PGE₂, PGI₂, and thromboxane A₂ (TXA₂) play in the local modulation of many important cellular functions, this mechanism of action is probably sufficient to explain the clinical effects of NSAIDs.

Administration of PGE₂ and PGI₂ causes erythema, an increase in local blood flow, and in concert with other inflammatory mediators (e.g., bradykinin), hyperalgesia and enhanced vascular permeability.¹ Moreover, PGE₂ interacting with its EP₃ receptor can produce fever. Thus, prostanoids reproduce the main signs and symptoms of the inflammatory response. Because of the redundancy of mediators of this response, it is not surprising that NSAIDs exert only a moderate antiinflammatory effect, are effective only against pain of low to moderate intensity, and reduce fever but do not interfere with the physiologic control of body temperature.¹

Production of the prostanoids involved in these responses appears to be triggered by the immediate availability of constitutively expressed COX-1 and to be amplified and sustained by the local induction of COX-2 in response to inflammatory and mitogenic stimuli.² Although the analgesic, antiinflammatory, and antipyretic actions of traditional NSAIDs are largely reproduced by coxibs (a class of selective inhibitors of COX-2), this finding does not exclude a potential role for COX-1 in mediating, at least in some individuals, the PG-dependent contribution to pain and inflammation.³

The ability of acetaminophen to inhibit COX-1 and COX-2 is importantly conditioned by the peroxide tone of the local environment.⁴ This may explain, at least in part, the clinical observation that although sharing the analgesic and antipyretic effects of NSAIDs, acetaminophen has relatively poor antiinflammatory activity at conventional doses. High concentrations

of leukocyte-derived peroxides accumulate at sites of inflammation and may impair the ability of acetaminophen to inhibit COX-2.⁴ However, circulating plasma levels of the drug following the administration of 1000 mg systemically inhibit COX-2 activity to a comparable degree as traditional NSAIDs and coxibs.⁵

CYCLOOXYGENASE ISOZYME SELECTIVITY

PGG/H synthase is found in two isoforms that are products of two different genes (see Fig. 53.1): PGHS-1, or COX-1, which is expressed constitutively in all cells but is inducible under appropriate conditions, and PGHS-2, or COX-2, which is inducible in response to inflammatory, mitogenic, or hemodynamic stimuli but is also constitutively expressed in some tissues, such as certain areas of the human kidney and brain.^{2,3}

The COX isozyme selectivity of a particular drug is critically dependent on its concentration.³ One can describe the selectivity profile of different COX-2 inhibitors by plotting the drug concentrations required to inhibit the activity of human platelet COX-1 against those required to inhibit human monocyte COX-2 by 50% (IC₅₀) in whole blood assays (Fig. 53.2). This type of analysis establishes two important facts:

1. COX-2 selectivity is a continuous variable that does not justify a dichotomous definition of selective and nonselective inhibitors.
2. Substantial overlap in COX-2 selectivity is found with some coxibs (e.g., celecoxib) and some traditional NSAIDs (e.g., nimesulide and diclofenac).³

One can pragmatically characterize three levels of COX-2 selectivity in terms of the probability of sparing COX-1 at therapeutic plasma levels: low (e.g., acetaminophen), intermediate (e.g., celecoxib, nimesulide, and diclofenac), and high (e.g., rofecoxib, etoricoxib, and lumiracoxib).

PHARMACOKINETICS AND DRUG INTERACTIONS

The vast majority of NSAIDs are organic acids that are well absorbed orally, highly bound (i.e., 95% to 99%) to plasma proteins, metabolized by the liver, and excreted by either glomerular filtration or tubular secretion.¹ Most NSAIDs are rapidly and completely absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1 to 4 hours. Food tends to delay absorption without affecting peak plasma levels.¹

NSAIDs tend to accumulate at sites of inflammation, thus potentially confounding the relationship between plasma concentrations and duration of the antiinflammatory or analgesic effect. Some pharmacokinetic features of representative NSAIDs are listed in Table 53.1. Several traditional NSAIDs (e.g., ibuprofen and diclofenac) are characterized by very short half-lives (1 to 2 hours), which would hardly justify thrice- or twice-daily regimens of administration. To prolong the duration of action, some of these older NSAIDs (e.g., diclofenac) have been developed with formulations and doses that achieve high-grade and sustained inhibition of COX-2 in the systemic circulation. Although this may improve clinical efficacy, it may also influence COX-2-dependent untoward effects, such as cardiovascular toxicity (see later). Some NSAIDs, such as sulindac and nabumetone, are administered as inactive prodrugs that are converted in the large intestine or the liver (or both) into the active metabolites that are largely responsible for COX inhibition. Some of these redox reactions are reversible. Enterohepatic recycling of indomethacin and sulindac can occur and contribute to sustained plasma concentrations of the NSAID.¹

TABLE 53.1

Main chemical classes and representative nonsteroidal antiinflammatory drugs along with selected pharmacokinetic and pharmacodynamic properties

Chemical class and representative drugs	Time to peak plasma concentration (hr)	Half-life (hr)	Dosing regimen	Cyclooxygenase isozyme selectivity
Salicylates				
Aspirin	0.5-1	0.3	q4-6h	COX-1 = COX-2
Diflunisal	2-3	12	q8-12h	NA
Para-aminophenol				
Acetaminophen	0.5-1	2	q4h	COX-2 > COX-1
Acetic acid				
Indomethacin	1.5	2.5	q12h	COX-1 > COX-2
Sulindac	8 (active metabolite)	13 (active metabolite)	q12h	NA
Etodolac	1	7	q6-8h	COX-2 > COX-1
Anthranilic acid				
Mefenamic acid	2-4	3-4	q6h	NA
Sulfonanilides				
Nimesulide	1-3	2-5	q12h	COX-2 ≫ COX-1
Heteroaryl acetic acid				
Diclofenac	2-3	1-2	q8-12h	COX-2 ≫ COX-1
Ketorolac	0.5-1	5	q4-6h	NA
Arylpropionic acid				
Ibuprofen	1-2	2	q6-8h	COX-1 > COX-2
Naproxen	2	14	q12h	COX-1 > COX-2
Ketoprofen	1-2	2	q6-8h	NA
Enolic acid				
Piroxicam	3-5	45-50	qd	COX-1 > COX-2
Meloxicam	5-10	15-20	qd	COX-2 > COX-1
Alkanones				
Nabumetone	4-5	24	q12-24h	COX-1 = COX-2
Coxib				
Celecoxib	2-3	11	q12-24h	COX-2 ≫ COX-1
Etoricoxib	2-3	15-22	qd	COX-2 ≫ COX-1

NA, not available.

The pharmacokinetics of most NSAIDs can be affected to some extent by liver disease, renal disease, or old age. NSAIDs should either be avoided or be used with caution under these circumstances and the daily dose adjusted accordingly.¹

NSAIDs can modify the pharmacokinetics or pharmacodynamics of other drugs given concurrently and result in clinically important drug interactions (Table 53.2). Pharmacokinetic interactions are related to the capacity of NSAIDs to modify the metabolism (e.g., warfarin), protein binding (e.g., sulfonylurea hypoglycemic drugs), or renal excretion (e.g., lithium) of other drugs, which often results in supratherapeutic plasma levels of the latter; the dosage of such agents may require adjustment to prevent toxicity.¹

A pharmacodynamic interaction may occur between most NSAIDs and several classes of antihypertensive drugs. Reduced production of the vasodilator PGI₂ in the renal cortex and of the natriuretic PGE₂ in the medulla, as a consequence of COX-2 inhibition, results in vasoconstriction and sodium and water retention, which in turn tend to elevate blood pressure regardless of the mechanism of action of the antihypertensive drugs.¹ This pharmacodynamic interaction has been described with most traditional NSAIDs (including acetaminophen)⁶ and coxibs³ but not with low-dose aspirin.⁷

The pharmacokinetic interaction between NSAIDs and warfarin that may result in supratherapeutic plasma concentrations of the latter because of its displacement from plasma protein binding and reduced metabolism is

further complicated by the fact that NSAIDs may transiently inhibit platelet function in some patients and thus amplify the impairment of primary hemostasis induced by warfarin.

Some NSAIDs favoring COX-1 versus COX-2 inhibition, such as ibuprofen and naproxen (see Fig. 53.2), may interfere with the antiplatelet effect of low-dose aspirin by competing with acetylsalicylic acid for a common docking site (arginine 120) within the COX-1 channel.⁸ Previous occupancy of Arg-120 by an NSAID will prevent aspirin from acetylating a serine residue (Ser-529) just below the COX catalytic site of the enzyme, which forms the basis of the unique mechanism of action of aspirin that results in permanent inactivation of platelet COX-1.⁷ Drugs favoring COX-2 versus COX-1 inhibition, such as acetaminophen and diclofenac, do not interfere with the pharmacodynamic effect of low-dose aspirin, similar to celecoxib and rofecoxib (Fig. 53.3).⁸ Based on current analysis of the data available, the Food and Drug Administration has issued a statement informing patients and health care professionals that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/day), thus potentially rendering aspirin less effective when used for cardioprotection and stroke prevention (available at www.fda.gov/cder/drug/infopage/ibuprofen/default.htm).

Low-dose aspirin can cause upper gastrointestinal bleeding.⁷ In two large outcome trials, subgroup analyses suggested that aspirin may attenuate the gastrointestinal safety of coxibs as compared with traditional NSAIDs.^{9,10}

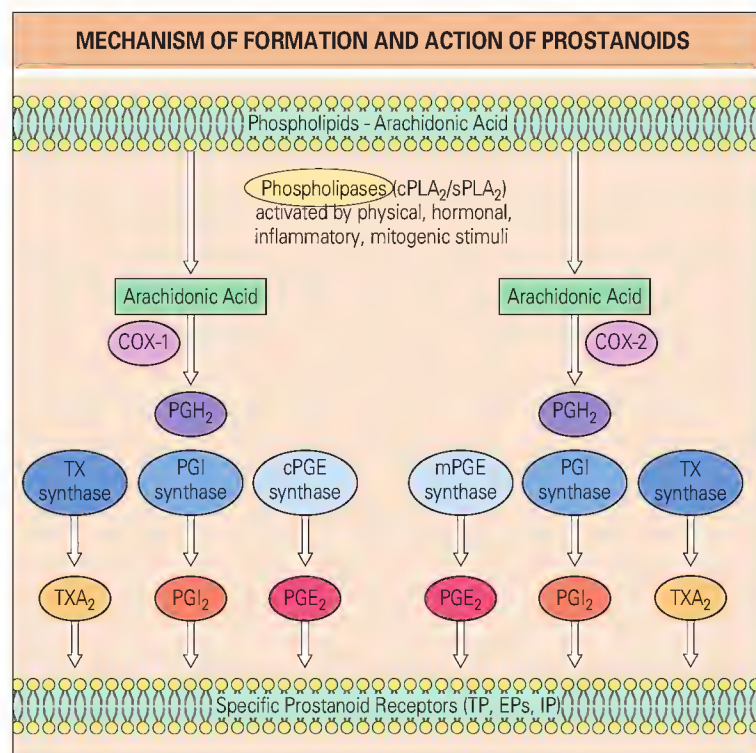


Fig. 53.1 Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the sn2 position in membrane phospholipids by phospholipases, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin (PG) G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase activity, to the unstable intermediate PGH_2 . The synthases are colloquially termed cyclooxygenases and exist in two forms: COX-1 and COX-2. PGH_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell membrane receptors of the superfamily of G protein-coupled receptors. TX, thromboxane.

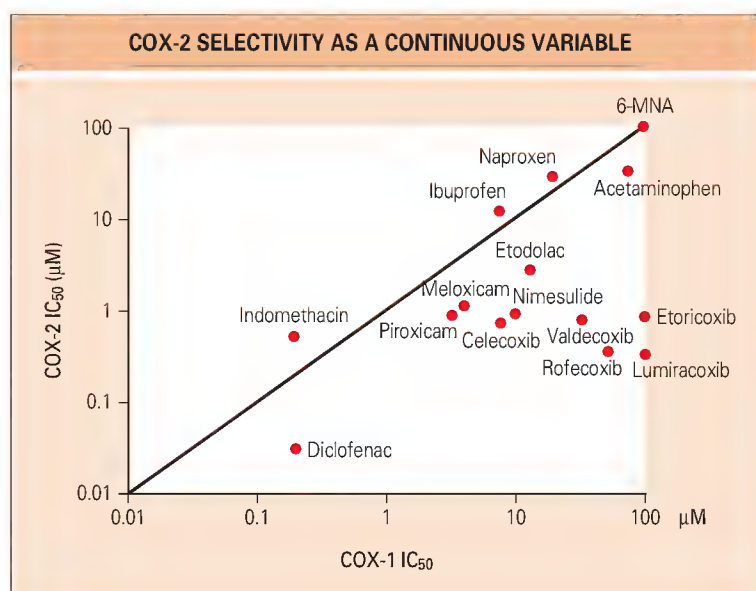


Fig. 53.2 The concentrations of various cyclooxygenase-2 (COX-2) inhibitors needed to inhibit the activity of platelet COX-1 and monocyte COX-2 by 50% (IC_{50}) are plotted on the abscissa and ordinate scales, respectively. The solid line describes equipotent inhibition of both COX-1 and COX-2. Symbols to the left of this line denote greater inhibition of COX-1 than COX-2. Symbols to the right of this line indicate progressively greater inhibition of COX-2 than COX-1, that is, increasing degrees of COX-2 selectivity. 6-MNA denotes 6-methoxy-2-naphthylacetic acid, the active metabolite of nabumetone. (Data from FitzGerald GA, Patrono C. *The coxibs, selective inhibitors of cyclooxygenase-2*. *N Engl J Med* 2001;345:433-42; and García Rodríguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol* 2008;52:1628-36.)

CLINICAL EFFICACY

NSAIDs are most widely used as analgesic and antiinflammatory agents for the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. The clinical efficacy of these drugs is related to symptomatic relief of the pain and inflammation associated with these musculoskeletal disorders. However, NSAIDs are not disease-modifying agents and do not arrest progression of tissue injury.¹

The results of phase 3 efficacy studies in osteoarthritis, rheumatoid arthritis, and various models of acute pain have established that the analgesic and antiinflammatory effects of coxibs are indistinguishable from those of several NSAID comparators (often, diclofenac, ibuprofen, or naproxen), consistent with similar COX-2 inhibition at comparable doses.³

Potential variables contributing to different COX-2-dependent effects include the daily dose of the inhibitor, which determines the extent of COX-2 inhibition; the half-life and dosing interval of the inhibitor, which determines the duration of COX-2 inhibition; and the patient's substrate inasmuch as the importance of COX-2-dependent prostanoids is likely to vary in different clinical settings.³

NSAIDs are particularly effective when inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. The pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibers and enhanced pain sensitivity (hyperalgesia), in part as a consequence of the increased excitability of central neurons in the spinal cord.¹

The choice among different NSAIDs for the treatment of osteoarthritis and rheumatoid arthritis remains largely empirical and based on efficacy, but it may be guided rationally by safety considerations (see later). Substantial differences in clinical response have been noted among individuals treated with the same NSAID and within an individual treated with different NSAIDs. This may be related to the quite substantial interindividual variability in the pharmacokinetic and pharmacodynamic relationship, as noted earlier.

If the patient does not achieve therapeutic benefit from a 2-week trial with one particular NSAID, another should be tried. Combination therapy with more than one NSAID has no scientific rationale, and the risk for adverse effects is at least additive.

ADVERSE EFFECTS

Shared adverse effects of NSAID therapy are listed in Table 53.3. The list includes minor symptomatic disturbances, as well as serious and life-threatening complications. The latter represent a growing safety concern, particularly in elderly patients, because age is associated with an increased probability of serious adverse reactions to NSAIDs.¹¹ When assessing clinically relevant outcomes of NSAID therapy, one should consider the variable incidence rate of these outcomes in the general population (Table 53.4). No placebo-controlled trials of adequate size and duration have been performed with traditional NSAIDs to reliably evaluate the excess of these serious outcomes attributable to NSAID therapy. Thus, we have to rely almost entirely on the results of observational studies that give a quantitative assessment of the risk for important outcomes (see Table 53.4). If the associations found in epidemiologic studies were causal, approximately 300 upper gastrointestinal bleeding or perforation events, a similar number of hospitalizations for congestive heart failure and nonfatal myocardial infarction, 5 acute liver injuries, and 4 to 8 hospitalizations for acute renal failure per 100,000 persons per year would be attributable to NSAID therapy.¹¹

Gastrointestinal

The most common symptoms associated with NSAID therapy are gastrointestinal, including nausea, abdominal pain, and diarrhea. These symptoms do not necessarily reflect NSAID-induced mucosal lesions or ulcers because they occur commonly in placebo-treated patients. Gastrointestinal ulcers, as assessed by endoscopy, are detectable in 30% to 50% of NSAID-treated patients and develop in a dose- and time-dependent fashion. However, less than 10% of NSAID-treated patients have symptomatic ulcers, thus emphasizing the poor correlation between upper gastrointestinal symptoms and lesions. Gastrointestinal ulcers may be single or multiple and can be accompanied by gradual blood loss leading to anemia or by life-threatening bleeding. The risk for NSAID-induced ulceration is increased in patients infected with *Helicobacter pylori*, heavy alcohol drinkers, or those taking concomitant low-dose aspirin, clopidogrel, warfarin, or glucocorticoids.¹

Coxibs have been shown to be associated with a lower incidence of endoscopic gastroduodenal ulcers than equally effective doses of traditional

TABLE 53.2

Interactions between nonsteroidal antiinflammatory and other drugs

Drug affected	NSAID implicated	Effect	Approach to management
Oral anticoagulants	Phenylbutazone Oxyphenbutazone Azapropazone	Inhibition of the metabolism of S-warfarin, which increases the anticoagulant effect	Avoid NSAIDs if possible Use careful monitoring when use is unavoidable
Lithium	Probably all NSAIDs	Inhibition of renal excretion of lithium, which increases lithium serum concentrations and the risk for toxicity	Use sulindac or aspirin if an NSAID is unavoidable Closely monitor the lithium concentration and appropriate dose reduction
Oral hypoglycemic agents	Phenylbutazone Oxyphenbutazone Azapropazone	Inhibition of the metabolism of sulfonylurea drugs, which prolongs the half-life and increases the risk for hypoglycemia	Avoid this group of NSAIDs if possible; if not, monitor the blood glucose level closely
Phenytoin	Phenylbutazone Oxyphenbutazone Other NSAIDs	Inhibition of the metabolism of phenytoin, which increases the plasma concentration and risk for toxicity Displacement of phenytoin from plasma protein, which reduces total concentrations for the same unbound (active) concentration	Avoid this group of NSAIDs if possible; if not, intensify therapeutic drug monitoring Avoid aspirin; closely monitor the plasma concentration if another NSAID is used
Methotrexate	Probably all NSAIDs	Reduced clearance of methotrexate (mechanism unclear), which increases the plasma concentration and risk for severe toxicity	This is relevant only to the high-dose methotrexate used in cancer chemotherapy
Sodium valproate	Aspirin	Inhibition of valproate metabolism, which increases the plasma concentration	Avoid aspirin; closely monitor the plasma concentration if another NSAID is used
Digoxin	All NSAIDs	Potential reduction in renal function (particularly in the very young and very old), which reduces digoxin clearance and increases its plasma concentration	Avoid NSAIDs if possible; if not, perform frequent checks of the plasma concentration of digoxin and the plasma creatinine level
Aminoglycosides	All NSAIDs	Reduction in renal function in susceptible individuals, which reduces aminoglycoside clearance and increases the plasma concentration	Closely monitor plasma concentration and dose adjustment
Antihypertensive agents: β -blockers, diuretics, ACE inhibitors, vasodilators	Indomethacin Other NSAIDs	Reduction in hypotensive effect, probably related to inhibition of renal prostaglandin synthesis (which produces salt and water retention) and vascular prostaglandin synthesis (which produces increased vasoconstriction)	Avoid all NSAIDs in patients with cardiac failure; monitor for clinical signs of fluid retention
Diuretics	Indomethacin Other NSAIDs	Reduction in natriuretic and diuretic effects; may exacerbate congestive cardiac failure	Avoid NSAIDs in patients with cardiac failure; monitor for clinical signs of fluid retention
Anticoagulants	All NSAIDs	Gastrointestinal tract mucosal damage, together with inhibition of platelet aggregation, which increases the risk for gastrointestinal bleeding in patients taking anticoagulants	Avoid all NSAIDs if possible
Low-dose aspirin	Ibuprofen and naproxen	Prevention of irreversible inactivation of platelet COX-1	Use NSAIDs with some degree of COX-2 selectivity

ACE, angiotensin-converting enzyme; COX, cyclooxygenase; NSAID, nonsteroidal antiinflammatory drug.

NSAIDs.³ Prophylaxis with a proton pump inhibitor, such as omeprazole, or a prostaglandin analogue, such as misoprostol, has been shown to reduce the risk for NSAID-induced, endoscopically verified ulcers.¹

Upper gastrointestinal complications (bleeding, perforation, and obstruction) occur in 1% to 2% of NSAID-treated patients. The mortality rate associated with hospitalization for major gastrointestinal events is 5% to 6% in recent studies.¹² Mortality rates associated with upper or lower gastrointestinal complications secondary to NSAIDs are similar.¹² The major risk factors for upper gastrointestinal bleeding are older age and a previous history of gastrointestinal disorders (Fig. 53.4).¹¹ Male gender, cigarette smoking, and heavy alcohol intake increase this risk by less than twofold, as do oral glucocorticoids. Oral anticoagulants, thienopyridines, and low-dose aspirin increase the risk for NSAID-induced bleeding complications by twofold to threefold.¹¹ The excess of these complications attributable to traditional NSAIDs has been estimated to range between 3 and 30 events per 1000 patients treated per year,¹¹ depending on the absence or presence of risk factors.

Because of the low event rate of ulcer complications, very large sample sizes or prolonged drug exposure is needed to detect differences between drugs. Four large (8000 to 35,000 patients) randomized trials of 6 to 18 months' duration have compared the gastrointestinal safety of coxibs with that of traditional NSAIDs: CLASS (Celecoxib Long-term Arthritis Safety Study—celecoxib versus ibuprofen and diclofenac),⁹ VIGOR¹³ (Vioxx Gastrointestinal Outcomes Research—rofecoxib versus naproxen), TARGET¹⁰ (Therapeutic Arthritis Research and Gastrointestinal Event Trial—lumiracoxib versus ibuprofen and naproxen), and MEDAL¹⁴ (Multinational Etoricoxib and Diclofenac Arthritis Long-term program—etoricoxib versus diclofenac). The main characteristics of the approximately 69,000 patients enrolled in these studies are detailed in Table 53.5. The rate of ulcer

complications associated with traditional NSAIDs in these trials ranged between 5 and 15 per 1000. As can be appreciated in Figure 53.4, these values are consistent with the rates of upper gastrointestinal complications predicted by analysis of epidemiologic data for a comparable low-risk population (i.e., women aged 60 with a largely negative previous gastrointestinal history).¹¹ Both in VIGOR and TARGET, a highly selective COX-2 inhibitor was associated with a statistically significant 50% to 66% relative risk reduction in ulcer complications as compared with naproxen or ibuprofen.^{10,13} Based on recently completed meta-analyses of individual participant data from all the available randomized trials, the risk for upper gastrointestinal complications was almost twice as high for naproxen as for ibuprofen and diclofenac (Coxib and traditional NSAID Trialists' [CNT] Collaboration).¹⁵ The gastrointestinal risks of all the NSAIDs were evident within the first 6 months of treatment.¹⁵

When contrasting the options of using a highly selective COX-2 inhibitor or a traditional NSAID plus a proton pump inhibitor, the following points should be borne in mind:

1. In contrast to coxibs, proton pump inhibitors have not been demonstrated to reduce the risk for NSAID-induced ulcer complications in adequately sized randomized trials.
2. Whereas coxibs have been shown to reduce the risk for both upper and lower gastrointestinal events, proton pump inhibitors would not be expected to protect against the latter.

Finally, it should be emphasized that any COX-2-selective inhibitor may eventually inhibit COX-1 in some patients (because of interindividual variability in pharmacokinetics or pharmacodynamics) and that there may be untoward COX-2-dependent effects (e.g., interference in ulcer healing) that are shared by all COX-2 inhibitors regardless of selectivity.³

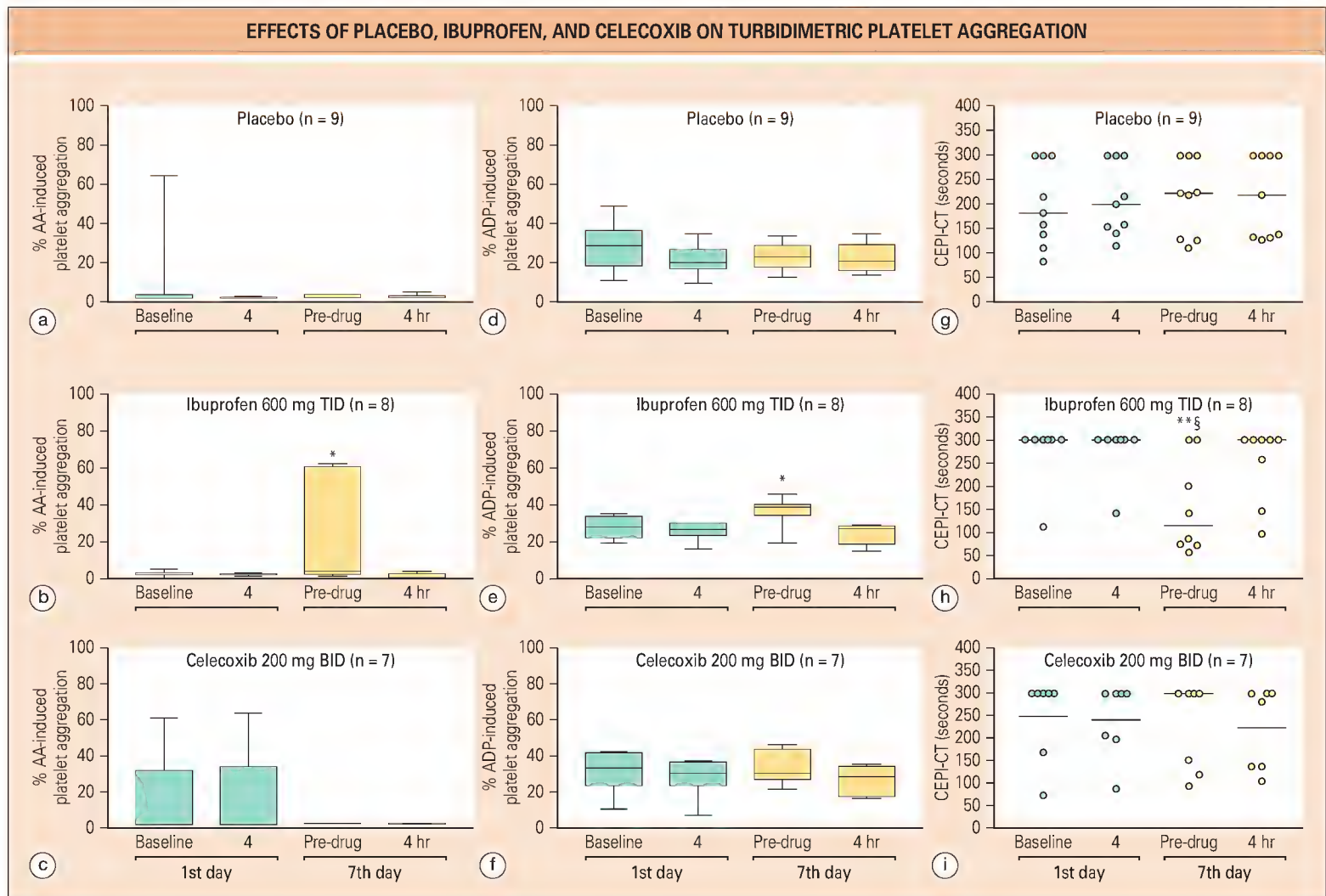


Fig. 53.3 Ibuprofen, celecoxib, and the antiplatelet effect of low-dose aspirin in patients with osteoarthritis and ischemic heart disease. Platelet cyclooxygenase-1 activity, as assessed by measurement of serum thromboxane (TX)B₂ levels, in aspirin-treated patients randomized to receive placebo (a and d), ibuprofen (600 mg 3 times daily [TID]) (b and e), or celecoxib (200 mg twice daily [BID]) (c and f) for 7 consecutive days. Median values (and interquartile range) are depicted in panels a, b, and c. Individual data points (and median values, as depicted by horizontal bars) are reported in panels d, e, and f with values of serum TXB₂ expressed as percentage of baseline (i.e., prior to randomized treatment). (Data from Renda G, Tacconelli S, Capone ML, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. *Clin Pharmacol Ther* 2006;80:264-74.)

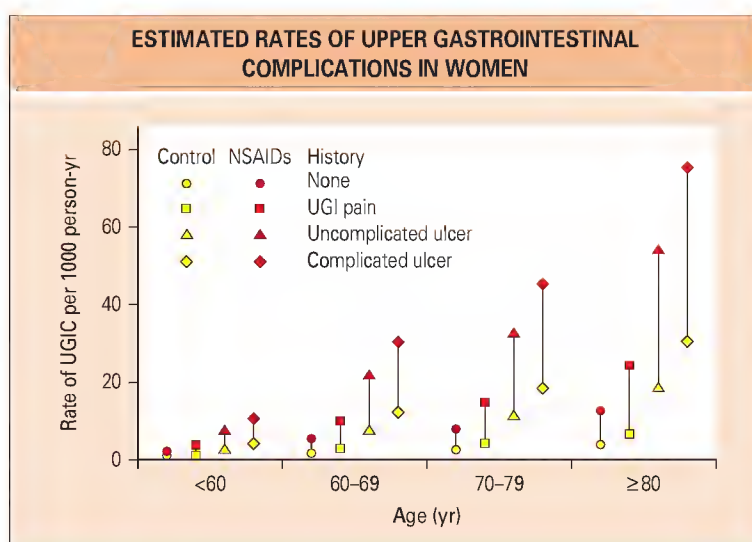


Fig. 53.4 Upper gastrointestinal complication (UGIC) rates were estimated in women according to age and the presence or absence of a history of such complications and regular use of traditional nonsteroidal antiinflammatory drugs (NSAIDs). The solid lines connecting each pair of green (control) and blue (NSAIDs) symbols depict the excess risk for complications related to NSAID therapy. (Data from Hernández-Díaz S, García Rodríguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001;110[Suppl]:20S-27S; and unpublished results of S. Hernández-Díaz and L.A. García Rodríguez.)

Cardiovascular

Persistent (throughout the dosing interval and beyond) and virtually complete (i.e., greater than 97%) inhibition of platelet COX-1 by any commercially available dose of aspirin is associated with a 20% to 30% reduction in major vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death), as demonstrated by more than 50 placebo-controlled randomized trials involving approximately 100,000 subjects at high cardiovascular risk.⁷ Traditional NSAIDs have long been thought to pose no cardiovascular hazard or to be somewhat cardioprotective, even in the absence of any randomized study supporting this widely held assumption. Because of their reversible mechanism of action in inhibiting platelet COX-1 and their short half-lives (see Table 53.1), most traditional NSAIDs inhibit TXA₂-dependent platelet activation only transiently and incompletely in the vast majority of users (Fig. 53.5). A notable exception is provided by naproxen, which has been shown to inhibit TXA₂ biosynthesis *in vivo* to the same extent as low-dose aspirin when administered regularly at 500 mg twice daily,¹⁶ consistent with its relative COX-1 selectivity and longer half-life than other commonly used NSAIDs.

Three placebo-controlled trials have revealed a twofold to threefold increased risk for vascular events in approximately 6000 patients treated short-term (10 days) with valdecoxib¹⁷ or long-term (up to 3 years) with celecoxib¹⁸ or rofecoxib,¹⁹ both with and without concomitant aspirin treatment. These findings are consistent with a mechanism-based cardiovascular hazard for the coxib class.²⁰ In fact, coxibs depress the biosynthesis of vascular PGI₂, an important modulator of blood pressure and thromboresistance, without concomitant inhibition of platelet activation.^{21,22} A meta-analysis of tabular data from 138 randomized trials of five different coxibs involving approximately 145,000 patients has revealed that in placebo comparisons, allocation to a coxib was associated with a 42%

increased incidence of vascular events with no statistically significant heterogeneity among the different coxibs.²³ This excess risk for vascular events was derived primarily from a twofold increased risk for myocardial infarction. Overall, no significant difference was found in the incidence of vascular events between a coxib and any traditional NSAID, but there was evidence of significant heterogeneity between naproxen and the other traditional NSAIDs (largely represented by ibuprofen and diclofenac).²³ The apparent lack of a significant difference in the rate of vascular events between patients treated with any coxib and those treated with other NSAIDs, as

reported in this meta-analysis, is confirmed by the cardiovascular findings of the MEDAL program.²⁴ In this prespecified pooled analysis of data from three trials that included 34,701 patients with osteoarthritis or rheumatoid arthritis treated on average for 18 months, the hazard ratio for thrombotic cardiovascular events was 0.95 (95% confidence interval, 0.81 to 1.11) for etoricoxib versus diclofenac. The results of an updated meta-analysis

■ **TABLE 53.3**

Shared side effects of nonsteroidal antiinflammatory drugs

System	Manifestations
Gastrointestinal	Abdominal pain
	Nausea
	Anorexia
	Erosions or ulcers in the small and large bowel
	Anemia
	Gastrointestinal hemorrhage and perforation
Renal	Diarrhea
	Salt and water retention
	Edema, worsening of renal function in renal/cardiac and cirrhotic patients
	Acute renal failure
Central nervous system	Hyperkalemia
	Headache
	Vertigo
	Dizziness
	Confusion
	Depression
Blood platelets	Lowering of the seizure threshold
	Inhibited platelet activation
	Propensity for bruising
	Increased risk for hemorrhage
Uterus	Prolongation of gestation
	Inhibition of labor
Hypersensitivity	Vasomotor rhinitis
	Angioneurotic edema
	Asthma
	Flushing
	Hypotension
	Shock
Cardiovascular	Closure of the ductus arteriosus
	Precipitation or worsening of heart failure
	Myocardial infarction
	Hemorrhagic stroke
Liver	Transient rise in enzymes
	Cholestasis
	Acute liver injury
Skin	Photosensitivity
	Erythema multiforme
	Urticaria
	Toxic epidermal necrolysis

■ **TABLE 53.5**

Baseline characteristics of patients with osteoarthritis or rheumatoid arthritis and rates of ulcer complications associated with 6- to 12-month treatment with nonsteroidal antiinflammatory drugs in coxib gastrointestinal outcome trials

Trial	Mean age (yr)	Women (%)	Previous gastrointestinal history (%)	Aspirin use (%)	NSAID UGIC rates per 1000 patient-years
CLASS	60	69	9.6	20	15
VIGOR	58	80	7.8	0	14
TARGET	63	76	0	24	9.1
MEDAL	63	74	7	35	4.7

CLASS, Celecoxib Long-term Arthritis Safety Study; MEDAL, Multinational Etoricoxib and Diclofenac Arthritis Long-term program; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event Trial; UGIC, upper gastrointestinal complication; VIGOR, Vioxx Gastrointestinal Outcomes Research.

REVERSIBLE VERSUS IRREVERSIBLE INHIBITION OF PLATELET COX-1 ACTIVITY BY ASPIRIN AND A TRADITIONAL NSAID

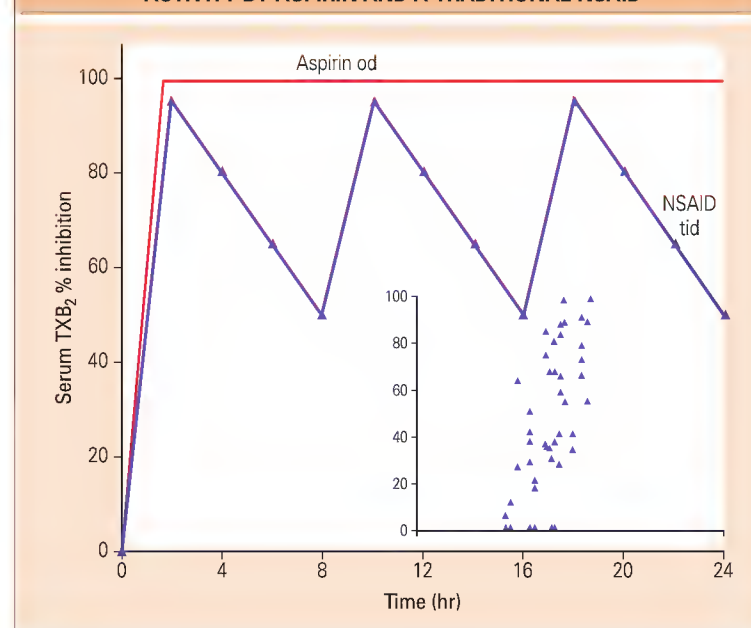


Fig. 53.5 The average time course of inhibition of serum thromboxane B₂ (TXB₂), an *ex-vivo* index of platelet cyclooxygenase-1 (COX-1) activity, is depicted over a 24-hour period after the administration of low-dose aspirin once daily and a traditional NSAID with a short half-life given every 8 hours. The inset depicts interindividual variability in the relationship between NSAID plasma levels plotted on the abscissa log scale and the corresponding level of inhibition of platelet COX-1 plotted on the ordinate. Only 2 of 44 individual blood samples achieved greater than 95% inhibition of platelet COX-1 activity.

■ **TABLE 53.4**

Incidence rates of major events possibly caused by traditional nonsteroidal antiinflammatory drugs as assessed in observational studies in the general population

Event	Incidence rate per 1000 patient-years	Increased risk	Hospitalizations per 100,000 NSAID users
Heart failure	2-4	2-fold	300
Myocardial infarction	1-4	2-fold	300
Upper gastrointestinal bleeding	0.6-1.7	4-fold	300
Acute renal failure	0.02-0.08	2-4-fold	4-8
Acute liver injury	0.02-0.04	2-fold	5

of coxib trials²⁵ that included the MEDAL²⁴ and ADAPT²⁶ (Alzheimer's Disease Anti-inflammatory Prevention Trial) studies confirmed the statistical heterogeneity between coxib versus naproxen and coxib versus other NSAID comparisons.

Given the nonlinear relationship between inhibition of platelet COX-1 activity and inhibition of platelet activation *in vivo*,²⁷ it is perhaps not surprising that the cardiovascular safety profiles of coxibs and some traditional NSAIDs appear similar in that they both fail to inhibit platelet activation adequately irrespective of their COX-2 selectivity.

Thus, coxibs and some traditional NSAIDs moderately increase the risk for vascular events, particularly myocardial infarction, but there remains considerable uncertainty about the magnitude of this hazard for particular drug regimens and patient subgroups. Early appearance,²⁸ dose dependence,²⁹ and slow dissipation²⁸ of risk appear to be important features of COX-2-related cardiotoxicity.

Use of NSAIDs can lead to the development of congestive heart failure in susceptible individuals.³⁰ Based on epidemiologic studies,^{11,30} current users of NSAIDs are estimated to have a twofold increased risk of hospitalization for congestive heart failure. The effect is greater in patients with preexisting heart disease. The risk appears to be dose dependent and somewhat higher during the first month of therapy.^{11,30}

A meta-analysis of individual participant data from all the available coxib and NSAID randomized trials¹⁵ has largely confirmed the main features of cardiovascular toxicity associated with COX-2 inhibition (Fig. 53.6). Moreover, coxibs, diclofenac and ibuprofen increased the risk for vascular death by 50% to 60% but had no significant effect on nonvascular causes of death.¹⁵

Renal

Both traditional NSAIDs and coxibs have been associated with renal and renovascular adverse events, consistent with the important role of constitutively expressed COX-2 in sustaining the physiologic production of vasodilator and natriuretic prostanoids in the human kidney.^{1,3}

COX-2 inhibitors have little effect on renal function or blood pressure control in healthy subjects. However, in patients with chronic glomerular disease, hepatic cirrhosis, congestive heart failure, hypovolemia, and other states of activation of the sympathoadrenal or renin-angiotensin systems, maintenance of renal blood flow and the glomerular filtration rate is critically dependent on renal PG synthesis.^{1,3}

Some studies evaluating the risk for chronic renal conditions (e.g., analgesic nephropathy) associated with traditional NSAIDs, including aspirin and acetaminophen, have found that NSAID users have a twofold increased

risk for these conditions. The risk increases with age and is related to dose and duration of NSAID intake.^{11,31}

The incidence rate of hospitalization for acute renal failure among non-users is approximately 2 per 100,000 persons per year. Current users of NSAIDs are estimated to experience a twofold to fourfold increased risk of hospitalization for acute renal failure. The risk is dose dependent and is considerably higher during the first month of therapy.^{11,31}

Other risk factors for acute renal failure are male gender, older age, cardiovascular comorbidity, renal diseases, concomitant use of other nephrotoxic drugs, and recent hospitalization for disorders other than renal disease.^{11,31}

Respiratory

Asthma is most common with salicylates but may be precipitated or exacerbated by other NSAIDs. Symptoms may be mild or severe, and fatal attacks of bronchospasm have been precipitated by a single dose of an NSAID. If aspirin-sensitive asthmatic patients require an NSAID, a low dose should be administered in a controlled environment equipped with facilities to reverse bronchospasm. Pulmonary alveolitis has also been reported with NSAID therapy and, though rare, should be considered when an illness suggestive of pulmonary infection but failing to respond to antibiotic therapy develops in a patient taking an NSAID. Limited data suggest that coxibs can be used safely in asthmatics.³² Nonacetylated salicylates are often used in this situation.

Hepatic

Both traditional NSAIDs and coxibs are among the most common agents associated with drug-induced liver injury ranging from asymptomatic elevations in aminotransferase levels to serious liver injury with acute hepatic failure. Observational studies have reported nimesulide, sulindac, and diclofenac to be associated with the highest risk for liver injury, and the only risk factor consistently identified in these analyses is the concomitant use of other hepatotoxic drugs.^{11,33} In the MEDAL program,²⁴ diclofenac caused elevations in aminotransferase levels more frequently than etoricoxib did, generally during the first 4 to 6 months of therapy, although clinical liver events requiring hospitalization were relatively rare.

Nimesulide has been withdrawn in Finland and Spain because of hepatotoxicity, but it continues to be prescribed in Italy and Portugal with some restrictions.

RATIONAL SELECTION OF NONSTEROIDAL ANTIINFLAMMATORY DRUG THERAPY

Patients with rheumatic disease have quite substantial interindividual variability in their response to NSAIDs. The therapeutic challenge in each case is to find the right NSAID and appropriate dosing regimen that provide an acceptable level of pain relief while minimizing the risk for serious adverse events.

Because gastrointestinal and cardiovascular adverse events contribute the largest share of NSAID-induced toxicity, careful consideration should be given to assessment of risk factors for these complications in the individual patient.

Because of the nature of serious complications that could be caused or prevented by one particular NSAID versus another, patients' values and preferences should be considered in the choice of NSAID therapy. Moreover, patients should be adequately informed about the balance of benefits and risks to obtain their cooperation in achieving the following goals:

- Minimizing the level and duration of drug exposure
- Avoiding concomitant over-the-counter analgesic medications
- Complying with prescribed dietary, physical, and pharmacologic means in managing modifiable cardiovascular risk factors (i.e., cigarette smoking and higher than optimal blood pressure, cholesterol, and body weight).

In light of the heterogeneous regulatory and marketing environment in the United States versus Europe (Table 53.6), uniform treatment recommendations are difficult to make. Although some preferred treatment options have been suggested^{32,34-36} according to the level of cardiovascular and gastrointestinal risk, these are based largely on expert opinion. However, the most recent analyses based on individual patient data suggest that the cardiovascular and gastrointestinal risks associated with both coxibs and traditional NSAID regimens are approximately proportional to the estimated baseline risk for each type of event and can therefore be predicted.¹⁵

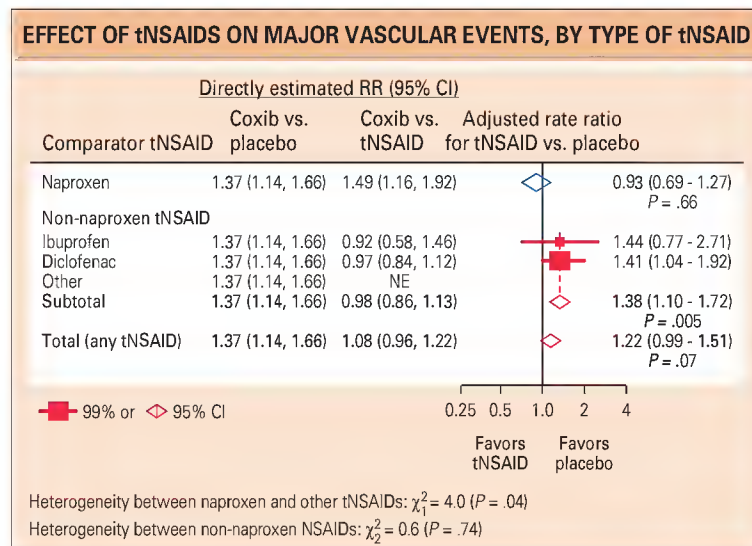


Fig. 53.6 Rate ratios (RRs) are for comparisons of a traditional nonsteroidal antiinflammatory drug (tNSAID) versus placebo, calculated indirectly from ratio of RRs for a coxib versus placebo and RRs for a coxib versus tNSAID, each of which is shown in the vertical columns. Event rate ratios, with 95% confidence intervals, are indicated by a diamond; rate ratios for individual tNSAIDs, with 99% confidence intervals, are indicated by a square and horizontal line. Diamonds to the right of the solid line indicate hazard with tNSAIDs versus placebo, but this is conventionally significant only if the diamond does not overlap the solid line. (Adapted from Coxib and traditional NSAID trialists' (CNT) secretariat, unpublished. Courtesy Dr. Colin Baigent.)

TABLE 53.6

Elements of a heterogeneous and evolving scenario concerning nonsteroidal antiinflammatory drug therapy in the United States and Europe

Variable	USA	Europe
Marketing scenario	Celecoxib is the only marketed coxib. Some COX-2-selective NSAIDs (e.g., nimesulide) are not marketed.	Celecoxib and etoricoxib are marketed in most countries. Nimesulide is marketed in some countries but has been withdrawn in others.
Regulatory scenario	Etoricoxib and lumiracoxib have not been approved. Celecoxib is not contraindicated in patients at high cardiovascular risk. Cardiovascular warning has been placed on celecoxib and all traditional NSAIDs except aspirin.	Celecoxib, etoricoxib, and diclofenac are contraindicated in patients at high cardiovascular risk. No such contraindication is on the label of other traditional NSAIDs.

COX, cyclooxygenase; NSAIDs, nonsteroidal antiinflammatory drugs.

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54

Systemic glucocorticoids
in rheumatology

■ KENNETH G. SAAG ■ FRANK BUTTGEREIT

- Glucocorticoids act via a number of pathways including inhibition of transcription factors nuclear factor- κ B and activator protein 1.
- Glucocorticoids decrease synthesis of proinflammatory cytokines and proinflammatory enzymes, decrease T-cell function, and reduce Fc receptor expression.
- Short-term use of low-dose glucocorticoids in rheumatoid arthritis decreases clinical disease activity. These agents also have a beneficial effect on radiographic activity.
- Adverse events are common with these drugs, and many of the side effects are dose dependent. Careful titration of dose and strategies to minimize toxicity are essential when glucocorticoids are used.

INTRODUCTION

Discovered over 50 years ago, synthetic cortisone was first shown to be remarkably effective in relieving the inflammation associated with rheumatoid arthritis (RA).¹ This pioneering work by Hench, Kendall, and colleagues subsequently resulted in a Nobel Prize in Medicine. Despite the advent of many disease-specific therapies, the use of synthetic glucocorticoids in rheumatology remains a common, albeit controversial, therapy for many inflammatory disorders.

NOMENCLATURE AND PHARMACOLOGY

Preparations and structure

The term *corticosteroid* is often used synonymously with *glucocorticoid*, although glucocorticoid is the preferred designation when using exogenous agents therapeutically because corticosteroids encompass both glucocorticoid and mineralocorticoid hormones.² A variety of synthetic glucocorticoid preparations are commercially available and have variable chemical structure (Fig. 54.1), potency, and half-life (Table 54.1). The 11 β - and 17 α -hydroxyl groups are important for glucocorticoid activity, and prednisone, a synthetic analogue of cortisone, is also hydroxylated before becoming biologically active. The additional double bond in ring A of the resultant prednisolone enhances glucocorticoid activity without increasing mineralocorticoid activity, an effect that is increased by 6 α -methylation (to produce methylprednisolone) or 9 α -fluorination (triamcinolone) or both (dexamethasone). In rheumatology, the most commonly used oral glucocorticoids are prednisone and prednisolone, whereas methylprednisolone is the predominant preparation used parenterally.

Dosing

Thresholds for low, medium, and high dose are not well defined. Some rheumatologists consider 10 mg/day prednisone equivalent as the upper threshold of a low dose, whereas others use 7.5 mg/day³; this is actually somewhat above the daily endogenous production of cortisol (hydrocortisone) by the adrenal glands, which averages 5.7 mg/m²/day.⁴ A European League Against Rheumatism (EULAR) standing committee defined *low dose* as up to 7.5 mg/day, *medium dose* as more than 7.5 mg/day but less than or equal to 30 mg/day, *high dose* as more than 30 but mg/day less than or equal to 100 mg/day, and *very high dose* as more than 100 mg/day prednisolone

equivalent.² Dosing designations were considered based on the percent binding of the glucocorticoid receptors and the risk of perceived adverse effects. These dosing conventions are used throughout this chapter.

Bioequivalence and bioavailability

The different preparations of glucocorticoids have the same rate of gastrointestinal absorption. Most commercially available prednisone tablets are bioequivalent, independent of tablet strength,⁵ and the systemic bioavailability of prednisone and prednisolone are similar. Glucocorticoid bioavailability does not appear to be affected by pregnancy.

Metabolism and drug interactions

In contrast to endogenous cortisol, which is 80% bound, synthetic glucocorticoids bind poorly to cortisol-binding globulin (CBG, or transcortin). Prednisolone has about 60%, prednisone 5%, and methylprednisolone, dexamethasone, betamethasone, and triamcinolone less than 1% of the affinity of cortisol for CBG. Half-life ranges from about 1 hour for prednisone to over 4 hours for dexamethasone. Prednisone is rapidly metabolized in the liver by CYP3A4 (a cytochrome P450 isoform) to prednisolone; the elimination of prednisone is approximately 13 times faster than the elimination of prednisolone.⁶ Hyperthyroidism and nephrotic syndrome increase clearance, whereas aging and liver disease impair clearance. Prednisolone is preferred to prednisone in patients with significant hepatic dysfunction.

Enhancement of the rate of metabolism of some glucocorticoids has been noted with concurrent administration of phenobarbital, phenytoin, and rifampin (rifampicin). Concurrent use of aspirin and glucocorticoids decreases salicylate levels by causing an increased rate of salicylate metabolism.

Clearance and dose timing

The elimination half-life of prednisolone is approximately 3 hours.⁷ Total prednisolone clearance increases by 75% as the intravenous dose increased from 5 to 40 mg.⁸ Clearance also varies with the time of day. Both prednisolone and methylprednisolone clearance is up to 25% lower in the morning than in the evening.⁹ This property, in combination with the disruption of the usual cortisol diurnal rhythm by exogenous glucocorticoids, results in variations in efficacy when glucocorticoids are administered at different times during the day.¹⁰ Administration of short-acting glucocorticoids very early in the morning, in contrast to later in the day, better complements the normal diurnal variation in endogenous hormones and further blocks production of proinflammatory cytokines such as interleukin-6 (IL-6)¹¹ and inflammatory symptoms.¹² For example, a low-dose prednisone compound incorporating a modified-release mechanism (MR prednisone, i.e., drug is released 4 hours after ingestion) when taken in the evening reduced RA morning stiffness more than placebo at 12 weeks.^{13,14}

MR prednisone plus disease-modifying antirheumatic drug (DMARD) therapy resulted in significantly higher ACR20 response rates (percentage of patients achieving a 20% improvement in signs and symptoms according to American College of Rheumatology criteria) and a greater relative reduction in morning stiffness than placebo plus DMARD.¹⁵ Significantly greater reductions in severity of RA and fatigue, and a greater improvement in physical function also were seen at week 12 with MR prednisone compared with placebo.

Timing of administration of the glucocorticoid dose also influences toxicity. For example, daily split-dose therapy is more immunosuppressive and should be used for a shorter duration due to its more profound disruption of the normal hypothalamic-pituitary-adrenal (HPA) axis function.

STRUCTURE OF SOME NATURAL AND SYNTHETIC GLUCOCORTICOIDS

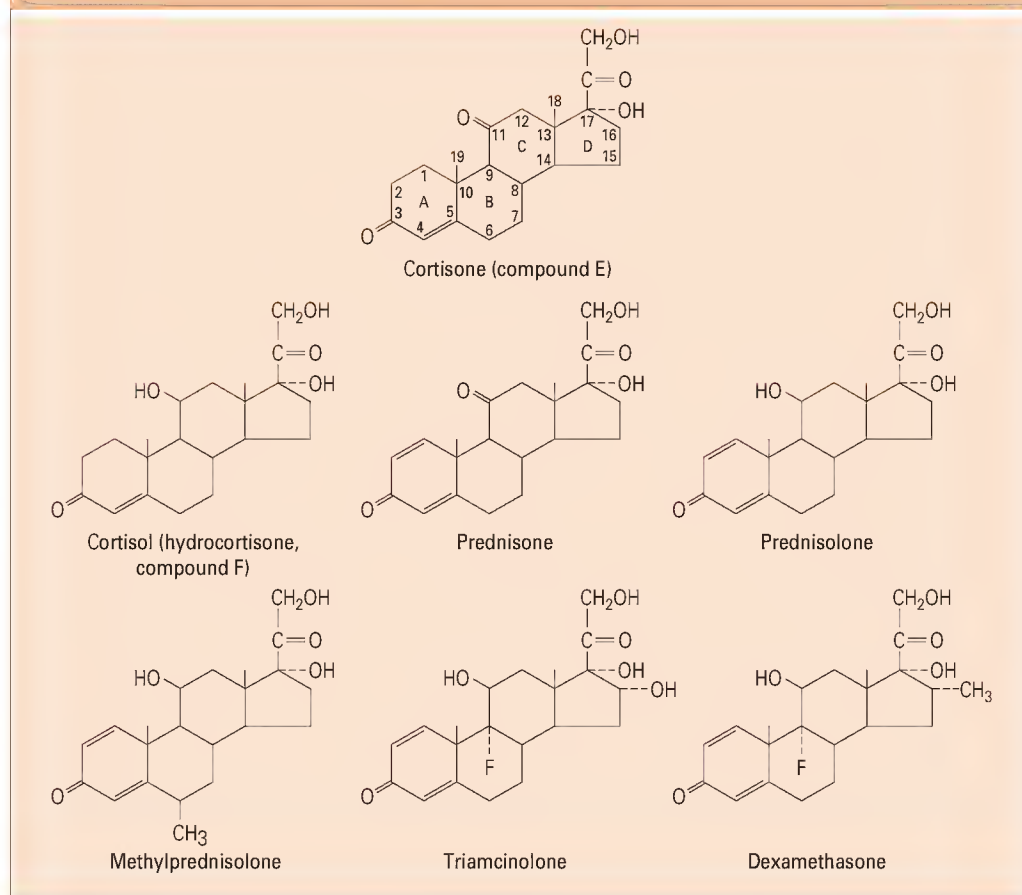


Fig. 54.1 Structure of some natural and synthetic glucocorticoids.

TABLE 54.1
Some commonly used glucocorticoids

Glucocorticoid	Equivalent oral dose (mg)	Plasma half-life (minutes)	Relative antiinflammatory effect	Relative mineralocorticoid effect
Cortisol	20	90	1	1
Prednisolone/prednisone	5	200	4	0.8
Methylprednisolone	4	200	5	0.5
Triamcinolone	4	200	5	0
Dexamethasone	0.75	300	25	0

One study found no differences between MR prednisone and standard prednisone with regard to influence on the HPA axis as measured by corticotropin-releasing hormone tests. In both treatment groups, there was a normal response in 50% of the patients, the response was suppressed in about 37%, and there was no response in about 13%.¹⁶

MECHANISMS OF GLUCOCORTICOID ACTION

Glucocorticoids act as antiinflammatory mediators via a number of pathways that continue to be further elucidated.¹⁷⁻²² Oral glucocorticoids at dosages of less than 30 mg/day prednisone equivalent circulate in the plasma and diffuse through the plasma membrane where they bind to the cytosolic glucocorticoid receptor, a 95-kDa phosphorylated protein. Diversity in the function of the glucocorticoid receptor is influenced by variations in genetic transcription mediated by alternative splice sites. The relative levels of the α and β receptors influence the sensitivity or resistance of cells to glucocorticoids. Glucocorticoid resistance is reported in patients with severe RA and has been associated with higher levels of glucocorticoid receptor β , activation of mitogen-activated protein kinases (MAPKs) that inhibit glucocorticoid signaling, or antibodies to lipocortin-1.²³⁻²⁶ Individuals with glucocorticoid receptor polymorphisms have higher sensitivity to exogenously administered glucocorticoids.²⁷ Persons with relative glucocorticoid resistance may have diminished *in-vitro* response of their peripheral blood

mononuclear cells to glucocorticoid stimulation.²⁸ Imbalances in the two isoforms of 11 β -hydroxysteroid dehydrogenase may play a central role in glucocorticoid resistance.²⁹

Glucocorticoids act on the cell through genomic and nongenomic paths in at least three ways (Fig. 54.2).²¹

- Heat shock protein chaperons the glucocorticoid/glucocorticoid receptor complex to the nucleus, where it binds reversibly and exerts potent effects on transcription via binding to positive and negative glucocorticoid response elements in promoter or suppressor sites of target genes. The detailed mechanism of a direct transrepression via the binding of glucocorticoid receptors to simple DNA binding sequences has been elucidated.³⁰
- The glucocorticoid/glucocorticoid receptor complex inhibits transcription factors such as nuclear factor- κ B (NF- κ B) and activator protein 1. Most antiinflammatory effects are thought to occur due to inhibited gene transcription via these effects on NF- κ B (transrepression), whereas the adverse effects of glucocorticoids, such as metabolic side effects, are mediated in large part via activation of transcription of certain genes (transactivation) (Fig. 54.3). However, this concept has recently been challenged.^{30a}
- Glucocorticoid signaling occurs through membrane-associated receptors and second messengers (nongenomic pathways). The glucocorticoid receptor gene encodes for both cytosolic and membrane-bound

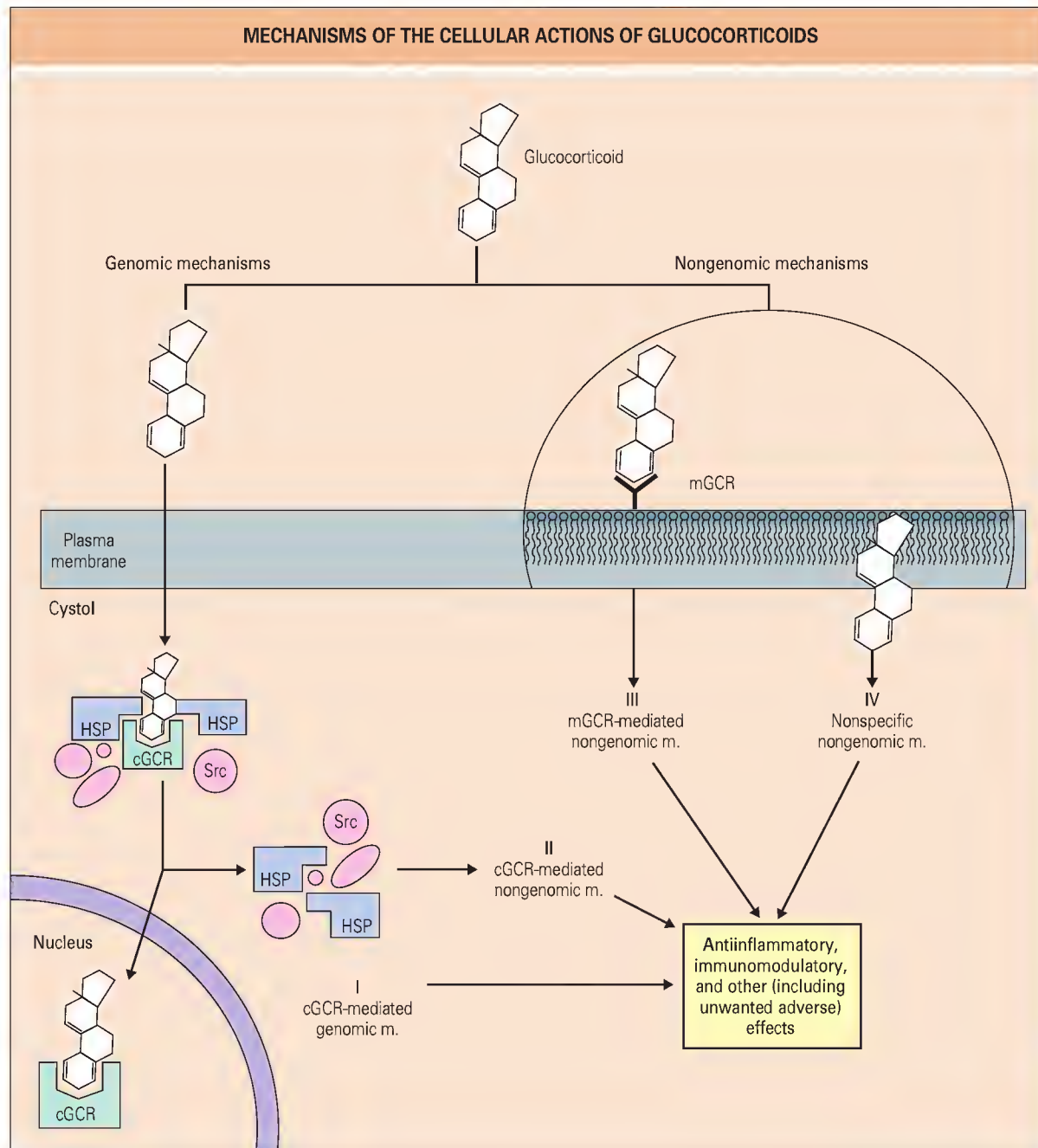


Fig. 54.2 As lipophilic substances, glucocorticoids pass very easily through the cell membrane into the cell, where they bind to ubiquitously expressed cytosolic glucocorticoid receptors (cGCRs). This is followed either by the classic cGCR-mediated genomic effects (I) or by cGCR-mediated nongenomic effects (II). Moreover, the glucocorticoid is very likely to interact with cell membranes, either via specific membrane-bound glucocorticoid receptors (mGCRs) (III) or via nonspecific interactions with cell membranes (IV). HSP, heat-shock protein; m., mechanism. (Adapted from Buttgerit F, Straub RH, Wehling M, Burmester GR. Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. *Arthritis Rheum* 2004;50:3408-17.)

glucocorticoid receptor.³¹ At high glucocorticoid dosages (more than 100 mg/day prednisolone equivalent), glucocorticoid receptors become saturated and these nongenomic effects emerge. They are also mediated by incorporation of glucocorticoid molecules into cell membranes.¹⁹

The relative contributions of these three mechanisms are not yet fully understood, but in combination they result in the decreased synthesis of proinflammatory cytokines such as IL-1, IL-2, IL-2 receptor, interferon- α , IL-6, and tumor necrosis factor- α (TNF- α).^{17,18,32} Glucocorticoids increase the rate of synthesis of lipocortin (annexin I), which inhibits phospholipase A₂. Phospholipase A₂ converts membrane-bound phospholipids into arachidonic acid with the subsequent intracellular production of prostaglandins, leukotrienes, and oxygen radicals.³³ Glucocorticoids also induce MAPK phosphatase 1 (which inactivates all proteins of the MAPK family including Jun N-terminal kinase), and glucocorticoids repress transcription of cyclooxygenase 2.³⁴ Independent of change in gene expression, glucocorticoids exert rapid effects via activation of endothelial nitric oxide as well as

activation of β -adrenoreceptors, endonucleases, and neutral endopeptidases, which explains other observed effects.³⁵ Glucocorticoids, even in very low concentrations, inhibit the synthesis of a variety of proinflammatory enzymes including the macrophage products collagenase, elastase, and plasminogen activator.³⁶ Glucocorticoids have a direct effect on lymphocytes by decreasing T-cell function and circulating number. They further inhibit Fc receptor expression (reducing clearance of antibody-coated blood cells), increase the number of circulating neutrophils, and affect leukocyte adhesion to endothelial cells.³⁷

Drug development efforts are attempting to exploit an improved knowledge of the molecular biology of glucocorticoids. Selective glucocorticoid receptor agonists that differentially affect levels of transactivation and transrepression have been under development.^{38,39} In preliminary experiments some compounds appeared to exhibit antiinflammatory effects similar to those of traditional glucocorticoids but may have fewer adverse effects such as blood glucose elevation or skin thinning.^{40,41} Liposomal glucocorticoids are being developed with the aim of providing more prolonged

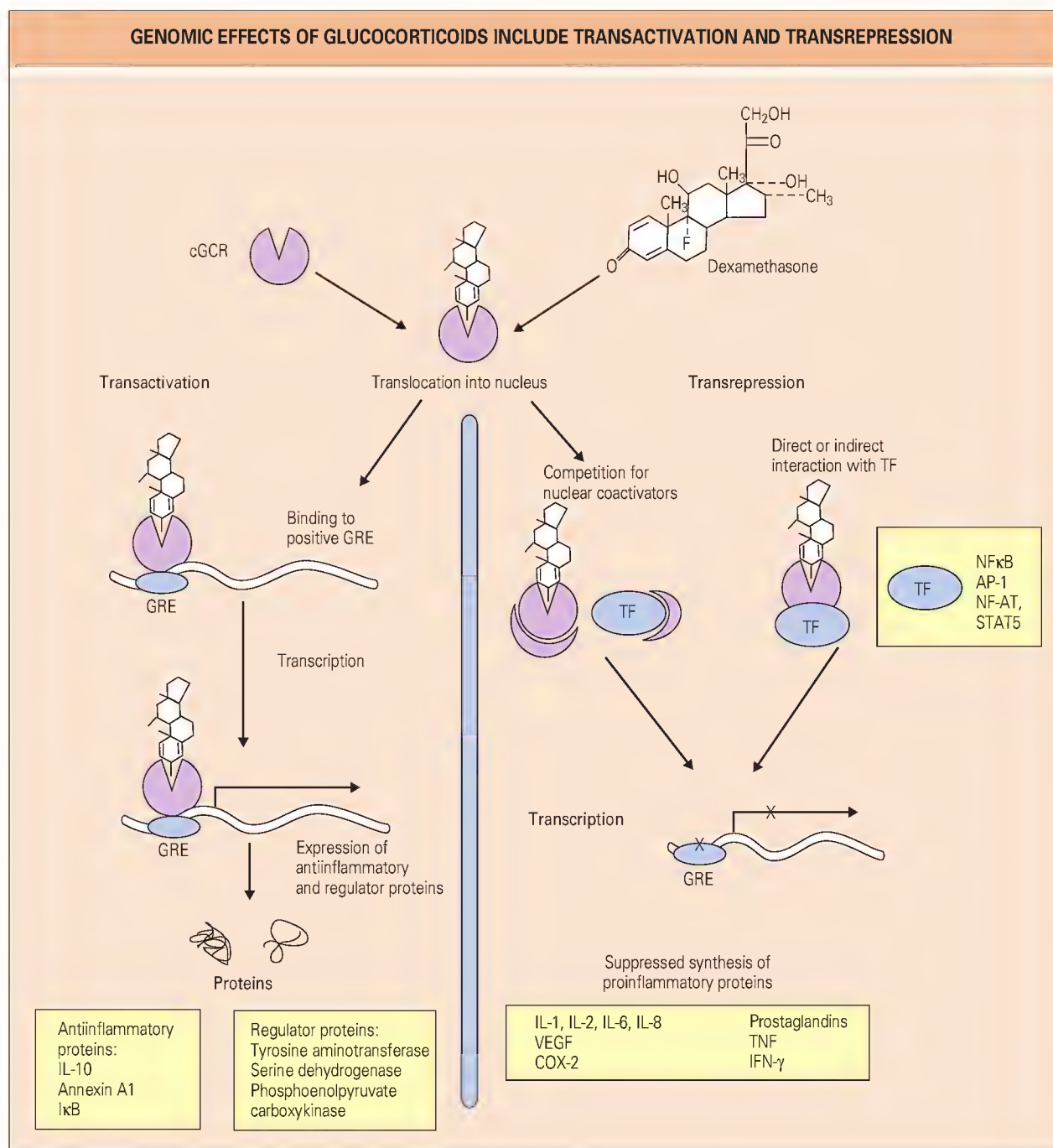


Fig. 54.3 Binding of the glucocorticoid/cytosolic glucocorticoid receptor (cGCR) complex to glucocorticoid response elements (GREs) leads to expression of antiinflammatory and regulatory proteins such as interleukin-10 (IL-10) or IκB (transactivation). A suppressed synthesis of proinflammatory proteins (transrepression) is caused by competition for nuclear coactivators or by direct or indirect interaction with transcription factors. AP-1, activator protein 1; COX-2, cyclooxygenase 2; IκB, inhibitor of NF-κB; IFN-γ, interferon-γ; NF-AT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; STAT5, signal transducer and activator of transcription 5; TF, transcription factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. (Adapted from Stahn C, Buttgerit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* 2008;4:525-33.)

concentrations of glucocorticoids at the site of inflammation and lower plasma levels. Part of their mechanism of action may be via insertion of higher concentrations of glucocorticoids into cell membranes.⁴²

EFFICACY

Efficacy in rheumatoid arthritis

Short- to moderate-term glucocorticoid studies reveal improvement in disease activity and functional status compared with control therapy.^{43,44} In many past studies, the antiinflammatory benefits of glucocorticoids declined after the first year⁴⁵⁻⁴⁷ and often were not seen even beyond 5 months.^{48,49} In contrast to earlier reports, three more recent randomized controlled trials

showed that at 2 years treatment with either 5 mg or 7.5 mg of prednisone^{50,51} or 10 mg of prednisone⁵² resulted in variable levels of improvement in joint indices, functional status, and remission criteria compared with placebo.

In addition to disease activity, joint damage as assessed by radiographic criteria (bony erosions and joint space narrowing) is a critical efficacy outcome. Although it is known that methotrexate, the anti-TNF agents, and newer biologic response modifiers are DMARDs in RA, there is now consensus that glucocorticoids function similarly. Many of the RA studies evaluating the effects of glucocorticoids on radiographic progression are summarized in Table 54.2. Findings that DMARDs, biologic agents, and glucocorticoids had similar effects on radiographic progression in RA were confirmed in a meta-analysis.⁵³ Many of the studies investigating the efficacy of glucocorticoids allowed concomitant use of DMARDs, which makes it

TABLE 54.2
Studies of oral glucocorticoid therapy and radiographic progression in rheumatoid arthritis (RA)

Study	Experimental group	Control group	Study type (no. of subjects)	Effect on radiologic progression	Comments
MRC (1955) ¹⁴⁹	Cortisone (69 mg/day)	ASA	CT (100)	No difference	Trend toward protective effect
MRC (1959) ¹⁵⁰	Prednisolone (initially 20 mg, 12 mg/day by yr 1, 10 mg/day by yr 2)	ASA	CT (77)	Reduction after 2 yr, less after 3 yr	Control patients offered prednisolone in yr 3
Berntsen & Freyberg (1961) ¹⁵¹	Various glucocorticoids, dose not reported	IM gold, analgesics	Retrospective (388)	Deterioration in all groups	Other treatments had already failed in many patients
Harris et al (1983) ¹⁵²	Prednisone (5 mg/day) & DMARD	PBO & DMARD	DB RCT (34)	No significant difference	Trend toward reduction
Million et al (1984) ¹⁵³	Prednisolone (10.3 mg/day) & DMARD	No prednisolone	RCT (103)	Significant reduction	10-yr study
Kirwan (1995) ⁴⁵	Prednisolone (7.5 mg/day) & DMARD	PBO & DMARD	DB RCT (106)	Significant reduction	
Boers et al (1997) ⁴⁸	Prednisolone (60 mg/day with taper) & MTX, SSZ	PBO & SSZ	DB RCT (102)	Significant reduction	
Hansen et al (1999) ⁴⁹	Prednisolone (6 mg/day) & DMARD	DMARD	RCT (102)	No significant difference	Trend toward reduction
van Everdingen et al (2002) ⁹⁶	Prednisolone (10 mg/day) & SSZ as rescue	PBO & SSZ as rescue	DB RCT (81)	Significant reduction	Only study since the MRC studies not allow to background DMARDs; SSZ allowed after 6 mo
Cappell et al (2004) ⁹⁵	Prednisolone (7 mg/day) & SSZ	PBO & SSZ	DB RCT (167)	No significant difference	Discordance between readers in radiographic interpretations
Wassenberg et al (2005) ⁵¹	Prednisolone (5 mg/day) & either AU or MTX	PBO & either AU or MTX	DB RCT (166)	Significant reduction	Relatively new-onset RA; one of lowest dosages to show radiographic protection
Svensson et al (2005) ⁵⁰	Prednisolone (7.5 mg/day) & DMARD	No prednisone & DMARD	Open RT (225)	Significant reduction	Early RA
Bakker et al (2012) ⁵²	Prednisone (10 mg/day) & MTX	PBO & MTX	DB RCT (236)	Significant reduction	Early RA; tight RA control sought with monthly methotrexate dose adjustments

ASA, high-dose aspirin; AU, auranofin; CT, controlled trial; DB, double-blind; DMARD, disease-modifying antirheumatic drug; IM intramuscular; MRC, Medical Research Council; MTX, methotrexate; PBO, placebo; RCT, randomized controlled trial; RT, randomized trial; SSZ, sulfasalazine.

difficult to discern the independent effects of glucocorticoids. Although many of the earlier investigations failed to demonstrate a benefit of low-dose glucocorticoids on radiographic progression, an increasing number of placebo-controlled randomized or open-label clinical trials have now demonstrated that low-dose glucocorticoids prevent radiographic joint destruction in RA. Although the overwhelming majority of glucocorticoid use internationally in RA is via lower-dose oral therapy,^{3,54} a few RA studies have examined other approaches such as pulse-dose and intramuscular depot administration.^{55,56} The addition of prednisone to a methotrexate-based therapy aimed at “tight control” resulted in a significantly greater reduction in radiographic damage.⁵²

Efficacy in systemic connective tissue disorders and vasculitis

Medium- to high-dose glucocorticoids are the therapeutic mainstay in rheumatology for managing serious inflammatory disorders with life- or organ-threatening manifestations. Glucocorticoids have been used to treat serious extraarticular manifestations of RA including interstitial lung disease, bronchiolitis obliterans with organizing pneumonia, pericarditis, scleritis, and vasculitis.⁵⁷

For these serious sequelae of RA, and in other major inflammatory disorders such as systemic lupus erythematosus (SLE), inflammatory myopathy, and systemic vasculitis, glucocorticoids are typically started at dosage in the range of 1 mg/kg/day of prednisone equivalent. Although highly effective in producing remission or improving control of these disorders, glucocorticoids do not inhibit the generation of platelet-derived thromboxane, and in certain forms of vasculitis patients can develop progressive ischemia despite glucocorticoid therapy.⁵⁸

For life- or organ-threatening complications, intravenous pulse therapy is used at dosages of 250 to 1000 mg/day of methylprednisolone for a typical treatment period of 3 days. The intent of pulse therapy is to rapidly and aggressively suppress severe systemic inflammation while minimizing exposure to prolonged very-high-dose therapy. Rapidly progressive glomerulonephritis as well as pulmonary and central nervous system vasculitis are among the disorders for which very-high-dose pulse therapy has been

advocated.^{59,60} Compared with prednisolone, methylprednisolone has more than threefold more nongenomic effects at equivalent dosages, which contributes to the preference for methylprednisolone over prednisone in this setting.⁶¹

Efficacy in polymyalgia rheumatica and large-vessel vasculitis

Glucocorticoids are the mainstay of therapy for polymyalgia rheumatica (PMR), giant cell (temporal) arteritis, and Takayasu arteritis.^{62,63} Due to the older age of most people with PMR and giant cell arteritis, glucocorticoids need to be used cautiously and monitored more closely in this population. Although a variety of other immunosuppressive agents have been tested as possible glucocorticoid-sparing agents, there are few compelling data that these agents are effective alternatives to glucocorticoids for treatment of these disorders. A typical prednisone starting dosage in giant cell arteritis is 60 mg/day, whereas 15 to 20 mg/day is usually adequate for PMR. Although efforts to taper glucocorticoids are initiated early in the disease course, over 6 months may be necessary to reach a low dose in persons with giant cell arteritis.⁶⁴ It is not uncommon for patients with giant cell arteritis to require in excess of 2 years of glucocorticoid therapy. Glucocorticoid-tapering regimens for PMR are not well standardized, and symptoms often wax and wane over many years, remaining partially responsive to low-dose prednisone. Guidance from a meta-analysis suggests that once a prednisone dosage of 10 mg/day is reached, tapering by 1 mg/mo or less results in fewer relapses.⁶⁵

ADVERSE EFFECTS

Despite the considerable benefits of glucocorticoids in controlling serious inflammation and improving functional status in a plethora of disorders, serious adverse effects dampen enthusiasm, particularly for its long-term use. Most studies of glucocorticoid toxicity tend to be retrospective and observational. The difficulty in differentiating adverse outcomes attributable to glucocorticoids from those occurring due to the underlying diseases or

other comorbidities confounds potential associations. A strong physician selection bias for glucocorticoid use exists because physicians are inclined to treat patients with more severe disease with glucocorticoids (i.e., confounding by indication). The use of glucocorticoids at variable points in the disease course, limited data defining the threshold dose for particular adverse events,⁶⁶ and toxicity reports for a heterogeneous group of glucocorticoid-treated diseases all further hinder interpretation of these data.

Several large retrospective reviews indicate that long-term, relatively low-dose glucocorticoid use is a significant independent predictor of numerous potentially serious adverse events.^{58,67-69} Lending further credibility to causality is the fact that the association between glucocorticoid use and adverse events was both dose and time dependent (Fig. 54.4). Both cumulative and mean glucocorticoid dose are independently associated with adverse

events. There appear to be two distinct dose-related patterns of adverse events⁷⁰: (1) a linear increase with increasing dose was found for a cushingoid phenotype, ecchymosis, leg edema, parchment-like skin, and sleep disturbance; (2) a threshold pattern showing an elevated frequency of events beyond a certain threshold value was observed for glaucoma, depression and listlessness, and increases in blood pressure. Dosages of 5 mg/day or more were associated with epistaxis and weight gain (Fig. 54.5).

Less serious adverse effects (e.g., skin thinning, cushingoid appearance) are often of great concern to patients, whereas more debilitating toxicities, such as vertebral fractures and cataracts, initially may be unrecognized or asymptomatic.⁷¹ Compared with other antirheumatic agents, glucocorticoids have a low incidence of short-term symptomatic toxicity, and patients uncommonly discontinue therapy for this reason. What follows is an overview of the most common adverse effects that have been associated with glucocorticoid use. Recent international recommendations provide guidance on the safe use of glucocorticoids.⁷²

Bone and muscle effects

Glucocorticoid-induced osteoporosis is the most potentially devastating complication of protracted glucocorticoid therapy. It is estimated from observational studies that as many as 40% of glucocorticoid users develop bone loss leading to fracture.⁷³ Although glucocorticoids diminish sex hormone production and decrease circulating levels of receptor activator of NF- κ B ligand (RANKL), both of which lead to enhanced osteoclast-mediated bone resorption, a direct glucocorticoid-induced defect in bone formation is thought to be the predominate pathway of importance.^{74,75} Glucocorticoid-induced osteoporosis initially affects trabecular bone. However, with long-term glucocorticoid use, cortical bone at sites such as the femoral neck is also affected.⁷³ Comparison of the results of studies examining the bone effects of glucocorticoids is made difficult by the differences in timing of glucocorticoid initiation, variable dosing regimens, and use of different bone mass measurement techniques and disparities in the sites of measurement.

Observational studies of RA and other glucocorticoid-requiring diseases show a mean first-year loss of bone ranging from 1.5% to 20% at a dosage of 10 mg/day or less of prednisone.³⁸

With continued use, bone loss remains greater than normal and is estimated to be approximately 1.5% to 3% per year, depending on dose, in subsequent years. Although a decline in bone mineral density (BMD) is strongly correlated with fracture risk, the rate of bone turnover, bone quality, and other factors also play important roles.⁷⁶ Some data suggest that at very low doses, glucocorticoids prevent bone loss in RA because of their inhibitory effects on proinflammatory cytokines that modulate osteoclast activity as well as their beneficial effects on functional status, which promotes more weight-bearing activities.^{77,78} Several studies including a meta-analysis have failed to demonstrate an association of low-dose glucocorticoid use with low axial BMD, even in the setting of an increased fracture rate.⁷⁸⁻⁸¹ However,

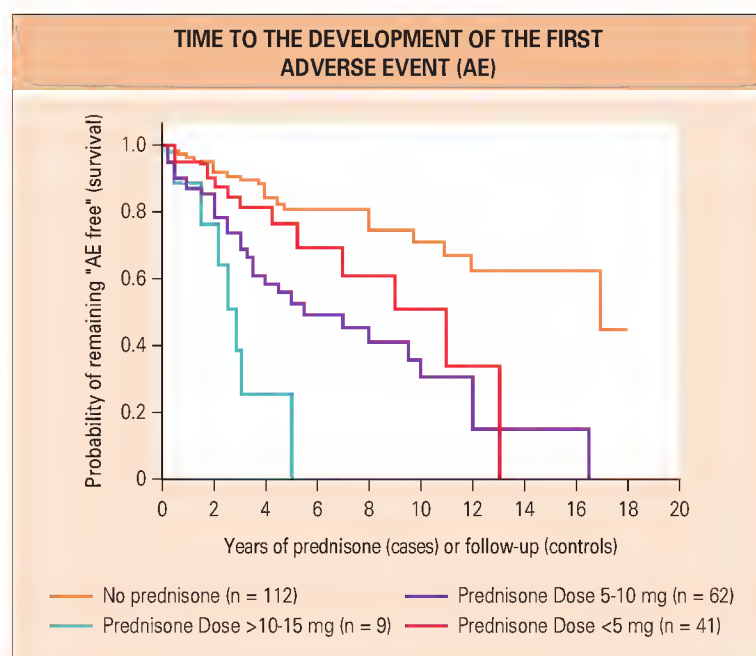


Fig. 54.4 Probability of remaining free from adverse events (AEs) over time in patients receiving low-dose (less than 5 mg), intermediate-dose (5 to 10 mg), or high-dose (more than 10 to 15 mg) prednisone compared with a control group. (Adapted from Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994;96:115-23.)

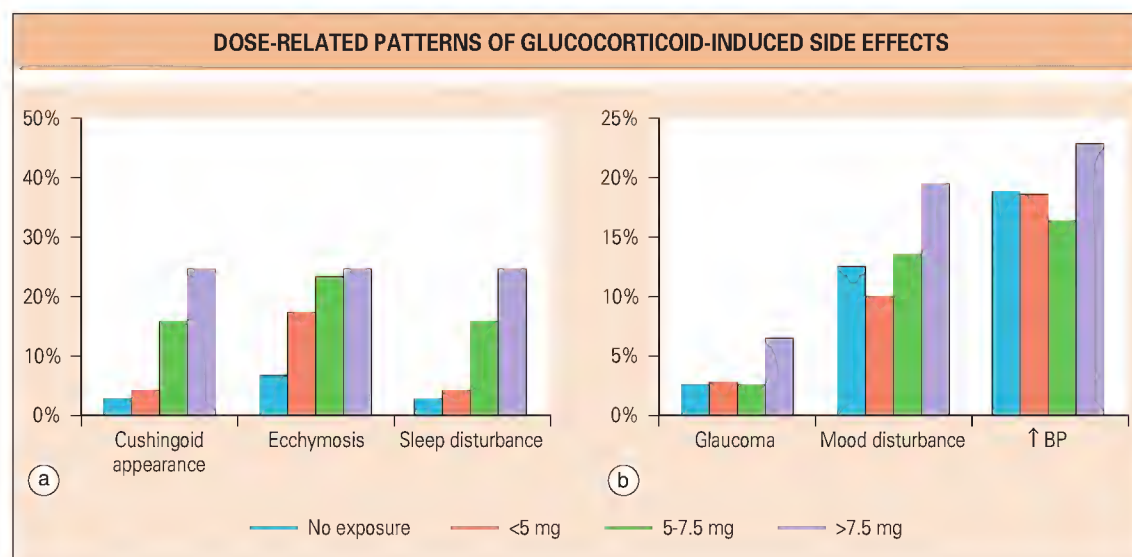


Fig. 54.5 Two distinct patterns of glucocorticoid-induced adverse events related to dose and duration of glucocorticoid intake have been observed: a linear pattern (a) and a threshold pattern (b). Graphs show percentage of unselected patients with rheumatoid arthritis in routine practice who experienced various health problems while taking glucocorticoids based on self-report (n = 1066). BP, blood pressure. (Adapted from Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009;68:1119-24.)

the presence of biochemical changes in bone remodeling with very-low-dose oral⁸² or even intraarticular⁸³ administration argues against a “safe” glucocorticoid dose from the standpoint of bone.⁸⁴

The confounding effects in trying to identify an association between glucocorticoid treatment and osteoporosis in RA relate to two principal issues: the heightened risk of osteoporosis caused by the RA disease process itself⁸⁵⁻⁸⁷ and a higher rate of osteoporosis in postmenopausal women, the demographic group with the highest prevalence of RA.⁸⁸

Given the inconsistent findings of BMD studies and the knowledge that fractures in glucocorticoid-treated patients occur at a higher BMD and depend on other factors,^{89,90} it is necessary to examine long-term studies that evaluate actual fracture incidence. In a large cohort of RA patients,⁹¹ 34% of more than 300 women taking a mean dose of prednisone of 8.6 mg/day had a self-reported fracture within 5 years. Two case-control studies of hip fracture in patients both with and without RA showed a twofold increased risk even after adjustment for the presence of RA.^{85,92} Cohort studies identify fractures as one of the most commonly documented complications of supraphysiologic glucocorticoid use.^{67,68,93} Hip and other nonvertebral fractures occur with glucocorticoids in both a dose- and time-dependent fashion.^{84,94} Nevertheless, randomized controlled trials involving the most common glucocorticoid-requiring illness, RA, have not confirmed an increased rate of fracture.^{45,50,51,95,96} However, none of these trials has been large enough or long enough to fully clarify the magnitude of the fracture risk, some have not systematically assessed fracture outcomes in all patients, and in at least one,⁹⁵ patients were allowed to use bone-protective medications.

Considerable advancement has occurred in the development of antiosteoporotic therapies, and numerous clinical trials have specifically tested such therapies in patients newly initiating glucocorticoid treatment and receiving long-term glucocorticoid therapy. All RA patients with or at risk of glucocorticoid-induced osteoporosis should receive initial therapy with adequate calcium and vitamin D,^{97,98} and strong evidence-based consideration should be given to the addition of a bisphosphonate⁹⁹⁻¹⁰³ or even potentially raloxifene as an alternative.¹⁰⁴ Teriparatide, which may directly inhibit glucocorticoid-mediated deleterious effects on bone formation, is another treatment option for glucocorticoid users at high risk of fracture.¹⁰⁵ Internationally, a variety of specialty societies have promulgated recommendations for appropriate testing and treatment to prevent glucocorticoid-induced osteoporosis.¹⁰⁶⁻¹¹¹

Osteonecrosis is a significant problem in patients receiving high-dose glucocorticoids, particularly for treatment of SLE. Osteonecrosis is more strongly associated with the peak dose of glucocorticoid than with the cumulative dose,¹¹² perhaps owing to osteocyte and osteoblast apoptosis.⁷⁵ The presence of antiphospholipid antibodies contributes to osteonecrosis independent of glucocorticoid use. Osteonecrosis is seldom seen when the prednisone dosage is maintained at less than 20 mg/day.¹¹³

Like osteonecrosis, myopathy occurs very rarely in patients receiving glucocorticoids at low doses. In patients with inflammatory myopathy it is often difficult to disentangle ongoing muscle inflammation from glucocorticoid myopathy. Gradual muscle improvement with dose reduction is often a diagnostic clue because electromyography and muscle biopsy findings are often insufficiently specific to differentiate these two entities. Based on small studies, fluorinated glucocorticoid preparations, such as triamcinolone, are more strongly associated with myopathy than prednisone.¹¹⁴ Myopathy has been reported to occur at a dosage as low as 8 mg/day of triamcinolone after only 3 months of treatment. In general, myopathy attributable to prednisone requires a higher dose and longer duration of treatment.

Cardiovascular effects

Glucocorticoids at medium to high dose promote fluid retention based in some¹¹⁵ but not all^{116,117} studies. This can be problematic for patients with underlying heart or kidney disease, although susceptibility is modified by both glucocorticoid dose and dietary factors. Patients with essential hypertension require closer surveillance of blood pressure and may need modification of their antihypertensive regimens while receiving glucocorticoid therapy. In some studies glucocorticoids, at even low or moderate doses, have been associated with hypertension, but this may be a reflection of channeling bias due to RA disease severity.¹¹⁸ Glucocorticoids can cause sodium retention and can potentiate vasopressor response to catecholamines and angiotensin II. In patients receiving less than 10 mg/day, age and elevated pretreatment blood pressure likely better explain significant hypertension than the use of glucocorticoids.¹¹⁹ There is inconsistent information on the effects of glucocorticoids on serum lipid profiles.¹²⁰⁻¹²³ To date, randomized controlled trials have not identified low-dose glucocorticoid therapy as an additional risk factor for dyslipidemia.

Another difficult-to-study potential toxicity of low-dose glucocorticoids is the development of premature atherosclerotic vascular disease. Increasing attention to the importance of accelerated atherosclerotic disease in RA and other inflammatory conditions has raised interesting questions about the role of chronic inflammation on the vascular endothelium.¹²⁴ Although atherosclerotic vascular disease is known to be accelerated in patients with Cushing disease and at least one study showed increased carotid plaque and decreased arterial compressibility in RA patients receiving glucocorticoids,¹²⁵ there are insufficient data to confirm an independent risk in patients taking low-dose glucocorticoids, in particular. A systematic review of low-dose glucocorticoid therapy,¹²⁶ somewhat in contrast with the lipid results, reported that four out of six studies reviewed found low-dose glucocorticoid therapy to be associated with major cardiovascular events, including myocardial infarction, stroke, mortality and a composite index of cardiovascular events. Nonetheless, one of the largest and most carefully conducted cohort studies did not find an increased cardiovascular risk with dosages of less than 7.5 mg/day of prednisone.¹²⁷ There is also evidence that glucocorticoids may tend to have a protective vascular effect in persons with polymyalgia rheumatica.¹²⁸

Cardiac arrhythmias have been described during pulse-dose glucocorticoid therapy. This rare occurrence, reported mostly in patients with renal disease, calls for a preinfusion check of serum electrolyte levels and strong consideration of cardiac monitoring during infusion. The use of slower infusion rates (administration over 1 to 2 hours) may reduce this concern.

Dermatologic effects and appearance

Even at a low dose, skin thinning and ecchymoses are one of the most common glucocorticoid adverse events. A cushingoid appearance manifests as moon facies, truncal obesity, and buffalo hump and is very troubling to patients, but it is uncommon at doses below the physiologic glucocorticoid replacement range. Moon facies develops in slightly over 10% of patients receiving even short-term low-dose therapy. Use of an alternate-day schedule decreases the incidence of cushingoid appearance. Steroid acne and, to a lesser extent, hirsutism and stria are other undesirable dermatologic adverse effects that can occur even at lower doses. Glucocorticoids also impair wound healing by inhibiting the synthesis of matrix metalloproteinases and collagen.¹²⁹ Weight gain and fat redistribution occur at moderate to high doses, in particular. The effects of hyperinsulinemia on leptin, increased adipocyte conversion of cortisone to cortisol, and increased appetite all contribute to weight gain and fat redistribution.

Gastrointestinal effects

Although glucocorticoids are considerably less toxic to the upper gastrointestinal (GI) tract than nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids slightly increase the risk of adverse GI events such as gastritis, ulcers, and GI bleeding. The increased risk of GI events with glucocorticoid use is very small, with estimated relative risks varying from 1.1 (not significant) to 1.5 (marginally significant).^{130,131} In addition to reports of upper GI morbidity, there are case reports of intestinal rupture, diverticular perforation, and pancreatitis thought to be caused by glucocorticoids. Glucocorticoids frequently are used concurrently with NSAIDs in rheumatology, and the combination synergistically results in a higher risk of GI adverse events. Glucocorticoids cause a nearly twofold increased risk of GI adverse events among NSAID users,¹³² and the combined use of NSAIDs and glucocorticoids results in a more than fourfold increased risk of GI adverse events compared with nonusers.¹³¹

Infectious diseases

Moderate- to very-high-dose glucocorticoid therapy leads to an increased risk of serious infections. However, no studies have adequately explored the risk of infection in patients treated with low-dose glucocorticoids. The risk of infection appears to be lessened by initiating alternate-day therapy. The association of glucocorticoids with infectious adverse events becomes an even greater concern if glucocorticoids are used in combination with biologic antirheumatic agents.¹³³ Among patients in the Consortium of Rheumatology Researchers of North America registry who were prescribed methotrexate, TNF antagonists, or other DMARDs, low-dose prednisone use overall was not associated with increased risk of infection.¹³⁴ In a nested case-control study, the adjusted relative risk increased from 1.10 for dosages of less than 5 mg/day to 1.85 for dosages of more than 20 mg/day. Although the overall relative risk was low at 1.20, the absolute risk was high, with one additional infection seen for every 13 patients treated with glucocorticoids (at all dosage levels) for 1 year.¹³⁵ In a study of RA patients comparing

infection risk with biologic therapies to that with nonbiologic DMARDs, glucocorticoid use was the factor most associated with serious infection outcomes.¹³⁶ A meta-analysis of 71 controlled clinical trials involving over 2000 patients randomly allocated to receive systemic glucocorticoids in the setting of different diseases, the relative risk for infectious complications overall was 1.6 (95% confidence interval, 1.3 to 1.9). The rate was not increased in patients given a daily dose of less than 10 mg or a cumulative dose of less than 700 mg of prednisone.¹³⁷ Similarly, a different systematic review identified 15 studies assessing infection risk of low-dose glucocorticoid therapy in RA patients and did not find consistent associations between infection risk and low-dose glucocorticoid treatment.^{35,134-137} At higher doses, glucocorticoids appear to be a risk factor for tuberculosis.¹³⁸

Metabolic and endocrine effects

Glucocorticoid users with diabetes mellitus commonly have higher blood glucose levels while taking glucocorticoids. Moreover, in patients with early diabetes or glucose intolerance new-onset hyperglycemia or, rarely, a non-ketotic hyperosmolar state can develop *de novo*. Ketosis is very rare in glucocorticoid-associated diabetes, because the gluconeogenic and glycogenic effects of glucocorticoids offer protection against this complication. It is uncommon for frank diabetes to develop as a result of glucocorticoid therapy. A recent, small, randomized trial of short-term treatment with prednisolone 60 mg or 30 mg per day demonstrated no deterioration of glucose tolerance in patients with active RA.^{138a}

A significant concern with long-term glucocorticoid use is HPA insufficiency. HPA insufficiency is both dose and duration specific. High-dose therapy results in protracted suppression of adrenocorticotrophic hormone release and adrenal hyporesponsiveness in as little as 5 days. More typically, adrenal suppression can be detected in 6 weeks at 10 mg/day and in 4 weeks at 15 mg/day.⁶⁶ Spontaneous recovery of the HPA axis is normal in patients taking 5 mg or less of prednisone; however, even subphysiologic dosages (less than 7.5 mg/day) given for long periods may lead to HPA blunting.¹³⁹ HPA suppression is worsened if glucocorticoids are given twice daily.

Neuropsychiatric effects

Patients taking even low-dose glucocorticoid therapy report a slight increase in their overall sense of well-being, which appears to be independent of improvement in disease activity. Symptoms of akathisia (motor restlessness), insomnia, and depression are also occasionally observed in patients taking low-dose therapy. Memory impairment can occur even at low doses, particularly in older patients. Daily split-dose therapy, in particular, tends to be troublesome because the evening dose promotes sleep disturbances. True glucocorticoid psychosis is distinctly uncommon at dosages of less than 20 mg/day of prednisone.

Ophthalmologic effects

The development of posterior subcapsular cataracts is a well-described complication of prolonged glucocorticoid use. There is no minimal safe dose with respect to this complication, and reports exist of cataract formation even with the use of inhaled glucocorticoid preparations.¹⁴⁰ Although a very-low-dose glucocorticoid threshold was seen for cataracts (less than 5 mg/day) in one study,⁵⁴ cataracts rarely occur in patients taking less than 10 mg/day for less than 1 year.^{141,142} Nearly a third of RA patients taking a mean dosage of 8 mg/day for an average of 7 years developed cataracts.⁶⁷ Cortical cataracts also have also been associated with glucocorticoid use.¹⁴³

In addition to cataracts, glucocorticoid-treated patients can develop increased intraocular pressure, which can lead to visual disturbances. The development of frank glaucoma is rare, particularly with low-dose therapy, and it tends to appear in patients who are otherwise genetically predisposed.

GLUCOCORTICOID USE IN PREGNANCY

Glucocorticoids are often used in pregnant patients to control peripartum inflammatory disease activity. Although glucocorticoids are safer than many other antirheumatic agents during pregnancy, their use can cause fetal growth retardation and low birth weight of offspring. It is difficult, however, to fully discern whether these adverse fetal outcomes are caused by the glucocorticoids or by the underlying chronic inflammatory disorder. Prednisone or prednisolone is preferred over other glucocorticoids if the aim is

to treat a pregnant mother, because the placenta will convert active prednisolone back to prednisone and thereby limit fetal exposure. The American Academy of Pediatrics considers prednisone and its active metabolite prednisolone to be compatible with breastfeeding. Even at dosages above 1 mg/kg/day, the amount of glucocorticoid secreted into the breast milk is less than 10% of a nursing infant's endogenous cortisol production.

PRACTICAL RECOMMENDATIONS

Evidence-based treatment guidelines

In an era of internationally rising health care costs and highly efficacious but very expensive biologic disease-modifying agents, glucocorticoids provide an apparently inexpensive approach to management of inflammatory and autoimmune disorders. Although the cost per dose of oral glucocorticoid is low, other costs such as those associated with adverse effects must also be considered.¹⁴⁴ Monitoring for glucocorticoid adverse effects, as suggested by groups such as a EULAR task force,¹⁴⁵ may mitigate some but not all toxicities.

Once the decision is made to initiate glucocorticoid treatment, every effort should be made to use these agents as safely and effectively as possible. Accumulating data argue that more aggressive use of glucocorticoids earlier rather than later in the course of RA might be best. However, practitioners skeptical of the disease-modifying benefits of glucocorticoid therapy or excessively concerned about glucocorticoid adverse effects should strive to use the lowest effective dose. Despite the evidence and an international call to action to prevent glucocorticoid-induced osteoporosis among even long-term glucocorticoids users, fewer than half of all long-term glucocorticoid users are receiving adequate bone prophylaxis or evaluation.¹⁴⁶

Perioperative and stress-dose considerations

Long-term glucocorticoid users preparing for major surgery or undergoing considerable physiologic stress associated with severe illness should receive prophylactic stress-dose glucocorticoids, commonly in conjunction with a mineralocorticoid. Hydrocortisone at a dosage of 100 mg three times per day is empirically recommended, but for patients taking low-dose glucocorticoids or undergoing less significant physiologic insult, half this dose is often sufficient. Identifying which patients require stress-dose glucocorticoids requires consideration of both dose and duration of glucocorticoid use. Guidelines for low-dose use were discussed previously. Any person who has received more than 20 mg/day of prednisone equivalent for longer than 3 weeks or who has developed clinical Cushing syndrome should receive prophylaxis. If clinically feasible, the need for stress-dose glucocorticoids can be determined by testing for the responsiveness of the HPA axis using a low-dose synthetic adrenocorticotrophic hormone (cosyntropin) stimulation test.

Glucocorticoid use in children

Growth retardation can occur in children receiving glucocorticoids because these agents inhibit linear bone growth and delay epiphyseal closure. Regular daily administration of more than 7.5 mg prednisolone is associated with inhibition of linear growth. The mechanism of action is unknown, although suppression of growth hormone secretion and other metabolic effects can contribute. Alternate-day administration of the same total dose reduces this effect¹⁴⁷ and is preferred, if clinically practical.

Glucocorticoid withdrawal regimens and alternate-day therapy

There is little science to guide the necessary but challenging process of glucocorticoid dose reduction. In conditions such as RA, a very subtle dose reduction is most effective in promoting eventual glucocorticoid discontinuation. In SLE and other diseases in which immune complexes play a significant role in pathogenic consequences, alternate-day therapy is a consideration once disease control is achieved. Alternate-day therapy serves to minimize HPA axis suppression and, in turn, certain adverse effects, and it affords a reduction in cumulative glucocorticoid dose. In RA, however, alternate-day therapy often is not well tolerated due to an increase in joint symptoms on days off therapy.

Steroid withdrawal syndrome is not clearly associated with HPA insufficiency but presents as extreme weakness and arthralgias. Glucocorticoid tapering from 20 mg/day by increments of 2.5 mg/day every 2 weeks resulted in rebound deterioration in over half of RA patients.⁴⁶ Although

convenience and individual patient disease response should be accommodated, a relatively stable decrement of 10% to 20% of glucocorticoid dose every 1 to 2 weeks is recommended until the dose reaches 10 mg; then tapering should proceed more slowly for long-term users. Indeed, the difficulty in withdrawing patients from glucocorticoids is sometimes cited as a compelling reason for not initiating them.¹⁴⁸ Many rheumatologists report significant difficulties in tapering glucocorticoids in most RA patients, and

abrupt withdrawal can result in dramatic flares in disease activity. Thus it is recommended that in patients receiving long-term low-dose glucocorticoids for inflammatory arthritis or polymyalgia rheumatica the dose be lowered in increments as small as 1 mg/mo (sometimes facilitated by cutting the dose on alternate days) to maximize their prospects for successful withdrawal. However, further research on appropriate tapering regimens is greatly needed.

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Nonimmunosuppressive disease-modifying antirheumatic drugs

■ VIVIAN P. BYKERK

- Several nonimmunosuppressive disease-modifying antirheumatic drugs (DMARDs), including antimalarials, parenteral gold, sulfasalazine, tetracyclines, and bucillamine, are still actively being used and continue to be investigated for the treatment of rheumatic diseases.
- Rheumatic diseases amenable to treatment with these nonimmunosuppressive DMARDs include rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, and in some cases, osteoarthritis.
- DMARDs have a superior safety profile from the standpoint of risk for infection or malignancy.
- DMARDs also have relatively low cost.
- Because the precise role of DMARDs in the sequence of treatment strategies is still not entirely agreed on, further studies are needed. For example, the comparative effectiveness of combinations of DMARDs versus newer biologic therapies or immunosuppressive oral therapies should be studied in the context of cost-effectiveness, ability to halt damage and improve function and quality of life, and relative safety.
- Of all these DMARDs, the role of hydroxychloroquine is most intriguing given its potentially additive metabolic benefits.

INTRODUCTION

During the last 10 years, paradigm shifts in treating rheumatoid arthritis (RA) have included a treat-to-target approach in which the goal of therapy for RA has been to achieve remission and, when not possible, achieve a state with low disease activity instead.¹ Although most practice recommendations and guidelines propose that methotrexate (MTX) should be the first-line therapy for inflammatory arthritis, nonimmunosuppressive disease-modifying antirheumatic drugs (DMARDs) have an ongoing role in the treatment of RA, inflammatory arthritis, and in the case of hydroxychloroquine (HCQ), systemic lupus erythematosus (SLE) as well. Furthermore, in some patients who cannot tolerate MTX or its use is contraindicated, other nonimmunosuppressive DMARDs can be viable and effective therapeutic options.

Some of these DMARDs have been studied more recently, such as HCQ and sulfasalazine (SSZ), whereas for others such as parenteral gold, tetracyclines, and bucillamine (BUC), fewer recent studies have been conducted and these drugs are being used less often for a variety of reasons. Although they are unrelated, all have the ability to suppress inflammation, improve symptoms and function, and possibly limit joint damage as evidenced by reduced progression of radiologic damage on radiographs of patients with RA.

Unlike the newer biologic drugs and corticosteroids, these DMARDs have a slower onset of action. Patients often need to wait at least 12 weeks for these agents to take effect and reduce the signs and symptoms of the inflammatory manifestations of arthritis and rheumatic diseases. These agents may also be reserved for the management of early and milder disease. In the case of moderate to severe RA, other therapies such as MTX are more often recommended because the DMARDs described in this chapter typically have a more delayed action, insufficient suppression of disease activity when used as monotherapy, and limited evidence of prevention of progression of joint damage. The exception is parenteral gold salts, which are the only agents that have been shown to slow radiographic damage and induce

remission in early RA. Interest in antimalarials, primarily HCQ, has been renewed because they have benefits in a number of rheumatic diseases and may have additional metabolic and antithrombotic benefits. Antimalarials and SSZ are no longer the initial treatment of choice as monotherapy for RA. Nonetheless, when taken in combination with MTX, these agents are still often used for the treatment of inflammatory arthritis and related conditions. Gold salts, tetracyclines, and BUC are being used less often for rheumatic diseases but merit discussion as treatment options. Based on published evidence over the past 15 to 20 years, tetracyclines, particularly minocycline, are used as an alternative to MTX for early arthritis, primarily as a result of a series of studies indicating a positive effect on RA. Studies of doxycycline have generated interest in their use as possible adjunctive therapy for osteoarthritis (OA), although it is doubtful that these agents are having an antimicrobial effect. In this chapter nonimmunosuppressive DMARDs are reviewed.

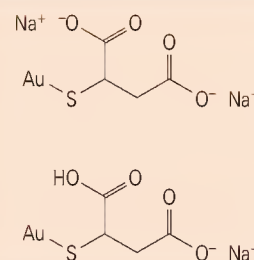
PARENTERAL GOLD

Introduction

Since 1935, following a report from Jacques Forestier,² injectable gold compounds came into use and have been successful in treating RA. Gold sodium aurothiomalate has been the most extensively studied by scientists and clinicians. In the 1980s, the oral gold compound auranofin was used temporarily as an alternative to injectable gold but fell out of favor because of its lower efficacy and higher rate of side effects. Of the injectable gold compounds, gold sodium thiomalate, which is 50% gold by weight, continues to be the preferred gold compound for the treatment of RA. The application of gold compounds is called “chrysotherapy.”

Use of gold is now uncommon despite evidence of the clinical efficacy of injectable gold sodium aurothiomalate. However, several authors contend that given the benefits shown in several placebo-controlled trials, injectable gold compounds can still play a valuable role and indeed may be the correct first choice for the management of RA.³

STRUCTURE OF SODIUM AUROTHIOMALATE



Pharmacology

After intramuscular (IM) injection, gold is rapidly absorbed into the circulation, where most of it is bound to albumin.⁴ Its peak serum concentration is reached within 2 to 4 hours after injection.⁵ Gold is slowly eliminated from the body, mostly via the kidney and the remainder in feces. It can be found in tissues up to 20 years after the last dose.⁶

Mode of action

The exact mechanisms responsible for the therapeutic effects of gold on RA are not fully understood. Several lines of evidence suggest that the free thiol group plays a key role in reducing oxidative stress.⁷ Studies evaluating the effect of gold in the synovium suggest that it reduces monocytes and macrophages, as well as the proinflammatory cytokines interleukin-1 α (IL-1 α), IL-1 β , IL-6, and tumor necrosis factor- α (TNF- α).^{8,9}

Efficacy

IM gold reduces the number of inflamed joints and decreases laboratory measures of inflammation when compared with placebo. In a study comparing IM gold with MTX 15 mg/wk, IM gold appeared to be as effective as MTX.^{10,11} Observational studies and short-term trials indicate that gold slows radiologic progression.¹² In a 2-year, randomized, placebo-controlled multicenter trial of combination MTX and IM gold therapy, 65 RA patients who had a suboptimal response to 12 weeks or more of MTX therapy were randomly assigned to add weekly IM gold or placebo to MTX. Adding IM gold weekly resulted in significant clinical improvement. Named for the American College of Rheumatology, the ACR20, ACR50, and ACR70 response rates in the IM gold patients compared favorably with those in the placebo group. IM gold–related adverse events led to discontinuation in 11% of the gold group over the course of the study.¹³

Toxicity

In general, IM gold leads to higher dropout rates because of its side effects in comparison to other DMARDs, including MTX.¹⁴ In one study 19% of patients had reactions to gold sodium aurothiomalate.¹⁵

The most common complications are dermatitis (rash, pruritus) and stomatitis; however, serious renal and hematologic reactions can occur (Table 55.1). Cutaneous reactions and occasionally proteinuria and a reduction in white cell counts can often be managed by temporarily stopping use of the drug and continuing at a lower dosage.^{16,17} Proteinuria occurred in clinical trials in less than 5% of patients. Mild proteinuria may resolve spontaneously even after decreasing the dose, but nephrotic syndrome has been described and aurothiomalate should be stopped if severe proteinuria develops.¹⁸

Approximately 5% of patients treated with aurothiomalate experience nitritoid reactions consisting of transient symptoms of flushing, sweating, dizziness, nausea, hypotension, and malaise that occur within minutes of drug administration.¹⁹ Patients who use angiotensin-converting enzyme inhibitors appear to be especially at risk and should receive gold therapy while in the recumbent position. Aplastic anemia is the most serious and rarest complication of gold treatment. Between 1965 and 1971 the British Committee on Safety of Medicines reported nine fatal episodes of aplastic anemia in patients treated with injectable gold. Thrombocytopenia, the most common hematologic effect that occurs with injectable gold therapy, occurs

in less than 5%. It will usually develop within the first 6 months of treatment and is generally related to immune-mediated destruction with an active bone marrow.²⁰ Other rare complications that have been described are enterocolitis, hepatotoxicity, pancreatitis, peripheral neuropathy, cranial nerve palsies, and a Guillain-Barré–like syndrome. Chrysiasis, a slate-gray skin pigmentation of sun-exposed skin that develops after long-term parenteral gold therapy, was recently reported to occur in a patient after laser therapy.²¹ Limited published information is available on the safety of gold in pregnancy,²² but it may be a treatment option in women planning pregnancy.²²

Dosage and monitoring

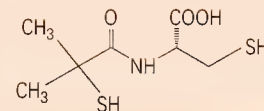
An initial dose of 10 mg, followed by a 25-mg dose the next week, is typically given to test for possible hypersensitivity. Thereafter, 50 mg/wk is given until disease activity is sufficiently reduced or until 20 weekly doses of 50 mg have been administered. Clinical effect may be delayed for 12 to 20 weeks. Once a good clinical response is achieved, the dose should be reduced to a maintenance level (often 50 mg monthly) by increasing the interval between injections up to once per 6 weeks. Regular blood tests to detect thrombocytopenia, anemia, and leukopenia and urinalysis to check for proteinuria are recommended before each injection.

BUCILLAMINE

Introduction

BUC is a DMARD known to be an analogue of D-penicillamine that was introduced in the 1980s for the treatment of RA. D-Penicillamine was historically used as a DMARD in many Western countries during the 1970s and 1980s. Because of only moderate efficacy and a disproportionately high incidence of side effects, it was effectively abandoned in place of more effective DMARDs such as MTX. BUC reportedly has fewer side effects than D-penicillamine does and has been used widely as one of the first-line DMARDs for RA in Japan and Korea. It is approved in Asia only for the treatment of RA.

STRUCTURE OF BUCILLAMINE



■ TABLE 55.1

Adverse reactions reported with the use of parenteral gold

Skin and mucous membranes	Pruritus and rash (30%) ranging from simple erythema to exfoliative dermatitis and mucous membrane lesions (20%), including stomatitis
Hematologic	Leukopenia (2%), thrombocytopenia (<5%), eosinophilia, agranulocytosis, and rarely aplastic anemia
Renal	Proteinuria (10%-15%), nephrotic syndrome, acute renal failure
Allergic	Anaphylactoid and vasomotor (nitritoid) reactions (5%)
Gastrointestinal	Metallic taste, diarrhea, enterocolitis, cholestatic jaundice, transaminitis, pancreatitis (<5%)
Chrysiasis	Affects skin and mucous membranes. Corneal gold deposits have been noted in some patients
Neurologic (rare)	Peripheral neuropathy, cranial nerve palsies, a Guillain-Barré–like syndrome, encephalitis
Miscellaneous rare reactions	Pulmonary infiltrates

Modified from <http://products.sonofi.co/en/myochrysine.pdf>.

Pharmacology

BUC, a thiol compound [N-(2-mercapto-2-methylpropionyl)-L-cysteine], differs from D-penicillamine by the presence of two free sulfhydryl groups and has two S-H bonds in its chemical structure.²³

Mode of action

BUC is considered to be a DMARD with immunologic effects. It has been shown to suppress IL-6 and IL-8 production by synovial cells in vitro and is thought to have pharmacologic actions that are different from those of D-penicillamine.²⁴ In an in vitro study of its effect on T-cell proliferation, cytokine production, and migration of T cells, BUC significantly inhibited T-cell proliferation, reduced the expression of CD44 on T cells, and inhibited the production of IL-2, interferon- γ (IFN- γ), TNF- α , and IL-6, thus indicating that it is an inhibitor of type 1 T helper–type cytokine production, proinflammatory cytokine production, and transendothelial migration of T cells.²⁵ The latter appears to be mediated partly through the reduced expression of CD44, an adhesion molecule on the T-cell surface.

Efficacy

The beneficial effects of BUC for the treatment of RA have been published in several observational studies and clinical trials, with varying effects reported. In a retrospective cohort study of 86 patients with active RA who

received BUC between 1998 and 2004, 20% reported improvement from 44% to 56% in ACR core set measures 6 months after initiation of therapy, 50% reported improvement of between 22% and 34% in ACR core set measures, and 70% reported improvement between 11% and 19% in ACR core set measures 6 months after initiation of therapy.²⁶ A 16-week open-label trial of BUC (300 mg/day) suggested that this agent is effective as a slow-acting drug for RA in patients who had previously failed gold salt or D-penicillamine therapy.²⁷ In a small randomized controlled trial (N = 46) of D-penicillamine and BUC, BUC was found to be at least as effective as D-penicillamine in improving the swollen joint count, tenderness score, morning stiffness, modified health assessment questionnaire, and erythrocyte sedimentation rate (ESR). It was more effective in terms of improvement in the tender joint count, grip strength, C-reactive protein, and rheumatoid factor titer. However, responses were low, with only 27% of the BUC group and 33% of the D-penicillamine group responding to treatment.²⁸

In a cross-sectional analysis from the IORRA study, a long-term observational database, responses to BUC treatment were noted to be better in males, in patients with a shorter duration of illness, and in those who were rheumatoid factor negative. In a longitudinal analysis from the same study, European League Against Rheumatism improvement criteria were higher in patients receiving BUC (41.0%) than in those receiving MTX (33%) or SSZ (26%).²⁹

A multicenter trial of BUC known as the SNOW study was conducted in patients with early RA. In this 24-month study of 81 DMARD-naïve patients with early RA, 87.5% showed moderate improvement in their 28-joint disease activity score (DAS28). After 24 months of BUC therapy, 7 patients (43.8%) met the remission criterion of a DAS28 lower than 2.6, and 60.5% of patients continued BUC either as monotherapy or in combination with other DMARDs after 24 months.³⁰ A multicenter, double-blind controlled trial studying a combination of MTX and BUC was performed in 71 patients with active early RA within 2 years of onset. Patients received 8 mg MTX with 5 mg folic acid per week, 200 mg BUC per day, or both. After 96 weeks they noted an ACR20 response rate of 79.2% in the combination group but only 44% in the MTX group ($P = .01$) and 46% in the BUC group ($P = .02$). Also, the combination group exhibited significantly less radiographic progression (total Sharp score over a 96-week period of 12.6 ± 9.0 versus 28.0 ± 28.3 for the single-therapy arms; $P = .05$). No increased rate of adverse events was noted in the combination group in comparison to the single-therapy group.³¹ However, in a recent review examining changes in the use of nonbiologic DMARDs in Japan, use of BUC alone appeared to be decreasing and use of MTX appeared to be increasing. BUC was also being more often used in combination with MTX.³²

Adverse effects

Proteinuria is reported to be the most frequent adverse effect of BUC. In one report, 10 cases of nephrotic syndrome were noted. Most cases occurred within the first 4 months of use. Discontinuation led to resolution of this complication within 1 year. In patients with BUC-induced proteinuria and membranous nephropathy, immediate withdrawal of BUC resulted in complete resolution of the proteinuria without any deterioration in renal function. Thus, monitoring of urinary protein is important when using this agent.³³ BUC-induced yellow nail syndrome (a triad of yellow nails, lymphedema, and pulmonary manifestations) was recently described in a review of 36 cases reported mostly in Japanese medical journals.³⁴ Most of these patients (90%) showed improvement in their yellow nails after discontinuation of BUC, but the lymphedema and pulmonary manifestations improved only in 31% and 35% of patients, respectively. Other rare side effects include skin disorders manifested as a rash, which can be vesicular or involve swelling of the lips. Less frequently reported adverse effects include hepatitis³⁵ and bone marrow suppression.³⁶ At least 15 cases of BUC-induced pulmonary injury have been reported. Advanced age was associated with the development of severe interstitial pneumonia, and pulmonary complications were reported to be resistant to corticosteroids and life-threatening, especially in the elderly.^{37,38} One case of bronchiolitis obliterans-organizing pneumonia has been reported during treatment with BUC.³⁹

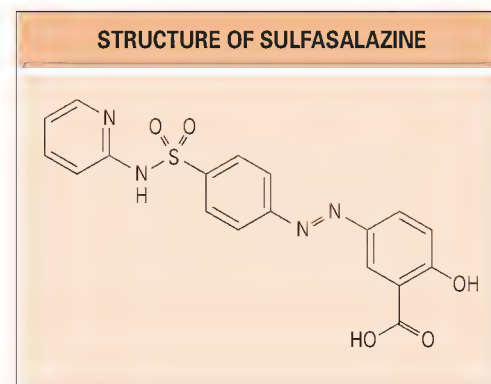
Dosage and monitoring

Typical doses of BUC range from 100 to 300 mg daily. Monitoring should include regular assessment of blood counts and urinalysis for proteinuria. Patients should be evaluated for efficacy by 3 months to determine their response to this therapy.

SULFASALAZINE

Introduction

In 1938 Svartz⁴⁰ first synthesized what is now called SSZ. SSZ was introduced as a drug for RA only in the late 1970s. McConkey⁴¹ and others reported beneficial effects of SSZ for RA with fewer side effects than with the then-standard drugs gold and penicillamine. Because of initial underwhelming responses to SSZ in patients with severe RA, it fell out of favor and became a treatment of inflammatory bowel diseases. Studies in the Netherlands in patients with new-onset RA demonstrated it to be effective, however, and it continues to be studied and used in combined regimens to this day.^{42,43}



Pharmacology

SSZ is a prodrug that is metabolized in the large intestine by bacterial enzymes into sulfapyridine, which is absorbed, and 5-aminosalicylic acid (5-ASA), which is excreted mostly via the bowel. Any intact SSZ that is absorbed is highly protein bound and excreted unchanged in urine with an elimination half-life of 5 hours.⁴⁴ Sulfapyridine and SSZ have been found in synovial fluid at slightly lower concentrations than in plasma.⁴⁵

Mode of action

The mode of action of SSZ is unclear. Intact SSZ, sulfapyridine, and 5-ASA are all biologically active, but sulfapyridine seems to be the most relevant component in the treatment of RA. Recent studies show scavenging effects of SSZ and its metabolites on reactive oxygen and nitrogen species, so SSZ may mediate its antiinflammatory effects through prevention of oxidative/nitrate/nitrosative damage.⁴⁶ Earlier studies suggested that SSZ may reduce inflammation in RA through the effects of sulfapyridine by reducing secretion of the inflammatory chemokines IL-8, GRO- α , and monocyte chemoattractant protein-1.⁴⁷

Efficacy

Placebo-controlled trials have shown a benefit of 2 g/day of SSZ in reducing the inflammatory activity and radiographic progression of RA.^{12,48} SSZ is likely to be as effective as lower doses of MTX, although it is usually no longer recommended as monotherapy for RA. It is still considered a treatment option as monotherapy for spondyloarthritis.^{49,50} In observational studies of RA, SSZ tends to be used in seronegative patients with lower disease activity, and even so, the effectiveness of SSZ is slightly less than that of MTX.⁵¹ Several randomized controlled trials of SSZ versus other DMARDs, either alone or in combination, have demonstrated effectiveness of this agent.⁵²⁻⁵⁵ A meta-analysis of four randomized trials studying the effect of combined MTX and SSZ versus SSZ monotherapy in naïve and experienced patients showed that the combination was more effective in patients who had an inadequate response to SSZ monotherapy. However, in patients who had never received either drug, responses to SSZ were similar to those to lower-dose MTX, and the combination of SSZ and MTX was more effective in SSZ/MTX-naïve patients.⁵⁶ Four randomized controlled trials were identified to compare the efficacy of combination MTX and SSZ with that of either drug alone. Two parallel trials were performed in patients naïve to both drugs, and two add-on trials were performed in SSZ failures. In the trials with naïve patients, the mean improvement in DAS with combination MTX and SSZ pointed to an additive effect by SSZ. In the trials with patients who previously failed to respond to SSZ, the mean changes in DAS for combination MTX and SSZ therapy also indicated additive efficacy. These authors concluded that in patients with RA, addition of MTX to SSZ is a beneficial therapeutic option for SSZ failures whereas the combination

of MTX and SSZ in DMARD-naïve patients has no added value. In a more recent trial of patients with very early RA, induction therapy with a combination of DMARDs, including HCQ and SSZ together with temporary use of glucocorticoids, was found to be better than MTX monotherapy in inducing remission in RA.⁴³

SSZ may be most effective in the treatment of RA when used in combination with other DMARDs as part of a dynamic treatment strategy aiming for tight control with the goal of reaching a target of low disease activity or remission. Overall, taking evidence of the efficacy of SSZ into account in the treatment of RA, current recommendations favor initial MTX over SSZ. If SSZ is to be used, it should be considered as part of combination DMARD therapy because of favorable long-term clinical and radiologic efficacy and low toxicity profile.⁵⁷⁻⁵⁹

In clinical studies of axial spondyloarthritis, modest benefits of SSZ have been demonstrated. In a recent study comparing the effectiveness of SSZ and etanercept, more patients receiving etanercept reached clinical and magnetic resonance imaging remission at week 48 than did SSZ-treated patients. However, no difference was found in the flare rate in patients receiving these two treatment options, thus suggesting that SSZ may have some efficacy in this disease.⁶⁰

Toxicity

The most common adverse effects of SSZ are minor gastrointestinal, central nervous system, and cutaneous side effects. The withdrawal rate because of side effects is approximately 25%.⁶¹ Symptoms include anorexia, headache, vomiting, diarrhea, gastric distress, and nausea. Pruritic rash occurs in about 5% of patients. Rash is more likely to occur in those with a history of sulfa allergy. Leukopenia occurs in less than 3% of patients and is usually mild and transient, but serious agranulocytosis, a rare event, has been observed, generally in the first 6 weeks of treatment.⁶² Less frequently reported problems include a decrease in immunoglobulins, megaloblastic anemia, hepatotoxicity (usually mild), eosinophilic pneumonia, and anaphylactic reactions.^{63,64} Temporary oligospermia may occur in men taking SSZ. SSZ is generally thought to be safe during pregnancy but should be given with a folic acid supplement. In some cases of milder disease it could be used as an alternative to MTX in women who want to become pregnant during treatment. SSZ should be used cautiously in women who are breastfeeding because sulfapyridine concentrations in breast milk are 40% to 50% of those found in maternal serum.⁶⁵

Dosage and monitoring

The standard dose of SSZ is 2 g/day, but it may be increased to 3 g/day. Nausea is usually transient during the first few days of treatment or when the dosage is increased and can be prevented by using a protocol of gradually increasing the dosage (e.g., start with 0.5 g/day and increase to 2 g/day over a period of 3 weeks). Patients who start SSZ should be instructed to consult a physician if they have a fever with or without a sore throat because this could be a manifestation of underlying agranulocytosis. Routine laboratory tests are recommended once monthly in the initial 3 months and once every 3 months during long-term treatment.

HYDROXYCHLOROQUINE

Introduction

Antimalarials have been used for rheumatic diseases since the early 1950s after several case series reported various antimalarials to be efficacious in

the treatment of RA. When compared with other immunosuppressive and biologic therapies, the relative effectiveness of HCQ is smaller; however, HCQ is often used as adjunctive therapy in combination regimens for RA and is the most common antimalarial used for SLE. Another antimalarial—chloroquine—though still available, is rarely used given the superior safety profile of HCQ.

Pharmacology

After oral absorption ($\approx 70\%$),⁶⁶ HCQ is cleared rapidly from plasma and distributed in tissues, including muscle, liver, spleen, kidney, lung, and hematopoietic cells. Steady-state concentrations are not achieved for at least 3 months.⁶⁷ Higher loading dosages are associated with more rapid beneficial clinical effects, but also with more frequent adverse gastrointestinal side effects, and are therefore not usually recommended. Excretion of HCQ is mostly by renal clearance. Its elimination half-life is approximately 40 days. Small amounts of chloroquine (a related antimalarial) were found in plasma, red blood cells, and urine several years after the last dose of chloroquine. HCQ may lead to increased plasma digoxin levels⁶⁸ and can increase the bioavailability of β -blockers.⁶⁹ Concomitant use of MTX does not appear to affect the pharmacokinetics of HCQ.⁷⁰

Mode of action

Antimalarials may have varying modes of action. Initially, antimalarials were thought to act by affecting phagosomal and lysosomal function.⁷¹ However, recent studies suggest that antimalarials exert an impact through inhibition of intracellular Toll-like receptors (TLRs), particularly TLR9.⁷² This effect on TLRs may mediate the effects of HCQ in patients with SLE, RA, and possibly also diabetes and hyperlipidemia.⁷¹ HCQ-related clinical improvement has also been correlated with reductions in IFN- α levels, thus underscoring the importance of these cytokines in the pathogenesis of SLE.⁷³ In addition, recent data have shown that antimalarials may have a potential role in treating antiphospholipid syndrome by affecting annexin-5 binding.⁷⁴ A recent study by Rand and colleagues⁷⁵ showed that HCQ abrogates the binding of aPL- β_2 GPI complexes to the phospholipid bilayer of target cells. Recent data in patients with SLE also suggest that those who reach a target blood concentration closer to 1000 ng/mL have fewer flares of SLE.⁷⁶

Efficacy

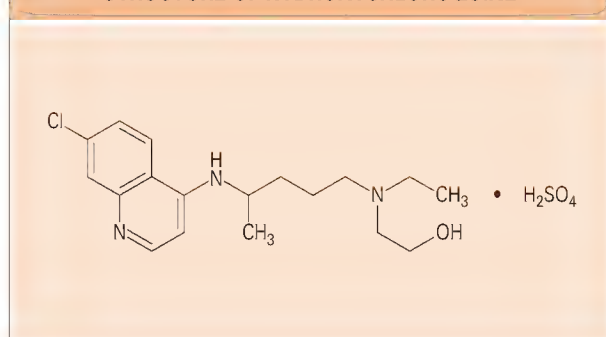
Rheumatoid arthritis

A meta-analysis evaluating the efficacy of antimalarials for RA indicated that they have moderate efficacy when used alone for the treatment of RA.⁷⁷ In an analysis of randomized trials of HCQ versus placebo in 300 patients assigned to HCQ therapy and 292 to placebo, a statistically significant benefit was observed when HCQ was compared with placebo. The standardized mean differences for the clinical outcome measures ranged from -0.33 to -0.52 , and these differences were statistically significant. Statistically significant differences were also observed for ESR. Overall withdrawals because of lack of efficacy were significantly more frequent in the placebo group. No differences were observed in withdrawals as a result of toxicity. Of note, no study has shown that HCQ monotherapy induces remission of RA or that it prevents radiographic damage. Currently, HCQ is typically part of a combined DMARD regimen for the treatment of RA known as “triple therapy,” which includes SSZ, MTX, and HCQ. This regimen has been included in several studies evaluating treat-to-target strategies. They were outlined in the section on SSZ in this chapter.

Systemic lupus erythematosus

Studies proving HCQ to be effective in the management of SLE were first reported in the early 1990s, and as a result, HCQ is commonly used for the treatment of joint and cutaneous manifestations of the disease, as well as to prevent disease flares.⁷⁸ HCQ is commonly used for SLE and has been shown to markedly improve disease prognosis.⁷⁹ A systematic review concluded that HCQ is an effective and safe medication to administer to patients with SLE and that its use should be encouraged at all stages of disease.⁸⁰ Despite data in animal studies proposing that there may be a rationale for HCQ playing a role in treating antiphospholipid syndrome, there is limited experimental and clinical evidence of its antithrombotic effects, and at this point it could be considered as adjunctive therapy because it is not associated with major bleeding side effects. Further controlled studies are needed to establish the efficacy and safety of HCQ for the management of refractory antiphospholipid syndrome.⁸¹

STRUCTURE OF HYDROXYCHLOROQUINE



Metabolic effects

In patients with comorbid cardiovascular disease, diabetes, and dyslipidemia associated with these diseases, there may be a rationale to use HCQ for its purported metabolic benefits.⁸² HCQ also has known benefits in reducing some traditional cardiovascular risk factors, such as hyperlipidemia and diabetes mellitus, and may have a role as an antithrombotic drug in patients with SLE and those with antiphospholipid antibodies.⁷⁹ In a retrospective cohort of 1127 adults with newly diagnosed RA studied in an administrative database, patients receiving HCQ had a lower incidence rate of diabetes than did those who did not receive it.⁸³ This benefit has also been confirmed in a larger study showing a reduced risk for diabetes in patients initiating HCQ versus other nonbiologic DMARDs.⁸⁴ Other studies suggest that HCQ may reduce the risk for future development of diabetes in RA patients.⁸³ It has also been associated with lower fasting glucose levels in both RA and SLE patients⁸⁵ and a more favorable lipid profile, including reduced low-density lipoprotein and triglycerides and increased high-density lipoprotein.⁸⁶

Toxicity

Antimalarials are considered to be among the safest of drugs used for RA. The most common side effects involve the gastrointestinal tract (nausea, anorexia, muscle-related abdominal cramps in <10%), the skin (especially a pruritic rash in <5%), and the eyes (<0.1%).⁸⁷ Retinopathy, which can lead to impaired vision, appears to be extremely rare, especially in the first 5 years of therapy.⁸⁸ Figure 55.1 shows examples of how the retina can be affected by antimalarials.⁸⁹ Screening guidelines tailored to different ages and risk groups have been published.⁹⁰ An uncommon but important side effect of antimalarials is neuromyotoxicity with proximal lower extremity weakness, normal creatine phosphokinase, and abnormal muscle and nerve biopsy results.^{91,92} Therapy with HCQ is thought to be safe during pregnancy and lactation.⁹³⁻⁹⁵



Fig. 55.1 Examples of retinal changes induced in susceptible patients treated with antimalarial agents. (From Shroyer NF, Lewis RA, Lupski JR. Analysis of the ABCR [ABCA4] gene in 4-aminoquinoline retinopathy: is retinal toxicity by chloroquine and hydroxychloroquine related to Stargardt disease? *Am J Ophthalmol* 2001;131:761-6).

Dosing of hydroxychloroquine

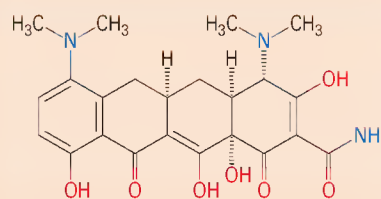
Revised recommendations have been published indicating that the dose of HCQ should be reduced to 6.5 mg/kg/day in people whose lean body weight is less than 60 kg (135 lb). Thus, most males less than 163 cm (5 feet 4 inches) tall or women less than 167 cm (5 feet 6 inches) tall would need their dose reduced.⁹⁰ Ototoxicity from antimalarials has been reported but is considered to be rare.⁹⁶ Symptoms of ototoxicity can occur quickly—within 24 hours after initiation of an antimalarial drug—but these complications are more often reported after at least 1 month of antimalarial drug use.

TETRACYCLINES

Introduction

Tetracyclines were first considered as possible antibiotic therapy for RA in the 1960s when RA was hypothesized to be caused by infection with *Mycoplasma* or similar organisms. Two decades later, Brown and Scammell used antibiotics (not only tetracyclines) for the treatment of RA and published their results in a lay textbook.⁹⁷ This caused significant interest in patients living with arthritis, and thus research involving antibiotics was reinitiated in the 1980s to test new semisynthetic tetracyclines for the treatment of RA when they were discovered to have antiinflammatory, immunomodulatory, and chondroprotective properties.⁹⁸ Minocycline and doxycycline were shown to have modest clinical benefit in RA. Yet despite positive reports of the benefits of tetracyclines, the use of MTX and biologic agents is greater given their additional benefit of halting radiographic progression and larger beneficial effects on clinical outcomes. Furthermore, the use of tetracyclines has been hampered by reports of hyperpigmentation and drug-induced lupus. In one report of 27 patients who experienced hyperpigmentation with minocycline, this was the main reason for stopping use of this drug (41%).⁹⁹ Hyperpigmentation has been reported in many tissues, including bone, as was reported in a 55-year-old woman undergoing total knee arthroplasty.^{100,101} Given what has seemed to be modest effects of these tetracyclines clinically and because of the unproven effect of their halting radiographic damage, it remains to be determined whether tetracyclines will have a significant role in patients with RA or other rheumatic conditions. Some propose that there may be potential for their use as a disease-modifying drug for OA because of their ability to inhibit matrix metalloproteinase (MMP). Others argue that therapies for OA directed at cartilage protection are essentially futile.¹⁰² This section of the chapter reviews issues involving the use of tetracyclines, particularly minocycline and doxycycline, for rheumatic diseases.

CHEMICAL STRUCTURE OF MINOCYCLINE



Pharmacology and drug interactions

Tetracyclines are readily absorbed from the gastrointestinal tract; they circulate bound to plasma proteins. Tetracyclines are concentrated in the liver in bile and excreted in both urine and feces in their active form (serum half-life of 11 to 22 hours in individuals with OA and normal renal function). In subjects with impaired renal or hepatic function, the half-life has been shown to vary from 11 to 69 hours. Absorption is not affected by most types of food but is impaired by aluminum-containing compounds and by calcium, magnesium, and iron preparations. Food containing calcium (dairy products) may also affect absorption. Tetracyclines form a stable calcium complex in bone-forming tissue and can cross the placenta, thus potentially negatively affecting development of the fetal skeleton. They may also produce permanent yellow, gray, or brown tooth discoloration and should not be administered to children or pregnant women.¹⁰³

Because tetracyclines can depress plasma prothrombin activity, patients taking warfarin may need their dose decreased. For reasons that are unclear, oral contraceptives have been shown to be less effective in patients treated with tetracyclines; additional contraceptive measures should be recommended in patients taking both together.¹⁰⁴

Tetracyclines for the treatment of rheumatoid arthritis

Efficacy data

Randomized controlled trials of minocycline

To date, four large double-blind, randomized clinical trials have used minocycline for RA.¹⁰⁵⁻¹⁰⁸ Three of these trials were conducted in the United States and one in Europe (Table 55.2). Overall, the results are consistent among the four studies and favor the use of minocycline for the treatment of RA to improve clinical and laboratory parameters. In a second study by O'Dell and colleagues from the RAIN Network, an even better response to minocycline than to HCQ was demonstrated. In two of these studies O'Dell and colleagues were able to gather longitudinal data on their patients.¹⁰⁹ Genetic studies were performed in the Minocycline in Rheumatoid Arthritis (MIRA) study; white subjects with the shared epitope were more likely to respond to minocycline treatment than were those without it.¹¹⁰

Randomized controlled trials of doxycycline

Two small double-blind, randomized clinical trials of short duration in which doxycycline was used for RA have also been published.^{111,112} In these studies doxycycline failed to reduce either disease activity or joint

destruction. Thus it is unlikely that further studies of doxycycline for the treatment of RA will be undertaken.

In one trial conducted for 2 years that included 66 early rheumatoid factor–positive DMARD-naïve patients with RA, subjects were randomized to (1) oral MTX alone, (2) 20 mg oral doxycycline twice daily with oral MTX, or (3) 100 mg oral doxycycline twice daily with oral MTX. The results showed that initial therapy with MTX plus doxycycline was superior (based on an ACR50 response) to treatment with MTX alone. These authors concluded that because the therapeutic responses to low-dose and high-dose doxycycline were similar, the antimetalloproteinase effects of tetracyclines may be a more important mechanism than the antibacterial effects in patients with RA.¹¹³

Meta-analysis of minocycline and doxycycline for rheumatoid arthritis

A meta-analysis of the treatment of RA with tetracyclines has since been conducted and has integrated the results from randomized controlled trials studying tetracyclines (one tetracycline study, six minocycline studies, and three doxycycline studies).¹¹⁴ It included a review of data reported on 535 patients. The investigators confirmed that a small reduction in tender and swollen joint counts was found in tetracycline-treated patients as opposed to those treated with placebo. In addition, a marked reduction in the ESR was noted in the tetracycline-treated group, although these effects were more evident in the subgroup of patients with early rheumatoid factor–positive disease (disease duration <1 year). Minocycline was found to be more effective than doxycycline. No difference was found in radiologic progression (erosions and joint space narrowing) between both treatment groups, which could be due to true lack of efficacy or the result of patient selection (milder disease activity). Moreover, radiographic outcome was not the primary endpoint, and these studies could have been underpowered to detect an effect. In summary, the data modestly favor the use of minocycline over the control treatment groups for RA.

Long-term data

Long-term efficacy data have been systematically assessed only in the studies of O'Dell and colleagues.^{106,109} Four years later, more patients randomized to minocycline in the first study were still receiving this compound or were in remission (or both) than were those randomized to placebo. Efficacy was still observed in the second study 2 years later.

Toxicity data

In terms of toxicity, the MIRA study reported some adverse reactions, but they were comparable in frequency and severity in the placebo- and minocycline-treated patients. In contrast, in the study from the Netherlands,

TABLE 55.2
Outcome data for randomized clinical trials of minocycline for rheumatoid arthritis

	Kloppenburg trial (N = 50) ¹⁰⁵	MIRA study (N = 219) ¹⁰⁷	RAIN network minocycline study 1 (N = 46) ¹⁰⁸	RAIN network minocycline study 2 (N = 80) ¹⁰⁶
Trial location	Netherlands	USA	USA	USA
Trial design	6-mo multicenter RCT; 200 mg minocycline vs. placebo	48-wk multicenter RCT	6-mo multicenter RCT, 100 mg minocycline bid vs. placebo	2-yr multicenter RCT, 100 mg minocycline bid vs. 200 mg hydroxychloroquine bid
Patient group	Established RA >10-yr duration, failed ≥1 DMARD	Established RA, failed ≥1 DMARD	DMARD naïve, IgM rheumatoid factor positive; <1 yr of disease duration	DMARD naïve, IgM rheumatoid factor positive; <1 yr of disease duration
Background DMARDs allowed	Yes	No	No	No
Results	Statistically significant reductions in Ritchie articular index, ESR, and IgM rheumatoid factor (all at least $P \leq .01$); radiographic outcomes showed no difference between study groups	More with reduced joint swelling (54% vs. 39%) and reduced joint tenderness (56% vs. 41%) in the minocycline-treated group ($P < .023$); more ESR normalization in the minocycline-treated group ($P < .001$)	65% of the minocycline group met 50% improvement for 6 mo vs. 13% treated with placebo ($P < .001$)	>60% ACR50 response at 2 yr in minocycline-treated patients vs. 33% in hydroxychloroquine-treated patients ($P = .04$); less prednisone in minocycline-treated patients ($P < .01$). More minocycline patients completely tapered off prednisone ($P = .03$)
Adverse events	GI, dizziness, headaches, pneumonitis			

ACR, American College of Rheumatology; bid, twice daily; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; RA, rheumatoid arthritis; RCT, randomized controlled trial.

some patients in the minocycline group experienced vestibular manifestations that led to falls and even some fractures. Rare manifestations associated with the use of minocycline include lupus-like syndromes. The original study from O'Dell's group demonstrated an impressive tolerability to minocycline, and only three patients (13%) withdrew from the 23 participants enrolled in the minocycline group, either because of cutaneous changes (fingernail discoloration and an erythematous rash) or dizziness. Of interest, in their second study, a 4 year follow-up, pigmentary changes were observed in four of the patients, out of the 30 in the minocycline group (13.3%); one patient chose to continue treatment with minocycline. In the meta-analysis 381 patients were included but there were no statistical differences in the risk for adverse events between both treatment groups.

Use of minocycline is well documented to cause cutaneous hyperpigmentation, although it is not frequently observed in initial clinical trials of RA. Four types of minocycline-induced hyperpigmentation are recognized, including (1) blue-black macular pigmentation confined to previous scars or inflammatory tissue on the face; (2) blue-black, brown, or slate-gray macules seen on healthy skin, mainly of the shins, forearms, or legs; (3) symmetric muddy-brown pigmentation of sun-exposed skin; and (4) blue-gray discoloration within scar tissue on the back.¹⁰¹ Figure 55.2 shows an example of these pigmentary changes in a patient with RA treated with minocycline for more than 5 years.

Dose-related toxicities associated with the use of tetracycline derivatives include vestibular dysfunction (dizziness, tinnitus, vertigo), gastrointestinal upset, pancreatitis, and hepatitis, whereas SLE, headaches, benign intracranial hypertension, and Stevens-Johnson syndrome are more rare and idiosyncratic.¹¹⁵



Fig. 55.2 Pigmentary changes in a patient with rheumatoid arthritis treated with minocycline for more than 5 years. (a) Pigmentation observed around a bunionectomy scar and on the shins after 5 years of treatment. Pigmentation over the bunionectomy scar worsened. (b) Pigmentation around the superior crux and conch of the pinna and oral mucosa after 5 years of treatment. (Courtesy Dr. Graciela S. Alarcón.)

Tetracyclines for the treatment of osteoarthritis

Efficacy data

In vivo studies have shown that oral doxycycline administration decreases the progression of OA in animal models. Thus, a multicenter, double-blind controlled study was conducted to compare oral doxycycline (100 mg twice a day) and placebo for 30 months in 431 obese women with unilateral knee OA confirmed by conventional standing views of knee radiographs (Kellgren grade II to III in the OA knee and 0 to I in the other).^{116,117} The primary outcome was changes in the joint space width of the medial tibiofemoral compartment.¹¹⁶ Patients in the doxycycline group experienced 33% less joint space narrowing in the OA knee (0.30 ± 0.60 mm versus 0.45 ± 0.70 mm, adjusted $P > .017$) but not in the contralateral knee as compared with the placebo group. No differences were noted in terms of pain score (Western Ontario and McMaster Universities [WOMAC] Osteoarthritis Index and 50-ft walk pain), WOMAC function, and median scores of patient and physician global assessment of disease activity between the doxycycline and placebo groups. Nonetheless, the frequency at which subjects reported a 20% or greater increase in knee pain (WOMAC pain score) in follow-up visits was reduced in the doxycycline group in comparison to the placebo group (23.8 ± 22.7 versus 30.2 ± 21.1 , $P > .004$). However, a recent triple-blind randomized trial of 100 mg doxycycline twice daily for OA showed that doxycycline was not effective in reducing symptoms in patients with knee OA over a 24-week study period and was associated with an increased risk for adverse events.¹¹⁸ Similarly, another study was unable to show clinical improvement in knee OA but did show slowing of joint space narrowing in a doxycycline-treated group versus a placebo-treated group.¹¹⁷ In terms of adverse events, photosensitivity, nonspecific gastrointestinal manifestations, and candidal vaginitis were reported more frequently in the doxycycline group than in the placebo group, but only a few patients discontinued the study prematurely because of these untoward events. Of interest, patients in the doxycycline group reported fewer urinary tract infections and a trend toward fewer upper respiratory tract infections. Thus, the data to date indicating whether doxycycline is a promising agent for the treatment of OA are not hopeful.

Dosing and monitoring

Dosing of minocycline can range from 50 to 400 mg taken once or twice a day; however, the dose studied for rheumatic diseases was 100 mg twice daily. Minocycline must be taken 2 to 3 hours before or after taking any medications containing magnesium, aluminum, calcium, iron, zinc, or sucralate, all of which can bind with minocycline and prevent its full absorption. Doses need to be reduced in patients with chronic kidney disease. Dosages of doxycycline are usually 100 mg twice daily. Absorption of doxycycline is not markedly affected by food, and therefore it can be taken with meals. Complete blood cell counts and chemistry profile should be monitored every 3 months while treatment is continued.

Summary

Minocycline may be a reasonable alternative as adjunctive treatment in patients who are not responding to standard therapy and are unable to afford or tolerate other DMARDs or in whom anti-TNF- α agents are not options because of increased risk for infection, such as in patients with chronic lung infection. In some instances minocycline may be considered for patients with early new-onset RA whose disease course is not thought to be aggressive and in whom HCQ may also have been considered.

The benefit of using doxycycline in patients with knee OA has been demonstrated, with one study indicating slowing of radiographic progression and data indicating that there may be an effect of reducing pain. These data need to be further validated with longer follow-up before doxycycline can be widely used as an option for patients with mild to moderate knee OA.

Despite limited data supporting the beneficial antirheumatic effects of tetracyclines and their derivatives, possibly resulting from their inhibition of MMPs and other proinflammatory mediators, only a few small trials have shown any significant clinical benefit of these agents in the treatment of RA or OA, and at this time they cannot be widely recommended for use in rheumatic diseases. Additional research is needed to further explore whether they have a role to play. Nonetheless, patients continue to request these drugs, particularly those who experienced transient improvements in their RA when they received antibiotics for other reasons.

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56

Methotrexate*

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- Methotrexate, a structural analogue of folic acid, can be administered orally or parenterally to treat a variety of rheumatic diseases.
- Although the exact mechanism of the therapeutic action of methotrexate is unknown, suppression of inflammation, mediated by increases in adenosine, may play a central role.
- The effectiveness of methotrexate in treating rheumatoid arthritis was established by four separate randomized controlled trials and confirmed by meta-analysis.
- Careful monitoring of methotrexate therapy is required, although most adverse events are mild and do not require discontinuation of the drug.
- Even though methotrexate hepatotoxicity is most widely discussed, serious liver disease is rare and the risk can be reduced with careful monitoring.
- Because methotrexate is a known teratogen, effective contraception should be used by women with the potential for pregnancy.

INTRODUCTION

Methotrexate (MTX), first used to treat malignant disease more than 50 years ago, is now the most commonly prescribed disease-modifying antirheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA). Low-dose MTX is highly efficacious and with monitoring has an excellent safety profile.

PHARMACOLOGY

MTX is structurally similar to folic acid; it differs only by the substitution of an amine for a hydroxyl group in the pteridine ring and by the addition of a methyl group on the 10th nitrogen of para-aminobenzoic acid (Fig. 56.1).

The bioavailability of low-dose oral MTX is relatively high, but individual patient variability exists. At 7.5 mg/wk, oral and parenteral absorption is the same, but at doses of 15 mg/wk or higher, oral absorption may be decreased by as much as 30% in comparison to parenteral dosing. At doses of 25 mg or greater, the bioavailability of oral MTX ranges from 0.21 to 0.96 relative to subcutaneous administration.² A greater clinical response is seen with subcutaneous than with oral MTX at doses greater than 15 mg/wk.^{3,4} Oral absorption is limited because MTX is absorbed from the gastrointestinal tract primarily via a saturable active transport system. Splitting the dose of oral MTX (25 to 35 mg) into two divided doses taken on the same day improves bioavailability by 28% and is comparable to subcutaneous therapy.⁵ Although oral absorption is not affected by food intake, it can be reduced in the setting of intestinal pathology.

After absorption, 10% of MTX is converted in the liver to 7-hydroxymethotrexate, predicted by animal models to be less efficacious in treating arthritis.⁶ This conversion has been shown to vary among treated patients, and folic acid may interfere with this metabolic step by inhibiting the enzyme responsible.⁷ Approximately 50% of MTX is bound to albumin, whereas 90% to 95% of 7-hydroxymethotrexate is bound to albumin.⁸ The serum half-life of MTX ranges from 6 to 8 hours, and it should be undetectable in serum by 24 hours. MTX and its metabolite 7-hydroxymethotrexate

are excreted primarily in urine, although a small portion is also excreted in bile. Renal clearance is due to a combination of filtration and secretion in the proximal tubule with subsequent reabsorption in the distal tubule. Renal insufficiency can lead to toxicity caused by impaired clearance of MTX. Because the drug is not cleared by dialysis, dialysis is an absolute contraindication to the use of MTX. Excretion of MTX is inhibited by weak organic acids such as aspirin, nonsteroidal antiinflammatory drugs, penicillin G, and probenecid. This is generally clinically relevant only with higher-dose MTX. Sulfonamides may also decrease renal tubular secretion and increase levels of MTX. Trimethoprim-sulfamethoxazole interferes with folic acid metabolism and may increase the risk for bone marrow suppression.⁹

Folates and antifolates enter the cell via two separate mechanisms. The reduced folate carrier (RFC) is a bidirectional anion exchanger that demonstrates higher affinity for MTX than for folic acid. In addition, MTX binds to folate receptors (FR- α and FR- β) and is transported inside the cell by endocytosis.¹⁰ Sulfasalazine is a noncompetitive inhibitor of the RFC and decreases the effects of MTX in cultured cells.¹¹ This inhibition of the RFC may decrease additive efficacy when combining sulfasalazine with MTX.

Inside cells, up to six glutamate residues can be added to MTX, but MTX PG₁ (native form) to MTX PG₅ have been reported to account for 99.6% of the total intracellular MTX polyglutamates¹² (Fig. 56.2). These polyglutamated forms are not readily transported across the cell membrane and can consequently accumulate intracellularly, with increased retention as the number of glutamate moieties increases.¹³ This modification is particularly important because polyglutamated MTX demonstrates significant increased affinity for certain folate-dependent enzymes, including thymidylate synthase, 5-aminoimidazole carboxamide ribonucleotide transformylase (AICAR transformylase), and glycylamide ribonucleotide transformylase (GAR transformylase)¹⁴ (Fig. 56.3). MTX in its ingested form is therefore essentially a prodrug, with its polyglutamated form being the active compound. The major determinants of MTX glutamate concentrations are age, renal function, and MTX dose.¹⁵

The concentration of intracellular MTX polyglutamates within red blood cells (RBCs) has been investigated as a biomarker of MTX efficacy. Although several cross-sectional studies involving RA have shown higher MTX polyglutamate levels in responders,¹⁶⁻¹⁸ in one study this relationship was not found.¹⁹ Two prospective longitudinal studies performed in patients starting MTX showed a correlation between RBC MTX polyglutamates and response,^{20,21} and in patients switching from oral to parenteral MTX, a selective accumulation of longer-chain MTX polyglutamates was demonstrated, which correlated with reduced disease activity.^{22,23} Of note, however, RBC steady-state concentrations were not achieved for at least 6 months after a change in dose.²² Determining whether MTX polyglutamate concentrations within RBCs can serve as a biomarker of MTX efficacy awaits larger, prospective, longitudinal studies. With the exception of a correlation between higher concentrations of MTX glutamate and gastrointestinal adverse events and elevated liver function test results in juvenile idiopathic arthritis,²⁴ no relationship between adverse events and MTX RBC glutamate concentrations has been found.

MECHANISM OF ACTION

MTX, an analogue of folic acid, can interfere with the ability of folic acid to serve as a cofactor for a variety of enzymes essential for purine and pyrimidine synthesis and cell replication. One of the first mechanisms proposed for MTX was inhibition of the proliferation of cells responsible for inflammation, such as lymphocytes. However, two findings have led to the suggestion of alternative hypotheses. First, the doses of MTX required to suppress inflammation are substantially lower than those used to treat

*Adapted from the authors' work in the book *Rheumatoid Arthritis*.¹

CHEMICAL STRUCTURES OF FOLIC ACID AND METHOTREXATE

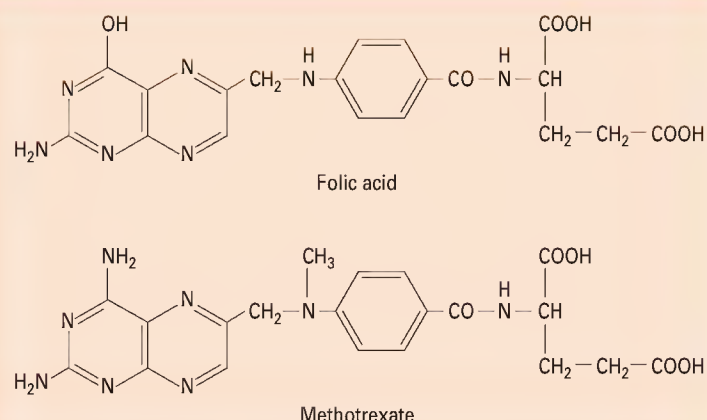


Fig. 56.1 Chemical structures of folic acid and methotrexate.

TRANSPORT AND GLUTAMATION OF METHOTREXATE

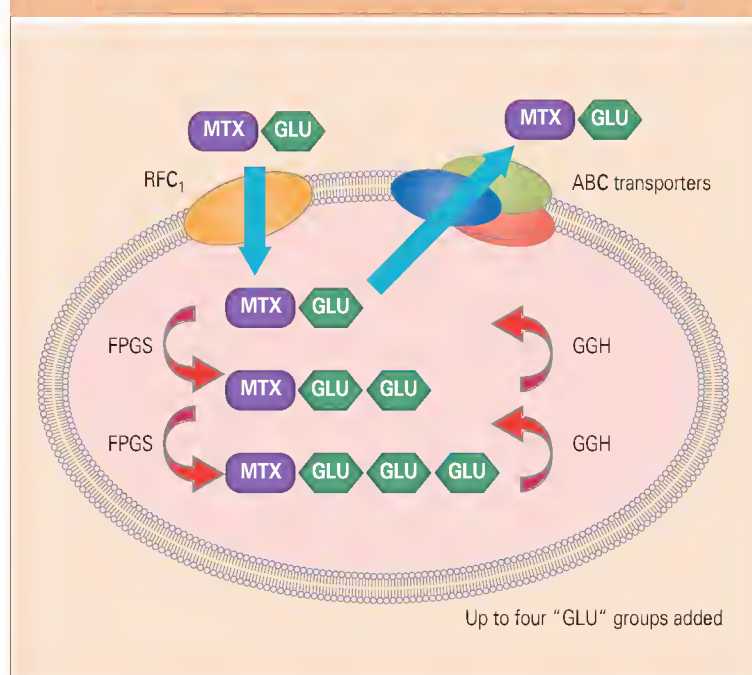


Fig. 56.2 Methotrexate (MTX), an analogue of dihydrofolic acid, is a prodrug that enters cells primarily through RFC1. Once inside the cell, MTX (also known as MTXGlu1 because it is a monoglutamate) is quickly converted to its active polyglutamated forms (MTXGlu2-5) by the enzyme FPGS. This sequential addition of up to four glutamate residues prevents efflux of MTX from the cell via a number of multidrug resistance proteins belonging to the ABC family of efflux pumps. Glutamation can be reversed by GGH. ABC, adenosine triphosphate (ATP)-binding cassette; FPGS, folypolyglutamate synthase; GGH, γ -glutamyl hydrolase; RFC1, reduced folate carrier 1. (Adapted from Stamp LK, Roberts RL. Effect of genetic polymorphisms in the folate pathway on methotrexate therapy in rheumatic diseases. *Pharmacogenomics* 2011;20:1449-63.)

malignant proliferative disorders. Second, folic acid supplementation can reverse the gastrointestinal and hepatic toxicities, which are probably secondary to the antiproliferative effects of MTX, but not the therapeutic effects, which are dependent on the antiinflammatory effects of MTX.²⁵

One alternative mechanism for the antiinflammatory actions of MTX has gained favor. MTX polyglutamates bind AICAR transformylase, which leads to increased levels of AICAR, an inhibitor of adenosine monophosphate (AMP) deaminase, and AICAR's dephosphorylated metabolite AICARiboside, an inhibitor of adenosine deaminase (Fig. 56.4). This inhibition increases levels of intracellular AMP and adenosine, as well as levels of

extracellular adenosine that will bind to cell-surface receptors.²⁵ Adenosine A_{2A} receptors are expressed on T cells, natural killer cells, monocytes, macrophages, and neutrophils and can therefore dampen inflammation by a variety of mechanisms, including suppression of T-cell activation and cell-mediated cytotoxicity, inhibition of the neutrophil oxidative burst, and suppression of nuclear factor- κ B and its downstream effects.²⁶ Major support for this hypothesis comes from animal models of inflammation in which adenosine receptors are blocked or deleted.²⁷ Because caffeine is a poorly selective adenosine receptor antagonist, the role of caffeine in abrogating the effects of MTX have been studied to lend support to the adenosine hypothesis *in vivo* in humans. Although initial studies in RA showed diminished effects of MTX in patients with high caffeine intake,²⁷ a larger prospective trial did not show any association between caffeine intake and MTX efficacy.²⁸ Patients with inflammatory arthritis treated with MTX (15 mg/wk), however, showed enhanced dipyridamole-induced vasodilation, an effect dependent on extracellular adenosine levels.²⁹

Other hypotheses to explain the immunosuppressive effects of MTX have been suggested and continue to be explored. For example, it was recently shown that MTX can increase the sensitivity of a cultured T-cell line to apoptosis via a Jun N-terminal kinase (JNK)-dependent mechanism.³⁰

EFFICACY IN RHEUMATOID ARTHRITIS

Initial use

The efficacy of aminopterin, the parent compound of MTX, in managing RA was first reported in 1951 when five of six patients treated with the drug at 1 to 2 mg/day demonstrated decreased joint pain and swelling.³¹ Subsequently, several positive open-label studies of weekly MTX were conducted in RA patients.³² In the 1980s, short-term placebo-controlled trials reported significant improvement with low-dose weekly MTX.³² A flare of arthritis was observed when MTX was stopped after short-term therapy (12 weeks)³³ or after longer-term therapy (36 months).³⁴ This flare generally occurred 4 to 6 weeks after stopping MTX.^{33,34}

Efficacy compared with nonbiologic DMARDs

MTX has the same or greater efficacy than most other synthetic DMARDs, including azathioprine, gold salts, and auranofin.³² For example, the American College of Rheumatologists 20% improvement (ACR20) response as calculated in a *post hoc* analysis of the MTX versus auranofin study³⁵ reported that an ACR20 response was achieved in approximately 68% of patients with MTX (maximum dose, 15 mg/wk) and in 30% with auranofin.³⁶ MTX was superior to leflunomide in improving disease activity measures after 1 year and radiographic progression after 2 years.³⁷ In most of these early comparison studies the maximum dose of MTX was 15 mg/wk. Intraarticular MTX is not effective in RA.³⁸

Efficacy compared with biologic DMARDs

MTX has been the active comparator in studies of biologic response modifiers. Inhibitors of tumor necrosis factor- α (TNF- α) have been evaluated against and in combination with MTX. In most of these studies the MTX dose was increased to 20 mg/wk. In a 24-month trial of etanercept versus MTX (7.5 mg escalating to 20 mg weekly) in patients with early RA, MTX was less effective than etanercept during the first 4 months of therapy but achieved efficacy similar to that of etanercept thereafter. At 12 months, an ACR20 response was seen in 72% with etanercept versus 65% with MTX. In another trial comparing etanercept, MTX, and the combination (TEMPO), an ACR20 response at week 52 was noted in 75% with MTX, in 76% with etanercept, and in 85% with the combination.³⁹ In patients with early (<2 years) RA, remission according to the 28-Item Disease Activity Score (DAS28) at 52 weeks was seen in 50% with etanercept plus MTX versus 28% with MTX therapy alone.⁴⁰ In another early RA study, escalation of MTX dosages to 20 mg/wk achieved an ACR50 response in more than 35% of patients.⁴¹ These studies have provided excellent data on the efficacy of MTX monotherapy, with ACR20 responses being achieved in 54% to 73% of patients (Table 56.1).³⁹⁻⁴⁴ In most of the direct comparison studies of MTX and biologic agents, MTX achieved a similar clinical response as biologics over time. Only in the tocilizumab monotherapy study did the biologic achieve a better response than MTX,⁴³ with an ACR20/50 response at week 24 being achieved in 69.9%/44% of patients with tocilizumab versus 52.5%/34% with MTX. Even though in some patients an initial response was noted as soon as 3 to 6 weeks after starting MTX therapy, a plateau in effect is not generally observed until after 12 to 16 weeks.

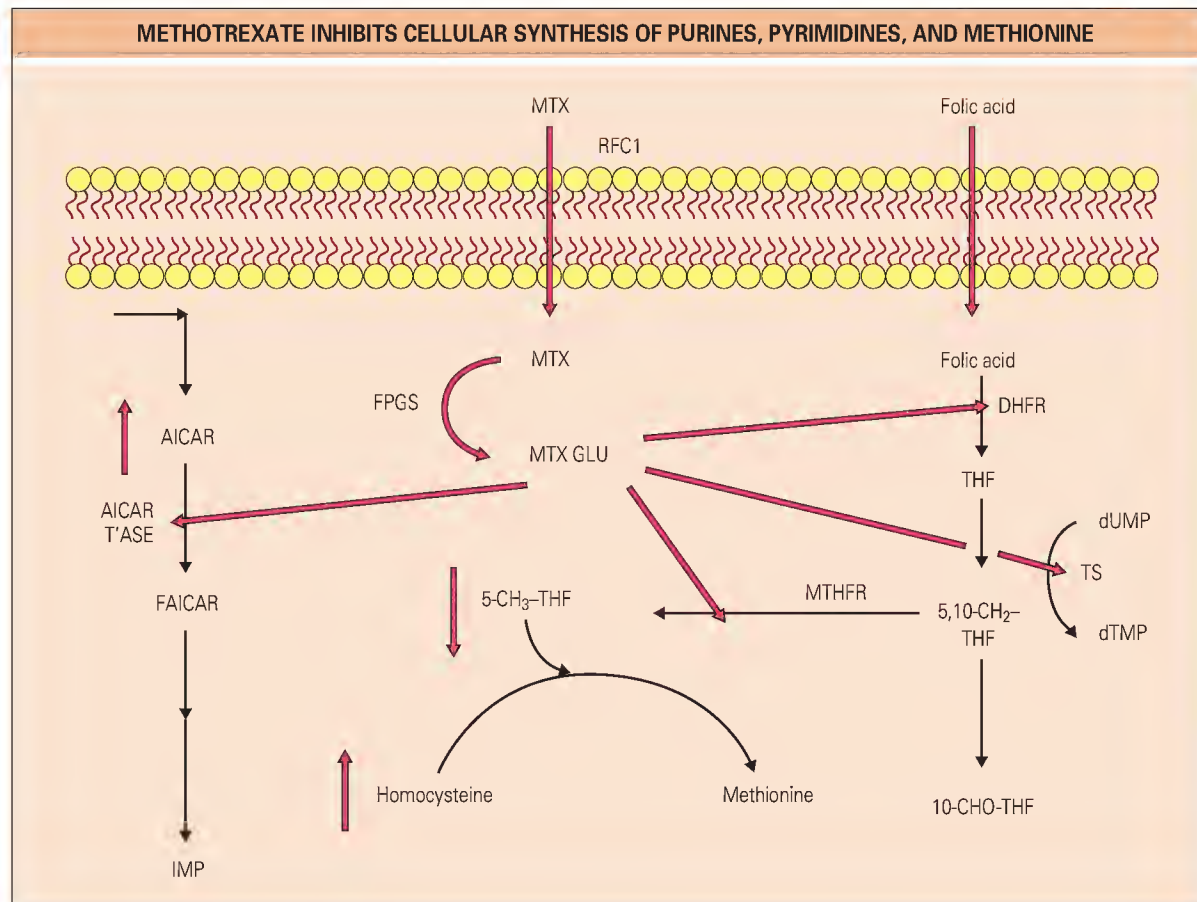


Fig. 56.3 MTX, an analogue of folic acid, can interfere with the ability of folic acid to serve as a cofactor for enzymes that are critical to purine and pyrimidine synthesis and cell replication. AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; AICAR T'ASE, AICAR transformylase; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FAICAR, 10-formyl AICAR; FPGS, folypolyglutamate synthase; IMP, inosine monophosphate; MTHFR, methylene tetrahydrofolate reductase; MTX, methotrexate; MTX GLU, methotrexate polyglutamate; RFC1, reduced folate carrier 1; THF, tetrahydrofolate; TS, thymidylate synthase. (Adapted from Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. *Pharmacol Rev* 2005;57:163-72.)

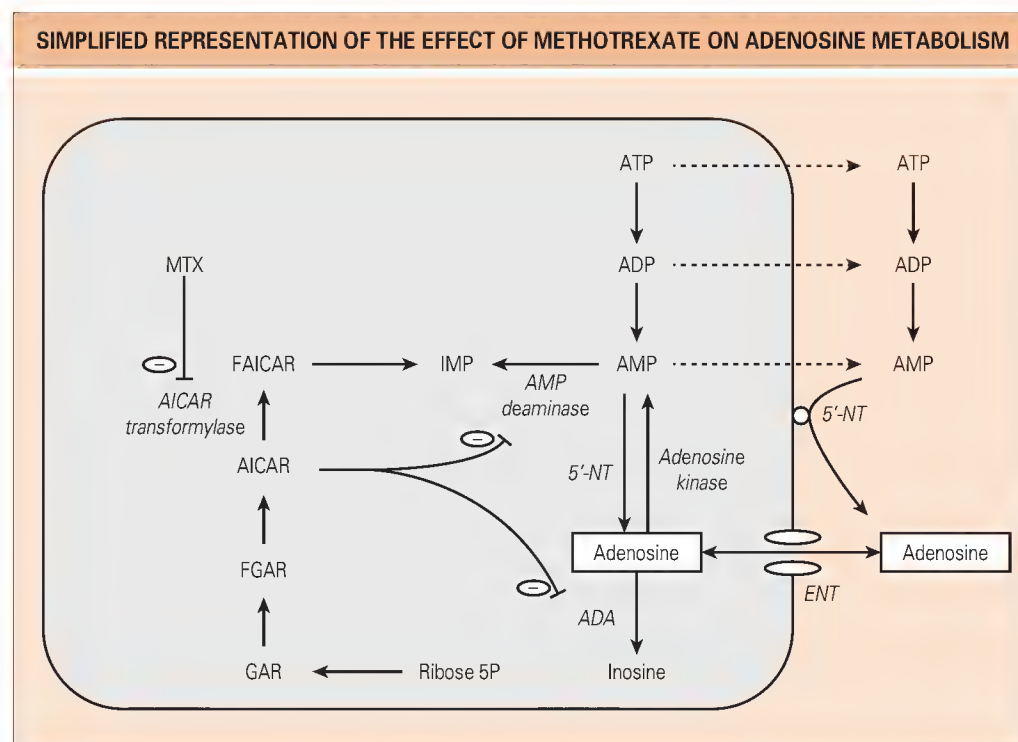


Fig. 56.4 Polyglutamate methotrexate inhibits AICAR transformylase, thereby resulting in intracellular accumulation of AICAR, which inhibits ADA and AMP deaminase. Consequently, irreversible degradation of adenosine to inosine is inhibited, as well as the conversion of AMP to IMP. Subsequently, AMP is extracellularly converted to adenosine by the ecto-5'-nucleotidase. ADA, adenosine deaminase; ADP, adenosine diphosphate; AICAR, 5-aminoimidazole-4-carboxamideribonucleotide; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ENT, equilibrative nucleoside transporter; FAICAR, 10-formyl AICAR; FGAR, 10-formyl GAR; GAR, glycinamide ribonucleotide; IMP, inosine monophosphate; 5'-NT, 5'-nucleotidase. (Adapted from Riksen NP, Barrera P, Van Den Broek PHH, et al. Methotrexate modulates the kinetics of adenosine in humans in vivo. *Ann Rheum Dis* 2006;65:465-70.)

TABLE 56.1
Efficacy of methotrexate as monotherapy in studies of biologics

	TEMPO*	PREMIER†	ASPIRE‡	COMET§	AMBITION¶	Abatacept study¶
ACR20 (%)	75	63	54	67	52	Not reported
ACR50 (%)	43	46	32	49	34	43
ACR70 (%)	19	28	21	28	28	27
DAS remission (%)	13	21	15	28	12	23

*Study comparing methotrexate, etanercept, and the combination of both drugs.³⁹

†Study comparing methotrexate, adalimumab, and the combination of both drugs.⁴¹

‡Study comparing methotrexate with methotrexate plus infliximab.⁴²

§Study comparing methotrexate with the combination of methotrexate and etanercept.⁴⁰

¶Study comparing methotrexate with tocilizumab.⁴³

¶Study comparing methotrexate with the combination of methotrexate and abatacept.⁴⁴

ACR, American College of Rheumatology; DAS, Disease Activity Score.

Efficacy in combination with nonbiologic DMARDs

The efficacy of MTX in combination with other synthetic DMARDs is variable.⁴⁵ The combination of azathioprine or auranofin with MTX was not superior to monotherapy. In patients with a suboptimal response to MTX, the addition of weekly intramuscular gold⁴⁶ or cyclosporine⁴⁷ resulted in increased efficacy. Triple therapy with MTX, hydroxychloroquine, and sulfasalazine was superior to MTX monotherapy and the combination of hydroxychloroquine and sulfasalazine.⁴⁸ MTX plus leflunomide showed increased efficacy for the combination, with an ACR20 response being achieved in 46.2% with the combination versus 19.5% with MTX alone.⁴⁹

Efficacy in combination with biologic DMARDs

The therapeutic effect is improved when anti-TNF therapy is added to background MTX, and the response is better than that with MTX or anti-TNF monotherapy.^{50,51} In the TEMPO study, the combination was more efficacious than either therapy alone, as evidenced by ACR20 responses at week 52 in 85% of patients given the combination versus 75% and 76% in the MTX and etanercept groups, respectively.³⁹ The combination was better in retarding joint damage, as assessed by the Sharp score, than was monotherapy with either drug. Greater efficacy was also observed when other biologics (i.e., rituximab, abatacept, tocilizumab) were added to MTX.⁵²⁻⁵⁴

Effect on structural damage

MTX slows the radiographic progression of RA.³² In one trial comparing MTX with the combination of etanercept and MTX for early RA, no progression was seen in 59% of the patients treated with MTX monotherapy⁴⁰; in addition, in an infliximab study, no progression was seen in 39% of the patients receiving MTX monotherapy.⁵⁵ Even though the radiographic effect is not as great as with the biologics, MTX can reduce and even halt radiographic progression in some patients.

Long-term studies

Long-term prospective studies show sustained effects on disease activity and reduction of radiographic progression. A cohort of 26 RA patients receiving MTX therapy was prospectively monitored over a period of 132 months.⁵⁶ For the 10 patients who completed the study at 132 months, significant improvement over baseline was noted in arthritis activity, including 50% improvement in the joint pain index and joint swelling index in more than 65% of the patients. There was no significant difference, however, in improvement in clinical variables between 12 and 132 months of therapy. In another prospective cohort study, 29 patients treated with MTX were followed for 156 months.⁵⁷ After 13.3 years a sustained clinical effect was still observed with MTX.⁵⁷ A large multicenter prospective trial monitored 123 patients taking MTX for 5 years and showed significant improvement in all clinical disease variables, functional status, and erythrocyte sedimentation rate in 64% of the patients who completed this study.⁵⁸

Biomarkers of response to MTX

MTX decreases markers of inflammation, including the erythrocyte sedimentation rate and C-reactive protein (CRP). There is a rapid decrease in CRP, with an effect being noted in one study by day 3 after MTX dosing.⁵⁹

To date, no baseline parameters have been shown to predict a positive response to MTX.^{60,61} A *post hoc* analysis of the TEMPO study³⁹ reported that after 12 weeks of MTX therapy, patients who had a CRP level lower than 0.67 mg/dL and a swollen joint count of greater than 1 or a CRP level lower than 0.67 and a swollen joint of greater than 10 had the worse radiographic progression at week 52.⁶²

Effect on mortality

Reduced mortality has been observed with MTX treatment of RA. In a retrospective study of 1240 patients with RA,⁶³ 44% of the 191 deaths were due to cardiovascular causes. When a weighted Cox proportional hazards model was used to adjust for potential confounders, including measures of disease activity, the adjusted mortality hazard ratio was 0.4 (0.2 to 0.8). The hazard ratio for cardiovascular mortality was 0.3 (0.2 to 0.7) versus 0.6 (0.2 to 1.2) for non-cardiovascular-related death. A systematic review plus meta-analysis of studies of MTX for chronic inflammatory diseases (primarily RA) was performed and showed a lower risk for cardiovascular disease with MTX. MTX was associated with a 18% reduction in myocardial infarction (MI) in the 10 studies analyzed.⁶⁴ A systematic review limited to RA also suggested that use of MTX was associated with a reduced risk for cardiovascular events,⁶⁵ probably related to the antiinflammatory effects observed with MTX. A large National Institutes of Health-funded study is currently under way to determine whether low-dose MTX reduces the rate of reinfarction in non-RA patients with a history of MI.

ADVERSE EFFECTS

Common adverse effects

The most common reactions associated with low-dose weekly MTX are anorexia, nausea, vomiting, and diarrhea, as reported in 31% of 3463 patients in a systematic literature review of 21 prospective studies⁶⁶ (Table 56.2).⁶⁷⁻⁷² Most of these reactions occurred shortly after initiation of MTX and were mild, although in one review 2.5% of patients discontinued MTX therapy.⁶⁷ In this same group of patients, stomatitis occurred in 6% and alopecia in 1%.⁶⁷ Folic acid or folinic acid can reduce many of these toxicities. Hematologic abnormalities were found in 5% of patients in the systematic review and included leukopenia (most common), anemia, and thrombocytopenia.⁶⁶ Risk factors for MTX-induced hematologic toxicity include drug overdoses, incorrect administration such as daily dosing, renal insufficiency, dialysis, hypoalbuminemia, and concomitant drugs such as trimethoprim-sulfamethoxazole. Folic acid and folinic acid therapy, laboratory monitoring, and patient education can reduce the risk of toxicity.

Hepatic toxicity

MTX liver toxicity was well known because of the experience with MTX in patients with psoriasis, in whom severe liver disease was reported in the 1970s and 1980s. The spectrum of liver injury ranges from asymptomatic elevations in serum transaminases to hepatic fibrosis and cirrhosis, with serum transaminase elevations being most frequent. The characteristic pathology seen with MTX toxicity is hepatic fibrosis and cirrhosis. This is fortunately rare in RA patients, unlike the earlier experience of MTX in those with psoriasis. Of 3808 patients reported in 27 prospective studies, an elevation in liver transaminases of up to two times the upper limit was reported in 13% of patients, and MTX was discontinued in 3.7% of these

TABLE 56.2
Adverse effects of methotrexate for rheumatoid arthritis

Adverse effect	Estimated incidence in rheumatoid arthritis
Gastrointestinal	
Anorexia, nausea, vomiting, diarrhea	10% ⁶⁷
Hematologic	
Leukopenia, anemia, thrombocytopenia	3% ^{67,68}
Hepatic	
Elevated transaminases	15% ⁶⁸
Cirrhosis/liver failure	0.1% 5-yr cumulative incidence ⁶⁹
Pulmonary	
Interstitial pneumonitis	2.1%-8% ⁷⁰
Epstein-Barr virus–associated lymphomas	Unknown
Accelerated nodulosis	8% ⁷¹
Central nervous system	
Dizziness, headache, mood alteration, memory impairment	25% ⁷²

patients.⁶⁶ In a large North America registry (CORRONA), of 1953 patients with RA treated with MTX, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased above the upper limit of normal in 22%, and 1% had a twofold increase in these enzymes.⁷³ Independent predictors of abnormal AST values were a lack of folate supplementation and untreated hyperlipidemia.⁶⁸ Even though elevations in serum transaminases occur frequently, especially in the first 6 months of MTX therapy, serious liver disease is extremely uncommon. A case-control study of serious liver disease in RA patients taking MTX identified 24 cases of cirrhosis and liver failure with a 5-year cumulative incidence of approximately 1 in 1000 treated patients. Elevations of serum transaminases above the upper limit of normal or low serum albumin was observed in the patients in whom serious liver disease developed versus the matched control group. Serial elevations in serum AST correlate with progression of histologic abnormalities.⁷⁴ The ability to use abnormal liver test results to predict pathology led to the recommendation for regular monitoring of serum transaminases and albumin. Late age at first use of MTX and duration of MTX therapy are independent predictors of serious liver disease.⁶⁹ The frequency of liver disease is lower in patients with RA than in those with psoriasis. Reasons for the higher rate in psoriasis could include higher alcohol consumption, higher mean body index with fatty liver disease, and higher doses of MTX.

A potentially serious complication can occur when MTX is used in patients infected with hepatitis B or C virus. Development of fulminant hepatitis after MTX withdrawal has been observed. Reactivation of the immune system by discontinuation of MTX is postulated as the cause.⁷⁵

Pulmonary toxicity

MTX can rarely cause lung injury, which is generally acute interstitial pneumonitis. In a systematic review of 3463 patients, pneumonitis was reported in 0.43%.⁶⁷ A retrospective combined cohort review and literature review identified 29 patients who had probable or definite MTX-related lung injury. Clinical features included shortness of breath (93%), cough (82%), and fever (69.0%) and occurred after a mean duration of MTX treatment of 78.6 weeks; however, 48% of the patients had been taking MTX for less than 32 weeks. Five patients died, and recurrent lung toxicity developed in four of six patients retreated with MTX.⁷⁶ A case-control study of patients reported that the strongest predictors of MTX-associated lung injury were older age, diabetes, rheumatoid pleuropulmonary involvement, previous use of DMARDs, and hypoalbuminemia.⁷⁷

Vaccination

In patients with RA and spondyloarthritis, treatment with MTX was a negative predictor of antibody response to the 7-valent pneumococcal vaccine.⁷⁸ However, a retrospective study found that patients with RA treated with MTX who received Pneumovax were protected from pneumonia when compared with those who had not been vaccinated.⁷⁹

Other adverse effects

Other adverse events seen with MTX include opportunistic infections such as *Pneumocystis carinii* pneumonia and herpes zoster infection, accelerated

nodulosis,⁷¹ gynecomastia, rashes including photosensitivity reactions, fever and a flulike illness, and nonspecific central nervous system effects such as dizziness, headache, mood alteration, and memory impairment.⁷² Fatigue is one of most common reasons that patients stop taking MTX—folinic acid may reduce fatigue.

An increased risk for melanoma (standardized incidence ratio, 3.0) has been observed in RA patients receiving MTX as compared with a normal population.⁸⁰ In general, an increase in other solid tumors is not associated with use of MTX based on the experience with high-dose MTX for malignancy or low-dose MTX for psoriasis. A higher rate of lymphoma was not observed in RA patients treated with MTX therapy alone versus RA patients never exposed to MTX therapy.⁸¹ There is increased risk for rare Epstein-Barr virus–associated lymphomas,⁸² which may occasionally regress with discontinuation of MTX.⁸³

Teratogenicity

MTX is a known teratogen that leads to multiple congenital abnormalities, especially of the nervous system (called the “aminopterin syndrome”), and higher-dose MTX is used to induce abortion. Even low-dose MTX can lead to fetal abnormalities.⁸⁴ MTX is labeled category X by the Food and Drug Administration. The sponsor package insert recommends that the use of MTX be stopped at least one menstrual cycle before attempting conception, but many rheumatologists recommend stopping it 3 months before attempting conception. There are few data to determine which recommendation is correct. MTX should not be used during lactation because the drug can be excreted in breast milk. In males with psoriasis, a reversible decrease in sperm count was seen. The package insert recommends that males stop taking MTX 3 months before attempting conception, but no firm data are available to support this recommendation.

FOLIC ACID SUPPLEMENTATION

To reduce the adverse effects of MTX such as nausea, diarrhea, stomatitis, hair thinning, fatigue, headaches, and hematologic toxicity, folic acid or folinic acid (leucovorin) is coadministered. Folic acid (5 mg or 27.5 mg each week) decreased MTX toxicity without reducing the efficacy of MTX in a randomized study.⁸⁵ Folic acid 1 mg/day or folinic acid 2.5 mg/wk reduced the incidence of elevated liver enzyme levels and decreased toxicity-related discontinuation but had no effect on gastrointestinal side effects. The mean dosages of MTX at the end of this 48-week study were higher in the folic acid and folinic acid groups than in the placebo group, thus suggesting that higher doses of MTX might be necessary for the same clinical effect.⁸⁶ Folinic acid (up to 30 mg/wk), as opposed to placebo, taken 24 hours after the MTX dose led to fewer adverse effects but no difference in disease activity when compared with placebo.⁸⁷ In contrast, in another placebo-controlled trial in which leucovorin (15 mg) was given 2 hours after MTX, the clinical and laboratory indices of disease worsened in the leucovorin group,⁸⁸ thus suggesting that the timing of folinic acid administration is probably important. Folinic acid should be taken 8 to 24 hours after MTX so that it does not block the efficacy of MTX but remains effective in reducing side effects.

PHARMACOGENOMICS

Although MTX is generally well tolerated, some patients experience adverse effects, and occasionally these are serious. In addition, even though MTX is efficacious in many patients, some patients do not respond. Therefore, ideally only patients who will tolerate and benefit from MTX should be treated. Because the critical proteins controlling the function and metabolism of MTX are known, it has been possible to study polymorphisms in some of these proteins to determine whether they influence the drug's effects.

The best-studied polymorphisms are in the methylenetetrahydrofolate reductase (*MTHFR*) gene. *MTHFR* is a critical enzyme associated with the regeneration of 5-methyltetrahydrofolate from 5,10-methylenetetrahydrofolate. 5-Methyltetrahydrofolate contributes a methyl group to homocysteine for regeneration of methionine, and deficiency can lead to hyperhomocysteinemia and methionine deficiency. More than a dozen *MTHFR* gene polymorphisms have been described, and two functional polymorphisms, 1298A→C and 677C→T, have been studied to determine whether they can influence patient response to MTX. Results have been conflicting, and currently there is no definitive evidence that these polymorphisms can predict MTX response or toxicity in patients with RA.⁸⁹ Many other polymorphisms in genes that encode proteins that control folate metabolism, MTX glutamation and transport, and adenosine metabolism

have been studied, but the results have been contradictory.⁸⁹ Understanding of the pharmacogenetics of MTX for RA awaits large statistically powered studies of functional polymorphisms.

USE OF METHOTREXATE FOR RHEUMATOID ARTHRITIS: RECOMMENDATIONS

MTX is usually started at a dose of 7.5 to 10 mg/wk, with escalation every 4 to 8 weeks until disease activity is controlled. The therapeutic dose generally ranges between 15 and 25 mg/wk. After the therapeutic dose is reached, it usually takes 4 to 6 weeks for a clinical effect to be noted. We typically start MTX at a dose of 10 mg/wk, but some clinicians start at 15 mg/wk. After 4 weeks, the dose is increased to 20 mg/wk unless toxicity is present. A systematic review supports monthly dose escalation.³ If a significant clinical effect has not been achieved, the dose can be increased to 25 mg and administered by subcutaneous injection. It is important to maximize the dose of MTX to achieve the greatest efficacy. The maximum dose of oral MTX is generally 20 to 25 mg/wk. MTX can be administered subcutaneously to patients with gastrointestinal intolerance or to nonresponders, with a predicted higher bioavailability than the with oral dosing. Splitting oral MTX (25 mg) into two divided doses taken on the same day improves bioavailability, but whether this provides the same efficacy as subcutaneous therapy is not known. The dose of MTX may be decreased over time in patients with an impressive clinical response, but most require ongoing therapy. Discontinuation of MTX is generally associated with a flare of arthritis 4 to 6 weeks after stopping the drug. Treatment with at least 1 mg of folic acid each day is used to reduce side effects. If adverse effects occur, folic acid should be increased to 2 mg/day. Outside the United States the folic acid dose is usually 5 mg 5 to 6 days per week. If side effects continue despite folic acid, folinic acid (leucovorin) beginning at 5 mg/wk should be used. The dose of leucovorin can be escalated to block side effects and should be given 8 to 24 hours after MTX. If administered within 8 hours of MTX, leucovorin may block the efficacy of MTX.

Patients should be aware of the adverse event profile. In general, MTX should be withheld during infections. We also withhold it the week of surgery and the first postoperative week, but this is not based on trial data. The ACR issued a consensus statement in 1994 that provided guidelines for monitoring liver toxicity (Box 56.1).⁹⁰ Although the 1994 statement recommends that AST, ALT, and albumin levels be monitored at intervals of every 4 to 8 weeks, a recent consensus statement recommends monitoring every 8 to 12 weeks after 3 months and every 12 weeks after 6 months of therapy.⁹¹ Routine surveillance liver biopsies are not recommended for RA patients taking traditional doses of MTX. However, biopsy should be performed in patients with persistent abnormalities on liver blood tests, defined as elevations in AST on 5 of the 9 determinations within a 12-month interval (6 of 12 if tests are performed monthly) or a decrease in serum albumin below the normal range.⁹⁰

Laboratory monitoring should be done on a regular basis. We monitor liver blood test results, creatinine level, and the complete blood count every 4 to 8 weeks, which is more conservative than the most recent recommendations.⁹¹ Patients should receive routine vaccinations, including influenza and pneumococcal vaccine, but should not receive live vaccines while taking MTX. MTX may impair antibody response to the pneumococcal vaccine, so to maximize the effect, the vaccine should be administered before starting MTX.⁷⁸ We recommend restricting the use of alcohol. Women of childbearing

potential must use birth control while taking the drug. An *ad hoc* group of international rheumatologists met to review the existing literature and published their own set of recommendations on the use of MTX for RA.⁹²

METHOTREXATE FOR OTHER RHEUMATIC DISEASES (Table 56.3)

Psoriatic arthritis

Although MTX is commonly used as a first-line agent for psoriatic arthritis, data supporting its efficacy for this disease are minimal, including several retrospective and observational studies; underpowered, double-blind, placebo-controlled trials; and studies using a maximum MTX dose of 15 mg/wk.¹⁰³ The current guidelines for monitoring hepatic toxicity when MTX is used for psoriasis have been modified by the National Psoriasis Foundation Consensus Conference.¹⁰⁴ In patients at low risk for liver disease, the guidelines no longer recommend routine surveillance liver biopsies but rather laboratory monitoring and following of the 1994 ACR guidelines.⁹¹ In high-risk patients, defined as those with diabetes, obesity,

BOX 56.1 RECOMMENDATIONS FOR MONITORING HEPATIC SAFETY IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) RECEIVING METHOTREXATE (MTX)

- A. Baseline
 1. Tests for all patients
 - a. Liver blood tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, albumin, bilirubin), hepatitis B and C serologic studies
 - b. Other standard tests, including complete blood cell count and serum creatinine
 2. Pretreatment liver biopsy (Menghini suction-type needle) only for patients with
 - a. Previous excessive alcohol consumption
 - b. Persistently abnormal baseline AST values
 - c. Chronic hepatitis B or C infection
- B. Monitor AST, ALT, albumin at 4- to 8-week intervals
- C. Perform liver biopsy if
 1. Five of 9 determinations of AST within a given 12-month interval (6 of 12 if tests are performed monthly) are abnormal (defined as an elevation above the upper limit of normal)
 2. There is a decrease in serum albumin below the normal range (in the setting of well-controlled rheumatoid arthritis)
- D. If results of liver biopsy are
 1. Roenigk grade I, II, IIIA, resume MTX and monitor as in B, C1, and C2 above
 2. Roenigk grade IIIB or IV, discontinue MTX
- E. Discontinue MTX in patients with persistent liver test abnormalities, as defined in C1 and C2 above, who refuse liver biopsy

Fram JM, Alarcon GS, Lightfoot RW Jr, et al. Methotrexate for rheumatoid arthritis. Suggested guidelines for monitoring liver toxicity. American College of Rheumatology. Arthritis Rheum 1994;37:316-28.

■ TABLE 56.3
Use of methotrexate for other diseases

Disease	Trial design	MTX dose (mg/wk)	Response	Reference
Ankylosing spondylitis	RCT	7.5-10	Not effective for spine disease	93
Felty syndrome	Case series	7.5-12.5	Increase in WBC count	94
ANCA vasculitis	Open and RCT	20-25	Noninferior to Cytoxan. As effective as azathioprine	95-97
PMR/GCA	RCT	7.5-15	Modest effect in PMR/GCA	98, 99
Myositis	Open	10-20	No RCT but consensus acceptance for myositis	100
Lupus	Open, RCT	15-20	Positive effects on joints and skin	101
CPPD	Open	5-10	Positive report	102

ANCA, antineutrophil cytoplasmic antibody; CPPD, calcium pyrophosphate dihydrate deposition disease; GCA, giant cell arteritis; MTX, methotrexate; PMR, polymyalgia rheumatica; RCT, randomized controlled trial; WBC, white blood cell.

abnormal liver test results, or significant alcohol intake, routine surveillance liver biopsies are still recommended in psoriasis patients treated with MTX.

Juvenile idiopathic arthritis

MTX is effective in various forms of juvenile polyarthritis, including oligo-articular arthritis and a subset of children with systemic juvenile idiopathic arthritis.¹⁰⁵ The dose in children, 8 to 12.5 mg/m²/wk, is higher than that used in adults. Significant additional improvement was not observed at a dose of 30 mg/m²/wk.¹⁰⁶

Other rheumatic diseases

MTX has been used for many other rheumatologic conditions, including ankylosing spondylitis, Felty syndrome, antineutrophil cytoplasmic

antibody-associated vasculitis, polymyalgia rheumatica/giant cell arteritis, systemic lupus erythematosus, scleroderma, myositis, and calcium pyrophosphate deposition disease with variable results (see Table 56.3).

CONCLUSION

MTX is now a first-line agent for the treatment of RA and is the “anchor drug” for combination therapy with other DMARDs. It has become the standard of care and the most widely used drug for the treatment of RA. When used appropriately, it has excellent efficacy and tolerability in the treatment of RA and is the DMARD to which all new therapies should be compared. The effectiveness of MTX for other rheumatic diseases still requires further study, but existing results suggest that MTX is a useful tool for the treatment of a variety of systemic rheumatic diseases.

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Leflunomide

■ BOULOS HARAOU

- Leflunomide inhibits pyrimidine synthesis, resulting in blockade of T-cell proliferation.
- Leflunomide is used in patients with moderate to severe active rheumatoid arthritis with early or late disease.
- Monotherapy with leflunomide has been shown to be as effective as methotrexate and sulfasalazine in improving symptoms and signs of rheumatoid arthritis.
- Leflunomide as monotherapy results in substantial inhibition of joint damage, as assessed radiologically.
- Leflunomide provides additional benefit in patients partially responsive to methotrexate.
- Leflunomide can be safely combined with tumor necrosis factor inhibitors or rituximab.
- Leflunomide is contraindicated in patients with interstitial lung disease or methotrexate-induced pneumonitis.
- The most common adverse effects of leflunomide are gastrointestinal symptoms and hepatotoxicity.
- Combination of leflunomide with methotrexate results in a significant increase in liver enzyme abnormalities.
- Leflunomide is teratogenic in animals and is therefore contraindicated in women who may become pregnant.

CHEMICAL STRUCTURE AND MODE OF ACTION

Leflunomide, N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide ($C_{12}H_9F_3N_2O_2$), is an isoxazole derivative with immunomodulatory and disease-modifying properties in rheumatoid arthritis (RA). It is a prodrug that is rapidly converted in the submucosal wall of the intestinal tract and after first passage in the liver into its active metabolite A77 1726, a manolonitrilamide. It appears that genetic polymorphisms in CYP1A2, a cytochrome P450 isoenzyme that may play a role in this transformation, could be linked to the pharmacokinetics and toxicity of leflunomide.¹

A77 1726 inhibits dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme that is critical for the *de novo* synthesis of pyrimidines (Fig. 57.1).² It is thought that this property effectively blocks the proliferation of human lymphocytes, which are highly dependent on this pathway for nucleotide synthesis.³ This leads to an arrest in the G1/S phase of the cell cycle. The concentration of A77 1726 needed to block T-cell proliferation after mitogen stimulation varies greatly among species and can be reversed *in vitro* by the exogenous addition of uridine in a dose-dependent fashion.^{4,5} Pyrimidines are also needed by proliferating cells to form the lipids and macromolecules essential to several cell functions such as cell-cell contact, diapedesis, and intracellular signaling (Fig. 57.2). Genetic polymorphism in DHODH has also been shown to play a role in leflunomide toxicity.¹

Furthermore, DHODH may be involved in other cellular mechanisms such as B-cell proliferation and immunoglobulin synthesis.^{6,7}

In several *in-vitro* stimulated and unstimulated cell lines, A77 1726 was demonstrated to inhibit two important transcriptional factors critical to the function of cells of the immune system and inflammation^{8,9}: tyrosine kinase activity and nuclear factor κ B (NF- κ B) activation and gene expression. It seems also that A77 1726 may directly block the JAK/STAT pathway,

inhibiting the production of interleukin-17 (IL-17), an effect that is not reversed by the addition of uridine¹⁰; it was also shown to suppress IL-1 β expression and matrix metalloproteinase-1 (MMP-1) production more efficiently than dexamethasone.¹¹ On the other hand, A77 1726 did not have any effect on IL-4 production or IL-2 receptor expression.¹² After 1 year of treatment with leflunomide, RA patients showed a reduction in the levels of interferon- γ (IFN- γ) but not of IL-6, which suggests a preferential effect on T cells.^{13,14}

Leflunomide has also been shown to inhibit chemotaxis of peripheral blood neutrophils in RA patients.¹⁴ Studies of synovial tissues in RA patients receiving leflunomide revealed a reduction in synovial macrophages as well as expression of intracellular adhesion molecule 1 and vascular cell adhesion molecule 1.¹⁵ A decreased ratio of MMP-1 to tissue inhibitor of metalloproteinase 1 was also demonstrated.

In vitro, the active metabolite A77 1726 was shown to directly inhibit both the generation and the activity of osteoclasts.¹⁶ This activity seems to be independent of its inhibition of uridine synthesis or the blockade of NF- κ B.

HUMAN CLINICAL PHARMACOKINETICS

Absorption and bioavailability

After oral absorption, leflunomide is rapidly metabolized to A77 1726 within the gut wall, plasma, and liver. The active metabolite is very highly bound to plasma protein (more than 99%) and, correspondingly, has a low apparent volume of distribution. At a dose of 20 mg/day, steady state is reached in 7 weeks, and the average plasma concentration of A77 1726 is approximately 35 mg/mL. Trough plasma concentrations are linearly related to the maintenance dose of leflunomide, which indicates linear pharmacokinetics.

A77 1726 undergoes enterohepatic circulation and biliary recycling, which contributes to its long elimination half-life of approximately 2 weeks. Therefore, to achieve a steady state rapidly, administration of a loading dose followed by a lower maintenance dose has been used.

It was also shown that certain transporters may play a role in leflunomide resistance or suboptimal response. One such transporter is ABCG2, which is part of the breast cancer resistance protein (BCRP) family.¹⁷

Metabolism and elimination

Almost half of the administered dose is excreted as unmetabolized A77 1726 in the feces. Glucuronide conjugates and oxolinic acid derivatives are the principal metabolites recovered in the urine. A77 1726 is still detectable in the urine 36 days after administration of a single dose. A77 1726 readily binds to orally administered activated charcoal and even more so to cholestyramine, which enhances its elimination; these characteristics are used in clinical situations whenever toxicity is present or rapid reduction of blood levels is required.

Drug interactions

In a clinical trial in RA patients, the pharmacokinetics of A77 1726 and methotrexate were not altered by concomitant administration.¹⁸ The maximum concentration of A77 1726 after the loading and maintenance doses remained within the range seen in patients treated with leflunomide alone.

In vitro, A77 1726 is an inhibitor of CYP2C9, through which warfarin, tolbutamide, phenytoin, and several nonsteroidal antiinflammatory drugs

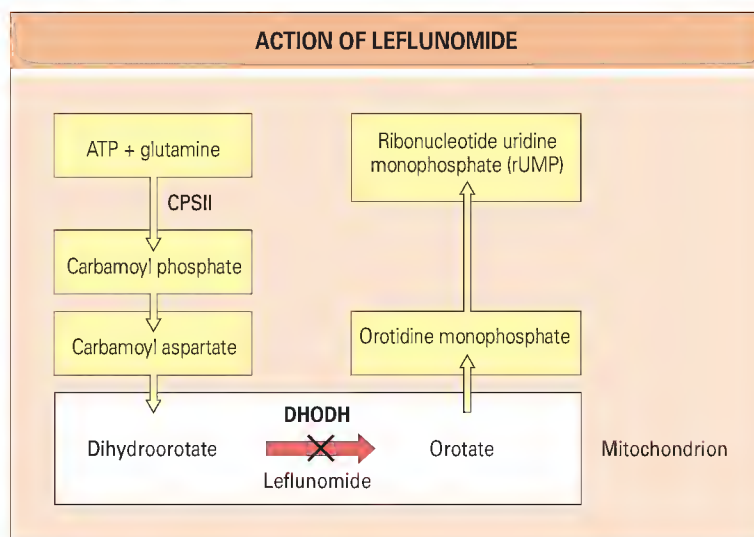


Fig. 57.1 Blocking of dihydroorotate dehydrogenase (DHODH), a key enzyme in the *de novo* synthesis of uridine, by leflunomide. ATP, adenosine triphosphate; CPSII, carbamoyl phosphate synthetase II.

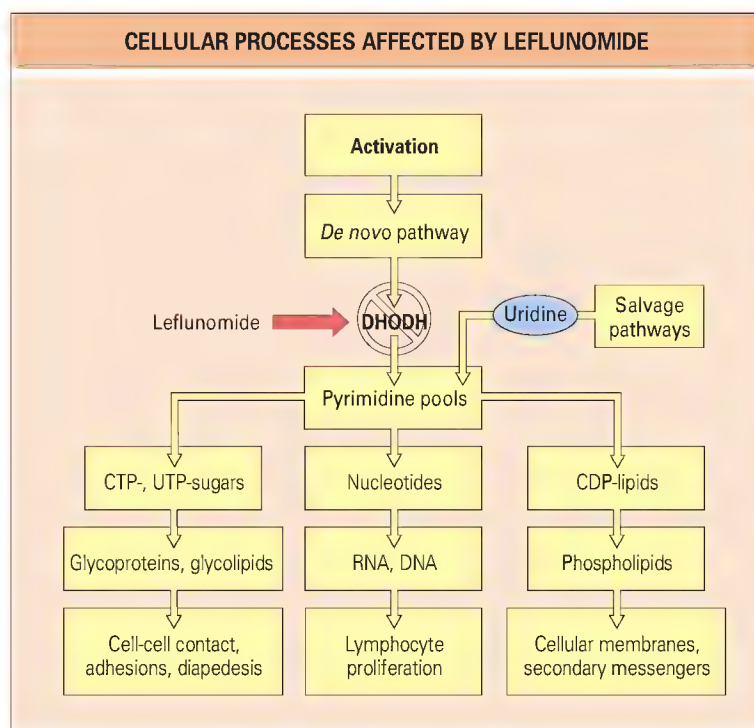


Fig. 57.2 Effect of Leflunomide on cellular processes through inhibition of *de novo* pyrimidine biosynthesis. CDP, cytosine diphosphate; CTP, cytosine triphosphate; DHODH, dihydroorotate dehydrogenase; UTP, uridine triphosphate.

are metabolized. However, in human *in-vivo* situations the free unbound drug is below the half-maximal inhibitory concentration (IC_{50}) for this enzyme, and no clinically significant drug interactions have been reported.

Based on recent pharmacokinetics studies in a pediatric population, the recommended daily dose of leflunomide is 20 mg for patients weighing more than 40 kg, 15 mg for those between 20 and 40 kg, and 10 mg for patients weighing less than 20 kg.¹⁹

EFFICACY

Monotherapy

Evidence from four multicenter, double-blind, randomized, controlled trials shows that leflunomide monotherapy is effective in the treatment of RA, is

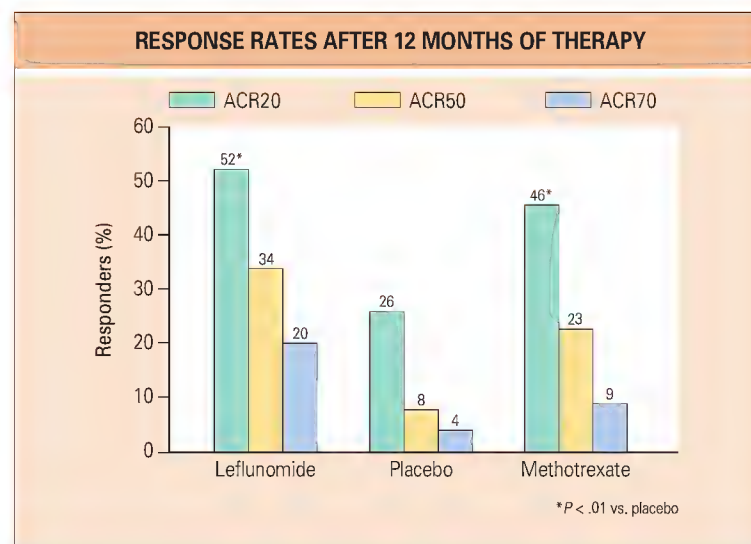


Fig. 57.3 Percentage of patients treated with leflunomide, methotrexate, or placebo who met the American College of Rheumatology (ACR) response criteria for improvement of 20%, 50%, 70%, or more (ACR20, ACR50, ACR70) at 12 months. (Data from Strand V, Cohen S, Schiff M, et al. *Treatment of active rheumatoid with leflunomide compared with placebo and methotrexate.* Arch Intern Med 1999;159:2542-50.)

significantly superior to placebo, and is similar in efficacy to sulfasalazine as well as moderate-dose methotrexate.

In the initial 6-month placebo-controlled dose-ranging study involving 402 patients (with a disease duration of 8.3 years), leflunomide was evaluated in doses of 5, 10, and 25 mg preceded by a single loading dose. In this study the two highest doses proved to be most efficacious.²⁰

In a subsequent 12-month study of leflunomide therapy in 482 patients (with a disease duration of 7 years), leflunomide at a dosage of 20 mg/day (after 100-mg loading doses on days 1 to 3) was compared with methotrexate (mean dose, 13.5 mg/wk) and placebo.²¹ When the less stringent ACR20 (American College of Rheumatology 20% improvement criteria) last observation carried forward analysis was used, leflunomide was found to be associated with a response rate of 52% compared with 46% for methotrexate. Response rates for both agents were higher than in the placebo group (26%) (Fig. 57.3). Clinically meaningful and statistically significant improvements in measures of function and health-related quality of life and work productivity were seen during treatment with leflunomide compared with placebo (Fig. 57.4). Leflunomide treatment resulted in significantly greater improvement in a number of the disability and quality of life measures.²² Leflunomide and methotrexate inhibited disease progression in approximately half the patients as measured by radiographic analysis (Fig. 57.5) and resulted in statistically significantly less radiographic progression compared with placebo at 12 months.²³

Longer-term efficacy was evaluated in a 12-month extension study in which patients who completed 52 weeks of treatment were given the option of continuing therapy for an additional year.²⁴ Patients receiving both leflunomide and methotrexate showed consistent improvement in signs and symptoms as well as in measures of function and health-related quality of life over the second year. The withdrawal rate in both groups of the year 2 cohort was low (<5%).

Leflunomide (20 mg/day) was also compared with methotrexate (10 to 15 mg/wk) in a head-to-head study involving 999 patients with shorter disease duration (3.7 years).²⁵ At 52 weeks, patients were given the option of continuing double-blind therapy for an additional 52 weeks. At the end of the first year more methotrexate-treated patients met ACR20 criteria (64.3%) than leflunomide-treated patients (50.5%) (Fig. 57.6). Improvement in signs and symptoms was also greater in the methotrexate-treated group after 1 year of therapy. As in the previous study, leflunomide elicited a more rapid response to therapy. Whether the higher methotrexate response rate in this study was a result of not including a folate supplement is unclear. In the subset of patients who elected to continue therapy for a second year, the ACR20 response rates were comparable for both drugs after 2 years of therapy. Disease modification as measured radiographically was similar with both drugs at 52 weeks but was more effective with methotrexate than with leflunomide after 2 years of therapy.

Leflunomide was also compared with sulfasalazine in a 6-month placebo-controlled study of 358 patients with a disease duration of 7 years.²⁶ At

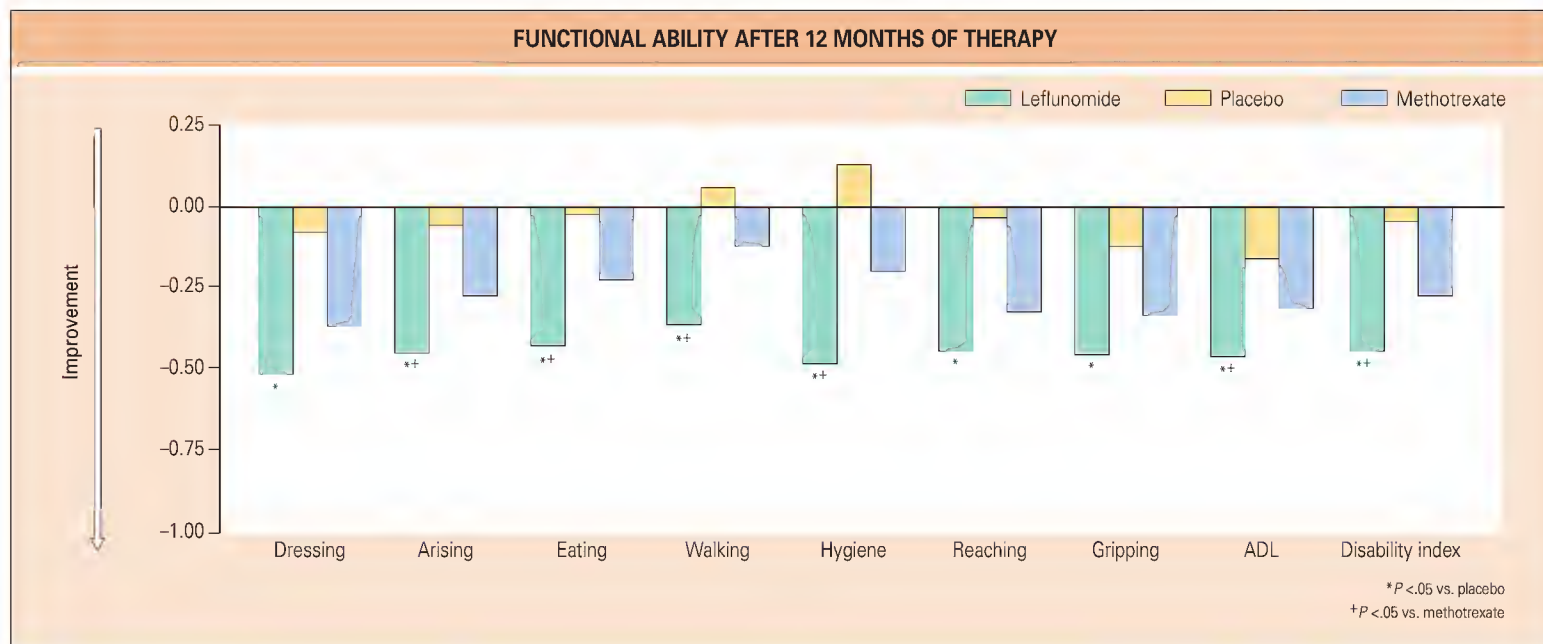


Fig. 57.4 Scores on individual subcategories of the Health Assessment Questionnaire after 12 months of therapy with leflunomide, methotrexate, or placebo. ADL, activities of daily living. (Data from Strand V, Tugwell P, Bombardier C, et al. *Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis*. *Arthritis Rheum* 1999;42:1870-8.)

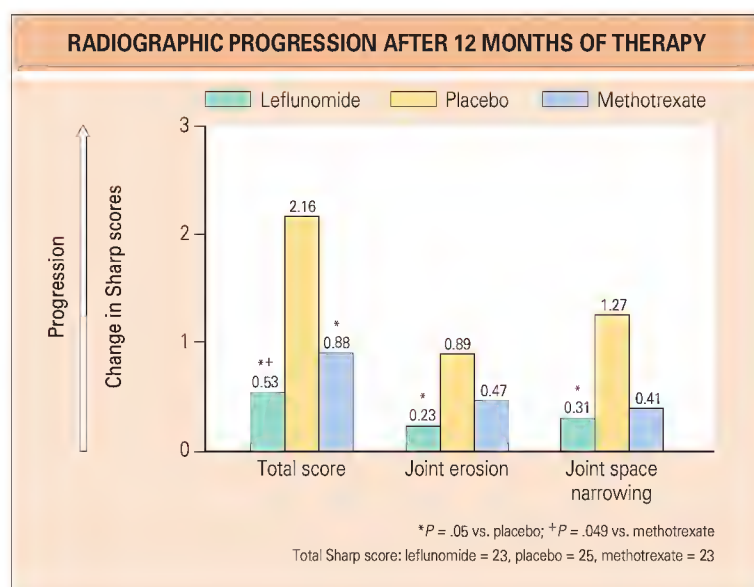


Fig. 57.5 Mean changes from baseline in total Sharp scores and erosion and joint space narrowing subscores for the intent-to-treat population. (Data from Strand V, Tugwell P, Bombardier C, et al. *Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis*. *Arthritis Rheum* 1999;42:1870-8.)

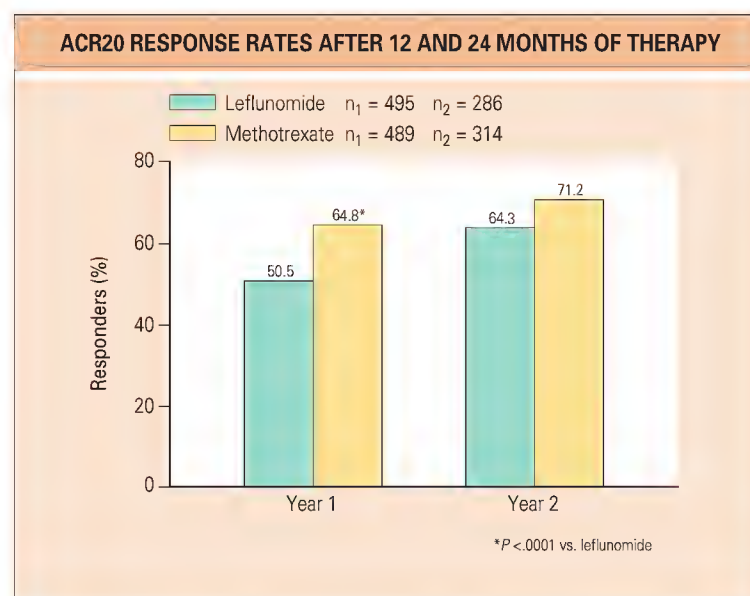


Fig. 57.6 Percentage of patients who met the American College of Rheumatology (ACR) response criteria for improvement of 20% (ACR20) after 12 and 24 months of therapy with leflunomide or methotrexate. (Data from Emery P, Breedveld FC, Lemmel EM, et al; Multinational Leflunomide Study Group. *A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis*. *Rheumatology* 2000;39:655-65.)

6 months, the ACR20 response rate was comparable for the groups treated with leflunomide (55%) and sulfasalazine (56%), and responses for both groups were superior to that for the placebo group (29%) (Fig. 57.7). Leflunomide demonstrated a more rapid onset of action, which was particularly evident after 1 month of therapy. At 6 months, both drugs inhibited radiographic progression to a similar extent. Patients completing the initial 6-month phase were given the option of continuing in a double-blind fashion in 12- and 24-month extension studies, with the placebo group switching to sulfasalazine. Leflunomide- and sulfasalazine-treated patients demonstrated a sustained response to 12 months, with the leflunomide cohort demonstrating a significantly greater ACR20 response rate than the sulfasalazine group at 24 months. Little disease progression, as determined radiographically, was observed at 1 year and 2 years in the cohort receiving leflunomide and in patients receiving sulfasalazine who remained on therapy (Fig. 57.8).

Combination therapy

Because methotrexate is thought to act primarily on the purine pathways of cellular metabolism whereas leflunomide inhibits pyrimidine pathways, the combination of leflunomide and methotrexate has the potential for synergy in inhibiting the proliferation of cells involved in the immune inflammatory response.

The safety, efficacy, and pharmacokinetics of combination therapy with leflunomide and methotrexate were initially evaluated in an open-label 52-week study of 30 patients who exhibited active disease despite receiving 17 mg/wk of methotrexate.¹⁸ After administration of a loading dose of 100 mg/day for 2 days, leflunomide was given in a dosage of 10 mg/day for 3 months and then increased as required to 20 mg in patients with persistently active disease.

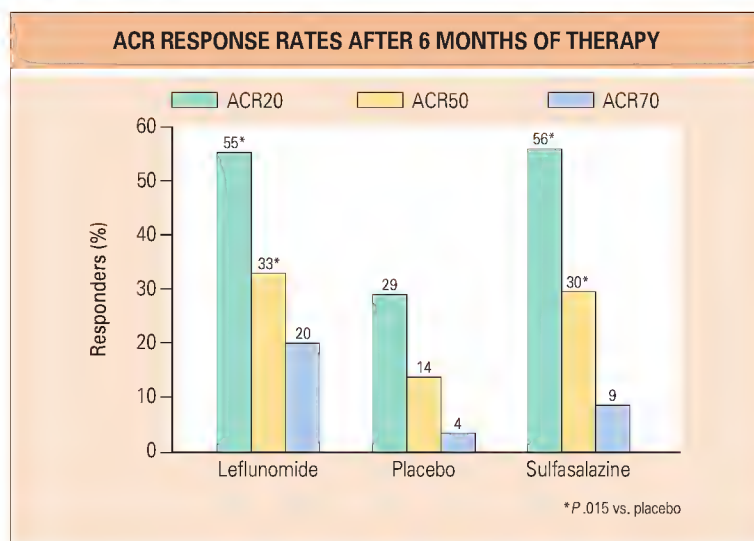


Fig. 57.7 Percentage of patients who met the American College of Rheumatology (ACR) response criteria for improvement of 20%, 50%, or 70% (ACR20, ACR50, ACR70) after 6 months of therapy with leflunomide, sulfasalazine, or placebo. (Data from Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulfasalazine in active rheumatoid arthritis: a double-blind randomized multicentre trial. *Lancet* 1999;353:259-66.)

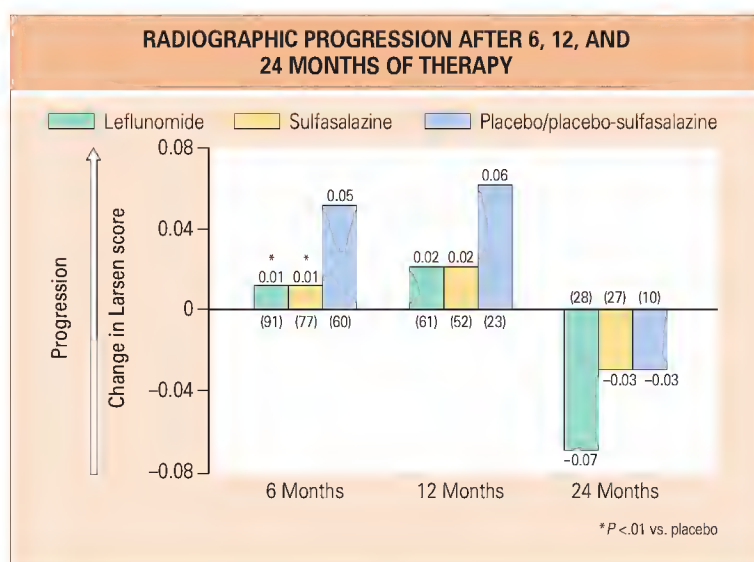


Fig. 57.8 Mean change in Larsen score for patients treated for 6, 12, and 24 months with leflunomide, sulfasalazine, or placebo. (Data from Scott DL, Smolen JS, Kalden JR, et al. Treatment of active rheumatoid arthritis with leflunomide: two-year follow-up of a double-blind, placebo-controlled trial versus sulfasalazine. *Ann Rheum Dis* 2001;60:913-23.)

There was no significant pharmacokinetic interaction between leflunomide and methotrexate. The combination was generally well tolerated; however, liver enzyme elevations were seen in the majority of patients (63%). Efficacy measures revealed a good response, with 53% of patients achieving ACR20 criteria. Liver biopsies in three patients with elevated liver enzyme levels revealed mild (not clinically significant) hepatic fibrosis in two patients and normal findings in one patient.

The combination of leflunomide and methotrexate was subsequently evaluated in a 24-week double-blind, placebo-controlled study of 263 patients with RA who exhibited an inadequate response to methotrexate.²⁷ Leflunomide was given in a dosage of 10 mg/day (after administration of two 100-mg loading doses) for 2 months, after which the dosage could be increased to 20 mg/day. The results showed that leflunomide provided additional benefit in 51.5% of patients who showed a partial response to methotrexate alone. Elevated liver function test results were observed in 28% of patients receiving combination therapy. These data suggest that the leflunomide-methotrexate combination can be used with appropriate liver

enzyme monitoring. A 6-month open-label extension was carried out in which patients receiving the combination of leflunomide and methotrexate continued treatment, whereas patients previously given methotrexate alone now received leflunomide (in combination with methotrexate) in a dosage of 10 mg/day without a loading dose, with subsequent dose adjustment based on the patient's response.²⁸ The combination of leflunomide and methotrexate continued to provide significant therapeutic benefit, and patients switching from placebo to leflunomide showed the same magnitude of response after 6 months despite the lack of a loading dose of leflunomide (Fig. 57.9). These data suggest that, in patients with an inadequate response to methotrexate, leflunomide is effective without the use of a loading dose. Another randomized controlled trial supported the concept that the combination of sulfasalazine with leflunomide was ineffective by demonstrating no significant difference in the Disease Activity Score when sulfasalazine was added to leflunomide compared with the use of sulfasalazine alone in patients who had previously shown inadequate response to leflunomide monotherapy.²⁹ However, a trend toward a higher response was seen, and the ACR70 response rate of the group given both drugs was superior to that of the group given sulfasalazine alone. A subsequent analysis of results for 968 patients with RA demonstrated that adding leflunomide or sulfasalazine to methotrexate rather than switching to monotherapy did not result in significantly different retention rates for leflunomide or sulfasalazine. Data from a large observational database encompassing 1214 RA patients were used to evaluate the clinical outcomes of two potential strategies in patients discontinuing disease-modifying antirheumatic drugs (DMARDs) because of ineffectiveness: switching to another DMARD, and step-up combination therapy with methotrexate, sulfasalazine, or leflunomide. Retention rates for leflunomide and sulfasalazine were similar for adding and for switching.³⁰

The efficacy and safety profiles of 10-mg versus 20-mg doses of leflunomide were evaluated in a 24-week multinational, randomized, double-blind, parallel-group study of 402 RA patients.³¹ Patients receiving 10 mg of leflunomide were given one 100-mg loading dose on day 3, whereas those receiving 20 mg were given a 100-mg loading dose on days 1 to 3. The results demonstrated superiority of the 20-mg dose.

Open-label and extension studies

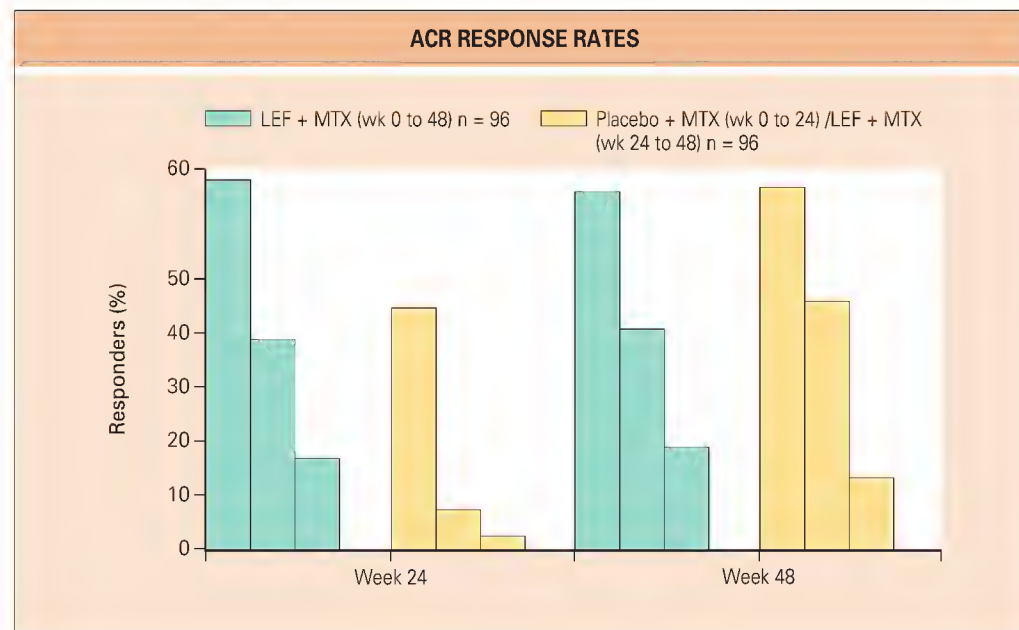
A 5-year open-label uncontrolled extension study demonstrated that the early efficacy of leflunomide based on ACR response rates and Health Assessment Questionnaire scores seen at 1 year was maintained for up to 5 years.³² The long-term safety profile was similar to that in previous studies. The sustainability of improvement in physical function and health-related quality of life (HRQOL) was examined in three phase 3 randomized controlled trials comparing leflunomide, sulfasalazine, and methotrexate. Over 24 months, improvements in physical function were shown to be sustained and reflected improvements in mental as well as physical domains of HRQOL.³³

Postcommercialization registries were started and observational studies conducted in several countries and were independently managed by local investigators, in most instances with financial or logistic support from the drug manufacturer. Data for one cohort of 285 patients were analyzed to determine the percentage of patients discontinuing leflunomide treatment over time compared with the percentage discontinuing treatment with other conventional DMARDs including methotrexate and sulfasalazine; leflunomide was associated with higher discontinuation rates due to toxicity but similar discontinuation rates due to lack of efficacy.³⁴

Several other open-label prospective studies have evaluated the efficacy and safety of leflunomide in real-life settings. One German study included 308 patients with early RA (disease duration of 1 year or less) who were treated for 24 weeks. All patients were eligible for leflunomide therapy according to the German prescription guidelines.³⁵ More than 50% were DMARD naive; 57% received a 3-day 100-mg loading dose, and the daily maintenance dose was 20 mg in 92% of patients. Leflunomide was administered in combination with methotrexate in 22% and in combination with another DMARDs in 5% of patients. At 6 months, 254 patients (82%) completed the study; 36.2% achieved a good EULAR response and 48.4% achieved a moderate response, with the vast majority reaching this level of response by 12 weeks. No new safety issues were raised.

A prospective postmarketing study was conducted in New Zealand and included 380 patients with long-standing RA (mean disease duration, 12.1 years); follow-up data were available for 244 patients.³⁶ The leflunomide loading dose was given to 90% of patients, and more than 80% received the 20-mg maintenance dose. Retention rates were 64% at 1 year and 49.4% at 2 years. Leflunomide was administered as monotherapy in 30%. Fifty-seven patients discontinued therapy because of adverse effects, the majority of which were gastrointestinal (49%). Seven patients required washout

Fig. 57.9 American College of Rheumatology (ACR) response rates at weeks 24 and 48 in patients receiving double-blind leflunomide (LEF) and methotrexate (MTX) from week 0 to 48 and in patients receiving placebo and methotrexate from week 0 to 24 followed by open-label leflunomide and methotrexate from week 24 to 48. (Data from Kremer J, Genovese M, Cannon G, et al. Combination of leflunomide and methotrexate [MTX] therapy for patients with active rheumatoid arthritis failing MTX monotherapy: open-label extension of a randomized, double-blind placebo controlled trial. *J Rheumatol* 2004;31:1521-31.)



procedures: two patients for Stevens-Johnson syndrome, two for diarrhea, and one each for abnormal liver function test results, skin rash, and desire to become pregnant.

The effectiveness of leflunomide was compared with that of infliximab and etanercept using survival on drug as an evaluation tool. Patients in a standardized clinical protocol were evaluated over 12 months. Patients not responding to DMARDs, including methotrexate, were treated with etanercept ($n = 184$), infliximab ($n = 223$), or leflunomide ($n = 114$). Rates of survival on drug as a percentage of the number of patients followed were 82%, 55%, and 32% at 12 months for etanercept, infliximab, and leflunomide, respectively. However, differences in patient selection and drug efficacy may have influenced the comparison between the tumor necrosis factor (TNF) blockers and leflunomide.³⁷ Similar data regarding the sustainability of leflunomide therapy were obtained in a prospective case series study in 136 patients initiating treatment with the drug. After a median follow-up of 317 days, 56% of patients receiving leflunomide withdrew from treatment, mainly because of adverse drug reactions (29%) or lack of efficacy (13%).³⁸

Combination therapy with biologic agents

The increasing use of biologic agents in RA coupled with the concept of combination therapy has resulted in increased use of a combination of leflunomide and biologic agents. All the data have been generated independently by investigators. Analyses of data from the Swiss (SCQM) and German (RABBIT) registries have compared the efficacy and safety outcomes of the combination of anti-TNF agents with methotrexate, leflunomide, or other DMARDs.^{39,40} Around 20% to 25% of patients were treated with TNF inhibitors and leflunomide compared with more than 70% who received anti-TNF agents with methotrexate. Both agents had comparable efficacy and retention rates.

More recently, an open-label prospective observational study of the random addition of an anti-TNF agent (etanercept, infliximab, or adalimumab) to either methotrexate or leflunomide in patients with inadequate response to the latter two drugs was reported.⁴¹ The 60 patients in each treatment group were assessed at 4, 12, and 24 weeks. Clinical efficacy and retention rates were comparable for the groups given methotrexate plus anti-TNF agent and leflunomide plus anti-TNF agent, with a slightly higher rate of discontinuation due to adverse effects in the leflunomide group.

The advent of biologic agents other than the TNF inhibitors has prompted interest in combining these agents, in particular rituximab, with leflunomide.⁴² The Collaborative European Registries for the Evaluation of Rituximab in Rheumatoid Arthritis (CERERRA) compared the clinical responses and safety profiles of rituximab when given in combination with methotrexate (1195 patients), in combination with leflunomide (177 patients), or as monotherapy (505 patients). More patients in the leflunomide combination group achieved good and moderate EULAR responses at 6 and 12 months and fewer patients required retreatment at 12 months than in the other two groups. Adverse events occurred in 10.2%, 13.2%, and 13.9% of patients in the rituximab plus leflunomide, rituximab plus methotrexate, and rituximab monotherapy groups, respectively.

Treatment of other rheumatologic conditions

Since the commercialization of leflunomide, clinicians in different countries have reported their independent experiences in using leflunomide for the treatment of other rheumatologic conditions in addition to rheumatoid arthritis. Although juvenile idiopathic arthritis is not an official indication for leflunomide therapy, its efficacy compared with methotrexate in treating this condition was demonstrated in a small randomized trial.⁴³ Leflunomide and methotrexate were dosed based on patient weight, with a full dose given to those weighing more than 40 kg. Methotrexate had numerically superior efficacy, with 89% of those in the methotrexate-treated group achieving a ACR Pedi30 response at 16 weeks versus 68% in the leflunomide group. With both drugs improvement was maintained to 48 weeks, and tolerability was comparable.

A retrospective analysis of the use of leflunomide was conducted that involved 48 patients with juvenile idiopathic arthritis who had switched from methotrexate, primarily because of adverse events, and an additional 10 patients in whom leflunomide was added to ongoing methotrexate therapy.⁴⁴ About 30% of patients attained remission; leflunomide was discontinued in 15 patients, in the majority (13) because of adverse effects.

The use of leflunomide in psoriatic arthritis has been evaluated in a large multicenter international study funded by the manufacturer.⁴⁵ In a 24-week controlled study of 188 patients with psoriatic arthritis, a modified ACR20 result was achieved in 36% of leflunomide-treated patients at 24 weeks compared with 20% in the placebo group. Fifty-nine percent of the leflunomide-treated patients compared with 30% of the placebo-treated patients achieved a psoriatic arthritis response (as judged by PsARC). The effect on psoriasis was also mild, with 17% of patients receiving leflunomide and 7% of those given placebo achieving a significant clearing of skin disease (as measured by PASI-75).

Encouraging results have been observed with leflunomide in combination with methotrexate or rituximab in antineutrophil cytoplasmic antibody-associated granulomatous vasculitis,^{46,47} Takayasu arteritis,⁴⁸ and sarcoidosis.⁴⁹ It was found to be ineffective in a pilot study in patients with primary Sjögren syndrome and a randomized controlled trial in patients with ankylosing spondylitis.

SAFETY AND TOLERABILITY

In clinical trials involving a total of 1339 patients treated with leflunomide monotherapy, the frequency of adverse effects and the safety profile of leflunomide are in general similar to those of moderate-dose methotrexate and sulfasalazine. However, the adverse effects tend to persist longer with leflunomide, even with dose reduction or discontinuation of therapy, because of the long half-life of the drug. The most common reported adverse effects are the following:

- **Gastrointestinal effects:** Gastrointestinal symptoms include diarrhea, dyspepsia, nausea, vomiting, and abdominal pain. Diarrhea is

generally mild to moderate and usually occurs within the first 3 months. In approximately 30% of patients, diarrhea resolves within 1 week, but in about 35% the symptoms persist for longer than 1 month. Nausea and vomiting are usually transient. Significant weight loss has also been reported in 7% of 70 patients beginning leflunomide therapy.⁵⁰ In a retrospective chart review encompassing 108 patients with inflammatory arthritis treated at UK centers with a combination of leflunomide and methotrexate, at a median of 24.5 months after initiation of therapy 51% of patients were still taking the drug combination. The most common reasons for discontinuation were nausea, vomiting, diarrhea, and abnormal liver function test results.⁵¹

- **Neurologic effects:** Nervous system effects of leflunomide include headache, dizziness, and paresthesia. The central nervous system adverse effects are usually mild to moderate and are not commonly a cause for stopping the drug. Case reports of peripheral neuropathy submitted to the U.S. Food and Drug Administration (FDA) in association with leflunomide have been reviewed.⁵² In the 80 reported cases, symptoms began after a mean of 6 months of treatment. Electrodiagnosis was consistent with distal axonal, sensory, or sensorimotor polyneuropathy in most patients. Patients withdrawing from leflunomide within 30 days were more likely to show improvement. In a study to monitor potential clinical neurotoxicity in 113 leflunomide-treated patients, eight incident cases of peripheral neuropathy and two cases of worsening of preexisting neuropathy were diagnosed by nerve conduction studies (incidence, 9.8%).⁵² Compared with patients not receiving leflunomide, patients receiving leflunomide were older (mean age, 69), more often diabetic (30%), and more often treated with potentially neurotoxic drugs (20%). At least one risk factor was found in 50% of patients with neuropathy (positive predictive value, 56%; negative predictive value, 96%). These results suggest the need for careful monitoring of the patient's neurologic status during leflunomide treatment. Patients have been reported to experience stabilization symptomatically and electrophysiologically on cessation of the drug.
- **Cardiovascular effects:** Hypertension is the most common cardiovascular effect of leflunomide. Data from clinical trials suggest that aggravation of existing hypertension is more likely to be a problem with leflunomide than new-onset hypertension.
- **Infection:** Clinical trials did not show a higher incidence of infection in patients receiving leflunomide than in patients receiving placebo. However, leflunomide is not recommended for patients with some immunodeficiency, substantial impairment of bone marrow function, or serious infections (i.e., those requiring intravenous antibiotics or hospitalization). If infection occurs in patients receiving combination therapy with another immunosuppressant such as methotrexate or corticosteroids, early and vigorous treatment should be considered. Leflunomide should be discontinued in the event of a serious infection and a washout procedure should be initiated. No cases of disseminated fungal or viral disease or opportunistic infections have been reported during clinical trials with leflunomide. A retrospective study of 201 patients revealed a higher risk of postoperative wound-healing complications after elective orthopedic surgery in patients receiving leflunomide therapy (40.6%) than in patients receiving methotrexate (13.6%) ($P = .01$).⁵³ Although it was recommended to interrupt leflunomide treatment preoperatively in this group of patients, the long half-life of leflunomide makes that impractical.
- **Cutaneous effects:** Leflunomide was associated with a higher rate of skin reactions compared with placebo in clinical trials, with an overall incidence of rash of 9.9%. Most rashes occurred between the second and fifth months of treatment and resulted in discontinuation of therapy in 1.3% of patients. Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. In all cases, patients were concurrently receiving other medication known to be associated with these skin lesions. Any suspicion of either of these conditions necessitates discontinuation of leflunomide and initiation of a cholestyramine washout procedure. Under these circumstances, reexposure to leflunomide is contraindicated. Alopecia was observed with low frequency and was reversible on discontinuing the drug. A small percentage of patients (fewer than 1.0%) withdrew because of alopecia. Mouth ulcers occurred at the same frequency as with placebo in these trials.
- **Respiratory effects:** Interstitial lung disease (ILD) has been reported in patients receiving leflunomide.⁵⁴ Baseline pulmonary disease and/or abnormal findings on chest radiographs or computed tomographic scans were observed in 69% of 29 patients before initiation of leflunomide. Prior methotrexate therapy was reported in 42% of patients. Forty-one percent of patients died. Most patients initially seek

treatment for acute pneumonitis, but a number of patients have slowly progressive ILD at presentation. In one report,^{54a} the mean duration of leflunomide treatment was 14.5 months before the onset of ILD. In another report,^{54b} pneumonitis occurred 12 to 20 weeks after the addition of leflunomide to methotrexate. A significant mortality rate, as high as 30%, has been associated with this pulmonary complication. Histologic findings include a mosaic pattern of acute and organizing diffuse alveolar damage. Treatment with early withdrawal of leflunomide, high-dose corticosteroids, and cholestyramine has been shown to be effective in some patients.⁵⁵ A population-based epidemiologic study using a claims database encompassing 62,734 RA patients demonstrated that the increased risk of ILD was associated with leflunomide use in patients with a history of methotrexate use or preexisting ILD, with a relative risk (RR) of 2.6 (95% confidence interval [CI], 1.2 to 5.6).⁵⁶ In patients with no previous methotrexate use or history of ILD the risk of ILD was not elevated (RR, 1.2; 95% CI, 0.4 to 3.1). The results were thought to be a consequence of the channeling of high-risk patients to leflunomide therapy. A postmarketing surveillance study of leflunomide use in 5054 Japanese patients was recently reported.⁵⁷ Sixty-one patients were reported to have lung injury with one third dying of it. Risk factors included preexisting ILD, use of a loading dose, history of smoking, and low body weight (40 kg or less). Recently, a review of the English literature found 32 cases of leflunomide-associated ILD, with the majority (82%) presenting within the first 20 weeks of therapy, and found the same risk factors of preexisting ILD or methotrexate lung toxicity; these two conditions should be considered contraindications to leflunomide use.⁵⁸ It seems that Japanese patients are more prone to such complications than are Western patients.

- **Hematologic effects:** Rare cases of pancytopenia have been observed in postmarketing experience, primarily in patients with known risk factors for blood dyscrasias; many cases were confounded by concomitant use of other medications. Significantly, leflunomide was not associated with an increased risk of lymphoproliferative disorders, which occurred at a frequency of 0.2% in around 2077 patient-years of exposure. This frequency was in line with the expected rate of lymphoproliferative disorders in RA of 0.2%. No increase in the incidence of malignancies has been demonstrated, with a reported rate of 1.3% for leflunomide compared with 1.2% for placebo.
- **Teratogenicity:** Leflunomide is teratogenic in animals and therefore is contraindicated during conception and pregnancy. The Organization of Teratology Information Specialists (OTIS) reported on the outcomes of 64 pregnancies in Canada and the United States in women exposed to leflunomide compared with outcomes in 108 women exposed to other DMARDs and 78 healthy controls.⁵⁹ There were 56 live births in the leflunomide group, comparable to the rates in the other two groups. Nearly all the women (95.3%) underwent at least one course of cholestyramine washout, and in a metabolite level below 0.02 mg/mL was documented. Birth outcomes were similar across the three groups.

Laboratory tests

The incidence of elevation of liver enzymes—alanine aminotransferase (ALT) and aspartate aminotransferase (AST)—with leflunomide therapy is similar to that observed with moderate-dose methotrexate therapy in patients receiving folate supplementation. ALT elevations of less than three times normal are usually reversed without discontinuation of leflunomide and may decrease with continued therapy or with dose reduction. Elevations of more than three times normal also reverse with dose reduction or discontinuation. Persistently elevated liver function test results should not be tolerated and should prompt drug withdrawal. Cholestyramine should be administered to patients with persistent elevation above three times normal levels despite withdrawal. A cholestyramine washout of 8 g three times daily for 11 days is generally adequate. Liver function abnormalities are generally asymptomatic and are not associated with decreased serum albumin level or prolonged prothrombin time. Because the active metabolite is cleared by the liver and biliary system, leflunomide is contraindicated in patients with impaired liver function. Liver function should be monitored on a regular basis.

Studies of combination therapy with leflunomide and methotrexate have found increased hepatotoxicity. In the larger study by Kremer and colleagues,²⁷ nearly 30% of patients exhibited an increase in AST or ALT levels at some time during the 6-month study, but only 1.5% and 3.8% demonstrated a threefold elevation of AST and ALT, respectively. The higher

incidence of elevated liver enzyme levels when leflunomide is combined with methotrexate for treatment of RA and psoriatic arthritis was confirmed in the analysis of the Consortium of Rheumatology Researchers of North America (CORRONA) database⁶⁰; a relation to the dose of methotrexate was also documented. The substantial proportion of patients who exhibit liver function abnormalities with the leflunomide-methotrexate combination suggests a need for careful monitoring of liver function with this combination. The data concerning serious liver toxicity reported to date for this combination (see earlier) have emphasized this requirement. A postmarketing report from the European Agency for the Evaluation of Medicinal Products detailed the experience in leflunomide-treated RA patients with a total drug exposure of 104,000 patient-years. The report described 296 cases of hepatic abnormality, including 129 cases of serious liver disease. The 296 cases included 232 patients with liver function abnormalities, 2 with cirrhosis, 15 with liver failure, and a total of 15 deaths. Most of the liver abnormalities occurred within the first 6 months of treatment without predilection for age or gender. Most of the patients with serious hepatotoxicity were also taking another potentially hepatotoxic drug (e.g., nonsteroidal antiinflammatory drugs and/or methotrexate) and had one or several comorbidities (including alcohol abuse; hepatitis A, B, and C; ILD; renal insufficiency; autoimmune liver disease; and pancreatitis).

After an extensive review of available data from clinical trials and several medical databases and postmarketing surveillance reports, the FDA Advisory Committee concluded that serious hepatotoxicity such as hepatocellular jaundice and acute liver failure is rare.⁶¹ Postmarketing surveillance spontaneous reporting by the FDA revealed that hepatic failure occurred with an incidence of 14 per 100,000 patient-years, similar to that observed with other DMARDs.⁶² A large claims database study demonstrated comparable results.

Treatment-related anemia was not observed with leflunomide. Some patients experienced transient reductions in white blood cell count without sustained leukopenia, as well as transient thrombocytopenia. In patients with recent or concurrent treatment with immunosuppressive drugs or with bone marrow toxicity potential or hematologic abnormalities, frequent hematologic monitoring should be performed. No clinically significant effect of leflunomide on levels of plasma electrolytes, total protein, creatinine, bilirubin, alkaline phosphatase, glucose, cholesterol, or triglycerides has been noted. A reduction in serum uric acid level was observed in 30% of treated patients, with an average reduction of 60 mm/L during therapy that was not associated with reduced calcium phosphate or bicarbonate levels. Uricosuria was related to inhibition of uric acid reabsorption. Renal function as determined by serum creatinine and urea levels was unaffected. However, given that leflunomide is partially eliminated by the kidney, it should be used with caution in patients with mild renal insufficiency. Leflunomide is contraindicated in patients with moderately severe renal impairment. Several case reports have addressed a potential interaction between leflunomide and warfarin. Such an interaction was at least partially responsible for an increase in international normalized ratio in a patient with a previously stable ratio. In patients taking both drugs clinicians should increase their frequency of monitoring of the international normalized ratio and adjust the warfarin dosage accordingly.

PRESCRIBING TIPS

Leflunomide is indicated for patients with moderate to severe active RA in both early and late disease. Because of its long half-life, leflunomide therapy

has been initiated with a loading dose of one 100-mg tablet/day for 3 days. However, because of toxicity concerns, many rheumatologists have stopped using the loading dose. Generally, a daily maintenance dosage of 10 to 20 mg/day is used. If dosing at 20 mg/day is not well tolerated clinically, the dosage may be decreased to 10 mg/day. In patients in whom the risk of toxicity is greater (e.g., those who are taking leflunomide in combination with methotrexate or those who are elderly) the maintenance dosage may be initiated at 10 mg/day for 2 months with a dose escalation to 20 mg if there is an inadequate response. Caution should also be exercised by using the lowest possible dose of methotrexate. As noted earlier, for patients not requiring a rapid response to therapy, consideration should be given to initiating therapy without a loading dose.

Before initiation of the drug a complete blood cell count, including a differential white blood cell and platelet count, and liver function tests, including AST and ALT levels, must be performed. According to the product monograph, a complete blood cell count and liver blood tests should also be performed every 2 weeks for the first 6 months and then every 8 weeks thereafter. More frequent early monitoring might be done if the drug is used in combination with methotrexate.

Patients experiencing a serious adverse effect of leflunomide should undergo a washout with cholestyramine (8 g three times daily) or activated charcoal (50 g four times daily) for 11 days. The metabolite of leflunomide, A77 1726, is not removed with peritoneal dialysis, although with hemodialysis A77 1726 is cleared somewhat more rapidly and with a shorter half-life. These findings suggest that dialysis is not an effective washout procedure.

Leflunomide is contraindicated in patients with impaired liver function, severe renal impairment, severe hypoproteinemia due to causes other than RA (e.g., nephrotic syndrome, serious infections, known immunodeficiency, bone marrow dysfunction, anemia, leukopenia, neutropenia, thrombocytopenia), or known hypersensitivity to the drug. Leflunomide should be used with caution in combination with methotrexate. It is contraindicated in serious infection, and patients should be advised to seek medical advice if they note worsening fatigue, bruising, sore throat, increased susceptibility to infection, or skin or mucous membrane lesions.

Leflunomide is teratogenic in animals and therefore should be used with caution in women of childbearing age. It should not be used in women who are, or may become, pregnant or those who are breastfeeding. In women contemplating pregnancy the plasma A77 1726 level should be checked to ensure that it is below 0.02 mg/L, which the manufacturer deems to present minimal teratogenic risk. Accelerated removal using cholestyramine (8 g three times daily for 11 days) or activated charcoal should be carried out, which shortens the clearance time to 3 months. After the washout, plasma levels of the active metabolite must be evaluated and must be less than 0.02 mg/L. This plasma level must be verified by a second test performed at least 14 days after the first plasma level of less than 0.02 mg/L is achieved. Women should be advised to be sure they are not pregnant before starting leflunomide therapy and to use reliable contraception while receiving the drug. Although no data exist, it is suggested by the manufacturer that men wishing to father a child discontinue leflunomide use and undergo an accelerated removal procedure.

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58

Immunosuppressives: cyclosporine, cyclophosphamide, azathioprine, mycophenolate mofetil

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- There is some evidence that cyclophosphamide (CYC) and cyclosporine (CsA) inhibit bony damage resulting from rheumatoid arthritis.
- CYC and CsA are associated with the most serious toxicity of the disease-modifying antirheumatic drugs.
- Mycophenolate mofetil and CYC are the drugs of choice for lupus nephritis.
- Cyclophosphamide is often used in various vasculitides.

INTRODUCTION

This chapter reviews the use of disease-modifying antirheumatic drugs (DMARDs) that are not covered in other chapters, namely, azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil.

Because the mechanisms of action of these drugs demonstrate some similarities (as well as differences), their mechanisms of action are addressed together (Table 58.1). Likewise, the pertinent pharmacokinetics of these medications is discussed in a single section. Thereafter, the evidence for the efficacy of these drugs and their toxicities as well as tips on their use are addressed for each drug each separately.

MECHANISMS OF ACTION

Azathioprine

Azathioprine (AZA) interferes with adenine and guanine ribonucleotide via suppression of inosinic acid synthesis. Its main active metabolite is 6-thioguanine. This, in turn, is a metabolic product of AZA's principal metabolic product, 6-mercaptopurine (6-MP).^{1,2} In rheumatoid arthritis (RA), AZA reduces the numbers of circulating B and T lymphocytes (particularly suppressor, or CD8+, cells), mixed lymphocyte reactivity, immunoglobulin M (IgM) and IgG synthesis, and interleukin-2 (IL-2) secretion.

Cyclophosphamide

Active metabolites of cyclophosphamide (CYC), principally phosphoramide mustard, cross-link DNA so that it cannot replicate. CYC is cytotoxic to both resting and dividing lymphocytes.^{1,3} In RA patients CYC (intravenous [IV] or oral) suppresses helper T cell (Th) functions, decreases the number of activated T cells by 30% to 40% (which correlates with clinical improvement), and dramatically decreases the number of B cells for months.⁴

CYC suppresses primary cellular and humoral immune responses, especially if administered immediately after an antigen challenge, but it can also inhibit an established humoral or immune response. It effectively suppresses many cell-mediated immune responses such as the reaction to the delayed hypersensitivity skin test and graft-versus-host reactivity, and it is antiinflammatory.³

Cyclosporine

Cyclosporine (CsA) complexes with cyclophilin (a cytoplasmic protein), which then binds calcineurin, an intracellular phosphatase. This in turn

regulates gene transcription coding for IL-2 and other cytokines.^{3,5} Further recent data demonstrate that CsA inhibits IL-17 production by Th17 cells.⁶ Additionally, CsA is antiangiogenic in rheumatoid synovial fibroblasts via inhibition of AP-1-mediated vascular endothelial growth factor expression,⁶ which demonstrates a possible mechanism to reduce synovial proliferation.

CsA blocks the amplification of cellular immune responses and the generation of T-cell effectors and other functions dependent on IL-2. It inhibits the B-cell production of antibody to T-cell-dependent antigens, interferon- γ production, and natural killer cell activity. Growth of bone marrow-derived myeloid, erythroid, or B-lymphocyte cell line responses to T-cell-independent antigens are not affected. CsA does not impair macrophage responses to lymphokines.³

Mycophenolate mofetil

Mycophenolate mofetil (MMF) breaks down rapidly to mycophenolic acid (MPA), the active form of this drug. MPA inhibits inosine monophosphate dehydrogenase. Cyclin-dependent kinase activity is inhibited and cyclin-dependent kinase inhibitor P27 elimination is blocked. This inhibits T-cell lymphocyte proliferation and downstream effects, such as intercellular adhesion to endothelial cells. *In vitro*, the expression of E-selectin, P-selectin, and intercellular adhesion molecule 1 on endothelial cells is markedly reduced. The complementary T-cell ligands leukocyte function antigen, very late antigen 4, and P-selection glycoprotein ligand 1 are functionally impaired, which reduces T-cell adhesion to and penetration through the endothelium and reduces lymphocyte recruitment to sites of inflammation.⁷

Enteric-coated MMF sodium (EC-MPA) was designed as an alternative to MMF. EC-MPA releases a different formulation of MPA. MPA dissolves slowly after reaching the small intestine, which delays the release of MPA. EC-MPA 720 mg twice daily is therapeutically equivalent to MMF 1000 mg twice daily in renal transplant patients and apparently decreases the adverse effects relative to the non-EC compound.

PHARMACOKINETICS

Table 58.2 summarizes the most pertinent pharmacokinetic properties of these drugs. Additional comments regarding the pharmacokinetics of each drug are outlined in the following sections.

Azathioprine

AZA is chemically cleaved to 6-MP, which is catalyzed to the inactive metabolite, 6-methylmercaptopurine (6-MMP), or is methylated to the active metabolites, 6-thioguanine nucleotides (6-TGNs) and 6-methylmercaptopurine ribonucleotides (6-MMPRs). The methylation of 6-MP to active 6-TGNs and 6-MMPRs is catalyzed by thiopurine methyltransferase (TPMT), an enzyme that exhibits a threefold difference in 6-TGN alleles and helps explain the large interindividual variations seen in efficacy and toxicity when AZA is used.⁸⁻¹⁰

Eighty-nine percent of white subjects have normal to high levels of TPMT activity, 11% have intermediate activity, and 0.3% have low or absent TPMT activity.^{9,11,12} Patients with intermediate levels of TPMT activity had a relative risk of 3.1 for development of severe adverse effects (predominantly gastrointestinal) in response to AZA compared with patients with high levels of TPMT activity in one study.¹² Another study documented only

an association between low or absent TPMT and neutropenia in patients receiving AZA.¹³ Despite some inherent problems regarding measurement of erythrocyte TPMT levels, this method is a useful guide to prevent neutropenia.¹²

Among patients with chronic inflammatory disease, those with TPMT activity below 11.9 nmol/mL red blood cells $\times$ h experienced more adverse effects (rash, cholestasis, and bone marrow toxicity).¹⁴ Because secondary intracellular metabolites are the source of AZA activity, measuring plasma levels of the parent compound is not useful.

Most pertinent pharmacokinetics are outlined in Table 58.2, but the pharmacokinetics of AZA in breast milk bears mentioning. Peak breast milk concentrations of AZA are about 10% of blood levels¹⁵ with small total amounts of AZA actually being absorbed (0.008 mg/kg of infant weight per 24 hours).¹⁶ Thus, despite the very low amount of AZA getting across in breast milk, one should proceed with great caution. This is because infants might rarely be TPMT deficient, which puts them at risk of aplasia.

An approximate doubling of the 6-TGN level 1 to 3 weeks after initiation of AZA in combination with infliximab for treatment of Crohn disease has been observed, but its clinical significance is unclear.¹⁷ The therapeutic level of AZA or 6-thioguanine (6-TGN) was assumed to be the same as that in inflammatory bowel disease, but this was shown inappropriate, at least for systemic lupus erythematosus, in which response was seen at “subtherapeutic” 6-TGN levels.¹⁸ On the other hand, high levels of 6-TGN correlated with a combination of abnormal results on liver function tests and neutropenia, so metabolite levels may help guide drug dosing.¹²

Cyclophosphamide

CYC itself is not cytotoxic, but it is enzymatically converted by hepatic microsomal (cytochrome P450) enzymes to multiple metabolites, of which phosphoramidate mustard is probably the most active urinary cytotoxic agent.^{1,19} CYC and its metabolites are excreted largely by the kidney. The drug is extensively metabolized before excretion, with less than 25% of the administered dose appearing in the urine unchanged. Of the urinary metabolites, carboxyphosphamide accounts for about 50% and 4-ketophosphamide

for about 15%.¹⁹ The concurrent use of sodium-2-mercaptoethane sulfonate (mesna) may detoxify acrolein (also a urinary metabolite), CYC's bladder-toxic metabolite, and thus reduce bladder toxicity.²⁰ Only small amounts of radioactively labeled drug or metabolite appear outside the urinary tract.^{1,21}

Because dialysis removes 72% of CYC, the drug should be administered after dialysis, and the dose should be reduced when CYC is administered to patients with renal failure. Allopurinol and cimetidine (but not ranitidine) inhibit hepatic microsomal enzymes, which results in increased CYC alkylating metabolite levels.¹⁹

Glomerulonephritis, including decreased serum albumin and increased urinary protein levels, as well as CYP2B6*9 and ABCB1 C3435T polymorphisms, increased CYC concentrations; the area under the curve increased ($r = -0.392$) and plasma CYC clearance decreased ($r = -0.392$). Special care should be exercised when using CYC in the presence of increasing glomerulonephritis.²²

Cyclosporine

Absorption of the usual CsA formulation is erratic and incomplete.^{23,24} The CsA microemulsion formulation is associated with a significant increase in the rate, extent, and consistency of absorption.²⁵ On a milligram-for-milligram basis, this has resulted in a 20% to 30% increase in exposure to CsA.²⁵ Preprandial treatment with the microemulsion further improves its efficacy in nephritic syndrome, improving outcome in 63% to 84% of patients.²⁶ CsA is a strong substrate for CYP3A4, so drugs that induce CYP3A4 (e.g., rifampin, phenobarbital, phenytoin) decrease its level, whereas drugs that inhibit CYP3A4 (ketoconazole, diltiazem) increase its level (Table 58.3). Grapefruit juice also increases drug level (by 62% in one study) because of its inhibition of CYP3A4 activity.²⁷ CsA is largely distributed outside the blood volume. It is highly bound to plasma proteins, erythrocytes, and lipoproteins.^{23,24} About 11% of a CsA dose is found in infant cord blood.²⁸ CsA is metabolized in the liver by the cytochrome P450

TABLE 58.1
Mechanisms of action

Drug	Active agent(s)	Mechanism
Azathioprine	6-thioguanilic acid, 6-methylmercaptopurine ribonucleosides	Interferes with adenine and guanine ribonucleotides
Cyclophosphamide	Phosphoramidate mustard (metabolite)	Cross-links DNA
Cyclosporine and other IL-2 inhibitors	Parent compound and up to 15 metabolites	Suppresses IL-2 synthesis and release Suppresses T-cell response and interaction
Mycophenolate mofetil	Mycophenolic acid	Interferes with inosine monophosphate Dehydrogenase inhibits T-cell and endothelial function

IL-2, interleukin-2.

TABLE 58.3
Drug interactions with cyclosporine

Drugs that increase IL-2 inhibitor concentrations (inhibit CYP3A4)	Drugs that decrease IL-2 inhibitor concentrations (induce CYP3A4)
Antacids: metoclopramide, cisapride	Anticonvulsants: phenytoin, carbamazepine, phenobarbital
Antifungals (azoles): ketoconazole, itraconazole	Antituberculosis drugs: rifampin
Antituberculosis drug: isoniazid	Antibiotics: nafcillin, aminoglutethimide
Calcium channel blockers: diltiazem (cyclosporine, rapamycin only), nifedipine, verapamil	Miscellaneous: St. John's wort
Antibiotics: ciprofloxacin, clarithromycin, erythromycin, doxycycline, protease inhibitors	
Miscellaneous: grapefruit juice, quinidine, diclofenac	

CYP3A4, cytochrome P450 isoenzyme 3A4; IL-2, interleukin-2.

TABLE 58.2
Pharmacokinetics of disease-modifying antirheumatic drugs

	Bioavailability	Clearance (mL/min/kg)	Serum elimination half-life (hr)	Unbound fraction	Routes of elimination	Site of metabolism
Azathioprine	0.8 (6-MP)	114 (6-MP)	1.2-1.5 (6-MP)	0.80 (6-MP)	Renal (20%-45%)	Liver, kidneys
Cyclophosphamide	0.97	1.2	2-8 8.7 (mustard)	0.87 0.45 (mustard)	Renal (cyclophosphamide 50%; metabolites 8%-35%)	Liver
Cyclosporine	0.2-0.5	2-32	10-30	0.10	Renal (6%) Bile (94%)	Liver
Mycophenolic mofetil	94	1.0	11.6	3	GI	Liver, GI tract

GI, gastrointestinal; 6-MP, 6-methylmercaptopurine.

mixed function oxidase to at least 15 known metabolites, some of which have immunosuppressive properties.^{23,24} CYP3A (hepatic metabolizing enzyme) activity correlates with CsA dosing requirement after renal transplant ($r = 0.55$).²⁹ At steady state, colonic tissue CsA concentrations are 50 to 250 times blood levels, which indicates significant tissue concentration of CsA. Elimination of CsA is primarily via the biliary system, with only small amounts appearing in the urine.^{23,24}

Administration of CsA with other nephrotoxic agents such as amino glycosides and nonsteroidal antiinflammatory drugs may increase its nephrotoxic potential.^{23,24} CsA may potentiate the action of methotrexate (MTX) by inhibiting metabolism of MTX to its less active forms.³⁰

Mycophenolate mofetil

MMF is rapidly changed to MPA, the active moiety. MPA is 93% bioavailable with a clearance of 11 L/hr and an elimination half-life of 11 to 16 hours.³¹ Although 90% is renally excreted, there is an enterohepatic recirculation that can supply a safety valve if renal insufficiency supervenes.³¹

The concentration of MPA correlates with serum bilirubin, creatinine, and albumin concentrations and thus is affected by both renal and liver disease.³¹ MPA pharmacokinetics was positively correlated with therapeutic responses of MMF in patients with biopsy-proven World Health Organization (WHO) class III or IV lupus nephritis.³² Monitoring the activity of inosine monophosphate dehydrogenase as a biomarker of MPA-induced immunosuppression is being considered as a novel approach in pharmacokinetics/pharmacodynamics-guided therapy.³³

Besides the degree of renal and hepatic disease (mentioned earlier), other factors such as bowel decontamination and enterohepatic recirculation affect MPA concentrations (contributing to a mean of 29% of MPA bioavailability).³⁴ CsA increases MPA concentrations, possibly by augmenting the bioavailability of MMF by inhibiting MPA glucuronidation.³⁴ Tacrolimus augments the bioavailability of MMF through inhibition of MPA glucuronidation.³⁵ Three clinical trials showed that patients concurrently receiving a proton pump inhibitor had MPA plasma concentrations that were significantly lower by approximately 43% at 2 g of MMF daily (but not at 3.0 g daily), possibly due to decreased absorption. At lower dosages, this increases the risk of treatment failure.³⁶⁻³⁸

Although these interactions speak to the need for monitoring MPA concentrations in transplant patients, monitoring of MPA levels in rheumatology is not common practice.

EFFICACY, TOXICITY, AND THERAPEUTIC USE

Azathioprine

Efficacy

AZA 1.25 to 3.0 mg/kg/day is more effective than placebo in treatment of RA^{1,2} (Table 58.4). There appears to be a dose-response relationship in RA, based on a comparison of placebo with AZA 1.0 mg/kg/day and AZA 2.5 mg/kg/day (although the data are not completely consistent).² A meta-analysis of three trials that included 81 RA patients who were treated with AZA reported that AZA was more effective than placebo (odds ratio, 1.45 to 10.50), as expected. Adverse reactions were also statistically more frequent in the AZA group.³⁹

In controlled trials comparing AZA with other DMARDs (CYC, CsA, chloroquine), results are inconsistent. However, AZA was not as effective as MTX in the treatment of RA.⁴⁰

A small placebo-controlled trial involving eight patients with reactive arthritis in a crossover design showed positive results over 4 to 6 months.⁴¹ A 16-patient controlled trial comparing AZA plus prednisone to prednisone

alone in polymyositis/dermatomyositis showed the superiority of AZA only after 3 years of follow-up; at 3 months no differences between the two regimens were discernible.² A placebo-controlled 2-year study of 73 patients with Behçet syndrome (37 of whom received AZA) concluded that AZA effectively controlled the progression of Behçet syndrome, especially the associated eye disease.⁴² A meta-analysis of studies using AZA for the treatment of renal systemic lupus erythematosus (SLE) reported that AZA plus steroids decreased renal SLE all-cause mortality (relative risk, 0.60; 95% confidence interval, 0.36 to 0.99) but did not alter renal outcomes; this combination treatment was not associated with increased infections compared with steroids alone.⁴³ An open 2-year study in 75 SLE patients demonstrated that AZA was equivalent to CsA in preventing lupus nephritis flares.⁴⁴ One study supported the use of AZA in scleroderma-associated lung disease.⁴⁵

In a prospective, open-label, multicenter, randomized trial, AZA (2.0 mg/kg/day) and MTX (25 mg/wk) for 12 months were shown to be equally effective alternatives for maintenance therapy in patients with granulomatosis with polyangiitis (previously known as *Wegener granulomatosis*) and microscopic polyangiitis. Among 159 eligible patients, 79% experienced remission after receiving corticosteroids and CYC as induction therapy. They were randomly assigned to receive either AZA or MTX ($n = 63$ per group). Those patients were followed for a mean of 29 months. Twenty-three patients who received AZA (37%) and 21 patients who received MTX (33%) experienced a relapse ($P = .71$); most (73%) experienced a relapse only after discontinuation of the study drug.⁴⁶

Toxicity

The most common adverse event seen with AZA is gastrointestinal intolerance, including nausea and diarrhea. Other toxic effects include rash, pancreatitis, cholestatic hepatitis, stomatitis, and perhaps viral infections¹ (Table 58.5). A 50-fold increase in relative risk of malignant disease (particularly non-Hodgkin lymphoma) was seen in AZA-treated renal transplant patients.² In RA, the AZA-related risk of lymphoma (and non-Hodgkin lymphoma) is confounded by an increased relative risk associated with RA itself.² Overall, there is probably a small added risk of developing some malignancy when using AZA in RA of 1.3 and a relative risk of between 2.2 and 8.7 for developing a lymphoproliferative disorder.^{1,2} Reversible lymphoma associated with Epstein-Barr virus infection has also been observed after AZA therapy.⁴⁷ Bone marrow toxicity has been associated with intermediate or reduced (especially low or absent) levels of TPMT in RA patients (see the section on AZA pharmacokinetics earlier).^{9,11,12,48}

Therapeutic use

Before AZA is used, a discussion of risks and treatment goals should be conducted and a good history taking, physical examination, and laboratory testing should be performed. Measurement of TPMT activity is useful to determine the likelihood of bone marrow toxicity.⁴⁸ However, TPMT levels are higher in new red blood cells, so the levels should not be determined shortly after bone marrow depression or during the posttransplant response of increased erythropoiesis.

An alternative to testing TPMT levels for predicting AZA sensitivity is to institute a daily dose of 25 to 50 mg for the first week followed by determination of a complete blood count. Thereafter, doses are increased regularly by 0.5 mg/kg/day every month, with a goal of 2 to 3 mg/kg/day. The dose may then be adjusted to the minimum effective dose.

Monitoring includes determination of hemoglobin level, white blood cell count, and platelet counts every 2 weeks while dosing regimens are being changed and every 4 to 12 weeks during stable regimens. Liver function tests can be performed every 6 to 12 weeks, after initial testing at 2 to 4 weeks. Monitoring for lymphoproliferative disease and other malignancy is appropriate but undefined, as is monitoring for pregnancy.

Cyclophosphamide

Efficacy

In five placebo-controlled trials in RA, oral CYC was consistently better than placebo when used in dosages of more than 1.5 mg/kg/day, both clinically and in terms of erythrocyte sedimentation rate (ESR) and rheumatoid factor levels.²⁰ It has not been consistently effective in dosages less than 1.0 mg/kg/day. CYC reached its peak effectiveness after approximately 16 weeks. In small studies, CYC retarded bone destruction.²⁰

Compared with other DMARDs, CYC is equal to AZA and is equal or superior to intramuscular gold with regard to both clinical and radiologic endpoints.²⁰ Due to toxicity issues and the availability of better newer agents, CYC is principally used now only to treat the extraarticular manifestations of RA (e.g., vasculitis or interstitial lung disease).

TABLE 58.4 Comparative efficacy of disease-modifying antirheumatic drugs in rheumatoid arthritis

Drug	Placebo	AZA	CYC
Azathioprine (AZA)	AZA > placebo	—	AZA = CYC
Cyclophosphamide (CYC)	CYC > placebo	CYC = AZA	—
Cyclosporine (CsA)	CsA > placebo	—	—
Mycophenolate mofetil (MMF)	MMF = placebo ¹⁰⁷	—	—

TABLE 58.5

Toxicity of disease-modifying antirheumatic drugs

	AZA (%)	CYC (%)	CsA (%)	MMF (%)*
Shared				
Dose-related marrow suppression	4-27	6-32	2-6	—
Leukopenia/thrombocytopenia	0-5	0-4	≤2	0-37
Susceptibility to infection				
Overall	0-9	0-22	0-6	0-68
Herpes zoster	0-6	5-30	0-3	3-30
Gastrointestinal intolerance				
Nausea, vomiting	9-23	19-45	4-40	0-34
Diarrhea	≤1	3-18	2-18	0-30
Rash	1-6	—	—	0-7
Not shared				
Hair				
Alopecia	—	7-80	—	0-16
Hypertrichosis	—	—	7-49	—
Stomatitis	0-5	—	0-8	5
Gum hyperplasia	—	—	4-12	—
Hepatic				
Abnormal liver function	0-5	—	0-8	—
Fibrosis/cirrhosis	—	—	—	—
Azoospermia/oligospermia	—	60-100	—	—
Amenorrhea	—	0-53	—	0-15
Cystitis	—	4-45	—	—
Teratogenesis	±	—	±	+
Neoplasia	—	—	—	0-7
Decreased GFR	—	—	50-87	—
Hypertension	—	—	33	—
Neurotoxicity	—	—	10-40	0-19.7
Pneumonitis	—	—	—	—

*Data from Touna Z, Gladman DD, Urowitz MB, et al. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. *J Rheumatol* 2011;38:69-78; Hoeltzenbein M, Elefant E, Vial T, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. *Am J Med Genet A* 158A:588-96; Epinette WW, Parker CM, Jones EL, et al. Mycophenolic acid for psoriasis: a review of pharmacology, long-term efficacy, and safety. *J Am Acad Dermatol* 1987;17:962-71; Riskalla MM, Somers EC, Fatima RA, et al. Tolerability of mycophenolate mofetil in patients with systemic lupus erythematosus. *J Rheumatol* 2003;30:1508-12. AZA, azathioprine; CsA, cyclosporine; CYC, cyclophosphamide; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; ±, additional studies and meta-analyses are needed to provide conclusive evidence.

Until recently, the treatment of choice for lupus nephritis (particularly [WHO] class III focal proliferative nephritis and class IV diffuse proliferative nephritis) was CYC. CYC was administered as 14 IV infusions of 0.5 to 0.75 g/m² over 30 months.^{43,49,50} In that protocol, the induction phase included the first six monthly CYC infusions, followed by a maintenance phase that included eight quarterly CYC infusions. Since publication of the results of randomized trials comparing MMF and CYC, the place of CYC as the drug of choice for SLE nephritis has been questioned.⁵⁰

High-dose IV CYC (50 mg/kg for 4 days, 200 mg/kg total dose) was compared with IV CYC 750 mg/mo for 12 months in a randomized clinical trial in patients with renal and central nervous system SLE.⁵¹ For the first 12 months the high-dose CYC group fared significantly better than the group receiving the monthly lower-dose CYC, although these differences disappeared by 30 months⁵¹ (Table 58.6).

A 10-year follow-up of the Euro-Lupus Nephritis Trial (ELNT) comparing low-dose IV CYC with high-dose IV CYC showed no significant differences between treatment groups in rates of all-cause death (5 of 44 patients [11%] in the low-dose group vs. 2 of 46 patients [4%] in the high-dose group), sustained doubling of serum creatinine level (6 of 44 [14%] vs. 5 of 46 [11%], respectively), and end-stage renal disease (2 of 44 [5%] vs. 4 of 46 [9%], respectively); similarly, there were no differences between groups in mean serum creatinine level, 24-hour proteinuria, and damage score at 10 years follow-up. This study confirms that a low-dose IV CYC regimen followed by AZA—the Euro-Lupus regimen—achieves good clinical results in the very long term.⁵⁰

A registry study examined the effect of CYC on pulmonary catastrophic antiphospholipid syndrome (p-CAPS) compared with SLE-CAPS.⁵² CYC treatment was associated with increased mortality in p-CAPS, whereas CYC improved survival in SLE-CAPS. Selection bias may have skewed the results, so these findings must be viewed very cautiously.

The treatment of the systemic vasculitides (antineutrophil cytoplasmic antibody [ANCA]-associated granulomatous vasculitis, microscopic polyarteritis, and crescentic glomerulonephritis) has been divided into the phases of remission induction and maintenance therapy. The induction phase has usually included CYC, AZA, or MTX.⁵³⁻⁵⁶ The rate of relapse was lower and the event-free survival was greater ($P < .05$) in patients receiving 12 monthly pulses of IV CYC than in those receiving 6 monthly pulses.⁵⁴ A 12-month open randomized trial comparing CYC and MTX showed the noninferiority of MTX to CYC for controlling ANCA+ vasculitis.⁵⁶ Unfortunately, the time to remission was longer in the MTX group, and the relapse rate after stopping MTX was higher than that of the CYC group.

Remission induced by CYC could be successfully maintained by therapy with AZA or MTX over 18 months, but relapse rate by 18 months was significantly higher when MTX was used for maintenance⁵⁴ than when CYC was continued. Another study comparing MTX with AZA for maintenance after induction with IV CYC showed that adverse events and efficacy were no different for the two therapies.⁴⁶

IV CYC (up to 900 mg/m²) without maintenance has real but limited usefulness in ANCA-associated granulomatous vasculitis, because 52% of patients experience relapse despite good initial response.⁵⁷ Comparison of daily oral CYC (2 mg/kg/day) with pulse CYC (15 mg/kg orally or intravenously every 2 to 3 weeks) in patients with ANCA-associated vasculitis who were taking prednisolone showed that the pulse CYC induced remission at a lower cumulative CYC dose and caused less leukopenia.⁵⁷ CYC added nothing to corticosteroids alone in the treatment of biopsy-proven Henoch-Schönlein purpura in an open-label trial involving 54 adults.⁵⁸ An eight-patient open trial of fortnightly administration of CYC (15 mg/kg IV) for treatment of pemphigus vulgaris indicated efficacy in all patients.⁵⁹

A 1-year placebo-controlled trial of oral CYC for systemic sclerosis (SSc)-associated interstitial lung disease showed a modest effect on forced vital capacity and more robust effects on dyspnea, ability to perform activities of daily living, quality of life, and skin thickening.⁶⁰ A double-blind, randomized, placebo-controlled trial in a group of 45 patients with SSc interstitial lung disease given 6 monthly IV CYC treatments, followed by 6 months of oral AZA, generally supported these results.⁴⁵ Open-label studies also supported the efficacy of CYC in SSc interstitial lung disease. The beneficial effects eventually faded after CYC was stopped.^{61,62} This suggests that immunosuppressive therapy may be needed for longer than 1 year (approximately 2 to 3 years) to prevent relapse.

Toxicity

CYC's significant toxicity is the major factor limiting its clinical use in the rheumatic diseases. A major toxicity is carcinogenicity (especially bladder cancer). Kinlen's experience with 643 RA patients suggests a relative risk of 1.8 for all cancers combined, a relative risk of 13.0 for non-Hodgkin lymphoma, and a relative risk of 12.8 for bladder cancer.⁶³ On the other hand, in a placebo-controlled trial of oral CYC for the treatment of SSc interstitial lung disease, most toxicities (including gastrointestinal) were equal to those with placebo over 1 year of treatment, and only the frequency of leukopenia was increased ($P < .0001$). After an additional 1 year in which patients were observed but were not treated with any study medication, there were no differences in the rates of cancer, serious adverse events, or deaths in the CYC group compared with the placebo group.⁶⁴

Irreversible azoospermia was regularly produced in adult males receiving a total dose of more than 18 g of CYC, although plasma testosterone levels remained normal. The risk of infertility and amenorrhea in women receiving CYC rises with increasing duration of therapy, dose, and age. In postpubertal females, both gametogenesis and hormonal function are altered adversely, and menopause occurs.

A study of 17 women demonstrated amenorrhea in all the patients receiving cyclophosphamide. In those given a luteinizing hormone-releasing agent, menstruation returned and ovarian dysfunction reversed when CYC was stopped. In those not given the agonist, ovarian function did not return.⁶⁵ Somers and coworkers also reported that ovarian function could be protected by a depot leuprolide acetate injection in SLE patients given CYC.⁶⁶

In a randomized clinical trial, women with granulomatosis with polyangiitis who had been exposed to CYC before study enrollment were found to have diminished ovarian reserve at entry and a higher rate of early menstruation cessation while being treated in the study. Among women with normal

TABLE 58.6
Randomized controlled trials for cyclophosphamide in systemic lupus erythematosus (SLE)

Study	Trial type	Trial duration (mo)	Disease manifestations	Drug	Dosage	No. pts	Efficacy outcome	Adverse events
Houssiau, et al. ¹⁰⁸	RCT	41	SLE proliferative GN	Group I: High-dose IV CYC followed by AZA* on a background of oral prednisolone†	8 pulses/yr IV CYC (6 monthly followed by 2 quarterly pulses); initial dose 0.5 g/m ² BSA increased to a maximum of 1500 mg/pulse 6 fortnightly 500-mg pulses IV CYC	46	Treatment failure in 16% of low-dose group and 20% of high-dose group ($P = .64$). Serum Cr, albumin, C3, 24-hr urinary protein, and DAS significantly improved in both groups during first year of F/U ($P = .005$). Renal flares in 27% of low-dose group vs. 29% of high-dose group ($P = .8$).	Episodes of severe infection twice as frequent in high-dose group ($P = .2$).
Mitwalli, et al. ¹⁰⁹	DB, RCT	42	LN WHO class IV	Group II: Low-dose IV CYC followed by AZA* on a background of oral prednisolone†	Group I: CYC + prednisolone, HCQ, and AZA† Group II: CYC + prednisolone, HCQ, and AZA†	73 44	Patients followed for 10 yr. Kidney survival over time equal in both groups ($P = .288$). ESRD: group I (13.9%) > group II (29.4%) ($P = .36$).	Gonadal toxicity and malignancy: group I > group II ($P = .0000$). Infections: group I (31.3%) > group II (31.6%) ($P = .019$). Amenorrhea: group I > group II ($P = .006$).
Petri, et al. ¹¹⁰	RCT	30	Renal lupus, neurologic lupus, or other organ system involvement with moderate to severe activity	Group I: IV CYC	750 mg/m ² BSA monthly × 6 mo then quarterly × 2 yr 50 mg/kg daily × 4 days	26 21	At 6-mo F/U, complete response [§] achieved in 52% of group II vs. 35% of group I ($P = .13$). At 30-mo F/U, complete response in 48% of group II vs. 65% of group II ($P = .13$).	Serious infections: 15 in group I vs. 11 in group II. Premature ovarian failure: 30% of group II vs. 43% of group I at 12 mo.
Austin, et al. ¹¹¹	RCT	12	LMN	Group I: CsA Group II: IV CYC Group III: prednisone	5 mg/kg body wt/day × 11 mo 0.5 to 1.0 g/m ² BSA every other mo × 6 cycles 1 mg/kg body wt every other day × 6 wk	12 15 15	At 1 yr, cumulative probability of remission of proteinuria was 27% with prednisolone, 60% with IV CYC, and 83% with CsA. Relapse of nephrotic syndrome occurred significantly more often after completion of CsA than after IV CYC ($P = .02$).	Infections: pneumonia (6.7% with prednisone and 16% with CsA), localized herpes zoster (13% with IV CYC), others.

*AZA (2 mg/kg/day) started in both groups 2 wk after the last injection of CYC and continued 30 mo after inclusion in study.

†All patients received 3 daily pulses of 750 mg of intravenous methylprednisolone, followed by oral glucocorticoid therapy (5–7.5 mg prednisolone/day). This dosage was maintained at least until month 30 after inclusion in study.

‡Maintenance therapy included the following: prednisolone 1 mg/kg/day started in both groups for 4 wk, tapered to 0.2 mg/kg an alternate days for 24 mo; HCQ 200 mg/day, AZA 1 mg/kg body weight/day for 24 mo.

§The major outcome measure was response as determined by the Responder Index for Lupus Erythematosus. This measure defined complete response, partial response, no change, or worsening for each organ manifestation.

||Complete remission was defined as proteinuria of <0.3 g protein/day. Partial remission was defined as proteinuria of <0.2 g protein/day with >50% reduction from baseline proteinuria.

¶Other infections were sinusitis, bronchitis, otitis media, dental abscess, upper respiratory tract infection, syphilis, pelvic inflammatory disease, cholecystitis, and herpes simplex virus skin infection.
 AZA, azathioprine; BSA, body surface area; Cr, creatinine; CsA, cyclosporine; CYC, cyclophosphamide; DAS, disease activity score; DB, double-blind; ESRD, end-stage renal disease; F/U, follow-up; GN, glomerulonephritis; HCQ, hydroxychloroquine; IV, intravenous; LMN, lupus membranous nephropathy; LN, lupus nephritis; pts, patients; RCT, randomized controlled trial; WHO, World Health Organization.

baseline ovarian function, six of eight who received CYC during the trial developed diminished ovarian reserve, compared with none of four who did not receive CYC ($P < .05$). Daily oral CYC, even when administered for fewer than 6 months, causes diminished ovarian reserve.⁶⁷

The urologic adverse effects of CYC are thought to be related to its urinary metabolite acrolein (see earlier section on CYC pharmacokinetics). Hemorrhagic cystitis has been reported in about one third of lupus nephritis patients receiving oral CYC daily, and there was a significant but much lower incidence of bladder fibrosis and bladder carcinoma.⁶⁸ In a cohort study of 119 RA patients, 9 developed bladder cancer during an average 13.1 years of follow-up, although three bladder cancers occurred after 14, 16, and 17 years.⁶⁹ Cystitis and bladder carcinoma are markedly reduced when CYC is used on an intermittent IV basis. Bladder toxicity can also be reduced by the concomitant administration of mesna.⁷⁰ Because mesna is administered intravenously, it is useful primarily when CYC is given intravenously.

Therapeutic use

Because CYC has significant toxicity, its use in RA should be limited to patients with extraarticular manifestations suggestive of polyarteritis-like disease and those for whom all other DMARDs, including biologics, have failed but who still have severe active RA. In these cases, oral CYC dosages of 2 mg/kg/day might be considered. An IV regimen of CYC has been suggested for management of rheumatoid vasculitis.⁷¹ In this regimen, 500 to 1000 mg of CYC and 500 to 1000 mg of methylprednisolone was given intravenously on days 1, 8, 29, and 58. Patients were continued on oral DMARDs. In either case, once the disease is under control, switching to a less toxic drug over a longer period should be considered.

Whenever CYC is used in the management of SLE-associated diffuse proliferative glomerulonephritis, it is usually started at 0.50 to 0.75 g/m² when the glomerular filtration rate (GFR) is greater than one third of the predicted normal value. When renal function is less than one third of normal, the starting dose is 0.5 g/m². CYC can be administered in 150 mL of a 5% glucose solution over 30 to 60 minutes. There are no established regimens for giving IV mesna with IV CYC to reduce bladder toxicity. The general rule, however, has been that its dose should be equivalent to the CYC dose and that it should be given in two to three divided doses over several hours.

Diuresis should be ensured by increased IV and oral fluids and possibly diuretics. Nausea and vomiting are common and may require antiemetic therapy (prophylactically and as needed). IV pulse methylprednisolone (10 to 100 mg) or dexamethasone (10 mg) may also be given. This may help decrease nausea and is also part of the treatment for glomerulonephritis.

As an induction therapy in SLE nephritis, IV pulse CYC (with or without IV methylprednisolone) may be given once every month for 6 months. After the completion of the 6-month induction period (using either CYC or MMF) there are three well-documented approaches to maintenance therapy: (1) IV CYC given every 3 months for up to 2 more years of therapy; (2) AZA; and (3) MMF. Maintenance therapy may be required for many years.

CYC given orally has been the preferred method for managing polyarteritis and ANCA-associated granulomatous vasculitis.¹ The initial dose should be 1 mg/kg/day with a goal of reaching 2 mg/kg/day (approximately 75 to 125 mg/day) and should be altered to maintain the white blood cell count at more than 3000/mm³.

Complete blood count, platelet count or estimate, and urinalysis with microscopic examination should be performed every 7 to 14 days initially and can be reduced to every 2 to 4 weeks once the disease and dose have been stabilized for 2 to 3 months.

Avoidance of pregnancy is strongly recommended. Consideration might be given to using oral contraceptives or gonadotropin-releasing hormone inhibitors if the patient is interested in preserving fertility, although the use of these medications in this context is still exploratory.^{67,72}

Cyclosporine

Efficacy

Placebo-controlled trials, including one trial in which a medium dose of CsA was compared with a low dose, have been performed and show that CsA is efficacious in treatment of RA.⁷³⁻⁷⁵ In these studies, nearly 400 subjects with RA received CsA in initial dosages of 1 to 10 mg/kg/day. CsA improved clinical symptoms and signs; however, no significant improvement was noted in laboratory parameters such as ESR or rheumatoid factor titers. On the basis of these studies and a meta-analysis,⁷⁴ patients treated with 2.5 to 4.0 mg/kg/day of CsA should show a substantial response within the first month. CsA and MTX was better than MTX or placebo in patients showing an incomplete response to MTX.⁷⁵ In a trial of sequential induction and maintenance treatment in patients with proliferative lupus nephritis and

preserved renal function CsA was as effective as CYC. Regimens containing CsA or IV CYC are each more effective than prednisone alone in inducing remission of proteinuria in patients with lupus nephropathy.⁷⁶

In children with steroid-resistant nephrotic syndrome, a high remission rate was achieved using a combined CsA/prednisolone treatment regimen in a 12-month prospective, multicenter trial involving 35 children. Major adverse events were severe bacterial infections (two patients) and posterior reversible encephalopathy syndrome (one patient).⁷⁷

A pediatric open, randomized, controlled trial in patients with Henoch-Schönlein nephritis pitted CsA (5 mg/kg/day) against methylprednisolone (3- to 30-mg/kg pulses followed by oral prednisone) over 12 months. In all 11 patients receiving CsA nephrotic-range proteinuria resolved by 3 months, whereas 6 of 13 methylprednisolone-treated patients failed to show a response. Biopsy-assessed response was similar over 2 years, and follow-ups to 6 years continued to show an advantage for CsA.⁷⁸ Two blinded trials found that CsA was superior to conventional therapy (colchicine or prednisone/chlorambucil) in the management of Behçet syndrome, particularly its ocular complications.^{5,79} CsA has been successfully used in open trials and anecdotal series for treatment of dermatomyositis,⁸⁰ ANCA-associated granulomatous vasculitis, and systemic sclerosis.⁸¹ In psoriasis, CsA appeared to be as effective as MMF.⁸² CsA seems to be effective in clearing cutaneous lesions in psoriasis⁵ and is a possible choice for treatment of psoriatic arthritis.⁸³

CsA was superior to MMF in treatment of skin and nail psoriasis in a multicenter, randomized, open-label trial of MMF (2 g/day; $n = 27$) versus CsA (2.5 mg/kg/day; $n = 27$) for 12 weeks; CsA improved the skin more than MMF ($P = .02$).⁸⁴ In a 12-week randomized controlled trial, CsA (5 mg/kg/day) significantly improved plaque psoriasis more than did MTX (15 mg/wk) and was equivalent with regard to patient quality of life and adverse events.⁸⁵ In a 24-week double-blind, randomized, controlled trial of a microemulsion formulation of CsA, patients with plaque psoriasis who had achieved remission while taking standard CsA were given the CsA microemulsion at 5 mg/kg/day for 2 days a week or placebo.⁸⁶ Results showed that CsA prevented clinical worsening in 69.9% of patients with baseline moderate or severe psoriasis versus 46.3% for placebo ($P = .01$). However, the results lost significance if patients with mild psoriasis were included ($P = .07$).⁸⁶

Toxicity

When CsA is used to treat rheumatic disease, adverse effects are generally mild and reversible at low doses.^{5,24} Dose-related decreases in GFR often occur with corresponding increases in serum creatinine level (the principal adverse effect). Over 12 months, a more than 30% increase in creatinine concentration was noted in 48% of the RA patients studied.⁸⁷ In patients taking more than 5 mg/kg/day, CsA renal biopsy specimens sometimes showed focal interstitial fibrosis, tubular atrophy, and/or arteriolar lesions. However, these did not occur if the dosage of CsA remained 5 mg/kg/day or less and if serum creatinine level did not rise more than 50% above baseline.⁸⁸ New-onset hypertension has been reported in about one third of rheumatoid and psoriatic arthritis patients treated with CsA. Although antihypertensive therapy may be required, potassium-sparing diuretics should be avoided because CsA may cause hyperkalemia. Because diltiazem (but not isradipine or nifedipine) may increase CsA levels by decreasing its metabolism, changes in CsA dosage may be required in patients using diltiazem.

Significant hepatotoxicity manifested as elevated levels of hepatic enzymes and bilirubin may be seen but usually only with higher CsA doses.⁸⁹ In psoriatic arthritis patients treated for up to 24 months, hypertrichosis occurred in 24%, neurologic disturbances in 7%, gum hyperplasia in 12%, and gastrointestinal complaints (mostly nausea) in 9% of patients.⁹⁰ Lymphomas have been observed with this drug, including reversible Epstein-Barr virus-associated lymphomas. In a secondary analysis of registry data, CsA was found to be associated with osteoporosis, although well-controlled trials will be necessary to confirm these data.⁸⁹ In a large randomized study, an increase in insulin-like growth factor (somatomedin C) levels and insulin-requiring diabetes was seen in RA patients⁹¹ during long-term CsA therapy. This, too, will need further study.

Therapeutic use

Consensus guidelines for the use of CsA in RA (for both conventional and microemulsion formulations) have been published and should be reviewed by any practitioner using CsA.⁸⁸ CsA should be avoided in patients with preexisting renal disease (creatinine clearance of less than 60 mL/min).

Both conventional and microemulsion formulations may be instituted at 2.5 mg/kg/day in two divided doses every 12 hours. The dosage may be cautiously increased by 0.5 to 0.75/kg/day every 4 to 8 weeks until a

maximum dosage of 5 mg/kg/day for the conventional formulation (or 4 mg/kg/day for the microemulsion) is reached, unless this is prevented by a rise in serum creatinine concentration of 30% or greater. Dosage reductions of 0.5 to 0.75 mg/kg/day are warranted if serum creatinine level increases above baseline by 30% or if uncontrolled hypertension appears (systolic pressure of more than 140 mm Hg and/or diastolic pressure of more than 90 mm Hg). Hypertension can usually be managed with calcium channel blockers (especially isradipine or nifedipine) and β -blockers.

Drug interaction

MPA delays CsA absorption, which indicates a potentially important drug-drug interaction. Thus the institution of CsA therapy may require adjustment of MPA dose when MPA and CsA are to be used together.

Mycophenolate mofetil

Efficacy

In one study (available in abstract only) there was no difference between 2 g and 4 g MMF daily for the treatment of RA.⁹² The response rate according to American College of Rheumatology 20% improvement criteria was 29% for 2 and 4 g MMF daily and 47% for 5 g daily.

A double-blind, randomized, controlled trial involving 227 patients with SLE renal disease showed that MMF (2 g/day) was superior to AZA (2 mg/kg/day) in "time to treatment failure" (defined as death, end-stage renal disease, doubling of serum creatinine level, need for rescue therapy, or renal flare).⁵⁰ Serious adverse events occurred in 33.3% of AZA-treated patients versus 23.5% of MMF-treated patients ($P = .02$).

Three meta-analyses were performed, each of which included data for several hundred patients with high-grade SLE nephritis. All meta-analyses showed a statistically significant ($P < .05$) advantage in remission rates for MMF with a relative risk of 1.5 to 3.0. All meta-analyses reported statistically significant lower rates of infectious complications with MMF (relative risk, 0.65 to 0.5) and a strong trend for less amenorrhea. On the other hand, there was a strong trend for increased rates of gastrointestinal adverse effects with MMF.⁹³

Double-blind studies using MMF in the treatment of lupus proliferative and membranous glomerulonephritis have shown this drug to be effective in these patients.^{50,94-96} In a meta-analysis encompassing 10 randomized controlled trials and 847 patients with SLE proliferative nephritis, renal remission rates were the same for CYC and MMF (relative risk, 1.052; 95% confidence interval, 0.950 to 1.166), as were the risks of death and end-stage

renal disease.⁹⁶ A meta-analysis of five studies stated that MMF is preferred over CYC in treatment of SLE nephritis.⁹⁷

Uncontrolled studies of children with lupus ($N = 52$) and some with renal lupus ($N = 31$) indicated that 69% to 85% of patients showed a response to MMF.^{98,99} MMF has been used in multiple other diseases, including bullous pemphigoid,⁸⁴ microscopic polyangiitis,¹⁰⁰ SSC cutaneous thickening and interstitial lung disease,¹⁰¹ and autoimmune hepatitis.¹⁰² In a controlled trial, patients in remission from ANCA-associated vasculitis (granulomatosis with polyangiitis or microscopic polyangiitis) received either AZA (2 mg/kg/day; $n = 80$) or MMF (2.0 g/d; $n = 76$), relapses were more common in those receiving MMF (60%) than in those given AZA (37.5%) (hazard ratio, 1.69; $P = .03$). Other outcomes, including severe adverse events, did not differ in the two groups.¹⁰³

Toxicity

Comparisons with AZA in the renal transplantation literature show that AZA and MMF have similar gastrointestinal, hematopoietic, and hepatic toxicity profiles.⁵⁰ Diarrhea is the most common adverse effect observed. Nausea, leukopenia, anemia, thrombocytopenia, thinning of scalp hair, pancreatitis, and bacterial and viral infections have also been seen. In a recent meta-analysis encompassing five trials and 683 patients, infections and gastrointestinal adverse effects occurred at similar rates in patients taking MMF and in those taking CYC, but leukopenia occurred less frequently in those taking MMF.⁹⁷ MMF was a greater risk in pregnancy than CsA, causing increased first-trimester pregnancy loss and multiple congenital malformations. It was also more often associated with herpes simplex and herpes zoster than CsA.¹⁰⁴

Therapeutic use

MMF is an immunosuppressive drug, but it also has effects on nonimmune cells (e.g., vascular smooth muscle cells, fibrocytes). It has therapeutic value in SLE-associated kidney disease and may replace CYC as the drug of first choice for lupus nephritis.¹⁰⁵ Systolic and diastolic blood pressure does not seem to be increased when MMF is taken.¹⁰⁶

The drug can be instituted at a dosage of 0.5 g twice daily for 1 week. The dosage can then be increased to 1.0 g twice daily for 1 week and then to 1.5 g twice daily, if one wishes. MMF can be taken before or with food.

In renal transplant patients, a dose of 720 mg of enteric-coated MPA has been demonstrated to be therapeutically equivalent to a 1000-mg dose of MMF. Laboratory monitoring for toxicity requires testing every 1 to 3 months for hematologic and hepatic toxicity.

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T-cell costimulation and other directed therapies

■ ERNEST H. CHOY

- T cells are pathogenic in rheumatoid arthritis (RA) and have an important role in sustaining synovitis even in established disease.
- Abatacept, a fusion protein of recombinant human cytotoxic T lymphocyte antigen 4 conjugated to the Fc portion of human immunoglobulin, blocks the costimulatory molecule CD28 binding to B7-1 and B7-2 and thereby modulates T-cell activation.
- Modulation of T-cell activity by blocking of costimulatory signals suppresses inflammation and improves prognosis in RA as evident from the efficacy of abatacept, which is licensed for the treatment of RA in patients who have failed to show a response to disease-modifying antirheumatic drugs or tumor necrosis factor antagonists.
- Adverse effects of abatacept include increased susceptibility to infection, infusion- or injection-site reaction, and reduced protective humoral response to vaccines.
- Recently a subcutaneous formulation of abatacept has been approved in the United States and Europe for the treatment of RA. Its efficacy and safety profile are similar to those of intravenous abatacept.

RATIONALE FOR TARGETING T CELLS IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease primarily affecting the articular joints. Although the cause of RA remains unknown, a considerable amount is now known about the pathologic processes involved in the disease. Because this has been addressed in detail elsewhere in this book, only a brief summary is given here. RA may be initiated by an unknown antigenic peptide derived either from an exogenous antigen (e.g., an infectious agent) or an autoantigen. The putative arthritogenic peptide is presented by the RA-associated major histocompatibility complex class II molecules, such as human leukocyte antigen (HLA)-DRB1*0404 or HLA-DRB1*0401, to arthritogenic CD4+ T cells. These CD4+ T cells become activated, release interleukin-2, and clonally expand. Their production of various other cytokines and growth factors activates other cell types, including B cells, monocytes/macrophages, and synovio-cytes, and enhances leukocyte recruitment into the joint. These processes together generate the immune-inflammatory cascade of synovitis. The beneficial effect of the anti-T-cell drugs cyclosporine A, tacrolimus, and recently the biologic agent abatacept (Orencia, Bristol-Myers Squibb, Princeton, N.J.), which inhibits T-cell activation by blocking costimulatory signals, even in patients with long-standing disease, argues strongly in favor of a continuing role for T cells.

COSTIMULATORY SIGNAL IN T-CELL ACTIVATION

The activation signal resulting when a T-cell receptor of a naive T cell binds to an antigenic peptide presented in the HLA groove of an antigen-presenting cell is known as *signal 1*.¹ However, signal 1 alone is insufficient for full T-cell activation, which is required for triggering cytokine production, clonal expansion, prevention of anergy, and resistance to apoptosis.¹ Full T-cell activation requires signal 2, provided by costimulatory molecules (Fig. 59.1). In the absence of a costimulatory signal, T cells not only will fail to activate but will become refractory to activation. A number of costimulatory molecules are expressed by T cells. One of these is CD28, which

binds to the B7 molecules B7-1 and B7-2 on antigen-presenting cells (see Fig. 59.1).¹ To counterbalance this activation state, cytotoxic T-lymphocyte antigen 4 (CTLA-4), a structural homologue of CD28 expressed by T cells, competes with CD28 for binding to B7-1/B7-2. Because CTLA-4 has higher binding avidity for B7-1/B7-2 than CD28, it acts as a suppressor of T-cell activation.²

ABATACEPT

Abatacept is a soluble human recombinant fusion protein in which the extracellular domain of CTLA-4 is conjugated to the Fc portion of human immunoglobulin. It binds to B7-1/B7-2 and prevents their interaction with CD28 on T cells, thereby modulating costimulation (see Fig. 59.1). In Europe, abatacept, in combination with methotrexate (MTX), is approved for treatment of moderate or severe active RA in adults who have shown an inadequate response to or intolerance of disease modifying antirheumatic drugs (DMARDs) and/or tumor necrosis factor- α (TNF- α) antagonists. Elsewhere, abatacept is also indicated for use as monotherapy in patients with moderate or severe active RA who have had an inadequate response to one or more DMARDs and/or TNF antagonists. It is also approved as a therapy for juvenile idiopathic arthritis. Abatacept is administered as a 30-minute intravenous injection on the 1st, 15th, and 30th days of treatment and thereafter once every 4 weeks. A dose of 500 mg is used for patients weighing less than 60 kg, 750 mg for those weighing 60 to 100 kg, and 1000 mg for those weighing more than 100 kg.

A subcutaneous formulation of abatacept administered weekly at a dose of 125 mg has been approved in the United States and Europe for the treatment of RA. An intravenous loading dose can be used in the subcutaneous regimen but probably is not needed.

Clinical efficacy

Intravenous abatacept

The tolerability and efficacy of intravenous abatacept was initially assessed in RA patients with active disease in whom treatment with DMARDs or etanercept had failed.³ Patients were randomly assigned to receive intravenous infusions of placebo or 0.5 mg/kg, 2 mg/kg, or 10 mg/kg of abatacept monotherapy on days 0, 15, 29, and 57. The primary endpoint was ACR20 response at day 85, and ACR20 criteria were met by 53% of patients receiving 10 mg/kg of abatacept and 31% of patients receiving placebo.

Combination therapy with methotrexate

In a phase 2 double-blind, randomized, controlled trial (RCT), patients who had active RA despite receiving MTX were randomly assigned to receive placebo or abatacept 2 mg/kg or 10 mg/kg.⁴ ACR20 criteria were met in 60% of patients in the 10-mg/kg group versus 35% in the placebo group. Subsequently, the efficacy of abatacept in RA was confirmed in the phase 3 RCT Abatacept in Inadequate Responders to MTX (AIM) in which patients with active RA despite MTX treatment were randomly assigned to receive either placebo or 10 mg/kg of abatacept.⁵ At 6 months, 68%, 40%, and 20% of patients in the abatacept group met ACR20, ACR50, and ACR70 criteria, respectively, compared with 40%, 17%, and 7% in the placebo-treated group. The differences were statistically significant. Along with improvement in symptoms and signs, abatacept-treated patients also had significant improvements in physical function and health-related quality of life as measured by the Health Assessment Questionnaire (HAQ) and Short Form-36 (SF-36), respectively. Abatacept reduced radiographic joint damage progression, with a median change in Genant-modified Sharp scores of 0.25 in the abatacept-treated group compared with 0.53 in the placebo-treated patients.

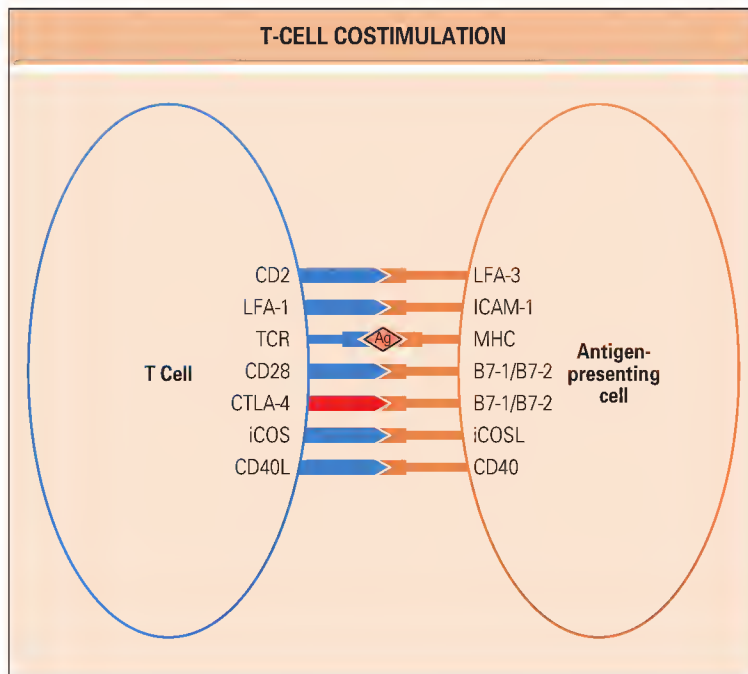


Fig. 59.1 T-cell activation requires costimulatory signals in addition to T-cell receptor engagement to major histocompatibility complex (MHC) and antigenic peptide. Ag, antigenic peptide; CD40L, CD40 ligand; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICAM-1, intercellular adhesion molecule 1; iCOS, inducible T-cell costimulator; iCOSL, inducible T-cell costimulator ligand; LFA, lymphocyte function-associated antigen; TCR, T-cell receptor.

Therapy after tumor necrosis factor antagonist failure

The Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN) was a 6-month RCT that examined the efficacy and safety of abatacept in patients who had shown an inadequate response to TNF antagonists and had active disease.⁶ At 6 months, ACR20 response criteria were met by 50.4% of abatacept-treated patients versus 19.5% of those in the placebo-treated group. DAS28 remission rates were 10% versus 0.9%, respectively. As in the AIM trial, there was statistically significantly greater improvement in SF-36 scores in those patients treated with abatacept than in those given placebo.

One common dilemma faced by clinicians in treating patients for whom TNF antagonist therapy has failed is whether to start treatment immediately or to allow a washout period before initiating abatacept. This issue was addressed by the Abatacept Researched in Rheumatoid Arthritis Patients with an Inadequate Anti-TNF Response to Validate Effectiveness (ARRIVE) trial,⁷ an open-label study in patients with RA who had shown an inadequate response to TNF antagonists. Patients were randomly assigned to undergo either washout (discontinuation of TNF antagonists for at least 2 months before treatment with abatacept) or direct switching (initiation of abatacept at their next scheduled TNF antagonist treatment). At 6 months, improvement in disease activity was similar in both groups. Importantly, rates of both adverse events and serious adverse events also were similar in the two groups: 78.0% in the washout group versus 79.2% in the direct-switch group and 11.1% in the washout group versus 9.9% in the direct-switch group, respectively. The conclusion of the ARRIVE trial is that a washout period is not necessary in patients who have not responded to TNF antagonists before initiation of treatment with abatacept.

Comparison with tumor necrosis factor inhibitors

Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating Rheumatoid Arthritis (ATTEST)⁸ evaluated the efficacy and safety of abatacept or infliximab (3 mg/kg) versus placebo in 431 patients with RA who had shown a partial response to MTX. Reduction in DAS28 score was significantly greater with abatacept and infliximab than with placebo (−2.53, −2.25 and −1.48, respectively; $P < .001$) at 6 months. Similar improvement in symptoms and signs, physical function, and health-related quality of life were seen at 1 year. Abatacept showed an advantage over infliximab in the rate of serious infections (1.9% in the abatacept group vs. 8.5% in the infliximab group), discontinuations due to adverse events (3.2% vs. 7.3%, respectively), and serious adverse events (2.6% vs. 3.6%, respectively).

Treatment of early rheumatoid arthritis

The Abatacept Study to Gauge Remission and Joint Damage Progression in MTX-Naïve Patients with Early Erosive RA (AGREE)⁹ was an RCT examining the use of abatacept in patients with early RA who had one of more poor prognostic factors including high levels of C-reactive protein (CRP), radiographic evidence of erosive disease, and seropositivity for rheumatoid factor or anti-citrullinated protein antibody. Patients were randomly assigned to treatment by either intravenous abatacept plus MTX or MTX alone. At 1 year, DAS28 (CRP)-defined remission was achieved more frequently in abatacept-treated patients than in those given placebo: 41.4% versus 23.3%, respectively ($P < .001$). ACR50 and ACR70 criteria were also more frequently achieved in those receiving abatacept than in those given placebo: 57.4% and 42.6% versus 42.3% and 27.3%, respectively. Radiographic damage measured by Genant-modified Sharp scores was statistically significantly lower in patients receiving abatacept plus MTX (0.63) than in those given MTX alone (1.06).

Subcutaneous abatacept

As noted earlier, a subcutaneous formulation of abatacept recently has become available. A number of RCTs have evaluated the efficacy and safety of subcutaneous abatacept in patients with RA.

Combination with methotrexate

A noninferiority trial comparing subcutaneous abatacept 125 mg weekly with intravenous abatacept 10 mg/kg every 4 weeks was conducted in 1457 patients with RA who had active disease despite receiving MTX.¹⁰ ACR20 response criteria were met by 76% of those receiving subcutaneous abatacept and 75.8% of those receiving intravenous abatacept, which confirms that the two formulations have similar efficacy. An open-label, single-arm study in which 123 patients with RA who had been receiving intravenous abatacept long term were switched to subcutaneous abatacept found that, at 3 months, 97.6% of patients were continuing to receive subcutaneous abatacept without loss of efficacy.¹¹

Comparison with tumor necrosis factor antagonists

The Abatacept versus Adalimumab Comparison in Biologic-Naïve Rheumatoid Arthritis (AMPLE) trial, a single-blind RCT involving 646 biologic drug-naïve RA patients being treated with MTX, compared concurrent administration of subcutaneous abatacept 125 mg every week without an intravenous loading dose with concurrent administration of subcutaneous adalimumab 40 mg every 2 weeks¹² in a study powered to demonstrate “noninferiority.” Patients were unblinded to the drug, but the investigators were blinded to the treatment regimen. At 1 year, abatacept plus MTX and adalimumab plus MTX showed similar efficacy, with ACR20, ACR50, and ACR70 response rates of 64.8%, 46.2%, and 29.2%, respectively, for abatacept versus 63.4%, 46%, and 26.2%, respectively, for adalimumab—results that demonstrated comparability or noninferiority. The kinetics of response was similar for both drugs, with similar responses noted by 4 weeks.

Radiographic damage was also similar in the two groups as assessed by the van der Heijde–modified total Sharp score (0.58 and 0.38 in the abatacept and adalimumab groups, respectively). Injection site reactions were less common in abatacept-treated than adalimumab-treated patients (3.8% vs. 9.1%, respectively; $P = .006$). Rates of adverse events, serious adverse events, and infection were similar in the two groups.

Safety

In RCTs, the rate of discontinuation of therapy due to adverse events in patients treated with intravenous abatacept ranged between 1.9% and 8.7%.¹³

Infusion-related reaction

Infusion reactions occur in approximately 10% of patients receiving intravenous abatacept. Most are mild, but rarely anaphylactic reaction occurs. Rate of discontinuation due to infusion-related reaction is low (<1%).

Infection

In the ATTAIN trial, infections were more common in abatacept-treated patients than in placebo-treated patients (37.6% vs. 32.3%, respectively). The majority of infections were mild to moderate. The rate of serious infections was the same in abatacept-treated patients (2.3%) and placebo-treated patients (2.3%).⁶ In the AIM trial, serious infections were more frequent in abatacept-treated patients than in placebo-treated patients: 3.9% versus 2.3%, respectively.⁵

The Abatacept Study of Safety in Use with Other RA Therapies (ASSURE), a large-scale safety study of abatacept in patients concurrently taking a

traditional DMARD and/or anticytokine agent,¹⁴ found that serious infection occurred in 2.6% of patients received abatacept plus a DMARD versus 1.7% of patients taking a DMARD only. The rate of serious infection was higher in patients taking abatacept with an anticytokine agent (5.8%) than in patients taking an anticytokine agent only (1.6%). Hence combining abatacept with anticytokines is not recommended in routine clinical practice.

Tuberculosis

Screening for tuberculosis is recommended before initiation of any biologic therapy for RA since reactivation of latent tuberculosis has been reported in patients treated with TNF antagonists.¹⁵ In RCTs of abatacept, all patients were screened for latent tuberculosis. In long-term extension studies of RCTs, including AIM and ATTEST, tuberculosis was reported in fewer than 1% of cases.^{5,6}

Vaccination

Abatacept was shown to reduce the protective humoral response to influenza vaccine in 11 RA patients receiving abatacept and DMARDs compared with 33 age-matched RA patients taking MTX and 55 healthy controls.¹⁶ Humoral response to vaccination was observed in 9% of RA patients receiving abatacept and DMARDs compared with 58% of RA patients receiving MTX and 69% of healthy controls ($P < .01$).

Malignancy

The risk of malignancy is a concern with the use of immunomodulatory treatment, since increased incidence of cancer has been reported with immunosuppressive drugs. The incidence of malignancy in patients with RA receiving abatacept in RCTs and open-label studies has been compared with that in patients receiving DMARDs in observational studies by Simon and colleagues¹⁷ and Khraishi and colleagues.¹³ The overall incidence was 0.63 (95% confidence interval 0.46 to 0.84) per 100 patient-years in abatacept-treated patients compared with 0.63 (95% confidence interval 0.26 to 1.5) patient-years in placebo-treated patients. However, the number of patient studied so far is too small for a definitive conclusion to be drawn.

Subcutaneous abatacept

In clinical trials, the rates of adverse events and serious adverse events were similar in patients treated with subcutaneous abatacept and those treated with intravenous abatacept: 65.2% and 4.9% versus 67.0% and 4.2%, respectively. Injection site reactions associated with subcutaneous abatacept therapy are mostly mild and occurred in fewer than 4% of patients.

Immunogenicity

Overall, the immunogenicity of abatacept is low. In phase 3 RCTs, antibodies against intravenously administered abatacept developed in fewer than 3% of patients.¹³ Abatacept induced antibodies in 1.1% of patients treated with the subcutaneous formulation compared with 2.6% of intravenously treated patients.¹⁰ Switching from intravenous to subcutaneous abatacept has limited effect on immunogenicity.¹¹ Immunogenicity was seen in 8 of 123 patients after switching, of whom 6 tested positive before changing to subcutaneous injection. In a follow-on study in which the effects of withdrawal and reintroduction of abatacept were assessed, a stop-start regimen was found to have little impact on efficacy, safety, and immunogenicity.

Biologic effects

Abatacept treatment is associated with changes in the number of CD4+ and CD8+ circulating T lymphocytes in the blood. Furthermore, reduction in interferon- γ expression in synovial tissue suggested reduction in T-cell activation. In animal models of autoimmune diseases, costimulatory blockade induces anergy/tolerance. Hitherto, anergy/tolerance had not been demonstrated in clinical trials of patients with RA. However, an exploratory trial in which patients with undifferentiated inflammatory arthritis were randomly assigned to receive either placebo or abatacept therapy for 6 months found that, at the end of 1 year, numerically more placebo-treated patients (66.7%) than abatacept-treated patients (46.2%) developed RA, although the difference was not statistically significant.¹⁸

TABLE 59.1

Anti-T-cell strategies in rheumatoid arthritis

Strategy	Agent(s)
T-cell subset depletion	Anti-CD7, ²⁰ CD5-plus (XOMA Corp, Berkeley, Calif.), ²¹ IL2-DAB (Pfizer, New York), ²² Campath-1H (anti-CDw52, Alemtuzmab, Sanofi, Paris), ²³⁻²⁵ and anti-CD4 monoclonal antibodies (Centocor, Malvern, Pa.) ²⁶⁻³²
T-cell immunomodulation	Nondepleting anti-CD4 monoclonal antibodies: IDEC-CE9.1/SB-210396 (SmithKline Beecham, Philadelphia), ³³ 4162W94 (Glaxo Wellcome, London) ²⁷ MTRX1011A (Genentech, South San Francisco, Calif.) ³⁴
Vaccination	T cells ^{35,36} T-cell receptors (IR501, Immune Response Corp., New York) ³⁷ MHC peptides: HLA-DRB1*0404/B1*04041 peptide (Anergen, part of GSK, UK) ³⁸ and HLA-DRB1*0404/peptide from HC gp-39 (AG4263) ³⁹
Oral tolerance	Chicken collagen ⁴⁰⁻⁴⁵ Bovine collagen ⁴⁶⁻⁴⁸
Increasing CD4+ regulatory T-cell number	CD28 superagonist (TGN1412, TeGenero Immuno Therapeutics, Würzburg, Germany) ⁴⁹

HC gp-39, human cortiloge glycoprotein 39; IL2-DAB, interleukin-2 diphtherio fusion protein; MHC, major histocompatibility complex.

Conclusions

RCTs of abatacept have shown that selective modulation of T-cell costimulation is an effective treatment strategy in patients with RA with consistent efficacy and safety profile across many clinical studies.

OTHER T-CELL-DIRECTED THERAPIES

Ideally, T-cell-directed therapy should target, primarily or exclusively, the arthritogenic T cells. Clearly, such specific therapy would be less toxic than a general anti-T-cell therapy. However, this type of therapy is more difficult to achieve, especially in established disease, since the arthritogenic peptide- and disease-specific T cells in RA remain unknown. Both depletion and immunomodulation therapies against T cells have been tested in RA (Table 59.1). The development of these strategies has been not continued due to either toxicity or limited efficacy.

FUTURE OF T-CELL TARGETING

In animal models, nonmitogenic, nondepleting anti-CD3 monoclonal antibody can induce immunologic tolerance.¹⁹ Research into the use of a nonmitogenic, nondepleting anti-CD3 monoclonal antibody in RA is being conducted.

CONCLUSION

Current evidence suggests that T cells are pathogenic in RA and play an important role in sustaining synovitis, even in established disease. Modulation of T-cell activity by costimulatory blockade suppresses inflammation and improves disease. In animal models of RA, immunomodulation of T cells can indeed produce prolonged disease remission; however, this has yet to be demonstrated in human disease.

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B-cell depletion

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- B-cell depletion therapies are used for the treatment of various rheumatic diseases, and rituximab is currently the agent most widely used.
- Rituximab depletes B cells by targeting CD20, although the level of B-cell depletion varies between patients.
- Rituximab is licensed for the treatment of severe, active rheumatoid arthritis (RA) in patients who have had an inadequate response to anti-tumor necrosis factor therapy and for the treatment of antineutrophilic cytoplasmic antibody-associated vasculitis.
- For RA, rituximab is given as a course of two infusions, which may be repeated after 6 months if disease activity is ongoing or later if and when disease activity worsens after the initial response; a similar paradigm has been adopted for connective tissue diseases, but the duration of response may be longer than for RA.
- The safety profile of rituximab does not indicate a significant increase in risk for infection, although lower than normal levels of immunoglobulin develop in some patients after several courses. Isolated cases of progressive multifocal leukoencephalopathy have been reported.
- Rituximab has been used for the treatment of systemic lupus erythematosus and Sjögren syndrome, although further studies are required in this area.

INTRODUCTION

Therapeutic B-cell depletion with monoclonal antibodies was originally developed as a treatment of B-cell malignancies and is now being used for the management of several rheumatic diseases.

After an initial case report of improvement of rheumatoid arthritis (RA) in a patient treated with a combination of rituximab and other chemotherapeutic agents,¹ promising results in a small case series of patients² led to the conduct of pivotal multicenter, randomized, controlled trials.

B-cell depletion targeted at CD20 is temporary because of the sparing of stem cells. An initial expectation of many was that temporary clearance of B cells would be sufficient to eliminate the pathogenic clones and lead to sustained remission after repopulation with a new diverse population of B cells. However, in all rheumatic diseases treated, patients ultimately relapse, albeit after a variable interval following B-cell repopulation, and repeated cycles are required to recapture response. Furthermore, clinical responses to depletion vary, thus implying potential pathogenic or pharmacodynamic differences between subgroups of patients.

The response to rituximab therefore established a different therapeutic paradigm than for other immunosuppressive therapies. Clinical questions of importance include the efficacy and safety of repeated cycles of therapy, choosing an appropriate dose and retreatment interval, and defining subgroups of patients likely to respond.

ROLES OF B CELLS IN AUTOIMMUNE DISEASES

B lymphocytes are generated in bone marrow with specific antigen reactivity and negative selection against autoreactive B cells. They are then released into the circulation as transitional cells and ultimately become mature naive

B cells. Naive B cells become activated on meeting their cognate antigen and then participate in germinal center reactions, which involve an interaction of B and T cells arising from B-cell presentation of the antigen, along with other co-stimulatory molecules. In certain instances, B cells may be activated in a T cell-independent manner, such as by bacterial polysaccharides via B-cell and Toll-like receptors. However, HLA associations imply that this is less relevant to the rheumatic diseases usually treated by B-cell depletion.

B-cell activation may lead to multiple memory and effector mechanisms. Memory B cells are generated, as well as short- and long-lived plasma cells that secrete antibody.³ Memory B cells contribute to immune memory by requiring a lower threshold for reactivation on reencountering their cognate antigen and thereafter rapidly differentiating into plasma cells. Short-lived plasma cells provide an immediate antibody response that may be generated without T-cell help. Long-lived plasma cells persist for many years after migrating to bone marrow and hence contribute to both immune memory and maintenance of normal immunoglobulin levels. Finally, T-cell activation following interaction with B cells may activate other effector mechanisms besides B and plasma cells, such as release of inflammatory cytokines.

Hence, B cells may mediate autoimmune disease by production of autoantibodies or immune complexes via plasma cells; by presenting antigen to T cells, which leads to T cell-mediated inflammation; or by producing inflammatory cytokines.

RA is associated with the autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated protein antibody, and T-cell activation in RA may require antigen presentation by B cells.⁴ Autoantibodies may be expressed years before clinical symptoms,⁵ and their exact role in synovitis remains unclear. Systemic lupus erythematosus (SLE) and Sjögren syndrome are associated with antibodies to nuclear components. There is evidence of immune complex deposition at sites of disease, but again, B cells may also have antibody-independent effects, at least in animal models.⁶ In antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis, antibodies are directed against the proteinase-3 and myeloperoxidase located in neutrophils and neutrophil extracellular traps, which may be found in the glomerulus.

B-cell depletion with rituximab generally reduces autoantibody titers, thus indicating their production by short-lived plasma cells, and targeting of long-lived plasma cells is not necessary in most patients. However, antibody status and changes only partially explain the clinical response.

Targeting CD20

CD20 is a 33- to 37-kDa, nonglycosylated phosphoprotein expressed on the surface of mature naive B cells that have exited the bone marrow to enter blood. It is expressed neither on stem cells nor on plasma cells that have returned to bone marrow (Fig. 60.1). This selective expression on mature B cells but not on precursors such as stem cells or on antibody-secreting plasma cells makes it an attractive target, particularly from the point of view of theoretic safety concerns. Depletion via CD20 permits B-cell regeneration and prevents reduction of immunoglobulin levels, at least with initial therapy. Furthermore, on binding antibody, CD20 did not initially appear to be shed from the cell surface or be detectable in serum and is not internalized.⁷ However, evidence from hematology patients has shown that targeted epitope expression may decline after the infusion of monoclonal antibodies. It has been demonstrated *in vitro* that rituximab/CD20 complexes may be removed from B cells by THP-1 monocytes via FcγR, thereby preventing their killing—"CD20 shaving."⁸ CD20 appears to have no natural ligand, and CD20 knockout mice display an almost normal phenotype,⁹ but *in vitro* evidence suggests that it regulates intracellular calcium.

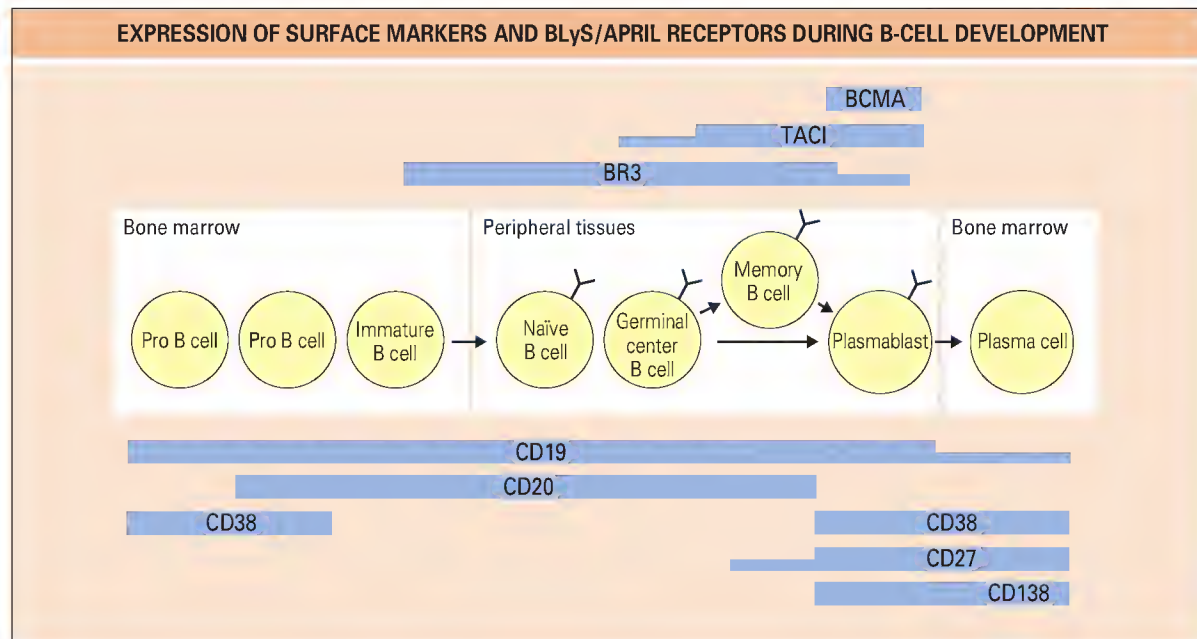


Fig. 60.1 During normal maturation and differentiation of B lineage cells surface marker expression changes. These markers are used for B cell subset identification in flow cytometry. CD20 expression spares Pro B cells and plasma cells in bone marrow, accounting for recovery of B cell numbers and preservation of immunoglobulin titres. BLYS/APRIL receptor expression changes reflect the changing dependence of B cells on these survival factors as the differentiate (see text for details).

Rituximab

Rituximab, the first anti-CD20 monoclonal antibody to be used therapeutically, consists of fusion of the light- and heavy-chain variable regions of a murine antihuman monoclonal anti-CD20 antibody with human immunoglobulin κ light-chain and $\gamma 1$ heavy-chain constant regions.¹⁰ It was originally developed for the treatment of refractory CD20+ B-cell non-Hodgkin lymphoma (NHL)¹¹ and has demonstrated efficacy against other B-cell malignancies such as B-cell chronic lymphocytic leukemia and diffuse large B-cell lymphoma. B-cell killing *in vivo* is achieved by antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells, complement-dependent cytotoxicity, and apoptosis. ADCC is thought to be its most important mechanism of cell killing¹² (Fig. 60.2).

Rituximab is formulated for intravenous administration over a period of several hours. Clinical pharmacokinetic data are available for two consecutive doses of 500 mg (RTX500) and two doses of 1000 mg (RTX1000) given on days 1 and 15. The mean terminal elimination half-life ranged from 16 to 16.5 days (after the second infusion) for the former dose and 18 to 21 days for the latter. No difference in pharmacokinetics was seen between the first and second cycles of treatment. Because of the risk for infusion-related reactions, rituximab should be administered in clinical environments in which full resuscitation facilities are available, although severe infusion reactions are uncommon in the treatment of autoimmune diseases. Prophylaxis with paracetamol (1 g) and diphenhydramine HCl (25 to 50 mg or equivalent dose of a similar agent) should be initiated 30 to 60 minutes before infusion of rituximab.¹³

Rituximab biosimilars

Roche's patents on rituximab expire in 2014-2015, and several manufacturers are developing "biosimilars"—molecules based on the same amino acid sequence but potentially different manufacturing processes (and therefore posttranslational modifications) in an attempt to match the overall characteristics of marketed rituximab as closely as possible.

Second- and third-generation anti-CD20 molecules

Ofatumumab is a fully human anti-CD20 antibody that binds to a different epitope than rituximab does; it is licensed for resistant chronic lymphocytic leukemia and has shown evidence of efficacy in treating RA.¹⁴ Obinutuzumab is a humanized anti-CD20 antibody that also binds a different epitope than rituximab does; it has phase 1 efficacy and safety data published for NHL.¹⁵ Ocrelizumab is a humanized anti-CD20 antibody that binds to an overlapping CD20 epitope to rituximab with increased ADCC and reduced complement-dependent cytotoxicity, also developed by Roche. It met endpoints in clinical trials involving RA and was used in trials for SLE.¹⁶ Development for these indications ended after evidence of an increased rate of

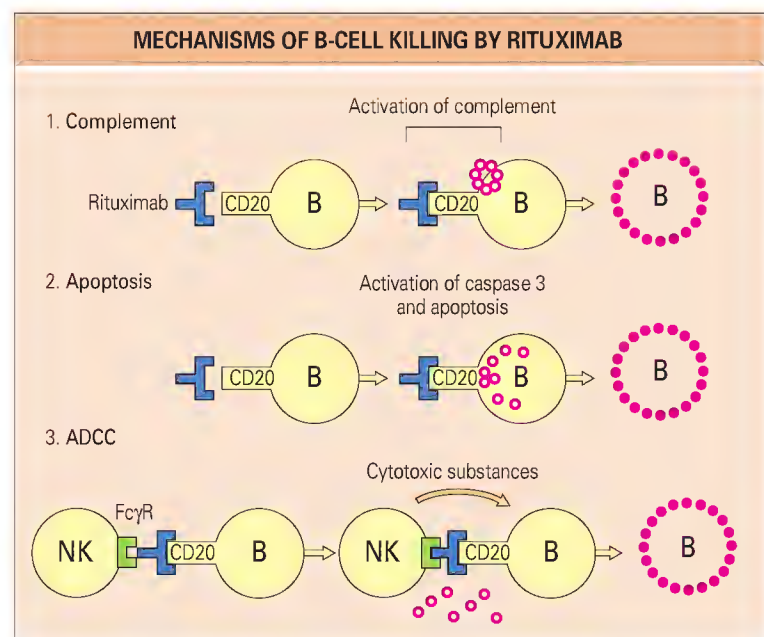


Fig. 60.2 There are three possible mechanisms of cell killing for anti-CD20 antibodies: ADCC (antibody-dependent cell-mediated cytotoxicity); Complement-dependent cytotoxicity and induction of apoptosis. However, there is only indirect evidence for which is most important *in vivo*. ADCC is generally thought to be the predominant mechanism. Cell killing depends on Fc-gamma receptor bearing NK cells or monocytes following the binding of rituximab to CD20. NK, natural killer.

opportunistic infection. The drug is being still developed for the treatment of multiple sclerosis.¹⁷

Efficacy for rheumatoid arthritis

Open-label series initially reported regimens containing variable doses of rituximab, cyclophosphamide, and high-dose corticosteroid to be efficacious. The efficacy of rituximab has since been tested in a series of randomized controlled trials¹⁸⁻²³ (Table 60.1). In all these studies rituximab was administered as two infusions 2 weeks apart, each preceded by 100 mg

■ TABLE 60.1

Summary of efficacy data in rituximab in rheumatoid arthritis: randomized controlled trials

Study	Population	Randomization	Endpoints	Key findings	Reference
Edwards et al.	MTX-IR RF positive	1: MTX (n = 40) 2: RTX1000 (n = 40) 3: RTX1000 + CyP (n = 41) 4: RTX1000 + MTX (n = 40) All groups had PO-CS and IV-CS	1: ACR50 at wk 24 2: DAS28, EULAR, and ACR responses at 24 and 48 wk	All RTX arms superior to MTX at 6 mo Only arms 3 and 4 significantly superior at 12 mo B cells depleted in all RTX groups for 24 wk RF reduced; total Ig remained stable	18
DANCER	MTX-IR or TNF-IR RF/CCP positive or negative	1: Placebo 2: Placebo + IV-CS 3: Placebo + IV-CS + PO-CS 4: RTX500 5: RTX500 + IV-CS 6: RTX500 + IV-CS + PO-CS 7: RTX1000 8: RTX1000 + IV-CS 9: RTX1000 + IV-CS + PO-CS All groups had MTX Total N = 465 Retreatment on relapse	1: ACR20 at wk 24 2: DAS28, EULAR, and ACR responses at wk 24; HAQ, FACIT-F, safety, Ig, HACA	All RTX arms superior to placebo Time to best response 12-24 wk Numerically higher ACR70 and EULAR good response in RTX 1000 groups vs. RTX 500 CS did not influence efficacy endpoints IV-CS reduces infusion reactions, no added benefit with PO-CS HACA rate: placebo = 0.7%, RTX 500 = 4.2%, RTX 1000 = 2.7%, but no clinical sequelae	19
REFLEX	TNF-IR RF/CCP positive or negative	1: Placebo + MTX (n = 209) 2: RTX1000 + MTX (n = 311) All groups had PO-CS and IV-CS Retreatment on relapse	1: ACR20 at wk 24 2: DAS28, EULAR, and ACR responses at wk 24 Other: HAQ, FACIT-F, radiographic, safety	RTX superior to placebo: ACR20 = 51% vs. 18% Trend to less progression in total Genant-modified Sharp score Significantly less progression in joint space narrowing score Nonserious AEs other than infusion reactions balanced Serious infections: placebo = 3.7, RTX = 5.2/100 patient-yr	20
SERENE	MTX-IR RF/CCP positive or negative	1: Placebo + MTX 2: RTX500 + MTX 3: RTX1000 + MTX Retreatment from wk 24 unless in remission	1: ACR20 at wk 24 2: DAS28, EULAR, and ACR responses; HAQ, SF36, FACIT-F	Confirmed similar level of efficacy at wk 24 as REFLEX study Further improvement in response rates following retreatment No difference between rituximab doses Better responses if RF or CCP positive at baseline	21
MIRROR	MTX-IR or TNF-IR RF/CCP positive or negative	1: RTX500 then RTX500 2: RTX500 then RTX1000 3: RTX1000 then RTX1000 Treatment at 0 and 24 wk in all patients All patients received MTX	1: ACR20 at wk 48 2: DAS28, EULAR, and ACR responses; HAQ, SF36, FACIT-F	Numerically higher ACR response at 48 wk in arm 3 vs. other 2 arms Statistically better EULAR response at 48 wk in arm 3 46% of ACR20 nonresponders at 24 wk responded at 48 wk (arm 3) Fewer patients had worse response at 48 wk in arm 3	22
IMAGE	MTX naive RF-negative patients needed erosions to enroll	1: Placebo + MTX 2: RTX500 + MTX 3: RTX1000 + MTX Retreatment from wk 24 unless in remission	1: Change in mTSS at wk 52 Other: major clinical response (maintenance of ACR70 >6 mo). DAS28, EULAR, and ACR responses; HAQ, SF36, FACIT-F	RTX + MTX superior to MTX alone in MTX-naive RA ACR and EULAR responses not affected by RTX dose mTSS progression only significantly better with RTX 1000	23

ACR, American College of Rheumatology; AE, adverse event; CCP, cyclic citrullinated protein; CS, corticosteroid; CyP, cyclophosphamide; DAS28, 28-joint disease activity score; EULAR, European League Against Rheumatism; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue subscale; HACA, human antichimeric antibody; HAQ, Health Assessment Questionnaire; Ig, immunoglobulin; IV-CS, intravenous methylprednisolone 100 mg days 1 and 15; mTSS, total Genant-modified Sharp score; MTX, methotrexate; PO-CS, oral prednisolone 60 mg days 2-7, 30 mg days 8-14; RA, rheumatoid arthritis; RF, rheumatoid factor; RTX500, 2 × 500 mg rituximab; RTX1000, 2 × 1000 mg rituximab; TNF, tumor necrosis factor.

methylprednisolone. However, rituximab doses, other concomitant therapies, and retreatment intervals varied.

Rituximab was licensed by the U.S. Food and Drug Administration (FDA) and European Medicines Agency for the treatment of severe active RA in patients with an inadequate response to anti-tumor necrosis factor (TNF) therapy.

Radiographic outcomes

Data on radiographic progression following rituximab are available from the REFLEX²⁰ and IMAGE²³ studies. The patient populations in these studies were quite different. The former enrolled patients with a relatively long disease duration (approximately 12 years) who had already had an

inadequate response to anti-TNF therapy. In the latter, patients had much a shorter disease duration (mean duration, 0.9 months) and had not yet received methotrexate. In the REFLEX study, patients were taking methotrexate and were then randomized to receive either rituximab (1000 mg for two doses) or placebo. Retreatment with the same dose was given when patients flared after their initial response; patients randomized to placebo could be given rescue treatment with rituximab, but for the purposes of analysis, such patients were still considered part of the “placebo” group. Radiographs of patients’ hands and feet were obtained at baseline, week 24, and week 56 and scored with the Genant-modified Sharp method. Patients who received rituximab had significantly less radiographic disease progression than did those who received placebo. The mean change from baseline

in the total Genant-modified Sharp score at week 56 was significantly lower in patients treated with rituximab (1.00 versus 2.31, rituximab versus placebo, $P = .005$); changes in erosion scores (0.59 versus 1.32, rituximab versus placebo, $P = .011$) and joint space narrowing (0.41 versus 0.99, $P < .001$) were significantly in favor of rituximab. Patients treated with rituximab whose clinical outcomes were no better than those receiving placebo still had less radiographic progression.

The IMAGE study of methotrexate-naïve patients with early RA measured similar outcomes in 715 patients randomized equally to three arms: methotrexate alone, methotrexate plus RTX500, or methotrexate plus RTX1000.²³ At 52 weeks, patients who received higher-dose rituximab (i.e., 2×1000 mg, repeated at 6 months in patients not in remission and given to patients in remission at 6 months if and when their disease activity score [DAS] later worsened) had significantly lower changes in the mean total Sharp score (mTSS) (0.359 versus 1.079, $P < .001$), and more patients had no progression in the mTSS when treated with that dose of rituximab (63.5 versus 53.4, $P < .05$). Although statistically significant differences were not observed between patients receiving methotrexate alone and those treated with the lower dose of rituximab, a numeric difference favored the lower dose of rituximab over methotrexate alone.

Outcome of repeated cycles

Patients from the original large randomized studies were followed in open-label extension studies. Patients who were deemed to be responders (by predefined criteria) were eligible for retreatment with a further cycle of two infusions of RTX1000 with preceding methylprednisolone if they subsequently had deterioration in disease activity. Data for up to five courses of therapy²⁴ are reported. The median treatment interval between the first, second, and third courses in patients with previous anti-TNF exposure remained stable at approximately 30 weeks (Fig. 60.3). Clinical responses were also sustained. American College of Rheumatology (ACR) and DAS responses were similar after the first and second courses, and the proportions of patients achieving ACR70, 28-joint Disease Activity Score (DAS28) low disease activity (DAS28 <3.2), and DAS28 remission (DAS28 <2.6) increased after the second course. The change in DAS28 from baseline after each course was consistent, thus implying a cumulative progressive reduction in disease activity with repeated treatment.

The most commonly used paradigm for rituximab therapy, therefore, is repeated therapy if a patient deteriorates after initially improving. Inherent in this paradigm is a degree of instability with potential clinical implications such as more short-term steroid use, and this may also potentially be detrimental to long-term outcomes. Results from the studies listed in Table 60.1 have been compared. Control of disease activity and safety both

appeared to be better in patients receiving fixed retreatment protocols, although this is confounded by differences in inclusion criteria.

Effect of rituximab dose

Existing data from four randomized controlled trials that used both rituximab doses have yielded conflicting information on their comparative efficacy, possibly because these studies recruited different patient populations and had different retreatment frequencies and outcome measures. The DANCER study recruited patients with established RA after failure of methotrexate or one or more TNF inhibitors and showed that single cycles of RTX500 or RTX1000 were both superior to placebo.¹⁹ There was no statistical comparison between these arms, but rates of “high-hurdle” endpoints were numerically higher after RTX1000 (European League Against Rheumatism [EULAR] good response: 14% versus 28%; ACR70: 13% versus 20% for RTX500 and RTX1000, respectively).¹⁹ The SERENE study recruited patients who had previously failed methotrexate only and used rituximab every 6 months unless in remission.²¹ This study found no substantive or significant differences between rituximab doses. Interestingly, however, the ACR70 rate was not significantly superior to placebo at either dose of rituximab in this study, in contrast to DANCER.¹⁹ The MIRROR study recruited patients who had failed methotrexate and either none or one TNF inhibitor and were treated with rituximab at baseline and 6 months.²² This study found a significant difference in the EULAR response rate between RTX500 and RTX1000 at 52 weeks (72% versus 88%; $P < .05$). However, ACR responses did not differ except in the subgroup previously treated with anti-TNF.²² The IMAGE study recruited methotrexate-naïve patients with early RA and included a radiographic primary outcome measure.²³ Clinical responses were not significantly different. However, only the RTX1000 group demonstrated significant inhibition of radiographic progression in comparison to placebo at 24 and 52 weeks. The mean change in total Sharp score was also significantly less in the RTX1000 than in the RTX500 group at 52 weeks.²³

One study reported that B-cell and plasmablast numbers, rather than dose per se, correlated with clinical response. Patients with low numbers of plasmablasts at baseline had complete plasmablast depletion and a good clinical response with RTX500.²⁵

Six months after treatment, B cells are approximately 10 times lower than at baseline and in many cases remain undetectable by conventional methodologies. Lower doses of rituximab might be equally effective in repeated cycles.²⁶

Retreatment of nonresponse

A single course of rituximab does not usually normalize autoantibody titers, and mechanistic studies demonstrate the persistence of B-lineage cells in peripheral blood and synovium in clinical nonresponders. One study targeted patients with an inadequate response to an initial cycle of rituximab for retreatment at 6 months in an attempt to increase B-cell and plasmablast depletion. Increased B-cell depletion was seen, and 72% of the nonresponders became EULAR moderate or good responders after retreatment, with the duration of response being equivalent to that of the initial responders.²⁷

Concomitant disease-modifying antirheumatic drugs and corticosteroids

The DANCER study reported that premedication with intravenous steroids appeared to reduce acute infusion-related reactions.¹⁹ However, the use of oral corticosteroids appeared to be unnecessary in terms of improving long-term outcomes and had no effect on infusion reactions after the second infusion. Steroids did improve the initial clinical response at 4 weeks after therapy; subsequently, clinical improvement (ACR20 response) continued before reaching a plateau at 12 weeks. The EULAR consensus statement regarding rituximab²⁸ recommends advising patients that they may experience an immediate but transient benefit after therapy followed by slower response that may take up to 12 weeks to become apparent. An open-label study in which premedication with oral instead of intravenous steroids was substituted suggested that the incidence of infusion reactions was not dissimilar between the two treatment approaches.²⁹

The DANCER study demonstrated the benefit of methotrexate in prolonging response. The duration of B-cell depletion after rituximab appears to be unrelated to the concomitant use of methotrexate,³⁰ although the data provided by highly sensitive flow cytometry to optimize detection of plasmablasts demonstrated a difference in immediate depletion.³¹ Use of other concomitant disease-modifying antirheumatic drugs (DMARDs)—in particular, leflunomide—in a small number of patients has been reported to be safe and effective and reproduces the effect of methotrexate on peripheral B-cell subsets.³²

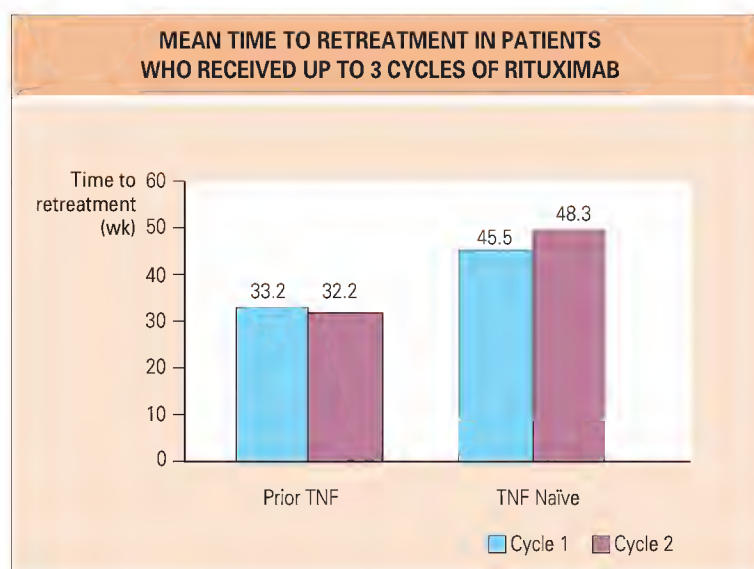


Fig. 60.3 Mean time to retreatment of patients who received up to three cycles of rituximab in long-term extensions of phase 2 DANCER and REFLEX studies according to previous TNF exposure. Error bars represent 95% confidence intervals. TNF, tumor necrosis factor. (From Keystone E, Fleishmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. *Arthritis Rheum* 2007;56:3896-908.)

Mechanism-of-action studies and prediction of response

Antibody status

The phase 2a study included only patients who were positive for RF; in DANCER, 380 patients were RF positive and 85 were RF negative; and in REFLEX, both RF-positive (81%) and RF-negative patients were also included. A meta-analysis of these studies indicated a modest additional increase in benefit in seropositive over seronegative patients—the reduction in the DAS28–erythrocyte sedimentation rate was on average 0.35 units greater in the former group (95% confidence interval, 0.12 to 0.84).³³ The effect of serologic status may be greater in patients who have received one or more anti-TNF agents than in those who are methotrexate naïve. Another study also reported that RF or anti-CCP antibodies and higher titers of total serum IgG were associated with response to rituximab.³⁴

Peripheral blood B-cell studies

Early studies indicated no correlation between total B-cell numbers and clinical response to rituximab.³⁵ A flow cytometry protocol that was optimized for detection of plasmablasts demonstrated that a higher number of these cells at baseline was associated with an inferior response to rituximab at 6 months.³⁶ Persistence of plasmablasts after the first infusion of rituximab was also associated with an inferior clinical response.³⁷

Genetic studies

Genetic studies have focused on Fcγ receptor polymorphisms and B-cell survival factors. The FCGR3A-158V/F polymorphism seemed to be associated in one study involving RA.³⁸

Safety in treating rheumatoid arthritis

No new safety signals have emerged from the use of rituximab for RA when compared with the extensive data available from hematology and oncology practice.³⁹

Screening before therapy

Patients should be screened by eliciting a history of chronic or concomitant comorbidity—with a focus on cardiovascular and pulmonary disease and infections. No increased risk for tuberculosis has been observed in lymphoma patients treated with rituximab.³⁹ Although screening for latent tuberculosis is not required, most rheumatologists routinely screen for it before starting rituximab therapy. Screening for hepatitis B infection is recommended because of reactivation of infection with fulminant hepatitis after rituximab therapy.⁴⁰ Patients with hepatitis B have been treated successfully with antiviral prophylaxis while taking rituximab,⁴⁰ and patients with hepatitis C have been treated without any prophylaxis.

Infusion reactions

Infusion reactions are the most frequent adverse events observed with rituximab therapy and include pruritus, urticaria, pyrexia, throat irritation, and hypotension and hypertension, but these reactions are usually mild to moderate in severity. It has been suggested that these reactions are due to release of cytokines following B-cell lysis.⁴¹ Such symptoms affect up to 30% of patients, but it should be noted that the incidence following the second infusion is much lower,¹⁹ possibly because B-cell numbers are already significantly reduced by the first infusion. The lower rate of infusion reactions in patients with RA than in those with NHL may also be related to this because the latter group often has a heavier B-cell load before therapy. A small number of patients (<1%) experienced serious infusion reactions (anaphylaxis and bronchospasm).

Intravenous steroid administration before infusion of rituximab reduced infusion reactions from 37% to 29% in patients receiving a first infusion of 1000 mg rituximab.¹⁹ Repeated courses are associated with fewer infusion reactions.²⁴ Infusion reactions can be managed with additional paracetamol, antihistamines, and if required, bronchodilators and steroids.

Infections

Rituximab therapy should be delayed until any active infections have resolved. Most infections after rituximab were minor and largely consisted of upper respiratory or urinary tract infections. There was a slight increase in serious infections (5.2 versus 3.7 per 100 patient-years) over placebo in the REFLEX trial. Limited data suggest an increased risk for opportunistic infections. A small number of patients with previous tuberculosis or a positive Mantoux test have been treated without reactivation of disease. A cumulative reduction in immunoglobulin levels occurs with repeated cycles of therapy. After a third course of rituximab, 23.5% of patients have lower than normal level of IgM (Fig. 60.4). No change was found in the incidence

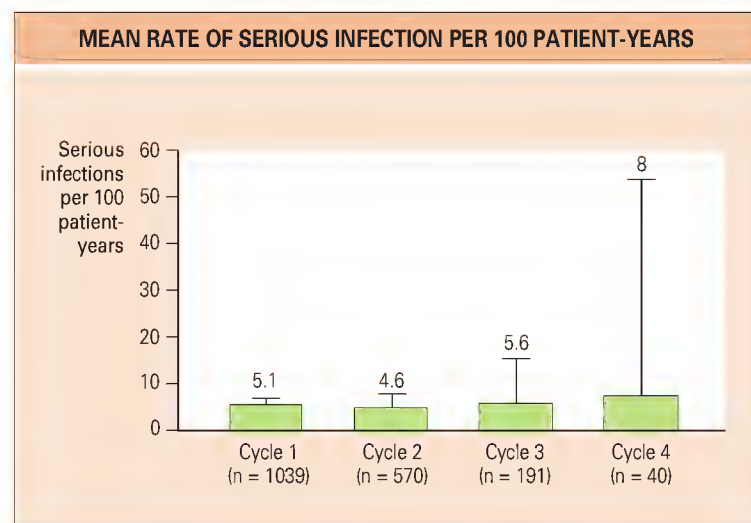


Fig. 60.4 Mean rate of serious infections per 100 patient-years in patients who received up to four cycles of rituximab in long-term extensions of phase 2 DANCER and REFLEX studies according to previous tumor necrosis factor exposure. Error bars represent 95% confidence intervals. (From Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. *Arthritis Rheum* 2007;56:3896-908.)

of infections in these patients before and after IgM fell below the normal limit. After cycles 3 and 4, approximately 5% of patients have low levels of IgG at any time. Data from the French AIR registry, however, indicate an increased rate of serious infections in patients with a low IgG level before receiving a first or repeated cycle of rituximab.⁴²

Vaccination responses and immunization following rituximab

A randomized controlled study (SIERRA) compared immunization responses in patients treated with combination rituximab and methotrexate and those receiving methotrexate alone.⁴³ All patients had similar effective responses to recall antigen (tetanus) and the ability to mount a cutaneous delayed-type hypersensitivity response to *Candida albicans* was similarly preserved, but responsiveness to pneumococcal vaccine (a polysaccharide antigen response) and a neoantigen (keyhole limpet hemocyanin) was diminished in rituximab-treated patients. It is recommended that vaccination be completed 4 weeks before rituximab therapy.

Progressive multifocal leukoencephalopathy

A small number of cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving rituximab for autoimmune diseases.⁴⁴ The incidence of PML is higher in patients with autoimmune rheumatic disease and in those receiving any form of immunosuppression. The incidence of PML in patients with RA treated with rituximab is quoted as being 1 in 25,000.⁴⁵ PML should be considered in the differential diagnosis of any patient treated with rituximab who is noted to have a change in neurologic status.⁴⁶

With regard to other potential side effects (malignancy, cutaneous and pulmonary) that have been observed with other biologic agents, limited data are available. No increased risk for malignancy was identified in one national cohort study of patients who had received one course of rituximab.⁴⁷ There have been case reports of psoriasis developing after treatment with rituximab.⁴⁸

Rituximab: use for connective tissue diseases

Rituximab has also been used increasingly widely for the treatment of connective tissue diseases. Randomized studies have been conducted in patients with SLE, primary Sjögren syndrome (pSS), and ANCA-associated vasculitis (AAV), and there are also considerable data from open-label series, often in patients with disease resistant to other therapies.

Systemic lupus erythematosus

Rituximab is used for SLE, but to date randomized controlled trials have not been positive. All open-label studies report a high degree of efficacy, including larger single-center series with a wide spectrum of

manifestations,^{49,50} a multicenter registry,⁵¹ and a systematic review of renal disease.⁵² Open-label series have reported rituximab to be efficacious for a range of disease manifestations,⁵³ including lupus nephritis, arthritis, hematologic disease (immune thrombocytopenia and autoimmune hemolytic anemia), cutaneous involvement, serositis, and cardiac, respiratory, and cerebral organ involvement. In these series most patients had received immunosuppression with DMARDs, including (but not always) cyclophosphamide, before treatment with rituximab. A variety of doses—usually either two infusions of 1 g rituximab or four infusions of 375 mg/m²—were used, as were different combinations of DMARDs, as well as rituximab monotherapy. Time to relapse is highly variable in SLE, with a subset of patients having much longer periods of remission (several years) in comparison to RA. Longer responses have been associated with negative antibodies to extractable nuclear antigens normal C3, and delayed repopulation of plasmablasts and memory B cells.^{50,54} Repeated cycles appear to be effective.⁵⁵

It has therefore been surprising that the first randomized controlled trial for SLE—“EXPLORER”—failed to meet any of its primary or secondary endpoints.⁵⁶ This discrepancy may be related to the endpoints used in the EXPLORER study and to the use of an active comparator. Patients were randomized to a high-dose corticosteroid regimen with tapering over a 6-month period combined with a conventional immunosuppressant with or without two infusions of rituximab at 0 and 6 months. The primary endpoint required patients to first meet a low-disease activity landmark at 6 months and then not flare in the second 6 months. However, the number of patients meeting the initial landmark in either arm was low, and in those who did meet that landmark, the subsequent flare rate was low even in the control arm. *Post-hoc* analyses of this study showed differences between rituximab and placebo in patients whose concomitant immunosuppressant was methotrexate, in patients of African ancestry, and in the British Isles Lupus Assessment Group A flare rate. A second randomized controlled trial of lupus nephritis also failed to meet its endpoints, but again, use of an active comparator may make interpretation difficult. These studies may therefore have been suggested to have underestimated the benefits of rituximab for SLE.

Sjögren Syndrome

Open-label studies of rituximab indicated improvement in sicca symptoms and objective measures, as well as in the histologic changes associated with MALToma.⁵⁷ A pilot randomized, double-blind, placebo-controlled trial of rituximab for pSS did show greater improvement in fatigue scores with rituximab than with placebo.⁵⁸

Vasculitis

Rituximab has been approved by the FDA for the treatment of AAV. A randomized, double-blind, double-dummy, noninferiority trial, the Rituximab in ANCA Associated Vasculitis study, was designed as a noninferiority

study to compare rituximab (four doses of 375 mg/m² intravenously) with cyclophosphamide (2 mg/kg/day orally) for 3 months followed by azathioprine.⁵⁹ Patients with either newly diagnosed or relapsing disease were eligible for entry. Intravenous and a tapering course of oral steroids were used in the same manner in both groups. The primary outcome was remission. One hundred ninety-seven patients with either granulomatosis with polyangiitis (75% of patients) or microscopic polyangiitis (24%) were enrolled in the study. More patients treated with rituximab were in remission (64% versus 55%, $P = .21$), and this difference met the criterion for noninferiority ($P < .001$). Rituximab was more efficacious than cyclophosphamide in patients with relapsing disease at baseline.

Rituximab appears to be an effective alternative to cyclophosphamide for AAV and may be more effective in patients who have relapsing disease.

A randomized, controlled trial in which rituximab was compared with cyclophosphamide for ANCA-associated renal vasculitis has also been undertaken.⁶⁰ All patients received a standard glucocorticoid regimen with either four infusions of rituximab 375 mg/m² given at weekly intervals along with two intravenous cyclophosphamide pulses or intravenous cyclophosphamide given for 3 to 6 months followed by azathioprine. No significant difference was found in the proportion of patients in both groups who were in sustained remission at 12 months (76% versus 82%, rituximab versus control group, $P = .68$), and the number of early severe adverse events was similar in both groups.

SUMMARY

B-cell depletion therapy with rituximab has proved to be a promising area in terms of both clinical management and research on disease pathogenesis. In RA, the clinical benefits of such therapy have been important for the significant number of patients who have active progressive disease despite conventional and biologic DMARDs; evidence of its benefit in populations with earlier disease is now accruing. There are also increasing data on structural benefit. Questions remain regarding the most appropriate dose and the frequency of repeated treatments. The safety profile has been reassuring, with the treatment being suitable for some patients who may have a contraindication to anti-TNF therapy for safety reasons. Immunoglobulin levels—particularly IgG after several cycles—will need to be monitored carefully, although with regard to safety, there does not appear to be a need to monitor CD19 levels in routine clinical practice.

Rituximab is now approved by the FDA for treatment of AAV. In terms of toxicity, rituximab may also be a better alternative than cyclophosphamide for the treatment of other rheumatic diseases, including SLE, although careful surveillance for infection, especially PML, will be required. In SLE and Sjögren syndrome, confirmation of efficacy through well-designed clinical studies is still needed.

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61

Cytokine neutralizers:
interleukin-1 inhibitors

■ CEM GABAY

- Interleukin-1 α (IL-1 α) and IL-1 β (also termed IL-1) are prototypic proinflammatory cytokines that activate effector cells by binding to IL-1 receptors.
- IL-1 is a very potent cytokine, the activities of which are tightly regulated by natural inhibitors such as IL-1 receptor antagonist (IL-1Ra), type 2 IL-1R, and soluble receptors. The balance between IL-1 and its natural inhibitor IL-1Ra has been shown to play a major role in the regulation of inflammatory responses.
- The production of mature and bioactive IL-1 β is regulated by two signals: signal 1 induces the production of pro-IL-1 β , a nonactive 31-kDa propeptide. Activation of the inflammasome, a cytosolic complex of proteins, leads to the activation of caspase-1, which causes processing of pro-IL-1 β into mature 17-kDa IL-1 β and its release outside the cells. In addition to caspase-1, other enzymes are also involved in the cleavage and maturation of IL-1 β .
- Exogenous microbial components and endogenous agents (monosodium urate and calcium dihydrate pyrophosphate crystals) can activate the NALP3 inflammasome. In addition, some mutations of NALP3 lead to spontaneous activation of the inflammasome and caspase-1 and overproduction of IL-1 β , which causes recurrent episodes of fever with inflammatory systemic manifestations.
- IL-1 inhibitors have been reported to be markedly effective in the management of systemic-onset juvenile idiopathic arthritis, adult-onset Still disease, crystal-induced arthritis, and periodic fever syndromes associated with either overproduction of IL-1 β or IL-1Ra deficiency.

INTERLEUKIN-1 FAMILY

Ligands and receptors

The IL-1 family includes three ligands: IL-1 α , IL-1 β , and IL-1 receptor antagonist (IL-1Ra).¹ IL-1 α and IL-1 β exert agonist activities and play critical roles in inflammatory responses. IL-1 α and IL-1 β are produced as 31-kDa propeptides. Pro-IL-1 β is biologically inactive and must be converted into mature IL-1 β to acquire the ability to bind to receptors and activate cells, whereas both pro-IL-1 α and mature IL-1 α are biologically active. However, the amino terminal region of pro-IL-1 α is also cleaved by Granzyme B, elastase, and calpain-1 proteases, which leads to marked enhancement of IL-1 α biologic activity.²

The IL-1 receptor family includes three receptors: type 1 IL-1 receptor (IL-1RI), type 2 IL-1 receptor (IL-1RII), and IL-1 receptor accessory protein (IL-1RAcP) (Fig. 61.1). Binding of IL-1 to IL-1RI leads to the recruitment of IL-1RAcP and cell signaling. IL-1RII has a short intracytoplasmic domain and is unable to transduce any intracellular signal and thus functions as a decoy receptor.³ Both membrane-bound and soluble IL-1RII can bind to IL-1 β and exert inhibitory functions (see Fig. 61.1).

IL-1Ra is structurally closely related to the other IL-1 ligands. IL-1Ra binds avidly to IL-1RI but fails to activate cells; it functions as a specific competitive inhibitor of IL-1. Several different isoforms of IL-1Ra are produced from the same gene, but the function of these intracellular isoforms remains unclear.⁴

Interleukin-1 plays a critical role in inflammation

In healthy human subjects, IL-1 β , contrary to other cytokines, is barely detectable in the bloodstream, thus suggesting that its circulating levels are below 10 pg/mL. Such low levels have to be maintained because of the tremendous potency of IL-1 β in inducing inflammatory responses.⁵ Experimental evidence indicates that IL-1 is involved in the development of arthritis.⁶ The importance of IL-1Ra as an endogenous modulator of inflammatory responses has been demonstrated by the use of gene knockout mice and more recently in humans genetically deficient in IL-1Ra. Breeding of IL-1Ra-deficient mice bred into the BALB/c background generates a spontaneous form of polyarthritis.⁷ The arthritis does not develop in germ-free conditions, and Toll-like receptor 4 (TLR4)-deficient mice have an attenuated form of arthritis, thus indicating the dependence of microbial flora. TLR4 signaling enhanced the disease by activating type 17 helper T cells (Th17) cells and increasing IL-17 production.⁸ Conditional knockout mice in which myeloid cell, including macrophages and dendritic cells, are selectively deficient in IL-1Ra exhibit an earlier onset and more severe form of collagen-induced arthritis with increased Th1 and Th17 responses.⁹ Finally, The occurrence of autoinflammatory manifestations in children deficient in IL-1Ra further supports the key regulatory role of this cytokine.^{10,11}

Regulation of interleukin-1 β maturation by the inflammasome

The mechanisms leading to the processing and release of mature IL-1 β have great relevance to many acute and chronic inflammatory diseases. It is currently hypothesized that two signals are required for release of IL-1 β from normal human monocytes. First, pro-IL-1 β synthesis is stimulated on binding of bacterial or endogenous components to the TLR. The second signal is NLR (NOD-like receptors)-induced IL-1 β processing and release through a caspase-1-dependent mechanism that is regulated by a multimeric cytosolic protein complex called the inflammasome. This complex contains caspase-1, the adapter protein PYCARD (also known as ASC), and a sensor protein belonging to the NLR family.¹² Activation of caspase 1 through the NALP3 inflammasome can be induced by stimulation with microbial molecules and endogenous molecules such as monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD)¹³ (Fig. 61.2). Interestingly, activation of the NALP3/cryopyrin inflammasome has proved particularly important for many diseases characterized by overproduction of IL-1 β , such as some periodic fever syndromes and crystal-induced arthritis.¹⁴ In addition, pro-IL-1 β can also be cleaved in the extracellular environment by different inflammatory proteases to yield active IL-1 β .^{15,16}

THERAPEUTIC INHIBITORS OF INTERLEUKIN-1 IN RHEUMATIC DISEASES

Figure 61.3 depicts the different strategies that have been developed to inhibit the biologic effects of IL-1. The subsequent paragraphs describe the effect of IL-1 antagonists in the different rheumatic diseases (Table 61.1). Descriptions of the different IL-1 inhibitors is detailed in the section on rheumatoid arthritis (RA) because they were all tested or at least initially examined in experimental models of RA.

Rheumatoid arthritis

Anakinra (Kineret) interleukin-1 receptor antagonist

The results of a randomized double-blind controlled clinical trial showed that administration of anakinra was superior to placebo according to the

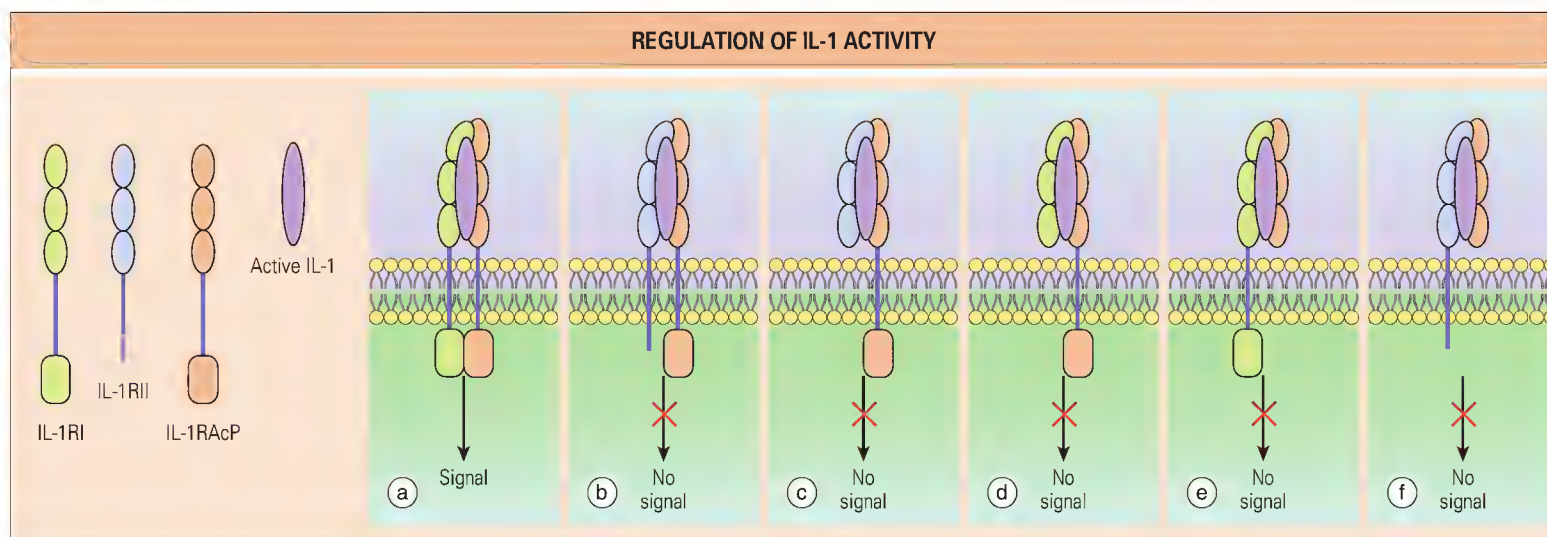


Fig. 61.1 Regulation of interleukin-1 (IL-1) activity by both membrane-bound and soluble forms of IL-1 receptors. (a) The biologic activities of IL-1, including membrane-bound pro-IL-1 α , mIL-1 α , and mIL-1 β , are mediated by binding to the cell surface receptor IL-1RI. Binding of IL-1 induces a conformational change in the extracellular component of IL-1RI that enables its interaction with IL-1RAcP, which is required for intracellular signaling. IL-1RII might act only as a decoy receptor either (b) on the cell surface or (c) as sIL-1RII in the extracellular environment after enzymatic cleavage of its extracellular domain. sIL-1RII contributes to IL-1 antagonism. IL-1RI (d) and IL-1RAcP (e) also exist as soluble forms that are produced by cleavage of the extracellular domain and alternative splicing, respectively. To date, the physiologic role of sIL-1RI is unclear. sIL-1RAcP can form an inactive complex with cell surface IL-1RI bound to IL-1 and (f) also increases the potency of sIL-1RII as an inhibitor of IL-1 action. IL-1RAcP, IL-1 receptor accessory protein; IL-1RI/II, IL-1 receptor type I/II; m, mature; s, soluble. (From Gabay C, Lamachia C, Palmer G. IL-1 pathways in inflammation and human diseases. *Nat Rev Rheumatol* 2010;6:232–41, copyright Nature Publishing group.)

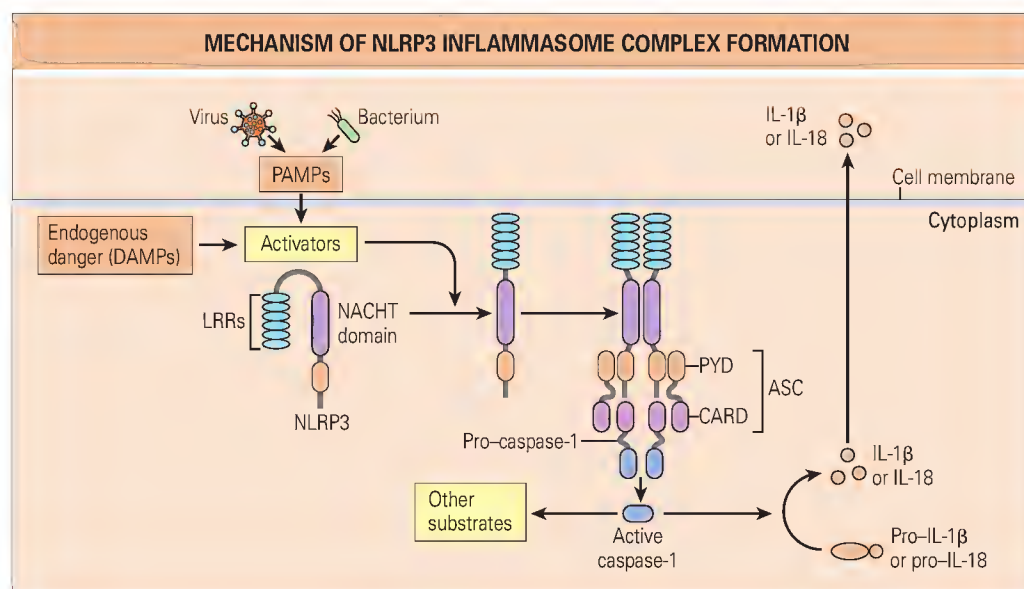


Fig. 61.2 Mechanism of NLR family, pyrin domain-containing 3 (NLRP3) inflammasome complex formation. Under healthy cellular conditions, NLRP3 is autorepressed because of an internal interaction between the NACHT domain and LRRs. This autorepression is removed in the presence of pathogen-associated molecular patterns (PAMPs) from microorganisms or damage-associated molecular patterns (DAMPs) from endogenous danger signals. This results in exposure of the NACHT domain. In turn, NLRP3 oligomerizes and recruits apoptosis-associated specklike protein containing a CARD (ASC; also known as PYCARD) and pro-caspase-1, which triggers the activation of caspase-1 and maturation and secretion of proinflammatory cytokines such as interleukin-1 β (IL-1 β) and IL-18. Other cytoplasmic proteins, such as enzymes of the glycolytic pathway, are also substrates of active caspase-1. CARD, caspase-recruitment domain; LRRs, leucine-rich repeats; NACHT, NAIP, CIITA, HET-E and TP1; PYD, pyrin domain. (From Tschopp J, Schroder K. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? *Nat Rev Immunol* 2010;10:210–15, copyright Nature Publishing group.)

American College of Rheumatology (ACR) response criteria¹⁷ in preventing the progression of structural damage.¹⁸ In patients with active RA despite methotrexate (MTX) therapy, the combination of anakinra and MTX resulted in better ACR responses than MTX alone did.¹⁹ Safety data from a larger population indicate that anakinra in combination with different disease-modifying antirheumatic drugs (DMARDs) is safe, with a rate of serious infections slightly higher in the anakinra than in the placebo group (2.1% vs. 0.4%).²⁰

The combination of anakinra and etanercept did not show any advantage over etanercept alone but was associated with a significant increase in the

incidence of serious infections.²¹ Use of anakinra in patients who had a previous incomplete response to tumor necrosis factor- α (TNF- α) inhibitors did not show any advantage either.²²

Soluble interleukin-1 receptors

Administration of soluble IL-1RI (sIL-1RI) administered either by intra-articular or subcutaneous injection was devoid of significant effect in patients with RA.²³ Despite some interesting preclinical results, no data are available on the use of sIL-1RII or sIL-1RAcP in patients with RA or other diseases.

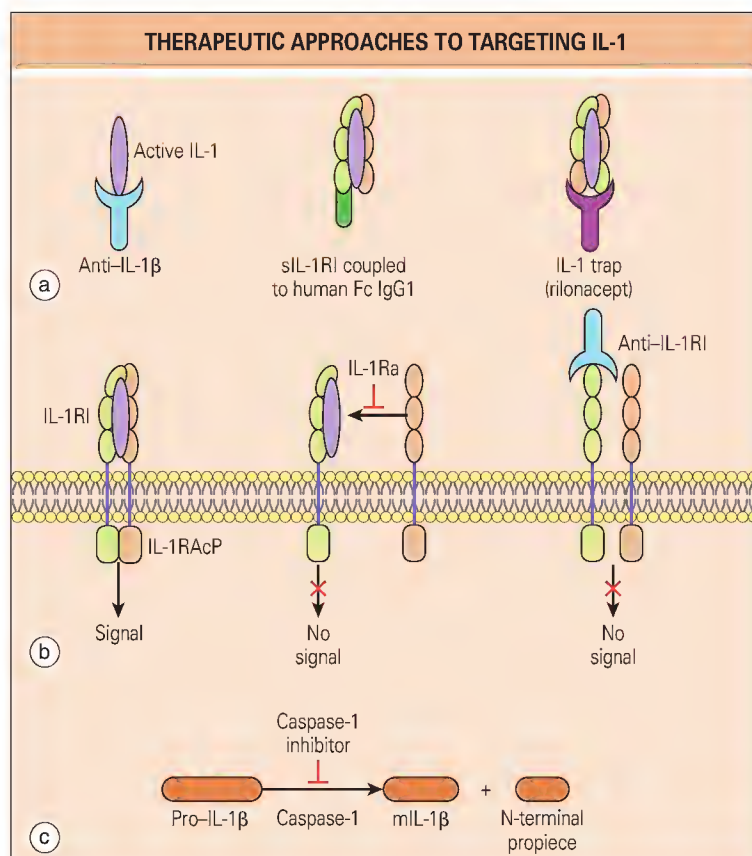


Fig. 61.3 (a) Anti-IL-1 β , IL-1 trap (rilonacept), and sIL-1RI can block extracellular IL-1 β . (b) Binding of active IL-1 to cell surface receptors can be inhibited by IL-1Ra and anti-IL-1RI antibodies. (c) Caspase-1 inhibitors can specifically inhibit the production of mature IL-1 β . IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein; IL-1RI, IL-1 receptor type I; m, mature; s, soluble. (From Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. *Nat Rev Rheumatol* 2010;6:232–41, copyright Nature Publishing group.)

IL-1 trap (rilonacept, Arcalyst) is a fusion protein containing some of the extracellular binding motifs of IL-1RI and IL-1RAcP coupled to the Fc fraction of human immunoglobulin IgG1. IL-1 trap has a prolonged circulating half-life ranging from 128 to 214 hours that permits once-weekly subcutaneous dosing. Administration of a murine form of IL-1 trap almost completely blocked the development of mouse collagen-induced arthritis.²⁴ Despite some encouraging results observed in a phase 1 trial,²⁵ a subsequent multicenter, randomized, double-blind, placebo-controlled phase 2 clinical trial failed to show a significant effect.

Monoclonal antibodies

The safety and efficacy of ACZ885 (canakinumab, Ilaris), an intravenously or subcutaneously infused, fully human monoclonal antibody that neutralizes the bioactivity of human IL-1 β , were examined in a 6-week randomized, placebo-controlled, dose-escalating, clinical trial that included 32 patients with RA and an incomplete response to MTX. When compared with MTX alone, a higher number of patients achieved an ACR20 response with the combination of MTX and the highest dose of canakinumab (10 mg/kg), although the difference was not statistically significant.²⁶

The safety and efficacy of AMG-108, a fully human anti-IL-1RI monoclonal antibody was examined in 813 patients with RA who had an inadequate response to MTX in a 24-week randomized, double-blind, placebo-controlled, parallel-dosing clinical trial. After 24 weeks, 40.4% and 20.2% of patients receiving the highest dose of AMG-108 achieved ACR20 and ACR50 responses as compared with 29.1% and 8.4% in those treated with MTX alone ($P = .22$ and $P < .001$, respectively). No difference was detected between the different groups regarding the ARC70 response. No notable differences were seen in either the frequency or type of adverse events.²⁷

Inhibition of interleukin-1 β production

The efficacy and safety of pralnacasan, a synthetic orally administered caspase-1 inhibitor, were examined in a 12-week phase 2, placebo-controlled

multicenter study in patients with RA receiving concurrent DMARDs. The ACR20 response rate was not significantly higher in patients treated with pralnacasan than in the placebo group.²⁸

Despite positive results in animal models of arthritis, the results of clinical trials using anakinra and other IL-1 inhibitors have shown only modest therapeutic effects in patients with RA.

Ankylosing spondylitis

Anakinra treatment was moderately successful as assessed by clinical and magnetic resonance imaging (MRI) parameters in a 3-month open-label study that included nine patients with ankylosing spondylitis.²⁹ In another 24-week open-label clinical trial that included 20 patients with ankylosing spondylitis refractory to nonsteroidal antiinflammatory drugs, ASAS20, ASAS40, and ASAS70 responses were achieved by five, four, and two patients, respectively. No change was observed in the serum levels of C-reactive protein and MRI scores.³⁰

Psoriatic arthritis

An open-label, proof-of-concept, single-center study of 12 patients with psoriatic arthritis demonstrated significant clinical benefits. After 12 weeks, 50% met the response criteria for psoriatic arthritis, but anakinra had no effect on the cutaneous manifestations of psoriasis.³¹

Systemic lupus erythematosus

Anakinra led to some positive results in a few patients with lupus arthritis.³²

Osteoarthritis

The results of a randomized, double-blind, placebo-controlled study failed to show positive effects with a single intraarticular injection of anakinra for knee osteoarthritis (OA) at the 12-week evaluation.³³ This result is not unexpected in view of the short half-life of IL-1Ra. Of note, a positive trend ($P = .051$) on the Western Ontario–McMaster Universities Osteoarthritis Index (WOMAC) pain score was noted at day 4 in the 150-mg anakinra group versus placebo. In patients with an acute anterior cruciate ligament tear, administration of a single intraarticular injection of 150 mg anakinra led to a rapid and significant reduction in pain and improvement in function when compared with saline injection in a small 2-week randomized, double-blind clinical trial.³⁴ AMG-108, an antibody against IL-1RI, was administered subcutaneously or intravenously to patients with knee OA in a randomized double-blind placebo-controlled study. The AMG-108 group had statistically insignificant, but numerically greater improvement in pain than did the placebo group as shown by WOMAC pain scores (median change, -63.0 vs. -37.0 , respectively).³⁵

Further studies should investigate the rationale of IL-1 targeting for the signs and symptoms of OA and in the prevention of cartilage damage.

Crystal-induced arthritis

MSU and CPPD crystals are the agents responsible for gout and pseudogout, respectively. MSU and CPPD crystals can stimulate the NALP3 inflammasome and thus lead to pro-IL-1 β processing and secretion of IL-1 β .³⁶ More recently, it has also been shown that MSU crystals induce the release of IL-1 α .³⁷ The basic calcium crystals that are associated with severe OA and periarticular inflammation can also stimulate the release of IL-1 β by cultured macrophages through activation of the NALP3 inflammasome.³⁸

In a multicenter, randomized, double-blind, dose-escalating controlled clinical trial, one subcutaneous injection of canakinumab, 150 mg, provided more rapid relief of pain in patients with acute gout and significantly reduced the risk for subsequent gouty flares when compared with one intramuscular injection of triamcinolone acetonide, 40 mg.³⁹ These positive results were confirmed in two subsequent multicenter, randomized controlled trials.⁴⁰ Canakinumab at a dosage of 50 mg or higher was superior to colchicine, 0.5 mg daily, in the prevention of gouty flares following the initiation of allopurinol.⁴¹ The use of rilonacept (IL-1 trap) in a multicenter clinical trial on acute gout has provided interesting preliminary results.⁴² Two subsequent clinical trials showed that rilonacept significantly reduces gout attacks following the initiation of allopurinol.^{43,44} Anakinra is efficacious in the treatment of acute pseudogout refractory to or intolerant of usual therapy,⁴⁵ as well as in the prevention of acute attacks.⁴⁶

TABLE 61.1

Interleukin-1 inhibitors in the treatment of rheumatic diseases

Disease	Biologic agent	Type of study	Primary outcome	Results
RA	Anakinra vs. placebo	RCT	ACR20 response criteria	Significant improvement ¹⁷
RA	Anakinra vs. placebo	RCT	Genant and Larsen scores	Limits structural damage ¹⁸
RA	Anakinra + MTX vs. MTX	RCT	ACR20 response criteria	Significant improvement ¹⁹
RA	Anakinra + etanercept vs. etanercept	RCT	ACR50 response criteria	No difference, but increased frequency of SIE ²¹
RA	Rilonacept + MTX vs. MTX	RCT	ACR20 response criteria	Nonsignificant effect [*]
RA	Canakinumab + MTX vs. MTX	RCT	ACR20 response criteria	Nonsignificant effect ²⁶
RA	AMG-108 + MTX vs. MTX	RCT	ACR20 response criteria	Nonsignificant effect ²⁷
RA	Pralnacasan + DMARDs vs. DMARDs	RCT	ACR20 response criteria	Nonsignificant effect ²⁸
AS	Anakinra	Case series	Multiple outcomes	Improvement ²⁹
AS	Anakinra	Case series	ASAS response criteria	ASAS20 in 5/20 patients ³⁰
PsA	Anakinra	Case series	Multiple outcomes	Improvement of arthritis but no effect on skin psoriasis ³¹
SLE	Anakinra	Case series	Multiple outcomes	Improvement in ⅔ of patients ³²
Knee OA	Anakinra vs. placebo	RCT	WOMAC questionnaire	Nonsignificant effect ³³
Knee OA	AMG-108 vs. placebo	RCT	WOMAC questionnaire	Nonsignificant effect ³⁵
Gout	Canakinumab vs. triamcinolone acetonide	RCT	Pain on visual analog score	Significant improvement ³⁹
Gout	Canakinumab vs. triamcinolone acetonide	2 RCTs	Pain on visual analog score + time to new flare	Significant improvement and reduction of new flares ⁴⁰
Gout	Canakinumab vs. colchicine	RCT	Prophylaxis for flare	Significant reduction of new flares after initiation of allopurinol ⁴¹
Gout	Rilonacept	Placebo controlled [†]	Pain on visual analog score	Improvement ⁴²
Gout	rilonacept vs. placebo	2 RCTs	Prophylaxis for new flares	Significant reduction of new flares ^{43,44}
Pseudogout	Anakinra	Case reports and patient series	Multiple outcomes	Improvement and prevention ^{45,46}
SOJIA	Anakinra	Case series	Multiple outcomes	Improvement ^{47,48}
AOSD	Anakinra	Case series	Multiple outcomes	Improvement ⁴⁹
FCAS, MWS	Anakinra	Case series	Multiple outcomes	Improvement ⁵⁰
FCAS	Rilonacept	Case series	Multiple outcomes	Improvement ⁵¹
FCAS, MWS	Rilonacept	2 RCTs	Composite validated score	Significant improvement ⁵²
CAPS	Canakinumab	Open label	Multiple outcomes	Improvement ⁵³
CAPS	Canakinumab	Phase 3, open label	Multiple outcomes	Improvement ⁵⁴
Behçet uveitis	Gevokizumab	Case series	Ophthalmologic evaluation	Improvement ⁵⁸

*Unpublished study.

†Nonrandomized, single-blind study.

ACR, American College of Rheumatology; AOSD, adult-onset Still disease; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; CAPS, cryopyrin-associated periodic syndromes; FCAS, familial cold autoinflammatory syndrome; HAQ-DI, health assessment quality-disability index; MWS, Muckle-Wells syndrome; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized placebo-controlled clinical trial; SOJIA, systemic-onset juvenile idiopathic arthritis; WOMAC, Western Ontario-McMaster Universities Osteoarthritis Index.

Systemic-onset juvenile idiopathic arthritis and adult Still disease

Treatment with anakinra was reported to be dramatically successful in nine patients with refractory systemic-onset juvenile idiopathic arthritis (SOJIA).⁴⁷ A recent observational study indicated that only 40% of patients with SOJIA had a marked and persistent response to anakinra that led to a reduction or discontinuation of co-medications, including corticosteroids. A higher neutrophil count and lower number of active joints were associated with a good response to anakinra.⁴⁸ Anakinra has been reported to be effective for adult Still disease, with responses that could be even better than those for SOJIA.⁴⁹ Currently in phase 3 clinical development, canakinumab was recently granted E.U. and U.S. orphan drug status for this condition, as well as for cryopyrin-associated periodic syndromes (see the next section). Early clinical trials have shown that administration of canakinumab every 2 weeks is safe and effective and thus offers a considerable advantage over anakinra.

Interleukin-1 inhibition for periodic fever syndromes

The term “cryopyrinopathies” or “cryopyrin-associated periodic syndromes” (CAPSs) was coined for a group of inherited disorders that includes

neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic, cutaneous, articular syndrome [CINCA]), Muckle-Wells syndrome (MWS), and familial cold autoinflammatory syndrome (FACS), a condition characterized by recurrent episodes of fever and inflammatory responses in multiple organs. All these diseases have been associated with mutations in the *CIAS1* or *NLRP3* gene, which encodes for cryopyrin or NALP3. Administration of anakinra to patients with MWS and FACS resulted in the cessation of symptoms within hours of the first injection along with a concomitant decrease in serum amyloid A, an acute-phase protein; normal levels were reached after 3 days of treatment.⁵⁰ Significant improvement in NOMID/CINCA with anakinra has also been reported. Rilonacept has likewise been tested with success in patients with FACS.⁵¹ These favorable results were confirmed by two consecutive randomized, placebo-controlled phase 3 clinical trials that included 47 adults with CAPS. The treatment was well tolerated except for injection site reactions and upper respiratory tract infections.⁵² These results led to the approval of rilonacept by the Food and Drug Administration for the treatment of FACS and MWS in adults or children 12 years or older. Canakinumab was administered in an open-label clinical trial as a single subcutaneous injection, with redosing on relapse in seven patients with CAPS. All patients achieved a complete response within 24 hours following canakinumab administration according to physician assessments. The response was sustained for a median time of 49 days.⁵³ The 2-year results of a multicenter, open-label

study conducted in 161 pediatric and adult patients with CAPS showed that among 109 patients who were naive to canakinumab, 85 (78%) achieved a complete response. Adverse events included infections and injection site reactions, which were reported in a minority of patients (8%). Immune responses to vaccination were normal.⁵⁴

Other autoinflammatory disorders

Several other disorders featuring periodic fever, joint symptoms, and systemic manifestations are also classified as “autoinflammatory diseases.”⁵⁵ The spectacular effect of treatment of CAPS with anakinra inspired several clinical trials in patients with other autoinflammatory syndromes. Regression of symptoms after anakinra treatment was observed in patients with pyogenic arthritis and pyoderma gangrenosum acne syndrome.⁵⁶ Anakinra and canakinumab have been used with success in patients with severe familial Mediterranean fever who did not respond to or were intolerant of colchicine.⁵⁷ Interestingly, anakinra also had a beneficial effect on TNF receptor-associated periodic syndrome (TRAPS), an inherited disease caused by a mutation modifying the control of TNF signaling. In addition to systemic autoinflammatory diseases associated with mutations in proteins related to the inflammasome, IL-1 inhibitors also displayed efficacy in patients with Schnitzler syndrome and neutrophilic skin disorders such as Sweets syndrome, pyoderma gangrenosum, and hidradenitis suppurativa. Finally,

gevokizumab, a humanized monoclonal antibody against IL-1 β , was efficacious in some patients with the refractory uveitis of Behçet syndrome.⁵⁸

General comment on available interleukin-1 inhibitors

Use of IL-1 inhibitors has been particularly successful in conditions associated with acute inflammatory flares, the presence of neutrophilic infiltrates, and also sometimes blood neutrophilia. Unfortunately, because blood levels of IL-1 are only marginally elevated or most often undetectable, they are of no value in predicting response to IL-1 inhibitors. In general, the response to IL-1 inhibitors is very rapid and occurs within days and sometimes a few hours after the initiation of therapy. Anakinra is used in general at a dosage of 100 mg via daily subcutaneous injections (children: 1 to 2 mg/kg). Canakinumab is administered subcutaneously at a dosage of 150 mg every 8 weeks (children: 2 mg/kg). Rilonacept is given as a loading dose of 320 mg followed by weekly subcutaneous injections of 160 mg (children: 4.4 mg/kg followed by 2.2 mg/kg, up to 320 and 160 mg, respectively). In patients with severe organ manifestations or residual inflammation, a higher dosage of IL-1 inhibitors may be required to obtain complete remission. IL-1 inhibitors are generally well tolerated, but the rate of infections, predominantly upper airway infections, and injection site reactions is increased. Combination with TNF antagonists should be avoided.

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Interleukin-6 inhibition

■ EDWARD KEYSTONE ■ MOHAMMED A. OMAIR

- Interleukin-6 (IL-6) is a multifunctional cytokine that plays a critical role in the pathogenesis of rheumatoid arthritis.
- Tocilizumab, a humanized monoclonal antibody directed against the IL-6 receptor, leads to significant improvement in clinical disease activity, functional state, and well-being, as well as inhibition of structural damage.
- Tocilizumab appears to have comparable efficacy when taken in combination with methotrexate and as monotherapy.
- Tocilizumab has demonstrated clinical benefit in patients with juvenile idiopathic arthritis, adult-onset Still disease, Takayasu disease, and giant cell arteritis.
- Serious adverse effects such as infection, colonic perforation, and malignancy are rare. More common nonserious adverse events include elevated liver transaminases, leukopenia, and hyperlipidemia.

INTERLEUKIN-6 AND INTERLEUKIN-6 RECEPTOR

Interleukin-6 (IL-6) is a member of the IL-6 family, which consists of polypeptide cytokines with a four- α -helix structure and a molecular mass of 21 to 28 kDa. Formerly named B-cell stimulatory factor 2, IL-6 is multifunctional cytokine produced by T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, and several tumor cells.¹ IL-6 receptor (IL-6R) belongs to the cytokine receptor class I family and has two components: an 80-kDa IL-6 binding protein (α chain) and a 130-kDa signal transducer known as glycoprotein 130 (gp130) (β chain).² IL-6R exists in two forms: a soluble IL-6 receptor (sIL-6R) and a membrane-bound (or transmembrane) IL-6 receptor (mIL-6R). IL-6 trans-signaling occurs through sIL-6R, which activates cells that express gp130, whereas classic signaling is limited to cells that express mIL-6R.³ Binding of IL-6 to IL-6R leads to homodimerization or heterodimerization of the gp130 subunit, which results in formation of the high-affinity IL-6/IL-6R/gp130 complex. This complex activates the Janus tyrosine kinase/signal transducer and activator of transcription (STAT) pathway. STAT and CCAAT enhancer binding proteins (C/EBPs) bind to DNA and regulate the expression of IL-6-type responsive genes. IL-6 has a wide range of biologic activities, including immune regulation, hematopoiesis, inflammation, and oncogenesis (Table 62.1).

TOCILIZUMAB**Mechanism of action**

Tocilizumab is a genetically engineered monoclonal antibody humanized from a mouse antihuman IL-6R antibody. Tocilizumab recognizes the IL-6 binding site of the human IL-6R and inhibits IL-6 signaling through competitive blockade of the IL-6 binding site. It can bind to both sIL-6R and mIL-6R, thus inhibiting both classic signaling and trans-signaling in cells that express mIL-6R or gp130, respectively (Fig. 62.1). Tocilizumab recognizes IL-6R and inhibits binding of IL-6 to its receptors while not blocking the signaling of other IL-6 family cytokines. It blocks the action of IL-6 without increasing its half-life. Despite being an IgG1 antibody, in humans tocilizumab causes no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity in cells that express IL-6R.

Pharmacokinetics

The half-life of tocilizumab in patients with rheumatoid arthritis (RA) depends on its concentration; the concentration-dependent apparent half-life is up to 11 days for 4 mg/kg and up to 13 days for 8 mg/kg administered every 4 weeks in patients with RA at a steady stage. The half-life of tocilizumab in children with systemic juvenile idiopathic arthritis (JIA) at steady state ranged from 18.4 to 22.7 days at 8 mg/kg in those with a body weight of 30 kg or greater and from 19.2 to 23 days at 12 mg/kg in those with a body weight lower than 30 kg.

Recommended dose and dose adjustment

Tocilizumab should be given in combination with methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs) or may also be given as monotherapy in patients intolerant of MTX or in whom MTX is not appropriate. The recommended starting dose in North America for adult patients is 4 mg/kg given once every 4 weeks as an intravenous infusion over a 1-hour period, followed by an increase to 8 mg/kg, depending on clinical response. For patients in Europe and Japan the starting dose is 8 mg/kg. It is recommended for patients who have had an inadequate response to one or more DMARDs or tumor necrosis factor (TNF) antagonists. In individuals whose body weight is greater than 100 kg, doses exceeding 800 mg per infusion are not recommended. Dose adjustments should be considered for the management of dose-related laboratory changes, including elevated liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), neutropenia, and thrombocytopenia.

Clinical trial results

The efficacy of combination therapy with tocilizumab in patients with moderate to severe disease has been demonstrated in several multicenter, double-blind, randomized controlled trials (DBRCTs) with MTX alone and with other conventional DMARDs.

One of the early studies was a 24-week, phase 2 DBRCT of 1220 patients receiving 8 mg/kg tocilizumab in combination with conventional DMARDs versus DMARDs alone.⁴ The American College of Rheumatology 20% improvement (ACR20) response of the group receiving tocilizumab plus DMARDs at 24 weeks was significantly greater than the response in the control group (61% versus 25%). ACR50/70 responses, 28-joint disease activity score (DAS28), DAS28 remission rates, European League Against Rheumatism (EULAR) responses, and changes in C-reactive protein (CRP) and hemoglobin demonstrated superiority of tocilizumab plus DMARDs over DMARDs alone. Another 24-week DBRCT confirmed these findings in 619 patients receiving conventional DMARDs with 8 mg/kg tocilizumab.⁵

In a 623-patient, 24-week phase 3 DBRCT of patients with an inadequate response to MTX, tocilizumab was examined at 4- and 8-mg/kg doses versus placebo plus MTX.⁶ At 24 weeks, ACR20 responses in the 8-mg/kg group (59%) and the 4-mg/kg group (48%) were superior to those in the group that received placebo plus MTX (26%). The time until maximum effect was 24 weeks, as demonstrated by a plateau of the mean DAS28 response. In this study the mean CRP level did not normalize in the 4-mg/kg group by 24 weeks, whereas it normalized in the 8-mg/kg group by 2 weeks. In another phase 3 study, 4- and 8-mg/kg doses of tocilizumab plus MTX were evaluated in a 2-year study of 1196 patients to examine structural damage.⁷ At 1 year significantly less progression in the Genant-modified Sharp score (G-SS) was seen in the 4-mg/kg (0.34 G-SS units) and 8-mg/kg (0.29 G-SS units) tocilizumab-plus-MTX groups than in the MTX-plus-placebo group (1.13 G-SS units). Superiority of tocilizumab was also confirmed for ACR20, ACR50, and ACR70 responses; the health assessment disability index; and DAS28 remission relative to the MTX-plus-placebo group (Fig. 62.2).

Tocilizumab also demonstrated dissociation between its clinical and radiographic outcomes, similar to what has been described with tumor necrosis factor inhibitors (TNFIs).

Tocilizumab in combination with MTX was also evaluated in patients refractory to TNFIs. In a 24-week, phase 3 study of 499 patients, the efficacy of tocilizumab was examined at doses of 4 and 8 mg/kg plus MTX versus placebo plus MTX.⁸ At 24 weeks, ACR20 responses were achieved in 50.0%, 30.4%, and 10.1% of patients in the 8- and 4-mg/kg tocilizumab and control groups, respectively. Patients responded regardless of the most recent TNFI or number of TNFI failures. To study whether patients with an inadequate response to 4 mg/kg would benefit from dose escalation to 8 mg/kg, a

post-hoc pooled analysis of clinical trial data was performed in those who responded inadequately to DMARD and TNFI; significant improvement in DAS28 occurred with escalation of tocilizumab from 4 to 8 mg/kg at 16 weeks.⁹ Slowing of radiographic progression was also demonstrated with dose escalation. These data suggest that in inadequate responders to DMARD and TNFI who do not achieve an adequate response to 4 mg/kg tocilizumab, escalation to the 8-mg/kg dose should be carried out.

It has been suggested that approximately a third of rheumatoid patients treated with biologics receive them as monotherapy without MTX. Tocilizumab monotherapy was found to be similar in efficacy to tocilizumab given in combination with conventional DMARDs, including MTX, in several studies. In one of the first DBRCTs, tocilizumab was evaluated in 359 patients at doses of 2, 4, and 8 mg/kg either as monotherapy or in combination with MTX; MTX plus placebo was used as control.¹⁰ An ACR20 response was achieved by 63% and 74% of patients receiving 4- and 8-mg/kg doses of tocilizumab with MTX, respectively, as compared with 61% and 63% of patients receiving monotherapy, respectively, and 41% of patients receiving placebo plus MTX. A dose-related reduction in DAS28 starting at week 2 was observed in all patients except those receiving 2 mg/kg tocilizumab monotherapy. The kinetics of the DAS28 response was similar with both the 4- and 8-mg/kg doses. The CRP level normalized in the first 2 weeks of therapy except in those receiving 2 mg/kg and those receiving 4 mg/kg as monotherapy. Patients treated with 4 mg/kg had a sawtooth pattern with a decrease in CRP 2 weeks after dosing and an increase before the next infusion. The 8-mg/kg dose produced a more sustained decrease. Similar results were achieved with tocilizumab monotherapy (8 mg/kg) in a 2-year open-label DMARD controlled trial of 306 patients; tocilizumab monotherapy reduced radiographic progression comparable to the DMARD combination group.¹¹ In a 24-week, double-blind study of 673 patients in whom MTX or biologic agents had not failed,¹² patients were randomized to either 8 mg/kg tocilizumab or MTX monotherapy (Fig. 62.3). Tocilizumab monotherapy was more effective than MTX, with a higher ACR20 response rate (69.9% versus 52.2%) and DAS28 score (33.6% versus 12.1%), respectively. In another study, 556 patients were randomized in a 2-year DBRCT to tocilizumab (8 mg/kg) monotherapy or to continue with tocilizumab in combination with MTX.¹³ At 24 weeks the DAS28–erythrocyte sedimentation rate (ESR) for tocilizumab monotherapy was not statistically different from that for the combination of tocilizumab and MTX (40.4% versus 34.8%). Even though the ACR responses were also comparable in the tocilizumab monotherapy and tocilizumab-plus-MTX groups, significantly more patients in the combination group achieved a DAS28 low disease state than did those in the monotherapy group (61.7% versus 51.4%). No difference in radiographic progression was noted in the two groups.

Because clinical trials may not always reflect clinical practice, several 24-week, multicenter open-label phase 3b studies were performed to examine tocilizumab in a setting closer to real-life medical care. In a study

TABLE 62.1
Effect of interleukin-6 on different cell lines during the immune response

Cell type	Effect
T cells	Proliferation and differentiation of T cells, including cytotoxic T lymphocytes and Th17 cells Augmentation of NK activity Inhibition of regulatory T cells
B cells	Increase immunoglobulin production (including rheumatoid factor)
Macrophages	Differentiation
Neutrophils	Increase demargination
Megakaryocytes	Enhancement of megakaryocytopoiesis Maturation of megakaryocytes
Hepatocytes	Stimulation of hepatocytes to produce acute-phase proteins such as CRP, fibrinogen, α_1 -antitrypsin, and serum amyloid A Stimulation of hepcidin Suppression of albumin production
Synoviocytes	Proliferation and pannus formation (inhibition of TNF- α -induced synovial growth) Production of VEGF
Osteodasts	Formation and differentiation leading to bone resorption
Endothelial cells	IL-8 production Activation of chemotaxis Production of adhesion molecules

CRP, C-reactive protein; NK, natural killer; Th17, type 17 helper T cell; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

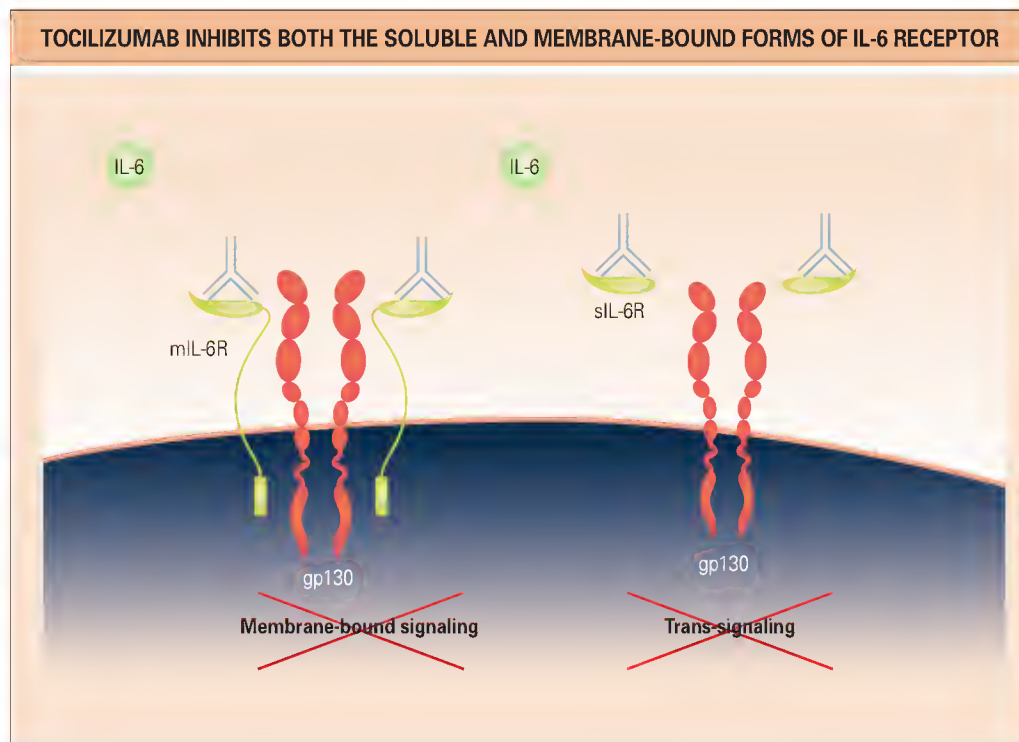


Fig. 62.1 Both the soluble (sIL-6R) and membrane-bound (mIL-6R) forms of the IL-6 receptor are inhibited by tocilizumab. gp130, glycoprotein 130. (With permission of Roche Global, Basel, Switzerland.)

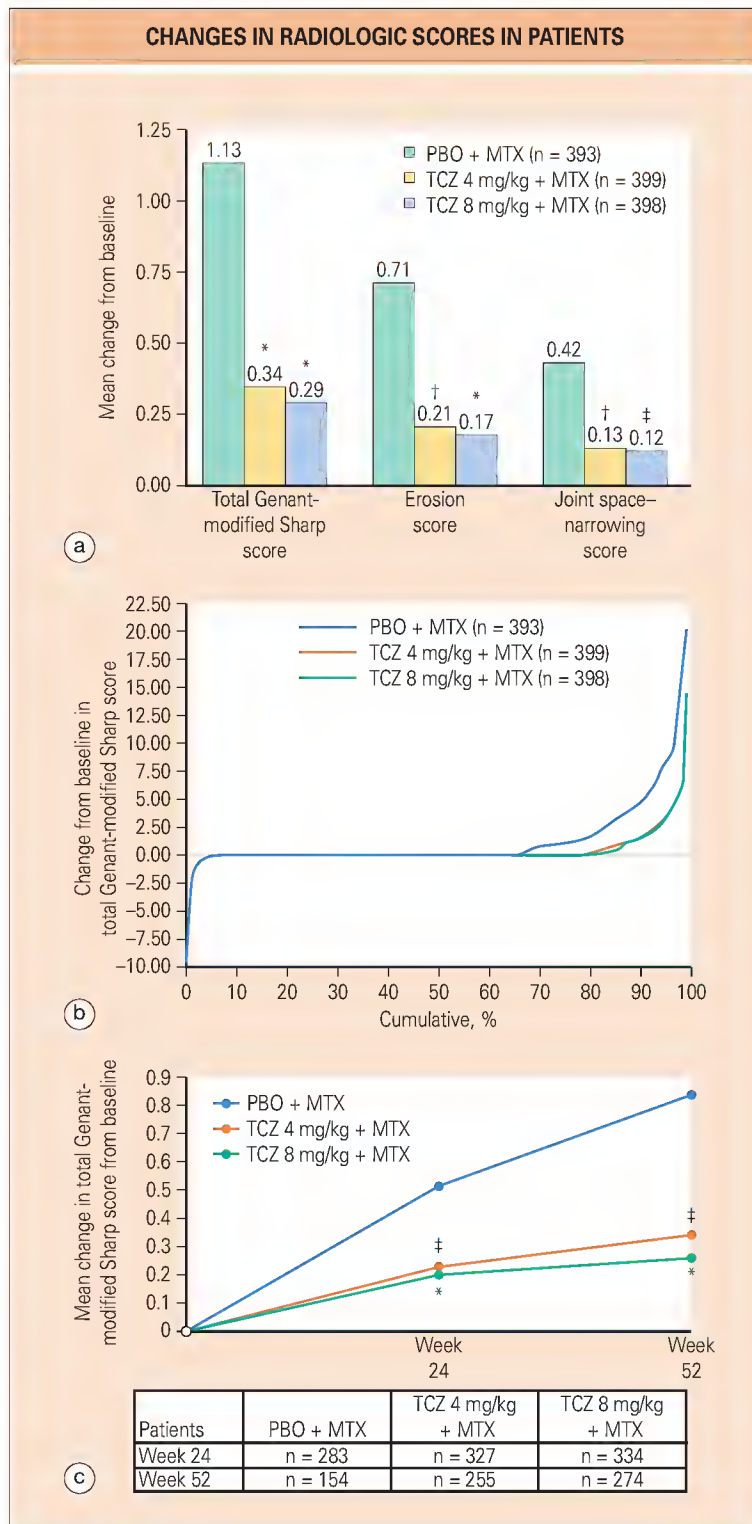


Fig. 62.2 Changes in radiologic scores in patients taking 4 mg/kg tocilizumab (TCZ) plus methotrexate (MTX), 8 mg/kg tocilizumab plus MTX, or placebo (PBO) plus MTX. (a) Mean change from baseline in the total Genant-modified Sharp score, erosion score, and joint space narrowing score at week 52 in the intent-to-treat (ITT) population. Data collected after withdrawal or while patients were receiving rescue therapy were excluded. Numbers at the top of the bars are the values represented by the bars. (b) Cumulative distribution of change from baseline in the total Genant-modified Sharp score to week 52 in the ITT population. Data collected after withdrawal or while patients were receiving rescue therapy were excluded. (c) Change in the total Genant-modified Sharp score over time in the ITT population (as-observed analysis [postwithdrawal, postrescue data excluded]). * $p < .0001$ versus placebo plus MTX; † $p < .05$ versus placebo plus MTX (the test failed, however, after a break in the hierarchic chain of the algorithm; therefore, statistical significance is not claimed); ‡ $p < .01$ versus placebo plus MTX. (From Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011;63:609-21.)

of 286 patients, tocilizumab at a dose of 8 mg/kg resulted in major improvements in patient-reported outcomes and DAS28 response.¹⁴ In another open-label study of 1681 patients, ACR responses, DAS28, clinical disease activity index (CDAI), and simple disease activity index (SDAI) remission with tocilizumab monotherapy (8 mg/kg) were found to be comparable to those achieved with tocilizumab-DMARD combination therapy at 24 weeks in inadequate responders to both DMARD and TNF.¹⁵ In an open-label, randomized U.S. study of previous inadequate responders to anti-TNF,^{16,17} patients treated with monotherapy or combination conventional DMARD therapy were randomized to 4 or 8 mg/kg tocilizumab and their current DMARDs, whereas those who previously received TNFI monotherapy were switched to 8 mg/kg tocilizumab alone. The efficacy of 8 mg/kg tocilizumab monotherapy and combination tocilizumab and conventional therapy was found to be equivalent in inadequate responders to TNFI.

Tocilizumab monotherapy (8 mg/kg) versus adalimumab 40 mg every 2 weeks was studied in a 24-week DBRCT.¹⁸ Three hundred twenty-six patients with a disease duration of 6.3 to 7.3 years who were intolerant of MTX or for whom continued treatment with MTX was inappropriate were enrolled in this study. The mean change in DAS28 at 24 weeks was significantly greater with tocilizumab (−3.3) than with adalimumab (−1.8). Tocilizumab demonstrated superiority over adalimumab with respect to DAS28 remission rates (39.9 versus 10.5), DAS28 low-disease state rates (51.5 versus 19.8), and CDAI remission rates (17.2 versus 9.3). The incidence of adverse events was similar between groups, although elevations in transaminases and low-density lipoprotein (LDL) and reductions in neutrophils were higher in the tocilizumab group.

In all the tocilizumab trials, DAS28 remission rates were higher with tocilizumab than the historical responses with other biologics despite similar remission rates as measured by the more stringent SDAI and CDAI criteria. The greater effect of tocilizumab through IL-6 inhibition than other biologics in reducing ESR and CRP coupled with high weighting of the acute-phase reactants in DAS28 accounts for the disparity.

Long-term effects

The long-term effects of tocilizumab were reported in 2904 inadequate responders to DMARD and 616 patients who had never been exposed to or failed MTX therapy (NE/NF).¹⁹ After a median of 3.55 years (range, 0 to 5.1 years), 30.0% of inadequate responders to DMARDs and 26.4% of NE/NF had withdrawn. Of patients who were still taking tocilizumab at week 216 in the group of inadequate responders to DMARDs, 73% achieved a DAS28 low-disease state and 53% achieved a DAS28 remission.

Safety

The most frequently reported adverse events in the clinical trial population treated with tocilizumab were upper respiratory infections, nasopharyngitis, headaches, increased transaminase levels, and upper abdominal pain.

Infections

In an integrated safety review of the core controlled clinical trial population (N = 4199), the most common serious adverse events reported (>0.3 per 100 patient-years [PY]) were pneumonia, cellulitis, urinary tract infection, gastroenteritis, sepsis, and herpes zoster.²⁰ Rates of serious infection in this controlled population were 3.5 per 100 PY for the control group, 3.5 per 100 PY for the 4-mg/kg tocilizumab group, and 4.9 per 100 PY for the 8-mg/kg group. In patients included in the controlled and extension phases of these trials, serious opportunistic infections were seen in 14 patients and included tuberculosis (TB), candidiasis (systemic, esophageal, gastrointestinal, osteomyelitis), fungal infections, and *Mycobacterium avium*, *Pneumocystis jiroveci*, and cryptococcal pneumonia. All opportunistic infections except one occurred in the 8-mg/kg tocilizumab group. Patients were screened for latent TB in the trials according to local country guidelines, and patients with pulmonary TB were from highly endemic areas. The rate of serious infection with tocilizumab therapy was comparable to that reported with other biologics used for RA. An update on long-term safety (median disease duration of 3.6 years) revealed stable rates of serious adverse events and serious infections with continued long-term tocilizumab exposure.²¹ With regard to viral infections, cases of herpes zoster were observed. No cases of hepatitis B occurred, but patients who screened positive were excluded. Data are not available on vaccination responses in patients receiving tocilizumab.

Gastrointestinal perforation

In the integrated safety analysis, 18 gastrointestinal perforations (including diverticular perforation in 11 patients) were identified,²⁰ the majority of which occurred in the colon. A systematic review of diverticular disease in

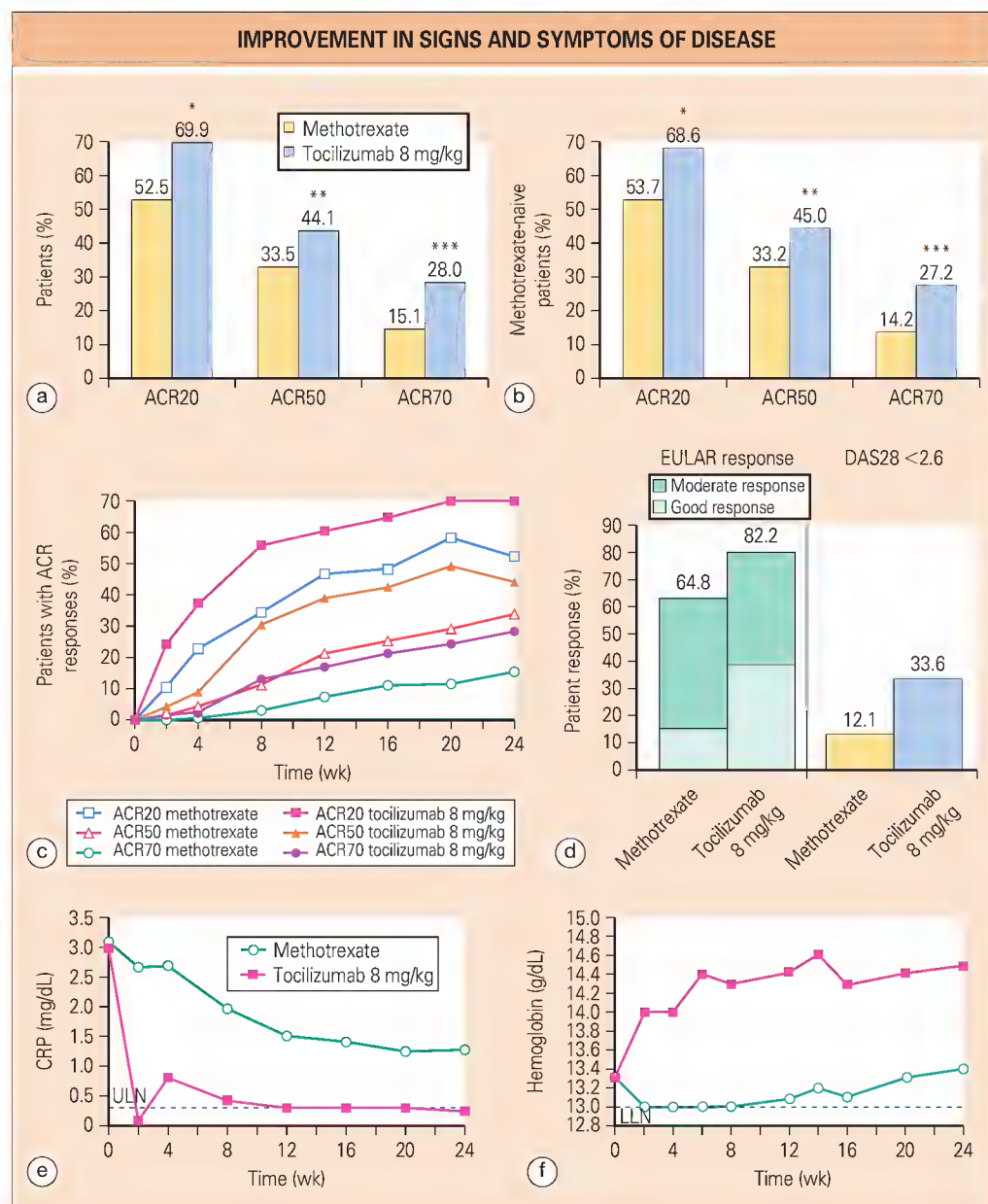


Fig. 62.3 (a) Proportion of patients achieving American College of Rheumatology 20% improvement (ACR20), ACR50, and ACR70 responses at week 24 (intent-to-treat [ITT] population). The results demonstrate that treatment with tocilizumab is significantly better than treatment with methotrexate (* $p < .001$; ** $p < .002$; *** $p < .001$). (b) Proportion of methotrexate-naïve patients achieving ACR20, ACR50, and ACR70 responses at week 24 (ITT population). *Weighted difference between groups = 0.15 (95% confidence interval [CI], 0.05 to 0.25), $p < .004$; **weighted difference between groups = 0.14 (95% CI 0.03 to 0.24), $p = .01$; ***weighted difference between groups = 0.15 (95% CI, 0.04 to 0.25), $P = .005$. (c) Time course for achievement of ACR20, ACR50, and ACR70 responses during 24 weeks of treatment with tocilizumab or methotrexate (ITT population). (d) Proportion of patients in clinical remission (DAS28 <2.6) and proportion of patients with a good or moderate European League Against Rheumatism (EULAR) response at week 24 (ITT population). (e) C-reactive protein (CRP) levels at each postbaseline visit during the 24-week study (ITT population). (f) Hemoglobin levels at each postbaseline visit during the 24-week study (safety population). LLN, lower limit of normal; ULN, upper limit of normal. (From Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;69:88-96.)

RA did not reveal evidence of diverticular perforation in DMARD-treated patients.²² In the 18 cases of lower gastrointestinal perforation with tocilizumab just noted, the rate of 1.9 events per 1000 PY was lower than that reported with corticosteroids (3.9/1000 PY), but slightly higher than the rate with TNFIs (1.3/1000 PY) in the United Health Care database. The majority of these patients were also concurrently receiving nonsteroidal antiinflammatory drugs and long-term glucocorticoids. Oral corticosteroid use and preexisting diverticulitis were independently associated with a higher risk for perforation with tocilizumab. A new onset of abdominal symptoms in tocilizumab-treated patients should therefore prompt evaluation for gastrointestinal perforation.

Malignancies

The overall rate of malignancy, including nonmelanoma skin cancer (NMSC), was 1.1 per 100 PY, with rates of 0.3 per 100 PY for NMSC alone, 0.7 per 100 PY for solid cancer, 0.1 per 100 PY for hematologic/lymphatic malignancy, and none for other cancers.²¹ The overall rate of malignancy in these subsets of malignancies remained stable with continued tocilizumab therapy. The standardized incidence rate of 1.1 for the malignancies occurring at the U.S. sites was comparable to the U.S. Surveillance, Epidemiology, and End Results database. The overall malignancy rate during the placebo-controlled period of the clinical trials was similar to that in the control population²⁰ (Table 62.2).

Cardiovascular events

Few cardiovascular events occurred during the placebo-controlled period, and rates with tocilizumab were similar to those in the control population.

In a recent long-term update of the all exposed population, the overall rate of myocardial infarction was 0.3 per 100 PY and that for stroke was 0.2 per 100 PY, both of which remained stable over time. These rates did not exceed those expected in the rheumatoid population (myocardial infarction, 0.4 to 0.8/100 PY; stroke, 0.5 to 0.9/100 PY).

Infusion reactions

The rate of infusion reactions reported with tocilizumab during or within 24 hours of infusion (8% with 4 mg/kg and 7% with 8 mg/kg) was only slightly higher than that reported in the DMARD plus placebo control group (5%). The development of hypertension and hypotension was similar with both doses (1%) and was the most frequently reported event during the infusion. The most frequently reported events within 24 hours of completing an infusion were headache and skin reactions (both 1% for both doses).^{22a}

In a 2011 consolidated safety reporting of five core phase III studies, eight patients experienced clinically significant anaphylactic reactions, seven of which occurred during the first four infusions of tocilizumab. Five events were reported in the 4 mg/kg group, and three events were reported in the 8 mg/kg group. All eight patients with anaphylaxis were required to discontinue tocilizumab treatment.^{22b} Postmarketing reports of anaphylaxis, including events with a fatal outcome, have been reported.

Hematology

A dose-related decrease in the mean neutrophil count has been observed in the first 2 weeks after drug initiation. The neutrophil count increased but did not normalize by 4 weeks and remained stable for up to 24 weeks in the clinical studies. Neutrophil counts between 500 and 1000/mm³ were

TABLE 62.2
Serious adverse events reported at a rate of 0.3 per 100 patient-years or greater in any group (all-control population)

	All-control population (N = 4199): rate per 100 patient-years (number of events)		
	Control (n = 1555)	Tocilizumab 4 mg/kg + DMARDs (n = 774)	Tocilizumab 8 mg/kg + DMARDs (n = 1870)
Pneumonia	0.6 (5)	0.7 (4)	0.9 (11)
Cellulitis	0.2 (2)	—	0.9 (11)
Gastroenteritis	0.2 (2)	0.5 (3)	0.1 (1)
Urinary tract infection	0.5 (4)	0.2 (1)	0.1 (1)
Sepsis	0.1 (1)	0.4 (2)	0.2 (2)
Herpes zoster	0.1 (1)	—	0.3 (4)
Fall	0.1 (1)	—	0.3 (4)
Pulmonary embolism	0.2 (2)	—	0.3 (3)
Basal cell carcinoma	0.1 (1)	0.4 (2)	0.1 (1)
Spinal compression fracture	0.1 (1)	—	0.3 (3)
Coronary artery disease	—	0.2 (1)	0.3 (3)
Back pain	0.1 (1)	—	0.3 (3)
Rheumatoid arthritis	0.4 (3)	—	—
Gastroenteritis viral	0.1 (1)	0.4 (2)	—
Prostate cancer	0.1 (1)	0.4 (2)	—
Neutropenia	—	0.4 (2)	0.1 (1)
Syncope	—	0.4 (2)	—
Tendon rupture	—	0.4 (2)	—
Interstitial lung disease	—	0.4 (2)	—
Anaphylactic reaction	—	0.4 (2)	—

DMARD, disease modifying antirheumatic drug; PY, patient-years.
 From Schiff MH, Kremer JM, Jhreis A, et al. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13(5):R141.

observed in 4.1% of the patients. Neutrophil counts lower than 500/mm³ were observed in 0.6% of patients, almost all of whom normalized with discontinuation of tocilizumab. The patients continuing on tocilizumab demonstrated improvement in their neutropenia—the majority returning to the normal range. No patient with a neutrophil count lower than 500/mm³ experienced a temporally associated serious infection, but by protocol, use of the drug was stopped. A decrease in the mean platelet count was observed at 2 weeks with tocilizumab treatment, but the majority of platelet counts remained in the normal range. Thrombocytopenia (<50,000/mm³) was observed in 0.8% of patients. Neutrophils and platelets should be monitored every 4 to 8 weeks. Tocilizumab therapy should be interrupted in patients with neutrophil counts between 500 and 1000/mm³ and restarted when the neutrophil count reaches 1000/mm³. It should be discontinued for counts below 500/mm³. Tocilizumab should be interrupted when the platelet count is between 50,000 and 100,000/mm³ and restarted at 4 mg/kg when the platelet count is higher than 100,000/mm³. For counts lower than 50,000, tocilizumab should be discontinued.

It is notable that an increase of approximately 1.0 g/dL in mean hemoglobin level was seen by 6 weeks, with the greatest improvement occurring in patients whose baseline hemoglobin was below the lower limit of normal.

Transaminase elevations

At least a single elevation in ALT of greater than one to three times the upper limit of normal (ULN) was observed in the first 6 months of treatment in 32% of patients treated with MTX monotherapy, in 19.1% of patients treated with non-MTX DMARDs, and in 33.8% of patients treated with 8 mg/kg tocilizumab. In patients treated with combination therapy, similar elevations in ALT levels were observed at least once in 42.8% and 45.9% of patients treated with 4 and 8 mg/kg tocilizumab plus DMARDs, respectively. Most ALT/AST elevations were transient and returned to normal without

dose adjustment or discontinuation of therapy. Elevated transaminases were not associated with clinically significant hepatitis, reduced liver function, or serious adverse effects. Because tocilizumab may unmask Gilbert syndrome, in patients in whom elevated bilirubin develops, measurement of indirect bilirubin should be done to confirm this diagnosis. This does not require stopping therapy.²¹

Dose adjustments are made for the management of elevated liver enzymes. For laboratory values higher than one to three times the ULN, the dose of the concomitant DMARD should be modified if appropriate. For persistent increases in this range, the dose of tocilizumab should be reduced to 4 mg/kg or its use interrupted until ALT/AST values have normalized. For ALT/AST higher than three to five times the ULN, tocilizumab dosing should be interrupted until lower than three times the ULN and the recommendations above followed for greater than one to three times the ULN.

Lipids

Total cholesterol, LDL, high-density lipoprotein, and apolipoproteins A-I and B were increased with tocilizumab in combination with DMARDs or as monotherapy at the first assessment at 6 weeks and remained elevated without a further increase for the duration of the treatment.²⁰ Similar elevations were seen in both the 4- and 8-mg/kg tocilizumab groups. In patients not receiving lipid-lowering agents, LDL cholesterol increased from less than 130 mg/dL at baseline to 130 mg/dL or higher in 14.2% of patients in the control group, in 25.1% in the 4-mg/kg tocilizumab group, and in 33.2% in the 8-mg/kg tocilizumab group. The significance of the lipid elevations with tocilizumab in patients with RA remains to be determined. Lipid parameters should be monitored every 4 to 8 weeks initially for 6 months and then every 6 months thereafter, and many rheumatologists initiate lipid-lowering therapies (i.e., statins) in patients in whom LDL higher than 130 mg/dL develops.

Indications and uses

Worldwide, tocilizumab is now approved for reduction of the signs and symptoms in adult patients with established moderate to severe RA who have demonstrated an inadequate response to one or more DMARD. It can be given as monotherapy or in combination with DMARDs. In the United States the recommended starting dose is 4 mg/kg intravenously every 4 weeks followed by an increase to 8 mg/kg based on clinical response, whereas in Europe and Japan the starting dose is 8 mg/kg with dose reduction for adverse events. Tocilizumab is administered over a 1-hour period. Doses higher than 800 mg per infusion are not recommended in adults with RA.

Tocilizumab is also indicated for patients 2 years and older with systemic JIA. The recommended dose for juvenile patients is 12 mg/kg every 2 weeks in those less than 30 kg weight and 8 mg/kg in those at or above 30 kg.

Use in specific populations

Pregnancy and nursing

Data on pregnancy outcomes in women exposed to tocilizumab during pregnancy are limited.²³ Evaluation in mice demonstrated no harm to offspring during the predevelopment and postdevelopment phases. There is no information on whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. The decision whether to discontinue nursing or tocilizumab must be balanced by the importance of the drug for the mother.

Use in the elderly

Of the 2644 patients receiving tocilizumab in clinical studies, 435 were 65 years or older, including 50 patients 75 years or older, and the frequency of serious infections was higher in such patients than in those younger than 65. This is not unexpected because the elderly population has a higher incidence of infection in general.

Hepatic or renal impairment

The safety of tocilizumab has not been evaluated in patients with hepatic impairment. According to current prescribing guidelines, tocilizumab should not be initiated in patients with an ALT level higher than 1.5 times normal. No dose adjustment is required in patients with mild renal impairment. Tocilizumab has not been studied in patients with moderate to severe renal impairment.

Other approved indications

Systemic-onset juvenile idiopathic arthritis

Tocilizumab received approval by the U.S. Food and Drug Administration for the treatment of systemic-onset JIA. Two phase 2 dose-escalating trials

in 18 white and 11 Japanese children^{24,25} and two phase 3 studies have been conducted. In the first phase 3 study, 56 Japanese children were included in a DBRCT withdrawal design. Of the 43 patients who were included in the double-blind phase, 4 (17%) of 23 patients in the placebo group maintained an ACR core set for a JIA30 response and a CRP concentration of less than 15 mg/L as compared with 16 (80%) of 20 in the tocilizumab group ($P < .0001$). At the end of the open-label extension phase, 47 (98%), 45 (94%), and 43 (90%) achieved an ACR core set for JIA30, JIA50, and JIA70 responses, respectively.²⁶ The largest phase 3 trial involved 112 patients, and at week 12 the primary endpoint (absence of fever and improvement of 30% or greater on at least three of the six variables in the ACR core set for JIA, with no more than one variable worsening by greater than 30%) was met in significantly more patients in the tocilizumab group than in the placebo group (64 of 75 [85%] versus 9 of 37 [24%], $P < .001$).²⁷ At week 52, 80% of the patients who received tocilizumab had at least 70% improvement with no fever, including 59% who had 90% improvement; in addition, 48% of the patients had no joints with active arthritis, and 52% had discontinued oral glucocorticoids. A reduction in joint space narrowing, erosions, epiphyseal irregularity, and subchondral cysts has been observed in other studies.^{28,29}

Castleman disease

Tocilizumab was approved as an orphan drug in Japan for the treatment of Castleman disease and was effective in improving a wide range of disease manifestations, including autoimmune hemolytic anemia, hepatosplenomegaly, pulmonary hypertension, lung lesions, cardiomyopathy, renal manifestations, and IgA nephropathy with cutaneous nodules.^{30,31}

Expanded unapproved indications

Polyarticular juvenile idiopathic arthritis

Tocilizumab was demonstrated to be efficacious in 19 children with polyarticular JIA who failed MTX therapy. At 48 weeks, 100%, 94.1%, 88.2%, and 64.7% achieved 30%, 50%, 70%, and 90% ACR pediatric response rates, respectively. Rheumatoid factor was positive in nine (47%) of the patients. In another report involving 12 children with polyarticular JIA refractory to MTX and other biologics, a good EULAR response was achieved in 9 (75%) of the patients.³²

Adult-onset Still disease

Tocilizumab was reported to be effective for resistant adult-onset Still disease (AOSD) in case reports. The patients included were refractory to corticosteroids, DMARDs, TNFIs, and anakinra. Tocilizumab was effective as monotherapy or when corticosteroids could not be used.³³ It was also successful in managing serious ASOD-related complications such as thrombotic thrombocytopenic purpura, aseptic meningitis, and macrophage activation syndrome.³³⁻³⁵

Systemic lupus erythematosus

The largest study evaluating IL-6 blockade in patients with systemic lupus erythematosus was a phase 1 dose-escalating trial in 16 patients with mild to moderate disease.³⁶ A third of these patients had renal involvement.

Arthritis improved in all the patients, along with a reduction in different serologic markers. Neutropenia occurred in 38% in the 4-mg/kg dose group and in 56% in the 8-mg/kg dose group and resolved after stopping therapy. Infection occurred in 11 patients; none was associated with neutropenia.³⁶

Spondyloarthritis

Several studies reported no benefit with tocilizumab for spondylitis. This has been observed in studies of other IL-6 inhibitors for ankylosing spondylitis. In a case report of two patients with psoriatic arthritis (PsA), tocilizumab failed to improve the skin lesions or arthritis,³⁷ whereas in another patient the psoriatic lesions improved.³⁸

Large-vessel vasculitis (Takayasu and giant cell arteritis)

A number of case reports have shown tocilizumab to be effective in improving ischemic symptoms, normalizing acute-phase reactants, and reducing inflammatory changes in blood vessels when assessed by ultrasound, magnetic resonance angiography, or positron emission tomography. In most of the patients described, the daily steroid requirement was stopped or tapered to a minimal dose. In one case series involving 10 patients (7 with giant cell arteritis, 2 with Takayasu arteritis, and 1 with polymyalgia rheumatica), tocilizumab was shown to be efficacious in all patients up to 6 months.³⁹ The demonstration of persistent large-vessel vasculitis at autopsy in one patient who exhibited a good clinical response implies close monitoring of patients in larger studies of tocilizumab. Disease progression at 1 year was also shown in another report despite clinical and biochemical improvement in a patient with Takayasu arteritis.⁴⁰

Case reports of Cogan syndrome,⁴¹ relapsing polychondritis,⁴² and hepatitis C–negative cryoglobulinemic vasculitis⁴³ state that tocilizumab improves amyloidosis-related symptoms and histologic deposition in the gut, kidney, and heart of patients with RA, JIA, AOSD, and PsA.⁴⁴⁻⁴⁷ Positive observations have also been reported in patients with idiopathic myositis,⁴⁸ Behçet disease,⁴⁹ and TNF receptor–associated periodic syndrome.⁵⁰ Confirmation is needed in all these cases before it is concluded that inhibition of the IL-6 pathway is relevant in these diseases.

EMERGING INTERLEUKIN-6/INTERLEUKIN-6 RECEPTOR INHIBITORS

Several agents are now in development to block the action of IL-6 through either targeting the molecule directly or targeting its surface receptor. Sarilumab is the first fully human IL-6 α monoclonal antibody in development, in contrast to tocilizumab, which is a humanized molecule. Phase 2b and 3 studies are under way to evaluate subcutaneous dosing weekly or twice weekly. Another IL-6 inhibitor, sirukumab, is a human anti-IL-6 monoclonal antibody that is in phase 3 trials to evaluate its efficacy in inadequate responders with RA to both DMARD and TNF; it is administered subcutaneously either twice or four times weekly. Other IL-6 monoclonal antibodies, olkizumab and clazakumab, are in earlier phases of development.

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63

Tumor necrosis factor–blocking therapies

■ PETER C. TAYLOR

- Tumor necrosis factor (TNF) has multiple proinflammatory effects and plays a key role in rheumatoid arthritis.
- Inhibition of TNF with monoclonal antibodies or the TNFR2 soluble receptor leads to a rapid and significant improvement in rheumatoid arthritis activity. Clinical effect is observed within weeks of starting therapy, with ACR20 criteria met in 50% to 70% of patients. Improvement in quality of life, functional status, and structural progression is observed with these therapies.
- Anti-TNF therapy appears more effective in combination with methotrexate than as monotherapy.
- Anti-TNF therapy also significantly benefits those with juvenile arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis.
- Serious adverse events are rare but include serious infection, tuberculosis, demyelinating syndromes, increased risk of certain malignancies, and drug-induced lupus.

INTRODUCTION

Biologic agents targeting tumor necrosis factor (TNF) have significantly modified the treatment paradigm for numerous inflammatory disorders and unequivocally validated TNF as a molecular target for therapy. The clinical success and impact of TNF inhibitors (monoclonal antibodies, Fab' antibody fragments or the p75 TNF soluble receptor) have fostered the development of other biologic and small-molecule modulators of proinflammatory cytokines. TNF inhibition is generally well tolerated and capable of ameliorating a variety of inflammatory disorders, although the range of disease phenotypes responding appears to differ with the two biologic approaches to TNF inhibition currently available, so that doses of etanercept effective in rheumatoid and other forms of inflammatory arthritis are not effective in granulomatous diseases such as inflammatory bowel disease, in distinction to the antibodies, which are.

Although TNF plays an important regulatory role in host defense, the amplified and dysregulated production of this cytokine mediates the inflammatory response that characterizes disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn disease, psoriatic arthritis (PsA), psoriasis, and other inflammatory disorders. Numerous studies have documented the excess production of local and systemic TNF and a reciprocal rise in TNF receptors (TNFRs) in these disorders. Byproducts of TNF-mediated proinflammatory events are also evident. Excessive levels of other proinflammatory cytokines, increased nitric oxide, collagenase, prostaglandins, increased adhesion molecule expression, and evidence of spontaneous erosive synovitis are all found in both human inflammatory diseases and transgenic mice overexpressing TNF.¹ Definitive verification of a primary role for TNF in these disorders came from clinical trials demonstrating the impressive amelioration of disease with TNF blockade.

TNF blockade in RA, PsA, and AS consistently decreases disease activity and improves quality of life, and it lessens radiographic progression of peripheral joint damage. Five biologic agents that inhibit TNF have been approved for use in RA: etanercept, a soluble dimeric TNFR2 immunoglobulin G1 (IgG1)–Fc fusion construct (Enbrel); infliximab, a chimeric anti-TNF- α IgG1 monoclonal antibody (Remicade); adalimumab, a human IgG1 anti-TNF- α monoclonal antibody (Humira); golimumab, a human IgG1 anti-TNF- α monoclonal antibody (Simponi); and certolizumab pegol, a TNF-specific, pegylated Fab' antibody fragment (Cimzia). [Box 63.1](#) lists the

several benefits seen with TNF blockade, including wide approval of these drugs for treatment of many inflammatory disorders, higher remission rates, protection against structural/radiographic deterioration, and possibly a reduced rate of cardiovascular events in RA patients.

MECHANISM OF ACTION

TNF and TNFRs are members of a family of molecules (including Fas ligand/Fas, CD40 ligand/CD40) possessing crucial regulatory functions that include cellular activation and apoptosis. TNF is an attractive therapeutic target owing to its abundant expression in the RA joint and plethora of proinflammatory effects that include regulation of other proinflammatory mediators.

TNF- α is made intracellularly, and the 26-kDa precursor transmembrane form is cleaved off by a specific metalloproteinase, TNF- α -converting enzyme, to produce soluble biologically active TNF. This molecule aggregates as a homotrimer in its active form. TNF- α and the closely related TNF- β (also known as *lymphotoxin- α*) equally bind the TNFR1 (p55, CD120a) and TNFR2 (p75, CD120b) receptors present on many cell types. The TNFR has an extracellular domain that can also be cleaved and released as a soluble TNFR and functions as a naturally occurring inhibitor.

The TNFRs differ in their binding abilities and signaling properties; these differences also reflect the differences in their primary functions. The presence of both receptors on nearly all cell types (except erythrocytes) underscores the wide-ranging biologic effects of TNF. Whereas TNFR1 is constitutively expressed on all cell types, TNFR2 is induced and expressed in larger amounts on hematopoietic and endothelial cells. Although binding of TNF to its receptor initiates a cascade of biologically profound events, both cell-bound and circulating TNF- α may also be bound to soluble TNFRs serving as natural, counterregulatory TNF antagonists. The extracellular domain of cell-bound TNFRs may be cleaved off (especially in an inflammatory milieu) to circulate in soluble form, where it binds TNF and ultimately is excreted by the kidney. The binding of TNFR1 and TNFR2 to TNF- α appears to be similar, with the main difference lying in the dissociation kinetics. Thus, although the binding of TNFR1 is static and almost irreversible (due to slow off-rate), the binding of TNFR2 is more dynamic owing to a more rapid off-rate. It appears that the physiologic activities of soluble TNF are largely mediated through the TNFR1 receptor, whereas TNFR2 is involved in ligand passing. The binding of TNF- α to its receptor can initiate several signaling pathways, including the activation of transcription factors (e.g., nuclear factor κ B), protein kinases (e.g., c-Jun N-terminal kinase [JNK], p38 MAP kinase), and proteases (e.g., caspases) that markedly impact immune and inflammatory responses.

TNF- α primarily mediates inflammation by promoting cellular activation and trafficking of leukocytes to inflammatory sites. The biologic properties affected by TNF are listed in [Box 63.2](#). TNF- α is produced primarily by monocytes and macrophages but may also be produced by other cell types (e.g., B cells, T cells, mast cells, fibroblasts). TNF- α may further contribute to the pathogenesis of RA by induction of proinflammatory cytokines such as interleukin-1 (IL-1) and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophils and eosinophils, induction of the synthesis of acute-phase reactants, and induction of tissue-degrading enzymes (matrix metalloproteinase enzymes) produced by synoviocytes and/or chondrocytes.

Although all biologic TNF inhibitors share many biologic, clinical, and adverse effects, there are differences among them beyond their pharmacokinetics. The monoclonal antibodies infliximab, adalimumab, golimumab, and certolizumab are specific for TNF- α ; etanercept binds both TNF- α and

lymphotoxin- α . Infliximab, adalimumab, and golimumab are IgG1 antibodies, and etanercept contains an IgG1 portion; certolizumab is a pegylated Fab' fragment lacking an Fc portion. In addition to sharing the ability to inhibit TNF, all five agents bind to TNF with high affinity, and all three monoclonal antibodies are virtually the same in their ability to neutralize soluble and transmembrane TNF. The induction of cell lysis in a cell line overexpressing TNF- α has been demonstrated in *in-vitro* studies of infliximab and adalimumab (Fig. 63.1).

The first formal proof that TNF- α regulates other proinflammatory cytokines *in vivo* was the observation that there is a rapid reduction in serum IL-6 concentrations, closely followed by falling serum C-reactive protein (CRP) levels, following administration of infliximab.^{2,3} Although IL-1 concentrations are often below the limit of detection in the peripheral blood of RA patients, when it is detectable, downregulation has been reported in a proportion of patients.⁴ In a small study in which repeat synovial biopsy specimens were obtained before and 2 weeks after a single infusion of 10 mg/kg of infliximab, computerized image analysis of sections stained for cytokine-producing cells demonstrated a reduction in synovial IL-1 α and IL-1 α in a subgroup.⁵ The benefits of anti-TNF therapy are not mediated by upregulation of endogenous proinflammatory cytokine inhibitors, because

circulating IL-1 receptor antagonist (IL-1ra) and soluble TNFR levels fall after infliximab infusion.³

A major mechanism of action of TNF inhibitors is likely to be modulation of inflammatory cell traffic. A dose-dependent rise in peripheral blood lymphocyte counts is observed following infliximab infusion, with a maximum rise within 24 hours of treatment.⁶ This is mediated by modulation of both arms of the inflammatory cell recruitment cascade. There is reduced histologic expression of synovial cytokine-induced vascular adhesion molecules, such as E-selectin and VCAM-1, following anti-TNF treatment,⁷ a significant dose-dependent reduction in soluble serum E-selectin and intercellular adhesion molecule 1 concentrations,⁶ and a significantly diminished immunohistologic expression of the chemokines IL-8 and MCP-1, with a trend toward reduction in a number of other chemokines.⁸

Infliximab therapy is also associated with a reduction in numbers of synovial tissue macrophages and lymphocytes.^{7,8} However, the definitive confirmation that TNF blockade reduces leukocyte traffic to inflamed joints was obtained in an open-label clinical trial demonstrating a 40% to 50% decrease in retention of autologous indium-111-labeled granulocytes in the hands, wrists, and knees 2 weeks after infliximab treatment.⁸ There is a reduction in the marginating granulocyte pool after infliximab treatment, an observation that would normally be associated with a rise in peripheral blood granulocyte counts.⁹ However, in contrast to peripheral blood lymphocyte counts, the numbers of peripheral blood granulocytes decrease after infliximab dosing with maximal changes within 24 hours. The reason for this is that myeloid cell production is reduced secondary to downregulation of granulocyte-macrophage colony-stimulating factor as a consequence of TNF blockade. Because of the short circulating half-life of the granulocyte of approximately 8 hours, a diminished rate of cell production dominates the peripheral blood picture.

One factor contributing to the rapid reduction in joint swelling after anti-TNF therapy is likely to be a reduction in tissue edema and capillary leak, mediated by vascular endothelial growth factor (VEGF), a cytokine implicated in new blood vessel formation and found to be elevated in the serum of RA patients.¹⁰ Serum concentrations of VEGF show a dose-dependent reduction following infliximab infusions, but without normalization. There is also reduction in synovial vascular density and in particular a reduction in angiogenesis, as assessed by diminished number of vessels expressing the $\alpha_v\beta_3$ integrin.¹¹ The vascular signal on quantitative power Doppler imaging is also significantly reduced following infliximab therapy.^{12,13}

A marked reduction in circulating concentrations of the precursors of the matrix metalloproteinase enzymes MMP-1 and MMP-3¹⁴ and a significant reduction in synovial tissue expression of matrix metalloproteinases was noted.¹⁵ Serum levels of osteoprotegerin (OPG) and soluble receptor activator of nuclear factor κ B ligands (sRANKL), both of which are elevated in RA sera compared with normal sera, are normalized following infliximab therapy without influencing the OPG-sRANKL ratio.¹⁶ These observations predicted the beneficial effects on radiographic erosions with anti-TNF inhibitors.

One hypothesis for the failure of etanercept to work in Crohn disease, in contrast to the marked benefits demonstrated with monoclonal antibodies to TNF- α , is that the antibodies may cause an increase in apoptosis of lamina propria and peripheral T cells through caspase-dependent mechanisms. This topic remains controversial, and the relevance of modulation of apoptosis

BOX 63.1 BENEFITS OF TUMOR NECROSIS FACTOR BLOCKADE

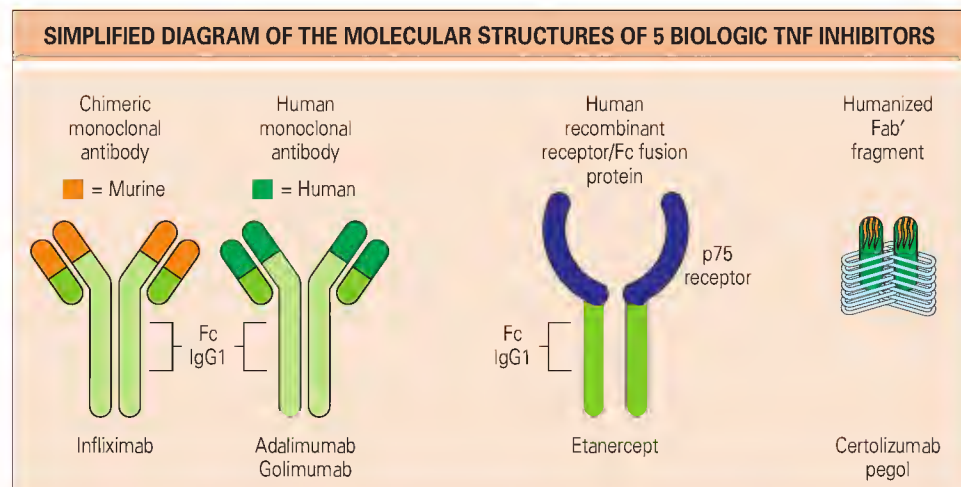
- Efficacy, safety, and approval for use in numerous inflammatory states: rheumatoid arthritis (RA), juvenile arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, and ulcerative colitis
- Increased odds of remission in both randomized controlled trials and clinical practice (in both early and established RA)
- Significant disease modification as assessed by radiographic studies
- Dramatic normalization of acute-phase reactants
- Reduced levels of serum rheumatoid factor and cyclic citrullinated peptide antibodies
- Decreased frequency of cardiovascular events in RA patients

BOX 63.2 BIOLOGIC EFFECTS OF TUMOR NECROSIS FACTOR- α

- Adhesion molecule expression (E-selectin, ICAM-1)
- Synthesis of other proinflammatory cytokines (IL-1, IL-6, GM-CSF)
- Synthesis of chemokines (e.g., RANTES, IL-8, MIP-1)
- Activation of numerous cell types (T cells, B cells, macrophages)
- Inhibition of regulatory T cells
- Matrix metalloproteinase induction
- Upregulation of RANK ligand expression
- Induction of apoptosis
- Antiviral and antitumor effects of tumor necrosis factor

GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MIP-1, macrophage inhibitory protein 1.

Fig. 63.1 Infliximab is a mouse/human chimeric monoclonal anti-tumor necrosis factor (TNF) antibody of immunoglobulin G1 (IgG1) isotype. Adalimumab and golimumab are fully human IgG1 monoclonal anti-TNF antibodies. Etanercept is a fusion protein of the p75 (TNF receptor 2) and the Fc portions of IgG1. Certolizumab pegol is a pegylated Fab' fragment of a humanized IgG1 monoclonal anti-TNF antibody.



as the mechanism of action of TNF inhibitors in RA is unclear. In one study, decreased synovial cellularity was reported as early as 48 hours after infliximab administration, but with no corresponding evidence of apoptosis.¹⁷ In another study, however, apoptosis in synovial macrophages was reported to be induced by both etanercept and infliximab, with a corresponding increase in active caspase-3 expression. No increase in lymphocyte apoptosis was observed, however.¹⁸

Approved indications and practical use

Table 63.1 details U.S. Food and Drug Administration (FDA)–approved indications for the use of anti-TNF therapy. TNF blockers were initially approved in RA, juvenile arthritis, and PsA for patients with moderately to severely active disease in whom an adequate trial of methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs) had failed. TNF blockers were also indicated for the control of signs and symptoms and the prevention of functional or radiographic deterioration in RA and PsA. Following the findings of large controlled trials in early RA patients, the FDA recommendations for infliximab, adalimumab, and etanercept were modified to allow their use as the initial DMARD in RA, and thus the requirement of failure of MTX (or other DMARD) was removed (see Table 63.1). Therefore, although MTX and TNF inhibitors appear to be equally effective in clinical trials, TNF inhibitor therapy has been established as yielding better radiographic outcomes (alone or in combination with MTX). Despite the clinical and radiographic potency of TNF blockade, particularly with concomitant MTX therapy, the circumstances in which this combination should be initiated as a first-line therapy have not been firmly established; a major consideration is the cost effectiveness of biologic therapies within the context of particular health care economies.

The optimal candidate for TNF inhibition has not been defined. The top indications for TNF inhibitor use in RA include (1) failure of MTX, (2) failure of multiple DMARDs, (3) physician assessment of active disease, (4) radiographic erosions, and (5) functional disability. The 2010 EULAR guidelines¹⁹ for management of RA recommend that, in patients showing insufficient response to MTX and/or other synthetic DMARDs with or without glucocorticoids, a TNF inhibitor be initiated and, unless contraindicated, be administered in combination with MTX.

Relative contraindications to TNF inhibitor use include overlap syndromes, a history of demyelinating disorder (multiple sclerosis, optic neuritis), congestive heart failure, and pregnancy. Absolute contraindications include untreated active or latent tuberculosis (Box 63.3). The clinician should always carefully consider the anticipated hazards versus potential benefits before proceeding with TNF inhibition.

Unless there is a contraindication to its use, MTX should be considered the front-line DMARD of choice in RA. Although other oral DMARD compounds may subsequently be considered as a monotherapy replacement,

TNF inhibitors are among the most effective second-line therapies available, especially in patients with active RA not controlled by MTX therapy at an adequate duration and dose.

In cases in which MTX therapy has been initiated and administered at appropriate dosages for no longer than 3 to 6 months but low disease activity has not been reached, it remains unclear whether a switch to combination DMARDs is as effective as addition of a biologic anti-TNF agent. Data from the BeST trial suggests that MTX plus TNF inhibitor is superior to add-on or sequential combination DMARD regimens.²⁰ In the SWEFOT trial, patients with early RA had initial MTX treatment, and only after this agent failed were they randomly assigned to two therapeutic strategies: the addition of sulfasalazine plus hydroxychloroquine, or the addition of infliximab.²¹ After 1 year, 25% of patients receiving the former combination and 39% of patients receiving the latter had achieved a EULAR good response, and the difference was statistically significant. Data from the Randomized Comparative Effectiveness Study of Oral Triple Therapy versus Etanercept plus MTX in Early, Aggressive Rheumatoid Arthritis (TEAR) suggested that treatment with the combination of MTX plus etanercept provided better radiographic benefit but similar clinical response compared with oral triple therapy.²²

DMARD-naïve patients with poor prognostic markers might be considered for combination therapy with MTX plus a biologic agent in very exceptional situations. However, the EULAR recommendations for treatment of RA consider that, in general, this approach is not cost effective.¹⁹ Such patients must manifest a weighty combination of risk factors that portends a severe outcome, including active polysynovitis, radiographic erosions, seropositivity for rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies, functional impairment, and sustained elevations of acute-phase markers. The identification of such high-risk patients mandates the combined use of MTX and TNF inhibition because studies have consistently

BOX 63.3 RELATIVE CONTRAINDICATIONS TO THE USE OF TUMOR NECROSIS FACTOR INHIBITORS

- Systemic lupus erythematosus, lupus overlap syndrome
- Multiple sclerosis, optic neuritis, demyelinating disorders
- Current, active, serious infection
- Recurrent or chronic infection
- Untreated latent or active mycobacterial infection
- Hepatitis B infection
- Congestive heart failure
- Pregnancy

TABLE 63.1

U.S. Food and Drug Administration–approved indications for tumor necrosis factor- α inhibitors

Indication	Etanercept	Infliximab	Adalimumab	Golimumab	Certolizumab
Rheumatoid arthritis	Yes ^a	Yes ^b	Yes ^a	Yes ^b	Yes
Early rheumatoid arthritis	Yes	Yes	Yes	—	—
Polyarticular juvenile arthritis	Yes ^c	—	—	—	—
Psoriatic arthritis	Yes ^d	Yes ^e	Yes ^e	Yes	Yes
Ankylosing spondylitis	Yes ^f	Yes ^f	Yes ^f	Yes	Yes
Psoriasis	Yes ^g	Yes	—	—	—
Crohn disease	—	Yes ^h	Yes ^h	—	Yes
Ulcerative colitis	—	Yes ⁱ	Yes	—	—

^aIndicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. It can be initiated alone or in combination with methotrexate (MTX).

^bInfliximab and golimumab are approved for use in combination with MTX only.

^cIndicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs.

^dOnly etanercept is indicated to inhibit the progression of structural damage and improve physical function in patients with moderately to severely active psoriatic arthritis. It can be used in combination with MTX in patients who do not show adequate response to MTX alone.

^eIndicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis.

^fIndicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

^gIndicated for the treatment of adult patients (>18 yr) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

^hIndicated for reducing signs and symptoms and inducing or maintaining clinical remission in patients with moderately to severely active Crohn disease who have had an inadequate response to conventional therapy. Also indicated for reducing the number of enterocutaneous and rectovaginal fistulas and maintaining fistula closure in fistulizing Crohn disease.

ⁱOnly infliximab is indicated for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

shown that clinical and radiographic outcomes are best when this combination is used instead of TNF inhibitor or MTX alone.

In addition to the rapid onset of effect is the enhanced well-being and improvement in fatigue reported by patients receiving TNF blockade. The mechanism for this effect is unknown. The popularity of these agents is evident from the growth in their use worldwide. Nonetheless, several factors have limited their more widespread use, including patient or physician reluctance, limited or variable coverage by third-party insurance carriers, toxicity concerns, and in particular, high costs.

ADALIMUMAB (HUMIRA)

Adalimumab was approved in December 2002 after an extensive development program.

Pharmacology

Adalimumab is a fully human IgG1 anti-TNF- α monoclonal antibody produced by phage display with a terminal half-life of 10 to 20 days (mean, 14 days), which permits every-other-week dosing. After a single 40-mg subcutaneous dose, the maximum serum concentration is achieved within 131 ($\pm$ 56) hours. The antibody binds circulating and cell-bound TNF- α and blocks its interaction with p55 and p75 receptors but does not interact with lymphotoxin (TNF- β). The drug induces cell lysis of TNF-expressing cells (in the presence of complement). Concomitant MTX therapy reduces the clearance of adalimumab by 29% to 44%. It is unknown if adalimumab pharmacokinetics is altered in the setting of renal or hepatic impairment.

Indications and use

Adalimumab is indicated to reduce signs and symptoms, inhibit radiographic damage or progression, and improve physical function in moderate to severe RA that is unresponsive to an adequate trial of one or more DMARDs. It is also approved for treatment of PsA, AS, psoriasis, Crohn disease, and ulcerative colitis. Adalimumab may be used as monotherapy or in combination with MTX; the recommended dosage is 40 mg administered subcutaneously every other week. Higher dosages (e.g., 80 mg every other week) were used during drug development but were not shown to be more effective in short-term trials. A minority of patients may require dose escalation (e.g., 40 mg weekly), in particular those receiving adalimumab monotherapy. In the PREMIER early RA trial, dose escalation was permitted for

those not meeting American College of Rheumatology 20% improvement criteria (ACR20). Patients receiving adalimumab monotherapy were more likely to need escalation to weekly dosing than those receiving combined adalimumab and MTX (25% vs. 11%, respectively).²³ Whether dose escalation to weekly adalimumab in patients taking MTX will lead to a better clinical response is less certain.

Adalimumab in rheumatoid arthritis pivotal trials

A single dose of adalimumab^{23a} produced significant and rapid clinical improvement, reduced acute-phase reactants, increased circulating lymphocyte counts, and significantly reduced systemic IL-6 and IL-1ra levels for at least 2 weeks. In controlled dose-ranging monotherapy studies, ACR20 response rates ranged from 46% to 73% (Table 63.2). In a placebo-controlled monotherapy trial involving 544 RA patients, a dose-dependent rise in ACR response rates was seen, with 46% of those receiving 40 mg every other week achieving an ACR20 response.²⁴

The ARMADA trial studied adalimumab in 271 RA patients with chronic disease and an inadequate response to MTX.²⁵ In this 6-month multicenter trial, patients continued to receive stable doses of MTX (mean, 16 to 17 mg/wk) and received placebo or 20 mg, 40 mg, or 80 mg of adalimumab every 2 weeks. ACR20 response rates were 14%, 48%, 66%, and 66% for those taking placebo, 20 mg adalimumab, 40 mg adalimumab, and 80 mg adalimumab, respectively. Another pivotal trial (DE019) examined efficacy and radiographic outcomes in a 52-week trial in 619 patients in which adalimumab 20 mg or 40 mg every other week or placebo was given to MTX partial responders.²⁶ ACR20 response rates after 52 weeks were 24%, 55%, and 59% in the placebo, 20 mg adalimumab, and 40 mg adalimumab groups, respectively. Responses were sustained in the 457 patients who went on to receive long-term open-label adalimumab. Radiographic progression, as measured by modified Sharp scores, was significantly worse in the placebo group (+2.7 Sharp units) compared with the groups receiving adalimumab 20 mg/wk (+0.7 Sharp units) and 40 mg every other week (+0.1 Sharp units).

The PREMIER trial established the efficacy of adalimumab in early RA (see Table 63.2). In this 2-year trial in patients with early RA (less than 3 years' duration), 799 DMARD-naïve patients received either adalimumab, MTX, or the combination of MTX and adalimumab.²³ Adalimumab and MTX were equipotent with regard to clinical outcomes (ACR20/50/70 responses, Disease Activity Score [DAS] remission), whereas the combined use of MTX and adalimumab was significantly better. ACR70 response rates and 6-month sustained, major clinical response rates were twofold higher with MTX plus adalimumab than with adalimumab alone (47% vs. 27% and

TABLE 63.2 Summary of pivotal adalimumab clinical trials in rheumatoid arthritis (RA)*

Trial	Van De Putte et al ²⁴	ARMADA ¹⁷	DE019 ²⁶	PREMIER ²³
Trial intervention	Adalimumab [†] monotherapy	MTX/adalimumab [†] combination	MTX/adalimumab [†] combination	Early RA MTX/adalimumab [†] combination
Trial duration	26 wk	24 wk	52 wk	24 mo
Number enrolled	544	271	619	799
Disease duration	12 yr	11-13 yr	11 yr	0.7 yr
ACR20	46%	67%	59%	73%
ACR50	22%	55%	42%	62%
ACR70	12%	27%	23%	46%
Rx effect	27%	53%	35%	NA
DAS remission	ND	ND	ND	49%
Change in HAQ score	-0.4	0.6	-0.7	-1.3
Mean TSS Δ	ND	ND	+0.1	+1.9
No Δ in TSS	ND	ND	62%	61%
Withdrawal rate	ND	ND	22%	24%
ISR rate	ND	15%	26%	ND
URI rate	ND	ND	19%	ND
SIE rate	ND	ND	0.06/patient-yr	0.03/patient-yr

*Multicenter, randomized, controlled trials.
[†]Reporting rates for group receiving 40 mg adalimumab every other week.
ACR20/50/70, American College of Rheumatology response criteria for 20%/50%/70% improvement; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; ISR, injection site reaction; MTX, methotrexate; ND, no data; Rx effect, active drug; SIE, serious infectious event; TSS, total Sharp score; URI, upper respiratory tract infection.

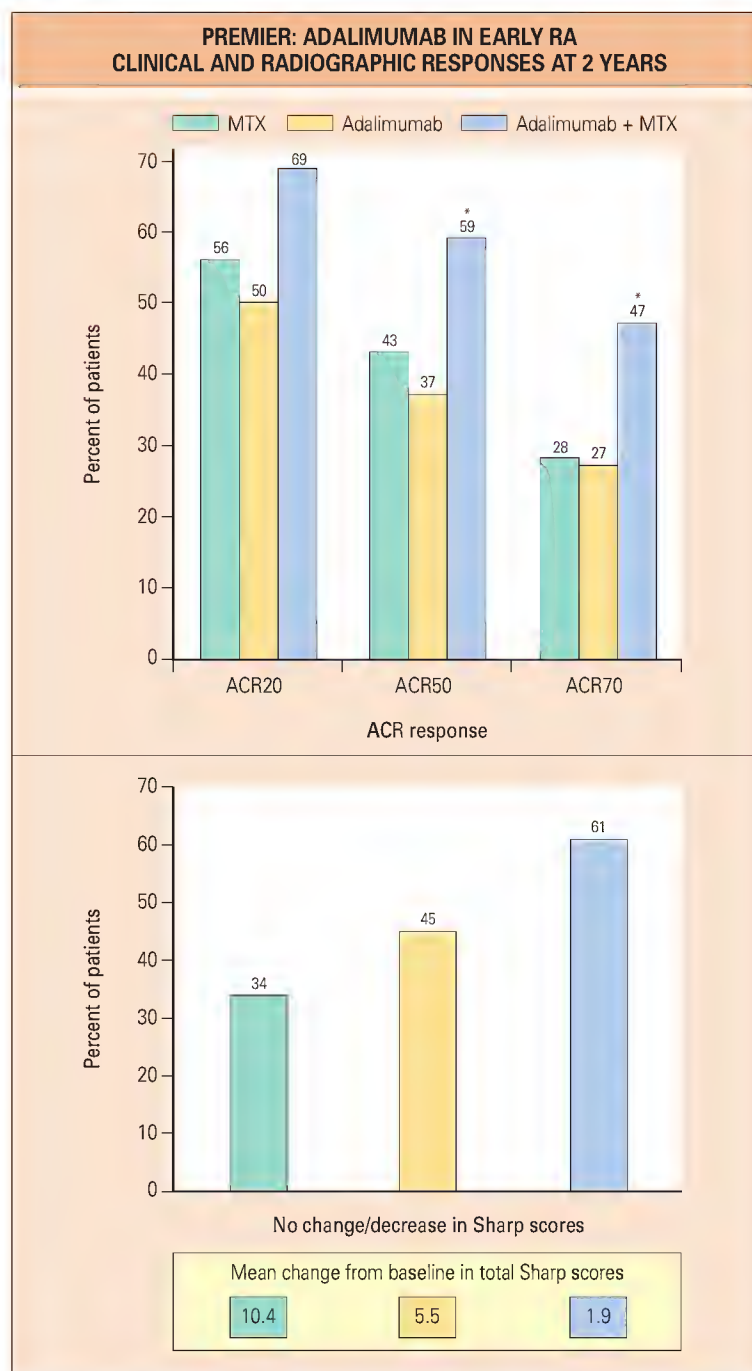


Fig. 63.2 * = $P < 0.001$ versus adalimumab alone and versus MTX alone. (From Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus MTX versus MTX alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous MTX treatment. *Arthritis Rheum* 2006;54:26-37.)

49% vs. 25%, respectively). Outcomes on primary measures included a 62% ACR50 response rate and a minimal change (+1.3 Sharp unit) in total Sharp score for those receiving MTX plus adalimumab for 12 months (Fig. 63.2).

ETANERCEPT (ENBREL)

In 1999 etanercept became the first anti-TNF therapy approved for RA by the FDA.

Pharmacology

Etanercept is a dimeric fusion construct that links two TNFR2 receptors to the Fc portion of IgG, containing domains CH2 and CH3 and the hinge region. Etanercept is produced in Chinese hamster ovary cells and has a

molecular weight of 150 kDa. It is capable of binding two circulating or cell-bound TNF- α molecules and inhibits the binding of TNF- α and TNF- β (lymphotoxin) to TNFRs. In contrast to the monoclonal antibodies, etanercept does not induce cell lysis or apoptosis of TNF-expressing cells. The half-life of etanercept in adult RA patients is 102 hours (± 30 hours) with a range of 4.1 to 12.5 days. Pharmacokinetics in children (older than age 4) is assumed to be similar to that in adults, although drug clearance may be reduced in children between the ages of 4 and 8 years. Steady-state serum concentrations were comparable in patients with RA treated with 50 mg once weekly and with 25 mg twice weekly. The route of clearance from the circulation is unclear, although it is thought to be mediated through Fc binding by the reticuloendothelial system. MTX has no effect on the pharmacokinetics of etanercept.

Indications and use

Etanercept is indicated in patients with established or early RA to reduce signs and symptoms, inhibit structural damage, and improve physical function in those with moderate to severe disease. Etanercept may be used alone or in conjunction with MTX. In adult RA patients, etanercept is given by self-administered subcutaneous injection at 50 mg once a week (or 25 mg twice weekly). In a controlled clinical trial, dose escalation to 100 mg weekly was not associated with increased efficacy in patients with active disease despite receiving long-term etanercept 50 mg/wk plus MTX.²⁷

Etanercept is also approved for use in patients with active, moderate to severe polyarticular juvenile arthritis, PsA, and AS (see Table 63.1). It is approved for moderate to severe plaque psoriasis at a higher dosage of 50 mg twice weekly for 3 months followed by a maintenance dose of 50 mg once weekly.

Etanercept in rheumatoid arthritis pivotal trials

The efficacy of etanercept was established in four pivotal clinical trials encompassing 1637 RA patients (Table 63.3). These trials consistently demonstrate impressive clinical outcomes, with ACR20 response rates ranging from 59% to 75% and ACR70 response rates of 15% to 40% after 6 to 12 months of therapy.

A 6-month randomized, controlled study compared placebo and etanercept (10 mg or 25 mg) subcutaneously twice weekly²⁸; 59% ACR20 and 15% ACR70 response rates were seen in patients taking etanercept 25 mg twice weekly, with lower responses seen with the 10-mg dose. When etanercept was added to long-term MTX, patients receiving etanercept and MTX showed a 71% ACR20 response rate compared with a 27% rate in the placebo plus MTX group.²⁹ Many of these patients were enrolled in a long-term open-label observational study and exhibited static ACR20, ACR50, and ACR70 response rates over 3 years. Importantly, sustained efficacy allowed for a 68% to 85% decrease in MTX or prednisone, and 39% to 59% of patients were able to discontinue MTX and prednisone use after 3 years.³⁰

Etanercept was the first biologic therapy tested head to head against MTX in an early RA (ERA) trial. This 12-month trial enrolled 632 patients with early RA (mean disease duration, 11 months), who received etanercept (10 or 25 mg twice weekly) or MTX 20 mg/wk.³¹ After 12 months, the MTX-treated and 25-mg etanercept-treated groups fared equally well, with ACR20 response rates of 65% and 72%, respectively. The only significant group difference in clinical effects was the more rapid onset of effect in those treated with etanercept in the first 4 months. Serious infectious events were infrequent in both groups (less than 3%). In the second year, a trend toward higher ACR20 response rates was seen in the etanercept group compared with the MTX group (72% vs. 59%).³²

The ERA trial showed that radiographic progression was diminished by both agents when assessed after 6, 12, and 24 months of therapy (Fig. 63.3). In the first year, modified Sharp scores showed little change in either the MTX group (1.3 units) or etanercept group (0.8 units), yet results for both were significantly better than their projected rates of radiographic deterioration (estimated to be approximately 9 Sharp units/yr). In the second year of the trial, significant differences were seen, with etanercept patients showing an increase of only 1.3 Sharp units (no progression in 63%) and MTX patients showing an increase of 3.2 Sharp units (no progression in 51%). The ERA trial was pivotal in demonstrating the potency of both MTX and etanercept in patients with early, aggressive RA. The additional radiographic advantage of TNF inhibition over MTX in early disease was seen largely in those with erosions at entry into the study.

The TEMPO trial reported the comparative efficacy of MTX, etanercept, and the combination of etanercept plus MTX in 682 patients with active RA with a mean disease duration of 7 years.³³ At both 12 and 24 months the combination of etanercept and MTX was significantly more effective than

TABLE 63.3

Summary of pivotal etanercept clinical trials in rheumatoid arthritis (RA)*

Trial	Moreland et al ²⁸	Weinblatt et al ²⁹	ERA ³¹	TEMPO ³³	COMET ³⁴
Description	Monotherapy	MTX/etanercept combination	Early RA, monotherapy	MTX/etanercept combination	Early RA, MTX/etanercept combination
Trial duration	6 mo	6 mo	12 mo	<24 mo	Reported to 12 mo, 24-mo study
No. enrolled	234	89	632	682	542
Disease duration	12 yr	13 yr	0.99 yr	7 yr	0.75 yr
ACR20 [†]	59%	71%	72%	86%	86%
ACR50 [†]	40%	39%	49%	71%	71%
ACR70 [†]	15%	15%	25%	49%	48%
Rx effect	48%	44%	NA	NA	NA
DAS remission	ND	ND	ND	38%	50%
Change in HAQ score	−0.6	−0.6	−0.7	−1.1	−1.0
Mean TSS Δ	ND	ND	Etanercept −1.3	−0.56	0.27
No Δ in TSS	ND	ND	72% no Δ erosion score	78%	75%
Withdrawal rate (etanercept)	28%	3%	7%	29%	19%
ISR rate	49%	42%	37%	11%	ND
URI rate	33%	22%	35%	ND	ND
SIE rate	ND	ND	<3%	6%	12%

*Multicenter, randomized, controlled trials (results shown for patients receiving etanercept 25 mg biweekly).
†At study end.
ACR20/50/70, American College of Rheumatology response criteria for 20%/50%/70% improvement; DAS, Disease Activity Score; HAQ, health assessment questionnaire; ISR, injection site reaction; MTX, methotrexate; NA, not applicable; ND, no data; Rx effect, active drug; SIE, serious infectious event; TSS, total Sharp score; URI, upper respiratory tract infection.

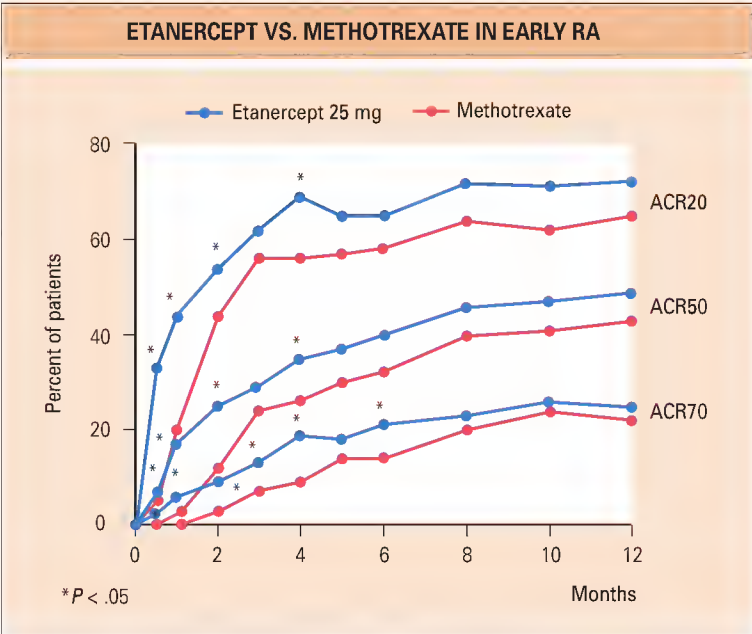


Fig. 63.3 ERA trial: etanercept in early rheumatoid arthritis. (From Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus MTX in patients with early rheumatoid arthritis: two year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443–50.)

monotherapy with either MTX or etanercept alone (see Table 63.3). At 24 months the combination group demonstrated impressive ACR20 (86%) and ACR70 (49%) response rates and DAS remissions (38%). Comparison of MTX-naïve and previously treated MTX patients failed to show significant differences in outcomes. The mean total Sharp score was decreased by 0.56 units in patients receiving combination etanercept plus MTX and 78% had no radiographic worsening. By comparison, total Sharp scores were increased in those taking etanercept alone (+0.5 units) or MTX alone (+2.8 units), and 60% to 68% showed no radiographic progression while taking MTX or etanercept, respectively. This study underscores the potential additive

clinical and radiographic protection afforded by the combination of MTX and TNF therapy, especially in patients with aggressive disease.

The COMET trial³⁴ compared the effects of a combination of etanercept and MTX with MTX alone in 542 MTX-naïve patients with early RA (duration of 3 months to 2 years). Half of the patients receiving combined treatment achieved DAS28 remission (less than 2.6) and 80% achieved radiographic nonprogression compared with 28% and 59%, respectively, of those taking MTX alone. For a majority of patients with early severe RA, clinical remission and radiographic nonprogression are achievable goals within 1 year of combined treatment with etanercept plus MTX.³⁴

INFLIXIMAB (REMICADE)

Infliximab was first approved for use in moderate to severe Crohn disease in 1998 and was approved in 1999 for use in RA.

Pharmacology

Infliximab is a chimeric anti-TNF monoclonal antibody that combines human IgG1K (constant region) with a murine Fv (variable) region and is produced in a murine myeloma cell line transfected with cloned DNA coding for cA2. Infliximab binds with high affinity to both soluble and membrane-bound TNF and is capable of neutralizing TNF *in vitro* and *in vivo*. This antibody can mediate cytotoxicity of TNF-expressing cells *in vitro* and is capable of inducing cell lysis of TNF-expressing cells via antibody-dependent cellular cytotoxicity *in vitro*. Infliximab binds TNF- α but not lymphotoxin (TNF- β). The median terminal half-life in patients with RA and Crohn disease is 8 to 9.5 days (mean, 210 hours) at doses of 3 to 10 mg/kg. Infliximab exhibits a linear dose-related pharmacokinetic profile at doses ranging from 3 to 20 mg/kg. Pharmacokinetic studies in the elderly and in patients with renal or hepatic dysfunction have not been done. Infliximab serum concentrations tended to be slightly higher when the drug is used along with MTX (7.5 mg once a week). The development of human antichimeric antibodies (HACA) has been shown to increase clearance and reduce serum levels of infliximab.

Indications and dosing

In established and early RA, infliximab (with MTX) is indicated to reduce signs and symptoms, inhibit radiographic progression, and improve physical

function in patients with moderately to severely active RA. Concurrent use of MTX (7.5 mg/wk) with infliximab has been shown to limit the immunogenic response to the construct (e.g., HACA formation). This is particularly relevant at lower doses (e.g., infliximab 3 mg/kg), at which immunogenicity is more likely than at higher doses (e.g., 10 mg/kg). Infliximab monotherapy (without MTX) is customary in Crohn disease, AS, ulcerative colitis and psoriasis, in which higher doses are usually employed.

In RA, the recommended dosage is 3 mg/kg given initially at weeks 0, 2, and 6 and thereafter every 8 weeks in combination with MTX. Infliximab is given as an intravenous infusion over 2 hours. Escalation of dose (up to 10 mg/kg) or frequency (every 4 to 6 weeks) may be necessary in some, but higher dosages may be associated with a higher frequency of serious infections (see later). Changes in dosing or dose intervals to maintain clinical efficacy may be needed. The loss of efficacy and the “dose creep” phenomenon are most common after the first year of therapy and may be due to physician-patient efforts to reduce the use of other adjunctive therapies (e.g., MTX, nonsteroidal antiinflammatory drugs, prednisone). Although 26% of patients receiving 3 mg/kg have undetectable infliximab levels at 8 weeks, shorter intervals (e.g., 4 weeks) and higher doses (e.g., 10 mg/kg) were less likely to result in undetectable levels.^{35,36} It was suggested that shorter dosing intervals would yield higher trough levels than would higher doses at the same intervals. For patients demonstrating a loss of efficacy, the clinician should first optimize the dose of MTX and then, if necessary, decrease dosing intervals (e.g., every 4 to 6 weeks) and then employ higher doses (up to 10 mg/kg).

Infliximab is also indicated for active adult and pediatric Crohn disease (including fistulizing disease), ulcerative colitis, AS, PsA, and psoriasis at a starting dose of 5 mg/kg. The initial dosing regimen is similar to that for RA (see earlier), and infliximab can be given every 8 weeks (or every 6 weeks in AS) thereafter.

Clinical efficacy of infliximab in rheumatoid arthritis

The efficacy and safety of infliximab in RA were initially established in monotherapy trials in which infliximab was administered after a DMARD washout. An 8-week open-label trial³⁷ demonstrated equivalent efficacy for two different regimens of infliximab: (1) two infusions of 10 mg/kg 2 weeks apart and (2) four monthly infusions of 5 mg/kg. Clinical benefits were noted after week 3 and were maximal by week 6 with normalization of CRP levels in nearly 90% of patients. Following the last infusion, clinical responses lasted a median of 14 weeks (range, 8 to 25 weeks). Another placebo-controlled monotherapy trial administering a single infusion of 1 mg/kg or 10 mg/kg demonstrated significant improvement by week 4, with Paulus 20% responses achieved in 44% and 79% of the low-dose and high-dose groups, respectively.³⁸ Eight responding patients went on to receive repeated infusions when clinical relapse became evident. In this group treated with infliximab alone, a trend toward shorter response intervals showed some correlation with the presence of HACA.

In another study the safety and immunogenicity of infliximab (1, 3, or 10 mg/kg) when given with or without MTX for 26 weeks was reported.³⁹ A Paulus 20% response was seen in 60% of patients receiving 3 or 10 mg/kg. Additive responses were seen with MTX (7.5 to 15 mg/wk) plus infliximab. After 26 weeks, HACA responses were seen in 53%, 21%, and 7% of those receiving 1 mg/kg, 3 mg/kg, and 10 mg/kg, respectively. The concurrent use of low-dose MTX further decreased HACA responses to 15%, 7%, and 0%, respectively. Larger multicenter trials further established the efficacy and safety of long-term infliximab administration on background MTX therapy in RA (Table 63.4). The ATTRACT trial was a 428-patient placebo-controlled trial of infliximab (3 mg/kg or 10 mg/kg) given every 4 or 8 weeks in patients with active RA receiving MTX weekly.⁴⁰ Patients who received infliximab (3 or 10 mg/kg) in addition to background MTX therapy showed significantly higher ACR20 responses (50% to 58%) than those taking MTX alone (20%) at 30 weeks. After 54 weeks ACR20 response rates were 42% to 59% in the 3-mg and 10-mg/kg groups.⁴⁰ Radiographic damage was progressive in the group receiving MTX plus placebo, increasing by a mean of 7 Sharp units at 1 year. By contrast, both the infliximab-treated groups (3 or 10 mg/kg) showed little change (1.3 and 0.2 units, respectively) after 12 months. At 2 years, 22% of placebo-treated patients showed no evidence of radiographic progression, whereas 43% to 47% of the 3-mg/kg group and 64% of the 10-mg/kg group showed no evidence of radiographic change. In patients without erosions at entry, infliximab plus MTX was revealed to be superior to MTX alone in halting further radiographic progression.⁴¹

The 12-month ASPIRE trial examined the effects of MTX and infliximab in 1049 patients with early RA with a mean disease duration of 7 months.⁴² All patients received MTX weekly (20 mg/wk) and either placebo or

TABLE 63.4
Summary of pivotal infliximab clinical trials in rheumatoid arthritis (RA)

Trial	ATTRACT ^{40*}		ASPIRE ⁴²	
Description	MTX*/infliximab combination		Early RA, MTX/infliximab combination	
Trial duration	54 wk		52 wk	
No. enrolled	428		1049	
Duration	8.4 yr		0.8 yr	
Dose (every 8 wk)	3 mg/kg	10 mg/kg	3 mg/kg	6 mg/kg
ACR20	42%	59%	62%	66%
ACR50	21%	39%	46%	50%
ACR70	10%	25%	33%	37%
Rx effect	25%	42%	NA	NA
DAS remission	ND		21%	31%
Change in HAQ score	−0.4		−0.8	−0.9
Mean TSS Δ	1.3	0.2	0.4	0.5
No Δ in TSS	54%		58%	59%
Withdrawal rate	21%		18%	20%
Infusion reactions	25% (2.3% withdrew)		21% (0.5% serious)	15%
URI rate	34%		25%	28%
SIE rate	6%		5.6%	5.0%
ANA/DNA positive	61%	10%	40%	24%
HACA	8%		14.5%	6.7%

*Results at week 54 presented for 3 mg and 10 mg administered every 8 weeks intravenously; mean MTX dose, 16 mg/wk.

ACR20/50/70, American College of Rheumatology response criteria for 20%/50%/70% improvement; ANA, antinuclear antibody; DAS, Disease Activity Score; HACA, human antichimeric antibodies; HAQ, health assessment questionnaire; MTX, methotrexate; SIE, serious infectious event; TSS, total Sharp score; URI, upper respiratory tract infection.

infliximab (3 mg/kg or 6 mg/kg). MTX/placebo-treated patients exhibited good ACR20 (54%) and ACR70 (21%) response rates and DAS remissions (15%); patients treated with MTX/infliximab showed significantly higher ACR20 (62% to 66%) and ACR70 (33% to 37%) response rates and DAS remissions (21% to 33%) at 54 weeks (Fig. 63.4). Radiographic progression was observed primarily in those patients treated only with MTX (see Fig. 63.4). Although 45% of the MTX/placebo-treated patients showed no progression, those receiving infliximab plus MTX demonstrated greater protection from progression in radiographic scores (no progression in 58% to 59%).

Two trials have suggested that the early use of infliximab in patients with new-onset RA may allow for its subsequent discontinuation with maintenance of efficacy using MTX therapy alone.^{20,43} A pilot study of 12 months of MTX and infliximab therapy in 20 high-risk patients with early RA resulted in clinical and magnetic resonance imaging (MRI) benefits that were sustained for a year after infliximab was withdrawn.⁴³ The BeST trial compared four treatment strategies for DMARD and biologic use in patients with early RA.²⁰ DMARD switch or add-on monotherapy was compared with a COBRA-like combination DMARD regimen and combined MTX and infliximab. The protocol called for the cessation of infliximab if remission was achieved after 9 months of therapy. After 4 years, more than half of infliximab/MTX-treated patients discontinued infliximab while maintaining a DAS of less than 2.4, and 18% of patients stopped both MTX and infliximab (drug-free remission) without recurrence or radiographic progression.⁴⁴ A *post-hoc* analysis of patient data for the four strategy limbs suggested that using MTX plus infliximab as initial treatment in patients with recent-onset RA is more effective than reserving MTX plus infliximab for patients in whom traditional DMARD therapy fails, with more improvement in HAQ scores over time, more infliximab discontinuation, and less progression of joint damage.⁴⁵ Initial combination therapy led to significantly faster improvement in all patient-reported measures.⁴⁶ The observation that drug-free or MTX-maintained remission may be maintained without ongoing TNF inhibition is an exciting development that requires further confirmation.

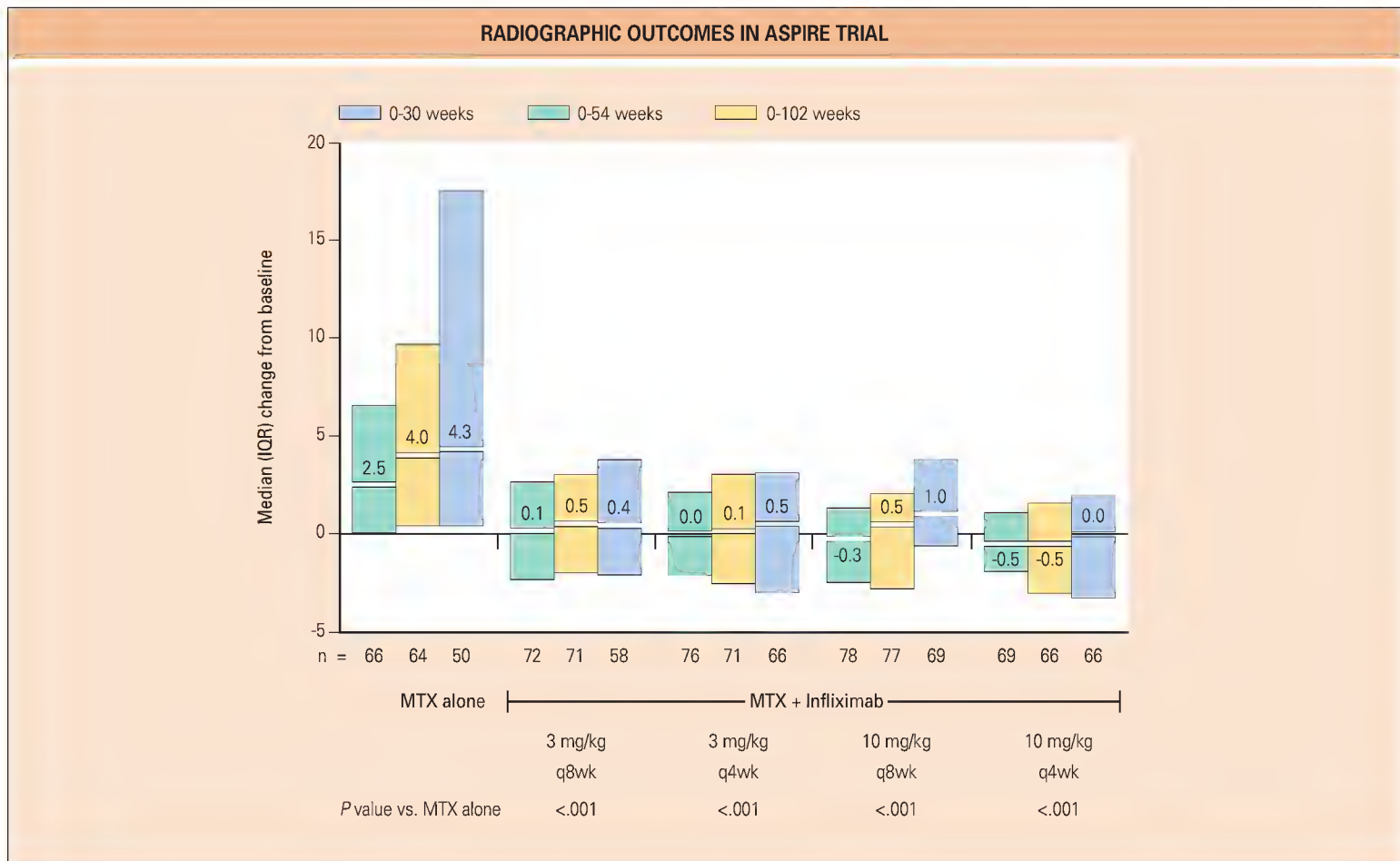


Fig. 63.4 ASPIRE trial: infliximab in early rheumatoid arthritis. MTX, methotrexate. (From St. Clair EW, Van Der Heijde DM, Smolen JS, et al; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and MTX therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:34320-43.)

CERTOLIZUMAB PEGOL (CIMZIA)

Certolizumab was first approved for use in moderate to severe Crohn disease in 2008 and was subsequently approved for treatment of RA in 2009.

Pharmacology

Certolizumab pegol is a TNF-specific, pegylated Fab' antibody fragment (see Fig. 63.1). The Fab' fragment was engineered with a single hinge-region free-cysteine residue, which enables site-specific attachment of polyethylene glycol (PEG) without affecting the ability of the Fab' fragment to bind and neutralize TNF. The attachment of a 40-kDa PEG moiety to the Fab' fragment markedly increases the half-life of certolizumab to one comparable with that of a whole antibody product. Because of the absence of an Fc region, certolizumab pegol does not mediate cell killing either directly through fixation of complement or via recruitment of effector cells.⁴⁷ Unlike the monoclonal antibodies adalimumab, infliximab, and golimumab, which are all bivalent with specificity for the monomeric subunit of homotrimeric TNF- α , certolizumab is univalent for the same ligand and therefore cannot cross-link membrane-bound TNF- α or soluble homotrimers, the consequence of the latter being that there is no formation of polymeric biologic-ligand complexes.

Clinical efficacy of certolizumab pegol in rheumatoid arthritis

In phase 2 studies, subcutaneous injections of increasing doses of certolizumab pegol were well tolerated in patients with active RA with rapid improvement in ACR responses.⁴⁸ In phase 3 studies, the RAPID 1⁴⁹ and RAPID 2⁵⁰ studies evaluated the efficacy and safety of lyophilized and liquid formulations, respectively, of subcutaneous certolizumab pegol (400 mg at weeks 0, 2, and 4 followed by 200 mg or 400 mg every 2 weeks) plus MTX versus placebo plus MTX for 24 weeks in patients with active RA receiving long-term MTX therapy. Among the 982 patients enrolled in RAPID 1, at week 24 the ACR20 response rates using nonresponder imputation for the

certolizumab pegol 200-mg and 400-mg groups were 58.8% and 60.8%, respectively, compared with 13.6% for the placebo group. Differences in ACR20 response rates in certolizumab pegol–treated versus placebo-treated patients were significant at week 1 and were sustained to week 52 ($P < .001$). The trial also showed that the drug improved physical function as early as week 1 and slowed mean radiographic progression from baseline by week 52, with an increase of 0.4 Sharp units in those receiving 200 mg certolizumab pegol and 0.2 Sharp units in those receiving 400 mg, compared with 2.8 Sharp units in placebo-treated patients ($P < .001$). Neither RAPID 1 nor RAPID 2 showed any advantage for 400 mg over 200 mg certolizumab pegol over 52 weeks after induction with 400 mg.

FAST4WARD was a 24-week randomized, double-blind, placebo-controlled study evaluating certolizumab pegol as monotherapy in 220 patients in whom treatment with one or more DMARDs had previously failed.⁵¹ The patients were randomly assigned to receive subcutaneous certolizumab pegol 400 mg ($n = 111$) or placebo ($n = 109$) every 4 weeks. The primary endpoint of achievement of ACR20 criteria at week 24 was reached by 45.5% of the certolizumab-treated group and 9.3% of the placebo-treated group ($P < .001$). Differences between the certolizumab pegol group and the placebo group in the ACR20 response rate were statistically significant as early as week 1 through to week 24 ($P < .001$). Significant improvements in ACR50, ACR components, DAS28(ESR)-3, and all patient-reported outcomes were also observed early in those treated with certolizumab pegol and were sustained throughout the study.

GOLIMUMAB (SIMPONI)

Golimumab was first approved for use in the treatment of RA, PsA, and AS in 2009.

Pharmacology

Golimumab is a fully human monoclonal antibody derived from TNF-immunized transgenic mice engineered to express human IgG. Its molecular characteristics include amino acid sequences that match those of human

germline IgG1, high affinity and neutralization capacity for human TNF- α , conformational stability, and high solubility. Golimumab is dosed every 4 weeks.⁵²

Clinical efficacy of golimumab in rheumatoid arthritis

Golimumab has been studied in both intravenous and subcutaneous formulations but currently is available only for subcutaneous use. Phase 3 RA studies have been reported in three important populations: MTX-naïve patients (GO-BEFORE), patients with active RA despite ongoing treatment with MTX (GO-FORWARD), and patients in whom previous anti-TNF treatment was ineffective (GO-AFTER). Patients receiving subcutaneous injections of golimumab 50 mg or 100 mg every 4 weeks and MTX weekly experienced significant improvements in signs and symptoms and physical function and decrease in disease activity.

In the GO-BEFORE study golimumab was administered once every 4 weeks by subcutaneous injection; MTX-naïve patients with active RA received either golimumab 100 mg alone, golimumab 50 mg or 100 mg in combination with MTX, or MTX alone. When data for three patients who did not receive the study drug but were included in the analysis as nonresponders were included, the primary endpoint, achievement of ACR50 criteria by intent-to-treat analysis, was not reached. However, when data for these three patients who did not receive golimumab were excluded, a modified intent-to-treat analysis showed that the proportion of patients achieving ACR50 criteria was statistically higher in those receiving golimumab 50 mg every 4 weeks plus MTX than in those receiving MTX alone.⁵³

In the GO-FORWARD study, 50-mg and 100-mg doses of golimumab were examined in patients whose disease was active despite ongoing treatment with MTX.⁵⁴ At week 14, 55% of patients receiving golimumab 50 mg plus MTX and 56% receiving golimumab 100 mg plus MTX achieved at least 20% improvement in signs and symptoms of RA (ACR20), compared with 33% of patients receiving placebo and MTX ($P < .01$ and $P < .001$, respectively). Improvements were seen as early as the first clinical assessment, which was 4 weeks after the first golimumab injection, and generally increased over time. At 24 weeks, 68% of patients in the golimumab 50-mg dosing group and 72% of patients receiving golimumab 100 mg experienced clinically relevant improvement in physical function compared with 39% of patients receiving placebo plus MTX ($P < .0001$).

GO-AFTER was the first large phase 3 randomized, double-blind, placebo-controlled trial to test the efficacy of anti-TNF switching in patients in whom the first anti-TNF agent failed.⁵⁵ Four hundred sixty-one patients who had previously received at least one anti-TNF agent, among whom 25% ($n = 115$) had been treated with two therapies and 9% ($n = 43$) with three, were enrolled in this study. Discontinuation of previous anti-TNF therapy was due to lack of efficacy (58%), intolerance (17%), or other reasons (40%). Patients received subcutaneous placebo, golimumab 50 mg, or golimumab 100 mg every 4 weeks. At baseline, 66% of patients were receiving MTX, 5% were receiving sulfasalazine, and 7% were receiving hydroxychloroquine. Among patients who discontinued a previous anti-TNF because of lack of efficacy, 35.7% and 42.7% of patients in the golimumab 50-mg and 100-mg groups, respectively, achieved ACR20 criteria at week 14 compared with 17.7% in the placebo group.

PHARMACOECONOMIC CONSIDERATIONS

Although the addition of TNF inhibitors has significantly impacted the lives of hundreds of thousands of patients worldwide, the addition of these agents to the arsenal of standard antirheumatic therapy has dramatically increased the cost of care in RA. The cost of having a chronic inflammatory disease is often overlooked in these deliberations. For example, in reaching their conclusions about the cost effectiveness of biologic anti-TNFs in the United Kingdom, NICE does not take into account the broader societal implications of the underlying condition such as loss of employment, loss of work productivity, the need for state benefits, and other indirect costs. There is a growing body of data confirming the substantial cost implications of autoimmune rheumatic diseases. For the TNF inhibitors, the notable clinical efficacy observed needs to be factored into a comprehensive assessment of their value. Results from a number of studies have begun to make a compelling case that these agents may have an incremental cost effectiveness within the range of currently accepted medical interventions. Pharmacoeconomic considerations are likely to remain a central factor affecting the use of novel therapies in rheumatology and other specialties. These considerations have led to several recent controlled trials addressing the feasibility of withdrawing TNF inhibitors in patients who achieve disease control. In a Japanese

study population, 9 of 56 patients whose RA was in remission after at least 24 weeks of infliximab therapy maintained remission for 1 year after discontinuation of the biologic; two showed no radiographic progression.⁵⁶ In the Optimal Protocol for Treatment Initiation with MTX and Adalimumab Combination Therapy in Patients with Early Rheumatoid Arthritis (OPTIMA) study, 926 patients with early RA received either MTX or MTX plus adalimumab.⁵⁷ At 24 weeks, patients who achieved low disease activity while receiving combination therapy were randomly reassigned, in a double-blinded manner, to continue the same treatment or withdraw adalimumab. Of those who discontinued adalimumab, 57% reached the composite endpoint of low disease activity with no radiographic progression after an additional year of therapy. Radiographic nonprogression was seen in 89.3% of those who continued adalimumab and 80.6% of those who did not.⁵⁸ In the PRESERVE study (a prospective, randomized etanercept study to evaluate reduced-dose etanercept 25 mg plus MTX versus full-dose etanercept 50 mg plus MTX versus MTX alone in patients with moderate RA), 604 patients received weekly etanercept in addition to background MTX. At 9 months, those with low disease activity either discontinued etanercept, continued etanercept at 50 mg/wk, or received a lower etanercept dose of 25 mg/wk in a double-blind study.⁵⁹ Over the next year, low disease activity was maintained in the majority of those who continued etanercept (82.6% of the 50-mg group, 79.1% of the 25-mg group), but in only 42.6% of those who discontinued etanercept. The mean change in modified total Sharp score was significantly greater in those discontinuing etanercept than in those continuing it (0.06 units/yr at the 50-mg dose, 0.5 units/yr at the 25-mg dose, and 0.6 units/yr without etanercept).

EXPANDED INDICATIONS

TNF- α inhibitors have been approved for use in juvenile arthritis, moderate to severe RA, early RA, PsA, psoriasis, AS, Crohn disease, pediatric Crohn disease, and ulcerative colitis. This approval is particularly important for PsA, spondyloarthritis, and AS (Box 63.4, Table 63.5) in which traditional DMARDs have been proven ineffective or potentially toxic. However, exploratory clinical trial results involving other disorders thought to be TNF mediated (e.g., multiple sclerosis, congestive heart failure, sarcoidosis, anti-neutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis) have generally been disappointing.

Ankylosing spondylitis

TNF inhibitors reproducibly induce substantial improvements in the signs and symptoms of AS and are significantly superior to placebo treatment.⁶⁰ Clinical response, as measured by ASAS20 and BASDAI 50 outcomes, appears comparable for all three agents, and a high-level response, defined as *partial remission*, may be seen. All TNF inhibitors improve spinal mobility measures, with the greatest changes noted in the cervical spine (occiput to wall measurement) and the least noted in the lumbar spine (Schober test).

Nonetheless, all AS patients appear to experience flare on discontinuation of therapy, with the mean time to flare ranging from 6 weeks with etanercept to 17.5 weeks with infliximab. Continuous therapy with TNF

BOX 63.4 INTERNATIONAL ASAS CONSENSUS STATEMENT ON THE USE OF TUMOR NECROSIS FACTOR INHIBITORS IN ANKYLOSING SPONDYLITIS

- Patients should meet modified New York criteria for AS.
- Active disease of longer than 4 weeks. Disease activity is defined as BASDAI greater than 40 (0 to 100).
- All patients should have had adequate therapeutic trials of at least two NSAIDs.
- Patients with pure axial manifestations do not have to take DMARDs before anti-TNF treatment can be started.
- Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate.
- Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine.
- Patients with symptomatic enthesitis must have failed appropriate local treatment.

AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

From Braun J, Davis J, Dougados M, et al. First update of the International ASAS consensus statement for the use of anti-TNF agents with ankylosing spondylitis. *Ann Rheum Dis* 2006;65:316-20. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;70:896-904.

TABLE 63.5 Use of tumor necrosis factor (TNF) inhibition in orphan disorders

TNF inhibitor use: unapproved indications and orphan use	
Large prospective, randomized, controlled trials or meta-analyses	
Benefits shown	Ineffective/equivocal findings
Anterior uveitis	Etanercept in ANCA-associated granulomatous vasculitis Sjögren syndrome
Limited reports of clinical benefits* Uncertain/equivocal benefits reported†	
Reactive/undifferentiated arthritis	Autoimmune inner ear disease
Pustular psoriasis	Sarcoidosis: pulmonary, ocular, resistant
Acrodermatitis continua of Hallopeau	Chronic obstructive pulmonary disease
Psoriatic onychopachydermoperiostitis	Asthma
Pyoderma gangrenosum	Aphthous stomatitis
Pemphigus	Sneddon-Wilkinson disease
SAPHO syndrome	Eosinophilic fasciitis
Hepatitis C virus infection	Panniculitis
Constrictive pericarditis	Eosinophilic fasciitis
Multicentric reticulohistiocytosis	Necrobiosis lipoidica diabetorum
Recurrent ovarian cancer	Hidradenitis suppurativa
Graft-versus-host disease	Idiopathic pulmonary fibrosis
Polyarteritis nodosa	Inclusion body myositis
Takayasu arteritis	Dermatomyositis
Behçet syndrome (ocular more than skin)	Polymyositis
Adult-onset Still disease	Scleroderma
Systemic juvenile idiopathic arthritis	Recalcitrant hand pompholyx
TNF receptor–associated periodic	Myelodysplastic syndrome (TRAPS)
Hyperimmunoglobulinemia D syndrome	Sciatica
PAPA syndrome	Discogenic spinal pain
Orbital myositis	Infertility
Amyloidosis	Endometriosis
ANCA-associated granulomatous vasculitis	Pulmonary tuberculosis
	Systemic lupus erythematosus
*Limited benefit: >1 positive, anecdotal, or uncontrolled report of benefit. †Uncertain/equivocal benefit: single limited and uncontrolled report of benefit or several negative or several conflicting reports. ANCA, antineutrophil cytoplasmic antibody.	

inhibitors will likely be necessary to maintain clinical benefit. TNF inhibitors also improve the quality of life among treated AS patients and may decrease extraarticular inflammatory involvement in some patients. In a systematic review that included data from randomized controlled trials and open-label experience, flares of anterior uveitis occurred less frequently with TNF inhibitor therapy (6.8 per 100 patient-years) compared with placebo (15.6 per 100 patient-years).⁶¹

MRI studies of AS patients treated with TNF inhibitors have shown attenuation of spinal inflammation.⁶⁰ Although suppression of inflammation was maintained for up to 2 years, it was not completely eliminated in most patients. However, TNF blockade does not prevent radiographic ankylosis over 2 years,⁶²⁻⁶⁴ although a recent study suggests that longer-term treatment (8 years) may reduce radiographic progression.⁶⁵ Guidelines for TNF inhibitor use in AS have been developed by an international group of rheumatologists (see Box 63.4).

Psoriatic arthritis

TNF inhibitors are effective in treating both the skin and joint disease (peripheral and spinal) in PsA. TNF inhibitor therapy also improves functional status, quality of life, dactylitis, and enthesitis,^{60,66,67} and diminishes the progression of radiographic peripheral joint disease in PsA.⁶⁰

Although improvement in cutaneous disease was seen in most trials of TNF inhibitor in PsA, these patients often had less baseline cutaneous

involvement (as measured by the Psoriasis Activity Severity Index) compared with those in the psoriasis trials. Although all TNF inhibitors tested ameliorate cutaneous disease and peripheral arthritis, the magnitude of improvement in skin disease appears to be greater with the monoclonal antibodies (infliximab, golimumab, and adalimumab) than with the soluble receptor construct (etanercept). Whether this difference relates to dosing, different mechanisms of action, or other factors, remains to be defined.

Other orphan disorders

The use of TNF inhibitors has rapidly spread to a growing list of uncommonly encountered inflammatory disorders (see Table 63.5). Reports of their usefulness in these “orphan” disorders are limited to investigator-initiated, single-center, open-label, and uncontrolled trials with few treated patients. Many of these reports have been presented only in abstract form and had not appeared in peer-reviewed publications. Moreover, assessment of outcomes suffers from the lack of standardized and validated measures. Table 63.5 lists those conditions in which TNF blockade has been attempted, has succeeded, or has failed.

Granulomatous disease

TNF-α plays a pivotal role in granuloma formation and stabilization, by promoting the differentiation of epithelioid macrophages to form granulomas capable of sequestering infected cells. For these reasons, anti-TNF therapy was postulated to be effective in diseases characterized by granulomatous inflammation. Although early uncontrolled reports have shown some therapeutic success in these disorders, subsequent research has undermined these as potential indications.

Antineutrophil cytoplasmic antibody–associated granulomatous vasculitis

Uncontrolled exploratory trials have shown that the addition of infliximab or etanercept lowers Birmingham Vasculitis Activity Scores or induces remission in granulomatous vasculitis.⁶⁸ Nonetheless, the efficacy of anti-TNF therapy in ANCA-associated granulomatous vasculitis was questioned when a large (n = 180 patients), 9-month trial of etanercept versus placebo in patients with active ANCA-associated granulomatous vasculitis failed to show any benefit of adding etanercept to background therapy and was associated with an increased number of malignancies compared with placebo treatment.^{69,70}

Giant cell arteritis

Despite anecdotal case reports of benefit of TNF inhibition in giant cell arteritis,⁷¹ an interim analysis of data from a controlled trial failed to show any benefit in 44 corticosteroid-treated patients who received either infliximab (5 mg/kg) or placebo. Relapse rates and rates of steroid reduction were the same in both groups after 54 weeks of observation.⁷²

Polymyalgia rheumatica

Open-label reports have suggested that infliximab may be effective in polymyalgia rheumatica. However, a 22-week placebo-controlled trial involving 51 consecutively treated patients with polymyalgia rheumatica failed to show any benefit of infliximab over placebo.⁷³

Sarcoidosis

Anecdotal reports suggested the efficacy of infliximab, etanercept, and adalimumab in sarcoidosis.⁷⁴⁻⁷⁶ Most patients showing a response were treated with infliximab and had extrapulmonary manifestations of sarcoidosis (skin [lupus pernio], ocular [uveitis], joint, or bone). A small, placebo-controlled trial in patients with ocular sarcoid failed to show any benefit of infliximab over placebo.⁷⁷ A 30-patient, prospective, open-label trial of etanercept in stage II pulmonary sarcoid produced negative results.⁷⁸ A large placebo-controlled trial showed modest but significant improvement in chronic pulmonary sarcoidosis patients treated with infliximab.⁷⁹

Pyoderma gangrenosum

Rapid resolution^{79a} of pyoderma gangrenosum lesions using single or multiple doses of infliximab 5 mg/kg (given at weeks 0, 2, and 6) has been observed. Continued therapy and occasional dose escalation were necessary to maintain control or remission in some of these patients.

Takayasu arteritis

There are limited reports of favorable outcomes when TNF blockade is used to treat Takayasu arteritis, a large vessel vasculitis. Open-label uncontrolled studies claimed efficacy in patients who had active disease despite

treatment with corticosteroids and MTX. All uniformly claimed amelioration of disease and a corticosteroid-sparing effect. Limited numbers and potential positive reporting bias should temper enthusiasm until controlled trials are done.

Inflammatory eye disease/uveitis

In juvenile arthritis and spondyloarthritis, joint indices responded well to anti-TNF therapy but variable ocular benefits were seen. A meta-analysis of AS trials using TNF inhibitors studied the pretreatment prevalence and posttreatment flares of anterior uveitis.⁶¹ The frequency of uveitis flares was 15.6 per 100 patient-years in placebo-treated patients and 6.8 per 100 patient-years in those receiving etanercept or infliximab. Nonetheless, these trials recorded several instances of new-onset anterior uveitis in patients while receiving etanercept or infliximab. Uncontrolled reports have claimed TNF inhibition also to be effective in the management of noninfectious refractory posterior uveitis.

Behçet syndrome

Anecdotal reports of the use of TNF inhibitors (primarily infliximab) in Behçet syndrome have suggested therapeutic benefits in difficult cases. In a 40-patient, placebo-controlled, 4-week trial, etanercept lessened the frequency of mucocutaneous manifestations in patients with Behçet syndrome.⁸⁰

Sjögren syndrome

A double-blind, randomized, placebo-controlled trial of infliximab failed to show any improvement in dryness, joint pain, fatigue, salivary flow rate, Schirmer test results, or CRP levels in patients with Sjögren syndrome.⁸¹ Similar negative results were seen in a placebo-controlled study of etanercept use in Sjögren syndrome patients.⁸² These data suggest that TNF inhibition is not an effective treatment for Sjögren syndrome.

Chronic lung disease

There have been uncontrolled reports of TNF blockade in patients with interstitial pneumonitis, but a placebo-controlled study failed to demonstrate efficacy in patients with chronic obstructive pulmonary disease (COPD) treated with infliximab.⁸³ TNF blockade in refractory asthma is not efficacious.^{84,85} There are rare reports of new-onset asthmatic flares, pulmonary infiltrates, granulomas, and fibrosing alveolitis in patients receiving etanercept, infliximab, or adalimumab.

Hepatitis B and C

Elevated TNF levels have been demonstrated in patients with hepatitis C. Hence a pathogenic role for TNF in hepatitis C virus (HCV) infection has been suggested but not clarified. Retrospective, open-label, prospective studies have not demonstrated worsening of hepatic enzyme levels or viral load titers with TNF inhibition. The potential adjuvant effect of etanercept therapy, combined with interferon and ribavirin, was studied in 50 nonarthritic patients with chronic HCV infection.⁸⁶ This 6-month, double-blind, placebo-controlled trial showed lower viral loads, normal hepatic enzyme levels, and fewer adverse events when etanercept was combined with this antiviral regimen. These data suggest that TNF inhibition may be used cautiously in HCV-infected patients with markedly limited treatment alternatives.

A rise in reports of hepatitis B virus (HBV) reactivation following TNF inhibition has led to the recommendation that patients be screened for HBV infection before use of anti-TNF therapy. For hepatitis B surface antigen (HBsAg) carriers, either anti-HBV treatment or prophylaxis is mandatory before anti-TNF therapy to prevent hepatitis reactivation. By contrast, TNF inhibition can be used with caution in HBsAg-negative patients who are nonetheless seropositive for antibodies to hepatitis B core antigen, although careful monitoring is recommended.⁸⁷

BASELESS USE OF TUMOR NECROSIS FACTOR INHIBITORS

The popularity of TNF blockade has often led to its application in a variety of conditions presumed to have an underlying inflammatory or immune-mediated pathogenesis. Table 63.5 lists many conditions for which the benefits of TNF inhibition are uncertain and unproven.

p55 TUMOR NECROSIS FACTOR INHIBITORS

Three different p55-directed TNF inhibitors have been studied but none is currently approved or actively under investigation for inflammatory indications. Onercept is a recombinant monomeric soluble TNFR1 (p55), lenercept is a recombinant fusion protein with two p55 soluble TNFRs fused to the Fc portion of IgG1, and pegsunercept is a recombinant monomeric p55 soluble TNFR with PEG linked to enhance its half-life. Reasons for the deferment of development of these p55 inhibitors are unclear but may relate to clinical trial results, toxicity concerns, or pharmacokinetic issues.

Tumor necrosis factor inhibitors in early rheumatoid arthritis

Numerous studies have confirmed the efficacy and safety of TNF inhibition in patients with new-onset RA^{23,31,42} and have led to FDA approval for use (as the initial DMARD) in patients with new-onset RA. Although entry into these early RA trials was limited to patients with a disease duration of less than 3 years, patients had a mean duration of disease of 6 to 12 months. Hence several large, randomized, controlled trials in early RA (ERA, ASPIRE, PREMIER, GO-BEFORE, BeST) have taught us that (1) ACR20 responses with TNF inhibitors are equivalent to, or in some cases better than, those with MTX; (2) the best responses (DAS remission, ACR70 response) are achieved when TNF inhibitors are combined with MTX; (3) TNF inhibitors are superior to MTX in halting radiographic progression (especially when combined with MTX); and (4) the safety of TNF inhibition in early RA appears to be equal to, or better than, that seen in established or severe RA. Due to cost issues it is generally accepted that patients with new-onset RA should initially receive MTX as their primary DMARD. TNF inhibition should be employed early when MTX cannot be used and/or when the patient is at high risk of severe RA or when patients are not fully responsive to MTX therapy.

Tumor necrosis factor inhibitors in children

The use of TNF inhibition in children with juvenile arthritis has been limited by the availability of few studies. Currently, only etanercept is approved for use in patients with active polyarticular juvenile arthritis after an inadequate response to MTX or other DMARD therapy. The safety and efficacy of etanercept was studied in 69 patients with polyarticular juvenile arthritis unresponsive to MTX.⁸⁸ Patients (4 to 17 years of age) received 0.4 mg/kg twice weekly for 90 days and showed a 74% response rate. After 90 days, patients who showed a response were randomly assigned to receive placebo or etanercept for 4 months and flare rates were assessed. The time to flare was much shorter for placebo-treated patients (28 days) than for those receiving etanercept (more than 116 days).

Tumor necrosis factor inhibitors in the elderly

Drug development pharmacokinetic studies of etanercept, infliximab, and adalimumab failed to show any influence of age or gender. During infliximab clinical trials in RA, efficacy and safety in 181 geriatric patients (older than 65 years) were similar to those in younger patients; however, both older infliximab-treated patients and older control patients exhibited more serious adverse events than did younger patients. Etanercept has been studied in older patients with RA and PsA in clinical trials demonstrating no difference in efficacy or safety between elderly and younger patients.

Because advancing age appears to be a risk factor for serious infection, TNF inhibitors should be used with caution in geriatric patients, especially those with comorbidities, debility, and a history of serious infection.

SAFETY OF ANTI-TUMOR NECROSIS FACTOR THERAPY

Advances in treatment afforded by TNF blockade have been tempered by safety concerns, many of which were reported in the controlled clinical trials. These clinical trials established the most common adverse events among thousands of patients who were selected because they had few or no comorbidities and met limitations on age, disease status, and background therapies. Identifying a real-world spectrum of TNF inhibitor-related safety concerns depends on a variety of pharmacovigilance efforts (e.g., open-label extension trials, phase 4 trials, postmarketing surveillance, passive physician and patient reports, disease databases and registries) involving less select populations with comorbidities and variable drug dosing and

background medications. In the postmarketing era, information on the safety of TNF inhibitors has accumulated with more than 15 years of experience and over 2 million patients treated worldwide. Although pharmacovigilance data may be limited by event underreporting, unverified diagnoses, duplicate reports, confounding comorbidities or medications, and uncertain temporal associations or causality, they offer our most comprehensive view of TNF inhibitor safety.

Box 63.3 details the relative contraindications to the use of TNF inhibitors. Moreover, the use of these agents in unapproved, rare, or orphan conditions may be associated with unexpected or unsatisfactory outcomes. Although many safety issues (e.g., the occurrence of tuberculosis, opportunistic infection, lupus) might have been predicted on the basis of preclinical studies, the development of unanticipated adverse events in newly exposed patient populations (e.g., demyelinating disease, heart failure, cytopenia) should temper inappropriate and widespread use of TNF inhibitors.

One indication of both efficacy and safety is the durability of an agent (e.g., how long a patient continues to receive such therapy). In randomized, placebo-controlled clinical trials, patients receiving TNF inhibitors consistently demonstrated higher study completion rates and lower dropout rates than those for placebo-treated or matched controls. Real-world observational studies have shown that the durability of the TNF inhibitors compares favorably with that of MTX, so that 65% to 80% of RA patients are still taking their TNF inhibitors 1 year after drug initiation.^{22,89} Dropouts for safety account for approximately 30% to 50% of those who discontinue TNF inhibitor therapy. Several studies consistently show the dropout rate for these agents to be nearly 10% to 15% per year in the first 2 years and roughly 10% per annum thereafter.

Infusion reactions

Infusion reactions to these parenterally administered agents are among the most common of adverse effects. Clinical trials reported that up to 20% of infliximab-treated patients experience an infusion reaction. However, fewer than 1% of infliximab-treated patients develop a serious infusion-related reaction, and only 2.5% of reactions are the cause of drug cessation. Most infliximab infusion reactions occur during infusion or within 2 hours after infusion. Common complaints include headache (20%), nausea (15%), urticaria, pruritus, rash, flushing, fever, chills, tachycardia, and dyspnea. In many, infusion reactions may be the result of a rapid infusion rate. The infusion reactions are usually transient, are rarely severe, and typically can be controlled by slowing the rate of infusion or treating with acetaminophen, nonsedating antihistamines, or short-acting corticosteroids. Premedication with the aforementioned agents is not routinely required but may be necessary in those who exhibit infusion reactions.

Rarely, severe or anaphylactic reactions occur in which findings of chest tightness, bronchospasm, hypotension, diaphoresis, anaphylaxis, or a feeling of impending doom may occur. In these individuals, infliximab therapy should be halted and supportive or emergent care administered until the patient's condition is stabilized. For these reasons infliximab infusions should be delivered only with appropriately trained medical personnel in attendance and with ready access to parenteral corticosteroids, diphenhydramine, and epinephrine.

Infusion reactions are twofold to threefold more likely if HACA are present. The immunogenicity of infliximab can be mitigated by concomitant MTX use or administration of higher infliximab doses. Experience with intermittent treatment of Crohn disease has shown reactions to be more likely when infliximab therapy is intermittent and suspended. In these patients, 25% developed delayed reactions (3 to 12 days after infusion) with symptoms of myalgia, arthralgia, fever, chills, rash, urticaria, edema, dysphagia, and sore throat.

Injection site reactions

During the RA adalimumab and etanercept clinical trials, cutaneous injection site reactions were seen in 20% and 37% of patients, respectively. However, these are less frequent in practice and rarely require drug discontinuation. Injection site reactions are usually mild or moderate and resolve within 7 days. They are most common during the first 4 to 8 weeks of use and do not correlate with drug dose, frequency of administration, or the presence of neutralizing antibodies. Patients may describe dysesthesia, bruising, erythema, pruritus, or urticaria at administration sites. Interestingly, in the TEMPO (etanercept) trial, fewer injection site reactions were observed in the MTX plus TNF inhibitor group than in those receiving the TNF inhibitor alone.³³ In the placebo-controlled trials of certolizumab, 6.4% of patients treated with certolizumab developed injection site reactions, compared with 6.5% of patients receiving placebo. In golimumab phase 3

trials through week 16 in RA, PsA, and AS, 5.8% of golimumab-treated patients had injection site reactions compared with 2.2% of control patients. In both the certolizumab and golimumab trials, the incidence of injection site pain was low at 1.5% or fewer patients, with no cases leading to withdrawal.

Infectious risk

In otherwise healthy individuals, TNF plays an important role in defense against infections, especially infection with intracellular organisms. In the context of infection, TNF enhances endothelial cell activation at the site of involvement, promotes inflammatory cell recruitment, and has a procoagulant role in limiting the spread of infection. It also increases the ability of activated macrophages to phagocytose and kill mycobacteria. Concerns that modulation of physiologic or excess TNF levels by specific inhibitors might promote infectious complications were heightened because of animal studies demonstrating the fatal effects of TNF inhibition in models of sepsis or endotoxic shock and the protective role of TNF with respect to opportunistic infections such as those caused by *Mycobacterium tuberculosis*, *Candida*, *Histoplasma*, *Leishmania*, and malarial organisms. Several early trials of TNF inhibition as a therapy for sepsis failed to show any consistent benefit or hazard to TNF neutralization.

RA patients have approximately twice the mortality rate of the general population, and serious infection (leading to hospital admission, intravenous antibiotic administration, or death) is a major contributing factor. In considering whether anti-TNF biologics raise infection risks, the higher background infection rates in RA need to be taken into account. Similarly, the influence of concomitantly administered drugs must also be considered. For example, a review of data from a large patient registry in the United States encompassing over 16,000 patients observed the risk of pneumonia requiring hospitalization to be 1.7 times higher in patients receiving corticosteroids.⁹⁰ Prednisolone at dosages of only 5 mg/day or less gave a hazard ratio of 1.4 (95% confidence interval [CI], 1.1 to 1.6).

Controlled trials have produced conflicting data with respect to the risk of serious infectious complications, and it must be remembered that registration clinical trials systematically exclude patients with significant comorbidities, so that the results may not be generalizable to RA patients as a whole. In the etanercept, infliximab, and adalimumab clinical trials, common nonserious infections (e.g., upper respiratory tract infections, bronchitis, sinusitis, pharyngitis, urinary tract infections) were seen in 20% to 37% of patients. Anti-TNF therapy was not suspended or stopped for these nonserious infections and patients responded well to either observation or symptomatic therapy.

Serious infectious events (e.g., pneumonia, cellulitis, joint infections) or death from infection were infrequently reported in the clinical trials before FDA approval and, overall, were not observed at a rate greater than that seen in placebo-treated controls. In the randomized placebo-controlled trials of all three TNF target agents (encompassing 6303 patients followed for 6 to 12 months), the rate of serious infectious events ranged from three to four events per 100 patient-years of therapy compared with two events per 100 patient-years in placebo-treated patients. Although many trials have shown no increase in serious infections (compared with placebo or active controls), several trials have shown higher rates of serious infections. For example, serious infections in the ATTRACT and ASPIRE trials were seen in 5.4% of infliximab/MTX-treated patients and 3.4% of patients treated with MTX alone.³⁹⁻⁴² Pneumonia was seen in 1.7% of infliximab-treated and 0.3% of placebo-treated patients (Table 63.6). Similarly, the DE019 trial found more serious infections in the adalimumab/MTX group (3.8%) compared with the MTX/placebo group (0.5%).²⁵ The PREMIER trial reported different serious infection rates in patients treated with MTX, adalimumab, and the combination of MTX/adalimumab (1.6, 0.7, and 2.9 events per 100 patient-years, respectively).²³ Postmarketing studies have also shown mixed results, with either equal or increased infection rates for TNF inhibitors compared with DMARD controls.⁹¹⁻⁹³ Reported serious infections include pneumonia, cellulitis, septic arthritis, prosthetic joint infections, postsurgical or wound infection, diverticulitis, pyelonephritis, abscess, and sepsis.

A meta-analysis of selected clinical trials of infliximab, etanercept, and adalimumab reported a pooled odds ratio of 2.0 for serious infections in patients taking anti-TNF antibodies compared with the control groups.⁹² As in the case of controlled trials, observational studies have produced conflicting data with respect to the risk of serious infectious complications with TNF inhibitors, with some studies suggesting increased serious infection rates and others no difference compared with groups not given TNF inhibitors. These apparent discrepancies may be due to many factors, including the variation in background rate of infection in different populations and locations, the duration of exposure to TNF inhibition,^{93,94} confounding

TABLE 63.6**Frequency of serious adverse events with the tumor necrosis factor (TNF) inhibitors infliximab, etanercept, and adalimumab**

	Infliximab*	Etanercept	Adalimumab
Pneumonia	1.7%*	<1%*	0.92%†
Tuberculosis	0.4%*	0.03%‡	0.23%†
Cytopenia§	0.9%-1.4%†	ND	0.08/100 patient-yr†
Lymphoma	0.31%‡	0.26%‡	0.41%†
Demyelinating disorders	ND	ND	0.08%†
Drug-induced lupus	0.2%	ND	0.05%†
Congestive heart failure	0.2%‡	0.06%‡	0.1%‡
Transaminitis (less than threefold)	34%‡	ND	ND
Hepatic failure	0.006†	ND	ND

*Package insert data from pivotal randomized clinical trial results.

†2004 Postmarketing data reported (data provided by manufacturer).

‡Data from 2003 Food and Drug Administration Arthritis Advisory Committee review of TNF inhibitor safety.

§Cytopenia includes leukopenia, neutropenia, and thrombocytopenia.

ND, no data.

concomitant therapy, and differences in disease severity between anti-TNF-treated and comparison cohorts. Another factor may relate to the biology of TNF inhibition. Evidence suggests that normalization of immune disequilibrium in RA may restore physiologic immune responses. For example, infliximab treatment in RA results in significant increases in circulating regulatory T cells and reversal of their anergic phenotype.⁹⁵ Thus it is possible that patients with well-controlled inflammation become less susceptible to infection than those with partially controlled inflammation or oversuppression of TNF.⁹⁶

A review of infectious risk data emerging from observational studies and the various national registries might suggest a variable level of risk. But when the incidence rate ratios are plotted against the duration of follow-up, a clear and consistent pattern emerges suggesting that risk of infectious complications is highest during the initial period of exposure to an anti-TNF and tends to decline after 6 months of therapy.⁹⁴ In patients enrolled into the German biologics register RABBIT (etanercept, *n* = 512; infliximab, *n* = 346; DMARD control, *n* = 601), the reported relative risk of serious infections was 2.2 (95% CI, 0.9 to 5.4) for etanercept (64 per 1000 patient-years) and 2.1 (95% CI, 0.8 to 5.5) for infliximab (62 per 1000 patient-years) compared with patients taking DMARDs only (23 per 1000 patient-years).⁹⁷ Despite the lower confidence intervals overlapping with 1.0, these findings suggest a trend toward increased risk of serious infection. This risk was independent of RA severity or duration, rheumatoid factor seropositivity, concomitant steroid use, diabetes, and lung disease.

A retrospective U.S. study encompassing 3894 person-years of anti-TNF therapy and 4846 person-years of MTX therapy over a median of 17 months reported the adjusted risk of hospitalization caused by bacterial infection, which was 1.9-fold higher in patients receiving anti-TNF agents (4.2-fold higher in the first 6 months).⁹⁸ The Spanish registry showed a 1.6-fold increase in the rate of serious infection with TNF inhibition in an analysis of 2868 patient-years of anti-TNF drug therapy compared with 2433 patient-years of controls.⁹⁹ A case-control cohort study of 23,733 RA patients suggested a twofold increase in risk of all infections in patients taking TNF blockers (infliximab and etanercept).¹⁰⁰ However, because of the limited number of patients receiving anti-TNF therapy (*n* = 261), the confidence interval was wide. Another retrospective study of 709 RA patients reported an incidence of serious infections of 3.4 per 100 patient-years before anti-TNF treatment and 10.5 afterward treatment.¹⁰¹ A meta-analysis of observational studies that restricted inclusion to studies reporting adjusted incidence rate ratios reported the pooled adjusted risk from five cohort studies and two case-control studies to be 1.37 (95% CI, 1.18 to 1.60).¹⁰²

The British Society for Rheumatology Biologics Register (BSRBR) reported the observations of a national prospective observational study of 7664 RA patients treated with anti-TNF agents and 1354 treated with DMARDs. No increase in serious infections in total was observed in anti-TNF-treated patients compared with patients given conventional DMARDs.¹⁰³ The incidence of serious infections in the anti-TNF group was 53.2 per 1000 person-years versus 41.2 in the control group. However,

serious skin and soft tissue infections were more frequent in anti-TNF-treated patients (incidence risk ratio, 4.2). A total of 19 serious bacterial intracellular infections occurred, all in patients in the anti-TNF-treated cohort. An extended analysis found an increased adjusted incidence rate of serious infection (ratio, 4.6; 95% CI, 1.8 to 11.9) over the first 90 days after starting anti-TNF drugs compared with DMARD therapy.⁹³

Another study followed 686 patients for 52 weeks and found no difference in the prevalence of serious infections in those receiving MTX and etanercept in combination compared with those receiving either drug alone (about 4% for all groups).¹⁰⁴ In a large cohort of 16,788 patients followed over 3.5 years, no increase in pneumonia risk with anti-TNF treatment was observed.⁹⁰ In a retrospective study involving patients older than 65 years of age, 1900 patients receiving MTX and 469 receiving anti-TNF drugs were followed for 0.2 to 1.3 years,¹⁰⁵ and no increase in infection rate in the anti-TNF group was found.

Despite apparently contradictory findings with respect to the risk of infectious complications of anti-TNF therapy based on observational studies and registry data, a more detailed analysis of available data suggests a more coherent pattern of an increased risk shortly after treatment starts.⁹⁴ Importantly, an analysis of RABBIT data found that this apparent reduction of risk over time was due in part to the removal of patients at risk of infection from the exposed cohort.¹⁰⁶

Current prescribing guidelines caution against the use of TNF inhibitors in patients with active serious infections or in those with chronic or recurrent infections, and patients should be monitored for signs and symptoms of infection while receiving TNF inhibitors. Even in patients with severe rheumatoid disease activity, there may be a point at which infection risks associated with TNF blockade outweigh any potential benefits. Moreover, the infectious risk may be heightened in the presence of well-known risk factors, such as advanced age, debility, extreme inflammatory activity, corticosteroid use (especially at higher dosages), comorbidities, skin breakdown, and planned major surgery (e.g., joint replacement). Increasing data suggest that higher dosages of TNF inhibitors may also increase the risk of infection.^{39,96} Serious bacterial infections may therefore be averted by proper patient selection, proper dosing, and TNF inhibitor avoidance if numerous risk factors for infection are present. Lastly, the combination of anakinra and a TNF inhibitor should be avoided because both open-label and controlled trials showed no clinical benefit but demonstrated an increased risk of serious infections (7% and neutropenia (2%)).¹⁰⁷ Similarly, abatacept (CTLA-4-immunoglobulin) should not be combined with TNF inhibitor therapy because this combination also yielded higher rates of serious infections (5.8% vs. 1.9%) in a randomized clinical trial.¹⁰⁸

Guidelines for the prevention and management of infections, especially serious infections, are currently lacking. Patients experiencing mild to moderate upper respiratory tract infection, bronchitis, or sinusitis can be symptomatically managed or closely observed without drug cessation. However, patients demonstrating high fevers or other suspicious symptoms should undergo temporary drug suspension and further evaluation. TNF inhibitors should be stopped when patients have a serious infection, hospitalizable infection, or opportunistic infection and should not be restarted until adequate control has been achieved. Patients undergoing elective major surgery (e.g., joint replacement surgery) may also benefit from suspension of the TNF inhibitor before surgery for at least one dosing cycle (e.g., 7 days for etanercept, 14 days for adalimumab, 6 to 8 weeks for infliximab), provided such cessation does not induce a major inflammatory flare, but this suggestion is not evidence based because of the limited number of studies in this area. Although one study showed that RA patients receiving TNF inhibitors had a fivefold increased risk of serious infection after joint arthroplasty,¹⁰⁹ further research is necessary to determine how best to manage these patients.

Tuberculosis

TNF antagonist therapy can interfere with the host's ability to protect itself from mycobacterial infection. TNF plays an important role in the formation and maintenance of granulomas. Tuberculosis (TB) and other opportunistic infections have been associated with all currently marketed TNF blocking agents. Hence therapeutic inhibition of TNF augments the risk of reactivation of latent mycobacterial (or fungal) infection. Interestingly, 30% to 50% of such patients have extrapulmonary, miliary, or disseminated and nonpulmonary presentations of TB. Although the risk of TB is increased in all patients receiving TNF inhibitors, even greater rates are seen in populations from geographic regions in which TB is endemic.¹¹⁰ All sources that have compared the risk of TB in anti-TNF-exposed patients with that in a reference rheumatoid population have found increased risk. There is clear evidence from the BIOBADASER database that application of TB screening guidelines significantly reduced that risk. Nonetheless, the risk across

various observational cohorts is increased 2.4- to 8.7-fold compared with nonexposed RA patients.¹¹⁰⁻¹¹²

Although no cases of TB emerged in the etanercept clinical trials, post-marketing analyses demonstrated 38 confirmed cases of etanercept-associated TB worldwide in the first 150,000 patients treated through December 2002. For infliximab, 441 cases of infliximab-related TB were reported among 492,874 treated patients worldwide, whereas there were only 6 infliximab-related TB cases reported in the clinical trials. Ninety-seven percent of the infliximab-related cases occurred within 7 months of treatment initiation, with a median time to onset of 12 weeks. The incidence of TB in clinical trials of adalimumab was higher in early clinical trials when the dose of adalimumab was higher and no screening procedures were used or enforced. The incidence of TB dropped 85% when adalimumab dose was reduced and screening measures for latent TB infection (purified protein derivative tuberculin [PPD] test, chest radiograph) were required before therapy. In one study, RATIO, the odds ratios for TB reactivation relative to that for etanercept were 13.3 (95% CI, 2.6 to 69.0) for infliximab and 17.1 (95% CI, 3.6 to 80.6) for adalimumab.¹¹³ In the BSRBR study, incidence rate ratios of TB for infliximab and adalimumab compared with etanercept were 3.1 (95% CI, 1.0 to 9.5) and 4.2 (95% CI, 1.4 to 12.4), respectively.¹¹²

The increased risk and extrapulmonary presentations of TB with TNF blockade mandate screening, close follow-up, and ongoing clinical suspicion. The risk of development of TB with TNF antagonist use is significantly reduced with screening and appropriate monitoring. Two different data sets have shown the preventive value of screening before drug initiation. In the adalimumab clinical trials, a TB infection rate of 1.3 per 100 patient-years was decreased to less than 0.11 per 100 patient-years with mandated screening (PPD test in North America and chest radiographs in Europe). A Spanish study reported a reduction of nearly 80% in active TB cases once screening and treatment of latent TB was implemented.¹¹⁰

Current guidelines from the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society recommend PPD skin testing before initiation of TNF antagonist therapy. Physicians who prescribe any TNF antagonist therapy should educate their patients about the symptoms of TB.

The reaction to the tuberculin (PPD) skin test must be read within 48 to 72 hours by a health care professional and is considered positive if induration is greater than 5 mm. Patients previously vaccinated with bacille Calmette-Guérin (BCG) should also be screened with a tuberculin skin test. The use of controls is not recommended because up to one third of RA patients may be anergic. Chest radiography is not routinely performed but should be done in those with a positive tuberculin skin test result, recent or past exposure to TB, signs or symptoms of TB, or history of travel to high-risk endemic areas.¹¹⁴ If results of the PPD test are positive and the patient is without signs, symptoms, or chest radiographic evidence of active infection, treatment for latent TB should commence before or with anti-TNF therapy. CDC guidelines suggest that 9 months of isoniazid therapy are optimal, although 6 months of isoniazid or other alternative regimens also have proven efficacy.

The PPD test is of limited benefit in immunosuppressed individuals, who often fail to mount a delayed-type hypersensitivity reaction. In such patients, newer interferon- γ -releasing assays may be a more robust method for diagnosis of tuberculosis and assessment of latent TB.¹¹⁵ These interferon-releasing assays are not confounded by prior BCG vaccination or exposure to environmental mycobacteria. However, it should be noted that a negative test result does not exclude infection with nontuberculous mycobacteria species, which are usually considered benign contaminants but are nonetheless increasingly recognized to be associated with pulmonary disease in immunocompromised hosts (see Chapter 67).

Other opportunist infections

Patients taking TNF inhibitors should be considered at risk for opportunistic infections, including infection with atypical mycobacteria, *Mycobacterium avium intracellulare*, *Mycobacterium kansasii*, and *Mycobacterium marinum*. Fungal and other opportunistic infections, including histoplasmosis, pneumocystosis, aspergillosis, coccidioidomycosis, sporotrichosis, nocardiosis, listeriosis, and cytomegalovirus infection, have been observed with all TNF inhibitors. Because no reliable skin or serologic testing exists to screen for these infections, clinicians must closely monitor patients for symptoms or signs of opportunistic infections, especially in endemic regions (e.g., Europe, South America, Ohio River Valley, San Joaquin Valley). It should be noted that long-term prednisone therapy may also predispose to such infections.

Immunity against viral infections has some similarity with that against intracellular bacterial infections. An increased risk of herpes zoster

associated with TNF inhibition was noted in the RABBIT registry; the increased risk of severe herpes zoster was seen with the monoclonal antibodies but not with etanercept.¹¹⁶

Neoplasia and lymphoma

Numerous population-based studies have generally shown that RA patients have an increased risk of lymphoma but are not at increased risk of other malignancies (e.g., solid tumors) and may in fact be at a lower risk of adenocarcinoma of the colon, presumably because of the use of nonsteroidal antiinflammatory drugs or cyclooxygenase-2 inhibitors. An overall twofold to threefold increase in lymphoma (primarily non-Hodgkin) has been shown in RA population studies. The lymphoma risk appears to increase with age and increasing inflammatory disease activity. In a 2003 FDA analysis of this issue, six lymphomas were found among 6303 RA patients treated with TNF inhibitors in controlled clinical trials, but none was observed in placebo-treated patients. A total of 23 lymphomas were observed during drug development (9 with etanercept, 4 with infliximab, 10 with adalimumab), which yielded an increased standardized incidence ratio (relative risk) of 3.47, 6.35, and 5.42, respectively. However, the 95% confidence intervals for these standardized incidence ratios were particularly wide and overlapping, so that it was not possible to separate lymphoma risk related to drug use from that associated with active RA alone.

Thus lymphoma rates in RA patients taking TNF inhibitors are elevated, but, as judged by data reported from two sources, ARTIS¹¹⁷ and the NDBRD,¹¹⁸ there is no evidence that the risk of lymphoma is increased in patients taking TNF inhibitors compared with that in RA patients treated with classical DMARDs, since the point estimate was 1.16, although the 95% confidence interval was from 0.72 to 1.60, so a small effect cannot be excluded.¹¹⁹ Data from safety registries suggest that it is disease activity rather than TNF inhibition that may account for the observed increase in lymphoma rates associated with TNF blockade.^{120,121} However, there are reports indicating an increased lymphoma risk related to anti-TNF treatment.¹²² The lag time from TNF blocker exposure to the onset of lymphoma varied, but most cases occurred after 6 to 24 months of TNF therapy. Hodgkin lymphoma occurred in 15%; the remainder were non-Hodgkin lymphomas, usually of the diffuse, large, B-cell class. Follicular, mantle, MALT, and T-cell lymphomas were uncommonly observed.²⁴ These issues merit continued scrutiny in long-term population-based surveillance registries of RA patients receiving biologic and nonbiologic DMARD therapy to provide a clearer understanding of the risk of lymphoma. There have been reports of rare and fatal hepatosplenic T-cell lymphoma in pediatric Crohn disease patients receiving infliximab and generally azathioprine or 6-mercaptopurine. These malignancies have not been observed with adalimumab or etanercept.

In registry studies, no overall increase in malignancy risk has been reported in RA patients whether or not exposed to TNF inhibitors.¹²³ In a recent systematic literature review and meta-analysis, the pooled estimate for the risk of malignancy from six studies was 0.94 (95% CI, 0.84 to 1.05). There was no evidence that longer duration of exposure to TNF inhibitors increased the risk of malignancy. In patients with prior malignancies, there was a higher risk of a new or recurring malignancy, but this risk was not increased further by exposure to TNF inhibitors.¹¹⁹ However, another meta-analysis of studies of patients taking TNF inhibitors (limited to the monoclonal antibodies) showed more malignancies (0.8%) compared with the placebo-matched population (0.2%), with a pooled odds ratio of 3.3 compared with placebo-treated patients. The risks appear to be dose dependent, with those receiving high-dose therapy (defined as 6 mg/kg infliximab or more every 8 weeks or 40 mg adalimumab or more every other week) having the greatest risk (odds ratio, 4.3; 95% CI, 1.6 to 11.8); no important increased risk was seen below these dosages.⁹² The lower than expected rate of neoplasia in the placebo group has been questioned and may relate to the inaccuracies arising from a shorter duration of placebo and TNF inhibitor exposure. There have been other studies demonstrating a higher rate of solid tumors. A 9-month, 180-patient trial examining the use of etanercept in ANCA-associated granulomatous vasculitis revealed six solid tumors in the etanercept group and none in the placebo group.⁶⁹ All six of these patients had received cyclophosphamide, so it may be that the addition of cyclophosphamide to etanercept increases the risk of malignancy. Additionally, a trial of infliximab in patients with severe COPD demonstrated an excess of solid tumors among patients receiving the TNF inhibitor. These analyses suggest that rates of solid tumors may be increased in certain at-risk populations.

Results from several studies concur that patients treated with TNF inhibitors have a significantly increased risk of developing a nonmelanoma skin cancer (relative risk, 1.45; 95% CI, 1.15 to 1.85). Additionally, patients are at increased risk of developing melanoma, because the pooled estimate from

two studies was 1.79 (95% CI, 1.18 to 2.64). Many rheumatologists are now recommending annual skin evaluations for patients receiving anti-TNF therapy. The pooled estimate for the risk of lymphoma was 1.11 (95% CI, 0.70 to 1.61).¹¹⁹

Antibiologic antibody responses

Biologic anti-TNF agents are large foreign proteins and as such are potentially immunogenic, even when the primary amino acid sequence is fully human. The clinical relevance of antidrug antibodies has been controversial, but nonetheless their occurrence might be anticipated to reduce response to treatment, either by inhibiting the functional part of the molecule or by accelerating drug clearance owing to the formation of immune complexes, which might also give rise to hypersensitivity reactions. Approximately 3% of etanercept-treated patients develop antibodies to etanercept. In one study, antibodies to infliximab developed in 53%, 21%, and 7% of patients receiving 1, 3, or 10 mg/kg of drug, respectively.³⁹ RA trials of infliximab therapy with or without concomitant MTX treatment revealed that immunogenicity was decreased by concomitant administration of MTX, due perhaps in part to the increase in the half-life of infliximab associated with MTX use. A multicenter trial of infliximab therapy in Crohn disease revealed that the induction of these anti-infliximab antibodies might have contributed to hypersensitivity reactions in some patients who had been treated with this drug. Although antibodies to adalimumab develop in about 12% of patients, the rate is reduced to 1% with concurrent MTX treatment. Routine testing for antibodies to these anti-TNF constructs is not currently recommended because the assays have not been standardized. However, as methods for testing for antibiologic antibodies have improved, the clinical consequences have become more apparent. Of 272 outpatients with RA treated with adalimumab and followed for over 3 years, 28% developed antiadalimumab antibodies, which were associated with lower adalimumab concentration and a decreased likelihood of minimal disease activity or clinical remission.¹²⁴

Autoimmune responses

Although nearly 40% of RA patients have serum antinuclear antibodies (ANA), the prevalence of ANA positivity increases with the use of anti-TNF agents. The mechanisms underlying autoantibody induction are uncertain but may relate to a compensatory increase in IL-10 or interferon- α , both of which are inhibited by TNF. Both can increase B-cell activity and are increased in patients treated with anti-TNF therapy. Antibodies to double-stranded DNA (ds-DNA) have also been reported to develop in about 5% to 10% of treated RA patients with all anti-TNF therapies. However, few (0.2% to 0.4%) develop symptoms consistent with drug-induced lupus.¹²⁵ Findings of ANA or dsDNA seropositivity are poorly predictive of subsequent toxicity, and thus pretreatment or routine monitoring of autoantibody levels is not recommended.

The rare occurrence of drug-induced lupus has been associated with all TNF inhibitors. Such patients need not meet criteria for lupus but must manifest a lupus-specific feature with evidence of ANA or dsDNA positivity and resolution with drug cessation. During drug development, there were few reports of TNF inhibitor-related rashes (discoid lupus, subacute cutaneous lupus, hypersensitivity vasculitis), serositis, cytopenias, and polyarthritides. Several points about drug-induced lupus related to the TNF inhibitors are worth summarizing:

- Common skin findings include malar rash, palpable purpura, or a “sunburnt” rash.
- The new onset of an acute large and small joint polyarthritis in a patient with previously stable RA treated with a TNF inhibitor may be an indication of drug-induced lupus.
- Fever, serositis, and cytopenias are common.
- ANA or dsDNA positivity is required to consider the diagnosis.
- Diagnostic confirmation rests with resolution of symptoms upon drug cessation.

Demyelinating syndromes

Multiple sclerosis (MS), optic neuritis, and other forms of demyelinating neurologic dysfunction have been described with TNF inhibitor use. This includes new-onset optic neuritis, *de-novo* MS, recurrence or flare of MS, encephalitis, myelitis, Guillain-Barré syndrome,¹²⁶ chronic inflammatory demyelinating polyneuropathy, neuropathy, transverse myelitis, seizures, and leukoencephalopathy. In most of these cases the disorder improved or resolved with discontinuation of TNF inhibitor therapy. It is unclear whether these rare events exceed those seen in the general or rheumatoid population,

and the epidemiology of demyelinating disorders in RA is also unknown. TNF antagonists may exacerbate existing demyelinating disease. A randomized study of the use of the p55 receptor lenercept in MS reported more flares in the patients receiving lenercept than in those receiving placebo.¹²⁷ Clinicians should exercise great caution when considering a TNF antagonist for a patient with preexisting or recent-onset optic neuritis, MS, or other demyelination disorder.

Congestive heart failure

TNF has been implicated in the pathogenesis of heart failure and cardiac cachexia. TNF levels are found to be consistently elevated in patients with congestive heart failure (CHF), and TNF has been shown to have negative inotropic effects on the myocardium and to cause myocyte dysfunction.

It was anticipated that TNF inhibition would improve cardiac outcomes in patients with CHF. However, clinical trials using high-dose infliximab (10 mg/kg) in patients with CHF were discontinued early because of an increase in death and worsening of CHF in patients with New York Heart Association (NYHA) class III or IV CHF.¹²⁸ Two large etanercept trials in patients with CHF were also terminated due to lack of efficacy and the observation that a high dose (25 mg three times weekly) was associated with worse cardiac outcomes. Despite the negative reported outcomes in CHF patients,¹²⁹ the use of TNF antagonists in RA patients was not associated with an increase in new-onset CHF in clinical trials. Caution is recommended when using anti-TNF agents in patients with CHF, especially those with NYHA class III and IV disease.

Cytopenias

Rare reports of pancytopenia and aplastic anemia have been described with anti-TNF therapy, and a minority of these cases resulted in death. Cytopenias developed in the first few weeks (median, 4 weeks) after initiation of TNF inhibitor therapy. Reasons for this sporadic association are unclear, but the occurrence of these cytopenias may be attributed to comorbidities or other myelosuppressive drugs in use. Periodic monitoring (every 3 to 6 months) of blood cell counts should be considered. Patients with features of blood dyscrasia (fever, pallor, bleeding, sore throat) should be evaluated for this complication.

Hepatotoxicity

Elevations in aminotransferase levels and hepatic failure have been reported with anti-TNF use (see Table 63.6). A 2003 FDA review of TNF safety revealed an unexpected 134 spontaneous reports of TNF inhibitor-related liver failure. When 50 cases were reviewed, confounding diagnoses or hepatotoxin exposure was found in 43 cases (e.g., sepsis, TB, isoniazid use, alcohol, viral hepatitis, graft-versus-host disease, use of hepatotoxic drugs). However, in seven cases (14%) no other cause could be identified, which suggests that TNF inhibitor use may have led to hepatic failure. In the clinical trials of infliximab and adalimumab, sporadic twofold to threefold elevations in liver function test values may have been attributable to the TNF inhibitor. There are also rare reports of hepatic failure with infliximab. Reactivation of chronic HBV infection has been reported following TNF inhibitor use. Hence patients at risk should be tested for HBV before drug initiation. One should be aware of these rare hepatic events, and hepatic enzyme levels should be monitored perhaps every 3 to 6 months.

Pregnancy and lactation

There are no controlled trials of TNF inhibitor therapy in pregnant women and there is a dearth of information on the use of TNF inhibitors in women who are or may become pregnant. Anti-TNF therapies are labeled by the FDA as a category B pregnancy risk. The BSRBR reported 88 live births from a total of 130 pregnancies in patients who received anti-TNF therapy before or during pregnancy. The rate of spontaneous abortion was highest among patients exposed to anti-TNF agents at the time of conception (with methotrexate or leflunomide, 33%; without methotrexate or leflunomide, 24%). This rate compared with 17% spontaneous abortions in those with prior exposure to anti-TNF agents and 10% spontaneous abortions in the control group. Ten terminations were performed.¹³⁰ The TREAT registry reported pregnancies in 66 patients with Crohn disease, 36 of whom were exposed to infliximab. No fetal malformations occurred, and no difference was seen between infliximab-treated and untreated patients in the rates of miscarriage ($P = .53$) and neonatal complications ($P = .78$).¹³¹

Placental transfer of maternal IgG antibodies to the fetus is an important mechanism that provides protection to the infant at a time when the fetal

humoral response is inefficient. IgG is the only antibody class that significantly crosses the human placenta mediated by FcRn expressed on syncytiotrophoblast cells. Thus it would be anticipated that biologics of the IgG class would cross the placenta. Unlike etanercept and the monoclonal antibody anti-TNFs, certolizumab lacks an Fc component. The U.S. drug label for certolizumab pegol states that, in an independent clinical study conducted in 10 pregnant women with Crohn disease treated with this drug, drug concentrations were measured in maternal blood as well as in cord and infant blood (n = 12) on the day of birth. The last dose of certolizumab pegol (400 mg for every mother) was given on average 19 days before delivery. Plasma certolizumab pegol concentrations were less than 0.41 to 1.66 µg/mL in cord blood, less than 0.41 to 1.58 µg/mL in infant blood, and 1.87 to 59.57 µg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in the mothers, which suggests low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 µg/mL over 4 weeks, which indicates that this biologic may be eliminated at a slower rate in infants than in adults.

The safety of anti-TNF therapy during lactation has not been established. Although it appears that the risk to the fetus and mother is negligible, further research is necessary. Many clinicians allow patients to conceive while receiving these therapies but stop the drugs at the time of conception. There are limited data on maintaining these drugs during pregnancy.

Cutaneous reactions

Rarely, cutaneous reactions have been ascribed to TNF inhibitors, including lupuslike rashes, hypersensitivity vasculitis, palpable purpura, urticaria, folliculitis, new-onset psoriasis, pernio, granuloma annulare, interstitial granulomatous dermatitis, lichenoid eruptions, bullous lesions, erythema multiforme, opportunistic skin infections, and cutaneous T-cell lymphoma (Box 63.5).

In a study of new-onset psoriasis reported as an adverse event among 9826 anti-TNF–treated and 2880 DMARD-treated patients with severe RA registered in the BSRBR, 25 incident cases of psoriasis were reported in patients receiving anti-TNF therapy and none in the comparison cohort. Furthermore, patients treated with adalimumab had a significantly higher rate of incident psoriasis compared with patients treated with etanercept or infliximab.¹³²

Unusual toxicities

One of the more unusual toxicities associated with TNF inhibitors is accidental injuries (e.g., falls, fractures) (Box 63.6). Improved well-being and resumption of physically aggressive activities appear to account for this unexpected occurrence. Also surprising are occasional reports of weight

gain with TNF inhibition. It is not clear if this is related to increased leptin levels or resolution of the anorectic effects of TNF.¹³³

Other unusual events reported with TNF inhibitor therapy include fibrosing alveolitis, adult respiratory distress syndrome, granulomatous lung disease, colonic perforations, vesicocolic fistula, paresthesia, neuropathy, seizures, foot drop, azoospermia, and glomerulonephritis (with and without lupus).¹³⁴⁻¹⁴²

Monitoring

Before initiating anti-TNF therapy, the clinician must weigh the potential clinical benefits of TNF-α inhibition against the potential adverse effects. Although specific laboratory monitoring is not mandated by current package labeling, physicians are strongly advised to order a complete blood count and liver function tests every 3 months (for the first 6 to 12 months) in patients treated with anti-TNF agents. Although autoimmune disorders (e.g., drug-induced lupus, multiple sclerosis) have arisen in anti-TNF–treated patients, there is no value in employing pretreatment or periodic serologic testing because these have no predictive value. In contrast, patients exhibiting signs of autoimmune disease should undergo serologic testing to help establish a diagnosis. Hepatitis B and C testing is also recommended before drug initiation. Patients should also be up to date with their immunizations before starting therapy, and inoculation with live vaccine should be avoided while the patient is receiving therapy.

At each visit the patient should be carefully evaluated for the risk or presence of infection, malignancy, demyelinating disorders, cytopenia, or any other comorbidities that may alter the patient's risk-benefit ratio. Physicians should suspend anti-TNF therapy and exercise caution when patients develop a serious infection.

CONCLUSION

Although currently available TNF blockers undoubtedly represent a considerable advance in the management of RA, future challenges remain. For example, further research is necessary to identify the ideal patient to receive

BOX 63.5 CUTANEOUS DISORDERS AND TUMOR NECROSIS FACTOR (TNF) INHIBITOR THERAPY

Anecdotal improvements with TNF	TNF inhibitor–induced cutaneous inhibitor therapy disorders
Pustular psoriasis	Lupus-like rashes
Acrodermatitis continua of Hallopeau	Hypersensitivity vasculitis, palpable
Psoriatic onychopachydermoperiostitis	Purpura
Pyoderma gangrenosum	Urticaria, angioedema
Pemphigus	Folliculitis
SAPHO syndrome	Interstitial granulomatous dermatitis
Graft-versus-host disease	Eosinophilic cellulitis
PAPA syndrome	Alopecia areata
Sarcoidosis	Pernio
Aphthous stomatitis	New-onset psoriasis
Sneddon-Wilkinson disease	Bullous lesions
Eosinophilic fasciitis	Granuloma annulare
Panniculitis	Lichenoid eruptions
Necrobiosis lipidica diabetorum	Erythema multiforme
Hidradenitis suppurativa	
Scleroderma	Scleredema
	Subcutaneous fat atrophy
	Opportunistic skin infections
	Cutaneous T-cell lymphoma
	Oral epithelial dysplasia

BOX 63.6 ADVERSE EVENTS ASSOCIATED WITH USE OF TUMOR NECROSIS FACTOR INHIBITORS

- Common**
- Injection site reactions
 - Infusion reactions
 - Upper respiratory tract infections
- Uncommon**
- Serious infectious events
 - Mycobacterial infection
 - Fungal infection
 - Opportunistic infections
 - Viral infection (herpes zoster, hepatitis B)
 - Lymphoma and malignancy
 - Autoimmunity, autoantibodies, and lupuslike disease
 - Heart failure
 - Cytopenias
 - Demyelinating disorders
 - Hepatotoxicity
- Rare or uncertain relationship**
- Accidental injury
 - Weight gain
 - Pulmonary fibrosis
 - Asthma
 - Adult respiratory distress syndrome
 - Granulomatous lung disease
 - Colonic perforations
 - Vesicocolic fistula
 - Paresthesia
 - Neuropathy
 - Seizures
 - Foot drop
 - Asthenozoospermia
 - Glomerulonephritis
 - Proliferative lupus nephritis

TNF inhibition, the patient in whom TNF inhibition should be avoided, and the patient in whom the dosage of TNF inhibitor can be reduced. The identification of demographic, clinical, laboratory, and genetic factors that would predict clinical response or toxicity to these agents is highly desirable.

In all, anti-TNF therapy has given much hope and needed relief of disease activity with reduction in disability in our patients. The future application of these agents is an evolving story.

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64

Kinase inhibition: a new therapeutic principle in rheumatology

■ RONALD FRITS VAN VOLLENHOVEN

- Tyrosine kinases are a large family of membrane-bound and intracellular enzymes with important regulatory functions in signaling cascades, including those involved in inflammatory responses. In recent years the blockade of tyrosine kinases has emerged as an important new therapeutic principle in many areas of medicine.
- Among tyrosine kinases, the four Janus kinases (JAKs) appear to be particularly suitable for therapeutic modulation in rheumatoid arthritis (RA) and other autoimmune inflammatory diseases.
- The JAK inhibitor tofacitinib was shown to be clinically effective at levels comparable to TNF-blockade. In 2012 it was approved by the U.S. Food and Drug Administration for the treatment of RA. Several other JAK inhibitors are currently in later-stage clinical development.

INTRODUCTION

If the advent of biologic treatments was the defining development in rheumatologic therapeutics over the past 20 years, it may well be that the second decade of the millennium will be the era of tyrosine kinase inhibitors. If so, this evolution will be in step with dramatic developments involving this very large class of molecules in other medical fields, most notably in oncology. More than a dozen such drugs have been approved in recent years for nonrheumatologic indications, in some instances opening up entirely new therapeutic possibilities. In rheumatology, the first tyrosine kinase inhibitor, tofacitinib, was approved in November 2012 by the U.S. Food and Drug Administration (FDA) for treatment of rheumatoid arthritis (RA), with more compounds under development.

TYROSINE KINASES

Tyrosine kinases are a group of around 90 enzymes capable of phosphorylating the amino acid tyrosine on another protein, which leads to conformational changes and typically activation of that protein. They are included in the much larger family of 518 kinases in the human “kinome”¹ (Fig. 64.1). Some tyrosine kinases are cell-surface receptors, whereas the nonreceptor tyrosine kinases serve as intracellular signal transducers, ensuring that binding of a transmembrane receptor for cytokines, growth factors, and so on, by its cognate ligand leads, by way of a sequence of activation events, to the initiation of transcription in the nucleus. For the future of therapeutics in rheumatology several tyrosine kinases are of paramount interest: the Janus kinases (JAKs), and the spleen tyrosine kinase (SYK).

Four tyrosine kinases comprise the JAK family: JAK1, JAK2, JAK3, and TYK2. The discovery of the critical role of the JAKs in human immunity represents a striking example of “bench-to-bedside” and then “bedside-to-bench” research, going from the identification of the JAKs as critical intracellular mediators in the intracellular process initiated by the binding of specific ligands to their cognate receptors on the cell surface^{2,3} to descriptions of genetic defects in the JAK3 enzyme in patients with severe combined immunodeficiency,⁴⁻⁷ which provided a link between the findings at the cellular and molecular level and the clinic. Subsequently, elegant work by multiple researchers clarified the precise role of the JAKs. A variety of mediator molecules, including some classical hormones such as prolactin,

growth factors such as erythropoietin, and around 60 immunologic mediators such as the interleukins and interferons, exert their effects by binding the type 1 and 2 cytokine receptors on the cell surface, containing the common γ chain; and the intracellular events following such binding, and leading to activation of specific transcription events, are critically dependent on the JAKs.⁸⁻¹² Thus, following binding of the receptor, a cascade of events is initiated to achieve the necessary activation (or suppression) of gene transcription in the nucleus. This cascade usually starts with the phosphorylation of the intracytoplasmic tail of the receptor molecules resulting in a conformational change, which in turn leads to the recruitment of various intracellular signaling molecules such as the signal transducer and activator of transcription (STAT) family of transcription factors. These are then phosphorylated as well, after which they dimerize and translocate to the nucleus where they initiate gene transcription. These events are summarized in Fig. 64.2. Table 64.1 lists some of the ligands dependent on the JAK activation pathway and adverse effects that can be expected when blocking these enzymes.

The spleen tyrosine kinase SYK is a nonreceptor tyrosine kinase with a key role in signaling following binding of several immunologically important receptors such as the B-cell receptor, the Fc γ receptor, and others. Thus SYK modulates intracellular signaling in cells bearing such receptors, including B cells, mast cells, macrophages, neutrophils, and synovocytes. SYK binds to the cytoplasmic region of these receptors through the immune receptor tyrosine-based activation motif (ITAM). Receptor binding results in ITAM phosphorylation activating SYK, which in turn activates various downstream tyrosine kinases including mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3'-kinase and phospholipase C; this leads finally to increased production of various cytokines (including interleukin-6 [IL-6]) and inflammatory pathway effector molecules (including matrix metalloproteinases).

TYROSINE KINASE INHIBITORS

Tyrosine kinases can be readily inhibited *in vitro* by rather simple small molecules. However, it was not immediately obvious that inhibition of tyrosine kinases would be a useful therapeutic principle: the essential physiologic roles of the various tyrosine kinases, and the lack of specificity for most of the molecules, suggested that significant problems could emerge when trying to block these enzymes in the patient. Nonetheless, in a relatively short span of time it has become clear that favorable efficacy-toxicity ratios can be achieved with tyrosine kinase inhibitors in various diseases; this was shown first and foremost in oncology, but more recently in multiple clinical trials in rheumatology. The classes of therapeutics of greatest interest at the current time are the JAK inhibitors (sometimes referred to as *jakinibs*) and SYK inhibitors.

JAK inhibition

Tofacitinib

Tofacitinib (Xeljanz), formerly CP-690,550 (Fig. 64.3), is a small molecule with high affinity for and inhibitory activity against JAK3 (with a 50% inhibition concentration of 2.2 nmol/L) and almost as high activity against JAK1. It has somewhat lower activity against JAK2 (5.0 nmol/L), very low activity against TYK2, and virtually none against other kinases. JAK3 blockade interferes with the actions of, among other cytokines, IL-2, IL-4, IL-15, and IL-21; blockade of JAK1 inhibits signaling by interferon- α ,

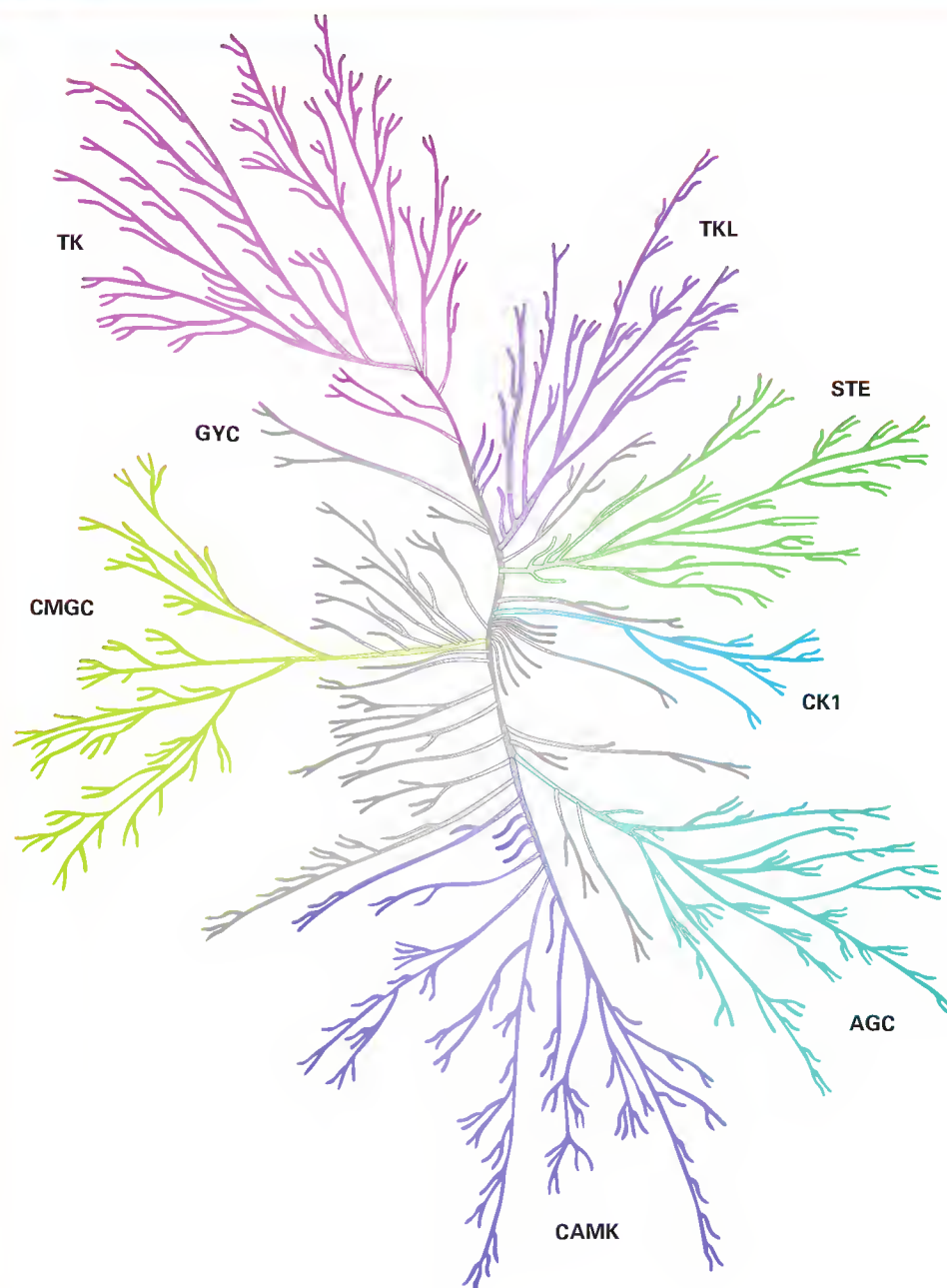


Fig. 64.1 The large group of protein kinase enzymes in humans (the “kinome”) can be depicted based on their structural relationships. Most relevant for rheumatology therapeutics are the tyrosine kinases (TK) in the upper left part of the figure. (Based on Manning C, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. *Science* 2002;298:1912-34.)

interferon- β , interferon- γ , IL-6, and others; and blockade of JAK2 decreases signaling of IL-3, IL-5, and interferon- γ but also the hematopoietic growth factors erythropoietin, thrombopoietin, and granulocyte-macrophage colony-stimulating factor. Tofacitinib was effective in animal models of arthritis¹³ and was studied in a large phase 1/2/3 program for treatment of RA, while also being developed for use in transplantation and inflammatory bowel disease. The RA development program, summarized later, led to approval by the FDA, and tofacitinib is currently under review by the European Medicines Agency.

The phase 2 program for tofacitinib, which consisted of three randomized trials,¹⁴⁻¹⁶ established 5- to 10-mg twice-daily dosing. The half-life of 2 to 5 hours is probably insufficient to allow once-daily dosing, and dosages higher than 10 mg twice daily were associated with increased adverse effects. Thus the large phase 3 program that included multiple randomized trials investigated the 5- and 10-mg twice-daily dosing regimens. Results of two of these trials have been published to date, and several others have been reported at international meetings.

In the ORAL-STANDARD trial¹⁷ patients with RA were included who had moderate or high disease activity (defined as having at least six swollen and at least six tender joints, plus at least one elevated acute-phase reactant) despite receiving stable treatment with methotrexate (MTX). Low-dose glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs) at stable doses were also allowed as concomitant medications, but no other disease-modifying antirheumatic drugs (DMARDs) or biologics were permitted. The patients were randomly assigned to receive placebo, tofacitinib

5 mg twice daily, tofacitinib 10 mg twice daily, or adalimumab 40 mg every other week. The primary outcome for the trial was achievement of 20% improvement according to the American College of Rheumatology scale (ACR20) after 6 months, which was reached by 28.3% of the placebo group, 47.2% of those receiving adalimumab, 51.5% of those given tofacitinib 5 mg twice daily, and 52.6% of those receiving 10 mg twice daily (Fig. 64.4). The active treatment groups fared statistically significantly better than the placebo group, and it was noted that the levels of improvement were numerically similar for all the active treatment groups. The same pattern was seen for a large number of secondary outcomes such as the ACR50 and ACR70 responses, European League Against Rheumatism responses, and so on. Thus the trial clearly established the clinical efficacy of tofacitinib, showing the clinical results to be numerically comparable to those of one of the most widely administered anti-tumor necrosis factor (anti-TNF) agents when used against a background of MTX. This trial did not assess the radiographic (structural) efficacy of tofacitinib.

The ORAL-SOLO trial¹⁸ investigated tofacitinib as monotherapy (allowing only NSAIDs and low-dose glucocorticoids as concomitant medications) compared with placebo. The standardized responses were significantly better with tofacitinib, with an ACR20 response rate at week 12 of 66%, 60%, and 27% for tofacitinib 10 mg, tofacitinib 5 mg, and placebo, respectively. In the ORAL-SYNC trial¹⁹ other DMARDs including MTX were allowed as background, and clinical efficacy over placebo was again demonstrated, so that at week 12 the ACR20 responses for tofacitinib 10 mg, tofacitinib 5 mg, and placebo were 58%, 53%, and 31%, respectively. In the

Fig. 64.2 Binding of a cytokine to its cognate receptor leads to phosphorylation of the intracellular domain of the receptor by specific Janus kinases (JAKs). Signal transducers and activators of transcription (STATs) are then recruited, bind to the receptor, and become phosphorylated by JAKs. This results in STAT dimerization, translocation, and regulation of gene transcription. Cytokines also activate PKB (AKT) and mTOR. Although not carefully studied, it is highly likely that blocking proximal cytokine signals will disrupt all downstream pathways. IFN, interferon; IL, interleukin. (From Kontzias A, Kotlyar A, Laurence A, Changelian P, O’Shea JJ. Jakinibs: a new class of kinase inhibitors in cancer and autoimmune disease. *Curr Opin Pharmacol* 2012;12:464-70.)

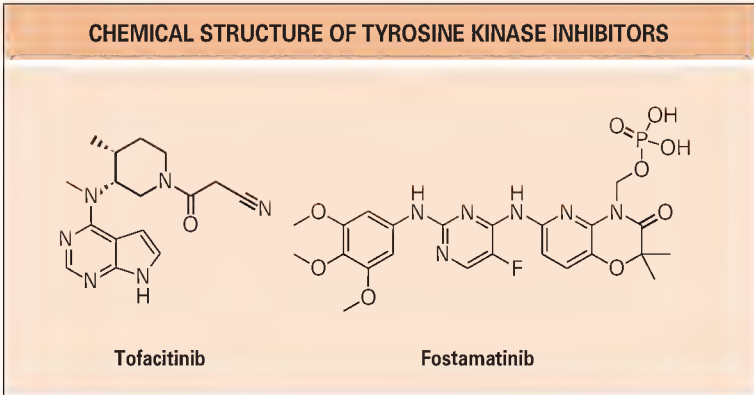
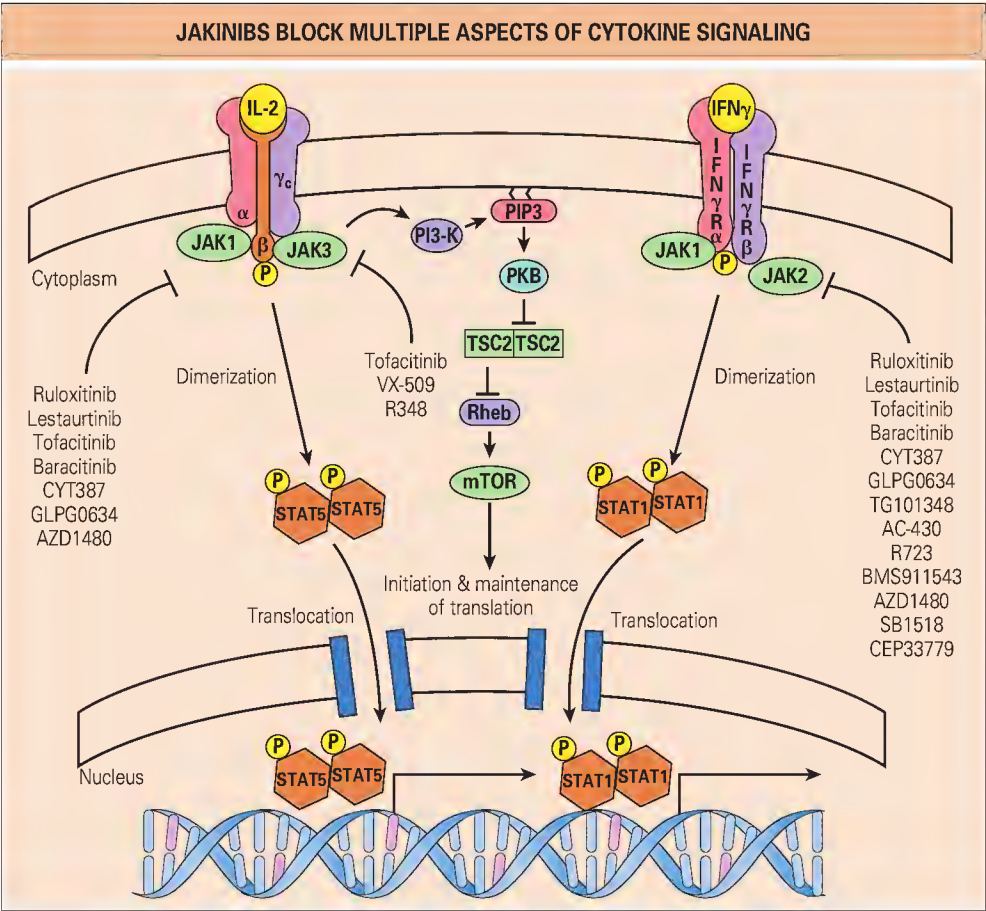


Fig. 64.3 Chemical structures of tofacitinib and fostamatinib, the tyrosine kinase inhibitors that are furthest along in clinical development for treatment of rheumatoid arthritis.

TABLE 64.1		
Main ligands dependent on the JAK activation pathway and adverse effects that can be expected when blocking these enzymes		
Ligands		Expected (“on-target”) adverse effects
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-11, IL-10, IL-15, IFN-α, IFN-β, IFN-γ	Immune suppression, hyperlipidemia
JAK2	EPO, TPO, GM-CSF, IL-3, IL-5, IFN-γ	Anemia, neutropenia, thrombocytopenia
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15	Immune suppression
TYK2	IFN-α, IFN-β, IFN-γ; IL-12	Immune suppression
SYK	Immunoglobulins	Immune suppression

EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; SYK, spleen tyrosine kinase; TPO, thrombopoietin.

ORAL-STEP trial²⁰ tofacitinib was compared with placebo over 6 months in 399 patients who had experienced treatment failure with at least one anti-TNF agent, with MTX used as background therapy; ACR20 responses at week 12 for tofacitinib 10 mg, tofacitinib 5 mg, and placebo were 48%, 41%, and 24%, respectively. In the ORAL-SCAN²¹ trial, in which tofacitinib was tested against placebo on a background of MTX therapy in 797 patients who had shown an incomplete response to MTX, not only the clinical but also the radiographic outcomes were analyzed. The latter were investigated using the van der Heijde modification of the Sharp score (SvdH score), measured at baseline and after 1 year of treatment. In this trial, the clinical effects were again clearly superior for tofacitinib compared with placebo, but for the radiographic outcomes a statistically significant reduction of progression in the SvdH score was seen only at the higher dosage (10 mg twice daily) and not at the lower one. Progression in the placebo group in this trial was rather limited, which makes it mathematically more challenging to demonstrate an improvement, and numerically the results were not very different for the two tofacitinib dosages. However, the FDA did not accept the radiographic findings as evidence for inhibition of radiographic progression and did not give the radiographic claim to tofacitinib. Finally, the ORAL-START trial²² included 952 patients with RA who had not yet been treated with MTX—which often, but not always, means relatively early RA. Patients were randomly assigned to receive either MTX at dosages increased stepwise to 20 mg/wk, tofacitinib 5 mg twice daily, or tofacitinib 10 mg twice daily. ACR20, ACR50, and ACR70 responses were achieved by a larger proportion of patients receiving either dosage of tofacitinib, and radiographic progression was significantly decreased, compared with those given MTX (Table 64.2).

The combined evidence from these trials shows quite clearly that tofacitinib has clinical efficacy in RA whether given as monotherapy or in combination with MTX or other DMARDs, and that the clinical efficacy with background MTX is numerically similar to that seen with the anti-TNF agent adalimumab. Radiologic efficacy was statistically seen only for the 10-mg dose in patients with established RA, but a clear trend was observed for the lower dose, and both doses were effective in this regard in MTX-naïve patients. In addition, these trials also demonstrated that the clinical effect is seen soon after treatment initiation and that the efficacy is maintained with continued treatment over the 1- to 2-year time frame for follow-up in these trials. Improvements in functional status and quality-of-life measures were also noted in the studies.

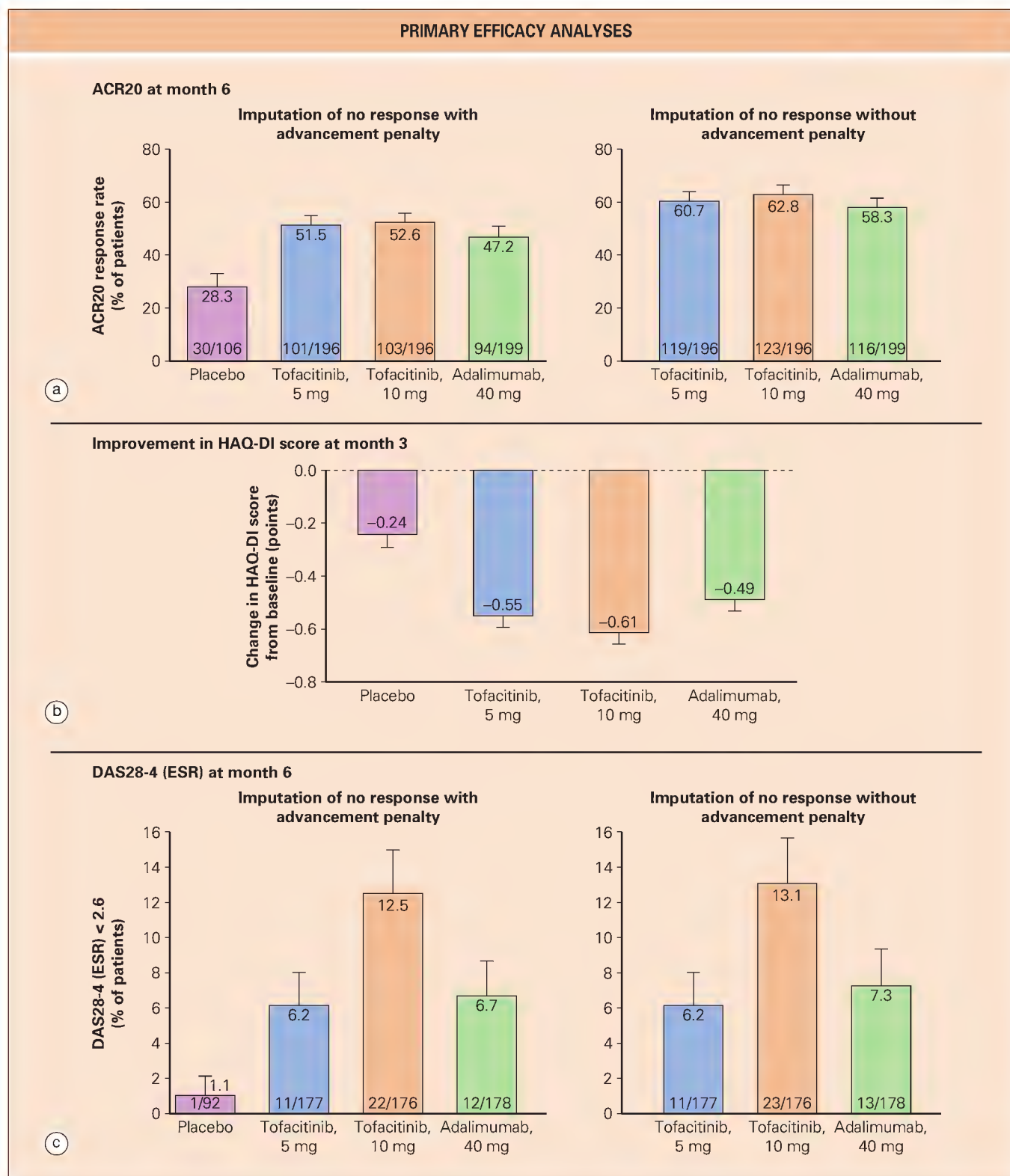


Fig. 64.4 Primary efficacy analyses of the ORAL-STANDARD trial of tofacitinib and adalimumab versus placebo in rheumatoid arthritis. (a) The numbers and percentages of patients with at least a 20% improvement as measured by the American College of Rheumatology scale (ACR20). The graph on the left shows the results of the analysis with imputation of no response with an “advancement penalty”; if the patient did not show a response to therapy by month 3, the treatment was considered to be a failure even if the patient had a response after month 6. $P < .001$ for the comparison of each active-treatment group with placebo. The graph on the right shows the results of the analysis with imputation of no response without the advancement penalty, these are the actual response rates at month 6 in the active-treatment groups irrespective of the response by month 3. The response without the advancement penalty cannot be calculated for the placebo group because patients in that group were blindly switched (“advanced”) to tofacitinib treatment if they showed no response by month 3. (b) Change in Health Assessment Questionnaire Disability Index (HAQ-DI) scores (which range from 0 to 3, with higher scores indicating greater disability) from baseline to month 3. A total of 98 patients in the placebo group, 188 in the 5-mg tofacitinib group, 185 in the 10-mg tofacitinib group, and 190 in the adalimumab group were included in this analysis. $P < .001$ for the comparison of each active-treatment group with placebo. (c) Numbers and percentages of patients with a Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4 [ESR]) of less than 2.6. Scores on the DAS28-4 (ESR) range from 0 to 9.4, with higher scores indicating more disease activity. As in (a), the graph on the left shows the results of the analysis with imputation of no response with the advancement penalty, and the graph on the right shows the results of the analysis with imputation of no response without the advancement penalty. For the graph on the left, $P < .05$ for the comparison of the 5-mg tofacitinib group and the adalimumab group with the placebo group, and $P < .001$ for the comparison of the 10-mg tofacitinib group with the placebo group. All data are expressed as means, with T bars indicating the standard error. (From van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508-19.)

TABLE 64.2
Results of the ORAL-START trial of tofacitinib versus methotrexate (MTX) in MTX-naïve patients with rheumatoid arthritis

	MTX	Tofacitinib 5 mg bid	Tofacitinib 10 mg bid
No. of patients	186	371	395
ACR20 response rate (%)	50.5	71.0	75.8
ACR50 response rate (%)	27.2	46.6	56.2
ACR70 response rate (%)	12.0	25.5	37.7
DAS28 < 2.6 (%)	7.6	14.6	21.6
Mean change in modified total Sharp score (least-squares method)	0.84	0.18	0.04

For each analysis shown, the difference between the tofacitinib-treated groups and the MTX-treated group was statistically significant.
 ACR20/50/70, American College of Rheumatology 20%/50%/70% improvement criteria; bid, twice daily; DAS28, 28-joint Disease Activity Score.
 From Lee EB, Fleischmann RM, Hall S, et al. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-naïve patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:S1049-5.

The safety and tolerability of tofacitinib were studied extensively in these trials as well as in longer-term extension studies²³ in which the medication was provided open label. The overall numbers of adverse events (where *adverse events* is the regulatory term indicating all medical events that occur during a trial, irrespective of attribution to the study drug; in other words, it is not the same thing as side effects) were generally slightly higher for tofacitinib than for placebo, with a suggestion that most of the increase was due to gastrointestinal symptoms and, to a lesser extent, to infections. The numbers of serious adverse events (defined as adverse events that lead to hospitalization, death, or various other serious long-term outcomes) were also somewhat higher for tofacitinib, as were the numbers of serious infectious events. The numerical increases in the latter were similar to those reported by clinical trials of many of the currently used biologics in RA, with rates of serious infectious events on the order of 4 to 6 per 100 patients per year. Because the background rate for patients with RA is not zero, this might be understood to mean that treatment with tofacitinib could lead to 1 to 4 serious infections per 100 patients treated for 1 year, an “attributable risk” quite similar to that seen with many of the currently used biologics in RA. During these trials, there were no major unexpected safety findings or “signals.” Cases of tuberculosis, other opportunistic infections, colonic perforations, and malignancies did occur, but to date the rates are similar to those seen with some or all of the biologics. However, there does appear to be an elevated rate of herpes zoster infection with tofacitinib.

Tofacitinib was also associated with various laboratory abnormalities. Elevations in liver enzyme levels were seen in around 5% to 10% of patients; most of the elevations were mild but some required dose adjustments or discontinuation. There were no cases of liver failure. Cytopenias including neutropenia, lymphopenia, anemia, and thrombocytopenia also occurred in 5% to 10% of patients, again with the majority being mild but with some more severe instances leading to discontinuation. These changes were reversible, and no major consequences were observed. In a limited number of patients severe anemia (hemoglobin level of less than 9 g/dL) was noted but resolved with drug discontinuation. Significant lymphopenia (fewer than 500 cells/mm³) was rarely seen. Tofacitinib should be temporarily withheld until there is recovery in the lymphocyte and/or absolute neutrophil count.

A very small but statistically significant increase in serum creatinine level was observed in the tofacitinib trials. The significance of this finding is unclear. Treatment with tofacitinib was associated with increases in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels and statin therapy may be required.

Overall, the laboratory abnormalities that are seen in the course of treatment with tofacitinib make it clear that such treatment will have to be monitored with laboratory testing. The cytopenias seen with tofacitinib can most likely be attributed to the weak JAK2-blocking effects of the molecule, whereas other laboratory abnormalities such as elevated lipid levels bear striking similarities to those seen with the anti-IL-6 agent tocilizumab. It is therefore reasonable to speculate that these adverse effects are a reflection of this particular action of the drug, and it might even be that many of the clinical benefits can be attributed to IL-6 blockade as well.

In November 2012 tofacitinib was approved for clinical use in the United States, but some questions remain at this time. While regulatory authorities

in other countries also approved this drug (Japan, Russia, Switzerland, as well as several countries in South America and the Middle East), the European Medical Agency did not grant approval, citing concerns on both efficacy and safety aspects.

The FDA approved the 5-mg twice-daily dosage as either monotherapy or in combination with MTX or other DMARDs in patients with active RA who had an inadequate response to or an intolerance of MTX. Measurement of complete blood count (CBC) and lymphocyte count as well as lipid levels is recommended at baseline and again at 4 to 8 weeks after initiation of therapy. CBC and lymphocyte count monitoring is recommended every 3 months thereafter. Routine monitoring of liver enzyme levels is also needed. Interruption of therapy is recommended if the absolute neutrophil count falls to between 500 and 1000 cells/mm³, and discontinuation is recommended if absolute neutrophil count or lymphocyte count is less than 500 cells/mm³. Interruption of therapy is also recommended for a hemoglobin decrease of more than 2 g/dL or a hemoglobin level of less than 8 g/dL.

It is evident that tofacitinib is an effective treatment with an adverse effect profile that is manageable in the context of rheumatology specialty care, so that the drug may reasonably be considered as an option for patients with active disease—and of course more so for patients who have not shown a response to other alternatives. The fact that tofacitinib is an oral agent may be attractive from the patient's point of view, and from a societal perspective it could be hoped that the simpler structure of the molecule compared with biologics would lead to a lower price. However, the current retail cost of the 5-mg twice-daily regimen is only marginally lower than that of the anti-TNF therapies.

Although tofacitinib is primarily being developed for use in RA (as well as transplantation, ulcerative colitis, Crohn disease, and psoriasis) additional rheumatologic indications for tofacitinib may emerge in the future, including spondyloarthritis, psoriatic arthritis, juvenile arthritides, and others. Additional studies will provide more information about questions such as whether dose escalation from 5 to 10 mg can induce a response in poor responders. Longer-term studies and greater patient exposure will provide important information about the drug's long-term safety profile, including risk of infections and malignancy. This information will be essential in determining the role and place of this agent.

Other JAK inhibitors

Several other JAK inhibitors are in clinical development for the treatment of rheumatic diseases (Table 64.3). The presence of divergent fine specificities for the different JAK enzymes could make important differences in the clinical benefits and risks, but only extensive clinical trials and, eventually, practical experience will allow a clear assessment of these compounds, which include the following:

- Decernotinib. Previously known as VX-509, decernotinib is a highly JAK3-selective inhibitor. In a phase 2 double-blind study, monotherapy with decernotinib at a range of dosages was tested against placebo in patients with RA who were biologic naïve and in whom DMARD treatment had failed. ACR20 responses for the highest dosages ranged from 61% to 66% compared with 29% for placebo. Some serious infections and liver enzyme elevations were noted, but there were no cytopenias and no effect on serum creatinine level.²⁴
- Baricitinib (LY3009104/INCB028050) blocks JAK1 and JAK2 and is a once-daily therapy. In a phase 2 trial involving 301 patients significant improvements were noted compared with placebo.^{25,26} At week 12 the ACR20 responses in the placebo group, the group given baricitinib 4 mg, and the group receiving baricitinib 8 mg were 41%, 75%, and 78%, respectively. As expected based on its JAK1, JAK2 profile some cases of anemia and elevated lipid levels were observed.
- Ruxolitinib is a JAK1/JAK2 blocker and the first such agent approved by the FDA for the treatment of myelofibrosis. Results of a phase 2 study of its use in RA were reported in abstract form²⁷ but never published. This compound is also being studied as a topical agent for treatment of psoriasis.
- GLPG0634 is a JAK1-selective agent. In a small proof-of-concept trial 24 patients were given GLPG0634 (half received 200 mg daily and half 200 mg twice daily), and 12 patients were given placebo. An ACR20 response was achieved by 83% of patients given GLPG0634 versus 33% of those given placebo. In this very small study, no anemia, increases in LDL level, elevated transaminase levels, or changes in creatinine level were seen.²⁸
- Several other JAK inhibitors are in development but with only animal data reported so far, including the JAK2 inhibitor CEP-33779^{29,30} and the combined JAK and SYK inhibitor R348.^{31,32}

TABLE 64.3

JAK inhibitors in clinical development

	Specific target(s)	Being developed for use in	Stage of clinical development
Tofacitinib	JAK3, JAK1 (JAK2)	RA, psoriasis, inflammatory bowel disease, transplantation	Phase 3
Decernotinib (VX-509)	JAK3	RA	Phase 2
Ruxolitinib	JAK2 (JAK1)	Myelofibrosis, polycythemia vera, essential thrombocythosis	Approved for myelofibrosis; phase 2/3 for other indications, unclear for RA
INCB18424 topical	JAK2 (JAK1)	Psoriasis	Phase 2
Baricitinib (INCB028050/LY3009104)	JAK1, JAK2	RA, psoriasis	Phase 2
CYT387	JAK2 (JAK1)	Myelofibrosis	Phase 2
GLPG0634	JAK1 (JAK2, TYK)	RA	Phase 2
AC-430	JAK2	RA, lymphoma	Preclinical

Additional JAK inhibitors for which preclinical data have been reported are R348, R723, BMS911543, AZD1480, and CEP33779. JAK, Janus kinase; RA, rheumatoid arthritis.

SYK inhibition: fostamatinib

Several inhibitors of the spleen tyrosine kinase (SYK) are also being developed for treatment of rheumatic diseases.

Fostamatinib (R788) is a prodrug; after oral administration it is rapidly converted to R406, an active inhibitor of SYK. It was effective in animal models of arthritis.³³ Three phase 2 trials of fostamatinib have been reported. In the first 12-week trial, and in a larger subsequent 24-week trial in patients who had never taken anti-TNF agents and had shown an incomplete response to MTX, good efficacy was seen, with a statistically significant higher level of improvement compared with placebo.^{34,35} In the 24-week trial ACR20 response rates at week 12 were 35%, 57%, and 67% in the groups receiving placebo, fostamatinib 150 mg once daily, and fostamatinib 100 mg twice daily, respectively. Clinical response was seen by week 1, and in most patients if a meaningful clinical response occurred it did so by week 8. However, a 3-month trial of fostamatinib in patients for whom prior anti-TNF therapy had failed did not demonstrate meaningful differences in the main clinical outcomes between the fostamatinib and placebo groups.³⁶ Subsequent analyses of the data for this nominally failed trial showed that patients with elevated C-reactive protein levels at baseline did benefit than patients who entered the trial with a normal C-reactive protein level but an elevated sedimentation rate, and an analysis of inflammation as documented by magnetic resonance imaging supported drug efficacy. It has been suggested that issues of trial design and baseline disease activity level contributed to the failure to show effects on the primary outcome. A recent press release announced that a fourth phase 2 trial had demonstrated the superiority of fostamatinib as monotherapy when compared with placebo but had failed to demonstrate equivalence with the anti-TNF agent adalimumab. An extensive safety follow-up of patients receiving fostamatinib therapy³⁷ demonstrated the occurrence of infections, neutropenia, and elevated liver enzyme levels, as well as a rather high frequency of diarrhea (27.6%) and hypertension (22.8%), but no anemia, increases in creatinine level, or increases in lipid levels. There were 14 malignancies reported in these trials. In June 2013 the phase 3 program for fostamatinib was terminated.

Other SYK inhibitors in the early stages of development include P505-15.

OTHER KINASE INHIBITORS

Although the JAK and SYK inhibitors have come the longest way in development as antirheumatic therapeutics, small-molecule inhibitors of other kinases are also being developed for various indications, and a use in autoimmune diseases may emerge.

Ibrutinib

Ibrutinib (PCI-32765) is a selective inhibitor of Bruton tyrosine kinase (Btk) and is being developed for treatment of several hematologic disorders. It was shown to have antiarthritic activity in an animal model.³⁸

p38 mitogen-activated protein kinases

A relatively large number of small-molecule compounds targeting the p38 mitogen-activated protein kinases (p38 MAPKs) have been evaluated over the past decade. p38 MAPKs are a group of protein kinases that are responsive to various stress stimuli. There are four p38 isotypes designated α , β , γ , and δ . Most compounds in clinical development targeted the α isoform. In preclinical studies in animal models many different p38 MAPK inhibitors showed evidence of a potential antiarthritic effect (reviewed by Bonilla-Hernán and colleagues³⁹). Some of these compounds were tested in early-phase trials and results were reported at international meetings but never published as full reports (reviewed in Bonilla-Hernán and colleagues³⁹ and in Genovese⁴⁰). A recurring finding in many of these trials was that an effect on C-reactive protein level was seen after only 1 to 2 weeks but abated after longer follow-up; clinical efficacy endpoints frequently were not met at longer time intervals, such as 12 weeks; and toxicities, including hepatotoxicity, were seen in many trials. Clinical results with the α -selective p38 MAPK inhibitor pamapimod were reported in more detail. In a phase 2 trial pamapimod was not significantly better than placebo,⁴¹ and in a double-blind, active agent-controlled phase 2 trial, pamapimod was less effective than MTX.⁴² Thus the initial optimism about these agents was followed by subsequent disappointment after many compounds failed in clinical testing.

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65

Emerging therapeutic targets:
GM-CSF, IL-17, and IL-23

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- Interleukin-17 (IL-17) is produced primarily by T cells. Granulocyte-macrophage colony-stimulating factor is produced primarily by activated T cells and macrophages. IL-23 is produced by antigen-presenting cells and tissue cells.
- Unique features of the biology and regulation of each cytokine point to specific strategies for either neutralization or downregulation by therapeutic biologics.
- In autoimmune diseases, cytokines function within a complex matrix of stimulatory and feedback loops such that perturbation of one cytokine is likely to influence the production and function of many others.

**POTENTIAL CYTOKINE TARGETS
IN RHEUMATIC DISEASES**

Multiple strategies can be used to inhibit the biologic effects of cytokines in rheumatic diseases, including monoclonal antibodies to cytokines or to their receptors, soluble receptors, and receptor antagonists. Additionally, cytokines can be inhibited by targeting their processing, intracellular signaling pathways, or synthesis (Table 65.1).

Design of inhibitors involves an understanding of their unique biologic activities, receptors, and signaling pathways while being mindful of potential complications that could result from their specific inhibition. Ideally, inhibitors of cytokines would be designed to alter the underlying immune dysfunction specific to a rheumatic disease while protecting the targeted tissues and allowing preservation of a host's immune defenses. As our understanding of the role of specific cytokines in rheumatic diseases evolves, more targets are being identified and potential new therapies are being tested for their safety and tolerability profiles.

**GRANULOCYTE-MACROPHAGE
COLONY-STIMULATING FACTOR****Description, receptor, function**

Granulocyte macrophage-colony stimulating factor (GM-CSF) is a cytokine produced primarily by activated T cells and macrophages. It mediates the activation of mature neutrophils, eosinophils, and macrophages to produce proinflammatory cytokines.¹ GM-CSF production is stimulated by lipopolysaccharide (LPS), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and IL-23. GM-CSF is a 23-kDa glycoprotein with a four- α -helical structure that signals through a heterodimeric receptor composed of an α subunit and the common β chain (the common β chain/ β c/GM-CSFR β).^{2,3} The α subunit binds GM-CSF with low affinity. Once dimerization of the α subunit with the common α chain occurs, high-affinity binding is generated, thereby allowing signal transduction. The GM-CSF receptor (GM-CSFR) is expressed on neutrophils, dendritic cells, macrophages, eosinophils, and endothelial cells. The GM-CSFR complex activates the Ras-MAPK and JAK2-STAT (STAT1, STAT3, STAT5)-SOCS (SOCS1, SOCS3) pathways.^{4,5}

GM-CSF has colony-stimulating effects on bone marrow. However, GM-CSF-/- mice have normal numbers of hematopoietic cells, including neutrophils, monocytes, and eosinophils.⁶ In the absence of GM-CSF,

defective maturation of alveolar macrophages can result in pulmonary alveolar proteinosis.⁷ It is not known whether blockade of GM-CSF will lead to altered clearance of surfactant in healthy lungs.⁴

GM-CSF in rheumatic disease

Two distinct macrophage lineages have been described but not defined in rheumatic diseases. The M1 classically activated macrophages are involved in inflammation and host defense, and the M2 alternatively activated macrophages have antiinflammatory properties and are involved in tissue repair. GM-CSF may promote the development of M1 macrophages at sites of chronic inflammation. GM-CSF is present in the synovial fluid and serum of patients with rheumatoid arthritis. Additionally, some patients with Felty syndrome have been reported to experience flares of arthritis when receiving treatment with GM-CSF.^{8,9}

Synovial macrophages produce inflammatory mediators, including TNF- α , IL-1 β , and IL-6. The degree of synovial macrophage infiltration correlates with the radiologic progression of joint destruction and joint pain in patients with rheumatoid arthritis. Reduction of macrophage numbers on synovial biopsy specimens is used as a biomarker for the effectiveness of antirheumatic therapy.¹⁰ Elevated levels of GM-CSF and GM-CSFR have been measured in the synovial fluid and plasma of patients with rheumatoid arthritis.¹¹⁻¹⁴ Taken together, these data suggest a role of GM-CSF in rheumatoid arthritis.

Clinical trials

Mavrilimumab is a fully humanized IgG1 monoclonal antibody that binds to the α subunit of GM-CSFR, thereby preventing interaction of GM-CSF with its receptor. In a phase 1 dose escalation study of 32 patients with rheumatoid arthritis, adverse events were reported with similar frequency in all treatment cohorts. One patient experienced face and neck urticaria during infusion of the 10-mg/kg dose that resulted in discontinuation of the infusion. The study was not designed to evaluate clinical efficacy, but no significant change in Disease Activity Score (DAS)28 was seen in any of the cohorts. In mavrilimumab-treated patients with moderate disease activity (DAS28 lower than 3.2) at baseline, mean DAS28 scores were significantly reduced at 28 weeks.¹⁵ A phase 2 study of mavrilimumab in patients with rheumatoid arthritis has been completed.¹⁶ In this 12-week, sequential ascending-dose study, 233 patients received either mavrilimumab (10, 30, 50, or 100 mg every other week) or placebo on a background of methotrexate therapy. The primary endpoint was the proportion of mavrilimumab-treated subjects achieving a decrease in DAS28-C-reactive protein (CRP) of 1.2 or greater from baseline versus placebo at week 12. By week 12, 55.7% of mavrilimumab-treated subjects met the primary endpoint (DAS28-CRP reduction of 1.2 or greater) versus 34.7% in the placebo group ($P = .003$). The 100-mg group showed significant improvement in comparison to placebo in the primary endpoint (DAS28-CRP); the American College of Rheumatologists (ACR) 20 response was 69% in the 100-mg group versus 40% in the placebo group ($P = .005$). Clinical response was observed by week 2. The short-term safety profile did not demonstrate any significant issues.

Namilumab, a humanized monoclonal antibody to GM-CSF, is undergoing a phase 1b dose escalation study in patients with rheumatoid arthritis.¹⁷ KB003 is a recombinant human anti-GM-CSF IgG1K monoclonal antibody. KB003 has undergone a phase 2b trial in patients with rheumatoid arthritis who failed previous treatment with a biologic agent. The results of the study have not been reported to date.¹⁸ MOR103 is a fully humanized monoclonal antibody to GM-CSF. A phase 1b/2a study involving an intravenous

TABLE 65.1
Cytokines, their sources, receptors, signaling pathways, and major functions

Cytokine	Cellular source	Receptor	Signaling pathway	Function
GM-CSF	Macrophages and activated T cells	GM-CSF α /GM-CSFR β	Ras-MAPK and JAK2-STAT1, STAT3, STAT5-SOCS1, SOCS3	Colony-stimulating factor on bone marrow; activation of mature neutrophils, eosinophils, and macrophages
IL-17A, IL-17F	T cells, $\gamma\delta$ T cells, NK T cells, neutrophils, eosinophils	IL-17RA/IL-17RC	TRAF6, MAPK, TAK1, NF- κ B	IL-6, IL-8, and GM-CSF production by epithelial cells and fibroblasts, production of IL-1 β and TNF- α from monocytes, MMP synthesis
IL-23	Macrophages, DCs, T cells, B cells, endothelial cells	IL-12RP1/IL-23R	JAK2, Tyk2, STAT3, STAT4	Maintains Th17 cells, induces memory T cells to proliferate and produce IFN- γ and IL-17

DCs, dendritic cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon- γ ; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF- κ B, nuclear factor-kappa B; NK, natural killer; Ras, rat sarcoma; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TAK, transforming growth factor- β -activated kinase; Th17, type 17 helper T cell; TRAF, TNF receptor-associated factor; Tyk, tyrosine kinase.

preparation has been completed in patients with rheumatoid arthritis. The results have not been published, but development of a subcutaneous preparation is under way.¹⁹

INTERLEUKIN-17

Description, receptor, function

The IL-17 family has six identified members designated A to F, of which IL-17A and IL-17F are the most studied. IL-17A and IL-17F are homodimeric cytokines, but human CD4+ T cells can also produce an IL-17A/F heterodimer that has inflammatory effects.²⁰ IL-17A and IL-17F are produced by activated CD4+ and CD8+ T cells. IL-17A is produced mainly by type 17 helper T cells (Th17 cells). Th17 cells are derived from CD4+ T cells that have been stimulated with IL-1 β and transforming growth factor- β (TGF- β), with roles for IL-6, IL-21, or IL-23.²¹ IL-23R is expressed by Th17 cells, and IL-23 is a survival factor for Th17 cells and induces the production of IL-17A from the Th17 cells. IL-17B and IL-17D are expressed in resting CD4+ T cells and can induce the secretion of IL-6, IL-8, and GM-CSF in fibroblasts, epithelial cells, and endothelial cells.^{22,23}

The IL-17 family members bind to a distinct class of cytokine receptors. IL-17RA is a subunit of a multimeric preformed receptor complex with IL-17RC. This complex undergoes a conformational change when bound.²⁴ IL-17R is expressed on monocytes, macrophages, chondrocytes, osteoblasts, and fibroblasts.²⁵

IL-17 is a proinflammatory cytokine that induces epithelial cells to produce IL-8, which is a chemoattractant for neutrophils, and IL-17 also induces the production of IL-1 β and TNF- α from monocytic cells.²⁶ Production of antimicrobial peptides is induced by IL-17 in epithelial cells, thus suggesting a role for IL-17 in host defense.²⁷

Interleukin-17 in rheumatic disease

High levels of IL-17A have been found in the sera, synovial fluid, and synovial biopsy specimens of patients with rheumatoid arthritis.²⁵ Additionally, increased levels of IL-17 expression in the synovium were predictive of more severe joint damage in a prospective study of patients with rheumatoid arthritis.²⁸ IL-17 contributes to cartilage and bone destruction through multiple mechanisms. It inhibits chondrocyte metabolism, causes proteoglycan breakdown, and induces the production of metalloproteinases associated with cartilage destruction.²⁵ IL-17 can trigger osteoclastogenesis by upregulating receptor activator of nuclear factor- κ B ligand (RANKL) on osteoblasts, which allows interaction with RANK on the osteoclasts responsible for bone erosion.²⁵ IL-17A can act synergistically with TNF- α and IL-1 β to induce inflammatory mediators in synoviocytes, osteoblasts, myoblasts, and chondrocytes.²⁴ IL-17RA and IL-17RC are overexpressed in rheumatoid arthritis.²⁴ Taken together, these findings make IL-17 and its receptor promising targets in the treatment of rheumatoid arthritis.

Clinical trials

IL-17A blockade with secukinumab, a human IgG1 κ monoclonal antibody to IL-17A, has completed phase 1/2 trials on rheumatoid arthritis. In the phase 1 trial on rheumatoid arthritis, the endpoint for efficacy, an ACR20 response, was met.²⁹ In a phase 2 study on rheumatoid arthritis, the primary efficacy endpoint, an ACR20 response at 16 weeks, was not reached. Upper respiratory infections and pharyngitis occurred more frequently in the

secukinumab-treated groups.³⁰ Efficacy, safety, and tolerability studies in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis are currently in progress.³¹⁻³³

Ixekizumab is a monoclonal antibody to IL-17A. A phase 1 placebo-controlled, proof-of-concept study was completed in patients with rheumatoid arthritis, with DAS28 at week 10 being the primary efficacy endpoint. Changes in DAS28 met significance only when the responses of all treated groups were combined and compared with the placebo group (−1.7) at week 10. The incidence of leukopenia and neutropenia was increased in ixekizumab-treated patients, but without any report of increased infection in active drug- versus placebo-treated patients.³⁴

In a randomized, phase 2 double-blind study, 260 patients naïve to biologic agents received subcutaneous placebo or ixekizumab (3, 10, 30, 80, or 180 mg), and 188 TNF-IR patients received placebo or ixekizumab (80 or 180 mg) at weeks 0, 1, 2, 4, 6, 8, and 10 with concomitant disease-modifying antirheumatic drug therapy. A significant dose-response relationship was seen in biologic-naïve patients at week 12. Significant differences versus placebo were seen for DAS28-CRP reductions in biologic-naïve patients and in TNF-IR patients at all ixekizumab doses, with a rapid onset of efficacy occurring within 1 week after the first dose. A reduction in DAS score of −1.8 was observed in the 180-mg biologic-naïve group versus −0.6 in the placebo group. The frequency of adverse events was similar across treatment arms.³⁵

INTERLEUKIN-23

Description, receptor, function

IL-23 is a member of the IL-12 cytokine family and is composed of two subunits, the p40 and p19 peptides. IL-23 is produced by macrophages and dendritic cells and binds to a heterodimeric receptor composed of IL-12R β 1 (shared with IL-12R) and IL-23R (Fig. 65.1).^{36,37} T cells, natural killer cells, monocytes/macrophages, and dendritic cells express IL-23R receptor.³⁸ IL-23 induces memory T cells to proliferate and produce interferon- γ , mediates the development and proliferation of IL-17-producing CD4+ Th17 cells, and stimulates antigen presentation by dendritic cells.³⁸ In a mouse model of demyelinating disease, IL-23 induced central nervous system and peritoneal macrophages to produce IL-1 β and TNF- α .³⁹ By inducing macrophages to produce IL-1 β and TNF- α , IL-23 may perpetuate a local proinflammatory environment. IL-23 signals through the JAK-STAT pathway. Binding of IL-23 to its receptor leads to activation of JAK2 and Tyk2, which phosphorylate and activate STAT3 and STAT4.^{36,40,41} The association of a STAT4 polymorphism marked by rs7574865 has been described in patients with rheumatoid arthritis, systemic lupus erythematosus, Crohn disease, and ulcerative colitis.⁴² Additionally, a polymorphism in the IL23R gene has been linked to susceptibility to Crohn disease.⁴³

Interleukin-23 in rheumatic diseases

IL-23 has been identified in the sera and synovial fluid of patients with rheumatoid arthritis, and expression of the p19 subunit is increased in the synovial fibroblasts of patients with rheumatoid arthritis.⁴⁴ IL-23 serum levels correlate with markers of rheumatoid arthritis disease activity, and IL-23 synovial fluid levels correlate with the presence of erosions in patients with rheumatoid arthritis.^{44,45} Cultured synoviocytes from rheumatoid arthritis patients produced IL-23 and IL-23R, and IL-23 blockade led to decreased production of TNF- α , IL-1 β , and IL-6.⁴⁶

IL-23 IS A MEMBER OF THE IL-12 CYTOKINE SUPERFAMILY

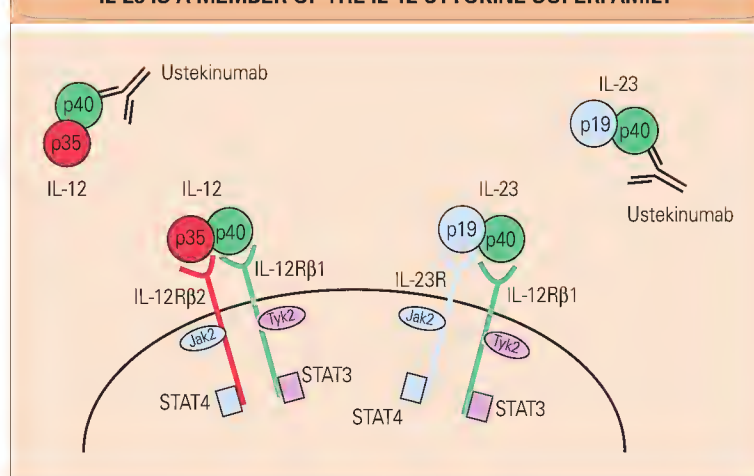


Fig. 65.1 Interleukin-23 (IL-23), a member of the IL-12 cytokine superfamily, is composed of two subunits, p40 and p19. IL-23 binds to a heterodimeric receptor composed of IL-12Rβ (shared with IL-12R) and IL-23R. Ustekinumab is a monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23. JAK2, Janus kinase 2; Tyk, tyrosine kinase 2; STAT4, signal transducer and activator of transcription 4.

Monocytes and dendritic cells in psoriatic skin plaques express high levels of the p19 and p40 subunits of IL-23.⁴⁷ Elevated serum levels of the p40 subunit of IL-23 were found to distinguish between patients with psoriatic arthritis and healthy individuals.⁴⁸

Patients with ankylosing spondylitis were found to have a higher proportion of IL-23R-expressing T cells in their peripheral blood because of a marked increase in IL-23R+ γδ T cells.⁴⁹ IL-23 serum levels were higher in patients with spondyloarthritis than in healthy individuals.^{50,51} Monocytes isolated from the peripheral blood of patients with ankylosing spondylitis that were differentiated into macrophages produced more IL-23 in response to LPS than did controls.⁵²

Infections with *Salmonella* and *Mycobacterium* have been described in individuals with homozygous mutations of either the *IL12B* gene, which encodes the p40 subunit common to IL-12 and IL-23, or the *IL12RB1* gene, which encodes a subunit of IL-12R and IL-23R.⁵³ This suggests that IL-23 may play an important role in defense against pathogens, with implications for safety issues in blockade of IL-23. Two recent meta-analyses performed to look for an association between blockade of IL-12/IL-23 for chronic plaque psoriasis and cardiovascular events had conflicting results; of note, both studies excluded trial data from patients with psoriatic arthritis.^{54,55} Further studies are needed to address this possible risk.

Clinical trials

An oral IL-12/IL-23 inhibitor, apilimod mesylate, was tested in patients with rheumatoid arthritis to determine safety, pharmacokinetics, and synovial tissue outcome but failed to induce a significant clinical response.⁵⁶

A phase 2 trial of ustekinumab, a human monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23 and blocks their signaling, was performed in patients with psoriatic arthritis. The primary endpoint was an

TABLE 65.2

Cytokines, potential inhibitors, and rheumatic disease targets

Cytokine	Method of inhibition	Disease targets
GM-CSF	Monoclonal antibody to GM-CSF Monoclonal antibody to GM-CSFRα	Rheumatoid arthritis
IL-17A, IL-17F	Monoclonal antibody to IL-17 Monoclonal antibody to IL-17R IL-17R fusion protein	Rheumatoid arthritis, psoriatic arthritis, spondyloarthritis
IL-23	Monoclonal antibody to the p40 subunit of IL-12 and IL-23 Monoclonal antibody to the p19 subunit of IL-23	Rheumatoid arthritis, psoriatic arthritis, spondyloarthritis

GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-17, interleukin-17.

ACR20 response at week 12, which was achieved by 42.1% of subjects in the treatment group and 14.3% of subjects in the placebo group ($P < .001$). Adverse event rates were reported to be similar in both groups.⁵⁷ Ustekinumab-treated patients experienced improved physical function and health-related quality of life.⁵⁸

A phase 3 trial of ustekinumab in patients with psoriatic arthritis has been completed.⁵⁹ Six hundred fifteen patients with active psoriatic arthritis were randomized to receive ustekinumab, 45 or 90 mg, or placebo at weeks 0 and 4 and every 12 weeks thereafter. Stable concomitant methotrexate was allowed. Previous anti-TNF therapy was an exclusion. The primary endpoint was the ACR20 response at week 24. A significantly greater proportion of patients treated with ustekinumab, 90 mg (49%), than placebo-treated patients (23%) achieved an ACR20 response at week 24. Nearly half the patients used concomitant methotrexate at baseline, but this did not alter the likelihood of benefit of ustekinumab versus placebo.

A second phase 3 study of ustekinumab is recruiting participants with and without previous exposure to anti-TNF agents. The primary outcome measure is the proportion of patients with an ACR20 response at 24 weeks.^{59,60}

A proof-of-concept study is recruiting subjects to investigate the safety and efficacy of ustekinumab in patients with active ankylosing spondylitis who have had an inadequate response to nonsteroidal antiinflammatory drugs.⁶¹

A phase 2 trial of ustekinumab and CNTO 195, an antibody to the p19 subunit of IL-23, is recruiting participants to evaluate the efficacy of these agents in patients with rheumatoid arthritis and concomitant methotrexate therapy. The primary outcome is the ACR20 response at week 28.⁶²

CONCLUSION

GM-CSF, IL-17, and IL-23 each have important proinflammatory roles in rheumatoid arthritis and other rheumatic diseases. Further understanding of these cytokines and their regulation has advanced rapidly. Notwithstanding potential safety concerns, careful therapeutic trials of blocking strategies directed against each of these molecules are justified by the available animal data, *in vitro* studies, and measurements performed in patients with rheumatic diseases (Table 65.2).

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66

Biosimilars in rheumatology

■ JEFFREY SIEGEL

- Recent legislation and guidelines provide an abbreviated path to approval of biosimilars.
- Because of the large size and complexity of biologics, the path to approval of biosimilars will be more complicated than that for generic small-molecule drugs.
- In rheumatology, demonstration of biosimilarity for approval will probably include clinical trials in most cases.
- Immunogenicity can have serious consequences for safety and efficacy and will be a key issue for approval of biosimilars.

Small-molecule drugs such as statins and nonsteroidal antiinflammatory drugs have a well-established pathway for the development and marketing of generic versions following a period of exclusivity for the innovator product. In contrast, until recently no similar pathway was available for the development of biosimilar versions of biologic drugs because of the complexity of their chemical makeup and manufacture. Recent developments have provided a legal and regulatory pathway for the approval and marketing of biosimilars, thereby increasing the likelihood that biosimilar versions of selected commonly prescribed biologics may become available in the not too distant future. These newer developments include the passage of legislation permitting the approval of biosimilars and the issuance of draft guidance by the U.S. Food and Drug Administration (FDA) on the process for demonstrating that a proposed biosimilar version of an approved biologic is, in fact, biosimilar to the innovator molecule. The criteria that will be applied for demonstrating biosimilarity are critical for assuring health care providers and patients that the biosimilar medications that patients receive have comparable safety and efficacy as the innovator product. The process of demonstrating biosimilarity is made more difficult by the large size and complexity of many biologics and by the propensity of many biologics to be immunogenic.

GENERIC DRUGS VERSUS BIOSIMILARS

When a new drug is approved, the manufacturer (sponsor) goes through a process of characterizing the product chemically and characterizing its toxicology in preclinical models, its pharmacokinetics, and its safety and efficacy in humans. After approval of a new drug by the FDA, a system of legal protections provides the pharmaceutical company sponsor a period of marketing exclusivity based on patent rights and on provisions that delay the marketing of generic versions until the period of marketing exclusivity is completed. The system is intended to reward innovation by companies that discover and develop new therapies in areas of unmet medical need. The Waxman-Hatch Act of 1984 (Drug Price Competition and Patent Term Restoration Act) allowed generic versions of small-molecule drugs to be approved in a simplified process when the marketing exclusivity and patent protection expire. The Waxman-Hatch Act defines a process for approving generics based on their bioequivalence to the innovator drug following submission of an Abbreviated New Drug Application (ANDA). In general, a sponsor submitting an ANDA provides evidence that the generic version has the same chemical structure as the innovator molecule and is bioequivalent in pharmacokinetic (PK) studies in humans. In this abbreviated pathway, if a generic drug is determined to be bioequivalent, the sponsor is not required to perform toxicology studies in animals or to conduct safety or efficacy studies in humans. This process allows generic drug manufacturers to market generic versions of drugs at lower cost to consumers.

Since ANDAs are not required to include studies of safety and efficacy in humans, the FDA relies on evidence of safety and efficacy for the approval of generic drugs that was not derived by the ANDA sponsor. For applications that rely solely on chemistry and bioequivalence, the FDA uses a provision termed 505(j) to allow the use of evidence not derived by the sponsor. In other situations in which a sponsor submits a New Drug Application (NDA) for a version of a previously approved drug, for which additional information beyond chemistry and bioequivalence are required, a similar provision, termed 505(b)(2), allows the FDA to rely on evidence not derived by the sponsor.

The term *biologic* refers to a number of different types of products, including therapeutic proteins, vaccines, blood products, and cell and gene therapies. In their practice rheumatologists prescribe several different types of biologics, such as vaccines, blood products (e.g., intravenous immune globulin), and therapeutic proteins, including monoclonal antibodies and soluble receptors (Fc fusion proteins). This chapter focuses on therapeutic proteins, although similar considerations may apply to other types of biologics. In contrast to small-molecule drugs, which are manufactured synthetically, biologics are made in biologic systems and the active moiety is then extracted and purified. Biologics are generally larger and much more complex molecules than small-molecule drugs. In addition, the properties of a biologic are sensitive to subtle changes in manufacturing that may not be apparent based on chemical characterization. Because of these important differences between small-molecule drugs and biologics, the Waxman-Hatch Act, which allowed approval of generic drugs, did not contain the necessary provisions to apply to biologics. Therefore, until recently there was no abbreviated pathway to approval of biosimilars.

WHY IS A DIFFERENT PROCESS NEEDED FOR BIOSIMILARS?

The abbreviated process for approval of generic small-molecule drugs relies on the idea that knowing that the chemical structure of a generic version and its distribution in the human body (bioequivalence) are the same as for the innovator product provides sufficient evidence to predict that its efficacy and safety will also be equivalent. The process of demonstrating chemical identity is made easier by the fact that small molecules are, by definition, small and have a relatively simple chemical structure. They are manufactured via chemical processes that are designed and carefully controlled to ensure that all molecules of the drug are identical. Strict controls are placed on the manufacturing process to make sure that other materials used in the chemical reactions are removed and any impurities are kept within specified, narrow limits. Of note, the manufacturing process for producing a generic is not usually the same as that for producing the innovator product, but chemical characterization and demonstration of bioequivalence ensure that the resulting molecules are sufficiently similar despite differences in their manufacture.

In contrast to small-molecule drugs, the composition and structure of therapeutic proteins and other biologics are much more complex (Table 66.1). To begin with, therapeutic proteins are much larger (typically 150 kDa for monoclonal antibodies versus less than 1 kDa for small-molecule drugs). In addition, knowing the primary structure alone (i.e., the amino acid sequence) does not allow prediction of the overall structure of the protein (Fig. 66.1). Rather, the amino acid residues in the nascent polypeptide chain interact with neighboring residues to form secondary structures (e.g., α -helices and β -sheets), and the protein folds to form its final structure in space (tertiary structure). Finally, many therapeutic proteins, including monoclonal antibodies, consist of multiple polypeptide chains interacting with one another in a specific manner to form its characteristic quaternary

Fig. 66.1 Protein complexity: structure.

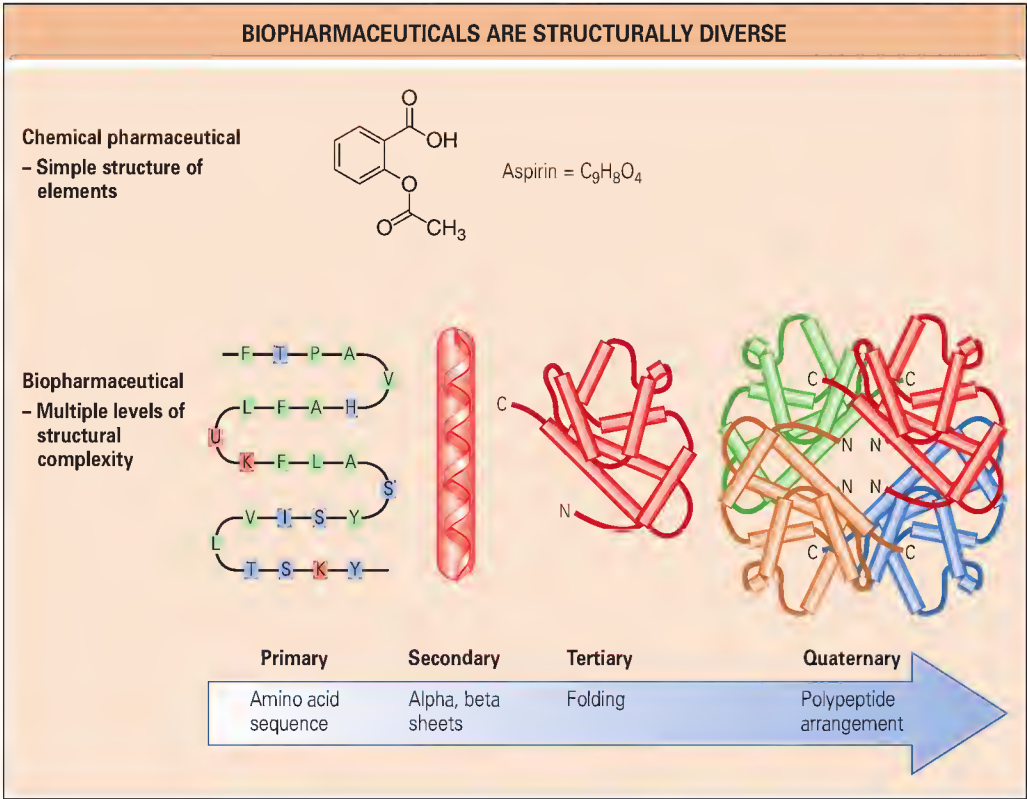


TABLE 66.1
Key differences between small-molecule drugs and biologics

Small-molecule drugs	Biologics
Generally small, less complex molecules	Large, highly complex molecules
Uniform	Complex mixture of related forms
Synthesized chemically	Produced in biologic systems
Generics process	Biosimilar process
Demonstration of similar structure, bioequivalence in pharmacokinetic studies	Demonstration of similarity in structure, function, preclinical studies, pharmacokinetics, pharmacodynamics, and clinical safety and efficacy
Immunogenicity—typically not an issue	Immunogenicity highly dependent on small changes in structure and on manufacturing
Interchangeable with the reference product	Requires independent demonstration of interchangeability

structure. The precise primary, secondary, tertiary, and quaternary structure of therapeutic proteins determines their biologic properties.

Biologics are not synthesized by using chemical methods; they are produced in living organisms. Monoclonal antibodies and other therapeutic proteins are typically grown in cell lines. The process begins with the introduction into cell lines of DNA coding for the polypeptide chains making up the therapeutic protein. The cell line transcribes the DNA and translates it into protein. The cell line is expanded in large incubators. The cells are then harvested and the therapeutic protein is extracted and purified. By allowing the cell line to produce the therapeutic protein, the same biologic control mechanisms that cells ordinarily use to ensure the proper sequence and folding of native proteins generate the proper sequence and folding of biologics in the engineered cell line.

The cell line also modifies the protein in a variety of ways, termed *post-translational modifications*, by using the same enzymes and processes that it uses in generating native proteins (Fig. 66.2). These modifications include the addition of sugars, such as mannose and sialyl residues, and modification of amino acid residues by oxidation or deamidation. These modifications are not absolutely uniform; that is, individual protein molecules may

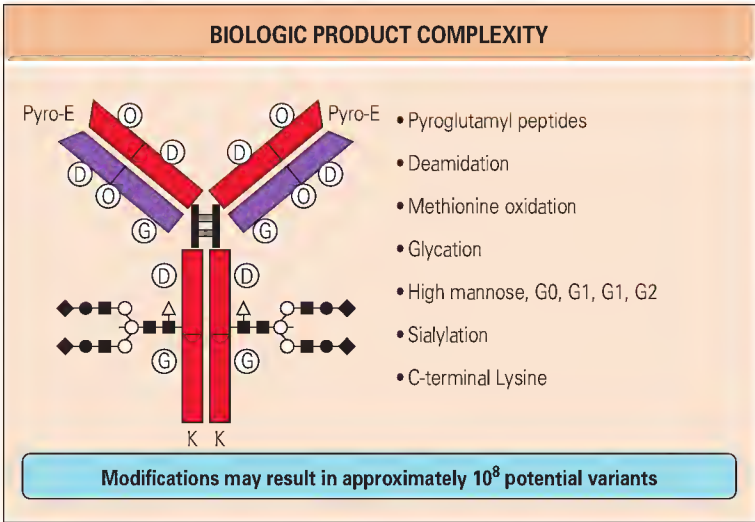


Fig. 66.2 Examples of modifications inherent or attributable to the manufacturing process. (Adapted from Steven Koslowski, Food and Drug Administration.)

differ from one another in their particular modifications, such as the extent of glycosylation. Further modifications may be contributed by the manufacturing process. As a consequence of these changes in the proteins, biologics are not generally composed of a uniform set of identical molecules as small-molecule drugs are. Instead, biologics are composed of an array of closely related molecules sharing a common amino acid sequence and similar structure but possessing a range of posttranslational modifications.

The considerations just mentioned illustrate why the pathway defined for approval of generic versions of small-molecule drugs would not work for biologics. Because of the complexity of biologics and the different manufacturing processes that the innovator and the biosimilar manufacturer would use, it is likely that a biosimilar would differ from the reference biologic in ways that could affect its biologic activity in unpredictable ways. Hence the safety and efficacy of a biosimilar cannot be assumed based on chemical characterization and PK bioequivalence alone. In the past a sponsor who wished to develop a biosimilar version of an innovator molecule after exclusivity had expired could have characterized the molecule in the same manner as for a new molecular entity (i.e., conducting studies

of toxicology in nonclinical models and safety and efficacy studies in humans). However, no abbreviated pathway for the development of biosimilars was available until recently with the approval of new legislation and guidance from the FDA.

LEGISLATIVE AND REGULATORY FRAMEWORK FOR BIOSIMILARS

After many years of consideration the U.S. Congress passed new legislation that provided for approval of biosimilars. The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) provided an abbreviated pathway for the approval of biosimilar versions of an FDA-licensed reference biologic that permits sponsors of biosimilars to use evidence that they had not derived themselves when the biosimilar version had been shown to be biosimilar to the reference biologic. However, even though the BPCI Act provided a pathway for approval of products shown to be biosimilar to or interchangeable with a reference approved biologic, it did not specify how biosimilarity or interchangeability would be determined. That awaited further communication from the FDA on how the BPCI Act would be implemented.

In February 2012, the FDA issued a draft guidance document titled “Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” which provides general principles regarding the evidentiary standard that the FDA will apply in reviewing applications for approval of biosimilars.¹ The draft guidance states that because of the complexity of the proteins, biosimilar products are unlikely to be identical to the reference product. Furthermore, minor differences in structure may have a significant impact on safety and efficacy. Hence, an approach such as that used for evaluating generic small-molecule drugs, which relies on demonstrating structural identity and bioequivalence based on PK studies, would not be sufficient for evaluating biologics. Rather, the draft guidance states that a 351(k) application for a biosimilar should contain evidence of biosimilarity based on analytic studies, animal studies, and one or more clinical studies of a condition of use for which the reference biologic is approved.

In its development program, a biosimilar sponsor would provide data to demonstrate that the biosimilar is very similar to the reference product. If the FDA reviewed the data and agreed that the product was biosimilar, it would conclude that the product met the standards for approval via the 351(k) pathway. What would happen if the differences were too large for the product to be deemed biosimilar? Would any other path to approval be available? In principle, the answer is yes. If a reference biologic is no longer under patent protection, a biosimilar manufacturer could follow the same pathway to approval as for a new molecular entity (NME) by conducting analytic studies and demonstrating safety and efficacy in animal and human studies. However, such a molecule could not take advantage of the abbreviated pathway of a 351(k) application. Approving such a product as an NME would be similar to the approach taken for biologics such as novel monoclonal antibodies that have the same target as an approved biologic but are derived independently and therefore have a distinct molecular composition. Similarly, the BPCI Act does not define an abbreviated path for products that are like a reference biologic but are designed to be improved in some manner, such as more potent or less immunogenic than a reference product. Such products are sometimes termed “biobetters” and would presumably need to follow the standard process for approval as an NME since the differences would preclude demonstrating similarity. Although it may seem counterintuitive that a more potent molecule would not meet the standards of biosimilarity, it must be kept in mind that a more potent product could have a different safety profile. In summary, a 351(k) application provides an abbreviated pathway for products that are versions of a reference product and in which any differences are so small they can be judged to be biosimilar.

MOLECULAR COMPLEXITY OF BIOLOGICS

In general, as detailed earlier, biologics are much more complex than small-molecule drugs. Their structure is determined not only by their amino acid sequence (primary structure) but also by their secondary structure (α -helix and β -sheet formation), tertiary structure (overall folding of the polypeptide chain), and the interaction between polypeptide chains making up the protein (quaternary structure). In addition, proteins undergo glycosylation and a variety of posttranslational modifications that have important implications for their structure and chemical and biologic properties. Structural analysis of protein biologics demonstrates that even after rigorous

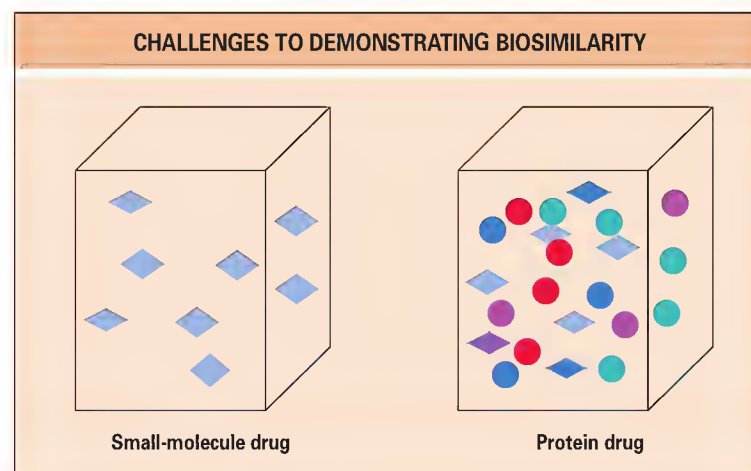


Fig. 66.3 Protein microheterogeneity.

purification a biologic is made up of a mix of molecules that vary within a range (Fig. 66.3). Based on the known variation it has been estimated that a given antibody molecule could theoretically have as many as 10^8 potential variants (see Fig. 66.2). Manufacturers of biologics carefully characterize the chemical and structural properties of their products and set specifications for the allowable amount of variation to ensure that a new batch is within the range of characteristics seen with previous batches. Only batches that fall within specifications are allowed to be marketed and prescribed.

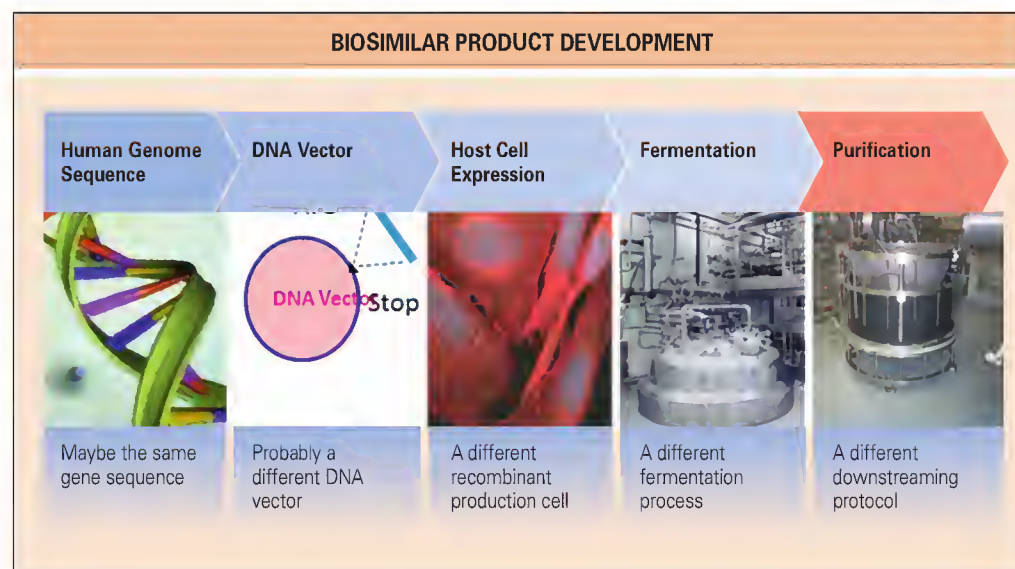
During the life cycle of a biologic the manufacturer will occasionally make changes in the manufacturing process, for example, to make the process more efficient or to reduce impurities. How do they make sure that the resulting product has the same properties as product from the previous manufacturing process? They do this by assessing comparability of the new and previous products. First, any process changes undertaken cannot fundamentally change the product. Otherwise, it would be considered a new product and would need to undergo testing as an NME. However, even seemingly small changes in manufacturing can lead to some change in the structural properties of the resulting product.² In general, if the two products are sufficiently similar, only biochemical characterization may be sufficient. If changes are present but they appear to be minor, bioequivalence studies may be required. Finally, if the changes are more than minor, clinical studies demonstrating similarity may be needed as well.

The process that manufacturers undertake when they make a manufacturing change in a biologic is highly regulated. The process is defined, in part, in documents such as the International Congress on Harmonisation (ICH) Q5E guidance document.³ This document acknowledges that because of the complexity of protein biologics, comparability does not necessarily mean identity. Rather, it means “. . . that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.” In particular, demonstrating comparability means having a detailed understanding of how the structural attributes of a protein relate to its function.

The variations observed in a protein molecule have important implications for the safety and efficacy of biologics. In some cases these variations determine the biologic activity of the resulting product. For example, experiments with human erythropoietin (HuEPO) have demonstrated that differences in its sialic acid-containing carbohydrate content have a direct relationship with its PK properties and bioactivity. Darbepoetin alfa is a recombinant human erythropoietin (rHuEPO) engineered to have two extra carbohydrate chains. Egrie and colleagues^{3a} showed that darbepoetin alfa had a longer half-life and was more potent than rHuEPO. Another example relates to monoclonal antibodies with antitumor activity, which are typically IgG1 antibodies possessing core fucosylation. Antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer (NK) and other cells is an important mechanism of tumor killing. Recent studies have shown that defucosylation of these antibodies leads to great receptor binding on NK cells and enhanced ADCC.⁴ Thus, glycosylation controls a property critical to the efficacy of these products.

Even though it is complicated for a manufacturer to demonstrate comparability after a change in manufacturing, it is much more complicated still for a biosimilar manufacturer to demonstrate biosimilarity to a reference biologic. When a biologic manufacturer makes a manufacturing change, everything is generally kept the same except for the change in the process

Fig. 66.4 Potential differences with a different manufacturer.



being undertaken. In contrast, when a biosimilar manufacturer undertakes to produce a biosimilar, many changes in the process with respect to the reference product will take place (Fig. 66.4). First, the sequence of the gene for the protein may or may not be the same as the reference product. In addition, to introduce the gene into cells it will probably have a different DNA vector. Then the host cell line used for expression will probably be different, with the potential for changes in protein processing within the cell. The cell lines will then be grown in a different process, and purification of the protein will probably differ. How much each of these differences will contribute to differences in the final product cannot be predicted.

In summary, the molecular complexity of biologics and the complex nature of the manufacturing process mandate a process for determining the similarity of biosimilars to reference biologics that is different from the process used for generic small-molecule drugs. Subtle differences in the molecular composition of biologics can have profound effects on their biologic activity. The FDA strictly regulates changes in the manufacturing process for approved biologics to ensure comparability.

CASE HISTORY: ERYTHROPOIETIN AND PURE RED CELL APLASIA

One important property of biologics that can interfere with their efficacy and safety is immunogenicity, namely, the ability to induce an immune response to the protein that results in antitherapeutic antibodies (ATAs). Many variables influence the immunogenicity of biologics, including the extent of foreign (i.e., nonhuman) sequences, route of administration, dose, concomitant medications, and disease status. The FDA requires careful assessment of immunogenicity for new biologics. The consequences of immunogenicity vary depending on the type of antibodies produced, their concentration and affinity, and the nature of the biologic in question. For monoclonal antibodies, ATAs can result in loss of efficacy either by binding to the active site of the biologic and thereby neutralizing its activity or by increasing its clearance in the body so that the concentration of the biologic falls below the therapeutic range. ATAs to monoclonal antibodies can also result in adverse events by inducing hypersensitivity reactions, vasculitis, or infusion or injection site reactions. Adverse events related to the immunogenicity of monoclonal antibodies generally dissipate when the biologic is cleared from the body.

For biologics that are also normal constituents of the human body, in addition to the aforementioned consequences of immunogenicity, there is the additional possibility of the ATA cross-reacting with the native protein and consequently reducing its concentration or neutralizing its activity with the potential for effects on normal physiology. When ATAs are produced to a biologic that is also a form of a naturally occurring protein and the ATAs cross-react with that native protein, the ATA may persist long after the biologic is cleared. If that native protein has a nonredundant function, the consequences can be serious. The occurrence of anti-EPO antibody-mediated pure red cell aplasia (PRCA) with certain products of rHuEPO illustrate the occurrence of ATAs and the potential consequences.

Several versions of rHuEPO have been approved for certain forms of anemia, including the anemia related to chronic kidney disease and the

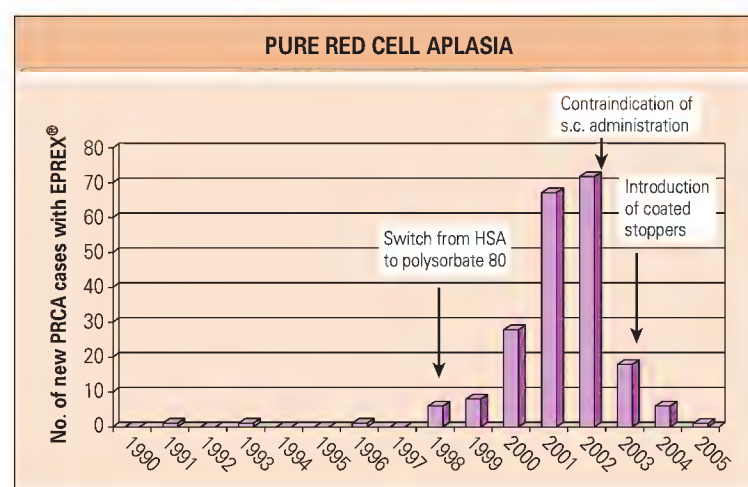


Fig. 66.5 Pure red cell aplasia (PRCA) with recombinant human erythropoietin. A small change in formulation led to unpredicted immunogenicity. HSA, human serum albumin; s.c., subcutaneous.

anemia related to the effects of concomitant myelosuppressive therapy. Initially, when rHuEPO was introduced into medical practice, the adverse event PRCA was observed rarely. Specifically, for the 10 years from 1988 to 1998, PRCA occurred in only three patients. This rare condition is caused by antibodies to rHuEPO that cross-react with and neutralize native EPO. Since the human body does not have alternative mechanisms for inducing erythropoiesis, these antibodies inhibit erythropoiesis and lead to selective loss of red cells. Beginning in 1998 an outbreak of PRCA was seen that was associated with the use of rHuEPO (Fig. 66.5).⁵ In the 2 years between 1998 and 2000, 13 cases of PRCA were reported in France—12 in patients receiving the product Eprex with the active ingredient epoetin alfa and 1 in a patient receiving NeoRecormon containing epoetin beta, both products that are marketed exclusively outside the United States. By 2004 a total of 175 cases had been reported for Eprex, 11 for NeoRecormon, and 5 for Epogen, another rHuEPO product.

What led to this dramatic increase in the occurrence of PRCA with rHuEPO? Several potential changes were identified that may have precipitated the change in immunogenicity. First, beginning in the 1990s there was a switch from administration by the intravenous route to subcutaneous administration. This may have contributed since the subcutaneous route of administration of proteins can be more immunogenic.⁶ However, alone it would not fully explain the observation that most cases occurred in Europe. In 1998 the formulation of Eprex was changed to substitute human serum albumin (HSA) because of concern on the part of European health authorities that HSA could transmit a variant of Creutzfeldt-Jakob disease. The reformulated, HSA-free version of Eprex contained polysorbate 80 as a stabilizer and had different recommendations for handling the product. In contrast, other rHuEPO products prescribed in the United States, Epogen

(epoetin alfa) and Aranesp (darbepoetin alfa), had always included HSA as a stabilizer. A variety of explanations have been offered on how changes in the formulation of Eprex marketed outside the United States could have led to an increase in immunogenicity. In general, the explanations center on the likelihood that the new formulation, because of either micelle formation, leachates from rubber stoppers, or a combination of both, was less stable and led to aggregate formation, which increased the likelihood of antibody formation. After recognition of the risk for PRCA, measures were taken to ensure proper storage, handling, and administration of Eprex, and the rubber plungers in the prefilled syringes were replaced by Teflon-coated plungers. After the institution of these new measures, the incidence of PRCA decreased by more than 80% worldwide.

The story of PRCA associated with a change in the formulation of an rHuEPO product illustrates several important principles. First, changes in the manufacture of a biologic may affect its biologic properties in important ways that cannot always be anticipated. Even the sophisticated structural studies used to characterize a biologic may not always detect changes that can affect important properties such as immunogenicity. The experience with PRCA and rHuEPO is relevant to the optimal approach to characterizing biosimilars since by its nature the production of biosimilars involves a change in manufacturing with respect to the reference product. In Thailand it was noted that the occurrence of PRCA was concomitant with the increased use of different follower rHuEPO products.⁷ To confirm the association between these products and PRCA, 30 patients who had experienced loss of efficacy with such rHuEPO products were studied. Of the 30, 23 had anti-EPO antibodies and PRCA. In response to this epidemic, the FDA of Thailand instituted a registry to estimate the immunogenicity and efficacy of rHuEPO products. Such follower products with inadequate approval as generics were not marketed in the United States. Another example of the important impact that subtle changes in manufacturing and administration of biologics can have on immunogenicity relates to HX575, a biosimilar rHuEPO approved for intravenous administration in Europe. When HX575 (Binocrit) was studied in a randomized trial by subcutaneous administration against Eprex, both products were able to raise hemoglobin levels to a similar degree with similar dosing. Nonetheless, the trial had to be stopped early because ATAs developed in two patients in response to subcutaneous HX575, one of whom also had PRCA.^{8,9}

WHAT WILL THE FOOD AND DRUG ADMINISTRATION REQUIRE TO APPROVE A BIOSIMILAR?

In the draft guidance the FDA described an approach to evaluate a proposed biosimilar product. This approach assumes that biosimilars are unlikely to be identical to the reference product. They proposed a stepwise approach that begins with analytic studies of the proposed biosimilar, followed by animal studies and then clinical studies in humans. Each step is intended to assess the extent of differences from the reference product. If analytic studies and animal studies indicate few differences, the likelihood of demonstrating biosimilarity on study in humans increases. In particular, if few differences are seen, the subsequent clinical studies may be more targeted. The FDA justified this stepwise approach by noting that “even minor structural differences” in a biologic can affect its safety, purity and potency. In particular, they noted that minor process impurities can increase the likelihood of an immune response to a biologic and that current analytic methods may not be sufficient to detect relevant differences.

The first step that the FDA recommended for assessment of biosimilarity is study of the structure and function of the molecule followed by animal toxicology studies to identify potential toxicities in humans and to make sure that no additional toxicities are seen beyond what was observed with the reference product. If these studies indicate similarity of the proposed biosimilar to the reference biologic, studies could commence in humans to assess pharmacokinetics, pharmacodynamics, and finally safety and efficacy for at least one of the approved indications. Of particular concern is immunogenicity since ATAs can influence both the safety and efficacy of a biologic and changes in manufacturing are known to have the potential to influence immunogenicity. Assessment of immunogenicity begins with study of the development of ATAs in animals. In general, immunogenicity of biologics in animals does not predict immunogenicity in humans. However, when assessing proposed biosimilars, comparison of the antibody response in animals to that of the reference biologic can identify differences that may predict the development of ATAs in humans. The next step in assessing immunogenicity is comparing ATAs in humans for the proposed product and the reference biologic in clinical trials conducted before approval (pre-market). The extent of premarket immunogenicity testing depends on a

variety of factors, including the potential consequences of ATAs, such as the possibility of anaphylaxis or situations in which the biologic is a form of a naturally occurring, nonredundant protein in the body (e.g., rHuEPO). Finally, additional postmarket testing for ATAs may be required.

In the end the agency states that it will consider the totality of the evidence in determining biosimilarity and making approval decisions. The FDA has discretion to not require one or more required elements. However, which elements that the FDA may not require in any given situation is unknown. Sponsors should meet with the FDA to discuss their program during development so that the FDA can offer advice on the sponsors' proposed development plan.

WHAT WILL A CLINICAL DEVELOPMENT PROGRAM FOR A BIOSIMILAR LOOK LIKE?

The final step in development is studies in humans. Since the objective of these studies is to demonstrate biosimilarity, they will by nature be comparative studies to the reference biologic. The clinical development program will begin with PK and pharmacodynamic (PD) studies. PK studies will serve to demonstrate that similar blood levels are observed with the proposed biosimilar and the reference product but will also assess whether there may be differences in the way that the human body handles the proposed biosimilar that could reflect subtle but potentially important differences in structure or formulation. PD measures assess drug effects on the body and are generally chosen to reflect the mechanism of action (e.g., the effect of tumor necrosis factor [TNF] inhibitors on C-reactive protein [CRP]). PD studies serve to determine whether there are any differences in the way that the proposed biosimilar affects the body in mechanistically important ways.

When PK and PD studies have been completed, the final step is one or more clinical trials for a relevant indication. The design of such a trial follows from the objectives of the trial, namely, to demonstrate similarity to the reference biologic. To illustrate some of the considerations in designing a clinical development program, let us consider a proposed biosimilar to a TNF inhibitor for rheumatoid arthritis (RA). The study arms would be the proposed biosimilar and the reference product at one or more of the approved doses. When the reference TNF blocker is approved both as monotherapy and in combination with methotrexate (MTX), the biosimilar sponsor would need to decide whether to study monotherapy, to enroll patients with background MTX, or to study both conditions of use. On the one hand, TNF blockers are frequently added to MTX in patients with an inadequate response to MTX.¹⁰ Immunogenicity can be higher with monotherapy than in combination with MTX for some products, and the guidance document recommends that when a sponsor wishes to extrapolate the immunogenicity findings from one indication to another, the condition of application that is most sensitive to detect a difference in immunogenicity should be used. In situations in which monotherapy with the reference product is more immunogenic, a study in monotherapy could be considered a more sensitive test for differences in immunogenicity.

Since the goal of a biosimilar development program is to show similarity, the FDA recommends the use of an equivalence design, which is closely related to the noninferiority design that is commonly used to compare a new product with an active control but with some important differences (Fig. 66.6). In a noninferiority study the new product is compared with the active control with the objective of showing that it is at least as good as the active control. Since it is statistically impossible to show that two products are exactly as good as each other, a noninferiority study instead aims to show that the new product is no more than a very small amount inferior. Because noninferiority designs generally do not include a concurrent placebo control, it is necessary to make an assumption about how well a placebo control would have done if one had been included. To design such a trial then calls for evidence from previous placebo-controlled trials about the effect size of the active comparator. For example, if the American College of Rheumatology (ACR) 20 response for the active comparator was 55% in previous trials and the placebo response was 20%, the effect size was 55% – 20% = 35%. Then the trial needs to set a noninferiority margin (i.e., the size of inferiority that must not be exceeded). In general, the noninferiority margin is based on what is a clinically acceptable margin of noninferiority by taking into account the fact that very small noninferiority margins require commensurately large sample sizes. If the study sets a noninferiority margin of 10%, a successful trial shows an effect size of 25% or more, thereby demonstrating preservation of at least 71% of the effect size of the reference product (25%/35%). A comparative trial of this type would also allow a comparison of the safety of the two products side by side.

An additional complexity of a biosimilar clinical development program is that the clinical trial should demonstrate that the proposed product is

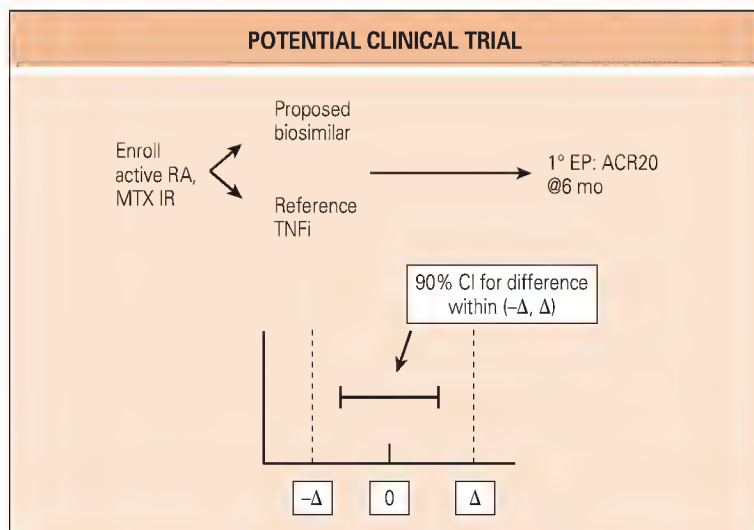


Fig. 66.6 Potential clinical trial to compare a proposed biosimilar with an approved tumor necrosis factor (TNF) blocker. ACR20, American College of Rheumatology 20% response; CI, confidence interval; EP, endpoint; MTX IR, methotrexate incomplete responder; RA, rheumatoid arthritis.

neither worse nor better than the reference product. Therefore, the optimal clinical trial design is actually an equivalence study rather than a noninferiority study. An equivalence trial would be designed to demonstrate that the proposed product is neither inferior nor superior to the reference product by the specified margin (e.g., 10%). Although this requirement may seem counterintuitive, the concern is that if a proposed biosimilar is actually more effective than a reference product, it may be more potent, in which case the safety of the product cannot be assumed to be the same.

A well-designed and well-conducted equivalence trial would provide clinical evidence that the proposed product behaves clinically like the reference product with respect to safety and efficacy, thus supporting the evidence of similarity provided by previous studies to support a conclusion of biosimilarity.

AREAS OF UNCERTAINTY

The FDA draft guidance document on biosimilars contains information on two additional important areas related to biosimilars: interchangeability and whether a biosimilar will receive all indications for which the reference biologic is approved or just a subset of the indications. These are both complex areas in which it is uncertain how the considerations described in the draft guidance will be applied in practice.

Interchangeability

Under most states' pharmacy substitution laws, pharmacists can substitute a generic for a reference product without requesting permission from the prescribing health care provider unless the prescriber specifically declines substitution. The scientific rationale for interchangeability for a generic small-molecule drug is that the approval process for the generic includes a review of evidence for structural identity and bioequivalence within the human body that ensures that the two products will behave every bit the same.

The FDA has a provision to allow interchangeability. Labels for biosimilars will contain a statement on whether the product has or has not been shown to be interchangeable with the reference product. However, the assumptions behind allowing an abbreviated pathway for approval of generic small-molecule drugs and biosimilars are distinctly different. Unlike proposed generic small-molecule drugs, proposed biosimilars are assumed to be likely not to be identical to the reference product. The process for assessment of biosimilars is a step-by-step procedure designed to show that the two products are very similar and that any small differences will not affect safety and efficacy. Whether the data that support biosimilarity are adequate to allow interchangeability is a different matter.

A key issue in concluding that the biosimilar can be interchanged with the reference product is whether the immunogenicity will be the same. If it is not, there is a risk that ATAs could develop in a patient who is switched to a biosimilar and prevent a clinical response to the reference biologic when

it is switched back. In addition to biosimilarity, to conclude interchangeability a biosimilar sponsor will need to provide evidence that after repeated administration the safety and efficacy of switching are no different from staying with the reference product. Although it makes intuitive sense that evidence of this type would support interchangeability, it is not at all clear at present how a sponsor would design a program to provide the necessary data. Among the questions a sponsor would need to answer are how safety and efficacy would be evaluated and how it would be demonstrated that immunogenicity after switching back is no different from that in patients who stayed with the reference product.

What indications will biosimilars be approved for?

When generic small-molecule drugs are approved, their label is derived from the label of the innovator product. With some exceptions the generic label lists the indications for which the innovator product is approved. One exception to this rule is that if the innovator conducted clinical trials to receive an additional indication, that additional indication may be protected for a time by exclusivity provisions. The BPCI Act allows approval of a biosimilar for additional indications beyond those studied in the clinical trials for approval by extrapolating from the indications that were studied and relying on evidence of safety and efficacy from the reference product. However, the decision to grant additional indications is not automatic. Rather, the sponsor will need to provide scientific justification for why similar safety and efficacy as the reference biologic would be expected for any additional indications. The rationale for this more cautious approach for biosimilars is that small differences are expected between reference biologics and proposed biosimilars and it is important to provide assurance that those small differences will not affect safety and efficacy for an indication (e.g., ankylosing spondylitis) for which a sponsor wishes to extrapolate safety and efficacy from another indication (e.g., RA).

For the biologics currently used in rheumatology, many are approved for multiple indications. The biosimilar draft guidance document specifies some of the considerations that the FDA will take into account in deciding which indications that a biosimilar will receive. Such considerations include any possible differences in mechanism of action, in PK characteristics, and in safety between the various indications. With respect to the mechanism of action, relevant considerations include the target or receptor for the relevant activity of the product, the location and expression of the receptor or target, binding of the product to the target, and what is known about the relationship between the structure of the product and its binding to the relevant target. For PK considerations the biosimilar sponsor will need to take into account how the PK properties of a reference biologic product differ between different indications, how the toxicities differ between different indications, and any other factors that may influence the safety and efficacy of a product differently in different indications.

Many examples of how biologics are used differently in different indications can be cited. Adalimumab is approved for RA, for Crohn disease, and for ulcerative colitis. However, the approved dose for RA is 40 mg subcutaneously every other week, whereas for Crohn disease a 160-mg loading dose on day 1 and then 80 mg on day 15 followed by 40 every other week beginning on day 29 is recommended. This difference in dosing presumably reflects a difference in the relevant targets in Crohn disease versus RA and the differential ability of a given concentration of adalimumab achieved in blood to block the target. For some biologics the rate of immunogenicity is lower when they are administered in combination with immunosuppressives than when administered as monotherapy. For these biologics the condition of use (concomitant immunosuppressives versus monotherapy) influences the rate of immunogenicity. In situations such as these, when the relevant properties of a biologic differ between indications, the draft guidance document recommends using the more sensitive condition for extrapolating from one condition of use to another. Thus, if immunogenicity is more frequent in one condition of use, study of that condition could allow extrapolation to the condition with less immunogenicity, but not vice versa. Similarly, if a particular toxicity is more frequent in one condition of use, it may not be possible to extrapolate safety from study of the indication in which that toxicity is less frequently observed.

One particular condition of use that is not addressed specifically in the draft guidance is use in children. For small-molecule drugs and biologics that are approved for adults, the Pediatric Research Equity Act (PREA) requires that the sponsor study the product in children with the same condition. On this basis several TNF blockers have been studied and approved for use in children with polyarticular juvenile idiopathic arthritis. It remains an open question whether the FDA would grant an indication for children without some study in pediatric patients. PK and PD studies in children could be carried out, but efficacy studies would be quite challenging since

comparative noninferiority or equivalence trials could require large sample sizes, which may be impractical. Whether pediatric studies would be required for biosimilars as they are for innovator biologics is an unanswered question.

Because biosimilars are not expected to be identical to the reference biologic and because small differences in structure can affect safety and efficacy in unpredictable ways, an approved biosimilar would not automatically receive all the indications as the reference product. Instead, the sponsor will need to provide scientific rationale to support approval for additional indications beyond the ones that they study directly. The extent of study required to obtain approval for other indications will depend on how close the proposed biosimilar is to the reference product and the likelihood that small variations could cause differences in safety and efficacy for the different indications.

APPROACH TO BIOSIMILARS IN OTHER REGIONS

The World Health Organization (WHO) and the European Union have also issued guidelines for the evaluation of biosimilars. The WHO guidelines, issued in 2009, provide a framework similar to that incorporated into the FDA guidance document.¹¹ The pathway defined by the European Union (Fig. 66.7) is similar but not identical to that in the United States and predates the U.S. legislation. Legislation allowing biosimilars was first passed in the European Union in 2004, and overarching guidelines describing the principles to be used when assessing biosimilars were released in 2005.¹² Guidelines have also been proposed for quality (i.e., product attributes) and for nonclinical and clinical considerations. Product-specific guidelines have been issued for insulin, somatotropin, granulocyte colony-stimulating factor, rHuEPO, and others. Somatotropin was the first biosimilar approved via this pathway in 2006. Currently, approximately a dozen biosimilars have been approved. The majority of them fall into the categories of somatotropin, rHuEPO alfa, and filgrastim. These molecules are smaller than monoclonal antibodies and are considerably less complex. At the time of this writing no monoclonal antibody or Fc fusion protein biosimilar has been approved in the European Union.

The process for demonstrating that a proposed biosimilar will have similar safety and efficacy as a reference product is generally similar in the European Union to the process described earlier in the United States, with some important differences. Both regions recognize that because of the complexity of biologics, the approach used for approval of generic small-molecule drugs is not scientifically appropriate. In both regions it is recognized that the differing manufacturing processes used by the innovator and biosimilar sponsor will lead to some differences between the two products. The E.U. guidelines recognize that although currently available assays are very good in discerning differences between protein molecules, it is not possible to predict how minor structural differences will translate into physicochemical or clinical differences.

In the European Union, approval of a biosimilar requires demonstration of the similar nature of the proposed biosimilar and the reference product. The biosimilar sponsor conducts comparability studies to demonstrate that the two products are sufficiently similar with respect to quality, safety, and efficacy. This is analogous to the FDA-defined process that calls for demonstrating that the two products are sufficiently similar to be deemed biosimilar, thereby ensuring that there are “no clinically meaningful differences . . . in terms of the safety, purity or potency of the product.” As in the United States, the assessment begins with studies of structure and function *in vitro*. At this point the degree of similarity that was demonstrated guides the need for subsequent studies. The E.U. guidelines allow the possibility that dose-comparative and highly sensitive PD studies could convincingly show comparability in a clinically relevant manner, thereby obviating the need for clinical trials. However, to use a PD study, the PD marker must be an accepted surrogate (i.e., evidence that an effect on the surrogate reliably predicts a corresponding effect on the clinical outcome measure). Since PD measures that are accepted surrogates are not available for most rheumatologic diseases, PD studies are unlikely to be the basis for approval of biosimilars for these indications. Therefore, normally it is expected that similar clinical efficacy between the proposed biosimilar and the reference product would be demonstrated in “adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blinded and normally equivalence trials,” which is very close to the standard enunciated by the FDA. Other aspects of the E.U. approach that are similar to the FDA approach include the recommendation to use the most sensitive model for PD and clinical studies and allowance of extrapolation to other indications with adequate justification.

The E.U. guidelines also specifically relate to assessment of the postmarketing safety of biosimilars. Pharmacovigilance may need to be greater than what is ordinarily called for, including the possibility of participating in new or existing registries. Sponsors must address how postmarketing safety will be assessed with respect to indications that used extrapolation but were not specifically studied with the proposed biosimilar, rare serious adverse events seen with the reference biologic, and new safety signals as with any marketed biologic. The brand name of the product given to a patient should be recorded to aid in traceability. Traceability could be important in situations in which one or more biosimilars are on the market along with the innovator product.

Guidelines of the European Medicines Agency (EMA) do not specifically offer recommendations concerning interchangeability. Rather, interchangeability (or substitution) is left to the member countries.

In the past, developing countries have allowed marketing of products that are purported to be biosimilars but have not undergone the rigorous evaluation described in the U.S., E.U., and WHO guidelines. It is not clear in all instances that these products are, in fact, biosimilar to the reference product. Key to the U.S. and EMA approval process for biosimilars is conduct of head-to-head studies comparing the proposed biosimilar with the reference product. In other countries with less rigorous regulatory processes, such studies may not be required for marketing. Studies evaluating alternative rEPO products outside the United States and European Union

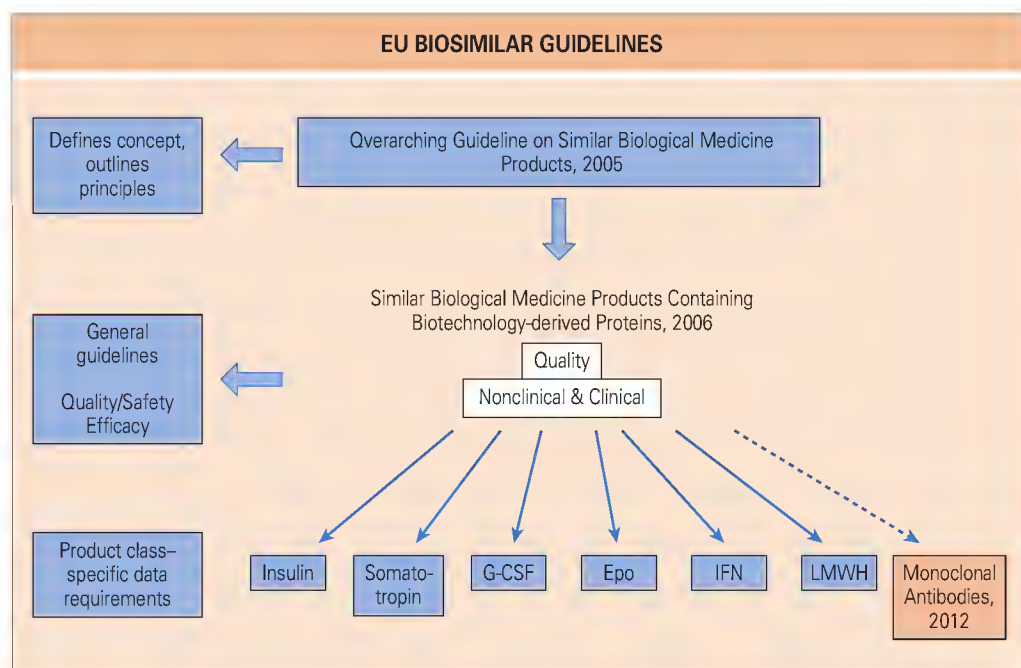


Fig. 66.7 Framework for E.U. assessment of biosimilar products. Epo, erythropoietin; G-CSF, granulocyte-colony stimulating factor; IFN, interferon; LMWH, low-molecular-weight heparin. (From McCamish M, Woollett G. *Worldwide experience with biosimilar development*. *MABs* 2011;3:209-217.)

by analytic techniques demonstrated that they were not comparable to the originator product.¹³ In contrast, analytic studies comparing E.U.-approved biosimilar versions of rHuEPO with the originator product have concluded that they were structurally similar.¹⁴ To avoid confusion, products that have not undergone rigorous evaluation of their similarity to the reference biologic with respect to structure, function, and nonclinical and clinical properties should not be referred to as biosimilars.

More recently, many developing countries have participated in discussions leading to the WHO guidelines on similar biopharmaceutical products, thus suggesting that they may adopt similar standards for approval fashioned on the WHO guidelines. Recently, the Korea FDA approved Remsima (Celltrion), a biosimilar version of Remicade (infliximab, Janssen). Although the full package submitted for approval is unknown, the sponsor conducted head-to-head studies against infliximab in the RA and ankylosing spondylitis populations consistent with the WHO guidelines. These studies showed generally similar response rates as the reference biologic.^{15,16}

IMPLICATIONS FOR HEALTH CARE PROVIDERS

Now that the United States has passed enabling legislation allowing an abbreviated path to approval of biosimilar products, it is only a matter of time before biosimilars appear in the marketplace. Given the prominent place of biologics in the armamentarium of rheumatologists, this will have an important impact in rheumatology. What do rheumatologists need to know about biosimilars to make sound, thoughtful decisions? Foremost in the mind of practicing physicians is knowing that they can count on the

safety profile and efficacy of products that they prescribe. In that regard the FDA has signaled that any biosimilar that appears on the market in the United States will have been rigorously tested side by side the innovator product as noted earlier.

State pharmacy laws have not yet been revised to address when automatic substitution of biosimilars for their reference products is permissible. Caution is warranted before permitting automatic substitution. The FDA has indicated that additional studies will be required for a biosimilar to be deemed interchangeable. Studies will need to be conducted to demonstrate that the outcome of switching to a biosimilar from the innovator and back is similar to what patients would have experienced if they had kept taking the innovator product. Particularly important in this regard is a demonstration that switching does not lead to greater immunogenicity than staying with the reference product does.

The introduction of biologics in the last decade has revolutionized clinical practice in rheumatology by allowing effective control of disease in many patients who had inadequate treatments available previously. Nonetheless, many patients who could benefit from biologics could not receive them because of their high price. Physicians are looking to biosimilars for a cost-effective alternative to the innovator molecules to allow more widespread access. The new legislation has provisions to continue to reward innovation for products that address unmet medical need while providing a path forward for products to be approved as biosimilars that meet the FDA standards for similar safety and efficacy. Knowledge of the process for assessing biosimilars and key differences between biosimilars and generic small-molecule drugs will allow physicians to determine when a biosimilar may be right for their patients.

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Infections and biologic therapy for rheumatoid arthritis: an update on risk and prevention

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- Patients with rheumatoid arthritis are at higher risk for infection because of disease and immunosuppressive therapies, including prednisone, biologics, and tofacitinib.
- The increased risk associated with biologics can be mitigated, however, when these agents improve control of disease and lead to reductions in prednisone use.
- At present, most biologics appear to be similar in their propensity to promote serious infection. Certain exceptions exist with regard to specific organisms (e.g., granulomatous pathogens) and specific therapies based on mechanism of action.
- Prevention of infection by screening and vaccination is an evolving strategy that serves to further mitigate risk.

RHEUMATOID ARTHRITIS AND BURDEN OF INFECTION

It is well known that patients with rheumatoid arthritis (RA) suffer greater morbidity and mortality from infectious diseases.¹⁻³ Although some of this increased burden is attributable to the immunosuppressive therapies used to treat RA (the focus of this chapter), it is likely that the underlying immune derangements of RA itself are also in part responsible.^{4,5} This immune system dysregulation potentially explains the nearly twofold increase in hospitalized infections observed in patients with RA, a risk that exists independent of immunosuppressive therapy. This was well documented during the prebiologic therapy era in the Mayo Clinic population when Doran and colleagues⁶ observed a hospitalized infection rate of 9 per 100 patient-years for RA patients and a clear elevated relative risk for pneumonia, skin and soft tissue infection, and bone and joint infection as compared with patients without RA. Importantly, these risks were independent of corticosteroid or other disease-modifying antirheumatic drug (DMARD) therapies in use at the time. Now, more than a decade later, the introduction and widespread use of biologic therapy have intensified the assessment of infection risk and prevention in the setting of RA, and although many unknowns still exist, our understanding of the infectious risk associated with these agents is more complete than ever, even as it continues to evolve over time.

PREDNISONE

There is little debate regarding corticosteroid's ability to cause infectious harm. Admittedly, clinical trial data with glucocorticoids do not support this perception,⁷ but data from observational studies ("real-world" populations) clearly and repeatedly suggest a dose-dependent elevated risk for hospitalized infections. The majority of studies suggest that patients taking prednisone have a 1.5- to 3-fold increased risk for serious infection.⁶⁻⁸ This increased risk has been noted even at doses considered "low."

In the United States, a 2006 study using the National Databank for Rheumatic Disease observed a nearly 1.5-fold elevation in risk for hospitalized infection even at doses lower than 5 mg/day.⁸ Other subsequent studies using registry, claims, and administrative data have found similar levels of

increased risk at doses of 5 mg or lower, as well as higher risk at higher doses in some cases.⁹⁻¹⁷

This includes a recent U.S. study that combined Medicare, Medicaid, health maintenance organization, and health plan administrative data (the Safety Assessment for Biologic thERapy [SABER] study) to form a cohort of more than 100,000 RA patients. Within this cohort, analysis of patients restricted to those starting new DMARDs and controlled for differences in RA disease severity and comorbidity (n = 10,000 RA patients included in the analysis) also found increased risk at prednisone doses lower than 5 mg and a nearly threefold elevated risk at average doses higher than 10 mg/day (Table 67.1).¹⁵

Similarly, other North American population-based studies report similar elevations in risk at doses lower than 5 mg and up to a fivefold higher risk when average doses of 20 mg or greater were studied.^{12,14} In Europe, observational studies report much the same. The German biologic registry for RA patients (Rheumatoid Arthritis oBservatiOn of Biologic Therapy, or RABBIT) identified an elevated relative risk for serious infection of between twofold and fivefold, depending on the average daily steroid dose, with the British Biologics registry documenting similar findings.^{16,18} Beyond bacterial infections, corticosteroids also raise the risk for opportunistic infections.¹⁹⁻²⁵ Similar to bacterial infections, these risks are dose dependent. Despite these infectious risks and the advent of newer biologic therapies, corticosteroid use in patients with RA remains common.²⁶

BIOLOGIC THERAPIES AND RISK FOR INFECTION

Our understanding of the relative infectious risks posed by biologic therapy is a moving target. Estimates of risk vary according to the type of study conducted (e.g., randomized controlled trials [RCTs] generally reveal lower risk than long-term extension studies do), and with time it is likely that patients and physicians have "learned" to use such therapies better (i.e., in safer fashion) such that more recent studies might not be comparable to those from earlier periods. Furthermore, it is clear that much of the variability in an individual's risk for infection is attributable to patient factors (e.g., age, chronic lung disease, and other comorbid conditions) and not necessarily the therapies (Fig. 67.1).^{12,16} In addition, biologic therapies can serve as corticosteroid-sparing agents and improve disease control (thereby lowering risk), and it can be difficult to estimate or model how infectious risk changes after treatment with a particular biologic is started. Despite these challenges, some general comments can be made. For anti-tumor necrosis factor (TNF) therapies, higher absolute infection rates among anti-TNF users have generally been observed, particularly in the first few months after initiation of drug therapy. Fairly similar rates of serious infection have been reported in clinical trials of different anti-TNF compounds, although not unexpectedly, absolute infection rates for these compounds observed in the "real-world" setting of population-based observational studies are typically higher than those reported from clinical trials. For the more recently approved classes of biologics for RA (i.e., abatacept, tocilizumab, rituximab) and for tofacitinib, rates of serious infection observed in clinical trials have largely been similar to those observed in anti-TNF trials. However, how these drugs behave in nonclinical trial populations is currently unknown. Population-based infection rates and risk estimates are largely missing because such observational registry or database studies of these therapies are still lacking for the most part.

TABLE 67.1

Dose-dependent increase in hospitalized infection rates observed with glucocorticoid use from the Safety Assessment for Biologic tHERapy (SABER) study, United States

Exposure	Events (No.)	Person-years (No.)	Rate per 100 person-years	Hazard ratio (95% CI) for propensity score–matched cohorts	Adjusted hazard ratio (95% CI)
Rheumatoid arthritis					
Nonbiologic regimens	326	4192	7.78	1	1
TNF- α antagonists	497	6089	8.16	1.05 (0.91-1.21)	1.05 (0.91-1.21)
Baseline glucocorticoid use, prednisone equivalents					
None					1
>0 to <5 mg/day					1.32 (1.10-1.58)
5 to 10 mg/day					1.78 (1.47-2.15)
>10 mg/day					2.95 (2.41-3.61)

CI, confidence interval; TNF, tumor necrosis factor.

From Winthrop KL, Baddley J, Chen L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. *JAMA* 2013;309:887-95.

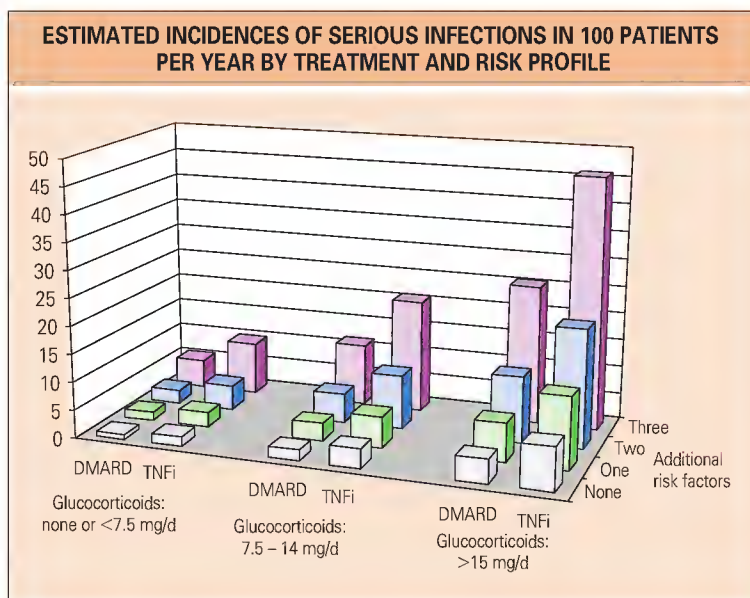


Fig. 67.1 Additional risk factors are one or two of the following: age older than 60 years, chronic lung disease, chronic renal disease, or higher number of treatment failures; three risk factors: two of the above risk factors plus previous serious infection. DMARD, disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor. (From Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011;70:1914-20.)

TUMOR NECROSIS FACTOR ANTAGONISTS AND RISK FOR INFECTION

As a group, anti-TNF therapies (etanercept, adalimumab, infliximab, golimumab, certolizumab) inhibit TNF- α , a cytokine expressed by activated macrophages and other immune cells that is known to play a crucial role in the host response to a variety of infections.²² The importance of TNF has been demonstrated in *in vitro*, animal, and human studies with a variety of organisms, and it is involved in the host response to both intracellular (e.g., *Mycobacterium tuberculosis* and fungi) and extracellular organisms (e.g., *Klebsiella pneumoniae* and *Streptococcus pneumoniae*).²⁷⁻³³

Not surprisingly, risk for infection is elevated with the use of these compounds; however, as discussed, precise infectious risks attributable to anti-TNF therapy are in some cases difficult to quantify. The results from meta-analyses of TNF antagonist trials are mixed. Although rates of serious infection are generally higher in biologic-treated patients, the relative risks observed in comparison to placebo are frequently small and not statistically

significant. Bongartz and coworkers³⁴ analyzed monoclonal antibody trials (infliximab and adalimumab only) in patients with RA and observed a twofold increase in risk for serious infection, whereas another meta-analysis that included etanercept, infliximab, and adalimumab found no statistically increased risk (relative risk, 1.08 [0.81 to 1.43]) in those treated with anti-TNF therapy versus placebo.³⁵ Interestingly, this study did reveal a significant twofold elevation in risk in studies using higher doses of infliximab or adalimumab. A recent Cochrane review of all TNF antagonists across disease indications found only infliximab (odds ratio [OR], 1.45 [0.99 to 2.1]) and certolizumab (OR, 3.5 [1.6 to 7.8]) to be associated with elevated risk for serious infection in comparison to placebo.³⁶ Taken together, these studies might imply a somewhat higher risk for some TNF antagonists. However, there are severe limitations in relying on such studies to understand the infection profiles of these drugs (e.g., low statistical power for individual trials, careful selection of patients for RCTs) and even greater difficulty in comparing drugs across trials (e.g., differences in inclusion criteria, populations, disease indications).

Because of these shortcomings and given the need for long-term monitoring of safety, a number of biologic treatment registries have been created in Europe, North America, and Japan from which cohort studies can be conducted. In addition, large, population-based, observational studies using health plan or administrative claims data have also assessed the risk for infection with these compounds. Even though such studies also have limitations (e.g., confounding by indication), a number of these studies have used sophisticated analyses (i.e., propensity scores) in an attempt to control for underlying and potentially confounding differences between patients who receive biologic DMARDs and those who receive nonbiologic DMARDs. Despite some heterogeneity in methods, these studies have typically reported somewhat similar estimates of serious infection in patients treated with anti-TNF therapies, typically between 3 and 8 per 100 patient-years (Table 67.2). Some of these studies show a higher and significantly elevated risk soon after initiation of TNF antagonist therapy that declines after 3 to 6 months of use, such that relative risk estimates are much lower when longer periods are assessed.^{11,12,13,37} Reasons for this decrease in risk are multifactorial and probably include a “survivor effect” (i.e., individuals in whom infection is more likely to develop become infected sooner and are censored), as well as improvements in RA disease activity and changes in concomitant therapies such as steroid reduction after commencement of biologic therapy.¹⁶ Several other large recent studies have produced conflicting results, although differences in their methodologies are worth noting. The aforementioned population-based SABER study from the United States¹⁵ was somewhat unique in that it compared only new users of anti-TNF therapy with new users of nonbiologic DMARDs. This comparison was made in a very specific setting because the patients starting treatment with a nonbiologic DMARD were already being treated with methotrexate (and presumably failing, hence the need for additional therapy). Accordingly, the study effectively compared RA patients starting infliximab, etanercept, or adalimumab therapy with similar patients (in terms of underlying disease severity and comorbid conditions) who started hydroxychloroquine, leflunomide, or sulfasalazine therapy after or during methotrexate use. A high rate of serious infections (8/100 patient-years) was seen in the RA population overall, but no increase in risk was observed in those starting TNF antagonists, including during the few months after initiation of drug therapy

TABLE 67.2

The biologic era: rates and relative risk for serious infections in patients with rheumatoid arthritis treated with anti-TNF therapy from European and North American observational cohort studies

Country/year	Crude incidence per 100 patient-years		Adjusted RR* (95% CI)
	Treated with anti-TNF	Nonbiologic comparator	
Germany, 2005	6.4, ETN 6.2, INF	2.3	2.2 (0.9-5.4), ETN 2.1 (0.8-5.5), INF
UK, 2007	5.5	3.9	1.3 (0.9-1.8) [†] 4.6 (1.8-11.9) [‡]
USA, 2007	2.9*	1.4*	4.2 (2.0-8.8) [§] 1.9 (1.3-2.8)
Sweden, 2007	4.7	NR	1.4 (1.2-1.7)
USA, 2007	4.9	3.8	1.3 (0.8-2.1)
USA, 2011	8.2	7.8	1.05 (0.9-1.2)
Germany, 2011	4.8	2.3	1.8 (1.2-2.7) [¶]
Japan, 2011	6.4	2.6	2.4 (1.1-5.05)*

*Relative rate with nonbiologic users as the referent.

[†]When restricted to the first 90 days of therapy and adjusted for age, sex, disease duration and severity, extraarticular rheumatoid arthritis, baseline steroid use, diabetes, chronic obstructive pulmonary disease, pulmonary disease, and smoking history.

[‡]Adjusted relative rate when not restricted to the first 90 days of therapy.

[§]Analysis restricted to the first 6 months after initiation of anti-TNF therapy.

^{||}Rate calculated at 1 year after starting treatment and adjusted for RA severity and comorbid conditions associated with infections.

[¶]Adjustment for time-varying risk factors, treatment adaptations, and dropout.

*Rate up to 1 year after starting drug therapy.

CI, confidence interval; ETN, etanercept; INF, infliximab; NR, not reported; RR, relative risk; TNF, tumor necrosis factor.

(see Table 67.2). The study also reported slightly higher and statistically significant infection rates in those who start infliximab therapy relative to those starting etanercept or adalimumab (rates were approximately 25% higher). However, infliximab users were more likely to be prescribed methotrexate after initiation of drug therapy than were those starting either etanercept or adalimumab, and it is unclear whether this could have contributed to the observed difference in risk. Other population-based studies have failed to find a similar increase in relative risk for bacterial infections with the use of infliximab as compared with other TNF blockers.^{10,37,38} The SABER study produced a number of subanalyses, and even though no increased risk with initiation of TNF antagonist therapy could be demonstrated in any of the inflammatory disease groups (patients with inflammatory bowel disease, psoriasis, and ankylosing spondylitis were also studied) or in stratified analyses, the study reiterated the importance of patient comorbidity and age to the risk for infection. For example, anti-TNF-treated patients with a history of chronic obstructive lung disease (COPD) had rates of serious infection of nearly 17 per 100 patient-years versus 7 per 100-patient years in those without COPD.

Taken together, these and other observational studies suggest that the net infectious risk associated with biologic therapy is neither straightforward to understand nor easy to calculate. To date, only one observational study has accounted for changes in disease activity and concomitant therapies that take place after starting biologic or nonbiologic comparator therapy. The RABBIT registry reported that anti-TNF therapy improved disease control and decreased prednisone use, both of which lower the risk for infection, but that even when controlling for these changes after initiation of drug treatment, anti-TNF therapy significantly increased the risk for serious infections 1.8-fold (see Fig. 67.1).¹⁶

Opportunistic infections with anti-tumor necrosis factor therapy

Since the early clinical trials, a number of intracellular infections have been reported in this setting, including infections with *M. tuberculosis*, nontuberculous mycobacteria (NTM), *Pneumocystis*, *Histoplasma*, *Coccidioides*, *Listeria*, *Salmonella*, and others.³⁹ Tuberculosis (TB) is most clearly associated with TNF blockade and has been reported with all five TNF antagonists.

TABLE 67.3

The biologic era: rates and relative risks of opportunistic infections in patients with rheumatoid arthritis treated with anti-TNF therapy from European and North American observational cohort studies

Country/year	Outcome studied	Crude incidence per 100,000 patient-years		Adjusted RR* (95% CI)
		Treated with anti-TNF	Nonbiologic comparator	
UK, 2006 ³⁷	OI	192* [†]	0*	NR
France, 2011 ⁴⁸	OI [‡]	152 [§]	NR	NR
USA, 2010 ⁴⁹	OI	3000*	1600*	1.7 (0.95-2.9)
UK, 2010 ⁴⁰	Tuberculosis	95*	0*	UNDEF
France, 2009 ⁵⁰	Tuberculosis	117 [§]	NR	NR
USA, 2011 ⁴¹	Tuberculosis	56*	9*	NR
USA, 2011 ⁴¹	NTM	105*	19*	NR
France, 2006 ^a	<i>Legionella</i> pneumonia	37.5 [§]	NR	NR
USA, 2009 ⁵³	Zoster	1060	1118	NR
Germany, 2011 ²⁴	Zoster	980*	560*	1.63
UK, 2013 ⁵⁴	Zoster	1600	800	1.7
USA 2013 ⁵⁵	Zoster	1210	1270	1.0

*Cohorts restricted to patients with rheumatoid arthritis.

[†]Rate not published but instead estimated from data provided within the paper.

[‡]OI outcomes did not include tuberculosis.

[§]Rate adjusted for age and sex.

CI, confidence interval; NR, not reported; NTM, nontuberculous mycobacteria; OI, opportunistic infection; RR, relative risk; TNF, tumor necrosis factor; UNDEF, undefined.

Adapted and updated from Winthrop KL. Infections and biologic therapy in rheumatoid arthritis. *Rheum Dis Clin North Am* 2013;38:727-35.

^aTubach F, Ravaud P, Salmon-Ceron D, et al; Recherche Axée sur la Tolérance des Biathérapies Group. *Clin Infect Dis*. 2006;43:e95-e100.

However, in population-based studies in which drug-specific risks have been studied, a clear distinction in risk can be made between the fusion receptor construct etanercept and the monoclonal antibodies infliximab and adalimumab. Although each of these drugs is associated with elevated risk for TB, the incidence of TB is threefold to fourfold higher in infliximab- and adalimumab-treated subjects than in those treated with etanercept.^{40,41} Animal and *in vitro* studies have provided potential explanations for this difference in risk, including differential downregulation of antigen-stimulated interferon- γ (IFN- γ), differential effects on antimicrobial-producing CD8 effector cells, and poorer penetration of the granuloma by etanercept.⁴²⁻⁴⁴ Even though TB has been reported in clinical trials of certolizumab and golimumab, population studies evaluating their relative risk for TB with the other TNF blockers have not yet been done.

The risk for TB with anti-TNF therapy not surprisingly varies according to the background prevalence of TB in the regional population, and risk estimates also vary according to when the studies were conducted. Early population-based studies conducted in low-prevalence TB regions and prior to the widespread introduction of screening for TB before initiation of biologic DMARD therapy generally reported rates of TB that were 5 to 20 times higher than in the background general populations, including early studies from the United States (incidence of 52/100,000) and Sweden (incidence of 118/100,000).^{45,46} In Spain, where background rates of TB are low (but severalfold higher than in the United States), investigators reported an incidence of TNF antagonist-associated TB of 1900 per 100,000 person-years, a rate that was 10 to 20 times higher than that found in RA patients not using anti-TNF therapy. After the subsequent widespread introduction of screening for TB before the use of biologics, Spanish investigators noted a dramatic decrease in the anti-TNF-associated incidence of TB.⁴⁷ The most recent observational studies conducted in the United States and Western Europe all document an elevated incidence of TB with anti-TNF therapy relative to either the general public or RA patients treated with nonbiologic DMARDs (Table 67.3).^{41,48-50} Furthermore, at least in the United States (and probably in other regions with low TB endemicity), disease with NTM is more prevalent than TB in the anti-TNF setting.^{41,51} Pulmonary NTM disease is probably also associated with RA independent of immunosuppressive therapy. These environmental organisms (most commonly *Mycobacterium avium* complex) are more likely to infect middle-aged and elderly

individuals, particularly women and those with chronic underlying lung disease.⁴¹ Finally, like TB, extrapulmonary manifestations of disease with NTM appear to be more common in patients treated with anti-TNF therapy.⁵²

For some other types of opportunistic infection, the overall picture is that anti-TNF therapy does increase risk, particularly those that involve granulomatous host responses. The risk for endemic mycosis (histoplasmosis, coccidioidomycosis, blastomycosis) varies according to geography and baseline risk. For some “opportunistic” infections that do not involve granulomatous responses, the question of risk is less clear. Reactivation of varicella zoster (i.e., shingles) is clearly the most common “opportunistic” infection in the anti-TNF setting because it occurs more frequently in RA patients (than in patients without RA) and its risk increases with advancing age. Risk for shingles is clearly elevated 1.5- to 2-fold with the use of prednisone, but studies assessing its relationship with anti-TNF therapy have produced conflicting results.²² Investigators from the German and British biologic registries have documented a small elevated risk with anti-TNF therapy; however, two large population-based studies in the United States found no increased risk with anti-TNF therapy (see Table 67.3).^{24,53-55} Together, these studies do suggest, however, that patients in whom shingles develops while being treated with TNF antagonists are no more likely to have disseminated or complicated zoster than patients in whom shingles develops while using nonbiologic DMARDs.^{22,24,53}

Abatacept, rituximab, tocilizumab, and anakinra

Given the mechanism of action of these biologics, a variety of related infections could be hypothesized. To date, RCT and open-label experience with these compounds has produced similar infection profiles as those with anti-TNF agents, though with some notable exceptions. Full understanding of their safety profiles still awaits further study since postmarketing experience and observational data are relatively recent with these compounds.

Risk for serious bacterial and opportunistic infections

Clinical trials of rituximab in patients with RA did not suggest a significantly increased risk for serious infection,⁵⁶ although further experience in long-term extension studies highlighted small subgroups of patients in whom persistently low IgG levels develop after rituximab treatment and who are at increased risk for serious infection.^{57,58} One observational study using administrative data evaluated hospitalized infection risk in TNF antagonist “failures” (i.e., patients switching to another biologic). The study observed higher rates of hospitalized infection rates in patients switching to rituximab versus other biologics, but after adjusting for other risk factors for infection, the risk was similar to that in those switching to etanercept, adalimumab, and abatacept (and significantly lower than in those switching to infliximab).⁵⁹ Limited data have been published with regard to opportunistic infections and rituximab. Mycobacterial case reports (both TB and NTM) exist for patients treated with rituximab, although these patients have also been taking methotrexate and prednisone.^{54,60} With regard to viral infection, rituximab clearly promotes the progression of chronic hepatitis B virus (HBV) infection, and its use should be avoided in such patients.^{36,61,62}

Progressive multifocal leukoencephalopathy (PML) has been reported in RA patients treated with biologics, including rituximab. Outside the human immunodeficiency virus setting, PML is quite rare and its incidence in patients with RA is 1 per 1,000,000.⁶³ To date, the U.S. Food and Drug Administration (FDA) has received reports of 14 cases of PML in patients treated with rituximab for autoimmune inflammatory diseases; however, only 1 of these patients lacked other risk factors for PML, and 10 were using other immunosuppressive therapies concomitantly.⁶⁴ The contribution of rituximab to the development of PML remains unknown, however, and reassuringly, the condition is quite rare in RA patients regardless of their therapy.

For abatacept, a small increased risk for serious infection was observed during clinical trials in some subsets of patients (e.g., those with COPD), and in those treated concomitantly with anti-TNF therapy, the incidence of serious infections was significantly elevated (such concomitant therapy was subsequently contraindicated).⁶⁵⁻⁶⁸ Meta-analyses of RCT and open-label extension data documented rates of hospitalized infection of 2.7 per 100 patient-years in patients treated with abatacept.⁶⁹ Opportunistic infections have also been reported, although their relative risk remains unknown. TB occurred at a rate of 60 per 100,000 patient-years in abatacept RA trials, but it is unknown how this compares with the background risk for TB in these populations, and patients were screened for latent TB before entry into these trials.⁶⁹ In animal studies, abatacept does not appear to negatively affect the immune system of mice who are exposed to TB.⁷⁰ At least one randomized trial has compared the efficacy and safety of abatacept with that of infliximab; at 1 year patients taking abatacept suffered significantly fewer serious infections than did infliximab-treated patients (1.9% versus 8.5%). No cases

of opportunistic infection were seen in the abatacept-treated group, whereas five such cases were seen in the infliximab group, including two cases of TB and one of *Pneumocystis jiroveci* pneumonia.⁷¹

For the interleukin-6 (IL-6) receptor antagonist tocilizumab, RCTs and long-term extension trials have revealed rates of serious infection of 4.9 per 100 patient-years in patients receiving 8 mg/kg, whereas lower rates (3.5/100 patient-years) were observed in those receiving placebo or low-dose tocilizumab.⁷² Population-based observational data are only now beginning to emerge, with one study recently published from Japan where this compound has been in use for a relatively longer period. Within their tocilizumab postmarketing surveillance program (N = 3881 patients), they observed a rate of serious infection of 9 per 100 patient-years. With regard to opportunistic infections, shingles occurred at a frequency of 6.1 cases per 1000 patient-years, and 4 TB cases were reported (incidence rate of 220/100,000 person-years). This TB rate is similar to that observed in the postmarketing experience for anti-TNF therapies in Japan, although the rate is 10-fold higher than that in the background Japanese population.⁷³

Tofacitinib

Few data have been published in the peer-reviewed literature on the infectious risk associated with tofacitinib, a recently FDA-approved small molecule that inhibits Janus activating kinases 1 and 3 (JAK1/3). *In vitro*, this drug has been shown to diminish CD4+ T-lymphocyte production of INF- γ and IL-17.⁷⁴ Rates of serious infection were reported in several published phase 3 studies, and they were similar to those seen in RCTs of biologics. Rates of shingles, however, were elevated in tofacitinib-treated patients in RCTs and long-term extensions trials, particularly within Asian regions, and higher than those observed in other studies of TNF antagonists.⁷⁵⁻⁷⁷ TB cases occurred infrequently during clinical trials, though more frequently in patients receiving higher tofacitinib doses and in countries with a higher prevalence of TB. Patients were screened and, when indicated, started treatment of latent TB infection before study entry.⁷⁸

Prevention of infection in patients treated with biologics (screening and vaccination)

The serious infections most common in the setting of biologic therapy and in patients with RA in general are skin and soft tissue infections and community-acquired pneumonia.^{8,10,79} Like skin and soft tissue infections within the general public, most are probably due to *Staphylococcus aureus* and *Streptococcus* species.⁸⁰ For community-acquired pneumonia, these infections are also probably due to the same organisms that cause pneumonia in general populations, and *S. pneumoniae*, *Haemophilus influenzae*, *S. aureus*, gram-negative bacilli, and influenza are among the most common causative pathogens.⁸¹ Strategies to reduce the risk for hospitalized pneumonia include both pneumococcal and influenza vaccination. Historically, the 23-valent pneumococcal vaccine (PPSV-23) [Pneumovax] has been used and recommended before initiating anti-TNF and other long-term immunosuppressive therapies, including methotrexate (primarily for protection against invasive pneumococcal disease).⁸² Immunogenicity to this vaccine is poor and diminished by methotrexate, as well as by some other biologic drugs (e.g., rituximab), but it is relatively unaffected by anti-TNF therapy.⁸³ The FDA has recently approved the new 13-valent conjugate pneumococcal vaccine (PCV-13) for use in adults, a vaccine that should theoretically provide longer and improved protection against pneumococcal disease than PPSV-23 does.⁸⁴ Currently, however, no data are available on whether PCV-13 produces more robust immune responses than PPSV-23 does in patients being treated with biologic or nonbiologic DMARDs. It is currently recommended, however, that PCV-13 be administered to all adults with immunocompromising conditions, including RA. Current data suggest that a vaccine strategy that begins with PCV-13 and then follows with a PPSV-23 booster provides higher levels of antibodies to pneumococcal serotypes, at least in the first year after the booster.⁸⁵

Intramuscular influenza vaccination should be given yearly to all patients with RA (except those with a history of anaphylaxis to egg products), and the vaccine generally provides effective immune responses even when administered during biologic therapy (with the exception of rituximab, which severely diminishes such responses).^{86,87}

Intracellular pathogens

TB is perhaps the opportunistic infection that is most clearly preventable in the setting of biologic therapy. Screening recommendations for latent TB infection before initiation of biologic therapy have been issued by a wide variety of professional societies and public health entities.^{26,36,88,89} In the last

5 years, more recommendations have incorporated the use of IFN- γ release assays (IGRAs), Quantiferon-Gold TB In-tube® (QFT-IT), or the T-SPOT. TB®, which have improved specificity for TB relative to the tuberculin skin test (TST). This is of particular relevance in patients with a history of bacille Calmette-Guérin (BCG) immunization, in whom the TST is less preferred because of the known ability of BCG to cause false-positive TST responses. However, current data suggest that neither IGRAs nor the TST alone sufficiently identifies all infected patients because false-negative results can occur with either test, particularly in immunosuppressed individuals.⁹⁰ A strategy that uses both tests (or in the case of a BCG-vaccinated individual, a dual IGRA strategy) is probably warranted, particularly in patients with risk factors for TB.

For NTM and fungal disease, there is little in the way of preventive tools for the clinician to use other than ruling out active infection before starting drug therapy. Pulmonary NTM has emerged as an infection with a predilection for RA patients, and presumably some of these patients are identified during screening for TB.^{41,91} Patients with chronic, unexplained cough or those with abnormalities on their baseline chest radiographs should undergo further workup (potentially including chest computed tomography, culture of respiratory specimens as appropriate, or both) before starting biologic therapy.⁹² For fungal disease with *Histoplasma* and *Coccidioides*, no clear utility of serologic or other screening before biologic therapy has emerged.

Geographically, the epidemiology of HBV closely mirrors that of TB, with similar regions of high prevalence around the world. Unlike hepatitis C virus, for which anti-TNF compounds appear to be relatively safe, HBV progression can occur in patients using anti-TNF therapy. Accordingly, all patients should be screened for HBV before using such therapies. In addition to evaluating hepatitis B serum antigen status (a marker of active infection), both core antibody and surface antibody evaluations should be conducted.⁹³ Furthermore, in patients who have evidence of previous infection (i.e., positive hepatitis B core antibody), HBV DNA should be checked before starting biologic therapy and thereafter at periodic intervals. For patients with active HBV, TNF antagonist therapy has been used safely with concomitant antiviral therapy in the context of close laboratory and clinical monitoring.^{93,94} For other biologics, there is less experience in patients with active HBV

infection. Several cases of HBV progression have been reported in patients taking abatacept and not being treated with concomitant antiviral therapy (and several patients were treated safely with concomitant antiviral therapy), and several patients with HBV have successfully used tocilizumab in the context of antiviral prophylaxis.⁹⁴ Rituximab, however, remains contraindicated in such patients because poor outcomes and death have been reported in those with active HBV infection.

Shingles remains a vaccine-preventable disease in patients with RA treated with biologic therapy, and it is clear that these patients suffer greater shingles morbidity, thus making them ideal candidates for vaccination. The vaccine Zostavax® is licensed for the prevention of shingles in patients older than 50 years and has been shown to reduce overall risk for zoster by 67% in those vaccinated.⁹⁵ However, because of the theoretic safety concerns associated with a live vaccine, it is currently contraindicated in those taking biologic therapy, which makes it difficult to vaccinate many RA patients. Given the high morbidity and prevalence of this disease in RA and the inability to currently vaccinate RA patients treated with biologic agents, effort should be made to evaluate the safety and efficacy of this vaccine in this context.

CONCLUSION

Patients with RA are at higher risk for serious infection and death from infection than the general public is. Prednisone and biologic agents increase this risk, although such risk can be mitigated when biologic agents act as prednisone-sparing therapies. Some of the important causes of infectious morbidity in this setting are preventable with screening (i.e., TB) or vaccination (i.e., herpes zoster).

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68

Drugs and pregnancy

■ BONNIE LEE BERMAS

- Pregnancy impacts each rheumatic disease differently.
- If possible, patients with inflammatory arthritis and systemic rheumatic diseases should have the disease under good control before conception.
- Patients who have preexisting renal disease, in the context of either systemic lupus erythematosus or another collagen vascular disease, should be in remission for 6 months before conception.
- Clinicians should not empirically treat diagnoses or a laboratory test result but rather treat symptoms and signs of active disease.
- Aspirin can be used throughout pregnancy and other nonsteroidal antiinflammatory drugs can be used from the time of implantation until the last trimester of pregnancy.
- Glucocorticoids can be used during pregnancy for disease flares. There is about a threefold increased risk of cleft palate formation in fetuses exposed to glucocorticoids during the first trimester. Maternal risks of the use of these medications later in pregnancy include glucose intolerance, hypertension, and osteoporosis.
- Antimalarials, sulfasalazine, azathioprine, and cyclosporine can be used during pregnancy.
- Gold, cyclophosphamide, methotrexate, and leflunomide should be avoided during pregnancy.
- Data on the use of anti-tumor necrosis factor therapy during pregnancy are limited, although evidence suggests that these medications may be used in some circumstances.
- Clinicians should review the potential toxicities of medications during pregnancy with patients before initiating therapy.

Rheumatologic disorders occur commonly in women during their reproductive years. Thus clinicians should be familiar with how to manage rheumatic diseases during pregnancy. The impact of a pregnancy on the mother's disease activity, coupled with the potential toxicity of many anti-rheumatic medications to both mother and fetus, make treatment challenging. Data on the potential toxicity of a particular pharmacologic agent are often limited. Commonly, we rely on animal studies that use superpharmacologic dosing to evaluate a drug for teratogenicity. Alternatively, we refer to case reports of drug exposure in a handful of pregnancies. Neither of these approaches adequately reveals the true risk of a particular therapy during pregnancy. The U.S. Food and Drug Administration (FDA) use-in-pregnancy ratings are likewise based on limited information (Box 68.1). The American College of Rheumatology last addressed this issue in its guidelines for monitoring drug therapy in rheumatoid arthritis (RA) published in 1996.¹ Since then, both the management of disease and our experience with commonly used medications during pregnancy has changed. This chapter discusses the treatment of the pregnant patient with a rheumatic disorder with special emphasis on medication safety during pregnancy and nursing. Medications reviewed in this chapter include aspirin and other nonsteroidal antiinflammatory drugs, glucocorticoids, antimalarials, gold salts, immunosuppressive agents, antimetabolites, cytotoxic agents, intravenous immune globulin, and biologics (Table 68.1). Treatment recommendations and approaches to patient care are described wherever possible.

PREGNANCY

For a pregnancy to be successful, the mother must tolerate the fetus, which is a hemi-allograft. Some theories of what happens to the immune system during pregnancy to promote fetal survival include expression of nonclassical major histocompatibility complex class I by the trophoblast and the attenuation of natural killer cell activity.² Recent murine data suggest that suppression of the maternal response to paternal alloantigens by extrathymic regulatory T cells also plays an important role in pregnancy immunology.³

Rheumatic diseases and pregnancy

Changes in the immune system during pregnancy may modify the disease activity of different rheumatic diseases in disparate ways (Table 68.2). Conventional wisdom is that up to 70% of patients with RA experience remission when pregnant.⁴ However, newer evidence suggests that the actual number of patients who improve during pregnancy may be closer to 50%.⁵ Why this amelioration of symptoms occurs is unclear, but it may be related to some of the alterations in inflammatory cytokine levels that are observed during pregnancy. For example, tumor necrosis factor- α and other cytokines are down-regulated during pregnancy,⁶ and this may have a positive impact on disease activity in RA.⁷

In contrast to the data for RA, the data for systemic lupus erythematosus (SLE) are unclear. Some studies suggest that SLE is not impacted by pregnancy, whereas other studies suggest that SLE is exacerbated by pregnancy.^{8,9} There is even more limited information regarding other rheumatologic disorders. Therefore the clinician may not be able to predict which patient with a rheumatic condition is likely to experience a flare during pregnancy.

There are several guiding principles in managing patients with rheumatic diseases during pregnancy (Box 68.2). First, the patient should be in clinical remission or have her disease under good control at the time of conception. Specifically, in patients who have lupus nephritis or another rheumatologic disorder with renal involvement, the kidney disease should be in remission for at least 6 months before conception. This approach should also be applied to those patients that have other significant organ involvement as part of their rheumatologic disease. Second, patients should be following a therapeutic regimen that can be continued during pregnancy. For example, in patients with RA, if the disease is under good control, one can consider discontinuing medications before pregnancy. On the other hand, in those patients with active disease, it may be prudent to continue their medications that are considered compatible with pregnancy. Third, the clinician should treat active disease symptoms and signs and not a clinical diagnosis or a laboratory test result. Thus there is no role for empirical immunosuppression in pregnant patients with rheumatologic disorder who are in clinically stable condition.

ASPIRIN, OTHER NONSTEROIDAL ANTIINFLAMMATORY DRUGS, AND CYCLOOXYGENASE-2 INHIBITORS

Aspirin, other nonsteroidal antiinflammatory drugs (NSAIDs), and the cyclooxygenase-2 (COX-2) inhibitors are the cornerstones of treatment for the pain and joint inflammation in arthritic conditions. In humans, exposure to high-dose aspirin *in utero* during 5128 pregnancies did not result in an increased rate of fetal malformation despite reports that high-dose aspirin exposure in animals can be teratogenic.^{10,11} Furthermore,

BOX 68.1 FOOD AND DRUG ADMINISTRATION USE-IN-PREGNANCY RATINGS

- A Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
- B No evidence of risk in humans. Either animal findings show risk but human findings do not, or, if no adequate human studies have been performed, animal findings are negative.
- C Risk cannot be ruled out. Human studies are lacking and results of animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
- D Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
- X Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

BOX 68.2 TREATMENT PRINCIPLES FOR PATIENTS WITH RHEUMATIC DISEASES DURING PREGNANCY

- Disease should be in remission or under good control at the time of conception.
- Medications should be minimized or discontinued as appropriate.
- The disease symptoms, not the diagnosis, should be treated (e.g., a patient with systemic lupus erythematosus does not need empirical steroid therapy during pregnancy unless the disease is active).

low-dose aspirin is part of the treatment regimen for pregnant women with antiphospholipid syndrome and obstetric complications.¹² The American Academy of Pediatrics concludes that aspirin is compatible with breastfeeding.¹³

In animals, high doses of some NSAIDs are teratogenic.¹⁴ In humans, NSAIDs do not cause fetal malformations but can cause premature closure of the ductus arteriosus when used during the third trimester.¹⁵ Therefore one can treat with NSAIDs during the first two trimesters of pregnancy, but these medications need to be discontinued during the third trimester. The American Academy of Pediatrics considers most NSAIDs to be compatible with breastfeeding.¹³

Data on the use of the newer COX-2 inhibitors during pregnancy are limited. To date, there are no reports of fetal malformations after exposure to these drugs *in utero*; however, there are insufficient data in humans to evaluate their safety during pregnancy. In animal studies COX-2 inhibitors can interfere with both ovulation and implantation.¹⁶ Because NSAIDs have both COX-1 and COX-2 inhibitory effects, patients should discontinue both NSAIDs and COX-2 inhibitors at the beginning of a menstrual cycle in which they plan to try to conceive. No data are available on the safety of the COX-2 inhibitors in breastfeeding mothers.

Aspirin and other NSAIDs can be used during the pregnancy. The NSAID should be discontinued during the third trimester, and both NSAIDs and COX-2 inhibitors should be held during a conception cycle.

GLUCOCORTICOIDS

Glucocorticoids are used to treat many rheumatologic disorders. Prednisone and prednisolone, the forms most commonly used in rheumatology, are not readily metabolized by the placenta and reach the fetus in low concentrations. In contrast, betamethasone and dexamethasone, the fluorinated glucocorticoids, reach the fetus at higher concentrations and can be used for treating fetal conditions such as lung immaturity.¹⁷ In animals, glucocorticoids have been shown to increase aggressive behavior in the mother and increase the incidence of cleft palate formation.^{18,19} In humans the data are more reassuring. In a large series of asthma patients who were treated with glucocorticoids (mean dose, 8 mg/day) during pregnancy the rate of fetal anomalies was not above the background level.²⁰ In contrast, a meta-analysis of the use of glucocorticoids during pregnancy found a 3.4-fold increase in risk of cleft palate formation in offspring who were exposed to glucocorticoids during pregnancy.²¹ This risk goes away after the first trimester. Glucocorticoids can contribute to premature rupture of the membranes and babies who are small for gestational age. Pregnant women who take

glucocorticoids are at increased risk of the development of gestational diabetes, hypertension, and osteoporosis.

Glucocorticoids can be used in pregnant patients for whom NSAIDs have failed or who require immunosuppression. Patients should be informed that there is a slightly increased risk of cleft palate formation in fetuses exposed to glucocorticoids during the first trimester. Clinicians should use the lowest possible dose of glucocorticoids that controls clinical symptoms. In patients who have been treated with glucocorticoids throughout pregnancy and who have a prolonged labor or require a cesarean section, stress doses of steroids (50 to 100 mg hydrocortisone sodium succinate intravenously every 8 hours) should be administered during labor and delivery.

Five percent of the glucocorticoid dose is secreted in breast milk. This is not an issue for lactating mothers who are taking less than 20 mg/day. However, in patients who are taking more than 20 mg/day, the recommendation is to pump and discard breast milk produced during the 4 hours immediately following the steroid dose.²²

ANTIMALARIALS

In rheumatology practices, the 4-aminoquinoline antimalarial agents hydroxychloroquine and chloroquine are used for the treatment of mild inflammatory arthritis, SLE, and connective tissue disorders. In animals, use of these medications during pregnancy can cause chorioretinotoxicity in the fetus.²³ Although the FDA classifies these medications as category C for use during pregnancy, substantial evidence now exists to show that these drugs are compatible with pregnancy. In lower doses, the antimalarials have been safely used in pregnancy for malarial prophylaxis.²⁴ In higher doses, these medications have been given to pregnant patients with SLE with no increased reports of fetal malformations. Khamashta and colleagues²⁵ reported on 33 women who safely took antimalarials during pregnancy, and Parke and Rothfield²⁶ reported on 16 lupus patients who took antimalarials during pregnancy with no adverse effects. Furthermore, there is some evidence that continuing hydroxychloroquine therapy in patients with SLE during pregnancy may improve maternal and fetal outcome.²⁷ A survey of North American rheumatologists revealed that 69% of these physicians maintain patients on this medication during pregnancy, a result that supports the concept that hydroxychloroquine is compatible with pregnancy.²⁸ Current evidence and practice suggest that antimalarials are compatible with pregnancy. Patients with lupus or connective tissue disease should be encouraged to continue these medications during pregnancy to ensure better outcomes. Those with inflammatory arthritis can opt to discontinue this medication because in these patients symptoms are likely improve during pregnancy.

According to the American Academy of Pediatrics, this medication can be used in nursing mothers.¹³

GOLD

Although gold salts were among the first effective treatments for RA and inflammatory arthritis, they are now rarely used due to the development of other disease-modifying agents. In animals, gold salts cross the placenta and can cause congenital abnormalities, including hydrocephaly and hydronephrosis.²⁹ In humans, the data are limited on the use of gold during pregnancy. There is one case report of congenital anomalies occurring in an infant in which the mother was treated with gold salts.³⁰ Gold therapy should be stopped during pregnancy, although the long half-life of gold salts means that there are usually significant body stores of this medication at the time of pregnancy. This medication is considered to be compatible with breastfeeding.

SULFASALAZINE

Sulfasalazine was initially developed in the 1930s to treat RA. However, until the past two decades, this drug has been used mainly to treat inflammatory bowel disease. Sulfasalazine crosses the placenta with its metabolite sulfapyridine. The latter can displace bilirubin from albumin, but this is not thought to be clinically relevant.³¹ Although there have been case reports of fetal malformations in humans after *in utero* exposure to sulfasalazine, a large meta-analysis did not show a statistically significantly increased risk of congenital anomalies after fetal exposure.³² Because sulfasalazine inhibits the absorption of folic acid, pregnant women should take supplemental folic acid beyond the dosages typically prescribed during pregnancy.³³ This medication may be used during pregnancy and is a good option for women who have active inflammatory arthritis.

TABLE 68.1
Toxicities of antirheumatic therapies in animals and humans

Drug	Animals		Humans		
	Embryotoxic	Fetal	Maternal	Fetal	Breastfeeding
Aspirin and NSAIDs	No	Teratogenic in high doses	No	Premature closure of the ductus arteriosus	Compatible
Glucocorticoids	No	Cleft palate Aggressive behavior	PROM Hypertension Glucose intolerance Osteoporosis Osteonecrosis	SGA Adrenal hypoplasia Promotes lung maturity Cleft palate* Stillbirth*	Crosses into breast milk at low concentration, well tolerated
Antimalarials	No	Chorioretinotoxicity	No	Case reports of pigment deposition in the retina, cochleovestibular paresis, dorsal column disease, and mental retardation	Crosses into breast milk, contraindicated
Gold	No		No		Compatible
Sulfasalazine	†	Teratogenic in rats	No	Cleft palate VSD Coarctation of the aorta Macrocephaly Oligospermia	Crosses the placenta, contraindicated
Azathioprine	Yes	Skeletal abnormalities Cleft palate Decreased thymic development and hematopoiesis	†	Diminished fertility in offspring*	Contraindicated†
6-Mercaptopurine	Yes	Cleft palate	†	SGA Prematurity Intrauterine growth retardation Cleft palate	†
Cyclosporine A	Yes	Renal tubular cell damage	Renal insufficiency	Spontaneous abortions	Contraindicated
Mycophenolate mofetil	†	†	†	Case reports: Shortened digits and hypoplastic nails Auditory canal atresia Cleft lip and palate Micrognathia Hypertelorism Ocular coloboma	Contraindicated
Methotrexate	Yes	Skeletal abnormalities Cleft palate	†	Embryotoxic Skeletal abnormalities Facial abnormalities	Contraindicated
Leflunomide				Multiple congenital anomalies	Contraindicated*
Cyclophosphamide	Yes	SGA Skeletal abnormalities Cleft palate Exophthalmos Decreased fertility	Decreased fertility in males and females	SGA Limb abnormalities Coronary artery agenesis Tumors in offspring*	Contraindicated
Intravenous immunoglobulin	†	†	†	SGA Autoantibodies	†
Etanercept, adalimumab, infliximab	†	†	†	VACTERL anomalies? Placental transfer?	†
Certolizumab					
Rituximab	†	†	†	†	†
Abatacept	†	†	†	†	†
Anakinra	†	†	†	†	†
Tocilizumab	†	†	†	†	†

*Theoretical risk or case reports only.

†No information available.

‡Conflicting information.

NSAIDs, nonsteroidal antiinflammatory drugs; PROM, premature rupture of the membranes; SGA, small-for-gestational age offspring; VSD, ventricular septal defect.

Sulfasalazine interferes with both spermatogenesis and sperm motility. Therefore discontinuing this medication for 3 months before attempting conception is recommended.³⁴ Due to a report of bloody diarrhea in a breastfed infant whose mother was ingesting sulfasalazine, the American Academy of Pediatrics warns against use of this medication by nursing mothers; nonetheless, in certain circumstances it may be appropriate to continue this medication in lactating women.^{13,35}

IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive agents are used in the treatment of rheumatic diseases to manage end-organ involvement and as steroid-sparing agents. Fortunately, we have a plethora of information on the use of these medications during pregnancy because of information gleaned from large transplant

TABLE 68.2
Rheumatic diseases during pregnancy

Disease	Activity during pregnancy
Rheumatoid arthritis	Remits in 50%-70% of cases
Systemic lupus erythematosus	Stable or worsens; active renal disease is particularly problematic
Psoriatic arthritis	Generally improves
Scleroderma	Limited data
Dermatomyositis	Limited data

registries. Azathioprine and its active metabolite 6-mercaptopurine, cyclosporine, and mycophenolate mofetil are the major immunosuppressive agents used in the treatment of rheumatic diseases. Their safety for use in pregnancy is discussed in the following sections.

Azathioprine and 6-mercaptopurine

The purine analogues azathioprine and its major metabolite 6-mercaptopurine have been used for the treatment of SLE, RA, and the spondylitic variants. In pregnant rats treated with high doses of azathioprine (20 mg/kg/day), trophoblastic damage was observed.³⁶ In humans, the placenta is unable to metabolize azathioprine into its metabolite 6-mercaptopurine, which suggests that little if any of the biologically active form of this medication reaches the fetus.³⁷ Although there have been case reports of infants born with pancytopenia, combined immunodeficiency, chromosomal abnormalities, and craniofacial malformations after *in utero* exposure to azathioprine,^{38,39} several large case series have failed to demonstrate an increased risk of congenital anomalies in exposed fetuses. In 142 transplant recipients who were given azathioprine during pregnancy, reported anomalies in infants included metatarsus adductus, kidney malformation, ventricular septal defect, patent ductus arteriosus, and a hearing deficit. Nonetheless, the number of observed anomalies was not above the background rate.⁴⁰ Moreover, patients were concomitantly receiving other medications such as glucocorticoids and cyclosporine, so attributing risk to any particular medication is difficult. Lower birth weights have been described in infants whose mothers took azathioprine during pregnancy; however, whether this is due to premature delivery or true small size for gestational age is a subject of debate.^{41,42} The rate of premature delivery is likewise difficult to interpret given that patient and physician preference for delivery time is often not discussed in these studies.

The FDA classifies this medication as risk category D for safety in use during pregnancy. Despite this classification, the existing data suggest that azathioprine does not increase the risk of congenital anomalies above background rates. This medication is considered a viable option for immunosuppression during pregnancy.

In animals, 6-mercaptopurine is teratogenic, inducing cleft palate formation, microcephaly, and dilatation of the cerebral ventricles.^{43,44} In humans, there are few case series available for review. In one case series of 155 patients with inflammatory bowel disease who took 6-mercaptopurine during pregnancy, no increase was seen in rate of conception failures or major congenital malformation.⁴⁵ Another reassuring study demonstrated no increase in congenital anomalies in 215 pregnancies in patients with inflammatory bowel disease treated with thiopurines.⁴⁶ The question of when to discontinue this medication in male patients who wish to father a child is important. In one series of 13 male patients who had taken this medication in the 3 months preceding conception, there were two spontaneous abortions among their wives and two offspring born with skeletal congenital anomalies.⁴⁷ Therefore this medication should be discontinued in men 3 months before a planned conception.

Both azathioprine and 6-mercaptopurine can cause immunosuppression in the newborn and should not be used by nursing mothers.

Cyclosporine

In rodents, cyclosporine crosses the placenta in very low concentrations.⁴⁸ Pregnant rodents administered high doses of cyclosporine (25 mg/kg/day) have increased fetal mortality and renal abnormalities, although other studies have not shown any impact on organogenesis.^{49,50} There are differing

opinions as to whether or not cyclosporine crosses the placenta in significant concentrations in humans.^{51,52} Regardless, there seems to be no increased risk of teratogenicity over background rates with *in utero* cyclosporine exposure. In one study of 154 pregnancies in renal transplant patients in which the mothers were taking cyclosporine, there was no increase in the incidence of malformations; however, the babies exposed to cyclosporine were smaller and more often premature, and the mothers had an increased incidence of maternal diabetes and hypertension.⁵³ In the U.S. National Transplantation Pregnancy Registry, 500 pregnancies have been reported in which the fetuses were exposed to cyclosporine. There was no increase in congenital anomalies, although the live birth rate was lower in those pregnant patients who received cyclosporine. Importantly, sicker patients tend to be taking cyclosporine, which may help explain this observation.⁵⁴ Finally, a recent meta-analysis concluded that cyclosporine does not appear to be a major teratogen, although it may be associated with increased rates of prematurity.⁵⁵

There is some concern that *in utero* exposure to cyclosporine may impair the development of T, B, and natural killer cells. Whether this will have long-term impact and whether immunization schedules in these infants should be modified is unclear.⁵⁶ The literature suggests that cyclosporine may be used for immunosuppression during pregnancy. This medication is not compatible with nursing because of the risk of immunosuppression in the offspring.

Mycophenolate mofetil

Mycophenolate mofetil is a purine synthesis inhibitor that has been used to prevent organ rejection. More recently, it has been used in the treatment of lupus nephritis.⁵⁷ In animals, this agent may cause premature meiotic maturation.⁵⁸ In a case series of 57 pregnancies in women taking mycophenolate mofetil a lower than expected rate of live births and a higher than expected rate of congenital anomalies (6 per 29 live births) was reported.⁵⁹ This medication is classified as a category C drug by the FDA. Given the high rate of reported anomalies, this medication should be avoided during pregnancy and nursing.

Methotrexate

Methotrexate is a folate antagonist that has been used widely over the past 2 decades for the treatment of RA and other inflammatory conditions. Current practice suggests that this medication should be the mainstay of therapy of RA.⁶⁰ In pregnant rodents, this agent causes skeletal abnormalities in the offspring and increased fetal resorption rate.^{61,62} In humans this medication is profoundly abortifacient and is commonly used for the non-surgical treatment of ectopic pregnancies.⁶³ It can also cause severe teratogenicity including craniofacial abnormalities and mental retardation.⁶⁴ Most of the toxicity appears to occur during the sixth through eighth weeks of gestation and at dosages higher than 10 mg/wk. There have been a few case reports of offspring in whom there was no teratogenicity when exposed to this medication before 6 weeks of gestation and at dosages lower than 10 mg/wk.^{65,66} Nonetheless, a recent review of this topic by Lloyd and colleagues⁶⁷ suggests that there is no safe window. In their series encompassing 42 pregnancies there were 10 fetal abnormalities after *in utero* exposure to methotrexate in the first trimester. They suggest that the washout period before conception in both men and women should be 6 months. Donnemfeld and associates⁶⁸ suggest that the medication should be discontinued 12 weeks before conception because of the high spontaneous abortion rate. The FDA has classified methotrexate as a category X risk for use during pregnancy. Thus it is imperative to counsel sexually active patients who have the potential to conceive about consistently using reliable birth control. The American College of Rheumatology recommends that men discontinue this medication 3 months before attempting conception. They suggest that women wait at least one ovulatory cycle after stopping methotrexate before trying to become pregnant. This medication is not compatible with breastfeeding.

Given the widespread use of methotrexate in rheumatic disorders, inadvertent *in utero* exposure can and does occur.^{65,66} Thus clinicians may be faced with how best to counsel patients regarding whether to proceed with a pregnancy or not. Reproductive choices are intensely personal and are based on cultural, religious, and individual belief systems. The role of the clinician is to provide as much information as possible on reported fetal outcomes after medication exposures so that patients can evaluate the potential risk to the fetus. In addition to providing this information, referring the patient for high-resolution fetal ultrasonography that can evaluate organ development can help the patient make an informed decision about how to proceed with the pregnancy.

LEFLUNOMIDE

Leflunomide is used to treat inflammatory arthritis, Behçet syndrome, and other disorders. This medication is extremely teratogenic (risk category X) and is contraindicated in pregnancy.

Recently there was a report on 45 pregnancies in which inadvertent exposure to leflunomide occurred either just before conception or during gestation. The authors reported that 2 of 16 offspring exposed to leflunomide *in utero* had major malformations and an additional three had minor anomalies.⁶⁹ Although the authors conclude that leflunomide is not a major teratogen, the numbers suggest a higher than background rate of congenital anomalies. Thus patients who are taking leflunomide should be carefully counseled regarding appropriate contraception. Because of its extremely long half-life, drug elimination with cholestyramine is recommended for women who wish to become pregnant. The manufacturer recommends that cholestyramine be given at a dosage of 8 g three times a day for 11 days and that drug levels then be measured. Without cholestyramine, it can take up to 2 years to eliminate this drug.

CYCLOPHOSPHAMIDE

Cyclophosphamide is a cytotoxic agent that is the backbone of many cancer chemotherapy regimens. In people with SLE and vasculitis, this medication has greatly reduced the morbidity and mortality of renal disease and other organ involvement.⁷⁰ In pregnant mice, cyclophosphamide causes chromosomal rearrangements and impairs blastocyst development in embryos.⁷¹ In humans, cyclophosphamide exposure during pregnancy can lead to problems with digit development and limb formation, iris development, and coronary artery abnormalities.^{72,73} Although there have been case reports of individuals being treated for granulomatosis with polyangiitis (at 17 weeks of gestation and beyond) and Hodgkin lymphoma (in third trimester) with no adverse outcomes, cyclophosphamide should be avoided during pregnancy.^{74,75} Patients who need to be treated with this medication during the first trimester and early second trimester of pregnancy should be counseled about the high risk of congenital anomalies in the fetus. Cyclophosphamide is transferred into breast milk and should not be used by nursing mothers.

Prolonged use of cyclophosphamide can also induce infertility in women. Risk factors for cyclophosphamide-induced infertility include age older than 30, more than 15 pulses of therapy, and a cumulative dose of more than 10 g. Concomitant use of leuprolide acetate or oral contraceptives may offset this effect.⁷⁶

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IVIG) is used for the treatment of dermatomyositis and other rheumatic conditions. Data on the use of this medication during pregnancy are limited. There have been several case reports about the safety of this medication during pregnancy. Moreover, this medication has also been used to manage the obstetric complications of antiphospholipid syndrome without inducing congenital malformations.⁷⁷ This medication is considered compatible with pregnancy.

TUMOR NECROSIS FACTOR- α BLOCKADE AND INHIBITORS

Biologics that are directed against the tumor necrosis factor- α (TNF- α) receptor or inhibit this cytokine are successful in treating RA.⁷ These medications are rated category B for use during pregnancy. Although there have been two reports to the FDA of potential congenital anomalies consistent with VACTERL syndrome,⁷⁸ the significance of this finding has been questioned.⁷⁹ A recent case series of 118 pregnancies in which there was exposure to anti-TNF- α agents either before conception or during pregnancy demonstrated a higher rate of spontaneous miscarriage (several of the patients were taking methotrexate and leflunomide as well) but no increased incidence of congenital anomalies.⁸⁰ Nonetheless, in most circumstances it is recommended that these medications be discontinued before pregnancy or at the time of a confirmed pregnancy test result. In cases of severe disease in which patients have previously not tolerated discontinuation of their TNF- α blockers, one can consider continuing these medications during pregnancy.

Animal data suggest that an anti-TNF- α pegylated Fab monoclonal antibody may not cross the placenta in significant concentration to accumulate in the fetus.⁸¹ More recent human data for 152 pregnancies in women exposed to certolizumab pegol, a pegylated anti-TNF- α agent, suggest no increased rate of congenital abnormalities or pregnancy complications when this medication is used during pregnancy.⁸²

RITUXIMAB AND OTHER EXPERIMENTAL THERAPY

Data on the safety of rituximab, abatacept, and other depleting therapies during pregnancy are limited. A recent review of data for 153 pregnancies involving fetal exposure to rituximab revealed 11 hematologic abnormalities, 4 neonatal infections and 2 congenital malformations in 90 live births.⁸³ The authors concluded that rituximab should be avoided for 12 months before conception. Given that immunoglobulins do not cross the placenta until after the first trimester, this may be overly conservative. Nonetheless, whether this medication can safely be used closer to pregnancy is unknown. Data on anakinra, abatacept, tocilizumab, and belimumab are limited, so no conclusions can be drawn. Current recommendations are to avoid these medications during pregnancy.

CONCLUSION

Managing the pregnant patient with an underlying rheumatologic disorder is challenging. Ensuring that the patient's disorder is in remission or under good control with medications compatible with pregnancy before conception is crucial for good maternal and fetal outcomes. The potential toxicities of medications to both the mother and the fetus must be weighed against the need for disease control in situations of disease flare. Often there is no ideal therapy for a given situation. One approach (Table 68.3) is to treat mild symptoms with NSAIDs (up until the third trimester) and/or low doses of glucocorticoids. If inflammatory arthritis is the major complaint, sulfasalazine and possibly TNF- α blockers can be used if disease is flaring during pregnancy. For some patients with extremely active arthritis, it may be difficult to withdraw medications before conception. In these patients, changing to medications compatible with pregnancy such as sulfasalazine and TNF- α blockers that may not cross the placenta may be the best approach. Patients with SLE should continue to take their antimalarials during pregnancy. For moderate disease, higher doses of glucocorticoids, azathioprine, and cyclosporine can be used. For severe diseases, pulse steroid therapy, IVIG, azathioprine, and cyclosporine can be used. Cytotoxic agents should be reserved for life-threatening situations. Limited data on biologics preclude their use during pregnancy in most circumstances. In all cases, the treating clinician and the patient should discuss the potential hazard to the mother and/or the fetus of any therapy.

TABLE 68.3

Treatment recommendations*

Symptom/condition	Treatment options
Mild arthralgias, arthritis, pleuritis, skin rashes	Nonsteroidal antiinflammatory drugs (first two trimesters only) Low-dose glucocorticoids (5-10 mg prednisone a day)
Inflammatory arthritis	Consider sulfasalazine in addition to above
Systemic lupus erythematosus or connective tissue disease	Consider antimalarials
Moderate disease	Glucocorticoids (higher doses), azathioprine, 6-mercaptopurine, cyclosporine
Severe disease	Pulse steroids, intravenous immunoglobulin, azathioprine, cyclosporine
Life-threatening disease	Cyclophosphamide

*Methotrexate and leflunomide should be avoided.

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69

Aspiration and injection of joints and periarticular tissue and intralesional therapy

■ ESPERANZA NAREDO ■ MARINA RULL

- Synovial aspiration is a basic bedside diagnostic tool in rheumatology.
- Major diagnostic errors can be made by simply assuming the nature of an effusion.
- Corticosteroid injection and infiltration and viscosupplementation are basic treatment tools in rheumatology, orthopedics, physiatry, and general medicine. These procedures pose minimal risk to patients when performed properly.
- Synoviorthesis, or medical synovectomy, may be achieved by the intraarticular injection of sclerosing agents or radioactive material but requires specialized knowledge.
- Rheumatologists trained in musculoskeletal ultrasonography are able to perform, at low cost and minimal risk to patients, procedures that in the past required expensive and even risky techniques.
- Ultrasound is a valuable bedside tool for guiding accurate and safe musculoskeletal fluid aspiration and perilesional or intralesional injections. Ultrasound provides confirmation of the clinical diagnosis and the indication for injection. Real-time ultrasound enables us to place the needle correctly, deliver medication accurately, and visualize the drug during and after the procedure.

INDICATIONS FOR ASPIRATING OR INJECTING MUSCULOSKELETAL TISSUES

Aspiration of fluid for diagnostic or therapeutic purposes

Joint aspiration has a number of major indications. In patients in whom infection, crystal, or blood is the suspected cause of monoarthritis or a bursal or tendon sheath lesion, aspiration and synovial fluid analysis are essential and obligated for diagnosis.¹⁻³ In patients with tense joint effusions, aspiration of synovial fluid provides prompt relief of pain and permits the patient to move or bear weight on the affected joint. Finally, in hemarthrosis or septic arthritis, the blood and pus within a synovial cavity may be damaging to the joint cartilage and synovial membrane, so evacuation of the fluid is necessary to avoid permanent joint damage. Large articular effusions should be drained as fully as possible to decrease pressure, improve synovial circulation, and prevent muscle atrophy. Synovial fluid analysis is discussed in Chapter 31.

Key practice issues

Procedure

Aspiration or injection of joints or soft tissues is an outpatient procedure that does not require equipment (Table 69.1) unless performed under ultrasound (US) guidance. The procedure must be explained fully to the patient. Universal precautions focused on sterilization must be followed during the procedure.

Blind aspiration

The patient should be in a supine position for lower extremity procedures and in a sitting position in a chair with armrests for upper extremity

procedures. Anatomic landmarks need to be identified by palpation and the needle site marked. The skin must then be cleaned carefully with antiseptic agents. For local anesthesia, the skin and subcutaneous tissue are infiltrated with 1% or 2% lidocaine without epinephrine (adrenaline) via a small-bore needle down to the level of the periarticular lesion or joint capsule. However, experienced physicians may use topical ethyl chloride or no anesthetic at all. With proper technique the needle passes freely through the extraarticular tissues and a “pop” may be felt as the needle enters the joint. The ease with which fluid can be withdrawn depends on the size of needle used, the viscosity of the fluid, and the presence of any fibrin clots or “rice bodies” in the joint fluid. Free flow of fluid is often suddenly interrupted because of clogging of the end of the needle by the synovial membrane or debris. Rotating the needle, withdrawing it slightly, or even reinjecting a little of the fluid will often help unclog the needle. If corticosteroids or other substances are to be injected, this should be done through the same needle without removing it from the joint.

Ultrasound-guided aspiration and injection

US can be a valuable bedside tool for guiding musculoskeletal fluid aspiration and perilesional or intralesional injections accurately and safely.^{4,5} US provides confirmation of the clinical diagnosis and the indication for injection. The characteristics of joint effusions (e.g., extension, solid or fluid content, internal synovial hypertrophy) that should be aspirated are visualized with US. This information is very useful for planning the best access to the fluid while avoiding synovial hypertrophy or solid material inside the fluid and for selecting the appropriate needle for the procedure. Real-time US enables correct placement of the needle and accurate delivery of any medication by visualizing the drug suspension during and after the procedure. Injections into anatomic structures adjacent to the intended target (e.g., vessels, nerves, subcutaneous fat) can be avoided because they are easily identified with US. The learning time for US-guided injections is usually short.

Several studies have demonstrated greater accuracy with US-guided joint aspiration and soft tissue injection than with blind injection.⁶ Although the impact of accurate needle placement on the therapeutic response to local corticosteroid injection needs further elucidation,⁷ it seems clear that US guidance, if available, can maximize accuracy of the injection into the intended target and minimize adverse effects related to the procedure.

The capability of US to guide injections is based on the easily detectable hyperechoic appearance of foreign bodies such as needles and other puncture devices. The needle is visualized as a bright hyperechogenic line, often with a posterior reverberation artifact, when it is directed parallel to the long axis of the contact surface of the transducer (i.e., probe) and perpendicular to the US beam. Needle imaging is possible with many superficial injections. When the transducer is placed transverse to the route of the needle, only the tip of the needle is detected as a bright hyperechogenic focus as it reaches the target under the probe. The echogenicity of the needle decreases when its direction is oblique to the US beam. The size of the needle does not significantly influence its visualization.

US-guided injections should be carried out by following five steps:

1. US assessment of the clinically pathologic area and confirmation of the clinical diagnosis and indication for injection
2. Planning of the injection route and needle characteristics
3. Sterilization of the patient's skin and probe
4. Skin puncture under US guidance



5. Confirmation of correct fluid aspiration or drug location (or both) with US before removing the needle

Two methods of guiding musculoskeletal needle placement with US are used:

1. Skin marking or indirect method (Fig. 69.1a and b). With this method, US is used to select the potentially most successful puncture site over the target but not to guide progression of the needle. After scanning the pathologic area, the target is imaged in two perpendicular planes. When the target is in the center of the screen in both the longitudinal and transverse planes, the edges of the probe are drawn on the skin with a skin-marking indelible pen. The depth of the target is measured perpendicular to the skin. The probe is then removed and a mark is drawn on the skin in the center of the previously drawn rectangle. After sterilization of the skin, the needle is inserted into the mark and directed to the target.
2. Needle guidance under direct US control (Fig. 69.2a and b). The patient's skin and the transducer are sterilized. Sterile gel is applied to the skin if the entry point chosen is close to the transducer. Some ultrasonographers use a sterile sleeve for the transducer (adequate transducer contact is provided by placing acoustic gel within the

sleeve). Continuous monitoring of progression of the needle under direct US visualization, although more experience and hand-eye coordination are required, provides more accurate control of progression of the needle from the skin to the target during the procedure. Aspiration of fluid (see Fig. 69.2c to e) and injection of medication can be seen in real time. Most ultrasonographers carry out direct US-guided injections via a freehand technique. A needle guide can also be installed on the transducer to hold and direct the needle for injecting deep lesions. However, these devices make the procedure more time-consuming and expensive and the approach less flexible.

At the end of any procedure, the needle should be withdrawn swiftly and light pressure placed on the needle site in the skin. Application of simple adhesive plaster (tape) for a few hours is all that is usually required thereafter.

Aftercare

In most cases it is sensible for patients to rest the affected joint for 24 to 48 hours after a therapeutic injection to minimize leakage of the therapeutic agent following lower extremity procedures and improve the antiinflammatory response.

TABLE 69.1

Equipment required for joint and soft tissue injections

Procedure	Details
Skin preparation	Antiseptic solution (povidone-iodine), alcohol swabs, 4 × 4 gauze pads
Local anesthetic	1% or 2% lidocaine without epinephrine
Needles	No. 23-27 for local anesthetic, 18 gauge for large to moderate-sized joints (knees, shoulders, ankles, etc.), No. 23-27 for small joints (wrists, metacarpophalangeal joints, etc.)
Syringes	3 or 5 mL for anesthetic-steroid injection and 10-50 mL for joint aspiration (sterile steroid–prefilled syringes are preferable when available)
Miscellaneous	Gloves, forceps for removing needles from the syringe, specimen tubes/plates for culture and fluid studies

All the supplies required should be assembled in advance. Importantly, the needle must be long enough to reach the intended place and have a caliber adequate for the nature of the fluid. Although standard needle lengths work well in thin patients, longer needles and even a spinal needle may be required in obese patients. On the other hand, a 1-mL syringe with a half-inch No. 27 needle is particularly useful for infiltrating superficial structures such as the interphalangeal, metacarpophalangeal, and metatarsophalangeal joints; the digital flexor tendon sheaths; the carpal tunnel; de Quervain tenosynovitis; and the elbow joint through the lateral approach. Purulent effusions require No. 18 or 16 needles. Failure to fully drain a septic joint indicates large debris or loculation and calls for tidal lavage, arthroscopy, or arthrotomy. All material should be new and sealed when used; do not use the rest of opened vials.

CONTRAINDICATIONS

There are few absolute contraindications to joint or soft tissue aspiration and injection; if infection is suspected, fluid should always be aspirated from a joint. For other indications, the procedure should probably be avoided if the overlying skin or subcutaneous tissue is infected or if bacteremia is suspected. The presence of a significant bleeding disorder or diathesis or severe thrombocytopenia may also preclude joint aspiration. However, if it is deemed necessary for diagnosis or therapy, the procedure may be carried out after appropriate coverage for the bleeding disorder. Warfarin anticoagulation with international normalized ratios in the therapeutic range is not a contraindication to joint or soft tissue aspiration or injection.⁸ Aspiration of a joint with a prosthesis is often best left to surgeons.

CORTICOSTEROID INJECTIONS

Corticosteroid injections are frequently used to achieve a local antiinflammatory response. Indications for their use include the presence of persistent inflammation at a single site. Synovial joints and other cavities (e.g., bursae, cysts) should generally be injected with a long-acting crystalline form of corticosteroid such as triamcinolone hexacetonide or methylprednisolone acetate. These crystals persist longer in the fluid than do mixtures of depot and soluble betamethasone⁹ and thereby allow continued local release into the targeted area. Only a relatively small proportion escapes into the general circulation, but during the first 24 hours after injection, patients may experience flushing or other evidence of a corticosteroid “pulse.” For periarticular injections, particularly subcutaneous bursae and de Quervain tenosynovitis,

Fig. 69.1 (a) Ultrasound-guided indirect method of injection into the right tibiotalar joint. An extended paper clip is displaced between the probe and the skin until its tip is imaged at the center of the target. The puncture point is marked in the patient's skin with the clip. (b) The needle is inserted perpendicular to the skin.



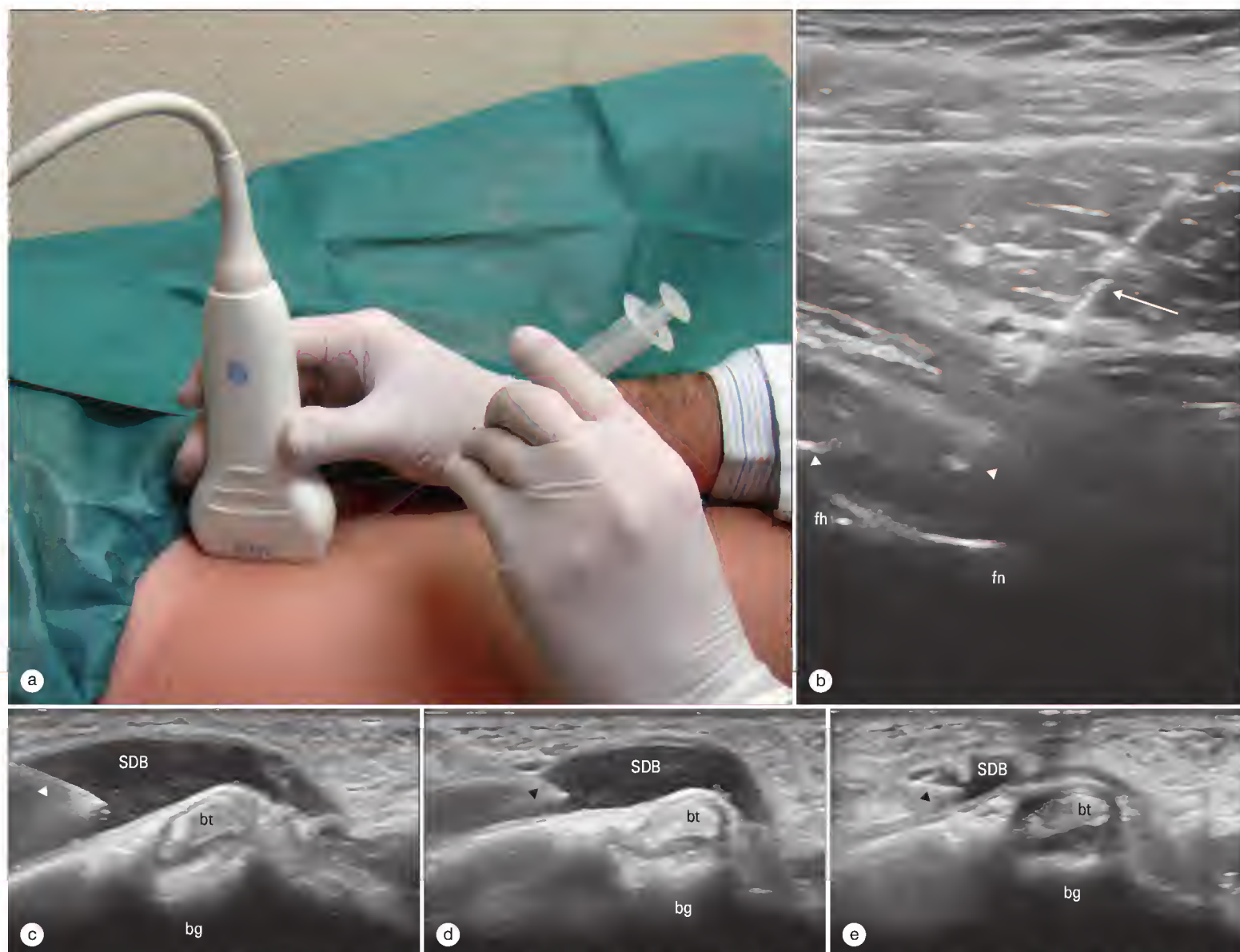


Fig. 69.2 (a) Ultrasound-guided direct method of injection of the right hip joint. The needle is inserted adjacent to the transducer and directed to the anterior recess of the hip. (b) On the ultrasound image the tip of the needle (arrowhead) has a hyperechogenic appearance inside the hip effusion. The needle (arrow) appears hyperacute in the iliopsoas muscle. fh, femoral head; fn, femoral neck. (c) Ultrasound-guided injection of subdeltoid bursitis. (d and e) Successful fluid aspiration can be visualized in real time. Arrowheads indicate needle tips. bt, biceps tendon; bg, bicipital groove; SDB, subdeltoid bursa.

methylprednisolone acetate should be used because the less soluble (and therefore more potent) triamcinolone hexacetonide is likely to induce skin atrophy.

Corticosteroid doses vary with the structure injected. For each of the procedures discussed, a dose range based on the use of methylprednisolone acetate is shown in each section. If the more potent triamcinolone hexacetonide is used, the lower dose of the indicated range should be chosen. Intracavitary position of the needle can be ascertained by withdrawing some joint fluid or checking to see whether the cavity distends as fluid is injected. In soft tissues, correct positioning may be ascertained by elimination of pain with a preceding lidocaine infiltration. However, if available and in procedures in which needle misplacement is common, US guidance gives the best results.¹⁰ Resting the injected site for 24 to 48 hours following the procedure is generally recommended.

The most common indications for aspiration and injection of the musculoskeletal system are presented in this chapter.

Complications of corticosteroid injections¹¹

- **Local bleeding.** In patients without a bleeding diathesis, pressing the puncture site with sterile gauze for about a minute—or longer in those taking prophylactic aspirin—stops the bleeding. In procedures on the upper extremity, arm elevation prevents venous bleeding.
- **Facial flushing.** Flushing occurs in perhaps 40% of cases. Transient and inconsequential, it may nevertheless worry unwarned patients.
- **Postinjection flare.** Corticosteroid crystal-induced synovitis occurs in approximately 5% of intraarticular injections. Pain appears several hours following the procedure and may last from a few hours to 1 day. Persistent pain and mounting swelling may indicate infection; these joints should be reaspirated for Gram stain and aerobic and anaerobic culture.
- **Skin atrophy.** This complication occurs frequently, particularly in elderly individuals and with superficial infiltrations. The condition is characterized by cigarette paper-like skin, recurrent ecchymosis, and chronic pressure pain.
- **Fat atrophy.** This complication may occur with repeated fatty tissue infiltration, such as for Morton neuroma and proximal plantar enthesopathy.
- **Skin hypopigmentation.** Superficial corticosteroid infiltrations such as for de Quervain tenosynovitis often result in a hypopigmented patch, which may be quite disfiguring in people with dark skin.
- **Embolia cutis, livedoid dermatitis, or Nicolau syndrome.** A rare adverse reaction to drug injections, including corticosteroids, this complication is characterized by microembolic obstruction of a dermal artery, which causes a livedoid lesion and necrotic ulcers. Pain is felt around the injection site, followed by a livedoid and hemorrhagic patch, and finally necrosis of the skin, subcutaneous fat, and muscle occurs.
- **Infection.** The reported rate of septic arthritis following corticosteroid injection has been on the order of five cases per 100,000 procedures

when the corticosteroid is aspirated from a vial and less than one case per 100,000 procedures when prefilled syringes are used.¹² Patients who have severe immunodeficiency problems, as well as those with implants, may be at greater risk. It is important to not reuse leftovers of open vials because of staphylococcal contamination.

- Tendon rupture. A ruptured tendon following a corticosteroid injection may indicate abuse of the procedure, intratendinous injection, or coincidental rupture caused by the very condition that led to the injection. Conditions that result in spontaneous tendon rupture include dorsal wrist tenosynovitis and posterior tibialis tenosynovitis in patients with rheumatoid arthritis (RA); degenerative changes in the supraspinatus, long biceps, or Achilles tendon; chronic corticosteroid use; fluoroquinolone-induced Achilles tendinopathy; uremia; hyperparathyroidism; and systemic lupus erythematosus.
- Corticosteroid arthropathy. Abuse of intraarticular injections may result in a Charcot-like arthropathy similar to that described with calcium pyrophosphate crystal deposition disease (see Chapter 190).
- Nerve damage. With knowledge of regional anatomy, this complication should largely be avoided. However, because anatomic variations are frequent, insertion of the needle should always be done cautiously.
- Osteonecrosis. This is a reported complication of articular or soft tissue corticosteroid infiltration abuse.
- Systemic complications. Corticosteroid injections cause pituitary inhibition, which recovers in 1 to 2 weeks,¹³ and in diabetics, transient hyperglycemia lasting 2 to 3 days; anaphylactic shock, albeit exceedingly rare, may also occur.¹⁴

OTHER THERAPEUTIC INJECTIONS

Viscosupplementation

Viscosupplementation is the term that describes the use of intraarticular hyaluronates for the treatment of pain in osteoarthritic joints. Two types of agents are in use. One is hylan G-F 20, a high-molecular-weight preparation (molecular weight of 6,000,000). The other type includes lower-molecular-weight hyaluronan preparations in the range of 800,000 to 2,000,000. Viscosupplementation is often effective in relieving pain in patients with osteoarthritis (OA).^{15,16} When compared with intraarticular corticosteroids, the beneficial effect of viscosupplementation is that it has delayed action but lasts longer.¹⁷ The relative merits of hylan G-F 20 and the lower-molecular-weight compounds are still in dispute.^{18,19} Although these agents were initially used for the knee, other joints such as the trapeziometacarpal joint, the shoulder, the hip, and the ankle have all been treated with benefit. Viscosupplementation is associated with several risks. Postinjection pain, not necessarily associated with a significant effusion, has been common in the authors' experience. Another complication is a pseudo-septic effusion associated with pyrexia.²⁰ These reactions require hospital admission and intravenous antibiotics pending the results of culture. A granulomatous reaction has also been reported.²¹ A further risk with viscosupplementation is an allergic reaction in patients with avian protein allergy (e.g., products, feathers). The usual indications for viscosupplementation include (1) patients who cannot tolerate antiinflammatory medications and whose pain is unrelieved with analgesics and (2) those with advanced OA who refuse or are not suitable candidates for surgery. The medication and administration costs of viscosupplementation are considerable. However, a Canadian cost analysis has shown superiority of viscosupplementation over appropriate care without viscosupplementation.²²

Synoviorthesis

Synoviorthesis, or medical synovectomy, may be achieved with the intraarticular injection of chemicals such as osmic acid, rifampicin, and rifamycin or radioactive colloids such as yttrium-90 (⁹⁰Y), erbium-169 (¹⁶⁹Er), dysprosium-165 (¹⁶⁵Dy), and gold-198 (¹⁹⁸Au), among others. The procedure may be used in patients with RA, OA, pigmented villonodular synovitis,²³ and other chronic effusive conditions, as well as in those with hemophilia to terminate recurrent hemarthrosis.²⁴ Chemical agents are believed to be less efficacious than radioactive colloids, and among these, beta-emitting radioisotopes such as ⁹⁰Y, ¹⁶⁹Er, and ¹⁶⁵Dy are preferred over gamma-emitting radioisotopes such as ¹⁹⁸Au, which cause total body irradiation. Few randomized controlled trials of radioactive and chemical synoviorthesis have been conducted.²⁵ Adverse effects of radioactive synoviorthesis are uncommon. A possible untoward local effect is a burning sensation in the needle track. This may be prevented by injecting a corticosteroid suspension while slowly removing the injecting needle. A greater concern has been

a possible oncogenic effect of the radioactive colloid. However, although chromosomal damage has been found rather frequently in peripheral blood following these procedures, a 30-year Finnish follow-up study of ⁹⁰Y synoviorthesis in more than a thousand patients failed to show excess cancer deaths.²⁶ Thus, radioactive synoviorthesis, a low-risk, relatively low-cost outpatient procedure that minimally disrupts the patient's activities, is a plausible alternative to surgical synovectomy in carefully selected patients. In hemophilia, according to experts, failure of three consecutive radioactive synoviorthesis procedures is an indication for open or arthroscopic synovectomy.

Other injections

Other medications that can be injected into the musculoskeletal system with controversial efficacy are sclerosants and platelet-rich plasma to ameliorate pain and improve healing of tendinoligamentous structures and botulinum toxin for the relief of muscle pain.

The next section of this chapter focuses on the most frequent procedures involving corticosteroid injection from an anatomic perspective.

WRIST AND HAND

Finger and metacarpophalangeal joints

Indications. Active Bouchard nodes, RA,²⁷ psoriatic arthritis. US guidance is not required.

Corticosteroid dose. 10 to 15 mg methylprednisolone acetate (No. 25 or 27 needle).

Approach. Dorsolateral with the digit in semiflexion (Fig. 69.3, Figs. e69.1 and e69.2). Note that in this and other clinical pictures the skin had been sterilized with alcohol and the needle seen in place was for injection of local anesthetic before injection of the steroid. Multiple joints may be injected during the same session.

Precautions. Do not overdilate the joint or joints. Fluid tends to back up; apply firm pressure with sterile gauze for at least 2 minutes following the procedure.

Complications. Joint hyperlaxity, capsular calcification (frequent but inconsequential).

First carpometacarpal joint

Indications. Painful OA. The efficacy of steroid injection has been disputed.²⁸ Viscosupplementation may be useful as an alternative to surgery.²⁹ US guidance is not required.

Corticosteroid dose. 15 to 30 mg methylprednisolone acetate (No. 25 or 27 needle).

Approach. A common entry site is at the anatomic snuffbox while flexing the thumb across the palm, which optimally exposes the joint just proximal to the protruding base of the first metacarpal (Fig. 69.4). A palmar approach is generally used to inject this joint under US guidance.

Precautions. Avoid the radial artery as it traverses the anatomic snuffbox.

Complications. None.



Fig. 69.3 Injection of the right fourth proximal interphalangeal joint in a patient with osteoarthritis.



Fig. e69.1 Injection of third metacarpophalangeal joint in a patient with rheumatoid arthritis.



Fig. e69.2 Injection of interphalangeal joint of the thumb adjacent to a Heberden node.

Wrist (radiocarpal and midcarpal joints)

Indications. For diagnosis of acute arthritis. Most cases of acute wrist arthritis are due to calcium pyrophosphate dihydrate pseudogout, gout, and septic arthritis. For injection in patients with RA, other sterile synovitis, and OA, US guidance is preferred. US allows identification of which wrist joint (e.g., radiocarpal, midcarpal) is more inflamed or has more fluid, which is important in determining the injection target.

Corticosteroid dose. 30 to 40 mg methylprednisolone acetate (No. 25 or 27 needle). Aspiration should be attempted before injection. For aspiration alone, use a No. 20 or 18 needle.

Approach with blind injections. The radiocarpal joint is approached dorsally just distal to the Lister tubercle (a bony prominence in the dorsal distal end of the radius) or at the midcarpal joint 1 cm ulnar and 5 mm distal to the Lister tubercle (Figs. e69.3 and e69.4). The wrist should be slightly palmar-flexed to assist in the procedure.

Precautions. No neurovascular structures of concern are located at this site.

Complications. None.

Trigger finger and trigger thumb

Indications. Only 30% of trigger fingers resolve spontaneously, and injections are highly efficacious.³⁰ A lower success rate of injections is seen in diabetics. US guidance is not required.

Approach. Just distal to proximal palmar crease (index) (Fig. 69.5), between the proximal and distal creases in the long finger (Fig. e69.5), and just distal to the distal crease in the ring and little fingers (Fig. e69.6) with the needle held at a 45-degree distal inclination; just proximal to the digital crease and aimed at sesamoids of the thumb (Fig. 69.6).

Corticosteroid dose. 15 to 20 mg methylprednisolone acetate mixed with 1 to 2 mL lidocaine (No. 25 or 27 needle).



Fig. 69.4 Injection of the left trapeziometacarpal joint in a patient with osteoarthritis.



Fig. 69.5 Injection of a right index trigger finger.

Precautions. Avoid intratendinous injection. Intratheath injection is not a requirement for success.³¹ Up to three injections given 3 weeks apart are allowed.

Complications. Focal palmar fat atrophy.

Digital flexor tenosynovitis

Indications. RA, psoriatic arthritis, and other inflammatory conditions.

Because the injection must be intratheath for flexor tenosynovitis, US guidance is preferred (Fig. 69.7, Fig. e69.7).

Corticosteroid dose. 15 to 20 mg methylprednisolone acetate mixed with 1 to 2 mL lidocaine (No. 25 or 27 needle).

Approach. If US is unavailable, inject as for trigger finger.

Precautions. Avoid intratendinous injection.

Complications. As with trigger finger, tendon rupture occurs occasionally.

Carpal tunnel syndrome³²

Indications. Injection is indicated for all causes of carpal tunnel syndrome except acute cases (hypoesthesia, severe pain, and tense bulging) caused by synovitis, fracture, hemorrhage, infection, and carpal tunnel syndrome in late pregnancy. US guidance is optional for routine cases but is a must for unilateral cases to rule out a mass lesion.³³

Corticosteroid dose. 30 to 40 mg methylprednisolone acetate, straight or mixed with 2 to 3 mL lidocaine (No. 25 or 27 needle).

Approach. About 10 mm proximal to the distal wrist crease and just medial to the palmaris longus tendon (Fig. 69.8, Fig. e69.8). If the palmaris longus is absent (14% of people), use a midline approach. The needle is inserted to a depth of 0.8 to 1 cm at a 45-degree distal inclination and a 45-degree lateral inclination. The corticosteroid is injected into the proximal extension of the ulnar bursa.

Precautions. Paresthesias indicate median nerve engagement; reposition the needle. Reciprocal needle motion with gentle finger motion indicates tendon engagement; reposition the needle. A wrist splint in neutral is a useful adjunct to the injection.

Complications. Pain, which may last 1 to 3 days, and a transient increase in paresthesias. The patient should be instructed to use an ice pack intermittently, 5 minutes on and 5 off, at the first hint of pain.



Fig. 69.6 Injection of a right trigger thumb.



Fig. 69.7 Same patient as in Figure e69.7. t, flexor tendon; s, steroid.



Fig. e69.3 Aspiration of the radiocarpal joint for gout, radial view.



Fig. e69.4 Aspiration of the radiocarpal joint for gout, dorsal view.



Fig. e69.5 Injection of a right middle trigger finger.



Fig. e69.6 Injection of a right ring trigger finger.

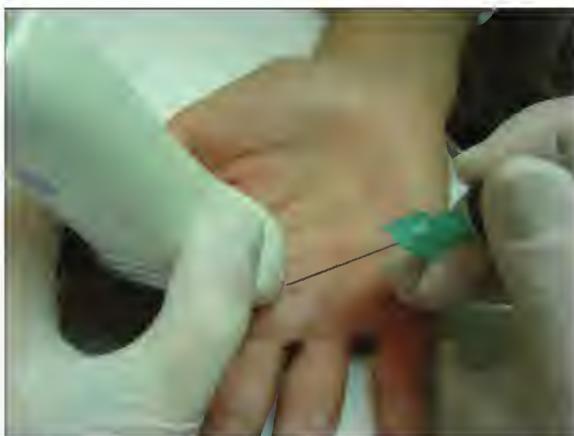


Fig. e69.7 Ultrasound-guided direct injection for flexor tenosynovitis of the hand.



Fig. e69.8 The tendons used as landmarks for injection into the carpal tunnel are seen clearly in this patient. To the left of the needle, past the vein, two tendons are seen: the palmaris longus and, radial to this, the flexor carpi radialis.

de Quervain tenosynovitis³⁴⁻³⁶

Indications. Steroid injection is the treatment of choice for this condition. US guidance is optional.

Corticosteroid dose. 15 to 20 mg methylprednisolone acetate (No. 25 or 27 needle).

Approach. The needle is aimed toward the radial styloid, which underlies the sheath (Fig. 69.9). The needle is then pulled back by the millimeter and injection is attempted. Successful injections distend the sheath of the abductor pollicis longus or extensor pollicis brevis (or both). Up to three injections given 3 weeks apart are allowed.

Precautions. The corticosteroid must remain within the sheath. Do not infiltrate grossly thickened sheaths because mycobacterial infection may be present.

Complications. Skin hypopigmentation and skin atrophy.



Fig. 69.8 Injection for right carpal tunnel syndrome.



Fig. 69.9 Injection for right de Quervain tenosynovitis.

Wrist extensor tenosynovitis

Indications. Sustained tenosynovitis in patients with RA and psoriatic arthritis, microcrystalline tenosynovitis. Failure of one injection is an indication for tenosynovectomy.

Corticosteroid dose. 15 to 20 mg methylprednisolone acetate. (No. 25 or 27 needle).

Approach. A direct US-guided injection is preferred (Figs. e69.9 and e69.10).

Complications. The extensor digital tendons are prone to spontaneous rupture in patients with RA. An intratendinous injection probably enhances this tendency. Whether to inject an extensor tendon sheath or proceed to tenosynovectomy should be discussed with a hand surgeon.

Ganglia

Indications. Local corticosteroids are highly effective in the treatment of routine dorsal ganglia. Ganglia within the carpal tunnel, those that impinge on neurovascular structures, and those larger than 3 cm in diameter should be injected under US guidance³⁷ or treated surgically.

Corticosteroid dose. Depends on the lesion; usually 15 to 20 mg methylprednisolone acetate (No. 20 or 18 needle; thinner needles may become clogged).

Approach. The needle is aimed at the center of the lesion, which is aspirated before injection. Ganglia contain a viscous, translucent fluid. Fluid with other characteristics indicates that the lesion is not a ganglion; the fluid should therefore be cultured and inspected for crystals.

US guidance for ganglia injections is especially valuable with deeply located lesions or when they are close to other structures that may be punctured incidentally (e.g., tendons, peripheral nerves or vessels) (Fig. e69.11 and Fig. 69.10a and b).

Precautions. With ganglia in the wrist and anatomic snuffbox, rule out radial artery aneurysm, which mimics a ganglion. These lesions are expansile with the pulse, as opposed to the focal pulsation caused by a normal adjacent radial artery.

Complications. None.

ELBOW REGION

Elbow (joint)

Indications. Aspiration for acute arthritis, injection for RA, and psoriatic arthritis.

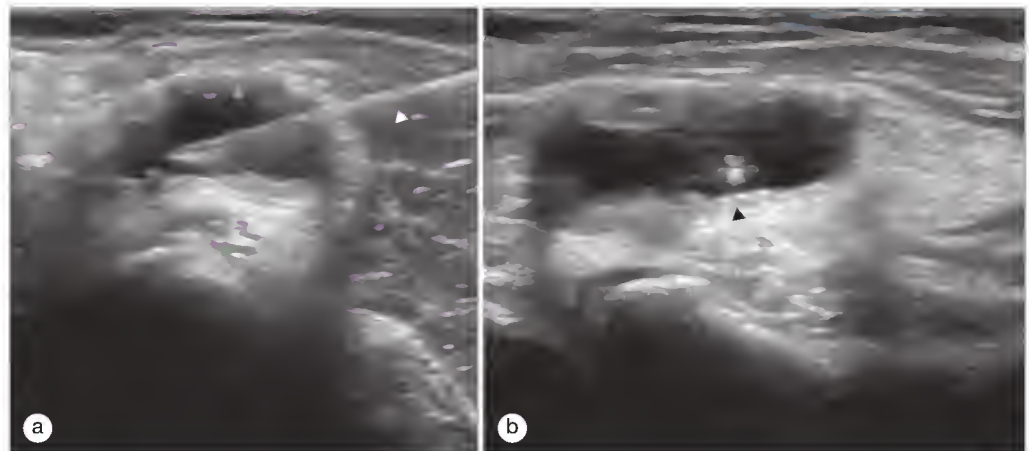
Corticosteroid dose. 30 to 40 mg methylprednisolone acetate (No. 22, 25, or 27 needle). Aspiration should be attempted before injection. For aspiration alone, use a No. 20 or 18 needle, depending on the suspected diagnosis. US guidance is optional.

Approach for blind injections. Two entries are commonly used; for both entries the elbow is held flexed at 90 degrees.

—Inferolateral approach. The midpoint cleft between the tip of the olecranon and the lateral epicondyle is palpated. The needle is then inserted perpendicularly and aimed at the center of the joint.

—Lateral approach. The radiocapitellar joint may be entered from the side just proximal to the radial head. The needle is passed perpendicular to the skin between the two bones (Fig. 69.11).

Fig. 69.10 Ultrasound-guided injection of a ganglion cyst at the anterior aspect of the elbow (i.e., radiohumeral joint) with the needle parallel to the long axis of the transducer (a) or perpendicular to the long axis of the transducer (b). The hyperechoic needle (a; arrowhead) or the tip of the needle (b; arrowhead) is seen inside the lesion.



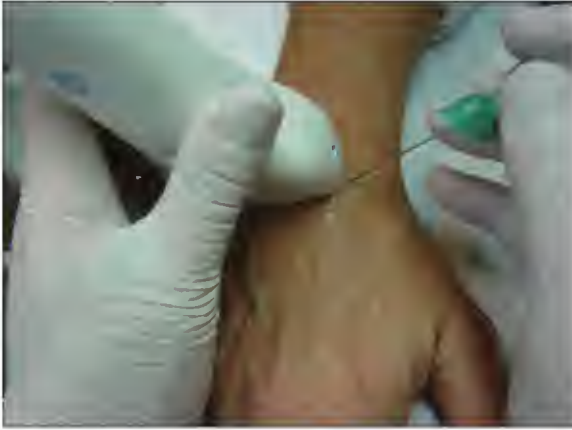


Fig. e69.9 The needle is inserted adjacent to the transducer and directed to the sheath of the fourth extensor compartment of the wrist.

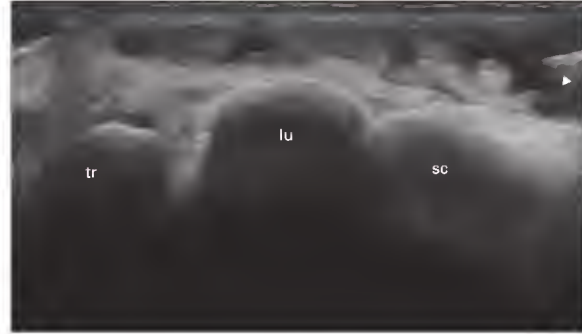


Fig. e69.10 Same patient as in [Figure e69.9](#). On the ultrasound image the needle (arrowhead) is introduced into the hypoechoic extensor tenosynovitis. lu, lunate; sc, scaphoid; tr, triquetrum.

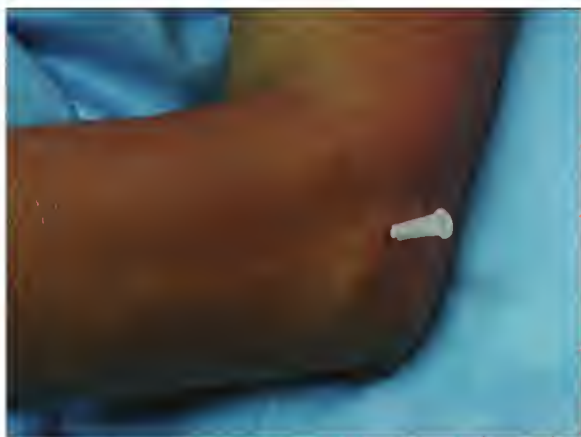


Fig. 69.11 Lateral (radiocapitellar) injection of the left elbow in a patient with rheumatoid arthritis.

If palpation-guided aspiration of the elbow joint is not successful, US-guided arthrocentesis can be carried out from an anterior or posterior recess, depending on the location and characteristics of the effusion. The brachial artery and median and radial nerves can easily be identified and avoided with the anterior needle route.

Precautions. No neurovascular structures are located in the vicinity.

Complications. None.

Olecranon bursa

Indications. For the diagnosis of effusion and for the treatment of refractory aseptic bursitis (traumatic or microcrystalline). A negative bursal fluid culture is required before steroid injection. US guidance is not necessary.

Corticosteroid dose. 20 mg methylprednisolone acetate (No. 20 or 22 needle). Empty the bursa before injection.

Approach. Lateral through normal skin and aimed at the center of the bursa (Fig. e69.12).

Precautions. Taps at the tip of the bursa may create a chronic leak. Medial entries may damage the ulnar nerve.

Complications. Injection of 20 mg methylprednisolone acetate has not caused complications.

Lateral epicondylar syndrome, or tennis elbow, and medial epicondylar syndrome, or golfer's elbow^{38,39}

Indications. Failure of conservative treatment. To shorten the symptomatic period (with the caveat that the long-term outcome may be worse in injected than in uninjected patients). US guidance is not necessary.

Corticosteroid dose. 10 to 20 mg methylprednisolone acetate (No. 25 or 27 needle).

Approach for the lateral epicondyle. At the most tender point (Fig. 69.12), pass the needle until contact with the periosteum is made and infiltrate with 1 mL lidocaine. Failure to eradicate pain on resisted wrist dorsiflexion indicates the wrong injection site; reposition the needle and reinfiltrate with lidocaine. The corticosteroid should be infiltrated deeply at the enthesis and radially within the proximal part of the tendon.

Approach for the medial epicondyle. Aim the needle toward the distal portion of the medial epicondyle where the wrist flexor muscles insert.

Avoid injecting the posterior surface of the epicondyle to stay away from the ulnar nerve (Fig. e69.13).

Precautions. Avoid injecting too superficially.

Complications. Transient increase in pain in 20% to 40% of patients. Repeated corticosteroid infiltrations may result in chronic pain.

SHOULDER REGION

Shoulder (glenohumeral joint)

Indications. Aspiration for acute arthritis; injection for RA, spondyloarthritis, and the initial stages of frozen shoulder⁴⁰; viscosupplementation for OA. US guidance is necessary for the latter indication and desirable for all of them.



Fig. 69.12 Injection for right tennis elbow (lateral epicondylar syndrome).



Fig. 69.13 Posterior approach to the right shoulder in a patient with a frozen shoulder.

Corticosteroid dose. 40 to 80 mg methylprednisolone acetate (No. 22 needle). Aspiration should be attempted before injection. For frozen shoulder, injection into the joint may be difficult because of the capsular restriction. For aspiration alone, use a No. 20 or larger needle.

Approach for blind injection. Two entries are described: the posterior approach, which is preferred by the authors, and the anterior approach.

—**Posterior approach** (Fig. 69.13, Figs. e69.14 and e69.15). With the patient sitting, the posterior margin of the acromion is palpated. The needle is then inserted posteroanteriorly 1 cm below and 1 cm medial to the posterior corner of the acromion and aimed toward the coracoid process until bone is touched at the articular space.

—**Anterior approach.** Again, the patient should be sitting with the arm hanging at the side of the body, elbow flexed 90 degrees, and forearm in the sagittal plane. The needle is inserted anteroposteriorly 1 cm distal and 1 cm lateral to the coracoid process. Once the bone is touched, the forearm is very gently and passively brought into internal rotation as the needle is pushed into the articular space.

The glenohumeral joint is usually injected from a posterior approach under US guidance. The needle is directed to the posterior synovial recess located at the superior angle of the posterior labrum.

Precautions. Use a chair with armrests; watch for fainting.

Complications. Vasovagal syndrome. Misplaced anterior injections may encounter neurovascular structures.

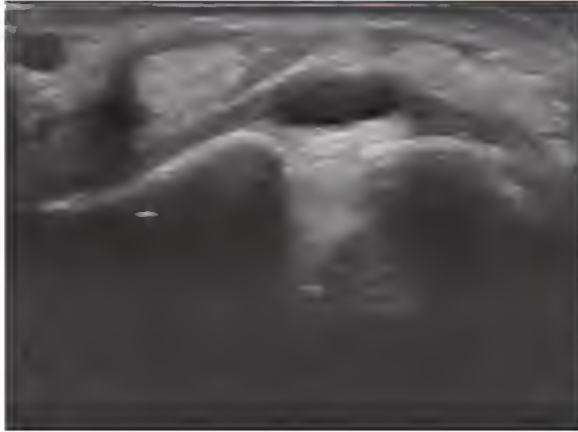


Fig. e69.11 Transverse ultrasound image of a scapholunate ganglion.



Fig. e69.12 Lateral needle entry for olecranon bursitis.



Fig. e69.13 Injection for right golfer's elbow (medial epicondylar syndrome).



Fig. e69.14 Posterior approach to the right shoulder, back view.



Fig. e69.15 Posterior approach to the right shoulder, superior-lateral view.

Acromioclavicular joint

Indications. Aspiration for acute arthritis; injection for OA, RA, and spondyloarthritis. US guidance is not required.

Corticosteroid dose. 10 to 20 mg methylprednisolone acetate (No. 25 or 27 needle). Aspiration should be attempted before injection. For aspiration alone use a No. 20 needle.

 **Approach.** Aim the needle perpendicular to the skin into the articular cleft; aspirate or inject to distend the joint (Fig. e69.16).

Precautions. The procedure is difficult because the acromioclavicular joint space is narrow and has a partial meniscus.

Complications. None.

Subacromial bursa¹⁰

 **Indications.** Injection may be indicated for rotator cuff tendinopathy and inflammatory and microcrystalline bursitis. US guidance is highly desirable (Figs. e69.17 and e69.18).

Corticosteroid dose. 30 to 40 mg methylprednisolone acetate (No. 22 or 25 needle).

Approach for blind injection. The needle is inserted laterally near the posterior angle of the acromion and aimed anteromedially while ensuring that it passes under the anterior half of the acromion. Easy flow and bulging outlining the bursa indicate bursal injection.

Precautions. None.

Complications. None.

Note: Only about 50% of blind subacromial bursa injections fall on target.

Rotator cuff calcific tendinitis

In patients with calcific tendinitis of the rotator cuff who do not respond to blind corticosteroid injections, US-guided puncture of the calcifications combined with local corticosteroid injection can be a successful therapeutic alternative.⁴¹ The needle should be directed to the subdeltoid bursa under continuous US guidance. After the bursa is anesthetized with lidocaine, the needle is introduced through the tendon until the calcium deposit is reached. Fragmentation and aspiration of at least part of the calcium deposit and later bursal and peritendinous corticosteroid injection are carried out. Calcification lavage can be facilitated by using two needles for the procedure.

HIP REGION

Hip joint⁴²

Indications. Diagnosis of septic arthritis, including the differential diagnosis of septic arthritis versus aseptic loosening in a prosthetic hip; viscosupplementation. US guidance is required.

Corticosteroid dose. Although the procedure is generally performed for diagnosis, there are proponents of steroid injection or, preferably, viscosupplementation for advanced hip osteoarthritis. The dose is 40 to 60 mg methylprednisolone acetate mixed with 3 mL of 1% lidocaine (No. 22 needle). Aspiration should be attempted before injection.

Approach. US guidance is required (see Fig. 69.2a and b).

Precautions. The danger of injuring the femoral neurovascular bundle is averted by guidance with US.

Complications. None.

Iliopsoas bursa

Indications. Painful iliopsoas bursitis⁴³ and bursal distention causing neurovascular compression.

Corticosteroid dose. 30 to 40 mg methylprednisolone acetate mixed with 3 mL of 1% lidocaine (No. 22 needle). Aspiration should be attempted before injection.

Approach. US guidance, as for the hip.

Precautions. As for the hip.

Complications. None.

Trochanteric syndrome

Indications. Lateral hip pain with trochanteric tenderness.⁴⁴ US guidance is not required. However, US allows differential diagnosis between trochanteric bursitis and gluteus tendinopathy-enthesopathy and, if present, facilitates injection inside the bursa.

Corticosteroid dose. 40 mg methylprednisolone acetate mixed with 5 mL of 1% lidocaine (No. 22, 1.5-inch needle; a longer needle may be required for obese patients).

Approach. With the patient lying on the opposite side, the greater trochanter is identified by distal-to-proximal palpation along the femur. The point of maximal tenderness is usually located at the posterior corner of the trochanter. The needle is inserted vertically until contact with the periosteum. The mixture of corticosteroid and lidocaine should then be infiltrated radially to cover the base of a cone 3 cm in diameter, half on bone and half in the proximal soft tissues (Fig. e69.19).

Precautions. The needle should be of sufficient length to reach bone.

Complications. None.

KNEE REGION

Knee (joint)

Indications. For diagnosis of any joint effusion; for corticosteroid injection in patients with RA, spondyloarthritis, OA, and occasionally, crystal-induced synovitis. For viscosupplementation, US guidance is not required.

Corticosteroid dose. 40 to 80 mg methylprednisolone acetate (No. 22 needle). Aspiration should be attempted before injection. For aspiration alone use a No. 20 or 18 needle depending on clinical suspicion.

Approach. Lateral, with the needle aimed at the patellar undersurface midway between the upper and lower poles of the patella⁴⁵ (Fig. 69.14a). When clinical attempts to aspirate a knee effusion are unsuccessful, confirmation of synovitis and guidance of the procedure can be achieved with US. The parapatellar recesses are more accessible to US-guided injection than the suprapatellar recess is (see Fig. 69.14b and c).

Precautions. Beware of superimposed septic arthritis in patients with RA. Postpone injection of an acutely inflamed joint until a negative synovial fluid culture result becomes available.

Complications. None.

Baker cyst

With very large cysts, direct aspiration through a large-bore needle followed by instillation of a corticosteroid is appropriate. US guidance is highly desirable (Fig. 69.15).

Medial knee pain and pes anserinus syndrome

Indications. Pain in the pes anserinus area.^{46,47} US guidance is not required.

Corticosteroid dose. 20 to 40 mg methylprednisolone acetate mixed with 2 to 3 mL lidocaine (No. 22 needle).

Approach. The injection site is best determined by following the medial tendinous border of the thigh (semitendinosus tendon), with the knee in semiflexion, to the tibia, where a mark is placed. The knee is then brought to extension and the needle inserted perpendicularly until contact with the tibia (Fig. 69.16). An area 3 cm in diameter is infiltrated adjacent to the periosteum.

Precautions. Paresthesias extending along the medial aspect of leg indicate engagement of the saphenous nerve; reposition the needle.

Complications. None.

ANKLE AND FOOT

Ankle (joint)

Indications. As for the knee. US guidance is preferable⁴⁸ (see Fig. 69.1).

Corticosteroid dose. 40 to 60 mg methylprednisolone acetate (No. 22 or 25 needle). Aspiration should be attempted before injection. For aspiration alone use a No. 20 needle.

Approach for blind injection. With the patient supine on the examination table, seek the cleft between the tibia and talus by gently flexing and extending the foot. Insert the needle vertically medial to the anterior tibialis tendon (Fig. e69.20).

The lateral and medial tibiotalar recesses, with avoidance of vessels and tendons, are the usual routes for US-guided injections into the ankle.

Precautions. Avoid the dorsalis pedis artery.

Complications. None.



Fig. e69.16 Injection of a painful acromioclavicular joint in a patient with osteoarthritis.



Fig. e69.17 Ultrasound-guided direct injection into the subacromial bursa.



Fig. e69.18 Same patient as in [Figure e69.17](#). The needle (arrowhead) is hyperechogenic with a posterior reverberation artifact inside the subdeltoid bursitis (SDB). bg, bicipital groove; t, biceps tendon.



Fig. e69.19 Steroid injection for trochanteric syndrome.

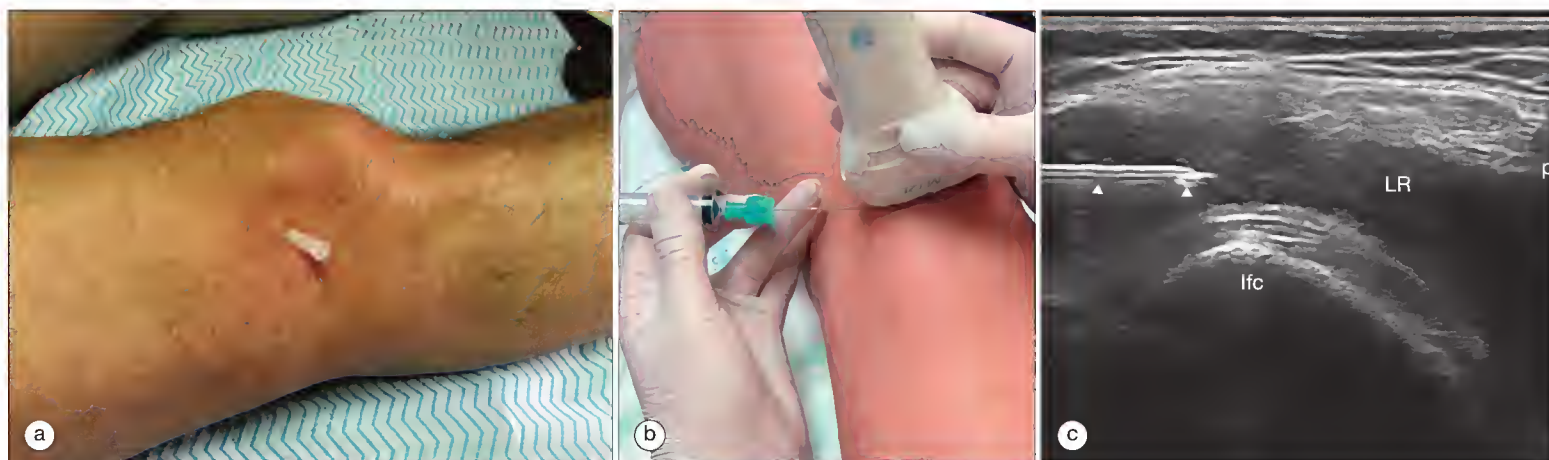


Fig. 69.14 (a) Knee injection, lateral approach, right knee osteoarthritis. (b) Ultrasound-guided direct method of injection into the knee. The needle is inserted adjacent to the transducer and directed to the lateral recess of the knee. (c) Ultrasound-guided injection into the lateral recess of the knee. The needle has a hyperechoic appearance (arrowheads) inside the lateral recess, which is distended by synovitis. lfc, lateral femoral condyle; LR, lateral recess; p, patella.



Fig. 69.15 Ultrasound-guided injection of a Baker cyst. The needle (arrowheads) has a hyperechoic appearance inside the Baker cyst (BC). mfc, posterior aspect of the medial femoral condyle.



Fig. 69.16 Injection for right pes anserinus syndrome.



Fig. 69.17 Aspiration of the left first metatarsophalangeal joint for gout.

Subtalar joint

Indications. As for the knee. US guidance is optional.

Corticosteroid dose: 20 to 30 mg methylprednisolone acetate (No. 22 needle). Aspiration should be attempted before injection. For aspiration alone use a No. 20 needle.

Approach. By gently inverting and everting the foot, find the soft cleft (sinus tarsi) anterior to the lateral malleolus. Insert the needle perpendicularly toward the tip of the medial malleolus. Aspiration of fluid proves an articular insertion. Inject under low pressure (Fig. e69.21).

Precautions. This procedure should be performed only by health professionals with a thorough knowledge of anatomy.

Complications. None.

Metatarsophalangeal joints

Indications. Aspiration for the diagnosis of gout (usually the first metatarsophalangeal joint). Injection for hallux rigidus, RA, and spondyloarthritis. US guidance is optional.

Corticosteroid dose. 10 to 20 mg methylprednisolone acetate (No. 22, 25, or 27 needle). Attempt aspiration before injection. For aspiration alone use a No. 22 needle.

Approach for blind injection. Dorsal, lateral, or medial to the extensor tendon. Slight passive plantar flexion facilitates the procedure (Fig. 69.17, Figs. e69.22 and e69.23).

Precautions. None.

Complications. None.



Fig. e69.20 Aspiration of the right tibiotalar (ankle) joint in a patient with gout.



Fig. e69.21 Injection of the talocalcaneal joint (subtalar) in a patient with rheumatoid arthritis.

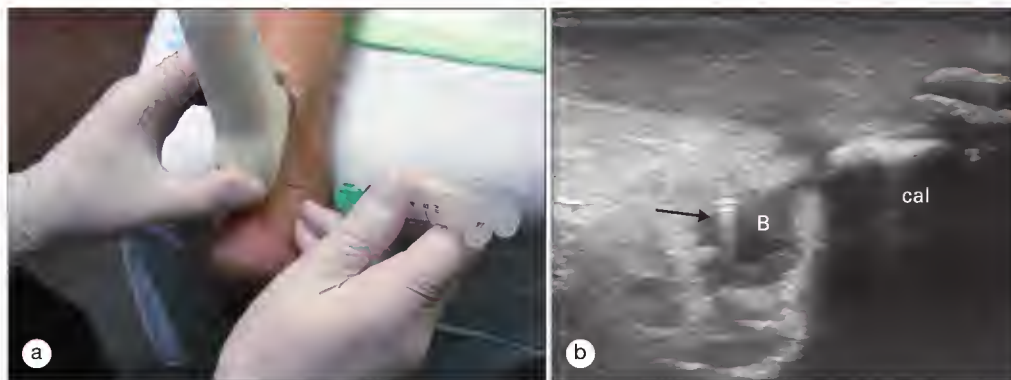


Fig. e69.22 Aspiration of second metatarsophalangeal joint for gout.



Fig. e69.23 Aspiration of fifth metatarsophalangeal joint for gout.

Fig. 69.18 (a) Ultrasound-guided direct injection into the retrocalcaneal bursa. The needle is inserted adjacent to the transducer and perpendicular to its long axis. (b) On the ultrasound image, the tip of the needle (arrow) is hyperechogenic inside the retrocalcaneal bursitis. B, bursa; cal, calcaneus.



Retrocalcaneal bursa

Indications. Refractory Achilles tendon enthesis, organ inflammation in spondyloarthritis, RA. Whenever possible this procedure should be performed under US guidance (Fig. 69.18a and b).

Corticosteroid dose. 15 to 20 mg methylprednisolone acetate (No. 22, 25, or 27 needle or butterfly). Aspiration should be attempted before injection. The presence of fluid (usually a trace) proves intrabursal location of the needle.

Approach for blind injection. Posterior approach.⁴⁹ The patient lies prone on the examination table with the foot outside the mattress. Allow calf relaxation. A 13-mm No. 27 insulin needle may be best suited for this procedure. The needle is advanced vertical to the skin, transtendinously, and aimed at the posterior superior calcaneal angle.

Precautions. This procedure should be performed only by health professionals with a thorough knowledge of anatomy.

Complications. Tendon rupture is possible and more than one reinjection is discouraged.

Posterior tibialis tendon sheath

Indications. Posterior tibialis tenosynovitis in patients with RA and spondyloarthritis; tarsal tunnel syndrome. US guidance is highly desirable (Fig. 69.19).

Corticosteroid dose. 20 to 30 mg methylprednisolone acetate (No. 22 or 25 needle).

Approach for blind injection. The patient lies supine with the injected leg resting on the contralateral knee. Have the patient invert the foot to identify the posterior tibialis tendon, which tents the skin. The needle is inserted tangentially, three fingerbreadths proximal to the tip of the medial malleolus. Inject under low pressure. Fluid may be seen and felt distending the sheath.

Precautions. Aspirate first to make sure that the posterior tibial artery has not been punctured. Plantar paresthesias indicate engagement of the posterior tibial nerve. This procedure should be performed only by health professionals with a thorough knowledge of anatomy.

Complications. The posterior tibialis tendon is prone to spontaneous rupture in patients with RA. A misplaced (intratendinous) injection probably enhances this tendency.

Plantar fascia calcaneal entheses^{50,51}

Indications. Refractory plantar fasciitis in patients with spondyloarthritis. US guidance is optional.

Corticosteroid dose. 20 to 30 mg methylprednisolone acetate diluted with 2 mL lidocaine (No. 22 needle).

Approach for blind procedure. Medial, needle parallel to the plantar skin 2 cm deep to the plantar surface. Aim the needle into the medial plantar tubercle of the calcaneus. Resilience indicates a fascial location. Relocate the needle and inject deeply and superficially to the fibrous fascia (Fig. e69.24).

Precautions. This procedure should be performed only by health professionals with a thorough knowledge of anatomy.

Complications. Repeated infiltrations result in fat atrophy and pressure-induced plantar heel pain. Rupture of the plantar fascia may also occur. Discourage more than one reinjection (2 to 3 weeks after the initial injection).

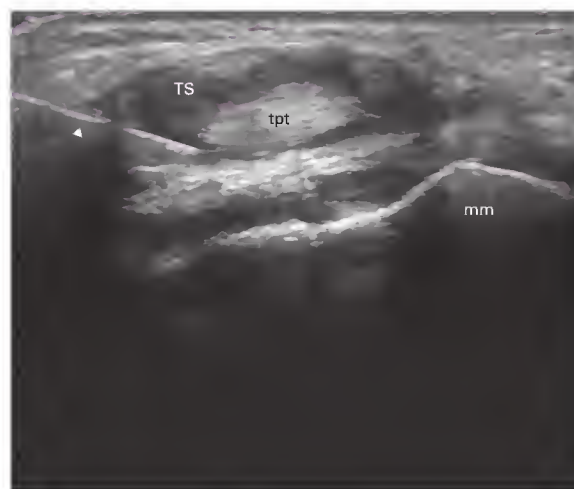


Fig. 69.19 Ultrasound-guided direct injection for tenosynovitis of the tibialis posterior tendon. The needle (arrowhead) is inserted within the distended tendon sheath (TS). mm, medial malleolus; tpt, tibialis posterior tendon.

Intermetatarsal bursae

Indications. Intermetatarsal bursitis in patients with RA (two or more toes spread apart). US guidance is optional.

Corticosteroid dose. 20 to 30 mg methylprednisolone acetate (No. 25 or 27 needle).

Approach. Dorsal to plantar with the needle aimed toward the space in between the metatarsal heads (Figs. e69.25 and e69.26).

Precautions. Plantar fat atrophy is minimized by using an insulin needle.

Complications. None.

Morton neuroma⁵²

Indications. Morton neuroma. US guidance is optional.

Corticosteroid dose. 20 to 30 mg methylprednisolone acetate mixed with 1 mL lidocaine (No. 22 or 25 needle).

Approach for blind procedure. Through the web space on the plantar side (Fig. 69.20). The needle is advanced in a distal-to-proximal direction and aimed at the neuroma (technique taught to one of the authors by Lilia Andrade-Ortega, MD, Mexico City).

Precautions. Inject under low pressure. This procedure should be performed by health professionals with a thorough knowledge of anatomy.

Complications. None are expected; up to two reinjections 2 to 3 weeks apart are allowed.

INTRALESIONAL CORTICOSTEROID TREATMENT

Intralesional corticosteroid treatment is sometimes used for discoid lupus,⁵³ medical treatment of rheumatoid nodules⁵⁴ (Fig. e69.27), nodular fasciitis,



Fig. e69.24 Injection for calcaneal plantar fascia enthesopathy.



Fig. e69.25 Intermetatarsal bursitis in a patient with rheumatoid arthritis. The third and fourth toes are spread apart along with soft tissue tenderness between the metatarsal heads.



Fig. e69.26 Same patient as in Figure e69.25. For steroid injection, the needle is inserted vertically into the intermetatarsal space.



Fig. e69.27 Corticosteroid injection of a rheumatoid nodule (see text for technique).



Fig. 69.20 Injection for Morton neuroma, right foot, third web space.

occasionally Sweet syndrome,⁵⁵ granulomatous disease including Crohn disease affecting the oral cavity,⁵⁶ tracheal granulomas in patients with Wegener granulomatosis,⁵⁷ eosinophilic granuloma of the skin,⁵⁸ and inflammatory eye conditions unresponsive to oral or parenteral agents.⁵⁹

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Perioperative care of patients with rheumatic disease

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- Careful preoperative evaluation, patient selection, and postoperative care are essential; coordination between the surgeon and rheumatologist is necessary.
- Orthopedic surgery can relieve pain and improve function.
- Joint replacement surgery, including hip, knee, ankle, shoulder, elbow, and wrist replacement, has been successful.
- Arthroscopy, synovectomy, osteotomy, and fusion procedures might be indicated in selected patients.

It is important for rheumatologists to understand the processes underlying the decision to proceed with orthopedic surgery and the needs of patients postoperatively. This chapter describes a stepwise approach to the preoperative medical evaluation and assessment of surgical risk in patients with chronic rheumatic conditions.

INDICATIONS FOR ORTHOPEDIC SURGERY

Indications for elective orthopedic surgery are refractory and intolerable pain and disability attributable to a well-defined and significant pathologic state that has become intolerable to the patient. The final decision for surgery requires agreement between the patient, the orthopedic surgeon, and often the physician that the positive effects of surgery outweigh the potentially negative consequences, a complex balance, especially in frail older patients with significant comorbid conditions such as rheumatic disease. Two of the most frequently performed major orthopedic procedures in the rheumatic disease population are total joint replacement and spine surgery. In addition to the broad indications just mentioned, the latter is indicated in those with a progressive or incapacitating neurologic problem that demands immediate treatment, such as severe radiculopathy (for example, acute footdrop) or myelopathy.

Patients and their clinicians have different perspectives that need to be considered in detail (Box 70.1).

PREOPERATIVE ASSESSMENT

Influence of changing medical practice

As a consequence of medical advances, as well as financial and resource constraints, there has been a substantial trend toward performing surgery in the ambulatory, outpatient setting, which in orthopedic practice reflects the growth in arthroscopic techniques.^{1,2} The interval between the decision for outpatient surgery and performance of the operation thus allows time for the multiple detailed assessments outlined in Box 70.1.

Although the efficacy of preoperative assessment has not been definitively established,^{3,4} the aging and increasing complexity of modern-day surgical patients justify the process. The Australian Incident Monitoring Study⁵ revealed that 11% of preoperative assessments were considered either inadequate or incorrect and contributed to 3% of the adverse postoperative events, with the majority being considered major morbidity and almost all of which were preventable. In another study of anesthetic-related deaths, more than a third of deaths involved suboptimal preoperative assessment

and management.⁶ Delays in surgery, subsequent complications, and unexpected postoperative admissions to higher levels of care have been shown to be reduced by preoperative evaluation.⁷ Furthermore, anxiety, pain, length of stay, and patient satisfaction are favorably influenced by preoperative evaluation and enhanced by patients meeting with the anesthesiologist preoperatively.⁸

Key desired characteristics of perioperative care

The literature supports various core principles that underlie effective medical consultation, including the following⁹:

1. Consultation by either a physician or appropriately trained health care professional, which increasingly in some health care systems involves adopting a comanagement strategy for the patient's postoperative care or in some instances assuming full responsibility for the patient after completion of the surgery
2. Particular emphasis on the challenges posed by the elderly with their comorbid conditions and restricted physiologic reserve (homeostenosis)

History and physical examination

A complete history and physical examination constitute the bedrock of preoperative evaluation and also provide justification for any necessary ancillary testing. The indication for surgery should be ascertained and considered alongside the magnitude, nature, and urgency of the selected procedure. Previous experience with surgery and anesthesia and the presence, severity, and stability of all comorbid conditions should be established. All prescription and over-the-counter medications, including the use of herbs and supplements, should be recorded along with their dosages and dosing schedules. The use of tobacco, alcohol, and other drugs should also be documented, as should the patient's allergic history.

In the preoperative context the physical examination should focus on patient characteristics that might have an adverse impact on the patient's postoperative course. Among the areas for specific focus is the patient's body mass index, which is not only associated with other chronic diseases but is also an independent risk factor for problems with surgery. Obesity, large neck circumference, and hypertension predict obstructive sleep apnea (OSA), an important but underappreciated problem in the postoperative setting. Second, careful auscultation of the heart is important because the presence of third and fourth heart sounds may indicate congestive heart failure, and depending on its nature and severity, valvular heart disease may compromise cardiac function at times of physiologic stress, such as surgery.

Laboratory studies

The role of routine preoperative investigations is unclear,¹⁰ with some evidence suggesting that routine testing may actually be harmful.¹¹ Abnormalities in test results are of much greater significance in patients with clinical findings¹² suggesting new or persistent abnormalities.¹³ An extensive literature has failed to demonstrate that routine testing improves surgical outcomes.¹⁴ In one study, guidelines designed to reduce preoperative testing did not result in untoward perioperative events or an increase in test ordering.¹⁵ In particular, in studies involving healthy patients undergoing minor procedures, routine preoperative laboratory testing appears to be unnecessary.^{16,17} Nonetheless, depending on the patient and the nature and magnitude of the planned surgery, a number of investigations may be considered appropriate and are commonly performed before major surgery (Table 70.1).

BOX 70.1 PERSPECTIVES OF PATIENTS AND THEIR CLINICIANS**Patient perspectives**

Uniformity of opinion that my pain and disability are not improved by conservative therapies?
 Risks associated with surgery and how they can be reduced given my health status?
 Specific needs related to underlying joint disease that increase the chance for complications?
 Requirements regarding current medications both preoperatively and postoperatively?
 Surgeon experience and expertise?
 Ability to communicate with the surgeon and opportunity to speak to a recent patient?
 Track record of the hospital in performing this operation, including medical and rehabilitation support?
 Support at home after the surgery?

Surgeon perspectives

Confidence in the type and extent of the musculoskeletal problem and exclusion of referred pain, infection, or fracture?
 Appropriate level of unsuccessful conservative care?
 Severity justifies surgery to achieve the patient's desired outcome?
 Are the patient's expectations appropriate?
 Patient's medical and psychological status?
 Any increased risk for thromboembolic phenomena and what prophylaxis is needed?
 What other potential complications might this patient face?

Need for another physician's opinion before surgery?
 Antibiotic prophylaxis needed and any allergy?
 Need for a rehabilitation center before discharge home and the nature of the home setting to ensure an optimal outcome?

Rheumatologist/internist perspective

Formal assessment of the musculoskeletal problem causing the pain and disability?
 Medical and psychological preparation for the planned surgery?
 Need to change the medication regimen?
 Preoperative assessments, such as to determine any increased risk for cardiovascular complications?
 Specific needs of patients with diabetes or those treated with corticosteroids?
 Need for thromboembolic prophylaxis and nature?
 Continuity of care and communication with the surgical team about problems arising in the hospital?

Anesthesiologist perspective

Communication with others involved in the patient's care or medical status/
 Discussion of the type of anesthesia with the patient and the medical and surgical team?
 Patient's use of current medications preoperatively?
 Specific issues related to diabetes or treatment with corticosteroids?
 Specific monitoring needed perioperatively for patients with cardiac, pulmonary, neurologic, or other medical problems?

TABLE 70.1
Recommendations for laboratory testing before elective surgery

Test	Incidence of abnormalities that influence management	LR[+]	LR[-]	Indications
Hemoglobin	0.1%	3.3	0.90	Anticipated major blood loss or symptoms of anemia
White blood cell count	0.0%	0.0	1.00	Symptoms suggest infection, myeloproliferative disorder, or myelotoxic medications
Platelet count	0.0%	0.0	1.00	History of bleeding diathesis, myeloproliferative disorder, or myelotoxic medications
Prothrombin time	0.0%	0.0	1.01	History of bleeding diathesis, chronic liver disease, malnutrition, or recent or long-term antibiotic use
Partial thromboplastin time	0.1%	1.7	0.86	History of bleeding diathesis
Electrolytes	1.8%	4.3	0.80	Known renal insufficiency, congestive heart failure, or medications that affect electrolytes
Renal function	2.6%	3.3	0.81	Age >50 yr, hypertension, cardiac disease, major surgery, or medications that may affect renal function
Glucose	0.5%	1.6	0.85	Obesity or known diabetes
Liver function tests	0.1%			No indication. Consider measurement of albumin for major surgery or chronic illness
Urinalysis	1.4%	1.7	0.97	No indication
Electrocardiogram	2.6%	1.6	0.96	Men >40 yr, women >50 yr, known CAD, diabetes, or hypertension
Chest radiograph	3.0%	2.5	0.72	Age >50 yr; known cardiac or pulmonary disease, symptom, or result of examination suggests cardiac or pulmonary disease

CAD, coronary artery disease; LR, likelihood ratio.

From Smetana GW, MacPherson DS. The case against routine preoperative laboratory testing. *Med Clin North Am* 2003;87:7-40.

Assessment of operative risk

Individual patient prediction

Rating systems have been developed to identify patients in whom postoperative complications are most likely to develop.

The best known and most widely used is the *American Society of Anesthesiologists Physical Status Scale*, an index that is highly correlated with a patient's postoperative course (Table 70.2).¹⁸ First proposed in 1941, a revision of the scale became the Physical Status Scale. Though criticized for the vagueness of its criteria, it has proved to be an extraordinarily durable and useful assessment tool. Nonetheless, the search for more robust prediction methodologies has continued, and considerable success has been achieved in the assessment of cardiac risk specifically.

The landmark work of Goldman on assessment of cardiac risk in patients undergoing noncardiac surgery can now be seen as having ushered in the field of perioperative medicine.¹⁹ The *Goldman Cardiac Risk Index* has undergone extensive study and subsequent revision.²⁰⁻²² The *Revised Cardiac Risk Index* is the most widely used scoring system to date (Table 70.3). It is

simple to calculate, with 1 point being assigned for each of six independent risk factors for major cardiac complications in patients undergoing noncardiac surgery (Table 70.4).

However, the search continues to develop more global indicators of risk. Holt and Silverman proposed a *resilience* score for organ systems compromised by an underlying disease process.²³ An overall resilience score for a given organ system is derived by adding the standard American Society of Anesthesiologists score to a surgical complexity score (rated 1 to 5). The maximum score is 10, and the higher the score, the more likely that a given organ system will suffer injury or fail when surgically stressed. Once calculated, the individual scores for each organ system assigned a score of 3 or higher can be added, with the total reflecting the impact of multisystem disease.

Risk from the epidemiologic level

Recent epidemiologic studies by Memtsoudis and colleagues^{24,25} provide an interesting context from which to examine trends in the performance and outcomes of orthopedic surgery, as well as useful information relevant to

TABLE 70.2
American Society of Anesthesiologists Physical Status Scale

Level of risk	Presence of a systemic disturbance	Associated surgical mortality
I	Absent	0.2%
II	Mild	0.5%
III	Severe/not incapacitating	1.9%
IV	Incapacitating/threat to life	4.9%
V	Moribund/survival <24 hr without surgery	N/A
E (subdesignation)	Emergency surgery	Doubles risk

N/A, not applicable.

Data from Prouse G, Rotzenhofer-Correnda B, Pierer G, et al. Can ASA grade or Goldman's cardiac risk index predict peri-operative mortality? A study of 16,227 patients. *Anaesthesia* 1997;52:203-6.

TABLE 70.3
Revised Cardiac Risk Index

High-risk surgery	Intraperitoneal, intrathoracic, suprainguinal, vascular
History of ischemic heart disease	Myocardial infarction, positive stress test, angina, nitrate therapy, pathologic Q waves
History of congestive heart failure	Congestive heart failure, pulmonary edema, paroxysmal nocturnal dyspnea, rales or S3 gallop, vascular redistribution on chest radiograph
History of cerebrovascular disease	Transient ischemic attack or stroke
Preoperative treatment with insulin	
Preoperative serum creatinine >2.0 mg/dL	

From Lee HT, Marcantania ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043-9.

TABLE 70.4
Incidence of complications in patients in a validation cohort

No. of risk factors	Incidence of complications
0	0.4%
1	0.9%
2	7%
3	11%

Data from Lee HT, Marcantania ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043-9.

assessment of perioperative risk. In an ongoing series of studies, observations concerning the outcome of specific orthopedic procedures are drawn from two large national data sets: the National Hospital Discharge Survey, which is composed of medical information collected annually since 1965 by the National Center for Health Statistics (a database of inpatient utilization), and the National Inpatient Sample, the largest annual all-payer database in the United States. The power of these studies is derived from the enormous size of the archive, which in one study involved nearly 7 million patient discharges.²⁴

Thus far this work has focused on lower extremity arthroplasty, specifically, the outcomes, complications, and mortality after total joint replacement (unilateral, bilateral, revision). Several broad themes relevant to perioperative care can be derived from the analysis. First, performance of total joint arthroplasty has increased over time, and trends in the prevalence of comorbid conditions has confirmed an increase in the frequency of hypertension, diabetes mellitus, hypercholesterolemia, obesity, pulmonary disease,

and coronary artery disease over time.²⁴ Overall complication rates have declined despite decreasing length of stay, except in the case of bilateral procedures. Indeed, in patients undergoing bilateral total joint arthroplasty, procedure-related complication rates were higher than in those undergoing unilateral procedures despite a younger average age and lower burden of comorbidity.²⁵ Mortality after total joint arthroplasty of the hip and knee was most strongly correlated with postoperative pulmonary embolism and stroke.²⁴ Preoperative risk factors for in-hospital mortality were revision total joint arthroplasty, advanced age (>85 years), and the presence of specific comorbid conditions (predominately dementia and renal and cerebrovascular disease). A steady decrease was noted in the risk for death over the time of the study (1990 to 2004). Extending this line of inquiry, Stundar and associates²⁶ compared perioperative outcomes in patients with rheumatoid arthritis (RA) and osteoarthritis after total hip replacement and reported higher rates of pulmonary and infectious complications in rheumatoid patients that resulted in longer lengths of stay and higher cost.

Finally, a recent study of patients with systemic lupus erythematosus (SLE) undergoing surgery also demonstrated increased risk for perioperative adverse events,²⁷ although all-cause postoperative mortality was significantly higher in women with SLE. Stratified according to their risk for cardiovascular events, patients with SLE undergoing low- and high-risk procedures had worse outcomes. Curiously, those undergoing surgery of an intermediate nature did not, a relevant finding because most orthopedic surgery falls into the intermediate category.

ANESTHESIA IN PATIENTS WITH RHEUMATIC DISEASE

A variety of issues, including airway considerations, the site and anticipated duration of surgery, existing comorbidity, and the patient's emotional state, are important determinants of the type of anesthesia that should be used, whether invasive monitoring will be necessary, and the length of time that the patient will spend in the recovery room after surgery.

Type of anesthesia

General anesthesia and regional anesthesia are commonly used in the surgical treatment of patients with rheumatic disease. General anesthesia with endotracheal intubation may pose a particular danger in patients with RA or ankylosing spondylitis (see later discussion on the cervical spine). In patients with cervical spine instability or a rigid airway, fiberoptic intubation may be required. Regional anesthesia may take the form of local anesthesia for minor procedures, peripheral nerve block for surgery on the upper and lower extremities, and epidural/spinal anesthesia for arthroplasty involving the lower extremity.

Many orthopedic surgical procedures are well suited to regional anesthetic techniques. Some evidence suggests that regional anesthesia does reduce the incidence of major perioperative complications such as blood loss,²⁸ deep venous thrombosis, and pulmonary embolism, as well as postoperative respiratory events and death.²⁹ Furthermore, postoperative pain management, a significant problem for patients with a painful rheumatic disease, may be best managed with regional anesthetic approaches.³⁰ Peripheral nerve blocks using longer-acting anesthetics and infusion methodologies are another consideration because they provide both excellent intraoperative anesthesia and postoperative pain relief.³¹

Monitoring techniques

Patients undergoing major surgery should have continuous electrocardiographic and pulse oximetry monitoring intraoperatively. At the discretion of the anesthesiologist, arterial and Swan-Ganz catheter monitoring may be helpful in selected patients such as those undergoing bilateral joint replacement surgery or those with a history of previous cardiac disease.

Postoperative analgesia

Postoperative pain can be controlled with traditional intravenous delivery, intramuscular routes (systemic), and epidural analgesia. Epidural patient-controlled analgesia is very effective in controlling pain postoperatively and can aid in facilitating postoperative physical therapy, which is important in restoring a patient's range of motion after orthopedic surgery. This method also reduces systemic absorption of analgesics and thus reduces the problem of narcotic-induced respiratory depression. Parenterally administered non-steroidal antiinflammatory agents are a useful alternative to traditional analgesia after surgery and can be used to reduce narcotic requirements after

major surgery. These drugs should not be given to patients with common contraindications to nonsteroidal antiinflammatory agents such as peptic ulcer disease, renal disease, ischemic heart disease, and the concomitant use of anticoagulants.

More recently, a multimodal approach to pain management has been embraced because of increased awareness of the range and severity of undesirable adverse effects that can occur with traditional postoperative analgesia.^{32,33} Adverse effects are particularly common in elderly patients, who are prone to narcotic-induced delirium, respiratory depression, and constipation. Multimodal methods use an array of agents, including nonsteroidal antiinflammatory drugs (usually cyclooxygenase-2 [COX-2] inhibitors), steroids (Decadron), narcotics, and peripheral nerve blockade. Acetaminophen is not often used despite its recently approved intravenous preparation. Even more innovative approaches are being studied, such as placing an indwelling catheter in the knee to deliver a continuous infusion of local anesthetic (ropivacaine) after knee replacement surgery. Alternatively, a high-volume infiltration can be administered as a single dose.³⁴ With both these approaches patient-controlled analgesia is not required, and usually only small doses of narcotic are needed.

PERIOPERATIVE MANAGEMENT OF COMORBID MEDICAL CONDITIONS

Several important comorbid conditions are encountered perioperatively that can cause potential problems in patients with rheumatic disease.

Ischemic heart disease

The contribution of cardiovascular disease to the risk associated with noncardiac surgery cannot be overstated. The number of persons older than 65 years in the United States is set to increase by 25% to 35% over the next 30 years—the patient group in which the majority of orthopedic surgery is performed.³⁵ The annual number of noncardiac surgical procedures performed in this age group could increase from 6 to 12 million per year during this time. Many of them are major surgical procedures (intraabdominal, thoracic, vascular, and orthopedic), so postoperative cardiovascular morbidity and mortality will remain a primary focus of those involved in perioperative medicine. Fortunately, cardiovascular disease is the most investigated and well-documented domain of perioperative medicine. Practical guidelines to direct physicians involved in the assessment and care of patients with cardiac disease are widely recognized and updated regularly as new evidence comes to light.³⁵ Prediction rules using readily available clinical data have been studied extensively, validated, and disseminated to the practicing community.

The predictive value of routine clinical assessment, history and physical examination, electrocardiography, and chest radiography, supplemented by other noninvasive methodologies, is well established in identifying preexisting cardiac disease. Defining disease severity, stability, and previous treatment is also important because these factors, together with clinical characteristics such as age, functional capacity, comorbidity, and type of surgery to be performed, ultimately define postoperative risk. A series of factors may predict postoperative myocardial infarction, congestive heart failure, and death after orthopedic surgery.

The American College of Cardiology/American Heart Association guidelines for perioperative cardiovascular evaluation for noncardiac surgery³⁵ provide algorithms for every level of decision-making in the clinical setting, including indications for preoperative exercise stress testing and coronary angiography. Multiple modalities for noninvasive cardiac evaluation are available; some assess cardiac function under resting conditions, whereas others “stress” the patient (via exercise or pharmacologic induction of physiologic stress). In patients with high exercise tolerance in their daily lives, little useful information is likely to be gained from such testing. In others, such as chronically ill patients with rheumatic disease, evaluation of cardiac function preoperatively may be useful because the illness may limit the natural physical “stress.” Such decisions should be made on an individual basis. Many studies have examined the correlation between impairment of left ventricular function and postoperative cardiac complications. However, most postoperative complications occur in patients with a left ventricular ejection fraction of less than 35%. Although this observation links such cardiac phenomena as ischemia, congestive heart failure, and death to impaired cardiac function, a resting echocardiogram has not proven a reliable predictor of postoperative ischemic events.^{36,37} Other noninvasive methods of detecting coronary artery disease that use exercise to improve sensitivity and specificity are widely available and covered in an extensive literature. Exercise stress testing, with or without nuclear imaging or

echocardiography, is widely employed to assess and detect coronary artery disease in general practice. Regardless of whether the method uses formal exercise (i.e., treadmill or bicycle) or pharmacologic (dipyridamole, adenosine) means for stress simulation, the goal of such testing is provocation of myocardial ischemia by increasing myocardial oxygen demand relative to supply. In these studies, fixed defects that do not change after exercise-induced redistribution of blood flow represent myocardial scar from previous infarction and have less predictive value for postoperative ischemic events. In patients with reversible abnormalities, cardiac risk increases with increasing size and number of reperfusion abnormalities. A meta-analysis of 68 studies involving 10,278 patients undergoing noncardiac surgery compared the predictive value of stress echocardiography and thallium imaging and showed that stress echocardiography had superior predictive capability for postoperative cardiac events.³⁸ Nonetheless, more than a third of the complications occurred in patients with negative test results. It remains unclear whether one approach to stress testing is definitively superior to another. They may all be reasonably good for preoperative assessment of risk, and the choice may be related to the patient's physical capacity to participate in stress induction and the availability of such testing. The former is particularly true in disabled rheumatic disease or orthopedic patients. The important question is not which test should be performed but which patients will benefit from such assessments?

Strategies to reduce cardiac risk during noncardiac surgery may involve medical therapy or invasive cardiac interventions performed preoperatively, alterations in anesthetic technique, and aggressive management of adverse hemodynamic developments intraoperatively and postoperatively. For an internist rheumatologist who evaluates a patient preoperatively, the relevant approach includes medical management, specifically, the use of β -blockers, antiplatelet agents, and statin therapy. The widespread use of cardiac stents has become an important preoperative management problem. On occasion, coronary revascularization is considered before noncardiac surgery.

The most significant advance in perioperative medical care is recognition of the protective role of β -blockade. β -Blockers protect the heart by improving myocardial oxygen balance by slowing the heart rate and reducing contractility. Slowing the heart rate has additional benefits—an improvement in diastolic filling while decreasing myocardial oxygen consumption. Though used widely in the treatment of coronary artery disease for decades, it was not until 1996 that a potential role of β -blockers in preventing postoperative cardiac complications was shown. Mangano and coworkers³⁹ examined the role of perioperative β -blockade in patients with known coronary artery disease or with significant risk factors. Patients were randomized to receive atenolol or placebo 7 days before surgery and for 1 month afterward. A significant reduction in cardiac events was noted postoperatively and remained significant for a 2-year period.⁴⁰ Subsequent work⁴¹ appeared to confirm the benefit of preoperative and postoperative administration of β -blockers in the noncardiac surgical setting, so its practice was widely promulgated. However, a large-scale randomized controlled trial has thrown this practice into question.⁴² This study, which involved 8351 patients at 190 centers across the globe, confirmed the findings of numerous clinical trials that prophylactic β -blockade significantly decreases the incidence of postoperative myocardial infarction. However, this benefit was negated by the higher incidence of death, stroke, clinically significant hypotension, and bradycardia, thus raising concern about the overall safety of this practice. This is the major current controversy in perioperative medicine and remains under active debate. The most prudent approach is to use perioperative β -blockade only in selected circumstances: for high-risk patients not already taking β -blockers, start therapy early (days to weeks before surgery), aim for a heart rate in the low 60-beat per minute range, and continue therapy for at least 1 week postoperatively.⁴³

Chronic aspirin (acetylsalicylic acid [ASA]) therapy for both the primary and secondary prevention of atherosclerotic cardiovascular disease and for the treatment of rheumatic disease is highly prevalent, so the use of ASA and other antiplatelet agents perioperatively is commonplace. Because of their perceived bleeding risk, use of such agents was, until recently, generally discontinued 5 days before surgery. As more evidence on the protective role of such therapy has come to light, the practice of discontinuing ASA therapy before surgery has been questioned. A meta-analysis of this issue demonstrated that ASA withdrawal preceded up to 10% of all acute cardiovascular events and that even though the frequency of ASA-related bleeding complications increased, the bleeding tended to be mild and not significant (except for intracranial surgery and transurethral resection of the prostate).⁴⁴ Other antiplatelet drugs (thienopyridines, clopidogrel, ticlopidine) are also in common use, although guidelines for perioperative application have not been established. Because of their longer half-life, general practice is to discontinue use of these agents at least 10 days before surgery.

A related problem of increasing prevalence is management of antiplatelet therapy in patients with intracoronary stents who are undergoing noncardiac surgery. Reports of stent thrombosis in the perioperative period in patients who have had such therapy discontinued preoperatively have raised concern about the attendant risks.⁴⁵ Such thrombosis is associated with high rates of myocardial infarction (up to 50%). Two major classes of stents are currently used, bare metal stents (BMSs) and drug-eluting stents (DESs). The latter contain drugs that prevent endothelialization of the stent and hence restenosis. Because the use of antiplatelet agents (usually dual antiplatelet therapy) significantly reduces the incidence of stent thrombosis, the protective influence of such medication is important. Furthermore, the risk for stent thrombosis varies with the type of stent used; BMSs are associated with lower risk when antiplatelet therapy is discontinued. The heightened risk for thrombosis with DESs can persist for up to a year. According to a recent advisory statement, for patients who require surgery and have had a DES placed in the preceding 12-month period, ASA alone should be maintained and use of the other antiplatelet agents stopped 7 to 10 days before surgery.⁴⁶

Last are the statins, medications known to have both lipid-lowering and antiinflammatory activity, the latter of which stabilizes coronary plaque, improves endothelial function, and inhibits platelet aggregation. Coupling these theoretic benefits with a number of clinical trials suggesting a cardioprotective effect perioperatively,⁴⁷ perioperative statin therapy should be continued despite the well-known potential complications of such therapy (hepatotoxicity, myositis, rhabdomyolysis).

Because of the effective treatment strategies now available, fewer patients with inflammatory arthritis or spondyloarthritis are undergoing orthopedic surgery. Nonetheless, some patients will still require surgery, and their particular cardiovascular risks need to be appreciated. Two converging lines of evidence confirm that patients with chronic rheumatic disease, particularly those with inflammatory disorders, are high-risk surgical candidates.^{48,49} Once viewed as a biochemically bland (though potentially clinically aggressive) lipid storage disease, observations derived from basic science now endorse the central role of inflammation in the initiation and progression of atherosclerosis.⁵⁰ The rheumatic disease literature is full of observations showing the contribution of the atherosclerotic process to the morbidity and mortality associated with these disorders.^{51,52} This is an important, if underappreciated relationship from the perspective of perioperative medicine. Moreover, from a clinical standpoint it may not be as obvious because the limited exercise capacity of these patients can mask the traditional signs and symptoms of coronary artery disease.

RA results in the premature development of arterial stiffening, atherosclerosis, and myocardial infarction. Congestive heart failure is likewise independently related to RA, possibly because of impaired left ventricular diastolic filling. Although effective control of disease activity may be beneficial in ameliorating vascular and myocardial disease, patients with severe disease are the most likely to have subclinical coronary disease. Like RA, SLE results in similar cardiovascular phenomena. Left ventricular hypertrophy may develop unrelated to traditional stimuli, probably because of inflammation-related arterial stiffening.⁵³ All COX-2-selective and traditional nonsteroidal antiinflammatory drugs increase the risk for ischemic heart disease and should be factored into the perioperative risk assessment.

Other cardiovascular diseases

Hypertension

The prevalence of hypertension perioperatively is 20% and it is associated with coronary artery disease, thus making it a risk factor for adverse outcomes after surgery. It has been shown to be one of five independent predictors of postoperative myocardial ischemia and one of three predictors of postoperative mortality. Nonetheless, clinical experience suggests that the magnitude of risk conferred by elevations in blood pressure alone appears to be small, and current practice is that surgery should not be postponed in patients with mild to moderate elevations in blood pressure. One large study of patients with chronically elevated blood pressure demonstrated no significantly different outcomes based on whether surgery was cancelled for those with diastolic blood pressure in the 110- to 130-mm Hg range.⁵⁴ Surgery in patients with greater elevations in blood pressure or those with major end-organ (cardiac, neurologic, renal) complications of the disorder should probably be cancelled until their pressure is under better control.

Valvular heart disease

Dysfunction of the cardiac valves is not uncommon in patients with connective tissue disease.⁵⁵ Beginning with the classic descriptions of the Libman-Sacks vegetations of SLE, regurgitation of the mitral valve has also been reported with RA.⁵⁶ Aortic valve disease, particularly aortic

insufficiency, has been reported in patients with HLA-B27-associated spondyloarthritis.⁵⁷ In these conditions aortic regurgitation has resulted from aortitis and subsequent dilatation of the aorta.⁵⁸ In addition to these associations, there is a high prevalence of aortic and aortic valve involvement in the systemic vasculitides, including granulomatous disorders, systemic vasculitis, giant cell arteritis, and Takayasu arteritis. In these conditions the inflammatory involvement of the great vessels results in aneurysmal dilatation of the aorta, aortic root dilatation and insufficiency, and in some cases, aortic dissection. Along with perioperative prothrombotic issues, antiphospholipid antibodies in SLE are associated with mitral valve nodules and significant mitral regurgitation, possibly because of activation of valvular endothelial cells.⁵⁹

Surgical risk in patients with valvular heart disease depends on the valve affected, as well as the nature and severity of the valvular lesion. The lesion conferring the highest perioperative risk is hemodynamically significant aortic stenosis; fortunately, it is relatively uncommon in conjunction with connective tissue diseases (though relatively prevalent in an aging surgical population). Mitral valve disease and aortic insufficiency, if not severe, are usually well tolerated, although any valvular disease associated with significant left ventricular dysfunction (New York Heart Association class 3 or 4) increases the risk associated with surgery. Therefore, patients with a significant cardiac murmur accompanied by signs or symptoms of left ventricular dysfunction should undergo an echocardiographic assessment preoperatively, particularly if major surgery is planned. Invasive hemodynamic monitoring perioperatively may be indicated in patients at high risk.

Conduction abnormalities and arrhythmias

Although cardiac conduction system disease and arrhythmias are a frequent marker of underlying cardiac or pulmonary disease, metabolic abnormalities, or drug toxicity, they are more frequently seen in patients with connective tissue disease. This is especially the case with scleroderma, in which myocardial fibrosis is thought to compromise the cardiac conduction system and lead to heart block and a wide range of electrocardiographic abnormalities and arrhythmias.⁶³ When patients with this and other connective tissue diseases are seen preoperatively with apparent conduction problems, the clinician should search for such conditions and institute corrective action, if possible, before surgery.

A problem that commonly arises is a patient with chronic atrial fibrillation who is being treated long-term with anticoagulation. Because the risk for embolic stroke in such patients without anticoagulation is low, it is safe to temporarily discontinue warfarin (Coumadin) for a sufficient period preoperatively to allow normalization of the prothrombin time and international normalized ratio (INR). Five days before surgery is generally sufficient, and reinstitution on the night of surgery is safe.

Pulmonary disease

Postoperative pulmonary complications are frequent and important adverse events in the postoperative period.^{60,61} One large study (1055 patients) reported a 2.7% incidence of pulmonary complications in patients thought to be at low to moderate risk; patients in whom such problems developed had a significantly longer length of stay (27.9 versus 4.5 days).⁶² Indeed, problems such as atelectasis, pneumonia, aspiration pneumonia, respiratory failure, and exacerbation of chronic obstructive lung disease (COPD) may have more severe consequences than cardiac disease and have been shown to be more predictive of long-term mortality.^{63,64} Smokers have up to a fourfold increased risk for postoperative pulmonary complications.⁶⁵ COPD is the most important patient-related factor predictive of postoperative complications, with a 6% to 28% risk for pulmonary complications developing after surgery.⁶² Asthmatics are also at increased risk if their disease is not well controlled preoperatively. The implication of chronic pulmonary disease in the perioperative setting is further underscored by the increased prevalence of cardiovascular disease in these patients.

Chronic pulmonary disease can be divided into three categories: asthma, obstructive lung disease, and restrictive lung disease. Chronic obstructive lung disease (chronic bronchitis, emphysema) and asthma are the two most prevalent forms of chronic pulmonary disease and are the pulmonary problems most commonly seen preoperatively. Characterized by reduced forced expiratory volume in 1 second (FEV₁) coupled with a normal to increased lung capacity, these conditions are important predictors of postoperative pulmonary complications, which may be pulmonary or nonpulmonary. The frequency of minor pulmonary complications (atelectasis, bronchitis) is increased in patients who smoke, have a chronic cough, or have abnormal results on spirometry. The risk for severe postoperative pulmonary complications (pneumonia, respiratory failure) is increased mainly in patients with marked impairment in lung function (FEV₁ <1.5 L).

Restrictive lung disease, though generally less common, deserves special mention because of its prevalence in patients with connective tissue disease. Defined by a symmetric decrease in FEV₁ and forced vital capacity (FVC) along with a reduction in total lung capacity, such restrictive patterns of lung spirometry are characteristic of the functional abnormality seen in patients with conditions such as RA, polymyositis/dermatomyositis, and SLE.⁶⁶

Risk factors for the development of postoperative pulmonary complications are divided into two categories: patient and procedure related.^{63,67} Patient-related risk factors include age, existing COPD, cigarette use, congestive heart failure, comorbid conditions, functional capacity, obesity, sleep apnea, and cognitive impairment. In contrast, procedure-related risk factors include the surgical site (increased complication rate with procedures near the diaphragm), duration of surgery, anesthetic technique, and emergency surgery. Even though attempts to develop an overall pulmonary predictive risk index similar to the Goldman Cardiac Risk Index have been unsuccessful, two separate pulmonary risk indices have been published, one to predict postoperative pneumonia⁶⁸ and the other for respiratory failure after surgery.⁶⁹

Two other pulmonary-related conditions are increasingly being recognized for their contribution to postoperative complications: sleep apnea and chronic pulmonary arterial hypertension (PAH). Sleep apnea syndrome is defined as 5 or more apneic events (airflow stops for 10 or more seconds despite continued respiratory effort) or 15 or more hypopneic events per hour (airflow lessens >50% for ≥10 seconds) during a 7-hour sleep study. Although three types are recognized, obstructive (OSA), central, and mixed, it is usually the obstructive form that comes to light postoperatively.⁷⁰ Typically, morbidly obese patients with no documented history of the condition are observed in the recovery room to experience upper airway obstruction suggestive of OSA. Other physical characteristics associated with OSA include a neck circumference of 17 inches or greater, craniofacial abnormalities affecting the airway, anatomic nasal obstruction, and tonsils touching in the midline. A preoperative interview is an efficient way to screen patients. The Berlin questionnaire, 10 questions that pertain to risk factors for sleep apnea (snoring, wake time sleepiness/fatigue, hypertension), has been shown to be predictive of the condition.⁷¹ These patients present a number of management difficulties, beginning with an often challenging airway and intubation and, after surgery, such problems as hypoxemia, hypertension, atrial fibrillation, and heart failure. PAH may also arise as a consequence of long-standing, untreated OSA.

An increasingly recognized perioperative challenge, PAH is also seen in association with connective tissue disease and is most often due to the pulmonary disease accompanying these conditions. Its association with conditions such as scleroderma and mixed connective tissue disease is well known to rheumatologists. In the surgical setting, PAH is an especially treacherous problem that challenges medical and anesthesiologic management and is associated with substantial mortality.⁷² A pathophysiologic state characterized by elevated right heart afterload, decreased venous return, reduced cardiac output, and deficient oxygen saturation,⁷³ PAH is categorized according to its underlying etiology: primary pulmonary hypertension, or PAH, arises as a consequence of left heart disease, hypoxic pulmonary disorders (e.g., OSA), or chronic thromboembolic phenomena.⁷⁴ The sustained elevations in pulmonary vascular resistance and pulmonary artery pressure, coupled with impaired vascular reactivity, may result in significant systemic hypotension in the setting of anesthesia. The negative inotropic effects of some anesthetic agents may exacerbate this tendency and precipitate right heart failure. The adverse consequences arising on the left side of the circulation (systemic hypotension) are further exacerbated by concomitant right-sided responses, where the pulmonary vessels constrict in response to the resultant hypoxia and thereby promote the development of hypercapnia, acidosis, hypothermia, and release of catecholamines. If allowed to progress too far, this cascade of events may result in further hemodynamic deterioration and frank circulatory collapse.⁷⁴ Although new and effective vasodilator medications (endothelin receptor antagonists and prostaglandins) can significantly decrease pulmonary artery pressure,⁷⁵ PAH remains a potent risk factor for adverse outcomes after surgery. It demands a knowledgeable and collaborative group of physicians to make medically sound decisions on behalf of such patients.

The general risk for perioperative lung dysfunction depends on the type of surgery performed. Patients with severe lung impairment can tolerate minor procedures, even under general anesthesia. The risk for pneumonia following major hip or knee surgery is low, even in patients with chronic lung disease. This is in marked contrast to intraabdominal or intrathoracic surgery, which is associated with a high risk for atelectasis or pneumonia, particularly in patients with severe COPD. Regional anesthesia for surgery on the extremities circumvents many of these problems. However, an interscalene block may transiently paralyze the ipsilateral diaphragm and reduce FVC by 30% to 40%. Patients with COPD undergoing shoulder surgery, for

which an interscalene block is used frequently, should have pulmonary function studies performed preoperatively. In patients with severely impaired pulmonary function (FEV₁ <1 L), an interscalene block should be avoided completely. Patients with COPD fare well with this anesthesia, especially in the sitting position.

Patients who have been taking bronchodilators on a chronic basis before surgery should have their standard dose the night before surgery; bronchodilator therapy should be administered postoperatively either systemically or by nebulizer. Incentive spirometry 10 times daily and early mobilization are helpful in preventing postoperative atelectasis.

Endocrine problems

Diabetes mellitus

Diabetes mellitus is one of the most common and important endocrine disorders encountered in surgical populations. In the postoperative setting it increases the risk for complications such as myocardial infarction, stroke, infection, and even death.⁷⁶ In orthopedic surgery, more than 8% of patients undergoing total hip and knee arthroplasty have diabetes, which results in higher postoperative complications and mortality.⁷⁷ Diabetic patients with autonomic insufficiency (e.g., postural hypotension, impotence, nocturnal diarrhea) may be at risk for sudden cardiopulmonary arrest postoperatively.⁷⁸ Diabetes is included as one of the risk factors in the Revised Cardiac Risk Index. Given the high prevalence of coronary artery disease in patients with diabetes, cardiovascular risk assessment is a focal point of the preoperative evaluation in these patients. It should be approached as outlined in the section on patients with established cardiac disease. Otherwise, the main perioperative consideration is to manage the underlying metabolic disease by glycemic control, which is often challenging. Because of a complex interplay of factors, the stimulatory effects of anesthesia and surgery enhance the production of counterregulatory hormones such as glucagon, epinephrine, cortisol, and corticotropin while decreasing the endogenous production of insulin. These responses, coupled with an increase in lipolysis and ketogenesis and poor caloric intake after surgery, result in significant derangements in overall glycemic control, which often drives blood sugar levels higher. The value of tight glucose control in the surgical setting has not been established. An important clinical trial on this problem showed that in critically ill surgical patients, tight glucose control may reduce postoperative mortality by a third.⁷⁹ Nonetheless, a recently published meta-analysis of tight glucose control in critically ill patients failed to show any benefit (reduced mortality, reduced need for dialysis), whereas such treatment increased the risk for hypoglycemia.⁸⁰ No prospective trials have shown that controlling glucose or decreasing hemoglobin A_{1c} preoperatively improves outcomes before elective surgery. Indeed, many of the fundamental questions concerning perioperative diabetic management remain unanswered, including whether there is a preoperative glucose (or A_{1c}) level above which surgery should be delayed and whether insulin should be started in an insulin-naïve, poorly controlled patient before surgery. Even the preoperative management of oral hypoglycemic agents and insulin is not clear. Even though the advantages of good perioperative control remain open to debate, three primary observations lend support to this practice. First, many patients with diabetes are at high risk in the surgical setting, and effort to reduce such risk is justified. Second, it is a common clinical problem because around 25% of patients with diabetes require surgery in their lifetime. Third, good glycemic control perioperatively may reduce the rate of wound infection, vascular complications, and death. However clinical trials report that 40% to 80% of blood sugar determinations fall outside the target range,⁸¹ so achieving good control is difficult.⁸²

Box 70.2 summarizes the clinical considerations important for perioperative decision-making in patients with diabetes.⁸³ These considerations add to the routine assessment for patients without diabetes. Long-term (end-organ) complications of this disorder (microvascular, macrovascular, neuropathic) must be considered, with particular attention directed to cardiovascular and renal disease. It is important to characterize the type of diabetes (types 1 and 2), determine the specifics of the patient's treatment (medications, timing and adherence to therapy), and establish the degree of glycemic control (blood sugar history and A_{1c}). The occurrence and frequency of hypoglycemia should also be ascertained. A clear understanding of the nature and magnitude of the type of planned surgery is likewise important. Practically speaking, glycemic criteria for proceeding with elective surgery are as follows: a preoperative hemoglobin A_{1c} level lower than 7% is considered satisfactory diabetic control, and levels greater than 10% provide grounds for cancelling routine surgery. If the patient's control is suboptimal, institution of oral agents (Amaryl 1 mg or Glucotrol 5 mg) or insulin (Lantus 20 units at nighttime) is a reasonable approach. Morning doses of intermediate- and long-acting insulin should be reduced by 25%

to 50% on the day of surgery to avoid inducing hypoglycemia; regular and short-acting insulin, generally given to provide nutritional coverage, should be withheld in patients fasting in preparation for surgery.

Patients treated with insulin pumps should maintain the basal infusion rate before and throughout the surgical procedure. Surgery should be scheduled early in the day to avoid the prolonged fasting that increases the risk for hypoglycemia.

Recommendations for perioperative diabetic management should be based on safety considerations (avoidance of hypoglycemia) and maintenance of stable glucose levels. So-called glycemic targets have been promoted, with desirable glucose estimates ranging between 90 and 110 (low) and upward to between 140 and 180 mg/dL. Numerous regimens have been recommended for the perioperative management of patients with diabetes,

BOX 70.2 PREOPERATIVE ASSESSMENT OF SURGICAL CANDIDATES WITH DIABETES MELLITUS

Operative risk assessment

Routine risk factors

- Cardiac
- Pulmonary
- Renal
- Hematologic

Diabetes-related risk factors

- Macrovascular complications
- Microvascular complications
- Neuropathic complications

Diabetes therapeutic regimen

Reestablish the correct diagnostic classification of diabetes

Pharmacologic regimen

- Medication type
- Dosage
- Timing

Meal plan

- Carbohydrate content
- Timing of meals

Activity level

Hypoglycemia

- Frequency
- Awareness
- Severity

Anticipated surgery

- Type of surgical procedure
- Inpatient or outpatient
- Type of anesthesia
- Start time
- Duration of the procedure

From Jacober SJ, Sowers JR. An update on perioperative management of diabetes. *Arch Intern Med* 1999;159:2405-11.

and the approach used is influenced by the type and severity of the diabetes. Regardless of disease severity, management should be proactive as opposed to reactive.

During the immediate postoperative period, blood sugar may be unstable and insulin supplementation is often required temporarily. This is best achieved with exogenous insulin to mimic physiologic insulin activity. This regimen is built on three components: *basal* insulin, *nutritional* (prandial/meal) insulin, and *correction-dose* (supplemental) insulin.⁸⁴ The patient's daily insulin requirement is the total of these components—the amount of insulin required in 24 hours with adequate nutrition. Basal insulin is secreted on a continuous basis and suppresses glucose and ketone production, nutritional insulin is secreted in response to food ingestion, and correction-dose insulin corrects hyperglycemia. Half the total daily insulin is basal insulin; it is provided by long-acting, low-peaking preparations (Lantus, Levemir), which results in stable insulin levels. According to the “50/50” rule, the other half is nutritional and is provided in a bolus fashion with rapidly acting insulin (NovoLog, Apidra, Lispro) administered at meal-time. Correction-dose insulin is the small supplemental dosages of rapidly acting insulin that are given intermittently to correct hyperglycemia. Finally, continuous insulin infusions are occasionally used postoperatively in patients with severe, brittle disease.

Chronic corticosteroid therapy

Many patients with rheumatic disease take corticosteroids, so management of steroid therapy perioperatively is a frequently encountered problem. Five milligrams to 7.5 mg daily of prednisone approximates the normal daily adrenal output of cortisol (30 mg), and dosages in this range are sufficient to result in chronic suppression of adrenocorticotrophic hormone production and adrenal cortical atrophy; the heightened risk for adrenal insufficiency is due to physiologic stress from surgery. Patients thought to be at increased risk include those currently taking more than 20 mg prednisone daily for longer than 3 weeks, those who have taken such doses for more than 2 weeks in the preceding year, and those who are receiving replacement corticosteroid therapy for known adrenal insufficiency. Although surgery may produce sufficient “stress” to provoke adrenal insufficiency, surgeries vary in the physiologic perturbations that they produce, and cortisol levels usually normalize within 24 to 48 hours in most patients after surgery.⁸⁵ Supplementation should depend on the anticipated degree of stress (a function of the duration and severity of the surgical procedure) and the chronic daily steroid dose. Table 70.5 provides recommendations for perioperative glucocorticoid coverage according to the magnitude of the planned surgery.

Gastrointestinal disease

Gastrointestinal problems, both exacerbations of chronic conditions and problems arising *de novo*, may complicate the postoperative period and produce significant morbidity. Postoperative nausea and vomiting (PONV) is a common problem that arises in 20% to 30% of patients,⁸⁶ an outcome rated by patients to be 1 of the 10 most undesirable consequences of surgery.⁸⁷ PONV is thought to be multifactorial in etiology, with an array of patient, surgical, and anesthetic factors contributing to its development. Patient factors often cited as risk factors include female sex, need for opioids for postoperative pain relief, and a history of motion sickness or PONV with previous surgery. The presence of none, one, two, three, or four such risk

TABLE 70.5
Recommendations for perioperative glucocorticoid coverage

Surgical stress	Target hydrocortisone equivalent	Preoperative steroid dose	Intraoperative steroid dose	Postoperative steroid dose*	Postoperative steroid dose on day 1*	Postoperative steroid dose on day 2*
Minor (e.g., inguinal herniorrhaphy)	25 mg/day for 1 day	Usual daily dose of steroid	None [†]	None [†]	Usual daily dose [†]	
Moderate (e.g., colon resection, total joint replacement, lower extremity revascularization)	50-75 mg/day for 1-2 days	Usual daily dose of steroid	50 mg hydrocortisone	20 mg hydrocortisone every 8 hr	20 mg hydrocortisone every 8 hr	
Major (e.g., pancreaticoduodenectomy, esophagectomy)	100-150 mg/day for 2-3 days	Usual daily dose of steroid	50 mg hydrocortisone	50 mg hydrocortisone every 8 hr	50 mg hydrocortisone every 8 hr	50 mg hydrocortisone every 8 hr

*If postoperative complications occur, continued glucocorticoid administration will be necessary commensurate with the level of stress. From Salem M, Tainsh RE, Bromberg J, et al. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. *Ann Surg* 1994;219:416-25.

[†]If the postoperative course is uncomplicated, patients can resume their usual steroid dose on postoperative day 1. From Sweitzer BJ. Preoperative assessment and management. Philadelphia: Walters Kluwer Lippincott Williams & Wilkins; 2008, p. 409.

factors is associated with an incidence of 10%, 21%, 39%, 61%, and 79%, respectively.⁸⁸ Such difficulties often herald the onset of more significant problems, specifically, postoperative abdominal ileus.

Impaired gastrointestinal motility after surgery is a relatively common complication that is not restricted to patients with chronic gastroenterologic problems. Characterized by constipation, accumulation of gas and fluid in the bowel and the development of abdominal distention, and intolerance of enteral feeding, postoperative ileus is generally a self-limited condition that lasts for 3 to 5 days.⁸⁹ Perturbations in gastrointestinal motility after surgery arise from a number of adverse influences occurring in the postoperative period. Some of these perturbations are external, such as narcotic analgesia and anesthesia, the fasting state, and reintroduction of oral feeding. Others are internal or physiologic responses to surgery. Such influences include surgery-related increases in sympathetic nervous system tone, hypothalamic release of corticotropin-releasing factor, and release of nitric oxide, all of which have a negative influence on motility of the gastrointestinal tract. Careful consideration should be given to the optimal timing for resumption of oral intake of both liquids and solids, and potent narcotic therapy should be weaned as quickly as possible, particularly in patients with chronic gastrointestinal conditions. Early mobilization is also an effective preventive strategy. In addition, a number of pharmacologic approaches are commonly required to resolve such problems, including the use of agents acting on the autonomic nervous system (bethanechol, carbachol, methacholine) and, more recently, the role of cholinesterase inhibitors such as neostigmine.⁹⁰ The latter is generally reserved for severe cases of adynamic ileus with massive dilatation of the colon in the absence of mechanical obstruction (Ogilvie syndrome), a highly threatening complication with a mortality of 50%.⁹¹ For motility problems that are more directly a consequence of postoperative narcotic therapy, the μ -opioid receptor antagonist methylnaltrexone (Relistor) is useful.⁹² Another simple and novel preventive approach is the use of chewing gum as a stimulant of gastrointestinal motility.⁹³

Other gastrointestinal conditions may also occur postoperatively. Intestinal volvulus is usually seen in patients with a history of abdominal surgery, chronic diverticular disease may flare up, and even colon cancer may declare itself at this time. Indeed, all three may mimic and be manifested as abdominal ileus. A fourth and important consideration is the development of *Clostridium difficile*-induced colitis.⁹⁴ Because of an increasing prevalence of this organism in the population and the subsequent colonization of hospitals (as a result of the widespread use of antibiotics), severe infectious colitis has been seen increasingly postoperatively, when patients are potentially debilitated and highly vulnerable. *C. difficile*-induced colitis may be asymptomatic, cause diarrhea alone (without colitis), or occur as acute pseudomembranous colitis progressing to life-threatening toxic megacolon. Treatment requires aggressive fluid support and institution of oral antibiotic therapy, either metronidazole (250 mg four times daily) or vancomycin (125 mg four times daily). More resistant cases have recently been described,⁹⁵ and new antibiotics are available for patients unresponsive to the aforementioned medical therapy. Rarely, in the most severe cases, surgery, including total colectomy, may be required. The simple preventive measure of handwashing can significantly decrease the transfer of this organism from patient to patient.

Peptic ulcer disease, a common problem in the orthopedic/rheumatic disease population because of the high use of nonsteroidal antiinflammatory agents and steroids, may become active after surgery; it is particularly problematic in patients who require anticoagulation prophylaxis, such as those who have undergone total joint arthroplasty. Patients with a history of peptic ulcer disease, gastrointestinal bleeding, or active dyspepsia should receive a prophylactic proton pump inhibitor or H2 blocker postoperatively. In the presence of strong clinical suspicion that an active peptic process is ongoing, the surgery should be canceled, a workup performed, and treatment instituted before proceeding. In patients at risk for the development of gastrointestinal bleeding after surgery, serial stool guaiac tests are a good surveillance approach.

Genitourinary conditions

Because of bed rest, narcotic use and epidural anesthesia, and the presence of prostate disease, urinary catheters are frequently placed in patients after major surgery. These catheters should generally be removed as early as possible and a surveillance urine culture performed to rule out urinary tract infection. Removing urinary catheters within 48 hours of surgery and avoiding urinary retention reduce the risk for urinary tract infection.

Prostatic hypertrophy leading to obstruction of urinary outflow is a common problem in men after surgery. In patients with chronic symptomatology, urologic consultation should be obtained before surgery and treatment (including transurethral resection of the prostate) performed if

necessary. In patients with a propensity for urinary retention and those with enlarged prostate glands who report obstructive symptomatology, therapy with agents such as terazosin (Hytrin) and tamsulosin (Flomax) could be instituted before or at the time of surgery. Dehydration should be avoided in patients with a history of nephrolithiasis to prevent acute renal colic.

Prevention of postoperative infection

The risk for infection in a prosthetic joint is a major concern in patients undergoing total joint arthroplasty. Effort to prevent and detect any infectious processes preoperatively and postoperatively is of utmost importance. The skin and urinary tract are sites of specific concern, and infection can be ruled out with a careful physical examination and routine preoperative urine culture. In addition, formal dental consultation may be appropriate in patients with poor oral hygiene and dentition.

Prophylactic antibiotic therapy for patients undergoing total joint arthroplasty should begin less than 2 hours before surgery and continue for 24 hours. The recommended protocol at the Hospital for Special Surgery involves cefazolin (Ancef) 1 g every 8 hours (total of three doses) or, in patients allergic to penicillin, vancomycin 1 g every 12 hours (total of two doses).

Neurologic problems

Postoperative delirium

Delirium, an acute confusional state often seen in patients with systemic illness, may arise postoperatively, particularly in the elderly. These patients have an altered level of consciousness and diminished ability to maintain and focus attention and often have hallucinations, delusions, and agitation; the delirium may have a diurnal variation (onset and more severe at night) and unpredictable duration.⁹⁶ A number of factors increase the risk for delirium after surgery: acute infections; drug (psychoactive, analgesic, anesthetic) and alcohol toxicity or withdrawal; dehydration; fluid, electrolyte, and metabolic disturbances; and states of low perfusion (heart failure and shock). In some postoperative settings this is a common problem; in patients undergoing surgical repair of a fractured hip, postoperative delirium developed in 37% of the nondemented patients.⁹⁷ Among those who experienced delirium after surgery, frank dementia developed in 69% over a 5-year follow-up period (as opposed to 20% of those without postoperative delirium). Additionally, patients with postoperative cognitive dysfunction at discharge are more likely to die within the first year after surgery.⁹⁸

Acute delirium is usually transient, but clinicians should focus on detection and treatment of correctable causes that may arise in this fashion, particularly in geriatric patients. Such causes include metabolic disturbances (hyponatremia, hypoxemia), medications (use of which might be discontinued), infection, and various acute conditions (respiratory failure, myocardial infarction, cardiac arrhythmias, congestive heart failure, pulmonary embolism, and fat embolism syndrome [FES]). Likewise, elderly patients and those with underlying neurologic dysfunction (e.g., alcoholism, parkinsonism) are at increased risk for postoperative delirium. Formal neurologic consultation and workup are occasionally necessary, though generally unrevealing. Specific alcohol withdrawal protocols should be developed and used because overall mortality is higher in these patients. Proactive geriatric consultation can significantly reduce the incidence of postoperative delirium.⁹⁹

Peripheral nerve injuries

Peripheral nerve injuries are common after upper and lower extremity surgery because they usually result from excessive traction on the nerve or compression from positioning of the extremity during surgery, tourniquet use (in total knee replacement), or a cast. Early detection and intervention are critical to the ultimate outcome. Patients with antecedent neurologic disease (e.g., peripheral neuropathy) are at particular risk. Patients with diabetes and patients with lumbar or cervical stenosis are at increased risk for nerve injury.

Emotional/psychiatric problems

Patients with chronic rheumatic diseases or disabling orthopedic conditions may suffer emotional difficulties as a result of chronic pain, disability, impaired social interactions and personal relationships, and constrained career opportunities. Because surgery is stressful, these individuals may require additional emotional support perioperatively. Furthermore, these patients may be taking or require antidepressant or anxiolytic medication. Though rare, patients being treated with monoamine oxidase inhibitors should discontinue use of their medication 10 to 14 days before surgery,

and the anesthesiologist should be alerted to the situation because these patients are at risk for circulatory instability with general anesthesia and certain narcotics, especially meperidine.

Management of specific clinical problems

Patients benefit from perioperative management of the following clinical problems, discussed in order of how commonly they occur.

Venous thromboembolism

Venous thromboembolism after orthopedic surgery is the most thoroughly studied potential postoperative complication.^{100,101} Pulmonary embolism, perhaps the most dreaded complication of orthopedic surgery, remains an important cause of postoperative mortality.¹⁰² Even though most of the literature on this problem has concentrated on lower extremity arthroplasty, a recent study suggests that these treatment paradigms should also be considered after total shoulder arthroplasty, for which the risk for thromboembolism may be higher than generally thought. Because surgery sets up some degree of a prothrombotic state, it is not whether prophylaxis should be considered but which method should be. In orthopedic surgery, a complicated balance exists between possible life-threatening pulmonary embolism and potential bleeding to a degree that compromises the surgical outcome. Numerous protocols have documented efficacy in minimizing this risk. Prevention begins at the time of the procedure. Expedient surgery reduces the risk for deep venous thrombosis following operations such as total hip replacement. The type of anesthesia used is also important; epidural anesthesia reduces the risk for proximal deep venous thrombosis following total hip replacement by twofold to threefold and also reduces the overall risk for deep venous thrombosis by at least 20%.¹⁰³ Other intraoperative interventions, such as hypotensive anesthesia and intraoperative heparin administration, further reduce thrombogenesis.¹⁰⁴

Mechanical methods can also reduce the risk for thromboembolism and include pneumatic compression boots, foot pumps, compression stockings, foot flexion/extension exercises, and early ambulation. These maneuvers are safe and effective and do not increase the risk for bleeding.¹⁰⁵ Inferior vena cava filter placement is another nonpharmacologic approach to prevent pulmonary embolism. Invasive devices should be used in high-risk surgical candidates, such as those with a history of thromboembolic episodes despite adequate therapy and those with a contraindication to anticoagulation. The mainstay of treatment is some form of anticoagulation. Prophylactic anticoagulation should be started immediately after surgery. Regimens include ASA, warfarin (Coumadin) with a target INR of 2.0 to 2.5, and low-molecular-weight (LMW) heparin, with several newer medications, either factor Xa or direct thrombin inhibitors (rivaroxaban, dabigatran, apixaban), having recently received approval by the U.S. Food and Drug Administration.¹⁰⁶ ASA is also effective when combined with other modalities and is often useful in low-risk patients. A multimodal approach that combines intraoperative modalities, postoperative mechanical devices, early ambulation, and low-intensity postoperative anticoagulation is preferred for most patients.^{107,108}

Fat embolism syndrome

Embolization of fat in the circulation is a well-described complication of skeletal trauma and surgery, as well as procedures involving instrumentation of the femoral medullary canal.¹⁰⁹ Although this occurs in most patients who sustain hip or femoral fractures, the development of frank FES occurs in relatively few. FES develops in 1% to 3% of patients undergoing joint replacement surgery (particularly simultaneous bilateral procedures, where it is presumably a “dose” effect) and in 5% to 10% of patients who have sustained multiple long-bone fractures.

The signs and symptoms of FES involve the respiratory, neurologic, hematologic, and cutaneous systems. Time of onset is variable; hemodynamic instability may develop almost immediately (presaged by a rise in PAH when the prosthesis is cemented) or more insidiously over the first few postoperative days. In the latter group it is often unclear what is happening early because patients gradually become moderately to severely hypoxic after surgery, may be hypotensive, and in the elderly, often become confused. Hematologic abnormalities such as transient thrombocytopenia are seen commonly. Respiratory signs are the most common manifestation of FES. Mild to moderate hypoxemia and some radiographic changes (mainly bilateral alveolar infiltrates) develop in the majority of patients. Life-threatening adult respiratory distress syndrome will develop in a minority and requires aggressive supportive measures and intubation. Manifestations range from mild drowsiness, to an acute confusional state, to severe obtundation and coma, all consequences of the associated hypoxemia, as well as the direct effect of embolization of fat on the brain.¹¹⁰ Skin eruption, rare

in patients undergoing total joint arthroplasty, takes the form of a petechial rash involving the conjunctiva and oral mucosa and is distributed over the folds of the neck and axillae. Retinal edema and hemorrhage are also common.

The pathophysiology of FES remains unclear, although it is thought to involve mechanical or biochemical factors (or both). According to the mechanical theory, when intramedullary pressure exceeds venous pressure, fat globules will be embolized and ultimately become lodged in the pulmonary capillary bed. Pulmonary hypertension then develops and opens the foramen ovale, which allows fat globules to pass into the arterial circulation. These globules lodge in the cerebral, retinal, and dermal capillaries and produce their end-organ effects. Alternatively, the biochemical theory states that embolized fat globules initiate an inflammatory response that produces the adverse clinical phenomena associated with this condition. These theories are not mutually exclusive, and the pathophysiologic mechanisms may be acting in concert. Other observations concerning age-related factors and specifically marrow fat also have pathophysiologic implications. FES is less common in children, whose primary marrow-derived lipids (palmitin and stearin) are less likely to produce emboli than the lipid olein found in adult bone marrow.¹¹¹

Patients in whom FES is suspected to have developed need to be monitored closely, but in most instances such embolic events are generally clinically benign. Treatment is supportive and includes the administration of increased concentrations of inspired oxygen (possibly via a ventilator), prevention of pulmonary hypertension by fluid restriction and the use of diuretics and venodilators, and pain control. Corticosteroid therapy is not recommended because there is no evidence of its benefit. In most patients the condition resolves within 3 to 7 days, although in severe cases the mortality rate remains at 5% to 15% even with modern aggressive therapy.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a condition consisting of vascular thrombosis (with or without pregnancy-related morbidity) arising as a consequence of the presence of antiphospholipid antibodies, usually lupus anticoagulant or anticardiolipin antibodies.¹¹² The primary form is not associated with any underlying connective tissue disease, whereas the secondary form arises in conditions such as SLE. Patients with APS who are undergoing surgery are at increased risk for postoperative thrombosis as a result of their general hypercoagulability. Their need for long-term anticoagulation challenges perioperative management because of the delicate balance between their propensity for thrombosis and the risk for postoperative bleeding as a result of their need for anticoagulation.

Recommendations have been published to guide medical management of patients with APS who are undergoing surgery.¹¹³ First, the important, adjunctive role of physical methods in the prevention of venous thrombosis should not be forgotten. Methods such as intermittent venous compression should be used aggressively preoperatively and postoperatively. Second, the perioperative period without anticoagulation should be kept to a minimum. Thus, for patients maintained on chronic Coumadin therapy, use of the medication should be stopped 3 to 4 days before surgery to allow the INR to normalize while concomitant therapy with LMW heparin is instituted at therapeutic dosages (1 mg/kg every 12 hours) and continued until the night before surgery. For many surgical procedures, particularly orthopedic surgery, Coumadin can be restarted on the night of the surgical procedure. If no contraindication is present, LMW heparin in prophylactic dosages (30 mg every 12 hours) can be restarted simultaneously with Coumadin and maintained until a therapeutic INR has been achieved. Conventional dosages of these agents may result in “undercoagulation” of patients with APS, and larger dosages, if feasible, may be considered necessary postoperatively, irrespective of the bleeding risk.

Epidural anesthesia and spinal anesthesia are used frequently in patients undergoing orthopedic surgery, with the resulting risk for epidural and spinal hematoma. To avoid this serious complication, the heparin dose should be omitted the night before surgery and preferably not restarted until at least 4 hours after removal of the epidural or spinal needle.

Hip fracture

Hundreds of thousands of patients are admitted to hospitals in the United States annually for treatment of a fractured hip, which results in major cost to society, patients, and their families.¹¹⁴ Up to 20% of elderly patients with hip fractures die within the first year after the fracture. Of those who survive for 1 year after fracture, a sixth are confined to long-term care and a third require assistive devices or help in their daily activities. Risk factors thought to increase the need for nursing home care include living alone before the fracture, having no children, and female gender.

The majority of hip fractures occur as a result of falls in frail, elderly women with osteoporosis. Risk factors for hip fracture include increasing age, poor general health, maternal history of hip fracture, history of thyroid disease, poor depth perception, use of psychoactive medication, sedentary lifestyle, and major life events.¹¹⁵

Femoral neck and intertrochanteric fractures are equally common, and most require surgery to restore mobility and functionality.¹¹⁶ Though a matter of ongoing debate, more severe (i.e., displaced) intracapsular femoral neck fractures are often treated by joint replacement because such fractures may result in serious compromise of the blood supply to the femoral head and lead to osteonecrosis, collapse of the femoral head, and secondary osteoarthritis.^{116,117} Internal fixation is the usual surgical approach for these fractures, but in frail, elderly patients with lower anticipated functional requirements, total joint arthroplasty is an option.

Preoperative medical assessment and care of patients with fractured hips are challenging. Because of the patient's age, frailty, functional compromise, existing comorbid conditions, and poorer outcome when surgery is delayed,^{118,119} the opportunity to optimally evaluate and prepare patients before surgery is limited and relies more on general principles of perioperative care. Given the perioperative care demands that such patients impose, clinical pathways¹²⁰ and other integrated comanagement (medical-surgical) approaches have been reported both for hip fracture¹²¹ and for total joint arthroplasty,¹²² with variable results. Nonetheless, improvements in terms of length of hospital stay, postoperative complications and mortality, late readmission to the hospital, and functional recovery have been observed.

The cervical spine

Patients with RA, particularly those with advanced and aggressive disease, have significant cervical spine involvement, with instability arising from atlantoaxial or subaxial subluxation. This increases the risk associated with undergoing surgery and poses significant challenges for the anesthesiologist, particularly if endotracheal intubation is required. These patients have an increased risk for cord compression during intubation or from uncontrolled neck movement during positioning for surgery.

Cervical spine instability should be ruled out before surgery with flexion/extension films in patients with neck pain or crepitus on range-of-motion testing, radicular symptoms, or arm or leg weakness. Affected patients should wear a soft cervical collar to the operating room, both for neck

immobilization and as a warning to all involved to not overmanipulate the neck. When possible, epidural or spinal anesthesia should be used.

Additional problems arising from rheumatic disease include involvement of the temporomandibular joint, limiting jaw opening, and arthritis of the cricoarytenoid joints. These problems can influence the choice of airway management, so the anesthesiologist must be informed preoperatively.

Conversely, in patients with ankylosing spondylitis, the rigid cervical spine presents technical challenges for the anesthesiologist during intubation, so a fiberoptic method is often used.

Immunosuppressive/antiinflammatory therapy

The contribution of corticosteroids and other disease-modifying antirheumatic drugs to postoperative infections and wound dehiscence has long been recognized and a consensus on the perioperative management of these medications has gradually emerged (Table 70.6).^{123,124} The primary challenge is to achieve an optimal balance between maintaining control of the underlying disease and minimizing the risk for postoperative wound infection and wound breakdown.¹²⁵ Animal studies on wound healing¹²⁶ and clinical investigation of postoperative infection¹²⁷ have produced conflicting data. However, two international groups have published their recommendations: guidelines of the Club Rhumatismes et Inflammations in France¹²⁸ and the British Society for Rheumatology.¹²⁹ Focused on biologic agents, both groups recommend discontinuing anti-tumor necrosis factor therapy for short periods before surgery, generally 2 to 4 weeks. The French favor a 4-week interval for infliximab and adalimumab because of the longer half-lives of these agents. Approaching these decisions by considering the half-life of the medication is advocated by some, although recommendations vary. For orthopedic patients, Pappas and Giles recommend a three- to five-half-life preoperative interruption, with therapy resumed in 10 to 14 days¹³⁰; others argue for a shorter duration (discontinuation for one dosing cycle).¹³¹ There is no information concerning postoperative infection and wound healing with newer agents such as abatacept (anti-T cell), anakinra (anti-interleukin-1 [anti-IL-1]), tocilizumab (anti-IL-6), or rituximab (anti-B cell). A novel approach has been suggested for the latter¹³² that involves measuring immunoglobulin levels (especially IgG) before surgery (moderate to severe in intensity) and proceeding if the levels are normal and the last dosage of rituximab was more than 100 days (five half-lives) earlier; conversely, if levels are low or if a delay in surgery is not possible, intravenous immune globulin replacement is given.

TABLE 70.6

Medication management in the perioperative period

Medication	Mechanism	Half-life	Preoperative recommendation
DMARD agents			
Sulfasalazine (Azulfidine)	ASA release	6-10 hr	Continue
Hydroxychloroquine (Plaquenil)	Toll-like receptors		Continue
Azathioprine (Imuran)	Inhibits purine metabolism	5 hr	Continue
Leflunomide (Arava)	Inhibits the pyrimidine synthesis activity of tyrosine kinase and NF- κ B	15-18 days	2-3 days
Methotrexate (Rheumatrex)	Dihydrofolate reductase inhibition	7 days	Continue
Mycophenolate mofetil (Prograf)	Inhibition of purine synthesis	18 hr	Withhold for 2 days
Biologic agents			
Etanercept (Enbrel)	TNF inhibitor	3.5-5.5 days	Withhold for 1 wk
Adalimumab (Humira)	TNF inhibitor	10-20 days	Withhold for 2 wk
Infliximab (Remicade)	TNF inhibitor	9.5 days	Withhold for 6-8 wk
Certolizumab (Cimzia)	TNF inhibitor	14 days	Withhold for 2 wk
Golimumab (Simponi)	TNF inhibitor	14 days	Withhold for 2 wk
Abatacept (Orenica)	T-cell inhibitor	12-16 days	Withhold for 2 wk
Rituximab (Rituxan)	B-cell inhibitor	18-22 days*	See text
Tocilizumab (Actemra)	IL-6 receptor antagonist	11-13 days	Withhold for 2 wk
Anakinra (Kinert)	IL-1 receptor antagonist	4-6 hr	Withhold for 1-2 days

DMARD and biologic agents can be restarted 10 to 14 days postoperatively if no signs of infection are present and the wound is healing well.

*Effects on B cells may last 6 or more months.

ASA, acetylsalicylic acid; DMARD, disease-modifying antirheumatic disease; IL-6, interleukin-6; NF- κ B, nuclear factor κ B; TNF, tumor necrosis factor.

Adapted from Gardner GC. Management of medication in patients with rheumatic diseases during the perioperative period. In: Mandell B, editor. Perioperative management of patients with rheumatic disease. New York: Springer; 2012, p. 78, Table 6.3.

Of the older therapies, methotrexate is now thought to be safe perioperatively and does not need to be withheld preoperatively; likewise, sulfasalazine, hydroxychloroquine, and azathioprine can be continued. Based on scant data, some recommend withholding mycophenolate mofetil for two half-lives (2 days) before elective major surgery.¹³² Leflunomide is more problematic because of its long half-life (15 to 18 days), but withholding it for 2 to 3 days before surgery seems prudent.

Finally, patient-related considerations should also be taken into account for decision-making. In patients undergoing minor surgical procedures with a low risk for infection, continuing treatment through the perioperative period may be reasonable. However, other patient-specific characteristics such as diabetes or chronic corticosteroid use would argue for adherence to the aforementioned guidelines. A more in-depth and current appraisal of these considerations has been published.¹³²

The integument

Skin integrity may be compromised before and after procedures in patients undergoing orthopedic surgery because of chronic therapy (i.e., corticosteroids, immunosuppressive agents) or as a manifestation (i.e., decubitus

ulceration) of the underlying disease or orthopedic condition. In addition, delayed wound healing and a propensity for infection may result from these influences. Initiating preventive measures early to combat the development of decubitus ulcers (particularly of the heels and buttocks) is vital for an uncomplicated postoperative course.

The eye

Patients taking chronic optic medication should have their eye drops instilled before surgery, especially for prolonged procedures. The one exception is the use of phosphodiesterase inhibitors for the treatment of glaucoma because these agents may prolong the action of the neuromuscular blocker succinylcholine. This is particularly pertinent in patients with Sjögren syndrome, who require artificial tears to prevent perioperative conjunctival injury.

Patients in the prone position are at risk for ocular injury secondary to external pressure, and those with underlying vasculitis of the optic vessels are at particular risk for ischemic injury to the eye. The anesthesiologist must take particular care in these cases to position the patient carefully to avoid excessive pressure on the eye and provide appropriate eye protection.

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REGIONAL AND WIDESPREAD PAIN

71

Neck pain

■ LES BARNSELEY

- Neck pain is common regional pain syndrome that usually arises from an undefined mechanical or musculoskeletal disturbance.
- It occurs acutely and is associated with marked hypomobility.
- Chronic symptoms are poorly understood.
- Neck pain may be a manifestation of a serious underlying malignant, infectious, or inflammatory disorder.
- It can occur in association with neurologic involvement—myelopathy and radiculopathy.
- No examination or imaging findings are known that can reliably identify the source of neck pain.
- It may be investigated with techniques targeting the pain.

INTRODUCTION

The neck provides a link of great flexibility between the sensory platform of the head and the trunk. Simultaneously, it provides vital conduits for neural and vascular tissue between the brain and the rest of the body. These conflicting priorities are achieved through the structure of the cervical spine, which combines strength with an extraordinary range of movement. Strength is achieved through a bony tube made up of the individual vertebrae. Range of movement is achieved through a complex articular system involving ligamentous intervertebral disks and paired posterior zygapophyseal joints in the lower part of the neck and loosely constrained synovial joints at the upper levels. The disks fissure posteriorly as part of the normal aging process,¹ thereby permitting rotatory movement through an oblique axis.² The posterior zygapophyseal joints have no bony constraint, which facilitates a broad range of movement that involves gliding of flat surfaces in concert to permit flexion and extension and in opposite directions to produce rotation. This complex is subject to almost constant activity, with the neck being reported to move more than 600 times per hour or once every 6 seconds.¹

Pain perceived in the region of the neck encompasses local sources of pain among the intrinsic structures of the cervical spine and distant sources that refer pain to the neck. Though previously thought to be acute and self-limited, contemporary reviews suggest that a chronic relapsing pattern is more typical.³ Most instances of chronic neck pain will prove to be musculoskeletal in origin, but it is incumbent on the physician to exclude other serious and potentially treatable pathology. Fortunately, the history and physical examination typically permit ready differentiation of musculoskeletal from other causes of neck pain. Once non-mechanical-related conditions have been excluded, the second responsibility is to provide a diagnosis of the structure and pathology producing the neck pain. Only with a sound anatomic diagnosis can therapy be targeted and rational.

Frequently discussed in association with neck pain but really a separate problem is the question of cervical nerve root or cervical cord compression.

These problems warrant assessment on their own merit, independent of any associated neck pain, and are considered later.

EPIDEMIOLOGY

Incidence, prevalence, and risk factors

Though less common than low back pain, neck pain is a common human experience—its universality and unpleasantness are reflected by colloquial use of the term “pain in the neck” to describe a particularly disagreeable circumstance or individual. A comprehensive review of the epidemiology of neck pain revealed an incidence between 10% and 21% and a mean 1-year prevalence of 25.8%.³

The determinants of chronic, mechanical neck pain are still incompletely studied. There is no doubt that trauma, particularly whiplash injury, is an important contributor to the burden of chronic neck pain. A clear relationship has been demonstrated between the nature of an occupation and neck pain, with manual workers having higher frequencies of neck pain than those with sedentary jobs.⁴ Other positive associations with neck pain include a self-reported heavy workload, level of education, and depression. Chronic neck pain has also been associated with metabolic syndrome and a high body mass index.^{5,6} A longitudinal study of adolescents demonstrated that dynamic loading sports involving the upper limbs during adolescence were associated with a 40% reduction in risk for the development of neck and shoulder pain 7 years later but that psychosomatic symptoms were associated with up to a 10% increase in risk. Increased flexibility in adolescent boys has been shown to be protective of later neck symptoms in males, whereas in girls good endurance strength confers similar benefit.⁷ One of the strongest predictors of future neck and shoulder pain was frequent symptoms of neck and shoulder pain during adolescence.⁸ Neck pain also has substantial genetic components, with a twin study suggesting heritability in the range of 35% to 58%.

Natural history

Neck pain is divided arbitrarily into acute pain, which lasts less than 3 months, and chronic pain, which lasts longer than 3 months. For a given episode of acute neck pain, only 40% of patients will either recover fully or have mild symptoms.⁹

Chronic neck pain is weakly predicted by the concomitant presence of low back pain, older age, previous episodes of neck pain, and stable symptoms for 2 weeks before the assessment.

PATHOGENESIS OF NECK PAIN

The exact cause of most mechanical neck pain remains elusive. In the case of acute neck pain, it has been suggested that the pain and hypomobility may stem from entrapment of the intraarticular menisci of the cervical

zygapophyseal joint in the large capsular recesses of these joints, with inflammation, pain, and stiffness ensuing before the meniscus is “reduced.”¹⁰

The source of more chronic neck pain remains arcane. The pathologic data concerning necks focus on problems that lead to neurologic compromise. The use of techniques such as zygapophyseal joint blocks enables, at a minimum, the anatomic source of the pain to be detected in a significant proportion of cases. In the case of the disk, annular tears extending into the innervated outer third of the disk may well be the source of the pain, but why the normal age-related changes, including extensive posterolateral fissuring, fail to cause pain in a significant proportion of patients is not understood.¹¹ A variety of lesions resulting from trauma to the neck could affect the cervical zygapophyseal joints (see later). Many of these lesions could result in premature osteoarthritic changes, which can be expected to be painful. Alternatively, intraarticular adhesions, capsulitis (analogous to frozen shoulder), or ongoing synovitis may be responsible for chronic zygapophyseal joint pain. A broader view of neck pain should also incorporate the possibility that some chronic neck pain is a centrally mediated or multifactorial problem that represents a complex interplay between biologic, psychological, and social factors—the so-called biopsychosocial model. As discussed in Chapter 24, pain is recognized as a phenomenon arising from nociceptive excitation perceived in a psychological and social milieu. It is generally accepted that pain, particularly chronic pain, is frequently associated with impaired social functioning and psychological distress. It is therefore difficult to separate causative from incidental relationships. It has been noted that when chronic neck pain has been fully relieved, evidence of psychological distress disappears,¹² thus implying that in this highly selected group, psychological distress was a consequence rather than cause of the chronic pain.

CLINICAL ASSESSMENT

History

Neck pain may be classified as being referred from distant (noncervical) structures; as arising through involvement of cervical structures by neoplastic, inflammatory, or infectious disease; or as being mechanical or musculoskeletal in origin. Diseases that may refer pain to the neck are outlined in Table 71.1. Fortunately, these conditions usually have other clinical characteristics, such as exertion-induced pain with angina, thus highlighting the need to take a complete history. Table 71.2 considers conditions that can affect components of the cervical spine. The clinical history should cover characteristics of the pain outlined in Box 71.1 to facilitate detection of more serious conditions.

Onset of pain

The circumstances surrounding the onset of pain are helpful in suspecting a diagnosis of non-mechanical-related neck pain. Older age or a past history of malignancy, particularly of the lung, breast, prostate, thyroid, or kidney, should raise the possibility of metastatic bone disease. Previous surgery, immunosuppression, and past infections increase the risk for hematogenous osteomyelitis or septic arthritis. Inflammatory conditions such as ankylosing spondylitis, rheumatoid arthritis (RA), and polymyalgia rheumatica are suggested by involvement of areas other than the cervical spine, a history of pain and stiffness on first rising and after immobility (“gelling”), and systemic features such as weight loss or sweats.

Musculoskeletal pain typically arises following trauma or unaccustomed activity, and intrinsic disease processes, such as osteoarthritis, may be responsible for the spontaneous development of pain.

Quality of pain

The pain associated with mechanical musculoskeletal derangement is typically dull, deep, and aching. Exacerbations usually consist of short-lived sharp pains superimposed on the chronic symptoms. Pain that does not follow this pattern, for instance, pain that is shooting or electrical, should raise suspicion that neural structures are involved. Deep, unremitting pain is a sinister sign implying ongoing distention, deformation, or invasion of pain-sensitive structures, which may occur with malignancy.

Frequency and duration of episodes of pain

Mechanical or noninflammatory musculoskeletal pain is typically experienced in episodes that are related to movement and exertion. The pain is made worse by particular postures or exercises and is characteristically improved by rest and immobility. Pain that does not follow this pattern, that is, not altered by movement and worsens spontaneously, suggests a more sinister underlying cause.

BOX 71.1 FEATURES OF PAIN TO BE ELICITED FROM THE CLINICAL HISTORY

Mode and time of onset
Site of pain
Quality of pain
Radiation of pain
Frequency and duration of episodes of pain
Pattern of episodes
If periodic, mode of onset and time of onset
Aggravating factors
Relieving factors
Associated features

TABLE 71.1

Non-musculoskeletal-related sources of neck pain

Structure	Condition
Pharynx	Pharyngitis
Larynx	Laryngitis Carcinoma
Trachea	Tracheitis
Thyroid	Thyroiditis
Lymph nodes	Lymphadenitis
Carotid arteries	Carotidynia Dissection Inflammation
Aorta	Aneurysm Dissection
Heart	Angina Infarction
Pericardium	Pericarditis
Diaphragm	Inflammation by blood, infection

TABLE 71.2

Musculoskeletal structures and pathologic processes

Muscles	Joints	Disks	Bone	Dura	Ligament	Other
Infectious	Septic arthritis	Diskitis	Osteomyelitis	Abscess Meningitis		Epidural abscess
Neoplastic			Primary Secondary	Neurofibroma Meningioma		Spinal cord tumor
Inflammatory	Polymyositis/dermatomyositis, polymyalgia rheumatica	Rheumatoid arthritis				
Metabolic		Diskitis? Ankylosing spondylitis Paget disease Osteoporosis Osteomalacia				

Fig. 71.1 Red represents the site stimulated to produce the pain pattern represented by the shaded area. (a) Intervertebral disks. p The disks were probed in the midline anteriorly and lateral to the midline anteriorly. (b) Deep musculoligamentous tissue. The site of pain is consistently produced by the injection of 6% saline into the interspinous region, just to the right of midline, at cervical levels from C1 to C8. (c) Zygapophyseal joints. Sites of pain are consistently produced by distention of the cervical zygapophyseal joints from C2-3 to C6-7 through the intraarticular injection of contrast medium. (d) Upper cervical synovial joints. Sites of pain are consistently produced by distention of the atlantooccipital and atlantoaxial joints by the intraarticular injection of contrast medium. (a, Modified from Cloward RB. *Cervical diskography: a contribution to the etiology and mechanism of neck, shoulder, and arm pain.* Ann Surg 1959;150:1052-64; b, modified from Feinstein B, Langton NJK, Jameson RM, Schiller F. *Experiments on pain referred from deep somatic tissues.* J Bone Joint Surg Am 1954;36:981-97; c, modified from Dwyer A, Aprill C, Bogduk N. *Cervical zygapophyseal joint pain patterns. I: a study in normal volunteers.* Spine 1990;15:453-7; and d, modified from Dreyfuss P, Michaelsen M, Fletcher D. *Atlanto-occipital and atlantoaxial joint pain patterns.* Spine 1994;19:1125-31.)

Site, radiation, and source of pain

Musculoskeletal cervical pain is typically perceived over the posterior aspect of the neck and rarely radiates past the anterior border of the sternomastoid muscle. Pain in the anterior part of the neck usually indicates disease in one of the anterior structures (see Table 71.1). Intrinsic neck pain can radiate into the head and down onto the shoulders. Headache is particularly common in patients with upper cervical pathology, particularly at C3 and above. Pain from structures at these levels is often perceived in the distribution of the first division of the trigeminal nerve, or the back of the head and neck, and pain from lower cervical levels can be referred to the shoulder girdle, arm, interscapular region, and chest wall. It has been observed that the more severe the pain, the larger the area of referral.

The clinical history and examination do not allow a specific anatomic structure to be impugned as a source of the pain. However, studies of normal individuals have demonstrated patterns of pain referral stemming from noxious stimulation of cervical structures. Probing the anterior part of the cervical disks in awake subjects produced pain in the posterior aspect of the neck several segments below the level stimulated (Fig. 71.1a).¹³ Feinstein and associates¹⁴ revealed that injections of hypertonic saline into the deep cervical muscles produced distinct patterns of pain, again over the posterior aspect of the neck (see Fig. 71.1b). Dwyer and colleagues¹⁵ distended the capsules of the cervical zygapophyseal joints (C2-3 to C6-7) of normal volunteers. Each joint had a reproducible and characteristic pattern of pain referral (see Fig. 71.1c). Similar methodology was used by Dreyfus and coworkers to investigate referral patterns of pain from the atlantoaxial joint (AAJ) and the atlantooccipital joint (AOJ).¹⁶ Injecting these joints in normal volunteers produced pain in the suboccipital region (see Fig. 71.1d). There is extensive overlap between different structures and the same structure at adjacent levels. In particular, the upper cervical zygapophyseal joints and the AAJ and AOJ all refer pain to the suboccipital region.

Consequently, it is impossible to determine the site of origin of neck pain on the basis of the site of pain alone. The approximate level of involvement may be determined, but not the structure. Furthermore, a single source of pain may produce pain over a wide area through the enhanced receptive fields of spinal neurons such that the pain may appear diffuse and unfocused.

Pain can be referred to the neck from other musculoskeletal structures. In similar experiments on normal volunteers, injection of hypertonic saline solution into the acromioclavicular¹⁷ and sternoclavicular¹⁸ joints frequently produced pain in the neck, sometimes with little local discomfort over the target joint.

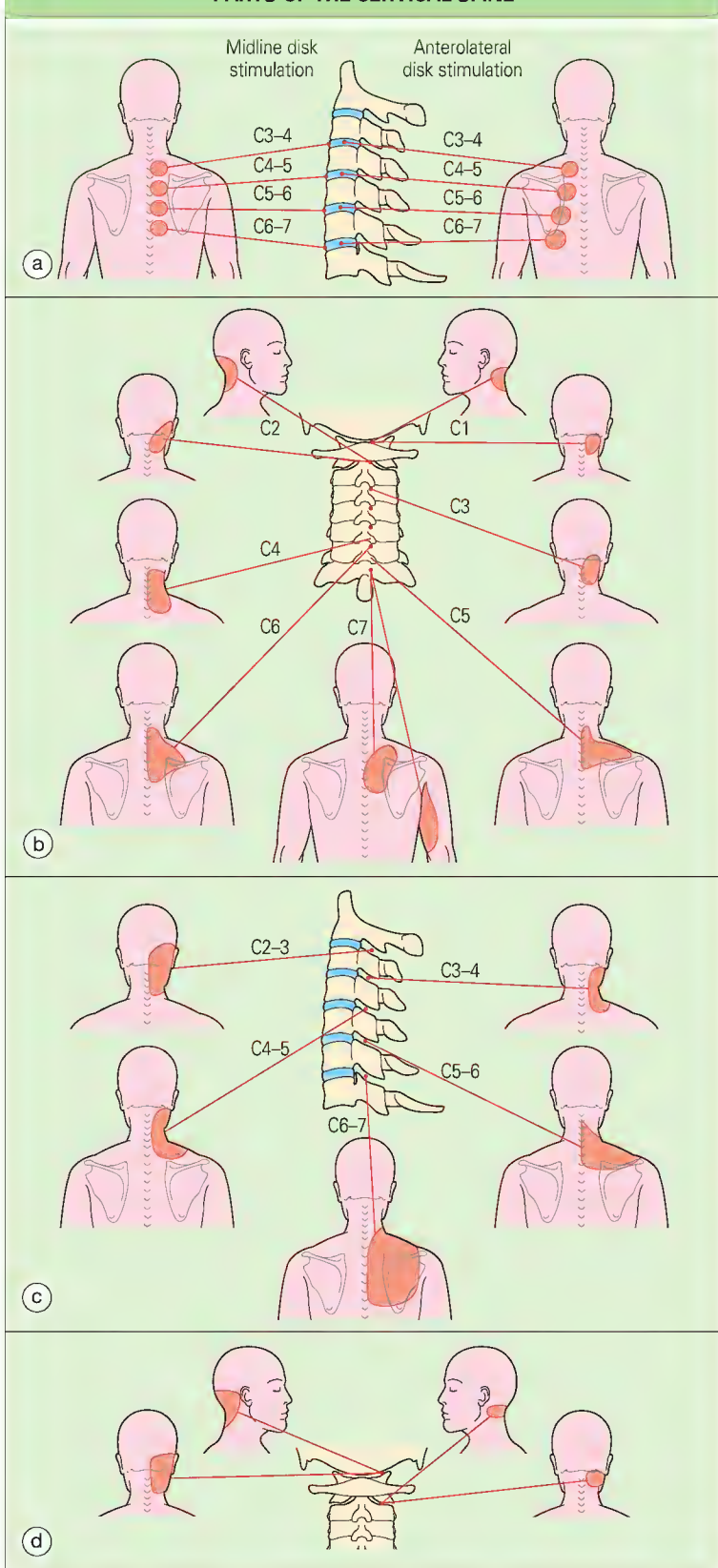
Associated features

Infections are typically accompanied by fever and malaise, as well as by specific features reflecting the tissues involved. Pain arising from malignant disease may be accompanied by paraneoplastic conditions such as peripheral neuropathy, hypercalcemia, or features of metastatic disease elsewhere.

Neurologic abnormalities

Neurologic symptoms such as paresthesia and subjective weakness may occur in patients with neck pain. Their significance depends on whether

PATTERNS OF PAIN ELICITED BY NOXIOUS STIMULATION OF DIFFERENT PARTS OF THE CERVICAL SPINE



they are accompanied by definite neurologic signs. Weakness in the absence of neurologic signs may seem to suggest a nonorganic basis for the complaints, but experimental studies have shown that pain has an inhibitory effect on motor neuron pools that results in a greater demand for effort and a consequent, subjective sensation of weakness. Paresthesia suggestive of nerve root irritation may arise as a result of functional thoracic outlet syndrome caused by spasm of the scalene muscle. Alterations in sensation have been described in patients with chronic pain states; such alterations take place as a result of complex interactions between nociceptive and other sensory pathways and lead to reports of altered sensation that do not correspond to the classic dermatomal or peripheral nerve distributions.

Hard neurologic signs are uncommon findings in patients whose primary complaint is neck pain, but if detected, the thrust of the investigation is to determine the site and nature of the lesion. Coexistent neck pain and neurologic deficit may be due to intrinsic involvement of the cord, dura, or nerve roots by neoplasia or infection (see Table 71.2) or to compression of neural tissue by bone or disks, which are themselves possible sources of pain. Clinical assessment should establish whether the spinal cord, nerve roots, or both are affected. The unexplained onset or presence of impaired sphincter function, lower limb weakness, and a sensory level is indicative of cord compression and demands urgent assessment, ideally by magnetic resonance imaging (MRI), to determine whether a reversible cause is present.

Signs of nerve root pathology, such as loss of a reflex, dermatomal sensory loss, or myotomal motor weakness (Fig. 71.2), may require confirmation by nerve conduction studies. Cross-sectional imaging often demonstrates the site and nature of the lesion and helps ascertain whether the problem is intrinsic disease of the nerve or external compression. These investigations are not justified for neck pain alone in the absence of neurologic signs.

Clinical examination

The principal role of the clinical examination in the setting of neck pain is to exclude other conditions contributing to the pain, such as infection, malignancy, or inflammatory arthropathy, or to exclude neurologic involvement. Once a diagnosis of mechanical neck pain is made, the diagnostic utility of clinical examination of the neck is limited.

General examination

A general examination is performed to exclude non-mechanical-related causes of neck pain. It should be particularly focused on any system or systems in which abnormalities have been suggested by the history. In addition, examination of temperature, skin, joints, lymph nodes, abdomen, and breasts should be performed. The yield from such assessment in the setting

of neck pain is not known and probably low, but the serious consequences of missing a potentially treatable systemic illness, malignancy or infection make performance of such an examination crucial. Inspection and palpation of cervical structures such as the thyroid, carotid arteries, and lymph nodes are indicated to exclude non-musculoskeletal-related conditions.

The neck should be examined for tenderness, which is best achieved by exerting pressure first on a control area such as the occipital protuberance. This pressure should then be applied along the spinous processes and then the articular pillars, as well as the trapezius muscles. This provides some standardization of the stimulus and permits some grading of response. Unfortunately, localization of the tenderness contributes little in the way of diagnostic information. No correlation has been demonstrated between tenderness in a particular area and a specific anatomic diagnosis.

Neurologic examination

The aims of neurologic examination in the setting of neck pain are to exclude cervical nerve root lesions (see later) or spinal cord lesions. The former requires detailed examination of the arms, including assessment of power, tone, reflexes, and sensory function. The lower limbs should be examined similarly, with the principal aim being exclusion of any upper motor neuron signs indicative of cord compression from the painful lesion in the neck.

Neck movement

Examination of the neck traditionally incorporates documentation of active and passive range of movement. However, basic research casts grave doubt on the diagnostic utility and reliability of such assessments. The detailed cineradiographic techniques used by Van Mameren and associates¹⁹ to assess flexion and extension have revealed that even normal individuals display marked variation in the pattern and amplitude of both segmental and total range of neck movement on different occasions. Therefore, only gross abnormalities in range of motion, such as reproducible asymmetry of movement, are likely to be assessed reliably. Furthermore, the clinical utility of assessment of neck movement is open to serious question. Biomechanical studies have shown that 50% of cervical rotation takes place at the AAJs.²⁰ The remaining rotation occurs in approximately equal proportions below C2 such that each segment contributes less than 7 degrees of movement. Consequently, even complete fusion of a segment below C1-2 may be clinically undetectable and will most likely fall within measurement error. At the same time it is conceivable that a painful lesion in the neck below C1-2 may produce marked loss of movement, in excess of 50% of range of motion, as a result of pain, fear of pain being produced, or local muscle spasm secondary to pain. At best, restriction of movement in the neck is indicative of one or more of the following: disturbance in neuromuscular control of the neck, a painful lesion aggravated by movement, or mechanical restriction

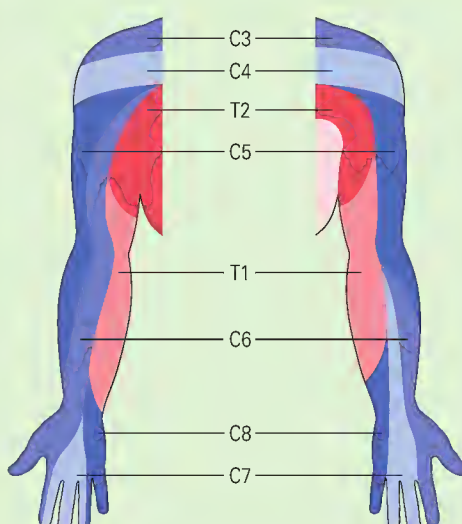
CERVICAL ROOT LESIONS			
Dermatome distribution		Root	Tendon reflex decreased
Anterior	Posterior		
		C5	Shoulder abduction Elbow flexion
		C6	Wrist extension/ pronation
		C7	Elbow/finger extension
		C8	Wrist/finger extension
		T1	Finger abduction Thumb adduction/ opposition

Fig. 71.2 Sensory and motor distribution of the cervical roots.

anywhere in the complex articular arrangements between two or more vertebrae.

CERVICAL NERVE ROOT COMPRESSION

Although it may not be a cause of neck pain, cervical nerve root compression is included here because suspicion of its presence dictates subsequent investigation.

Clinical features

Pain arising from overt compression or disease of the nerve root typically follows the appropriate dermatome and is therefore felt in the arm and not the neck. This pain will typically be radicular in quality, that is, pain that is perceived in a narrow band on the skin of the arm and that has electrical, radiating, or shooting properties. However, more somatic (i.e., deep, diffuse, aching) pain in proximal structures can be produced by nerve root compression.²¹ At the same time, pain that is perceived in the forearm or hand is unlikely to be somatic referred pain and more likely to be radicular in origin. Pain may be accompanied by neurologic symptoms such as numbness, paresthesia, altered sensation, and motor weakness. Pain may be perceived across the top of the shoulder from lesions involving C4 and in the face and head from lesions affecting C2 and C3. However, these levels are uncommonly affected, so much so that isolated lesions at these levels should prompt a systematic search for sinister, space-occupying pathology. The majority of cervical root lesions occur at C6, C7, and C8 and typically produce symptoms in the forearm and hand (see Fig. 71.2). Because of the extensive overlap of dermatomes in the arm and the complex central representation of the upper limb, pain referred to the arm from root irritation may be more diffuse than the traditional diagrams of dermatomes would suggest.

Unlike the lumbar spine, disk prolapse itself is not the predominant cause of cervical nerve root irritation. The nerve roots in the lower cervical spine lie in the inferior part of the foramina, at or below the level of the disk, and are susceptible to compromise by osteophytic involvement from the adjacent uncinate process or adjacent zygapophyseal joint.¹ Discogenic neural encroachment in the cervical spine is typically due to discrete fragments of the disk that herniate into the foramen.

Clinical examination

Supplementing the neurologic assessment described earlier, the most specific clinical test for nerve root entrapment is the compression or Spurling test. The patient's neck is moved passively into extension and rotated to the symptomatic side. Axial pressure is then applied to the neck by the examiner. This series of movements has been shown to narrow the intervertebral foramina. If the patient's radicular symptoms are reproduced, the test is positive.²² This test has good interrater reliability and is highly specific but relatively insensitive. The combination of a positive compression test and abnormal neurologic signs in the arm is strongly predictive of nerve root compression.

INVESTIGATIONS

Imaging

Radiographs

Plain radiographs of the cervical spine may be appropriate in patients with a history suggestive of severe trauma that is likely to produce fracture or severe subluxation or when major instability is suspected. The most useful views in these circumstances are lateral flexion and extension views, open-mouth views, and to a lesser extent, the anteroposterior view. To assess for subluxation, lines linking the anterior vertebral bodies, posterior vertebral bodies, and posterior border of the intervertebral canal on a lateral projection are constructed. These lines should describe a smooth arc (Fig. 71.3). The presence of a "step" in this arc is a sign of subluxation caused by either retrolisthesis or spondylolisthesis. Gross abnormalities in motion may be detected by comparing flexion and extension views, and instability can be demonstrated by comparing the construction lines described earlier on flexion and extension views. Of particular note is the issue of atlantoaxial instability. This is typically seen with RA but can occur in the presence of other destructive lesions affecting the odontoid peg or the transverse or alar ligament complex. It is assessed by comparing the gap between the anterior part of the odontoid peg and the posterior margin of the anterior arch of



Fig. 71.3 Plain lateral radiograph of a normal cervical spine. Lines joining the anterior part of the vertebral body (a), the posterior aspect of the vertebral body (b), and the anterior border of the laminae (c) should describe a smooth arc.

the atlas as seen on lateral flexion and extension views. The gap should normally be less than 5 mm (see Chapter 40).

Plain radiographs may also be useful in excluding primary bone disorders such as Paget disease, significant sclerotic malignant infiltration of bone, and destructive lesions such as osteomyelitis. However, standard views of the cervical spine are complex images with many structures being superimposed on all views. Consequently, radiographs are insensitive in detecting small abnormalities, such as purely lytic lesions without significant cortical bone destruction. When such lesions are suspected but not detected on plain films, further imaging with computed tomography (CT), MRI, or nuclear medicine techniques is desirable.

For patients with mechanical pain, the value of plain radiographs is much more limited. It has repeatedly been demonstrated that the presence of degenerative or spondylitic changes in the spine does not correlate with symptoms of neck pain. Friedenber and Miller studied the plain radiographs of 92 pairs of age- and sex-matched patients with and without neck pain.²³ The incidence of degenerative changes rose with age; was most common at the C5-6 level, at both the intervertebral disk and the zygapophyseal joints; but bore no relationship to the presence of neck pain.

Computed tomography

The principal value of CT in the assessment of cervical lesions is visualization of the bony conduits through which neural tissue passes. CT is of less value in assessing soft tissue. For neck pain alone without neurologic symptoms or signs and without clinical or plain radiographic evidence of a non-mechanical-related disorder, CT scans are not indicated.

Magnetic resonance imaging

MRI is highly specific and sensitive for disk herniations when compared with surgical findings (Fig. 71.4). It is particularly helpful in visualizing neural and soft tissue structures and intracord pathology in the cervical region (such as demyelination, intraaxial tumors, and spinal cord infarction) and enables accurate appraisal of developmental defects such as the Arnold-Chiari malformation. However, for assessment of neck pain of mechanical origin, MRI, like CT, has not been validated. It has been shown that nearly a fifth of all asymptomatic patients have abnormalities on MRI, with 60% of older patients having abnormalities of their intervertebral disks.²⁴ MRI should be reserved for patients in whom intraspinal pathology, neural compromise, or another neurologic disorder is clinically suspected.

Isotope scans

Bone scanning with technetium-labeled methylene diphosphonate (^{99m}Tc-MDP) is highly sensitive for the detection of bony pathology, with the notable exception of lesions that have a purely lytic pathology, particularly multiple myeloma (Fig. 71.5). However, for tumors that most commonly



Fig. 71.4 Disk herniation on magnetic resonance imaging (MRI). Axial (a) and sagittal (b) MRI scans of a 47-year-old man with neck pain, decreased left biceps jerk, and numbness over his thumb after a motor vehicle accident demonstrate a significant left posterolateral disk protrusion at C5-6 that is significantly compromising the exiting C6 nerve root.

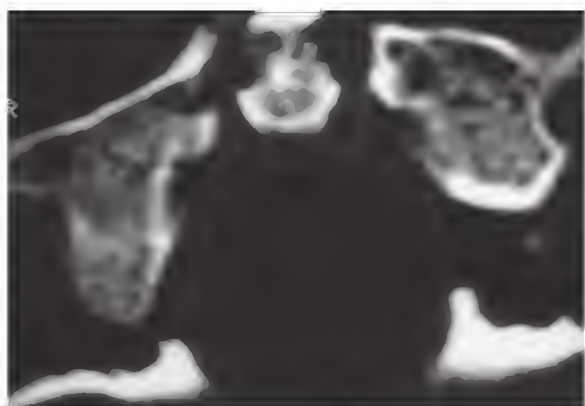


Fig. 71.5 Myeloma detected on a computed tomography scan of a 63-year-old man with known multiple myeloma in whom neck pain developed. Plain radiographs and a bone scan failed to demonstrate the osteolytic lesions affecting the odontoid peg.

metastasize to bone—lung, breast, prostate, thyroid, and kidney—bone scanning is the investigation of choice for the early detection of metastases. It may also be useful in the detection of infection, for which it shows avid uptake in the affected region. With early angiographic assessment during injection of the radiopharmaceutical and a blood pool image a short time later, increased vascularity can be assessed, which can help differentiate infection or inflammation from degenerative changes, where later bone-phase scans show uptake. Notable in the cervical spine is the normal, physiologically greater uptake over the C2 spinous process than over the lower cervical vertebrae. Anatomic localization can be facilitated with co-registered CT scanning.

Blood tests

Blood tests are indicated only when problems such as tumor or infection are suspected. The most useful investigations would be a complete blood count, erythrocyte sedimentation rate (ESR) or C-reactive protein (or both), and serum alkaline phosphatase. Infection and tumor are typically associated with an elevated ESR, infection with an elevated white blood cell count, and Paget disease with increased alkaline phosphatase. There is no evidence to advocate the use of these investigations for “screening.”

Investigations targeting pain

In the absence of reliable imaging correlates of mechanical neck pain it is necessary to target the pain itself to identify the painful structure. This can be accomplished either by stimulating a potentially painful structure and



Fig. 71.6 Arthrogram of the C2-3 zygapophyseal joint. A needle has been placed into the center of the joint, and injected contrast medium has filled the loose anterior and posterior recesses.

determining whether pain is produced or by anesthetizing a structure and determining whether the pain is relieved, thereby implicating that structure as a source of the pain.

Zygapophyseal joint blocks

Techniques for the diagnosis of cervical zygapophyseal joint pain rely on the principle that if a joint is a source of pain, anesthetizing that joint will relieve the pain. The cervical zygapophyseal joints can be anesthetized by injecting local anesthetic into the joint, or alternatively, the nerves that convey pain from the joint can be anesthetized.

Intraarticular blocks of the cervical zygapophyseal joints are performed under fluoroscopic control. A narrow-gauge spinal needle is directed toward the center of the target joint. Once the needle is felt to have pierced the joint capsule, a minimal volume of contrast medium must be injected to confirm intraarticular placement (Fig. 71.6). Thereafter, 0.7 to 1.0 mL of local anesthetic can be injected to anesthetize the joint.

The total volume injected should not exceed the capacity of the joint (generally accepted to be less than 1.0 mL) because distention beyond this volume may cause capsular rupture or extraarticular leakage, including epidural spread, which may compromise the specificity of an intraarticular block by anesthetizing structures other than the target joint.

Cervical medial branch blocks are a more expedient way to anesthetize a cervical zygapophyseal joint. They are easier to perform, are less painful to the patient, and provide the same diagnostic information.²⁵ They are performed under fluoroscopic control via either a posterior or lateral approach. These blocks take advantage of the anatomy of the nerve supply to the cervical zygapophyseal joints.

The cervical zygapophyseal joints are innervated by articular branches derived from the medial branches of the cervical dorsal rami. The C4-8 dorsal rami arise from their respective spinal nerves just outside the intervertebral foramina and pass dorsally over the roots of the transverse processes. The medial branches of the typical cervical dorsal rami course posteriorly around the waist of the articular pillars and are covered by tendinous slips of the origin of the semispinalis capitis (Fig. 71.7). Ascending and descending articular branches arise near the posterior aspect of the pillar to supply the joints above and below (see Fig. 71.7). Consequently, each typical cervical zygapophyseal joint receives dual innervation, from the medial branch above and from the medial branch below. A joint can be anesthetized or denervated by blocking both these nerves. The C2/3 joint receives its innervation from the third occipital nerve, which is the superficial medial branch of C3. After supplying the C2/3 joint, it furnishes muscle branches to the semispinalis capitis and becomes cutaneous over the suboccipital region.

The cervical medial branches below the third occipital nerve, (i.e., C3-7) can be anesthetized reliably by placing a small amount (0.25 to 0.5 mL) of local anesthetic onto the nerve as it passes across the waist of the articular

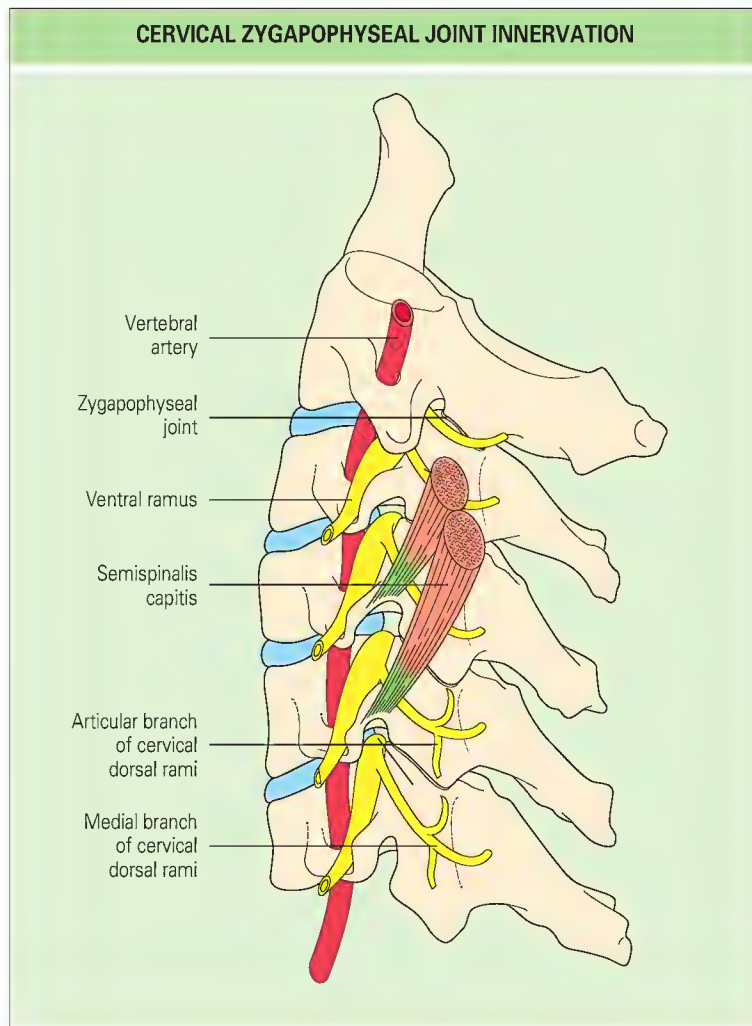


Fig. 71.7 A posterolateral drawing of the cervical spine illustrates the course of the medial branches of the cervical dorsal rami. All muscles except the origins of the semispinalis capitis at C4 and C5 have been removed. The medial branches of the cervical dorsal rami are seen to course across the waist of the articular pillars. At C4 and C5 they are shown covered by the tendinous origins of the semispinalis capitis. Articular branches arise from each medial branch, on the posterior aspect of the articular pillar, to innervate the zygapophyseal joints above and below. The medial branches are well away from the ventral rami of the spinal nerves and the vertebral artery.

pillar. Under image intensifier control a needle is placed onto the centrod of the articular pillar, usually from a lateral approach (Fig. 71.8). The third occipital nerve is anesthetized by placing local anesthetic onto the nerve as it passes across the C2-3 joint, with three injections used to cover its more variable course (Fig. 71.9).

The value of blocks as a diagnostic tool depends on correct interpretation of the patient's responses. Diagnoses based on a single block are compromised by a false-positive rate of between 27% and 45%.²⁶ To circumvent this problem, two blocks should be used, be administered on different occasions, involve anesthetics with different durations of action, and be delivered in random order under double-blind conditions. The veracity of the response is then adjudicated by the patient's report of the duration of pain relief afforded by the anesthetic given. Because the medial branches below the third occipital nerve do not have reliable cutaneous representation, the only way that a patient can tell which anesthetic was used is through the duration of pain relief. This approach has been formally tested and found to be a valid means of identifying cervical zygapophyseal joint pain.²⁷ A refinement of this process is the addition of a third, placebo injection with normal saline used as the injectant, which increases the sensitivity of the technique; any response to an anesthetic with no response to the saline is accepted as a positive test.

Studies using these techniques attest to a prevalence of cervical zygapophyseal joint pain of 54% in patients with chronic neck pain (whiplash) after motor vehicle accidents²⁸ and between 36% and 55% in less selected patients.^{29,30}

Other anesthetic blocks

Anesthetic blocks of other structures, such as the greater occipital nerve and ventral rami of the spinal nerves, may be useful in confirming or eliminating structures in their territories as causes of the pain, but in contrast to zygapophyseal joint blocks, these procedures do not have documented reliability, sensitivity, and specificity.

Provocation diskography

The only regularly used provocative test in the neck is provocation cervical diskography, in which a disk is punctured by a needle and distended by injecting contrast medium. A positive diskogram occurs when the procedure reproduces the patient's usual pain and implicates that disk as the source of the pain.³¹ The response can occasionally be confirmed by injecting local anesthetic in an attempt to abolish the pain. In practice the procedure itself can be quite painful, and it is often difficult for patients to judge whether it is their usual pain that is being reproduced. Furthermore, in a significant proportion of patients the pain reproduced by diskography can be eliminated completely by subsequent zygapophyseal joint blocks at that level,³² thus indicating a significant false-positive rate. On the basis of current evidence, diskograms should be considered true positives only if zygapophyseal joint blocks at that level are negative (i.e., no pain relief). The side effects of diskography have been assessed in an audit study in a single practice, which revealed the rate of diskitis to be 0.16% per injection.³³

TREATMENT—NECK PAIN

Treatment of neck pain secondary to infection, tumor, or inflammatory disease such as RA is necessarily treatment of the underlying disorder and is not further considered in this chapter. Treatment of mechanical neck pain can be divided into treatments that are not targeted at any particular structure and are therefore nonspecific and those that are targeted at a particular painful structure within the neck. The aim of treatment is to relieve pain and thereby improve function.

Nonspecific treatments

Analgesics

The most commonly used nonspecific treatments of neck pain are simple analgesics such as acetaminophen (paracetamol). These agents have an important role in acute neck pain and can also be used safely over long periods for more chronic problems when other treatment is ineffective. In patients with more severe pain, synthetic and nonsynthetic opioids such as dextropropoxyphene or codeine can be used, but the potential for abuse and dependency needs to be considered before they are prescribed. These concerns should not prevent the physician from treating severe, refractory, and incapacitating pain appropriately. Sustained-release oxycodone taken for 4 weeks has been shown to be superior to placebo in patients with flare of chronic neck pain; it decreases pain and results in improvement in quality-of-life scales.³⁴ Refractory neck pain may respond to the use of pregabalin.

Exercises

Neck exercises aim to restore range of motion and strengthen the neck musculature. The rationale for the latter is reinforced by observations that females with chronic neck pain have a smaller cross-sectional area of the cervical multifidus muscles than do those without neck pain.³⁵ In women with chronic neck pain, high-intensity strength training has been demonstrated to be superior to range-of-motion exercises and stretching in the control of pain,³⁶ and other studies have shown strengthening and endurance exercises to improve quality of life.³⁷ Expert panel recommendations derived from comprehensive literature reviews advocate a useful role for exercise-based therapy,³⁸ and other reviews have found strong evidence supporting the effectiveness of strengthening and proprioceptive training exercises for frequent (i.e., recurrent acute) and chronic neck disorders.³⁹

Physical therapy

Physical therapy incorporates a number of potentially therapeutic modalities such as heat, cold, interferential therapy, laser, ultrasound, traction, and massage. The undoubted fact that patients report modest and temporary benefit with these approaches has provided a pragmatic basis for pursuing formal studies. Low-level laser therapy was shown to provide short-term benefit in a randomized controlled trial,⁴⁰ and a systematic review of acupuncture attested to a limited analgesic benefit over no treatment.⁴¹ The most recent systematic review of massage finds little data to support massage as an individual therapy. These observations are reflected in the findings of the

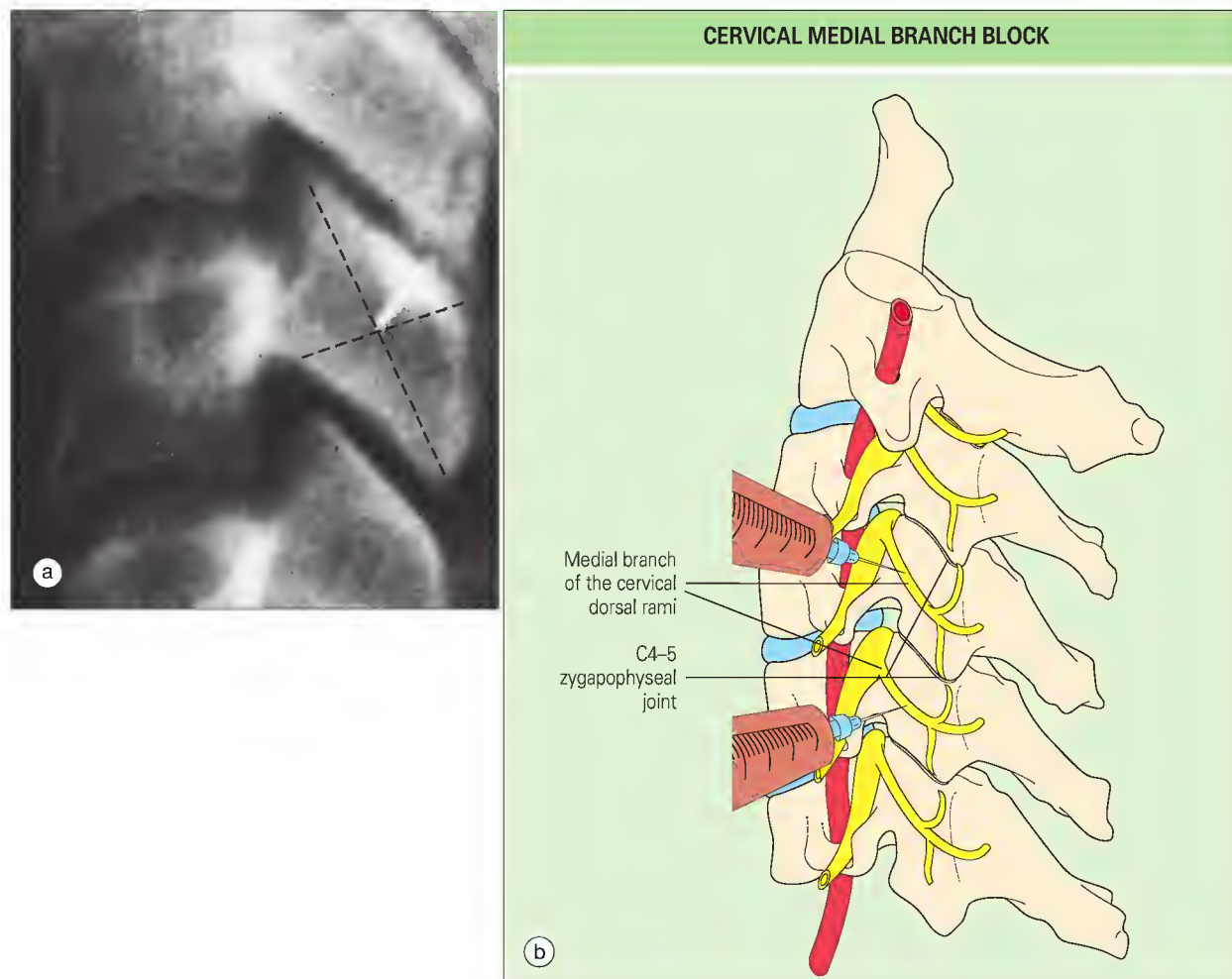


Fig. 71.8 (a) Radiograph illustrating a needle placed correctly for injection onto the medial branch of the C5 dorsal ramus. The target point is the centrod of the articular pillar as seen on a true lateral view. (b) Schematic diagram of medial branch blocks of the C4 and C5 dorsal rami to anesthetize the C4-5 zygapophyseal joint. Needles inserted from a lateral approach are positioned for infiltration of the medial branches of the cervical dorsal rami of C4 and C5. Note that the tips of the needles are proximal to the origins of the ascending and descending articular branches.

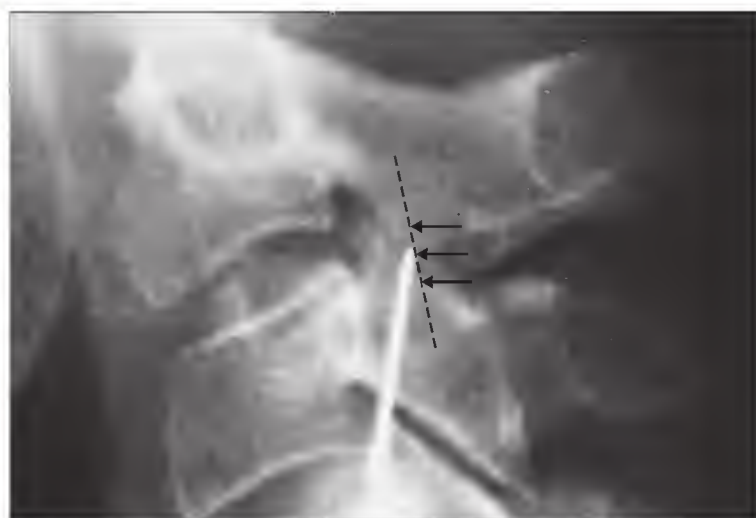


Fig. 71.9 Injecting the third occipital nerve. On a lateral radiograph of the cervical spine, arrows indicate the target points for injections to anesthetize the third occipital nerve and thus the C2-3 zygapophyseal joint. The points lie along a line that vertically bisects the articular pillar of C3 seen on a lateral projection. The middle point lies over the joint line, the upper point over the subchondral plate of the C2 inferior articular surface, and the lower point over the subchondral plate of the superior articular surface of C3.

best-evidence synthesis of the Bone and Joint decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders, which supports acupuncture and low-level laser therapy for patients with neck pain not related to trauma.⁴²

Manual therapy/manipulation

A variety of “hands-on” techniques have been described for the treatment of neck pain. The best studied and most widely practiced are short-lever, high-velocity “adjustments,” usually described as manipulations and used principally by chiropractors. The other leading technique is known as mobilization and involves oscillatory movements through both the physiologic and accessory movements of spinal joints. The aim is to stretch the tight joint capsules of symptomatic joints. Studies to date have lumped all patients with neck pain together and have also often included lumbar pain. These studies show small benefit that is of uncertain clinical significance for manual techniques over conventional physical therapy modalities and best medical care.⁴³ The use of mobilization or manipulative techniques for acute pain may be expected to have a modest effect.⁴⁴ The most recent Cochrane review of this subject concluded that manipulation or mobilization may provide beneficial short-term or immediate change but that no long-term data are available.

Attempts to quantify the risks associated with cervical manipulation have concluded on the basis of a number of assumptions that the risk for death or serious injury was on the order of less than 1 per 500,000 to 1,000,000 manipulations.

Pillows and posture correction

Emerging data are correlating increased thoracic-to-cervical angles and anterior scapular rotation with neck pain. There are a paucity of reliable data showing that either “posture correction” or the use of variously profiled pillows helps patients with chronic neck pain. However, these are benign

interventions, and in the absence of proven efficacious treatment, their use may be justified. Modification of workplace environments and practices to decrease extreme movements of the neck and reduce the amount of time spent in a fixed cervical posture may be helpful for neck pain. Water-based pillows have been shown to decrease waking pain in patients with chronic neck pain.⁴⁵

Specific treatments

Zygapophyseal joints

With a definitive diagnosis of cervical zygapophyseal joint pain, therapy can be targeted at the specific joint. A randomized controlled trial of corticosteroid injected into painful cervical zygapophyseal joints after whiplash injury showed no benefit over injection of local anesthetic, with neither group obtaining useful relief.⁴⁶ It is not known whether patients whose pain arises spontaneously respond to intraarticular corticosteroids.

Cervical zygapophyseal joint pain can be controlled by denervation of the joint through percutaneous radiofrequency neurotomy of the medial branches of the cervical dorsal rami. A randomized controlled trial of this technique demonstrated prolonged relief of zygapophyseal joint pain (a median of 263 days vs. 8 days in the control group).⁴⁷ Similar results have been reproduced by other groups^{48,49} and by published audits of the author's practice. The long-term effects of denervating a cervical zygapophyseal joint are not known, but clinical experience with limited numbers of patients has indicated no lasting adverse effects, and the procedure can be repeated safely for recurrence of pain over a period of several years. Surgical intervention for proven cervical zygapophyseal joint pain has not yet been described.

Intervertebral disks

The treatment options for proven disk pain are limited. By virtue of their diffuse innervation, they cannot be selectively denervated to control pain in a manner analogous to that for the cervical zygapophyseal joints. Moreover, the exact site of pain production within a painful disk cannot yet be determined, so sclerosis or excision of particular disk components is not currently a viable option. Current practice for the treatment of suspected or proven cervical disk pain is cervical disk excision, usually with fusion. The rationale for this approach is simple—remove the part that hurts—but empirical efficacy studies on the effects of cervical spine surgery on neck pain are not available. The only studies available are open and nonrandomized and constitute retrospective reviews of individual practitioners' experiences.^{50,51} Randomized, controlled studies of this operation on patients with proven disk pain are needed. For the time being, physicians contemplating such invasive intervention should ensure that the diagnosis of cervical disk pain is sound and that the patient is made aware of the potential risks associated with such operations, as well as the uncertainty of response.

TREATMENT—CERVICAL NERVE ROOT COMPRESSION

Natural history

The majority of patients with cervical radicular pain will experience resolution of their pain over a period of a few weeks or months. Over prolonged periods of observation, less than 10% of patients have persistent moderate or severe disability.⁵²

Treatment modalities

Very few interventions have been shown unequivocally to be any better than others in the treatment of cervical nerve root pain. In particular, a three-armed, randomized study failed to show any long-term differences between cervical collar physiotherapy and surgery.⁵³ However, it would appear that any reasonable treatment is better than no intervention, with patients in the treated arms of trials reporting better satisfaction than those in placebo arms. Typical treatments that can be expected to increase patients' perception of improvement include physiotherapy, traction, transcutaneous electrical nerve stimulation, analgesics, and isometric exercises. These types of interventions can be applied with the understanding that this pain generally has a favorable natural history and that there is no evidence of superiority of any one intervention over any other. The choice therefore hinges on minimizing harm.

Corticosteroid injections

Corticosteroid injections into the epidural space, either via an interlaminar route or into the root sleeve, have been advocated for radicular pain. The

rationale is to decrease inflammation around the nerve root. No randomized trials of transforaminal corticosteroid injections have been performed, and the generally favorable natural history makes interpretation of the benefits noted in cohort studies nearly impossible. Any enthusiasm for the technique needs to be tempered with the knowledge that serious, fatal, and disabling outcomes have been reported from such injections that are thought to be due to occlusion of radicular vessels supplying the spinal cord.^{54,55} The frequency of these events is not known, but in a series of more than 500 injections, no serious adverse events were reported.⁵⁶ Notwithstanding this, the procedure is clearly accompanied by a material risk that anybody considering administering or receiving such treatment should consider.

Surgery

Surgery has the potential to relieve compression on the affected nerve root and should therefore be able to “cure” cervical radiculopathy and pain from cervical nerve root entrapment. However, this does not seem to always be the case. Marshaling the available empirical evidence suggests that in the acute setting, surgery is likely to improve symptoms faster than conservative measures can but without making any long-term difference when compared with conservative treatment. In the chronic arena, surgery is likely to improve symptoms in the majority of patients but is unlikely to effect a “cure.”⁵⁷ In the absence of a serious underlying cause of radiculopathy (e.g., tumor, infection), reasonable indications for surgery would include a progressive neurologic deficit or refractory and disabling pain.

WHIPLASH

Whiplash injuries warrant particular mention in any discussion of neck pain. Even though whiplash injuries are undoubtedly a common cause of acute neck pain, the frequency with which they cause chronic pain still spawns vigorous debate.

Biomechanics

Biomechanical studies have demonstrated that the traditional view of hyperextension being the primary event in whiplash is unduly simplistic. It has been found that axial compression and unnatural, double curvatures of the cervical spine are important and potentially damaging components of the cervical spine's response to inertial loading. Cadaver experiments have demonstrated that after rear-end impact, the lower cervical spine is thrust upward and forward.⁵⁸ The neck is therefore compressed from below. The lower cervical segments are extended while the upper segments are relatively flexed, which results in an S shape during the first 50 to 75 msec. Thereafter, all segments are progressively extended until the head is thrown forward. A more detailed cineradiographic study of normal volunteers described the motion of individual cervical segments during the extension phase of whiplash.⁵⁹ Following an 8-kph impact that resulted in 4-g acceleration, the C6 vertebra was driven upward. As it moved, the C6 vertebra extended underneath the rest of the cervical spine, which caused the higher segments to undergo a small initial flexion, of some 2 to 5 degrees in amplitude, before undergoing extension. The net result was that the cervical spine assumed an S shape at about 100 msec as the lower segments commenced extension while the higher segments were still undergoing initial flexion (Fig. 71.10). These movements took place around abnormal axes of rotation, with the pathologic axes being higher than normal. As a result the anterior end of the vertebra separated from the vertebral body below, and posteriorly the tip of the inferior articular process chiseled into the supporting superior articular process. Subsequently, the cervical spine underwent extension, as described in the classic model. These observations provide a biomechanical substrate for injuries to several structures in the spine, most notably the cervical zygapophyseal joints, which seem to be particularly susceptible to damage via uncontrolled rotation through abnormal axes.⁶⁰

Pathology

Our understanding of the pathology of whiplash has languished behind that of other spheres of rheumatology, primarily because of the paucity of pathologic material and the generally benign nature of the condition. However, the existence of a number of pathologic entities has been determined through clinical, animal, cadaveric, and postmortem studies,⁶¹ as summarized in Figure 71.11.

Plain radiographs have been shown to be profoundly insensitive to the detection of all but the most severe bony injuries of the cervical spine. Twenty-two cervical spines were harvested from patients who had died of head injuries.⁶² The specimens were then radiographed under optimal

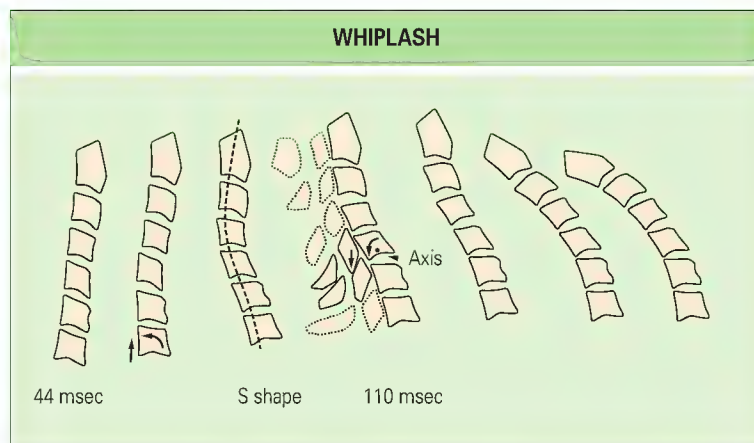


Fig. 71.10 Appearance of sequential radiographs of the cervical spine during the extension phase of whiplash. At 110 msec the C5 vertebra rotates about an abnormally high axis of rotation, which causes the vertebral body to separate anteriorly from C6 and the inferior articular process of C5 to chisel into the superior articular process of C6. (Modified from Barnsley L, Lord SM, Bogduk N, Teasell RW, Shapiro A. *The pathophysiology of whiplash*. In: Malanga, editor. *Cervical flexion-extension/whiplash injuries*. Spine: state of the art reviews. Philadelphia: Hanley & Belfus; 1998, p. 209-42; and Kaneoka K, Ono K, Inami S, Yokoi N, Hayashi K, editors. *Human cervical spine kinematics during whiplash loading*. International Conference on New Frontiers in Biomechanical Engineering. Tokyo: 1997.)

conditions. Subsequent photographs of submillimeter slices revealed 245 injuries to various structures. Only four were detected on plain radiographs, even on second look.

Natural history

The natural history of whiplash is, for the most part, benign. Most patients recover within a few weeks of injury and have no residual symptoms. The main physical risk factor for chronic neck pain after whiplash is the severity of the initial symptoms.⁶³ A best-evidence synthesis has highlighted the role of psychological factors such as passive coping style, depressed mood, and fear of movement in slowing recovery.⁶⁴ It has been argued that the apparent differences in rates of chronicity of whiplash in different countries are evidence that chronic whiplash is a socially programmed phenomenon that pivots on the presence of a compensation system.⁶⁵ However, careful analysis of the data reveals that many of the studies proffered to support this view were compromised by small sample size, poor study design, and inappropriate endpoints such as insurance claims rather than clinical information.^{66,67} Follow-up studies of an inception cohort of patients assembled in the United Kingdom in the early 1980s revealed that most patients destined to improve do so within a few months, with very little improvement noted after 2 years. After 15 years, well after completion of any compensation, approximately 25% still had intrusive symptoms.⁶⁸

Treatment of acute whiplash injury

Treatment of acute whiplash is aimed at preventing chronicity, minimizing symptoms, and improving function. A review of conservative treatment of acute whiplash found that treatments such as cervical collars, rest, and passive physical modalities were generally inferior to programs involving

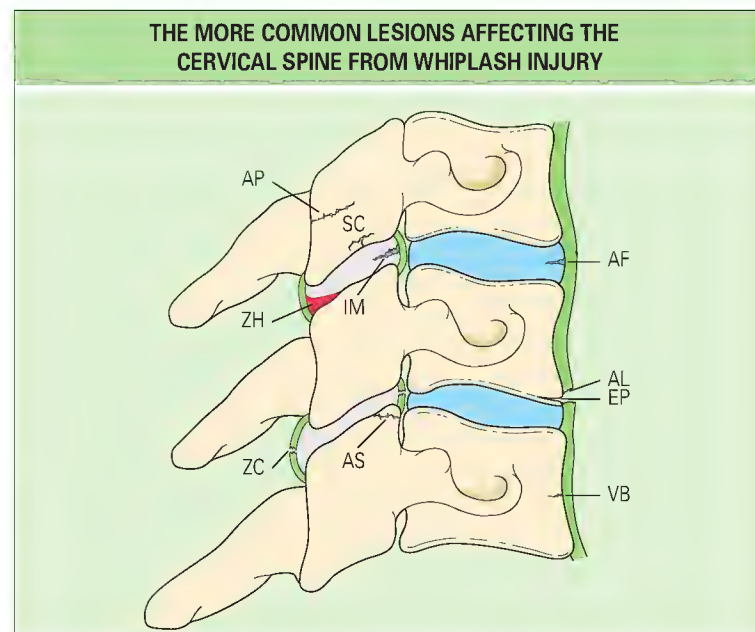


Fig. 71.11 AF, tear of the annulus fibrosus of the intervertebral disk; AL, tear of the anterior longitudinal ligament; AP, articular pillar fracture; AS, fracture involving the articular surface; EP, endplate avulsion and/or fracture; IM, contusion of the intraarticular meniscus of the zygapophyseal joint; SC, fracture of the subchondral plate; VB, vertebral body fracture; ZC, rupture or tear of the zygapophyseal joint capsule; ZH, hemarthrosis of the zygapophyseal joint. (Adapted from Barnsley L, Lord SM, Bogduk N, Teasell RW, Shapiro A. *The pathophysiology of whiplash*. In: Malanga, editor. *Cervical flexion-extension/whiplash injuries*. Spine: state of the art reviews. Philadelphia: Hanley & Belfus; 1998, p. 209-42.)

activation, multimodal interventions, simple reassurance, and encouragement to resume normal activities.⁶⁹

Treatment of chronic whiplash

Very few controlled studies of the treatment of chronic neck pain after whiplash injury have been conducted. The single most promising avenue has been percutaneous radiofrequency neurotomy, which was described previously.⁴⁷ This remains a palliative treatment, but one that is valuable for patients with constant and debilitating pain. Otherwise, the rather unsatisfactory options for the management of any chronic neck pain, as discussed earlier, can be applied.

CONCLUSION

Neck pain is a common disorder, but it is important to exclude serious underlying illness and neurologic involvement. Future progress in the field of chronic and refractory pain will depend on reliably identifying the source of pain, typically through invasive analgesic or provocation techniques, and testing potential treatments in methodologically sound studies in selected patients. Increasing sophistication of trials has enhanced the evidence base for some existing therapies, particularly activation for acute whiplash and exercise therapy for chronic neck pain.

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72

Lumbar spine disorders

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- Mechanical low back pain is the most common lumbar syndrome and a general category of pain that in severe refractory cases requires methodical evaluation.
- One of the most important roles of the physician is to recognize nonmechanical causes.
- Investigation is indicated for patients with persistent or progressive pain and those in whom a nonmechanical cause is suspected.

EPIDEMIOLOGY

Occurrence

Low back pain is the most frequent disorder of humanity after the common cold.^{1,2} Back pain develops in between 65% and 80% of the world's population at some point during their lives. More than 60 million adults in the United States report having back pain at some time in the past 3 months.³ The most prevalent impairments in people up to 65 years of age are musculoskeletal, with back and spine impairment being the most frequently reported subcategory at 51.7%.⁴ In the United States, mechanical low back pain is the fifth most common reason (2.8%) for physician office visits. Nonspecific low back pain accounts for 57% of these visits.⁵ Impairments of the back and spine are the chronic conditions that most frequently cause limitation of activity in people 45 years or younger, and they are the third most common reason for impairment in people aged 45 to 64 years.⁶

Impact

More than half of all patients with back pain improve after 1 week, and more than 90% are better at 8 weeks.⁷ The remaining 7% to 10% continue to experience symptoms for longer than 6 months. However, as many as 75% of individuals who improve are at risk of having a relapse of their back pain in the next 12 months.⁸ The high cost associated with low back pain is related to these individuals with chronic and recurrent pain. The cost of back pain in the United States is estimated to be higher than \$100 billion per year, the majority of which is indirect cost, including lost wages and lower productivity.⁹

Risk factors

Twin studies indicate that heredity plays a more important role than environmental factors do in disk degeneration, and it explains 74% of the variance in adult populations. Genetic influences have been confirmed by the identification of several genes associated with disk degeneration.¹⁰⁻¹²

Many of the environmental risk factors described for back pain involve occupational or psychological characteristics. Workers involved in heavy-duty labor who are older than 45 years have a 2.5 times greater risk for absence from work secondary to back pain than do workers 24 years or younger.¹³ Individuals with an initial episode of back pain lasting 3 months or longer have a 50% higher risk for recurrence in the following year than do those with an initial episode of only 1 day's duration.¹⁴

A number of psychological conditions are associated with back pain. Neurosis, hysteria, and conversion reaction are more frequently associated with acute back pain than depression is.¹⁵ Depression and anxiety are frequent complications of patients in whom chronic low back pain develops, and psychological distress predisposes to both a new episode and chronicity.

Although psychiatric comorbid conditions complicate treatment and can affect pain perception, true psychogenic pain is rare. Cigarette smoking is associated with increased risk for back pain, but the data are inconsistent.¹⁶ Although obesity is a minor factor in the causation of back pain, excessive weight is associated with longer episodes.¹⁷ Even though tobacco use, excessive weight, mood disturbances, and weakness of the core musculature have only weak associations with incident symptoms, they all represent modifiable factors.

CLINICAL EVALUATION

Introduction

Lumbar spine disorders can be categorized broadly as being mechanical, neuropathic, or medical in origin (Table 72.1). Up to 90% of patients with back pain have a mechanical or neuropathic reason for their pain.¹⁸ Mechanical implies that the pain is secondary to overuse of a normal anatomic structure, trauma, or deformity of an anatomic structure. Examples include discogenic pain, lumbar radiculopathy, spinal stenosis, facet syndrome, sacroiliac joint syndrome, and musculoskeletal sprain and strain. Neuropathic pain includes involvement of the peripheral or central nervous system either by direct compression of the spinal cord or spinal nerve roots or by changes in function of the neurologic system as a result of chronic pain. Given the difficulty of separating purely mechanical from purely neuropathic symptoms, many advocate the term *low back pain*. Patients with referred limb symptoms manifested as weakness, pain, sensory disturbances, or changes in reflexes caused by involvement of the spinal nerve are classified as having *radicular pain*. Defining a diagnosis is difficult because of the overlap of history, physical examination, and pain referral patterns of various pain generators and the high incidence of asymptomatic radiologic imaging findings.¹⁹ Frequently, however, no trauma or deformity can be identified with certainty in patients with low back pain. For the majority of patients with pain that responds to time, medications, and physical therapy, no specific diagnosis needs to be sought. Diagnostic functional testing with interventional spinal injection procedures is helpful in delineating the pain generator in refractory cases but requires thoughtful consideration of technical adequacy, placebo effect, and psychological pain behavior. Systemic illness accounts for the other 10% of adults with back pain.²⁰ More than 70 nonmechanical illnesses may be associated with back pain.²¹ Careful clinical evaluation helps distinguish patients with low back pain from those with systemic illness.

Evaluation of a patient with low back pain thus requires an organized approach that should be tailored to the specific complaints of the patient. Understanding the mechanism of pain generation helps determine what types of therapeutic exercise, activity modification, pharmacologic measures, spinal interventional procedures, and surgical options can be considered in the treatment algorithm.

History

The relevant medical history should be sought to evaluate for a possible underlying systemic illness.

A full occupational and social history is important to identify patients at risk for the development of low back pain. The association of work and the onset of pain is important in regard to compensation. The patient's opinion about the association of the pain and work must be determined, as well as the expectation of work-related sickness payments for injury and return to work.²²

TABLE 72.1**Categories of low back pain**

Category	Source/pathologic entity	Quality
Superficial somatic	Skin, subcutaneous tissue (cellulitis)	Sharp, burning
Deep somatic	Muscles, fascia, periosteum, ligaments, joints, vessels, dura (arthritis)	Sharp pain or dull ache, boring
Radicular	Spinal nerves (herniated disk, spinal stenosis)	Radiating, shooting, tingling
Neurogenic	Mixed motor sensory nerves (femoral neuropathy)	Burning
Visceral referred	Abdominal viscera, pelvic viscera, aorta (autonomic sensory nerves)	Boring, colicky, tearing
Psychogenic	Cerebral cortex (conversion reaction, malingering)	Variable

Site of pain

It is helpful to ask the patient whether the symptoms are predominantly axial or occur in the extremity (thigh, calf, or foot). The buttock region is often difficult to categorize because it can be affected by both axial low back pain and radicular pain secondary to irritation of the spinal nerve roots. Pain in the thighs or knees may be referred from elements of the spine, such as the intervertebral disks, zygapophyseal joints, sacroiliac joint, muscle, or ligaments, by somatic referral. Pain that radiates from the low back region to below the knees is usually radicular in origin and suggests a process affecting the spinal nerve roots.

Aggravating and relieving factors

Typically, disorders such as discogenic axial low back pain worsen with prolonged sitting, standing, and bending forward and improve with recumbency and changing position. Patients with disk herniations generally experience back and leg symptoms with sitting, driving, slouching, coughing, and sneezing. The symptoms are typically relieved by walking and shifting positions. Patients with spinal stenosis characteristically experience gluteal, thigh, and calf pain with standing, walking, and lumbar extension.

Some patients with medical disorders that affect the spine, such as osteoporotic compression fractures, traumatic fractures, pathologic fractures, or acute infection, may achieve pain relief with recumbency and even complete immobility, although some find no association with body position. Patients with spondyloarthritis classically report increased pain and stiffness when they remain in bed or seated for a few hours and relief with movement and exercise. Patients with spinal tumors often experience exacerbation with recumbency or nocturnally. Patients with viscerogenic pain may have symptoms that are worsened or exacerbated with meals or bowel movements, menstruation, or excess alcohol or nonsteroidal antiinflammatory drug (NSAID) consumption.

Physical examination**General examination**

When a medical or systemic cause of low back pain is suspected, a general physical examination should be completed in addition to examination of the spine. The objective of physical examination of the lumbosacral spine is to demonstrate static and dynamic abnormalities that can help sort out the disease entities that may be responsible for the low back pain.

Genital and rectal examinations should be performed in patients who have symptoms and signs suggestive of cauda equina syndrome or abdominal or pelvic pathology. These examinations may detect prostatic abnormalities, rectal cancer, or endometriosis. Low or absent rectal tone and absent voluntary anal contraction can be seen in patients with cauda equina syndrome. A number of ancillary physical examination tests may be used to confirm the abnormalities discovered during routine examination (Table 72.2).

Spinal examination

The spine is viewed for curvatures and postural deformities. A list is present if the first thoracic vertebra is not centered over the sacrum. Hyperlordosis or a flattened lumbosacral curve may be identified, and marked thoracic kyphosis is best noted from the lateral position. The spinous processes and sacrum can be palpated and percussed to determine whether any osseous injury is present. The ischial tuberosity and greater trochanter can be

TABLE 72.2**Ancillary tests for evaluation of low back pain**

Test	Tests for
Schober test	Lumbosacral motion
Contralateral straight leg-raising test	Nerve root compression
Bowstring sign	Nerve root compression (L5, S1)
Straight leg raise	Nerve root compression (L5, S1)
Femoral stretch test or hip extension	Nerve root compression (L2, L3, L4)
FABER test	Sacroiliac joint dysfunction, hip range of motion
Hoover test	Patient effort
Vertebral percussion	Osseous pain/fracture

FABER, flexion, abduction, external rotation.

TABLE 72.3**Lumbar root lesions**

Root*	Muscle weakness/movement affected	Tendon reflex decreased
L2	Hip flexion/adduction	
L3	Hip adduction Knee extension	Knee jerk
L4	Knee extension Foot inversion/dorsiflexion	Knee jerk
L5	Hip extension/abduction Knee flexion Foot/toe dorsiflexion	
S1	Knee flexion Foot/toe plantar flexion Foot eversion	Ankle jerk

**Cutaneous, motor, and reflex functions of the lower extremity.*

palpated for bursitis. The paraspinal muscles can be palpated for any areas of spasm, taut bands, or trigger points. In the supine position, leg lengths should be measured to document discrepancies.

Lumbar range of motion

The patient is asked to flex, extend, and laterally bend the lumbosacral spine. Patients with localized mechanical disorders maintain the lordosis while bending from the hips. Range of motion can be measured more precisely with an inclinometer.

Patients with spondyloarthritis may have an abnormal Schober test result. This test is performed by having the patient stand erect and marking the distance between the midpoint of the posterior superior iliac spines ("dimples of Venus") and 10 cm above that point. The patient is then asked to maximally flex forward while the more caudal spot is kept stationary. The more cephalad point on the tape measure should normally demonstrate at least 5 cm of excursion. This abnormality can also be seen with lumbar degenerative disk disease.

Classic teaching is that an increase in pain with forward flexion suggests an abnormality in the anterior elements of the spine, including the disk. This is probably mediated by increases in intradiscal pressure with forward flexion. Pain that is increased by extension suggests disease in the posterior elements of the spinal column, including the zygapophyseal joints.

Manual muscle testing

Of the possible neurologic abnormalities, persistent muscle weakness is the most reliable indicator of nerve compression.²³ It is useful to measure muscle strength on the Medical Research Council 6-point scale (muscle grade scores of 0 to 5). Examiner judgment is required to distinguish true weakness from pain-inhibited, apprehension-inhibited, or effort-dependent deficits in strength. At a minimum, the function of the three most commonly affected nerve roots should be tested (Table 72.3).

The L5 myotome includes the ankle dorsiflexors, great toe extensors, hip abductors, and ankle evertors. Asking the patient to heel-walk provides a

good screening test for the L5 nerve root. Severe weakness of the L5 myotome may be detected with the Trendelenburg test. The patient is asked to stand on one leg. Weakness of hip abduction is highlighted by sagging of the pelvis on the side opposite the affected leg. Patients may also have a Trendelenburg sign with hip osteoarthritis or synovitis, gluteal muscle tears, or a neurologic disorder.

The S1 myotome includes the gastrocnemius and hip extensors. Gluteus maximus strength is tested by having the patient lie prone and extend the hip against resistance with the knee bent. The gastrocnemius is not readily overcome with manual muscle testing even when weak, and a more sensitive screen for S1 weakness is completing more than 10 single-leg calf raises on each side.

The L4 myotome includes the quadriceps and ankle dorsiflexors. The L3 myotome includes the quadriceps but not the ankle dorsiflexors. Single-leg squatting is a good test to challenge the quadriceps muscle, which is often too strong to be overcome by the examiner's upper limb musculature.

The L1 and L2 myotomes include the hip flexors, which are tested by asking the supine patient to lift the thigh off the examining table. Having the hip externally rotated minimizes substitution of the rectus femoris of the quadriceps, which receives L2 through L4 contributions.

Neurologic examination

Upper motor neuron and peripheral nerve abnormalities may also cause neurologic dysfunction. Muscle spasticity, hyperreflexia, and the Babinski and Hoffman signs develop in patients with upper motor neuron dysfunction. Distinction among upper motor neuron, nerve root, and peripheral nerve lesions is essential for the differential diagnosis of back pain. Different disease processes preferentially affect the upper motor neuron (e.g., multiple sclerosis), nerve root (disk herniation), or peripheral nerve (diabetes).

Sensory examination

Sensory findings are less reliable than reflex or strength-testing findings. A given area of skin also receives innervation from two dermatomes, thus making sensory testing less specific for defining the affected nerve root. However, if a peripheral nerve is injured, a specific muscle may become paralyzed or specific skin areas may become anesthetic (Fig. 72.1). The L5 dermatome involves the buttock, lateral aspect of the thigh, lateral part of the calf, dorsal surface of the foot, and great toe. The S1 dermatome involves the buttock and the posterior thigh, posterior calf, and lateral foot areas. The L4 dermatome involves the anterior thigh region, anterior aspect of the knee, and pretibial region of the shin.

Deep tendon reflexes

Testing the deep tendon reflexes, especially the patellar reflex (L4) and Achilles reflex (S1), can be useful. However, no reliable reflex is available to test for L5. Older individuals may lose reflex function, particularly at the Achilles (which is likely to be symmetric), and previous episodes of nerve compression may have caused a loss of reflexes that may not return even with recovery of motor and sensory function.²⁴ Excessively brisk reflexes can be indicative of an upper motor neuron process such as cervical myelopathy.

Provocative maneuvers

The hip joints should be moved through their range of motion. Differentiation of hip pain from sacroiliac joint pain may be determined with the Patrick or "FABER" (flexion, abduction, external rotation) test. A Patrick maneuver producing low back pain suggests sacroiliac joint pain but can be nonspecific and is seen with spondylolisthesis, spinal stenosis, facet syndrome, and acute discogenic pain secondary to an annular tear. A Patrick maneuver producing groin or anterior thigh discomfort suggests hip disease. The greater trochanter can be palpated to determine the presence of bursitis. Sustained lumbar extension precipitating thigh or calf discomfort suggests lumbar stenosis.

Root tension signs

The straight leg-raising test detects irritation of the sciatic nerve (L5, S1). Passive raising of the leg with the knee extended stretches the sciatic nerve and its nerve roots and dural attachments. When the spinal nerve is inflamed and stretched, the patient will experience pain along its anatomic course. The pain associated with nerve root irritation is maximal between 20 and 70 degrees of elevation. Symptoms occurring at greater than 70 degrees of elevation may simply be related to mechanical pain secondary to muscle or ligamentous strain or joint disease.²⁵ Pain may also be experienced in the leg below the knee when the contralateral normal leg is raised, a finding known as the *crossed straight leg raise*. The crossed straight leg-raising test is insensitive but highly specific.²⁶

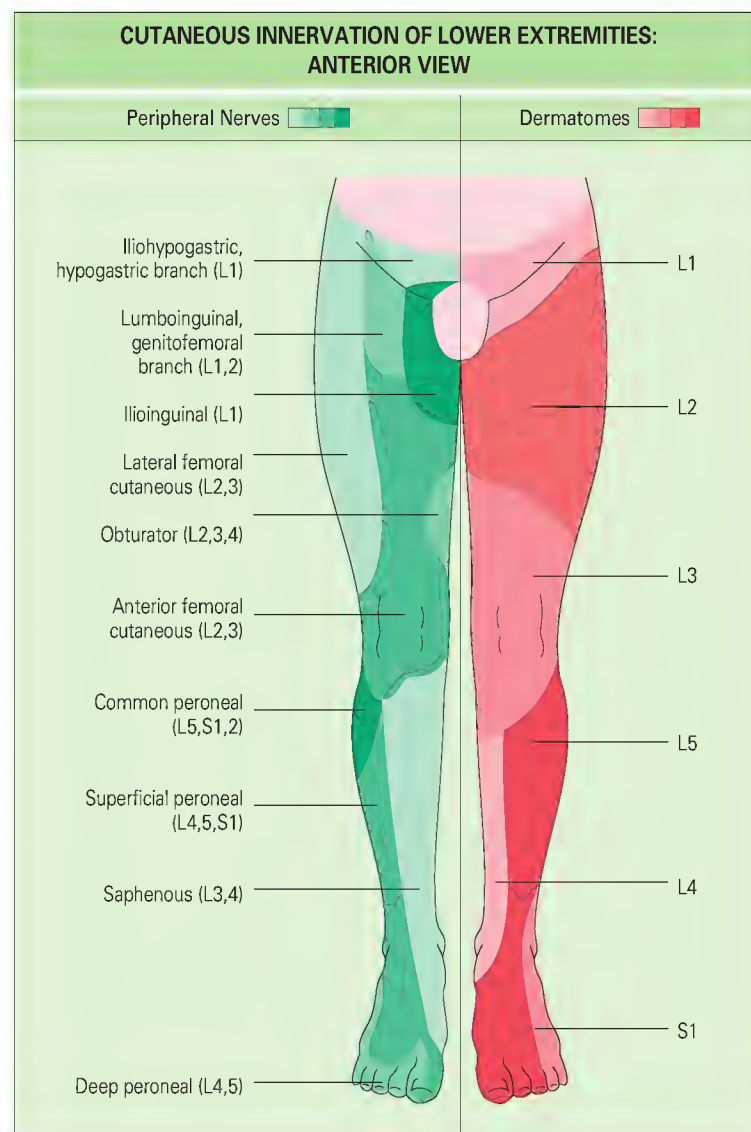


Fig. 72.1 Cutaneous sensory innervation. Anterior view of the lower extremities illustrating skin areas supplied by nerve roots (right) and peripheral nerves (left).

The neurologic examination is completed by testing for higher lumbar and sacral nerve root function. Dural irritation of nerve roots from L2 to L4 is tested by the femoral stretch test or reverse straight leg-raising test (Fig. 72.2). With the knee bent, the thigh is elevated from the examining table. The test is positive if pain is reproduced in the front of the thigh or the medial aspect of the leg.

Gait analysis

The patient's gait should be analyzed for heel and toe walking to screen for L5 and S1 myotomal deficits, respectively. Antalgia may be indicative of sacral, hip, knee, or foot and ankle injuries but can also be seen with acute radicular pain and with pain behavior. A forward stooped posture may be present in patients with spinal stenosis and in those with ankylosing spondylitis. A mechanical gait, which appears stiff and spastic, can be a component of cervical or thoracic myelopathy.

Reproducibility of physical signs

McCombe and colleagues²⁷ evaluated the reproducibility between three observers of 54 physical signs used for the evaluation of back pain. The signs that were adequately reproducible included measurements of lordosis and flexion range (Schober test), determination of the location of the pain with flexion and lateral bending, the straight leg-raising test, determination of the location of the pain in the thigh and legs, and sensory changes in the legs.

Nonorganic physical signs

Patients with psychological pain behavior often have subjective complaints that are much greater than their objective findings. Waddell and associates²⁸ described five tests that identify individuals with "functional" or

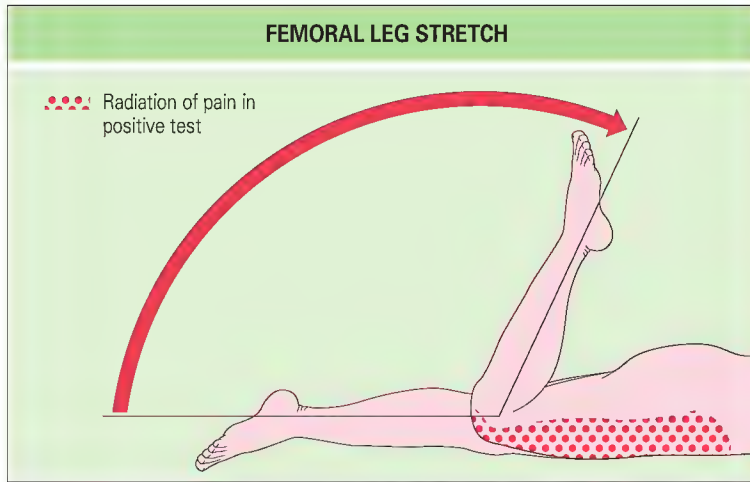


Fig. 72.2 In the femoral stretch test, the knee is flexed and lifted superiorly. Sharp pain generated in the anterior aspect of the thigh is considered to constitute a positive test.

“exaggerated” symptoms. A finding of three or more of the five signs is clinically significant. Patients who feign weakness during manual muscle testing may resist pressure for a few seconds and then release the muscle suddenly or in a manner resulting in a “cogwheel” or “give-way” effect. Because symptoms of psychological pain behavior do not exclude concomitant nociceptive pain and tissue injury, however, patients with psychological pain behavior warrant comprehensive treatment.

INVESTIGATIONS

Imaging

Plain radiographs

The Quebec Task Force on Spinal Disorders suggested that in patients without neurologic dysfunction, plain radiographs should not be obtained during the first week of an acute episode of back pain.²⁹ In adults younger than 50 years, the yield of unexpected important findings can be as low as 1 in 2500. By contrast, many individuals with radiographic abnormalities may be entirely asymptomatic.³⁰ Thus, congenital abnormalities, including spina bifida, transitional vertebrae, Schmorl nodes, and mild scoliosis, are only rarely causes of back pain.³¹ In normal persons older than 50 years, the prevalence of radiographic change is high: 67% have evidence of intervertebral disk degeneration, two thirds of whom are asymptomatic. In addition, osteoarthritis of the zygapophyseal joints noted on radiographs is not strongly correlated with symptoms.³²

When lumbar radiographs are obtained, a single lateral film offers the view with the highest yield in detecting vertebral compression fractures. Others have suggested that anteroposterior and lateral views are adequate for evaluation.³³ A coned lateral view of the lumbosacral junction and oblique views add little to the anteroposterior and lateral projections.³⁴ The anteroposterior and lateral views demonstrate the scoliotic curvature and sagittal balance, which can often help specialists in interpreting the biomechanics of the spine. Flexion and extension views can demonstrate segmental instability, a potential cause of unexplained back and radicular symptoms. Clinical practice guidelines have recommended that the criteria for obtaining plain films include older age, recent significant trauma, history of prolonged steroid use, previous cancer, recent infection, fever, intravenous drug abuse, unexplained weight loss, or pain with recumbency.³⁵ In a review of these guidelines, Suarez-Almazor and colleagues³⁶ reported that the recommendation for radiographs based on older age alone may result in excessive use of radiography during the initial visit. Use of the criteria of failure to respond to therapy and signs of systemic illness is more cost-effective. Patients with systemic illness and significant persistent symptoms often warrant imaging with magnetic resonance imaging (MRI) or computed tomography (CT), and negative plain radiographs do not provide sufficient reassurance of the absence of malignancy.

Radionuclide bone scintigraphy

Technetium-99m diphosphonate scans are useful in assessing for infection, tumors, inflammatory arthritis, and fractures.³⁷ The sensitivity of bone



Fig. 72.3 Technetium bone scan. Tracer activity throughout the axial skeleton is increased secondary to metastatic prostate cancer.

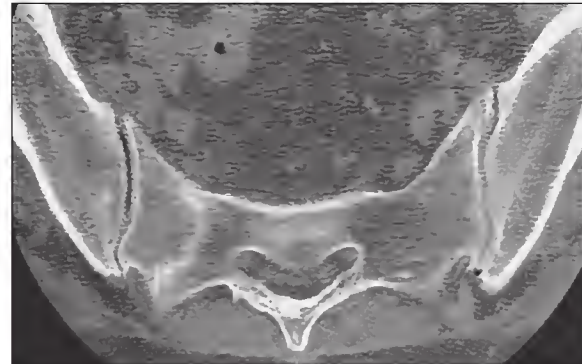


Fig. 72.4 Fracture. Computed tomography of the sacral spine demonstrates a sacral fracture not visualized with plain radiographs.



Fig. 72.5 Osteoid osteoma. Computed tomography of the thoracic spine demonstrates increased sclerosis associated with osteoid osteoma.

scanning is generally equal to that of MRI (90% vs. 96%), but it is less specific, for example, in detecting vertebral osteomyelitis (78% vs. 92%). Gallium and indium scans increase the specificity when used with a technetium scan but are less sensitive when used alone. Bone scintigraphy is better than MRI when evaluation of the whole skeleton is required, such as in patients with metastatic disease who may have unsuspected bone lesions in other parts of the skeleton (Fig. 72.3). The addition of single-photon emission computed tomography of bone can be useful for identifying facet pathology and predicting patients who will respond to intraarticular facet injection.³⁸

Computed tomography

CT is the best technique for assessing the bony architecture of the spinal column, including the sacroiliac joints, before changes are noted on plain radiographs.³⁹ In addition, the structural relationships of soft tissues (ligaments, nerve roots, fat, intervertebral disks) can be evaluated as they relate to their bony environment. CT is an excellent technique for identifying mechanical disorders, including spinal stenosis, spondylosis, spondylolysis, spondylolisthesis, trauma, congenital anomalies, and fractures (Fig. 72.4).⁴⁰ CT can visualize cortical bone destruction, calcified tumor matrix, and soft tissue extension of tumors affecting the spine and is superior to MRI in this regard (Fig. 72.5).⁴¹ CT can also be used in an outpatient setting to guide percutaneous needle biopsy of bony lesions.

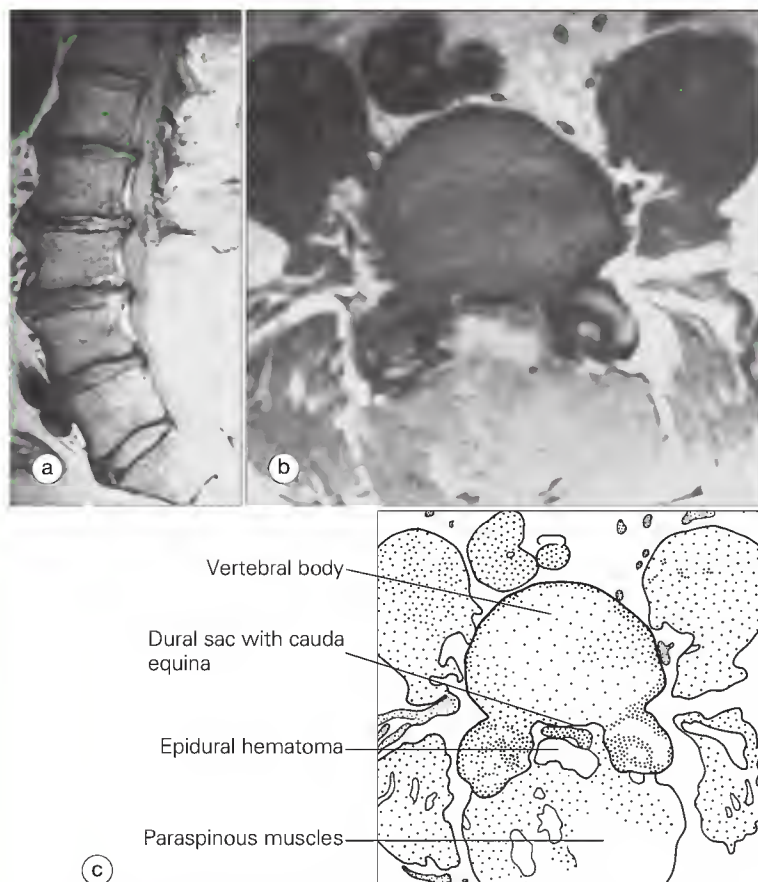


Fig. 72.6 (a to c) Epidural hematoma. Postoperative sagittal and axial magnetic resonance imaging shows an epidural hematoma compressing the cauda equina.

The clinical significance of abnormalities noted on CT must be evaluated in the setting of the patient's clinical findings. In one study of asymptomatic subjects older than 40 years, 50% had abnormal findings, including disk herniation, spinal stenosis, and zygapophyseal joint degeneration.⁴² Thus, CT (as with MRI) should be used as a confirmatory test and not solely as a diagnostic test.

Magnetic resonance imaging

MRI has become the imaging modality of choice to evaluate lumbar spine disorders.⁴³ Patients who are not candidates for MRI evaluation include those on life support systems and those who have a cardiac pacemaker or ferromagnetic clips in the abdomen or brain or on blood vessels.

MRI is an excellent technique to view the spinal cord. It identifies syringomyelia, atrophy, cord infarction, cord injury, multiple sclerosis, intramedullary tumors, and hematoma (Fig. 72.6).⁴⁴ Use of contrast media (gadopentetate dimeglumine) for MRI improves the characterization of spinal cord tumors.⁴⁵ MRI delineates the extent of extradural tumor invasion of the spinal canal and compression or displacement of the spinal cord. It can identify the vertebral bodies in which bone marrow has been replaced with tumor (Fig. 72.7).⁴⁶ Use of gadolinium in patients with renal failure has been associated with a scleroderma-like disorder called nephrogenic systemic fibrosis (see Chapter 170).⁴⁷

MRI is an excellent technique for detecting infection of the spine, including diskitis, osteomyelitis, epidural abscess, paraspinal abscess, and myelitis.⁴⁸ It is more sensitive in detecting vertebral osteomyelitis than plain radiography or CT is.⁴⁹ Changes in the vertebral bodies and adjacent intervertebral disk spaces are visualized on T1-weighted images as areas of low signal intensity. On T2-weighted images, high signal intensity is seen crossing the involved bone and disk space.

MRI is also a useful technique for evaluating mechanical disorders of the lumbosacral spine. Intervertebral disk herniations can be identified in the sagittal plane and confirmed on axial images.⁵⁰ MRI is likewise useful in assessing traumatic and nontraumatic vertebral fractures. MRI can identify degenerative vertebral endplate changes and categorize them as edema, fatty, or sclerotic. MRI can reveal high-intensity zone lesions representing annular tears and neovascularization.

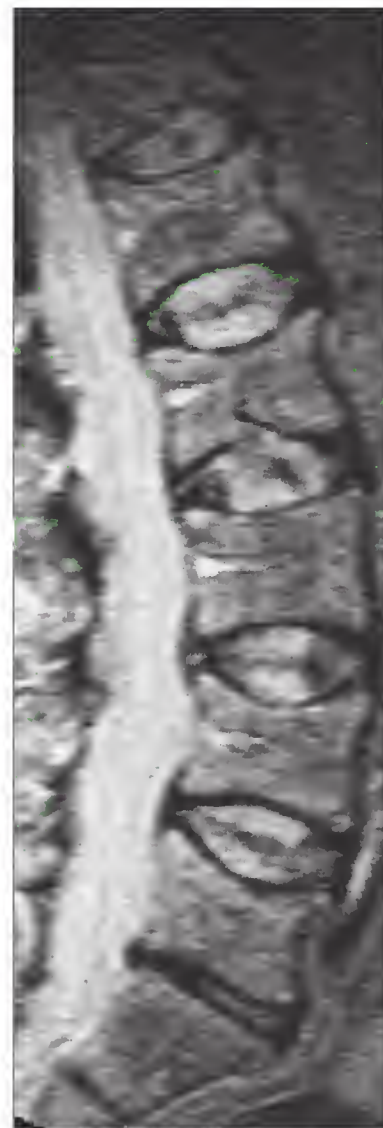


Fig. 72.7 Lumbar spine magnetic resonance imaging study of a patient with multiple myeloma and abnormal bone marrow signal throughout the vertebral bodies associated with remodeling and pathologic fractures.

Correlation between magnetic resonance imaging and clinical findings

As with CT and myelography, interpretation of the findings on MRI must take into account the clinical findings. Several separate studies have reported that in asymptomatic individuals, MRI identifies substantial abnormalities such as herniated disks (24% to 28% of the time), degenerative disk disease (>50%), and spinal stenosis (>5%).⁵¹

Comparison between magnetic resonance imaging and other modalities

In the diagnosis of herniated disks and spinal stenosis, MRI has a sensitivity equal to or greater than that of CT or myelography.⁵² In a study comparing MRI with contrast-enhanced CT for the diagnosis of a herniated disk confirmed at surgery, MRI had 90% accuracy, whereas CT had an accuracy rate of just 77%.⁵³ In addition, MRI was able to identify disk degeneration in 74 of 123 interspaces, whereas CT identified only 27. Currently, MRI is the technique of choice for investigation of spinal stenosis and disk degeneration. The major limitation of MRI is cost.

Other imaging techniques

A number of other radiographic techniques are available for evaluation of the lumbosacral spine. They are used infrequently in comparison to the techniques already discussed.

Spinal angiography permits identification of the arterial origins and the venous drainage of vascular lesions of the spinal cord and column.⁵⁴ Arteriovenous malformations are characterized by arteriovenous communication without an intervening capillary network.

Lumbar diskography is a procedure associated with the injection of contrast material through a percutaneous needle into the nucleus pulposus suspected of causing the back pain. Reproduction of the patient's pain is considered a positive test (Fig. 72.8). The test is used for patients with a degenerative disk who may be considered for spinal fusion, disk replacement, or intradiscal therapy because of persistent pain. Its clinical significance remains controversial.⁵⁵ MRI is equally sensitive in detecting disk degeneration by identifying high-intensity zones in an intervertebral disk (Fig. 72.9).⁵⁶ However, MRI is unable to reproduce the patient's symptoms. The role of diskography will be decided on the basis of its relevance to the patient's symptoms and the development of better nonsurgical therapies. Concerns are emerging about diskography potentially causing disk degeneration and herniations. A 10-year matched-cohort study by Carragee and coworkers⁵⁷ concluded that modern diskography techniques involving the use of a small-gauge needle and limited pressurization result in accelerated disk degeneration, disk herniation, loss of disk height and signal, and the development of reactive endplate changes when compared with match controls. Risk and benefit should be considered carefully when recommending procedures involving disk injection.

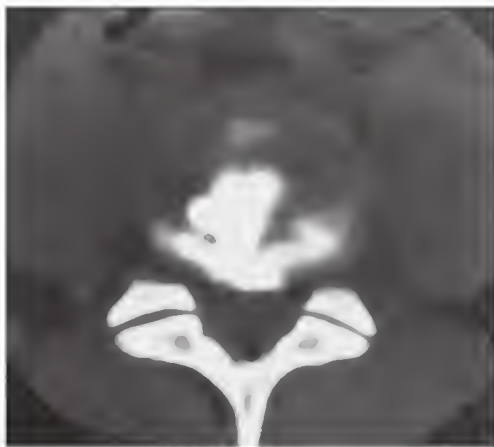


Fig. 72.8 Postdiskography computed tomography demonstrates painful grade 4 disruption of an annulus fibrosus.



Fig. 72.9 Disk degeneration. Magnetic resonance imaging demonstrates a high-intensity zone lesion in the L4/5 intervertebral disk.

CLINICAL LABORATORY TESTS

Patients with constitutional symptoms or who have failed conservative therapy may benefit from laboratory evaluation to exclude systemic processes such as infection, neoplasia, or visceral disease. The most useful tests in helping differentiate medical from mechanical low back pain is measurement of the erythrocyte sedimentation rate (ESR) or C-reactive protein level, which can suggest the presence of systemic inflammation.

Abnormalities in the complete blood count (hematocrit, leukocyte count, or platelet count) may be indicative of an inflammatory disorder, including neoplasms. Alterations in calcium concentration and alkaline phosphatase activity suggest diffuse bone disease (e.g., Paget disease, metastases). Elevated acid phosphatase activity may mirror the extent of metastases from prostatic cancer. Urinalysis can identify individuals with renal abnormalities (nephrolithiasis). Detection of occult blood in stool is a screening test for ulcers or gastrointestinal tumors.

ELECTRODIAGNOSTIC STUDIES

Electrodiagnostic studies can confirm the clinical suspicion of nerve root compression, define the distribution and severity of involvement, and document or exclude other disorders of nerves or muscles that can contribute to the patient's symptoms and signs. This tool is most helpful in cases in which peripheral entrapment, plexitis, anterior horn cell disease, or myopathy may be present. Electrodiagnostic tests can be helpful in identifying neurophysiologic abnormalities in patients in whom clinical examination (pain radiation, sensory changes, muscular weakness) does not necessarily indicate nerve root dysfunction.⁵⁸ Neurophysiologic tests can also document normal function in cases in which radiographic techniques have revealed anatomic abnormalities.

Electromyography

Electromyography (EMG) is the most sensitive tool for the diagnosis of radiculopathy.⁵⁹ EMG measures the action potentials of muscle fibers. As the nerve supplying a muscle becomes compressed, fibers to that muscle are lost and eventually replaced with regenerated fibers. This process of denervation and reinnervation occurs over time. EMG may not be able to document abnormalities until 3 to 4 weeks after the initial insult. A negative finding on EMG does not invalidate a patient's pain and sensory complaints but does make complaints of weakness and motor deficit much less likely to be based on spinal nerve injury.

Nerve conduction tests

In contrast to EMG, nerve conduction test results become abnormal as soon as nerve damage occurs.⁶⁰ Nerve conduction tests include evaluation of conduction velocity and amplitude along a segment of a peripheral nerve. They are helpful in distinguishing peripheral entrapment and neuropathy from radiculopathy. Changes on EMG may recede with resolution of the nerve impingement. However, patients in whom operative decompression provides relief of symptoms may have persistent abnormalities on EMG 1 year after surgery.⁶¹

NONMECHANICAL CAUSES OF LUMBAR SPINE PAIN

Most patients with low back pain have a mechanical cause of their symptoms and do not require any diagnostic tests (Table 72.4). However, a number of serious and potentially life-threatening disorders must be considered, including cauda equina compression, abdominal aneurysm, pancreatitis, infection, and neoplasm of various types. The first three are local disorders, but the latter often have systemic consequences. Clues to a potentially serious cause of back pain include the following:

- Constitutional symptoms: fever, weight loss, or increased pain on recumbency (e.g., sleeping in a chair) or nocturnally
- Acute, localized lumbosacral bone pain
- Visceral pain associated with alterations in gastrointestinal or genitourinary function

■ TABLE 72.4

Common degenerative causes of low back pain

	Muscle strain	Spondylolisthesis	Herniated disk	Osteoarthritis	Spinal stenosis
Age (yr)	20-60	20-40	20-60	>40	>50
Pain pattern					
Initial location	Back	Back	Leg > back	Back > leg	Leg > back
Onset	Acute	Insidious	Acute	Insidious	Insidious
Standing	+	+	—	+	+
Sitting	—	—	+	—	—
Flexion	+	—	+	—	—
Extension	—	+	—	+	+
Straight leg raise	—	—	+	—	—
Plain radiograph	—	+	—	+	+

BOX 72.1 INFECTIOUS DISORDERS AFFECTING THE LUMBOSACRAL SPINE*

Vertebral osteomyelitis

Bacterial

Tuberculous

Fungal

Spirochetal

Parasitic

Diskitis

Pyogenic sacroiliitis

*All these disorders may cause localized low back pain.

Cauda equina compression

Patients with cauda equina compression have a symptom complex that may include low back pain, bilateral sciatica, saddle anesthesia, or bladder and bowel incontinence. The most common causes of cauda equina compression include large central disk herniations, epidural abscess, hematoma, and tumor. MRI is the most sensitive diagnostic technique for detecting these lesions. Patients with cauda equina syndrome have the best opportunity for return of neurologic function if the cause of the compression can be eliminated within 48 hours.

Abdominal aortic aneurysm

An older patient with a history of vascular disease who is experiencing “tearing” or “throbbing” back pain with acute dizziness may have an expanding abdominal aneurysm. If patients complain of syncope or are hypotensive, they must be evaluated for an aneurysm on an emergency basis. Physical examination of the abdomen may reveal a pulsatile mass, abdominal bruits, and decreased pulsations in the lower extremities. Patients with expanding aneurysms may be evaluated with CT or ultrasonography, depending on the patient’s hemodynamic status. Those with an expanding aneurysm require surgical correction of the aneurysmal defect.

Infections

Patients with fever or weight loss (or both) may have an infection (or tumor) as a cause of their pain. The clinical findings in patients with a spinal infection depends on the infecting organism (Box 72.1). Bacterial infections cause acute, toxic symptoms, whereas tuberculosis and fungal infections are indolent. The pain associated with bacterial infections is persistent, present at rest, and exacerbated by motion. Physical findings include decreased range of motion, muscle spasm, and tenderness on percussion over the involved bone. Technetium bone scintigraphy or MRI can be used to investigate for the presence of local infection. MRI also detects soft tissue extension of lesions beyond the bony confines of the vertebral column. CT should be performed after MRI evaluation to delineate the bony architecture of lesions not visualized adequately with MRI (Fig. 72.10).

Definitive diagnosis of infection is based on recovery and identification of the causative organism from blood cultures or from aspirated material or

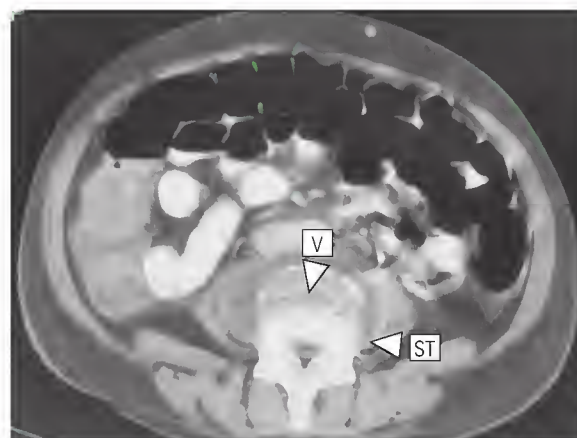


Fig. 72.10 Vertebral osteomyelitis. A computed tomography scan, axial view, demonstrates destruction of a vertebral body (V) with soft tissue extension (ST) into the paravertebral space.

biopsy samples of the lesion. Antibiotic therapy is adequate to cure most spinal infections. Surgical intervention for drainage is necessary if neurologic dysfunction has occurred or appears imminent secondary to the infection.

Vertebral osteomyelitis

Vertebral osteomyelitis follows hematogenous spread from an extraosseous source. Organisms may enter bone from nutrient arteries or from the venous plexus of Batson, a valveless system of veins that supplies the spinal column.⁶² Organisms that cause osteomyelitis include bacteria, mycobacteria, fungi, spirochetes, and parasites. The primary sources for spinal infections include the genitourinary tract, respiratory tract, and skin. The most frequently encountered organism causing infection is *Staphylococcus aureus* (in 60% of cases).⁶³ Gram-negative organisms may cause vertebral osteomyelitis in the elderly and in parenteral drug abusers (*Escherichia coli* and *Pseudomonas aeruginosa*,⁶⁴ respectively). In patients who have undergone surgery or suffered trauma to the spine, generally nonpathogenic organisms (diphtheroids, *Staphylococcus epidermidis*) may be associated with an indolent infection of the vertebral column.⁶⁵ Brucellosis may develop in workers in the meat-processing industry.⁶⁶ Tuberculous and fungal infections of the vertebral column occur most often in the elderly and other immunocompromised individuals. The clinical findings in a patient with tuberculous spondylitis are an insidious onset (potentially over a period of months to years) of pain over the involved vertebrae, low-grade fever, and weight loss (Fig. 72.11).⁶⁷

Disk infection

Spondylodiskitis occurs in the setting of concurrent extraspinal infection,⁶⁸ and in adults it is also associated with lumbar disk surgery. The ESR is almost universally elevated in the case of established disk space infections and often exceeds 100 mm/hr along with the presence of leukocytosis.⁶⁹ Plain radiographs may be normal at the onset of infection but will demonstrate increasing destruction with prolonged duration of infection



Fig. 72.11 Pott disease affecting the lumbosacral spine at L3 and resulting in rotatory scoliosis and lateral calcification.



Fig. 72.12 Infection of the intervertebral disk space. A plain lateral radiograph of the lumbar spine shows narrowing of the L5/S1 disk space with new bone formation at the L5 endplate (arrow) and a soft tissue mass pushing the great vessels anteriorly. This finding of narrowing of the disk space and new bone formation with displacement of the great vessels strongly suggests the diagnosis of spinal infection with a soft tissue abscess.

(Fig. 72.12). Radiographic evidence of established disk infection includes the following:

- Symmetric destruction of the adjacent endplate surfaces of two vertebrae
- Loss of disk height
- Reactive new bone formation
- Sclerosis of the bone endplates, with or without bone destruction or formation
- Soft tissue abscesses
- Kyphosis or subluxations after significant bone destruction has occurred

On CT, changes in the disk space and vertebral endplates can be seen, as can soft tissue abscesses (Fig. 72.13). The diagnosis is confirmed by identifying the causative organism from blood cultures, aspirated disk material, or biopsy specimens of infected adjacent bone. Six weeks of parenteral antibiotics and possibly additional oral antibiotic therapy usually provide adequate treatment for patients with radiologic evidence of disk space

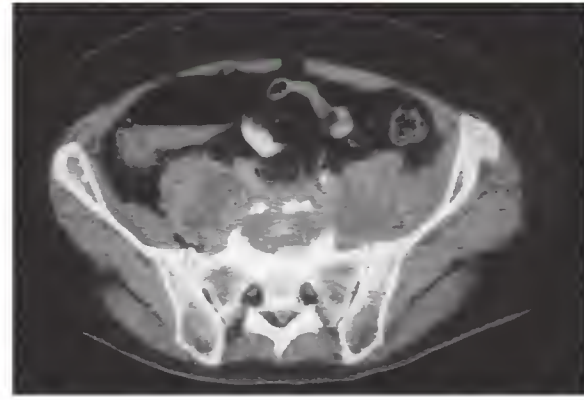


Fig. 72.13 Spinal infection imaged by computed tomography of the lumbar spine. At the L5/S1 level, lucent areas in both psoas muscles and destructive changes in the intervertebral disk space suggest the presence of spinal infection with bilateral abscesses.

infection and a positive culture. The ESR provides a method of assessing the efficacy of therapy in these patients.

Surgical intervention, including drainage and débridement of spinal infections, is indicated in patients in whom paraparesis or paraplegia develops. The following factors appear to increase the risk for neurologic deficits:

- Older age
- Cervical or thoracic infection
- Infection with staphylococci as opposed to other organisms
- Coexisting diabetes or rheumatoid arthritis

When surgical treatment is selected, controversy exists concerning the use of bone grafts to achieve bone fusion. The experience of the spinal surgeon at the time of surgical débridement can help determine the appropriate course of action.

Pyogenic sacroiliitis

Pyogenic sacroiliitis is an unusual form of septic arthritis.⁷⁰ The disease is associated with acute symptoms, severe sacroiliac joint pain, and fever. This entity can be seen in postpartum women and also in injection drug users. Diagnosis of the causative organism may be achieved by blood cultures, fluoroscopically directed fine-needle aspiration, or open biopsy. Antibiotic therapy for 6 weeks is usually adequate to eradicate the infection without the need for surgical drainage.

Neoplasms

Tumors of the spinal column or spinal cord may cause pain at night or during recumbency. Both benign and malignant neoplasms can cause these symptoms. Nocturnal pain may be due to swelling of neoplastic tissues associated with inactivity in the supine position or to stretching of neural tissues over the neoplastic mass. A number of benign and malignant tumors are associated with involvement of the lumbosacral spine (Box 72.2). Benign lesions tend to cause local pain and involve the posterior elements of vertebrae. Malignant lesions cause more diffuse pain and systemic symptoms and more typically involve the anterior elements of vertebrae.

Patients with malignancies have pain that is gradual in onset but persistent and increasing in intensity. Physical examination shows localized tenderness over the lesion along with neurologic dysfunction if neural elements are compressed. Radiographic evaluation is useful in detecting the location and characteristics of the neoplastic lesion.

Osteoid osteoma

Osteoid osteoma is a benign tumor of bone. Approximately 7% of osteoid osteomas occur in the spine, most frequently in the lumbar area.⁷¹ The pain is aching and boring and frequently worse at night. The appearance of marked paravertebral muscle spasm and sudden onset of nonstructural scoliosis in a young adult requires an evaluation for this lesion, which typically occurs on the concave side of the scoliosis. The pain is often relieved by low-dose NSAID therapy. Hyperemia of the tumor may cause swelling and erythema of the skin if the lesion is superficial.

The radiographic finding of a lucent nidus with a diameter of 1.5 cm and a surrounding well-defined area of dense sclerotic bone is virtually pathognomonic of osteoid osteoma (Fig. 72.14). Bone scan or CT should be

BOX 72.2 NEOPLASTIC LESIONS OF THE LUMBOSACRAL SPINE***Benign**

Osteoid osteoma
 Osteoblastoma
 Osteochondroma
 Giant cell tumor
 Aneurysmal bone cyst
 Hemangioma
 Eosinophilic granuloma
 Sacroiliac lipoma

Malignant

Multiple myeloma
 Chondrosarcoma
 Chordoma
 Lymphoma
 Skeletal metastases

Spinal cord tumors

Extradural metastases
 Intradural-extramedullary
 Neurofibroma
 Meningioma
 Intramedullary
 Ependymoma
 Astrocytoma

*All these lesions may cause localized low back pain.



Fig. 72.14 Osteoid osteoma. A plain radiograph of the thoracic spine demonstrates sclerosis affecting the right pedicle of T11.

performed if an osteoma is suspected and not found on plain radiographs (Fig. 72.15).^{72,73} Treatment of an osteoid osteoma is simple excision of the nidus and surrounding sclerotic bone.

Other primary spinal tumors

Neoplastic lesions may also occur inside the central spinal canal. These intraspinal neoplasms may be extradural, between bone and the outermost covering of the spinal cord (the dura); intradural-extramedullary, between the dura and the spinal cord; and intramedullary, in the spinal cord proper. Extradural tumors are most commonly metastatic in origin. Intradural-extramedullary tumors are primarily meningiomas, neurofibromas, or lipomas (Fig. 72.16). Intramedullary tumors are ependymomas or gliomas. MRI is useful in defining the location, size, and character of intraspinal lesions.

Multiple myeloma

Multiple myeloma is the most common primary malignancy of bone in adults and accounted for 27% of biopsied bone tumors in one series.⁷⁴ Patients typically range in age from 50 to 70 years. Low back pain is the initial complaint in 35% of patients. The pain is aching and intermittent at onset, aggravated by weight bearing, and improved with bed rest. Some patients may have radicular symptoms.⁷⁵ Significant neurologic dysfunction,



Fig. 72.15 Osteoid osteoma. Bone scintigraphy (posterior view) demonstrates increased uptake in T11. No other area of increased uptake in the skeleton is present.

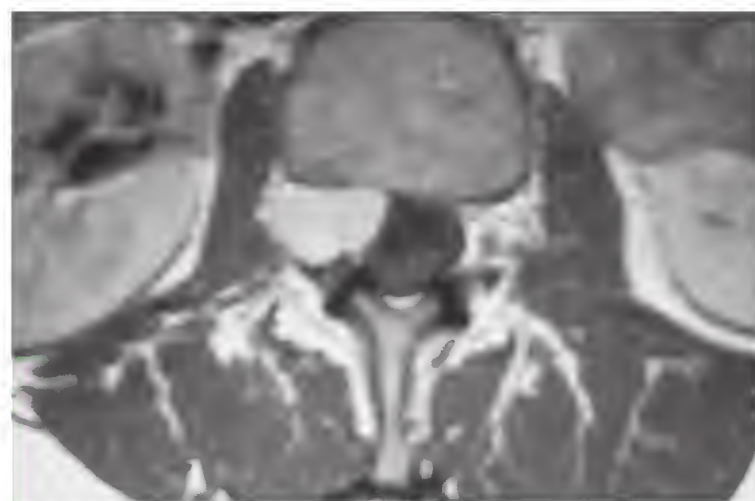


Fig. 72.16 Neurofibroma. A transverse T1-weighted magnetic resonance image following intravenous gadolinium administration shows an enhancing mass occluding the right neural foramen of L2. Note how local bone erosion has widened the neural foramen.

including paraplegia, occurs more commonly with solitary plasmacytoma than with multiple myeloma.⁷⁶ Physical examination may demonstrate diffuse bone tenderness, fever, pallor, and purpura in the later stages of the illness. Spinal cord compression may occur with vertebral body collapse. Abnormal laboratory results may include anemia, leukocytosis, thrombocytopenia, elevated ESR, hypercalcemia, hyperuricemia, elevated creatinine, and a positive Coombs test. An increase in serum proteins is secondary to the presence of abnormal immunoglobulins in any of the five classes. Urinalysis may detect Bence Jones protein formed by the production of excess immunoglobulin light chains. Bone marrow aspiration or biopsy reveals an excess number of plasma cells of varied histologic grades.

Plain radiographs demonstrate osteolysis without reactive sclerosis and sparing of the posterior elements of the spine (Fig. 72.17).⁷⁷ Bone scintigraphy does not detect myeloma because of the absence of a reactive component of osteoblasts to the myeloma cells. MRI and CT are better techniques for identifying the presence and extent of myeloma lesions in bone and soft tissues. MRI is able to detect spinal bone marrow involvement in patients with asymptomatic myeloma. Myeloma is treated with chemotherapeutic agents to control growth of the malignant plasma cells. In patients with cord compression, decompression laminectomy is indicated, with or without local radiotherapy.⁷⁸

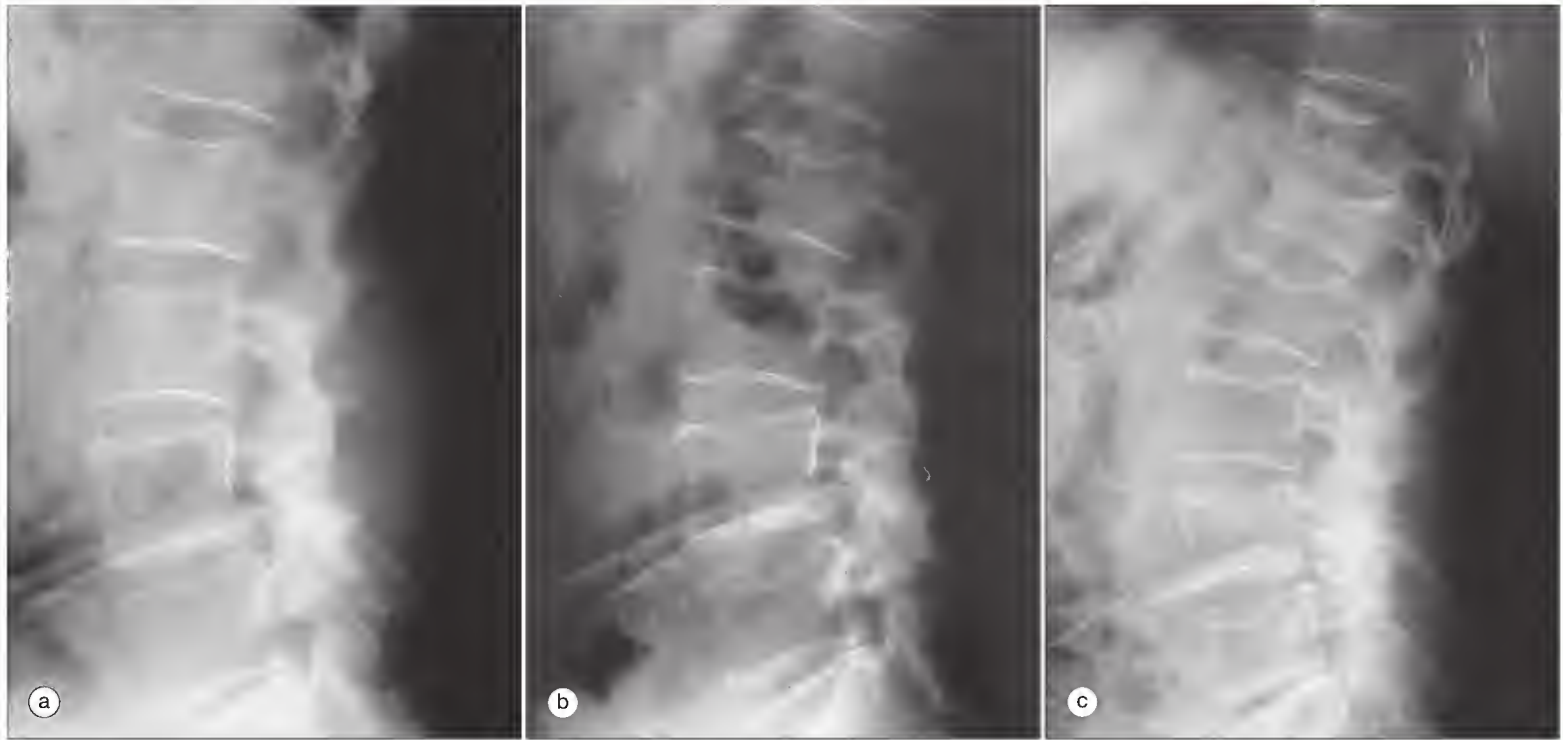


Fig. 72.17 Multiple myeloma. A series of plain radiographs taken over a 3-month period show progressive osteopenia and pathologic compression fractures. (a) Initial evaluation. (b) At 12 weeks. (c) At 14 weeks. The diagnosis was made 12 weeks after the initial evaluation.

Skeletal metastases

Skeletal metastases are 25 times more common than primary tumors as the cause of neoplastic lesions in the spine. Autopsy results demonstrate that metastases to the thoracolumbar spine develop in 70% of patients with primary tumors.⁷⁹ Common primary sources of skeletal metastases include tumors of the breast, prostate, lung, kidney, thyroid, colon, uterine cervix, and bladder. Physical examination may demonstrate pain on palpation over the affected bone. Neurologic abnormalities are indicative of nerve root or spinal cord impingement. Laboratory findings may be abnormal depending on the underlying malignancy. Histologic features of biopsy specimens may suggest the identity of the primary tumor, but some lesions are too undifferentiated for identification.

Radiographic abnormalities depend on the character of the underlying malignancy. Kidney and thyroid metastases are typically osteolytic, whereas colon lesions are osteoblastic. Mixed lytic and blastic lesions are noted with breast, lung, prostate, or bladder tumors (Fig. 72.18). Plain radiographs may not show any abnormalities until 30% to 50% of bone calcium is lost.⁸⁰ Bone scans are positive in more than 85% of patients with metastases. MRI is able to show tumor in the spinal cord, extraosseous extension, and bone marrow replacement, whereas CT is more helpful in detecting cortical bone involvement and bone mineralization.⁸¹

Treatment of metastatic disease of the spine is directed toward palliation of pain. Radiotherapy is useful to control spinal pain. Decompressive laminectomy is recommended for patients in whom neurologic dysfunction has recently developed.

Rheumatologic causes

There are a number of rheumatologic causes of back pain that are discussed in detail elsewhere in this volume, including polymyalgia rheumatica (Chapter 156), fibromyalgia (Chapter 80), and ankylosing spondylitis (Chapter 115).

Primary bone disorders

Acute localized bone pain is usually caused by a fracture or expansion of bone (Box 72.3). The medical history, including a review of systems, may suggest the underlying cause of the patient's back pain (kidney stones with hyperparathyroidism, chronic cough with sarcoidosis). Physical examination often shows localized tenderness, typically with surrounding muscle spasm. Anemia or an increased ESR should raise suspicion for an inflammatory process. Serum chemistry may detect abnormalities in calcium metabolism associated with vitamin D deficiency (osteomalacia) or an



Fig. 72.18 Metastatic prostate cancer. A plain radiograph demonstrates osteoblastic lesions replacing the lower lumbar vertebral bodies and most of the bony pelvis.

elevated parathyroid hormone level (hyperparathyroidism). Elevations in alkaline phosphatase may suggest increased bone activity associated with neoplasms or Paget disease.

Plain radiographs may show osteopenia (Fig. 72.19) and areas of sclerosis related to healed fractures or Paget disease (Fig. 72.20). Microfractures cause significant pain and may not be detected with plain films. Bone scintigraphy is useful in this context for detection of the increased bone activity associated with fractures, and MRI can detect abnormalities of bone marrow that are associated with alterations in bone mineral density.

Therapy for patients with acute localized bone pain must be tailored to the specific disease process causing the illness. In those with severe bony compromise, stabilization of the spine may require bone grafting or rod placement (or both) (Fig. 72.21). Vertebroplasty can be used to treat vertebral compression fractures that remain painful and disabling after 6 weeks.⁸² In this procedure, methylmethacrylate is injected through a cannula into

BOX 72.3 ENDOCRINOLOGIC, HEMATOLOGIC, AND MISCELLANEOUS DISORDERS AFFECTING THE LUMBOSACRAL SPINE***Endocrinologic/metabolic**

Osteoporosis
Osteomalacia
Hyperparathyroidism

Hematologic

Hemoglobinopathy
Myelofibrosis
Mastocytosis

Miscellaneous

Paget disease
Subacute endocarditis
Sarcoidosis
Retroperitoneal fibrosis

*All these disorders may cause acute localized bone pain.

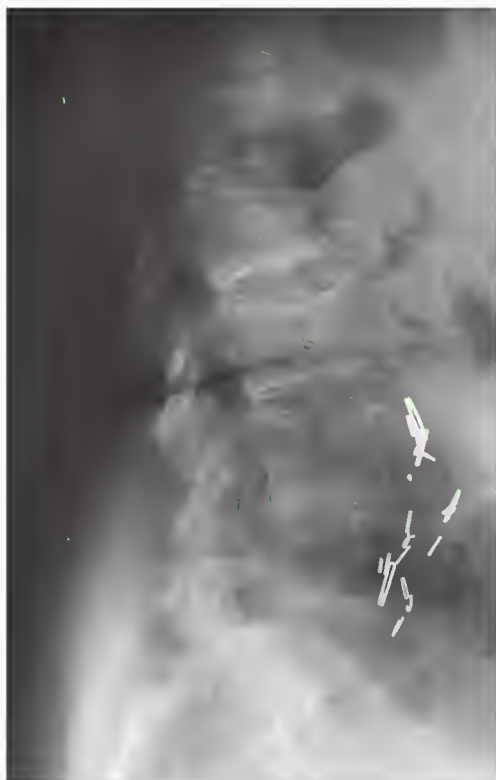


Fig. 72.19 Osteoporosis. A plain radiograph, lateral view, demonstrates diffuse osteopenia and multiple compression fractures.



Fig. 72.20 Paget disease. A plain radiograph demonstrates osteosclerotic alterations of the bony trabeculae in the L2 vertebral body. The body is slightly increased in size. This patient had an elevated serum alkaline phosphatase level.



Fig. 72.21 Plasmacytoma. A postoperative plain radiograph, lateral view, demonstrates placement of rods to stabilize the spine and prevent neurologic damage.

BOX 72.4 VISCEROGENIC PAIN REFERRED TO THE LUMBAR SPINE***Vascular**

Expanding aortic aneurysm

Genitourinary

Endometriosis
Tubal pregnancy
Kidney stone
Prostatitis

Gastrointestinal

Pancreatitis
Peptic ulcers
Colon cancer

*All these disorders can cause referred pain to the lower back region.

the collapsed vertebral body. The cement stabilizes the fracture and may result in rapid relief of pain. In rare circumstances the cement will escape from the vertebral body. Kyphoplasty uses an inflatable bone tamp to reduce kyphotic fractures.⁸³ These procedures may also be associated with rapid relief of spinal pain in individuals with acute and subacute osteoporotic compression fractures. The efficacy of bone augmentation procedures is debated.

Herpetic neuralgia

Herpes zoster, also known as *shingles*, results from reactivation of latent varicella zoster infection within the dorsal root ganglia. It is characterized by a painful, unilateral vesicular eruption, usually in a dermatomal distribution. The thoracic and lumbar dermatomes are the most commonly involved sites of herpes zoster. Approximately 75% of patients have prodromal pain before the rash appears, which leaves a time frame during which the source of the acute back pain can be misconstrued as a sprain or strain. A common consequence of herpes zoster is postherpetic neuralgia.⁸⁴

Pain referred from other visceral organs

Disorders of the vascular, genitourinary, and gastrointestinal systems can cause stimulation of sensory nerves and the attendant perception of pain both in the damaged area and in superficial tissues supplied by the same segments of the spinal cord (Box 72.4). Colicky pain occurs in peristaltic waves and is associated with a hollow viscus, such as the ureter,



Fig. 72.22 Herniated intervertebral lumbar disk. A sagittal magnetic resonance image demonstrates extrusion of the L4-5 disk.

uterus, gallbladder, or colon. Throbbing pain is associated with vascular structures.

MECHANICAL CAUSES OF LOW BACK PAIN

Low back pain (also commonly called axial low back pain, mechanical low back pain, or nonspecific low back pain) can be defined as low back pain originating from but not limited to the facet joint, intervertebral disk, sacroiliac joint, muscles, and ligaments. This definition excludes malignancy; infectious, inflammatory, and rheumatologic causes; radiculopathy; and myelopathy. Patients may commonly have low back pain concomitantly with radiculopathic pain from spinal nerve root compression. Patients may also commonly have concurrent myofascial and centrally mediated neuropathic pain. Although the majority of patients with radicular symptoms improve with time, those with axial low back pain account for the largest group of patients with chronic persistent pain.

Spondylolysis and spondylolisthesis

Spondylolysis is a break in the pars interarticularis. If the defect permits displacement of one vertebra on another, it is termed spondylolisthesis (Fig. 72.22). Spondylolysis, with or without spondylolisthesis, is a common structural abnormality; however, only 5% of patients with the condition become symptomatic. Most patients with symptomatic spondylolisthesis complain of pain when their spine is placed in extension (increased displacement) as opposed to flexion (which tends to normalize vertebral body position). Nonoperative measures include patient education, flexion exercises, and a flexion back support. The development of progressive intervertebral disk degeneration at the listhetic level in the third decade of life typically coincides with the development of increasing back pain. These individuals may benefit from spinal fusion.⁸⁵

Intervertebral disk disorder

Mechanisms of pain

Degenerative disk disease can be associated with back pain by several mechanisms. The outer third of the lumbar disk anulus receives innervation from the sinuvertebral nerve or recurrent nerve of Lushcka.⁸⁶ Injury to the annular fibers, in the form of either an annular tear or herniation of the nucleus pulposus, can cause local inflammation and thus both chemical and mechanical sensitization of these annular fibers. Disk herniations can put tension on and sensitize the posterior longitudinal ligament and cause pain. Neural and vascular ingrowth into regions of the annular tear can create a chronic nociceptor. Because of noxious stimuli, the vertebral segment may attempt to splint itself, which can result in limited range of motion, regional areas of tenderness in the back, muscle spasm, taut bands, and trigger points. Spasms, taut bands, and trigger points can be painful in and of themselves but often stem from injury to deeper spinal structures.

Clinical features

Symptoms are often first seen in the 20- to 50-year-old age group. They are typically worse with prolonged sitting, standing, and forward bending and



Fig. 72.23 Herniated intervertebral disk. Axial magnetic resonance imaging demonstrates a large left paracentral disk extrusion.

are often relieved with walking and frequent positional shift. Symptoms can radiate to the limb without nerve compression via somatic referral. A herniated nucleus pulposus is associated with leg pain exacerbated by flexion of the lumbar spine or prolonged sitting. Individuals may experience sensory or motor deficits, or both. Bed rest does not accelerate recovery.⁸⁷

Investigations

If the pain persists and the patient wishes to consider more invasive therapy (e.g., injections or surgery), MRI or CT evaluation should be performed (Fig. 72.23; also see Fig. 72.22). MRI can demonstrate disk desiccation, focal protrusions, high-intensity zone lesions, and vertebral endplate changes. Degenerative disk disease can also be an asymptomatic finding that needs to be taken into account when interpreting the imaging results.

Treatment

For patients with disk herniation, persistent pain, and limitations in function, fluoroscopically guided epidural corticosteroid injections may be useful.⁸⁸ Corticosteroid is injected into the epidural space transforaminally, close to the location of the nerve root compression. Approximately 66% to 84% of patients will have benefit that is sustained even at 1-year follow-up.^{89,90} Maximal benefit is typically noted after 4 weeks. Leg symptoms usually respond better than axial symptoms do.

If injections are effective in alleviating the leg pain, the patient should be encouraged to increase physical activity, though with limitation of activities that increase intradiscal pressure, such as heavy lifting or sitting for long periods.

If conservative measures have not been effective, the patient may consider surgical intervention. The choice of surgical procedure (laminectomy with discectomy vs. microdiscectomy) is beyond the scope of this chapter. Some studies have shown that discectomy produces better pain relief than nonsurgical treatment does over a 4-year period, but outcomes of operative and nonoperative therapy are similar at 10-year follow-up.⁹¹ The Spine Patient Outcomes Research Trial (SPORT) demonstrated that surgery may offer more rapid relief of radicular symptoms and that the symptomatic benefit of surgery, as compared with nonoperative therapy, extends to 4 years. Of note, the intention-to-treat analyses in SPORT are not readily interpretable because of high rates of crossover from operative to nonoperative and from nonoperative to operative therapy. Thus, the conclusions of the study are based on the more interpretable “as-treated” analyses, which afford less protection against bias.^{92,93} Needless to say, the success of any of these surgical procedures is dependent on choosing patients who require surgery. Surgery for radicular symptoms is helpful in relieving leg pain, but it has not been shown to improve back pain.

Zygapophyseal (facet) joint syndrome

The zygapophyseal joint can also cause low back pain. Articular degeneration with zygapophyseal joint sclerosis may be associated with back pain.

Patients with facet joint syndrome can often experience back and buttock pain that is worse with standing and walking or lumbar extension and alleviated with forward flexion. Diagnosis of symptomatic facet syndrome requires anesthetization of the joint via an intraarticular block or anesthetization of the joint's innervation. At least two blocks are required to be confident that the facet joint is mediating the pain because of the high incidence of non-specific or placebo effects.⁸⁴

Lumbar spinal stenosis

Spinal stenosis can be defined as narrowing of the spinal canal secondary to degenerative changes that occur in the spinal canal with time (Figs. 72.24 and 72.25). Other forms of spinal stenosis occur secondary to congenital abnormalities and traumatic, postsurgical, or metabolic disorders. Patients



Fig. 72.24 Spinal stenosis. Magnetic resonance imaging, axial view, of the L3/4 disk level demonstrates osteophyte overgrowth, disk degeneration, and ligamentous hypertrophy. The cauda equina is compressed in the central area of the canal.

with spinal stenosis experience leg pain with standing or walking—the classic syndrome of neurogenic claudication.

The prevalence of narrowing of the lumbar spinal canal increases with age. Midsagittal narrowing to less than 10 mm is abnormal.⁹⁵ Myelographic, CT, and MRI studies have all shown that 20% to 25% of asymptomatic individuals older than 40 years have marked narrowing of the lumbar spinal canal. These *in vivo* measurements support the conclusion drawn from postmortem morphometry studies that many cases of “morphologic” lumbar spinal stenosis have no recognizable clinical expression.

Etiology and pathogenesis

The lumbar spinal canal is bounded anteriorly by the lumbar disks, vertebral bodies, and the posterior longitudinal ligament; laterally by the laminae and facet joints; and posteriorly by the ligamentum flavum (Fig. 72.26). The nerve root canals through which the spinal nerves exit the spinal canal are bounded anteriorly by the posterior surface of disks and vertebral bodies, posteriorly by facet joints and the pars interarticularis, and medially by the central vertebral canal.⁹⁶ Stenosis develops when relative narrowing of the dimensions of the lumbar spinal canal occurs. Many cases of lumbar spinal stenosis syndrome are the result of both congenital and acquired narrowing of the lumbar spinal canal, thus limiting the utility of any rigid etiologic classification.⁹⁷

Pathologic studies of the lumbar nerve root canal show that lumbar spondylosis is associated with a reduction in the vertical dimension because of disk space narrowing, posterior bulging of the intervertebral disks, retropulsion of remnants of the annulus fibrosus, and the formation of

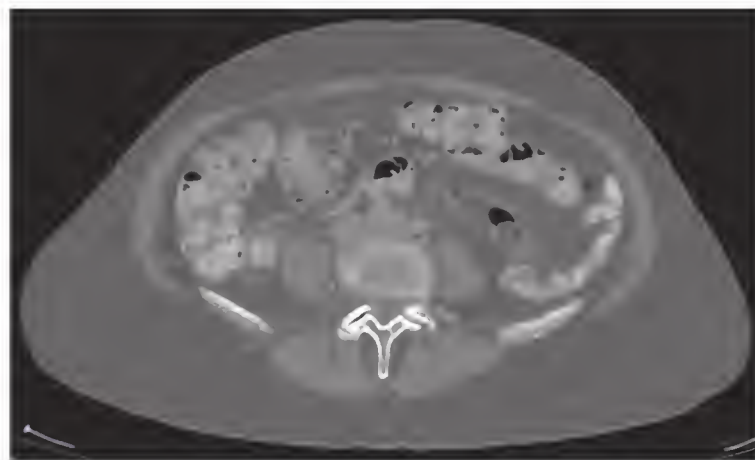


Fig. 72.25 Lumbar spine stenosis. Computed tomography shows a thickened ligamentum flavum, facet joint hypertrophy, and posterior disk bulging. Note the absence of epidural fat along with a trefoil deformity of the lumbar spinal canal.

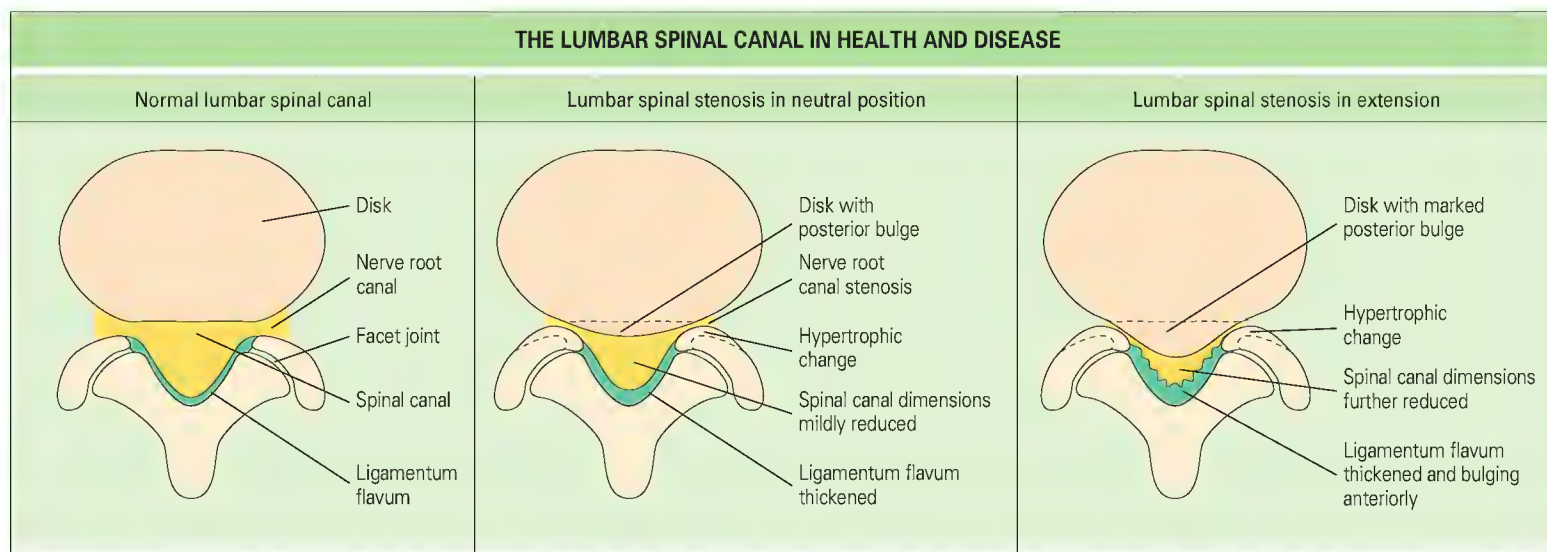


Fig. 72.26 (Left) The normal spinal canal. (Center) The spinal canal with central spinal and nerve root canal stenosis in the neutral position. (Right) The effect of lumbar extension on the spinal canal.

sclerotic ridges around the vertebral endplates. Osteoarthritic facet joints project osteophytes anteriorly from the superior articular processes, and synovial effusions, hemarthroses, and derangements of meniscal synovial folds are often present. Extension and rotation result in significant encroachment on the nerve root complex.⁹⁸ Flexion-extension myelography has shown consistent anterior displacement of the entire lumbar dural sac on extension as a result of shortening and thickening of the ligamentum flavum.⁹⁹

The precise mechanisms that produce neurogenic claudication are poorly understood. Neuropathologic assessment of patients has shown chronic segmental compression of nerves at regular intervals corresponding to the site of myelographic obstruction, together with confirmatory histologic features of nerve fiber damage. Abnormalities of the pial vessels have been reported,¹⁰⁰ and some patients have high cauda equina cerebrospinal fluid pressure.¹⁰¹ Any or all of these factors may play a role in the genesis of pseudoclaudication.

Clinical features

The most characteristic symptom is neurogenic claudication, defined as discomfort in the buttock, thigh, or leg on standing or walking that is relieved by rest and not produced by peripheral vascular insufficiency. Such discomfort is generally described as pain but is occasionally appreciated as numbness, weakness, or various combinations of these symptoms.

Neurogenic claudication is usually relieved by lying down, sitting, leaning forward on a shopping cart, or adopting a bent-forward position while walking (simian stance). The symptoms and signs typically affect multiple dermatomes. Some 40% of patients have bilateral symptoms. Restriction of straight leg raising (Lasègue sign) is present in only 10% of patients with lumbar spinal stenosis. Ankle jerks are absent in 40%, knee jerks are absent in 10%, and a small percentage have sensory loss or weakness.¹⁰² Anterior thigh numbness as seen in meralgia paresthetica can be produced by stenosis at the upper lumbar levels.¹⁰³

Bowel and bladder sphincter disturbances are relatively uncommon. Their presence constitutes an absolute indication for surgery to stabilize the deficit and allow some potential for recovery of bladder function.¹⁰⁴ Rarely, intermittent priapism has been reported as a manifestation of lumbar spinal stenosis.¹⁰⁵

A systematic review of the accuracy of clinical examination for the diagnosis of lumbar spinal stenosis that encompassed four studies and 741 patients found that having no pain when seated, improvement of symptoms when bending forward, the presence of bilateral buttock or leg pain, and neurogenic claudication were the most useful for diagnosing lumbar spinal stenosis. Additionally, having a wide-based gait and an abnormal Romberg test result also increased the likelihood of the clinical syndrome of lumbar spinal stenosis. Absence of neurogenic claudication decreased the likelihood of the diagnosis.¹⁰⁶

Investigations

The purpose of investigation is to confirm the diagnosis of lumbar stenosis syndrome and exclude other causes. Changes on plain films are insensitive for the diagnosis of spinal stenosis but provide information regarding alignment and general degenerative changes. Degenerative changes include narrowing of disk spaces, zygapophyseal joint osteoarthritis, and degenerative spondylolisthesis, commonly at L4/5.

CT can demonstrate articular facet hypertrophy, enlargement of laminae, hyperplasia, ossification of the ligamentum flavum, and disk prolapse. The technique allows definition of the osseous margins and the shape of the lumbar spinal canal. A trefoil shape of the lumbar canal is typical of severe lumbar spinal stenosis.

Contrast-enhanced myelography has largely been eclipsed by MRI and CT. Some physicians use contrast-enhanced myelography for surgical planning, however. Demonstration of obstruction to the flow of dye can be dependent on posture, with compression of the dural sac by the ligamentum flavum and disk being more severe in extension. The combination of contrast-enhanced myelography and CT directed at specific levels can demonstrate lateral recess or nerve root canal stenosis with greater definition than CT or myelography alone can.

MRI is the noninvasive study of choice. However, asymptomatic changes related to stenosis occur in 21% of subjects older than 60 years. MRI and contrast-enhanced CT are comparable in demonstrating spinal stenosis in any one segment.¹⁰⁷

Electrodiagnostic studies can also be helpful in the diagnosis of spinal stenosis. Of 37 patients with surgically proven lumbar spinal stenosis, 34 had an abnormality noted on EMG with evidence of one or more radiculopathies. Much of the usefulness of EMG lies in excluding peripheral neuropathy and peripheral nerve entrapment syndromes.¹⁰⁸

BOX 72.5 DIFFERENTIAL DIAGNOSIS OF LUMBAR SPINAL STENOSIS SYNDROME

Lumbar spondylosis without spinal stenosis
Herniated nucleus pulposus
Atherosclerotic occlusive peripheral vascular disease
Spinal tumors
Restless legs syndrome
Peripheral nerve entrapment
Cervical and thoracic spinal stenosis
Peripheral neuropathy
Anterior tibial compartment syndrome

Differential diagnosis

A number of conditions must be distinguished from lumbar spinal stenosis syndrome (Box 72.5). Peripheral vascular disease can be diagnosed on the basis of the history, physical examination, exercise, ankle brachial index, and vascular surgical consultation.¹⁰⁹ A herniated nucleus pulposus causing sciatica is associated with an abrupt onset. Patients with hip osteoarthritis have diminished range of motion and pain provoked by hip internal rotation. The possibility of two pain generators is common in this aging population. Trochanteric bursitis can cause regional thigh pain and can mimic radicular pain. Peripheral nerve entrapment may produce extremity pain. Lumbar spinal stenosis may be associated with stenosis in the cervical and thoracic areas, a combination that gives rise to complex manifestations. For example, myelopathy from more rostral narrowing of the spinal canal will result in difficulty walking and sphincter disturbance.¹¹⁰ Sacral fractures can entrap or irritate sacral nerve roots in the foramen and cause radicular pain referred to the buttock or thigh. Vascular disease can also be referred to the buttock and posterior part of the thigh. Hamstring injuries and ischial bursitis are soft tissue disorders that can refer symptoms to the posterior aspect of the thigh, whereas trochanteric bursitis and iliotibial band tightness can be associated with pain in the lateral aspect of the thigh.

MANAGEMENT OF LUMBAR SPINE DISORDERS

No single form of therapy is effective for all forms of back pain. Patients with systemic causes must be treated with specific therapies effective for their underlying disease as discussed earlier. The following section provides guidelines for the management of nonspecific back pain.

- Bed rest for more than 2 days is not helpful and may debilitate the patient. During the acute phase, patients are encouraged to ambulate as tolerated.
- Relief of pain may be accomplished most safely with nonprescription analgesics or nonsteroidal medication. Spinal manipulation may be helpful during the first 4 weeks in patients without radiculopathy.
- Low-stress aerobic activities can be started safely in the first 2 weeks of symptoms. Trunk muscle exercises should be delayed for at least 2 weeks.
- Patients should be encouraged to return to usual activities, both vocational and recreational, as soon as possible.

Frequently, the ability of patients to cope with their symptoms can be helped by careful explanation of the cause of the symptoms. The key to conservative management lies in the patient's acceptance of mild disability because most continue to be symptomatic in the longer term.

Conservative approaches

Components of a conservative management program for patients with low back pain include education, controlled physical activity, bed rest, exercise, and medication therapy in the form of NSAIDs and muscle relaxants. Bed rest should be kept to a minimum or eliminated. Scientific data support the recommendation to continue regular activity as tolerated rather than bed rest.¹¹¹

Physical modalities

Physical modalities may be used to diminish symptoms for short periods. Such forms of therapy include ice massage, hot packs, diathermy, ultrasound, and transcutaneous electrical nerve stimulation. These therapies may be applied by patients themselves or by a therapist. They are most useful as an adjunct to other treatments rather than as sole therapy.

Exercise

Physical therapy, particularly in the form of therapeutic exercises, may be particularly helpful in controlling mechanical low back pain.¹¹² As a generalization, patients with mechanical disorders of the disks prefer extension exercises, whereas those with stenosis prefer flexion exercises. In most circumstances, patients eventually perform a combination of both forms of exercise.

Patients may feel worse before they feel better following an exercise program. In one study of patients with chronic low back pain,¹¹³ 2 months was required before benefit was noted. The treating physician should find a physical therapist who is interested in taking care of patients with back pain and communicate concerns about patients to the therapist.

Exercises may also play a significant role in preventing back pain in asymptomatic individuals. In a comparison with educational strategies, mechanical support, and risk modification, exercises that strengthen the back and abdominal muscles were the only intervention associated with a decreased frequency and duration of low back pain.¹¹⁴

Oral drug therapy

The types of medication used for low back pain include analgesics, NSAIDs, muscle relaxants, and neuropathic pain medications. The potential toxicities must also be considered when choosing an agent for a patient.

Analgesics

Patients may benefit from acetaminophen. A slow-release form of the drug may allow a more prolonged analgesic effect in patients with back pain. The drug has a synergistic effect with NSAIDs and may be used in combination to increase analgesia without increasing toxicity.

Tramadol, a synthetic analgesic that binds opiate μ -receptors, is a useful agent that can be given independently or in combination with nonsteroidal drugs for the relief of chronic low back pain. This agent is most helpful for individuals who are unable to tolerate NSAIDs.

Narcotic analgesia should be reserved for patients with severe, functionally limiting pain and be used along with NSAIDs, other adjuvant analgesics, and a bowel regimen. Stronger narcotic analgesia should be reserved for patients who are unable to perform activities of daily living because of persistent pain. Continuation of narcotic analgesics in the outpatient setting should be discouraged unless the patient is committed to maximizing physical function through increased activity.¹¹⁵

Nonsteroidal antiinflammatory drugs

NSAIDs have analgesic properties in low doses and antiinflammatory properties at higher doses. The onset of action of the agents is important. With acute back pain, a rapid onset of action is important to control the symptoms quickly. With chronic pain, the onset of action is not as important as efficacy and safety over extended periods.

NSAIDs as a class of agents are effective therapy for low back pain.¹¹⁶ No specific selection criteria for the choice of a single agent have been established. Cyclooxygenase-2 (COX-2)-selective inhibitors are indicated for the treatment of low back pain in individuals with a history of peptic ulcer disease or gastrointestinal intolerance of dual COX-1/COX-2 inhibitors. Chronic use in the elderly is discouraged, and careful use of opiates may be safer.

Muscle relaxants

Muscle relaxants used for patients with low back pain work centrally to affect the activity of the muscle stretch reflexes. Drugs, including cyclobenzaprine, carisoprodol, and chlorzoxazone, have been shown to be more effective than placebo in treating patients with muscle spasm and, in combination with NSAIDs, augment the efficacy of the NSAID.¹¹⁷ The combination of an NSAID and a muscle relaxant offers significant relief of pain when compared with other combinations of therapies, including those with narcotics. The major side effects of muscle relaxants are drowsiness, headache, dizziness, and dry mouth.

Neuropathic pain agents

Tricyclic antidepressants have been shown in double-blind studies to relieve chronic pain. Low doses may be adequate to control symptoms.¹¹⁸ These drugs do not work immediately and may need to be continued for a number of weeks before decreased symptoms are noted. Selective serotonin reuptake inhibitors (sertraline, fluoxetine) are not as effective as tricyclics for relief of chronic pain.¹¹⁹ Mixed norepinephrine and serotonin reuptake inhibitors (venlafaxine and duloxetine) seem to have a more effective role in the management of chronic pain. Duloxetine has a Food and Drug Administration

indication for the treatment of chronic musculoskeletal pain and is often helpful for the treatment of chronic low back pain.

The second major class of neuropathic pain agents includes antiepileptic medications such as pregabalin, gabapentin, and carbamazepine. Neuropathic pain medications have a potential role when pain is mediated by both peripheral and central mechanisms. Chronic axial low back pain may also benefit from a trial of these agents. Strong evidence for the use of these agents is lacking, but judicious use can improve pain and quality of life and help restore sleep.

Injection therapy

Local or regional anesthesia given by injection is part of the therapeutic regimen for some patients with low back pain. The region injected may be an area of local trauma or a myofascial trigger point.¹²⁰ Trigger points are areas of the muscle that are painful at rest, prevent full lengthening of the muscle, weaken the muscle, refer pain in the muscle group on direct palpation, and cause a local contraction when palpated. A study by Garvey and colleagues¹²¹ suggested that needling the area with or without medication may have a beneficial effect. Injections may be given on a weekly basis for 3 to 4 additional weeks. It is controversial whether trigger point injections are beneficial.

Epidural injections

Epidural corticosteroid injections are used for patients with radicular pain who do not respond to less invasive management. The efficacy of these injections for the treatment of herniated disks and spinal stenosis with radiculopathy has been questioned, although they have been found to be effective in some patients.^{122,123} Benefits include decreased leg pain and more rapid return of sensory function. Epidural steroids may be administered via the interlaminar, transforaminal, and caudal routes. Fluoroscopic guidance improves the likelihood of delivering medication to the intended target, decreases the risk for vascular penetration, and enhances safety. Transforaminal epidural steroid injections place medication around the specifically involved nerve root and, in experienced hands, can offer effective treatment of radicular pain from a herniated disk.

Facet joint injection

Facet syndrome can mimic radicular pain. Diagnosis of facet syndrome is based on diagnostic anesthetization of the joint or its innervation. Corticosteroids can be injected to decrease pain.¹²⁴ These injections are done under fluoroscopic control to document appropriate placement of the needle. A facet joint receives innervation by the medial branches of the dorsal rami from the same level and the level above. If facet syndrome is confirmed on the basis of time-dependent medial branch anesthetic block, the medial branches can be denervated via radiofrequency ablation.^{125,126} The efficacy of facet injections and medial branch blocks has been questioned¹²⁷ and presents an area for further study.

Complementary therapies

Complementary therapies are used for a variety of medical problems, including low back pain. Therapies promoted for the treatment of low back pain include spinal manipulation, massage, acupuncture, and magnets.

Osteopathic physicians, chiropractors, and experienced physical therapists may offer manipulation as a therapy for low back pain. In a study of 215 patients who visited a physician and 242 who visited a chiropractor, overall satisfaction with care was three times greater with chiropractors than with physicians.¹²⁸ On the other hand, chiropractic care is associated with the greatest number of visits per episode and the highest outpatient cost when compared with other health care providers.¹²⁹

Therapeutic massage has benefit for individuals with chronic low back pain. Given once a week for a period of 10 weeks, this therapy has demonstrated benefit months after the last treatment. The efficacy of this form of treatment is limited to the availability of massage therapists.¹³⁰

Acupuncture is also commonly used for low back pain. A meta-analysis reported that for the primary outcome of short-term relief of chronic pain, acupuncture is significantly more effective than sham treatment and no additional treatment. Data are insufficient for drawing conclusions about acupuncture's short-term effectiveness relative to most other therapies.¹³¹

Another systematic review showed that for chronic low back pain, acupuncture is effective for relief of pain in the short term only. Acupuncture is not more effective than other conventional and "alternative" treatments. Data suggest that acupuncture and dry needling may be useful adjuncts to other therapies for chronic low back pain.¹³²

Surgical treatment

A small percentage of individuals with low back pain require surgical intervention to improve their condition. Indications for surgery vary according to the patient's characteristics but include sphincter and sexual dysfunction secondary to compression of the conus medullaris or cauda equina; severe radicular symptoms, particularly if progressive neurologic motor deficits are present; and radicular symptoms failing to respond to conservative management. Selection of the operative procedure is determined by the characteristics of the lesions and the skill of the surgeon with the specific technique.

With spinal stenosis, the success of surgical approaches depends on adequate decompression of areas of absolute stenosis and good judgment with respect to the adequacy of decompression of areas of relative stenosis. Surgery is most effective when patients have a clinical picture dominated by manifestations of nerve compression. The most common technical problem is inadequate neural decompression.¹³³ Comorbid conditions, including hip arthritis, osteoporosis, and cardiovascular disease, are associated with persistent pain after surgical correction.

Surgery for patients with radicular pain from a herniated disk primarily involves decompression; removal of the protruded, extruded, or sequestered disk material; and inspection and release of the tethered nerve root. Indications for concomitant spinal fusion remain controversial. Patients with spondylolisthesis, degenerative scoliosis, a history of previous surgery, segmental instability, or predominantly axial pain with concordant diskographic findings are possible candidates for concomitant fusion.

Patients with lumbar spondylolisthesis and symptoms of low back pain with or without neurologic symptoms from irritation of the spinal nerve roots may benefit from surgical fusion. In contrast, in patients with axial

low back pain and nonspecific degenerative changes, spinal fusion should be considered only after exhaustive attempts at nonoperative care and psychological counseling. In this small subpopulation, spinal fusion may be considered for patients with two or fewer adjacent degenerated disks demonstrated to be concordant for reproducing the patient's symptoms on non-sedated lumbar diskography with at least one asymptomatic level. Even in this highly selected population, concerns about adjacent-level degeneration and subsequent return of pain can occur. Prosthetic disks hold some promise in terms of reducing adjacent-level degeneration; their efficacy has been reported to be comparable to that of fusion.¹³⁴

The SPORT studies have shed additional light on the role of surgery in patients with back pain. The SPORT investigators performed three parallel studies involving patients with herniated nucleus pulposus and sciatica, patients with lumbar spinal stenosis and neurogenic claudication, and patients with degenerative spondylolisthesis and stenosis with neurogenic claudication. Each trial was compromised by high rates of crossover from one randomized group to the other. Essentially, about half of the SPORT subjects did not receive the intervention to which they were randomly assigned. Consequently, the investigators presented sophisticated as-treated analyses that took advantage of the unique SPORT data. These analyses consistently show that in the first 4 years of follow-up, outcomes are better following surgery than following nonoperative therapy. Longer follow-up will determine whether these differences persist.^{135,136}

Unfortunately, despite adequate conservative and operative management, some patients are left with ongoing severe back pain and limitation. Multidisciplinary pain management and functional restoration techniques should be considered for these patients, and management involves both physical and psychological assessment and treatment.¹³⁷

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73

The shoulder

■ SEAMUS E. DALTON

- Shoulder motion involves four articulations: the glenohumeral, acromioclavicular, sternoclavicular, and scapulothoracic.
- Stability of the shoulder is dependent on static and dynamic restraints.
- Common shoulder disorders include rotator cuff tendinopathy, capsulitis (frozen shoulder), glenohumeral arthritis, and acromioclavicular syndromes.
- Most shoulder conditions can be diagnosed clinically with a careful history and physical examination.
- Patients with tendinopathy have pain during active and resisted motion, but passive range of motion tends to be normal. Degenerative tendinopathy is common, age related, and often asymptomatic.
- In capsulitis and glenohumeral arthritis, active and passive motion is painful, there is no pain on resisted motion, and passive motion is decreased.

FUNCTIONAL ANATOMY

The clavicle, scapula, and humerus make up the bony skeleton of the shoulder girdle. Its relationship with the axial skeleton is maintained through muscular attachments and the articulation of the clavicle with the thoracic cage at the sternoclavicular joint. Shoulder movement occurs through motion at four articulations: the glenohumeral, acromioclavicular, sternoclavicular, and scapulothoracic. The scapula acts a mobile platform on which glenohumeral motion can take place. The glenohumeral joint is a multiaxial joint that allows the greatest freedom of movement of any joint in the body, though at the expense of stability. Ligamentous support is important in maintaining static stability of the joints of the shoulder and allowing synchronous movements to take place. Some constraint is also afforded to the head of the humerus through the subacromial joint by the overlying acromion and coracoacromial ligament. Muscles act as prime movers at the shoulder, as well as provide dynamic stability to the glenohumeral joint. The shoulder girdle also acts as a conduit for the brachial plexus and major vessels supplying the upper limb.

Glenohumeral joint

The glenohumeral joint allows a certain amount of translation, which increases when the musculoligamentous support is lax. Inherent bony stability is poor because of the shallow glenoid fossa and larger humeral head but is enhanced through a process of joint adhesion and negative intra-articular pressure. The glenoid labrum is a rim of fibrocartilage at the periphery of the glenoid that effectively deepens the glenoid fossa, thereby increasing its diameter and contact with the humeral head and affording some increased stability.

The joint capsule is thin and lax, especially inferiorly, which allows rotation and elevation, but becomes taut at the extremes of motion, with tensile load in one region of the capsule being associated with laxity in the contralateral region. In conditions in which the capsule contracts, glenohumeral motion is restricted. Restriction in the capsule posteriorly results in increased superior and anterior translation with forward flexion, which can lead to subacromial impingement and is also implicated in other clinical conditions of the shoulder.

Glenohumeral ligaments

The joint capsule thickens anteriorly to form separate components known as the glenohumeral ligaments, which act to strengthen the anterior and inferior capsule. The superior glenohumeral ligament (SGHL) runs from the anterosuperior aspect of the glenoid to the proximal edge of the lesser tuberosity of the humerus, with the middle glenohumeral ligament (MGHL) running just below this. The inferior glenohumeral ligament (IGHL) runs from the anteromedial aspect of the glenoid to the distal edge of the lesser tuberosity and proximal shaft of the humerus and has three components enabling it to sustain loading in multiple directions (Fig. 73.1). It is important in providing anteroinferior stability to the joint, particularly with the arm in abduction and external rotation, and is the major restraint of external rotation in the neutral and abducted position.¹ It has also been shown to provide some posterior stability, especially in flexion and internal rotation. The joint capsule functions like a hammock or cylinder, with many regions acting as a restraint to external rotation.

Anatomic variants in glenohumeral ligaments

Deficiencies in the glenohumeral ligament complex are important in the development of instability. Several studies have described a number of anatomic variations in the glenohumeral ligaments and capsulolabral attachments that need to be differentiated from truly pathologic conditions. With the advent of magnetic resonance imaging (MRI) and arthroscopy, these variants have been demonstrated in both the normal and symptomatic population (Fig. 73.2). An example is the variable development of the MGHL and anterosuperior labrum, with normal variants such as the Buford complex (absent anterior superior labrum and cordlike MGHL) and sublabral hole (or window) often mistakenly being identified as a pathologic lesion (e.g., a Bankart defect, or an isolated tear in the anterior inferior glenoid labrum).

Coracohumeral and coracoacromial ligaments

The coracohumeral ligament originates from the coracoid process with variable insertion into the rotator interval or anterior rotator cuff, and in conjunction with the SGHL it limits inferior translation and external rotation of the adducted shoulder. The coracoacromial ligament extends from the undersurface of the medial acromion to the superolateral border of the coracoid process, although several types have been described.² It acts as a tension band supporting the acromion and coracoid and has an important role in transmitting force from the surrounding muscles. Along with the acromion, it acts as a roof over the subacromial space under which the rotator cuff tendons slide, with the subacromial bursa lying between. This structure has been implicated in the pathology of impingement of the shoulder. The transverse humeral ligament runs between the greater and lesser tuberosities and covers the long head of the biceps tendon (Fig. 73.3).

Stabilizers of the shoulder

Stabilizers of the shoulder can be divided into two groups: static and dynamic (i.e., passive and active restraints). The capsule, labrum, glenohumeral ligament, and to a lesser extent, the coracohumeral ligament can be thought of as static stabilizers of the glenohumeral joint. There are two sleeves of muscles about the shoulder: superficial and deep. The outer sleeve of muscles comprises the deltoid, teres major, pectoralis major, latissimus dorsi, and trapezius muscles. They act as prime movers of the humerus, although the trapezius acts through movement of the scapula and clavicle. The deltoid muscle has three bellies—anterior, middle, and posterior—that respectively produce flexion, abduction, and extension of the shoulder. All three muscles converge to an insertion on the deltoid tubercle on the lateral aspect of the humeral shaft. The combination of these large muscles (which

provide abduction, flexion, extension, adduction, and a degree of rotation) with the deep layer of rotator cuff muscles (which provide more rotation of the humeral head and act as a stabilizing force) allows expansive movement of the arm for actions such as reaching behind one's back or behind the head. However, in certain positions, overactivity of these muscles,

notably the deltoid and pectoralis major, may actually reduce glenohumeral stability.³

The deep group comprises the rotator cuff muscles (supraspinatus, subscapularis, infraspinatus, and teres minor) and the tendon of the long head of the biceps. This layer acts dynamically to stabilize the humeral head in the glenoid fossa during shoulder movement while simultaneously providing rotation (through the subscapularis, teres minor, and infraspinatus) and abduction (through the supraspinatus).

Rotator cuff

The rotator cuff muscles originate from the scapula and attach to the greater (supraspinatus, infraspinatus, and teres minor) and lesser (subscapularis) tuberosities of the humerus. The rotator cuff has also been shown to provide some passive restraint to glenohumeral joint translation, especially posteriorly. During the initiation of shoulder abduction or elevation, the larger, more powerful deltoid muscle, if unopposed, would pull the humeral head superiorly toward the acromion. The rotator cuff muscles and the biceps tendon act as humeral head depressors to prevent such translational movement superiorly. This is known as the "force couple." The subscapularis also acts to resist the tendency of the humeral head to sublux anteriorly in the upper ranges of abduction, although its role is less important than previously thought and it has been found to be less effective at the extremes of motion.⁴ Dysfunction of the rotator cuff muscles, through either weakness or a tear, results in diminished stabilization of the humeral head, which leads to weakness of the arm in elevation, as well as superior migration of the humeral head, thereby increasing the likelihood of subacromial compression or impingement. Therefore, the four tendons of the rotator cuff grip the humeral head and act as guy ropes to stabilize it during shoulder movement and resist this sliding tendency within the joint.

A gap or thinning of the cuff is present between the supraspinatus and subscapularis tendons and is known as the "rotator interval," which is composed of the coracohumeral ligament, the SGHL, and part of the joint capsule. The rotator interval is of variable size, has a role in the prevention of inferior translation of the humeral head, and may be implicated in some patients with anterior glenohumeral instability. Two functionally different parts of the rotator cuff have been identified, and it has been reported that the coracohumeral ligament is an important structure in the rotator interval and, in conjunction with the SGHL, has a role in control of external rotation, as well as inferior translation, in the adducted shoulder.¹

Biceps tendon

The biceps tendon arises from the superior labrum or directly from the supraglenoid tubercle, although a number of variations in this attachment have been reported. The long head of the biceps has been described as a humeral head depressor in full abduction and has also been shown to contribute to anterior stability of the shoulder. It has been reported to be a significant dynamic restraint in the abducted shoulder near the end range of rotation. However, one study suggested that its role as a stabilizer of the

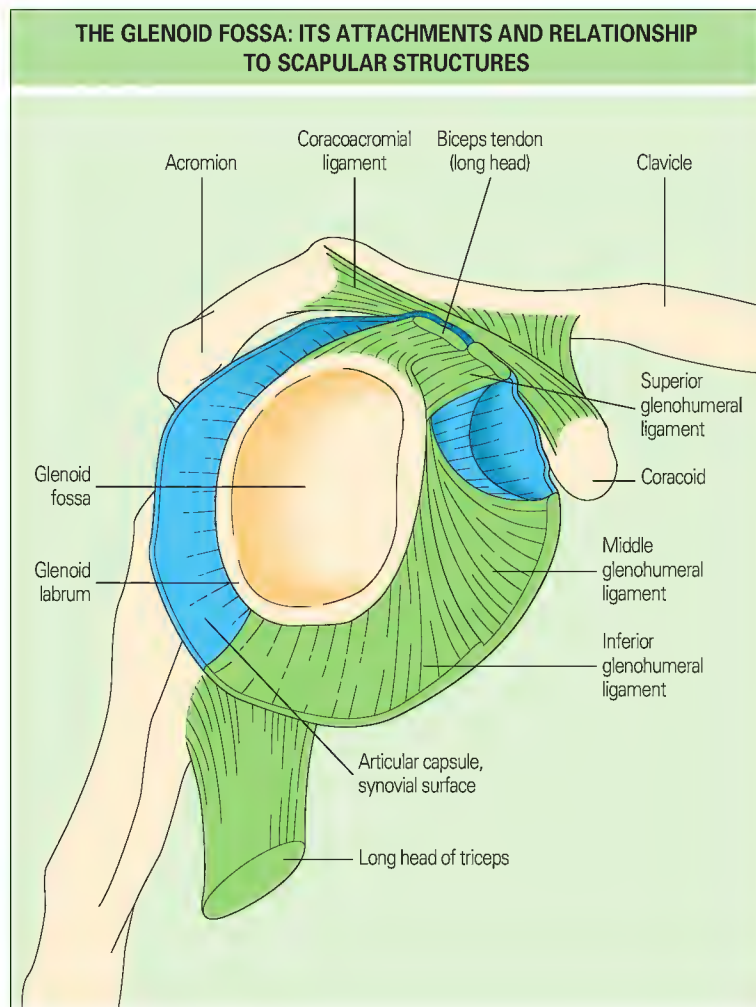


Fig. 73.1 The glenoid fossa: its attachments and relationship to scapular structures.

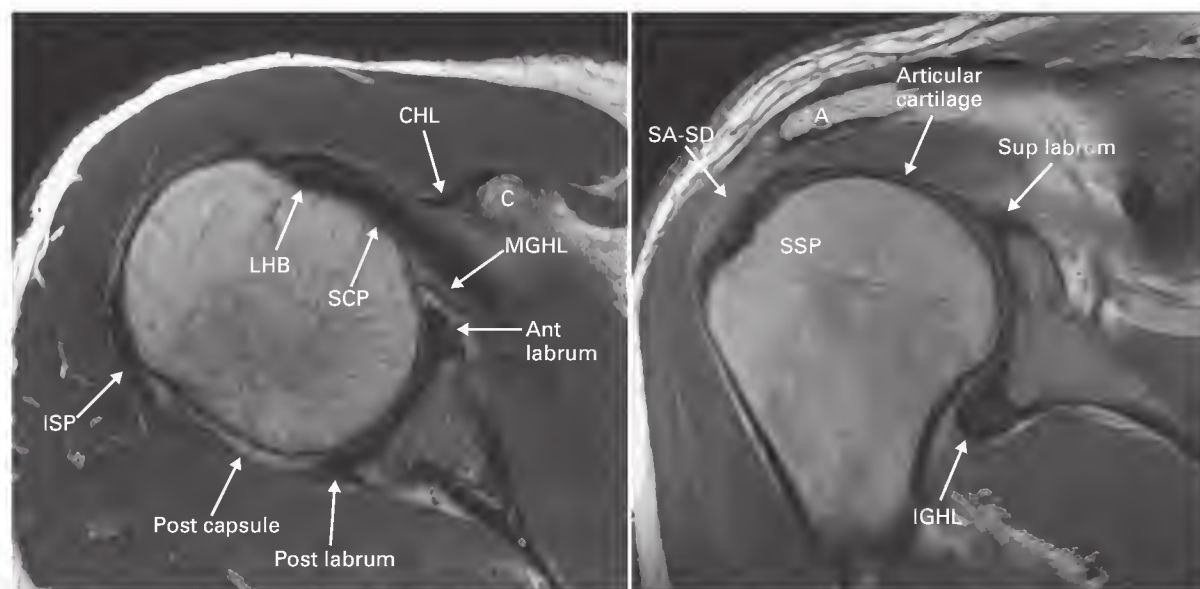


Fig. 73.2 Magnetic resonance imaging of the shoulder showing the anatomic features of the glenohumeral joint. A, acromion; Ant, anterior; C, cyst; CHL, coracohumeral ligament; IGHL, inferior glenohumeral ligament; ISP, infraspinatus; LHB, long head of bicep; MGHL, middle glenohumeral ligament; Post, posterior; SA-SD, subacromial/subdeltoid; SCP, subscapularis; SSP, supraspinatus; Sup, superior.

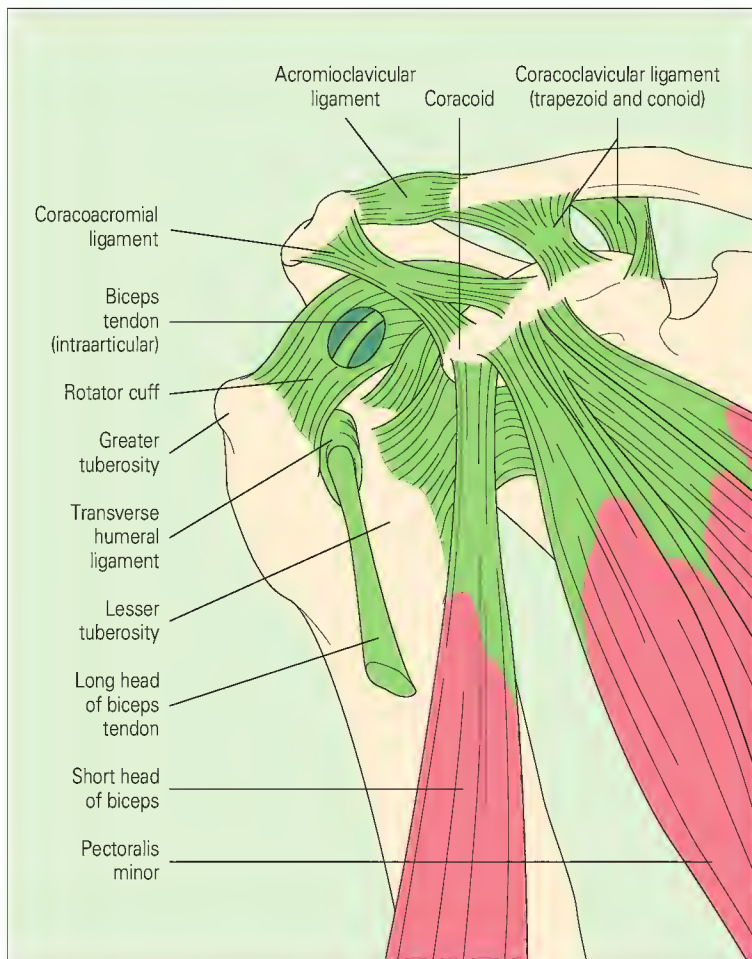


Fig. 73.3 Ligamentous and musculotendinous attachments about the shoulder joint.

glenohumeral joint is either a passive one or dependent on the tension associated with elbow and forearm activity.⁹

Nerve supply

The nerve supply to the glenohumeral joint is provided by the peripheral nerves supplying muscles acting on the joint: the axillary, suprascapular, subscapular, and musculocutaneous nerves. Innervation is via the fifth, sixth, and seventh cervical roots, and the brachial plexus passes anterior and inferior to the glenohumeral joint.

Other joints

Acromioclavicular joint

A fibrous disk separates the noncongruent surfaces of the distal end of the clavicle and the acromion and allows movement at this joint. During abduction and elevation the clavicle rotates through 30 to 40 degrees, and this rotation occurs largely at the sternoclavicular joint. There is a small amount of movement at the acromioclavicular joint, and compressive force is applied to the joint in full elevation and horizontal adduction, which is the basis of clinical stress tests applied to this joint. The joint is stabilized posteriorly by the posterior transverse ligament and inferiorly by the inferior ligament, and the deltoid and trapezius muscles provide some anterior and superior stability through their fascial layer. Of particular importance are the conoid and trapezoid (coracoclavicular) ligaments, which maintain the close relationship between the scapula and clavicle during shoulder movement.

Scapulothoracic joint

The scapula lies against the posterolateral aspect of the thoracic wall and rotates and slides laterally in abduction, elevation, and flexion. It provides the origin for the rotator cuff muscles, as well as the deltoid muscle, and the trapezius inserts along its superior aspect. The scapulothoracic joint represents the articulation between the scapula and the thoracic cage, and motion here is important for normal functioning of the shoulder.

Elevation and abduction of the arm involve synchronous motion at the glenohumeral and scapulothoracic joints. As elevation increases above 90 degrees, so does the proportion of scapulothoracic motion relative to

glenohumeral motion. Scapulohumeral rhythm is representative of the ratio between movement at these two joints and is important in several shoulder disorders. Disturbance of the normal scapulohumeral rhythm affects the biomechanics of the shoulder joint and may result in secondary impingement. This is seen in swimmers or participants in overhead sports, in whom muscle imbalances such as serratus anterior fatigue can lead to tendinopathy or impingement in this manner. Several muscles (levator scapulae, serratus anterior, trapezius, rhomboids) act to stabilize and move the scapula, and the balance between scapula elevators, rotators, depressors, retractors, and protractors determines scapulothoracic motion. Scapular control by these muscles is an important factor in glenohumeral instability and rotator cuff dysfunction. Muscle imbalance about the scapula can also lead to fatigue and overactivity of the levator and upper trapezius muscles particularly.

Sternoclavicular joint

Like the acromioclavicular joint, the sternoclavicular joint contains an intraarticular fibrous disk that allows rotation of the clavicle during abduction and elevation. Strong ligaments stabilize this joint anteriorly and posteriorly.

Bursae

The number and extent of bursae around the shoulder are variable. The subacromial bursa lies between the rotator cuff and overlying acromion but does not consist of a distinct sac, and its synovial layers blend in with and are firmly attached to the acromion and rotator cuff. In subacromial impingement there is reactive inflammation of this bursa, and the increased expression of cytokines in the synovium has been implicated in the pathogenesis of tendon degeneration. The subscapularis bursa communicates with the synovial joint cavity between the SGHL and MGHL, and the synovial membrane of the joint invests the tendon of the long head of the biceps. Other bursae include the subdeltoid, coracoid, infraserratus, and bursae at the insertion of the tendon of the trapezius and at the tendon insertions on the humerus.

HISTORY AND PHYSICAL EXAMINATION

History

Shoulder pain is seen in association with several medical conditions and may be referred from cervical, thoracic, or abdominal sources. Any history suggestive of such a secondary cause, such as diabetes or the Raynaud phenomenon, may be crucial in making the diagnosis. Similarly, the mechanism of any precipitating injury is of value. A fall on an outstretched arm can give rise to instability in a younger patient or a rotator cuff tear in the elderly. A fall on the point of the shoulder may result in injury to the rotator cuff or acromioclavicular joint. Throwing injuries tend to stress the capsulolabral complex and ligament attachments of the glenohumeral joint and can also give rise to rotator cuff or bicipital tendinitis.

A thorough history is essential because the location and type of pain vary between conditions. Pain referred from the cervical spine is often maximal over the suprascapular region, with associated paresthesia or pain referred to the upper limb. Although acromioclavicular and sternoclavicular pain is usually localized to the involved joint, it often radiates proximally, even into the neck. Pain from rotator cuff pathology is usually felt at the outer aspect of the upper part of the arm or the deltoid region. Adhesive capsulitis tends to give rise to an intense aching deep in the shoulder, although features similar to rotator cuff pathology are common in the early stages. Pain radiating into the arm may indicate cervical pathology, thoracic outlet syndrome, compressive neuropathy, brachial neuritis, or a neuropathic pain syndrome (e.g., complex regional pain syndrome). Night pain tends to be either sharp pain associated with movement, indicative of rotator cuff tendinopathy or acromioclavicular pathology, or a deep, constant ache more suggestive of capsulitis or a chronic tear of the rotator cuff.

Frequently, the severity and chronicity of a patient's pain do not correlate with the underlying pathology and presumed source of nociception. A process of central sensitization offers the best explanation for this, and early identification of neuropathic pain has important implications for the management of patients with chronic shoulder pain.

Examination

Inspection

Inspection should be carried out from the anterior, posterior, and lateral aspects. Difficulty undressing may indicate functional limitations. Areas of

erythema and bruising should be noted. Though uncommon, swelling of the shoulder joint may be seen anteriorly in the projection of the subscapularis bursa. Deformity of the shoulder girdle occurs with separation of the acromioclavicular joint or fracture of the clavicle or humerus. It is important to look for positioning of the shoulder such as asymmetric elevation or overprotraction. Neck position should also be recorded. Rupture of the long head of the biceps tendon is readily seen with anterior bulging in the upper part of the arm. Muscle wasting may be present in patients with cervical or brachial neuropathy (e.g., suprascapular nerve entrapment) but is also seen in the supraspinatus and infraspinatus muscle bellies with chronic rotator cuff tears. Scapulohumeral and scapulothoracic rhythm during elevation should be assessed and any asymmetry noted. A number of types of scapular dyskinesis have been described.⁶ Winging of the scapula, demonstrated by asking the patient to do a push-up against the wall, is indicative of serratus anterior weakness (as in long thoracic nerve palsy) but can also occur with muscular dysfunction. Excessive depression of the scapula (“dumping”) that is maintained through a range of abduction of the shoulder often indicates weakness of the upper trapezius or overactivity of the pectorals and latissimus and can lead to pain and symptoms of subacromial impingement or brachialgia and thoracic outlet syndrome.

Palpation

Palpation should be performed to identify tenderness, swelling, and instability of the acromioclavicular, sternoclavicular, and glenohumeral joints. Tenderness over the tendon of the long head of the biceps at the bicipital groove is common with bicipital tendinitis but may also occur with subscapularis tendinopathy, and comparison with the opposite shoulder is necessary because this region is often sensitive to touch. There may be tenderness over the rotator cuff insertions to the greater and lesser tuberosities, but this is not always present in rotator cuff tendinopathy. Acute calcific tendinitis results in exquisite tenderness over the involved tendon. The lateral margin of the subacromial joint can be palpated for swelling and tenderness, and the glenohumeral joint itself may be tender with acute instability or capsulitis. An effusion of the glenohumeral joint should be differentiated from subacromial swelling, although there may be communication between the two when a full-thickness tear of the rotator cuff is present. Osteophytes may be palpable at the margins of these joints, as well as crepitus, particularly with glenohumeral osteoarthritis.

Instability of the acromioclavicular and sternoclavicular joints is readily demonstrable, but glenohumeral instability requires a more detailed examination that combines assessment of laxity in the anterior, posterior, and inferior directions with stress and apprehension tests to determine the presence of symptomatic instability. Such assessment must be carried out in young adults with shoulder pain because underlying instability is a frequent cause of tendinitis around the shoulder. Muscles of the shoulder girdle and neck region should be palpated for trigger points and tender points, which are typically present with myofascial syndromes and fibromyalgia, respectively. Scapulothoracic crepitus is common and frequently found in association with muscular complaints and probably represents a frictional sound as the scapula glides across the underlying muscle layers. Rarely, it may reflect changes in the bony structure of the deep surface of the scapula or underlying ribs, such as an osteochondroma of the scapula or a rib exostosis, although these lesions tend to give rise to a more pronounced snapping sound and may result in deviation of the scapula away from the chest wall.

Range of movement

Active and passive range of motion should be assessed in the planes of abduction, forward flexion, and external rotation, both with the arm by the side and at 90 degrees of abduction. Internal rotation is frequently assessed as a combined maneuver with extension by bringing the hand up behind the back. Such movement is limited in many periarticular conditions, and true assessment of glenohumeral joint restriction is best done by measuring internal rotation with the arm by the side and the elbow extended. Internal rotation should also be assessed with the arm in abduction. Any limitation of movement should be noted, as well as any discrepancy between active and passive motion. Glenohumeral joint pathology is unlikely in the presence of a normal range of passive motion.

Further assessment should include passive adduction of the flexed and internally rotated shoulder to look for tightness of the posterior capsule and external rotators because such tightness is often seen in chronic conditions. Resisted shoulder movements are performed to assess the involvement of muscles and tendons. The patient is asked to resist a specific movement to elicit an isolated, isometric contraction in a particular muscle group. The supraspinatus is tested with the arm abducted to 90 degrees, flexed to 30 degrees, and internally rotated (i.e., thumb downward). The examiner then resists abduction from this position (“empty can” sign). However, in

symptomatic cases this test is frequently very painful, and resisted flexion (at 30 degrees of flexion) with the arm internally rotated is often a sensitive and less aggravating test of rotator cuff (particularly supraspinatus) function. Resisted internal rotation tests the subscapularis (best done with the hand behind the back or placed across the abdomen, known as the lift-off and belly press tests, respectively), and resisted external rotation tests the infraspinatus and teres minor (although 22% to 33% of the external rotation force can be attributed to the supraspinatus⁷). Resisted abduction should also be carried out with the arm by the side. Biceps function can also be tested by resisting shoulder flexion with the elbow extended (Speed test) or by resisting supination with the elbow flexed to 90 degrees (Yergason test), although the sensitivity and specificity of these tests are questionable. Any assessment must include an examination of the cervical spine to assess range of motion and the presence of any referred upper limb pain (see Chapter 71).

Special movements

Specific examination techniques are used to further localize the source of pain.⁸ Various tests for impingement have been described. In one, the arm is flexed to 90 degrees, adducted, and then forcefully internally rotated and slightly elevated by the examiner while the scapula is stabilized by the examiner's other hand (Fig. 73.4a). In another variation the arm is placed in the adducted, flexed, internally rotated position and the patient is asked to externally rotate the arm against resistance (see Fig. 73.4b). A further impingement test is carried out by passively forcing the arm into full forward flexion while the examiner stabilizes the top of the scapula with the other hand (see Fig. 73.4c). In all situations a positive test is recorded if pain is felt as the subacromial bursa and the rotator cuff are forced against the undersurface of the acromion, although it appears likely that these tests also provoke contact between anatomic structures associated with internal impingement.

A number of clinical tests for labral and biceps pathology have been described, but their diagnostic validity remains uncertain. The O'Brien test



Fig. 73.4 Impingement tests. (a) Forced passive internal rotation. (b) Resisted external rotation. (c) Forced passive full forward flexion.



Fig. 73.5 Adduction stress test of the acromioclavicular joint.



Fig. 73.6 The anterior draw test.

has been described as a provocation test for superior labral and biceps anchor pathology (superior labrum anterior to posterior [SLAP] lesions), but it also elicits pain in those with acromioclavicular joint disorders.

Pain at the acromioclavicular joint can be localized by performing various stress tests. In one, the arm is held with the elbow and shoulder extended and then passively adducted across behind the back (Fig. 73.5). In another less specific maneuver the arm is abducted to 90 degrees and then adducted across the patient's chest under the chin. In both tests pain is felt over an inflamed acromioclavicular joint at the limits of these movements. Assessment for thoracic outlet syndrome is difficult, and several maneuvers have been described that may provoke symptoms of neurovascular compression (see Chapter 81). A number of upper limb neural tension tests have also been described and are useful when assessing the etiology of diffuse or nonspecific upper limb pain.

Joint hypermobility

The patient should be assessed for the presence of joint hypermobility. Laxity of the glenohumeral joint in anterior and posterior directions is determined by performing draw tests in which the humeral head is gripped firmly and moved backward and forward in the glenoid fossa. This is best carried out with the patient lying supine and the abducted arm supported by the examiner's hand (Fig. 73.6). Inferior laxity is assessed by applying distal retraction to the arm while palpating the gap between the humeral head and acromion. The presence of a distinct gap can be felt and even seen and is referred to as a positive "sulcus" sign, which is indicative of multidirectional laxity of the joint. Anterior apprehension and stress tests are carried out with the examiner slowly extending and externally rotating the abducted arm with the patient supine. A positive test occurs when the patient experiences pain or apprehension during this maneuver and is confirmed when these symptoms disappear as the examiner's free hand applies a downward (i.e., stabilizing) force to the anterior aspect of the upper part of the humerus. This often allows further external rotation of the arm (Fig. 73.7). Symptoms return as this stabilizing force is slowly withdrawn. It is important to differentiate between a positive test eliciting pain alone and one eliciting apprehension, which may simply indicate internal impingement as opposed to true instability. A posterior stress test is carried out by applying gentle axial pressure on the humerus with the arm in the forward-flexed, internally rotated, and slightly adducted position, again in an attempt to reproduce pain and apprehension.

DIFFERENTIAL DIAGNOSIS OF SHOULDER PAIN

Shoulder pain typically arises from disorders affecting the shoulder joint or periarticular structures but can also be referred from other sites.

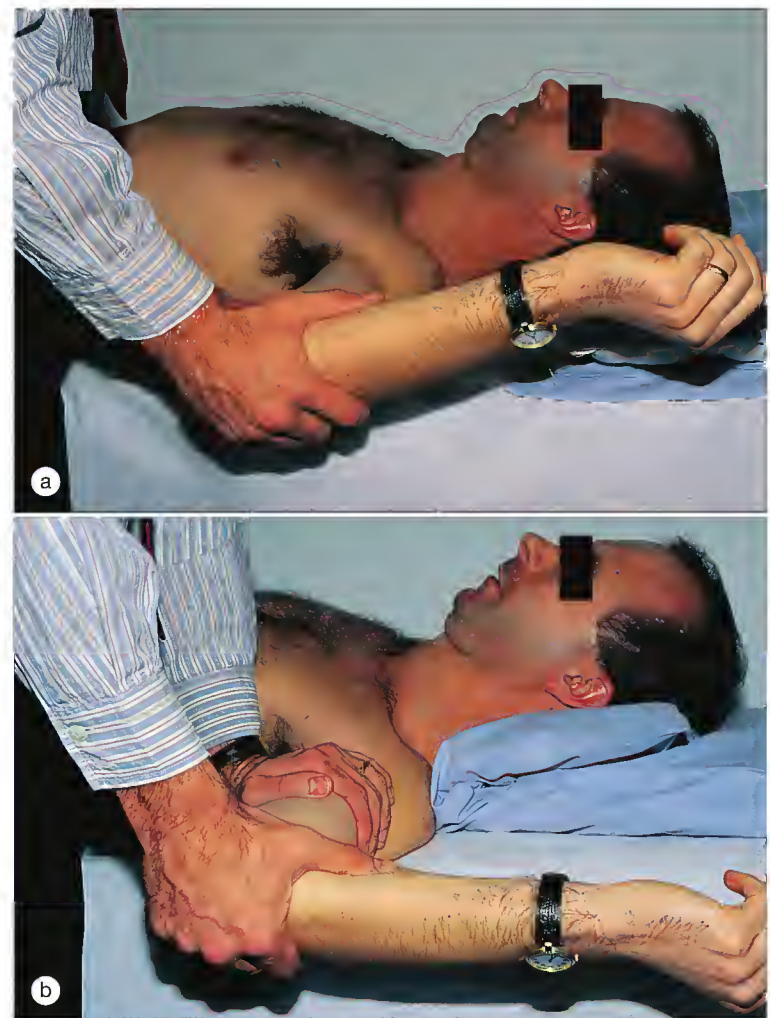


Fig. 73.7 Stress test for anterior glenohumeral instability. (a) The examiner slowly extends and externally rotates the abducted arm. (b) Containment sign. Applying pressure anteriorly relieves the symptoms and allows further external rotation.

The glenohumeral joint may be affected in a polyarthropathy such as rheumatoid arthritis or in isolation by conditions such as septic arthritis, neuropathic (Charcot) arthritis, osteonecrosis, and idiopathic destructive arthritis. Articular disorders of the shoulder may be accompanied by swelling, and invariably it has an effect on passive and active glenohumeral motion, with pain, restriction of movement, and often crepitus occurring.

Periarticular conditions affecting the shoulder can be loosely grouped into those with and without capsulitis. If no capsular involvement is present, passive joint motion is largely unaffected, whereas active movement may be limited by pain or weakness (e.g., rotator cuff disorders). Capsulitis causes multidirectional restriction of passive motion, and differentiation from articular conditions of the shoulder is made on clinical and radiologic grounds.

Referral of pain to the shoulder can occur with cervical disorders, Pancoast tumor of the lung, subphrenic pathology, entrapment neuropathies, and brachial neuritis. In these conditions passive and often active movements of the shoulder are largely unaffected, and usually little or no pain occurs when testing rotator cuff function. However, cervicobrachial pain is often associated with painful restriction of passive and active shoulder motion and may be confused with adhesive capsulitis. Differentiation from disorders of the shoulder is possible with an adequate history and examination (Table 73.1).

ROTATOR CUFF TENDINOPATHY

The term *tendinitis* is commonly used to describe patients with a painful tendon condition, although the classic inflammatory reaction is usually absent, especially in those with chronic tendinopathy. The spectrum of disorders affecting the rotator cuff ranges from mild transient tendinitis following an episode of glenohumeral instability in a young patient to a complete tear in the degenerative rotator cuff of an older patient. Subacromial impingement is not always present and can be a cause or result of rotator cuff dysfunction but is not in itself a clinical diagnosis, and it is important to appreciate that different pathologies can be accompanied by symptoms and signs of impingement.

Etiology

A number of extrinsic and intrinsic factors are involved in the etiology of rotator cuff tendinopathy. The anatomic configuration of the shoulder joint is such that the cuff is subjected to stress when the arm is in the elevated position. Impingement can occur as the supraspinatus tendon is compressed between the humeral head and the overlying anterior acromion, coracoacromial ligament, and even the inferior border of the acromioclavicular joint. Impingement may be structural secondary to the presence of an acromial spur or degenerative acromioclavicular joint, but it may also be functional and be caused by superior migration of the humeral head during abduction and elevation.⁴ Mechanical impingement by the coracoid process on the rotator cuff or rotator interval has also been recognized as a clinical entity, although the diagnosis can be confidently confirmed only at the time of surgery.⁹ Underlying glenohumeral instability can result in macrotrauma or microtrauma involving the rotator cuff and is a frequent cause of tendinopathy, particularly in a younger patient, as is eccentric overload in a throwing athlete, in whom the rotator cuff muscles act as decelerators of the throwing arm.

Pathology

As the rotator cuff becomes inflamed, thinned, or torn, its function as a humeral head depressor is compromised, and superior migration of the humeral head can occur through the unopposed action of the deltoid and give rise to further impingement. In a degenerative cuff with a complete tear this can eventually result in cuff arthropathy with osteoarthritis at the subacromial and glenohumeral joints. Impingement leads to inflammation of the subacromial bursa, but this is a reactive process and usually a secondary phenomenon, although primary subacromial bursitis can result from trauma.

Impingement has been shown to occur in forward flexion when the anterior margin of the acromion impinges on the supraspinatus tendon. Vascular studies have demonstrated a constant area of avascularity, or a "critical zone," extending from a point approximately 1 cm proximal to the point of insertion of the tendon into the greater tuberosity, and this compromised microvasculature is seen with the arm in the adducted (neutral) position.¹⁰ However, Iannotti and colleagues¹¹ detected substantial blood flow in this critical zone with laser Doppler, and the use of power Doppler has demonstrated hyperemia in acute tendinopathy. It has long been supposed that this region of relative hypovascularity is compromised during

elevation and abduction, thereby producing an inflammatory response and subsequent tendinitis. The bicipital tendon is frequently involved as part of this condition but is not usually the primary pathology. The pathology of this impingement syndrome was classified by Neer into three stages, but his initial proposal that rotator cuff tendinopathy resulted from subacromial impingement is an oversimplification of the pathogenesis of rotator cuff disease because both extrinsic and intrinsic mechanisms are clearly involved.¹²

Histologic studies have shown that degenerative changes are more prominent on the articular surface of the rotator cuff insertions,¹³ and a number of radiologic studies have confirmed the relative incidence of bursal, articular surface, intrasubstance, and lamination tears of the rotator cuff.

There appears to be progressive tendon failure leading to cuff rupture, with the prevalence of cuff tears increasing with age in the asymptomatic population.¹⁴ Full-thickness tears have been reported in 20% to 30% and partial-thickness tears have been found in a further 20% to 30% of people older than 60 years, with the prevalence of full-thickness tears rising to 50% in those older than 70. Possible etiologic factors include trauma, attrition, ischemia, and impingement, and a number of studies have looked at biochemical changes within the tendon matrix that may predispose to tendon rupture.¹⁵⁻¹⁸

The role of intrinsic factors in the pathogenesis of tendinopathy is becoming better understood. Recent studies have looked at various biologic factors, such as gene expression of growth factors and cytokines and their role in rotator cuff tendon degeneration. Increased matrix metalloproteinase (MMP) activity has been associated with degenerative tendinopathy and rotator cuff disease, and a number of cytokines and growth factors, including basic fibroblast growth factor, bone morphogenetic proteins, platelet-derived growth factor, and transforming growth factors, have been identified and may modulate tendon healing.¹⁹ This has led to the increased use of plasma- and platelet-derived growth factors in the biologic treatment of tendinopathy, although to date there is little evidence that such factors improve clinical outcomes and no consensus has been reached regarding the optimal concentration of platelets and leukocytes that should be administered.

History

The clinical findings depend on the age of the patient and the probable cause. Tendinopathy resulting from eccentric overload or glenohumeral instability in a young adult usually develops acutely following an activity such as throwing. In a middle-aged individual the onset may be more gradual and reflect the underlying chronic changes seen in the involved tendon. The patient may have aching and discomfort in the shoulder, pain on movement, and a history of repetitive or strenuous upper limb activity. An elderly patient may not have any history of antecedent trauma or repetitive activity, and there is usually a gradual onset of increasing shoulder discomfort, night pain, pain with movement, and weakness if a degenerative tear is present. Except for young patients with a history of explosive arm activity or trauma, the onset tends to be gradual and aggravated by movements such as abduction and elevation or sustained overhead activities, which are commonly sports or occupation related. Patients frequently complain that they have difficulty reaching up behind their back when dressing. The pain at night generally occurs when lying on the affected side and is typically felt in the deltoid region rather than the point of the shoulder. Active movements may be restricted by pain, and in more chronic cases secondary capsulitis can develop, thus further restricting movement at the shoulder.

Examination

Findings on examination include a painful arc of abduction usually occurring between 70 and 120 degrees. When lowering from full abduction, there is often a painful "catch," generally at midrange as impingement occurs and particularly in those with associated scapular dyskinesis. Passive motion tends to be full and pain free if adequate muscle relaxation can be achieved. Point tenderness over the greater tuberosity and distal rotator cuff may be present. The diagnosis is confirmed by reproduction of pain when resisting movement of the arm by the affected tendon and with impingement testing. In an older patient, arthritis of the acromioclavicular joint is often present, and there may be early joint stiffness. The probability of an underlying cuff tear increases with age.

Investigations

Plain radiographs may show evidence of rotator cuff degeneration, such as cystic and sclerotic changes at the greater tuberosity insertion, and calcification in the rotator cuff tendons may be seen in chronic

TABLE 73.1
Differential diagnosis of shoulder pain: clinical and radiographic features of common causes of shoulder pain

Diagnosis	Age	Type of onset	Location of pain	Night pain	Active range of motion	Passive range of motion	Impingement signs	Radiation of pain	Paresthesia	Weakness	Instability	Radiographic changes	Special features
Rotator cuff tendinitis	Any	Acute or chronic	Deltoid region	+	↓↓ guarding	Normal	+++	—	—	Only due to pain	Look for	In chronic cases	Painful arc of abduction
Rotator cuff tears (chronic)	>40 yr	Often chronic	Deltoid region	++	↓↓↓	Normal (may ↓ later)	++	—	—	++	—	+	Wasting of cuff muscles
Bicipital tendinitis	Any	Overuse	Anterior	—	↓ guarding	Normal	+	Occasionally into biceps	—	Only due to pain	Look for	None	Special examination tests
Calcific tendinitis	30–60 yr	Acute	Point of shoulder	++	↓↓↓ guarding	Normal except for pain	+++	—	—	Only due to pain	—	++	Tenderness ++
Capsulitis (“frozen shoulder”)	>40 yr	Insidious	Deep in shoulder	++	↓↓	↓↓	+	—	—	—	—	—	Global range of motion ↓
Acromioclavicular joint	Any	Acute or chronic	Over joint	Lying on side	↓ full elevation	Normal	—	—	—	—	—	In chronic cases	Local tenderness
Osteoarthritis of glenohumeral joint	>40 yr	Insidious	Deep in shoulder	++	↓↓	↓↓	—	—	—	May have mild	—	+++	Crepitus
Glenohumeral instability	Usually <25 yr	Episodic	Anterior or posterior	—	Only apprehension	Only apprehension	Possible	—	+ with acute episodes	+ with acute episodes	+++	Often	Stress tests
Cervical spondylosis	>40 yr	Insidious	Suprascapular	Often	Normal	Normal	—	++	+++	+	—	In cervical spine	Pain with neck movement
Thoracic outlet syndrome	Any	Usually with activity	Neck, shoulder, arm	—	Normal	Normal	—	++	++	++	—	—	Special examination tests

cases. Ultrasonography (US) and MRI can be used to identify rotator cuff tendinosis and partial tears, but in the case of US, interpretation is fairly observer dependent. Dynamic US can also demonstrate bunching of the subacromial bursa and impingement.

Differential diagnosis

Pain felt in the deltoid may suggest referred cervical pain, although such pain is more likely to be suprascapular pain referred down the arm. Pain on active movement and impingement testing with preservation of passive motion will differentiate rotator cuff tendinopathy from capsulitis. In cases of tendinopathy caused by underlying instability—which must be suspected in patients younger than 25 years—examination should confirm increased glenohumeral laxity and possibly symptomatic instability.

Management

Treatment of rotator cuff tendinopathy is difficult with continued participation in aggravating activities. Rest and modification of activities are necessary to prevent the problem from becoming chronic. Initial treatment should be directed at reducing inflammation when present with nonsteroidal anti-inflammatory drugs (NSAIDs). Little evidence supports the use of modalities such as US or laser,²⁰ although some evidence does support the use of extracorporeal shock wave therapy (ESWT) in the management of tendinopathy. When such means fail to resolve the symptoms and there is clinical and ultrasonographic evidence of subacromial bursitis or impingement, subacromial injection of corticosteroid can be used (see Chapter 69) while taking care to not inject the rotator cuff directly. A Cochrane review concluded that although such injections may be beneficial, their effect may be small and not well maintained.²¹ Subacromial injection of sodium hyaluronate has been suggested as an alternative treatment of rotator cuff lesions.²²

As well as reducing pain, treatment should be directed at restoring range of motion and the normal biomechanics of shoulder movement while paying particular attention to scapulohumeral rhythm. This is especially important in cases in which such a disturbance in biomechanics has aggravated or even precipitated the problem. Proprioceptive taping can be used to assess the role of scapular dyskinesis in the genesis of dynamic subacromial impingement and is a useful tool in the early rehabilitation of shoulder dysfunction. Once the pain has been reduced and normal shoulder, especially scapulohumeral, movement patterns have been restored, a strengthening program concentrating on rotator cuff exercises should be instituted to restore its function as a humeral head stabilizer and depressor, thereby reducing the likelihood of further injury. A review of level 1 and 2 studies in the literature has found that exercise is effective in reducing the pain in rotator cuff tendinopathy and impingement syndromes and that its effect may be augmented with manual therapy.²³ A younger patient with instability needs a comprehensive rehabilitation program and rarely requires injections in the shoulder. An older patient with a degenerative rotator cuff and associated acromioclavicular joint pathology may be resistant to conservative treatment.

Indications for surgery vary according to the age of the patient, stage of impingement or tendinopathy, and symptoms. The major indication is pain, and in the presence of an intact rotator cuff, failure to respond to a conservative program within 1 year is a reasonable indication for surgery. Surgery involves subacromial decompression and may consist of anterior acromioplasty with or without resection of the coracoacromial ligament, both of which can be carried out arthroscopically. Any impingement secondary to acromioclavicular joint pathology must also be addressed at surgery. The results of subacromial decompression have generally been reported as being good or excellent. However, there is a significant body of opinion that impingement usually results from a disturbance in normal glenohumeral kinematics attributable to capsular tightness, instability, scapulohumeral dysfunction, or loss of rotator cuff function as a humeral head stabilizer. In some cases, preservation of the coracoacromial arch is considered important in maintaining humeral head stability. Therefore, accurate clinical diagnosis and evidence of impingement at surgery are important in determining outcomes following subacromial decompression. In some patients, a capsular release or stabilization procedure may be more appropriate. In other words, subacromial impingement is frequently the result rather than the cause of shoulder dysfunction, and some think that decompression has little place as a stand-alone procedure.

Prevention

In a young patient or athlete, attention to proper preparation for exercise and correct technique is important. In many athletes, muscular imbalances

about the shoulder develop through either tightness or weakness, and secondary impingement and tendinopathy can result if these imbalances are not corrected. Serratus anterior fatigue results in loss of scapular stability and can lead to subacromial or internal impingement. In an older patient, avoidance of sustained above-shoulder activities or explosive lifting will help prevent this condition from deteriorating or perhaps even developing.

ROTATOR CUFF TEARS

Pathology

The incidence of degenerative cuff tears increases with age, as does the size of the tear.²⁴ Cuff tears are widely variable in type and extent. Full-thickness tears in one component of the rotator cuff often coexist with partial or intrasubstance tears in another area. Classification of the size and age of the tear, as well as the extent of tear retraction and fatty atrophy of the muscle belly, is important in planning treatment and predicting surgical outcomes. Superior migration of the humeral head against the undersurface of the acromion occurs as the incompetent rotator cuff fails to stabilize and depress the humeral head and therefore counteract the pull of the deltoid. This leads to degenerative changes both at the subacromial joint and secondarily at the glenohumeral joint, known as rotator cuff arthropathy. Neer estimated that 4% of cuff tears ultimately progress to cuff arthropathy,²⁵ although the true figure is probably greater.

Clinical features

Rotator cuff tears may be acute or chronic, partial or full thickness. Partial tears may occur in any age group following trauma, but a full-thickness tear is uncommon in patients younger than 40 years. In a young adult a partial tear can result from a fall or explosive shoulder movement and is manifested very much as an acute tendinopathy. Also, full active range of motion may be preserved. An acute complete rupture after trauma should be diagnosed readily. The mechanism of injury is usually a fall onto an outstretched arm, a hyperabduction injury, or a fall onto the side of the shoulder. Bruising is often delayed and occurs in the upper part of the arm, and there is usually immediate loss of active abduction and weakness of abduction and external rotation. Dislocation of the shoulder in patients older than 40 years is closely associated with partial or complete tears of the rotator cuff. In one review of 40 patients the prevalence of full-thickness tears was 90%.²⁶

Previous studies have recorded the incidence of chronic full-thickness tears found at autopsy,²⁷ although more recent MRI studies have reported a greater prevalence in the asymptomatic population, and many patients with a documented complete tear of the supraspinatus tendon have full active abduction, often in the absence of pain and even in the presence of abnormal glenohumeral kinematics and superior humeral head migration.²⁸ There may be no history of trauma, and symptoms frequently become apparent with increased activity, although the clinical expression of rotator cuff tears is variable.²⁹ The usual picture is pain on abduction and flexion with varying degrees of loss of active movement, depending on the size of the tear and the ability of the remaining rotator cuff to stabilize the humeral head. The patient may complain of weakness of abduction, flexion, and internal or external rotation, depending on the tendon involved.

Night pain is common and often severe. Examination reveals many of the features of rotator cuff tendinopathy, but the patient is often unable to maintain the arm in abduction when lowering from the elevated position (i.e., a positive “drop-off” sign). Subacromial crepitus and pain on impingement testing are usually present. A common clinical finding is wasting of the infraspinatus and supraspinatus muscle bellies, together with weakness of abduction, but more often weakness of external rotation reflects the size of the tear. Isometric measurement of rotation strength correlates well with the functional integrity of the rotator cuff, along with the patient's function and quality of life.³⁰ Rupture of the long head of the biceps tendon is frequently associated with chronic rotator cuff pathology.

Investigation

Features of chronic rotator cuff degeneration along with sclerosis and cystic changes at the greater tuberosity can be seen on plain radiography. Spur formation may be present along the anterior inferior acromion, often with osteoarthritis of the acromioclavicular joint. With a complete tear there may be superior migration of the humeral head and narrowing of the subacromial space (less than 6 mm indicates a tear). This finding, along with degenerative change, is seen in cuff arthropathy.

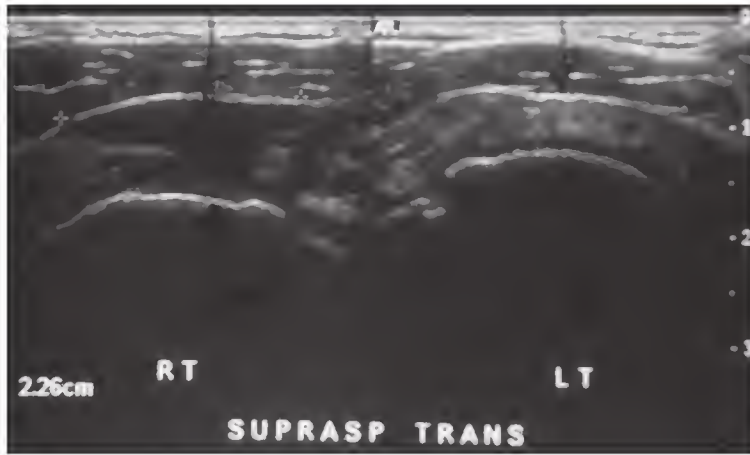


Fig. 73.8 Ultrasound of an acute full-thickness rotator cuff tear.



Fig. 73.9 Magnetic resonance image of a complete rotator cuff tear. The image shows a full-thickness tear of the distal supraspinatus tendon with early retraction of the articular side of the tendon.

Full-thickness tears are readily demonstrable with single- or double-contrast arthrography, with a sensitivity approaching 90%. Partial tears can occasionally be seen. However, estimation of the size of the defect with arthrography is unreliable, and it is rarely used unless in conjunction with computed tomography (CT) or MRI. US can identify and size tears, both full- and to a lesser extent partial-thickness tears (Fig. 73.8). MRI compares favorably with arthrography in the diagnosis of complete tears (Fig. 73.9). It is less consistent in the assessment of partial and lamination tears (Fig. 73.10) but allows assessment of tear retraction, muscle atrophy, and fatty degeneration in the rotator cuff muscles, which is important in the selection of patients for surgery. Arthroscopy may be used to establish the diagnosis in a patient with shoulder pain who requires further assessment. It is particularly useful in the assessment of instability while at the same time allowing visualization of the rotator cuff, subacromial bursa, intraarticular bicipital tendon, and glenoid labrum. It also allows estimation of the size of a tear before more definitive surgery, although cuff repairs are increasingly being performed arthroscopically.

Management

Initially, partial rotator cuff tears should all be managed conservatively, as for tendinopathy, although corticosteroid injection is not advisable within 4 to 6 weeks of an acute injury and there is less support for its use given the pathogenesis of tendinopathy. Growth factors and other biologic treatments are increasingly being administered, but evidence for their use is inconclusive. Despite the current lack of evidence, platelet-rich plasma and platelet-derived growth factors are often used to augment cuff repairs, and extracellular matrix scaffolds can be used as a means of delivery. Bursal and

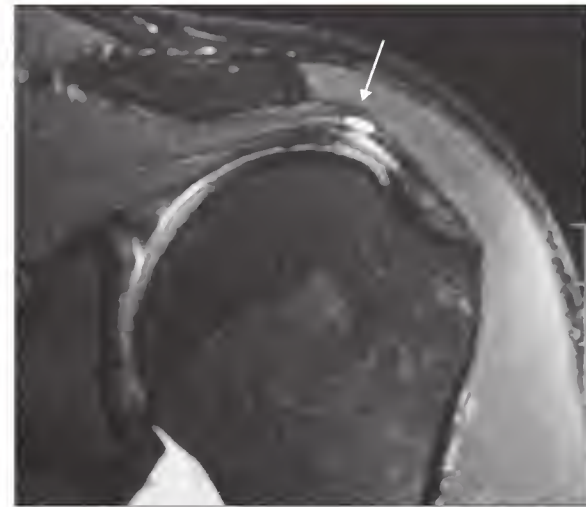


Fig. 73.10 Magnetic resonance image of complex rotator cuff pathology. The image shows a partial articular surface rotator cuff tear along with a laminar defect and small cyst in the distal supraspinatus tendon (arrow).

articular surface tears may be amenable to arthroscopic débridement, decompression, and possibly repair, but intrasubstance and laminar tears are best treated nonoperatively unless associated with subacromial impingement. Surgical management of partial or small full-thickness tears is somewhat controversial, and no consensus has been reached on when to intervene in these patients. Acute ruptures in a young or active patient should be managed surgically earlier rather than later. In an older or less active patient a trial of conservative management is reasonable, but if no substantial improvement occurs within 3 months, subacromial decompression with cuff repair is advisable.

Chronic complete tears are usually treated with an adequate conservative program initially. Failure to achieve pain relief is a major indication for surgical intervention. Any operative procedure should be directed primarily at relief of impingement, débridement of the cuff tear, and usually, but not always, repair of the defect. Surgery should also be considered in those with an associated rupture of the biceps tendon because cuff arthropathy appears to be more likely to develop in these cases, although in some patients bicipital tendinopathy is the primary pain generator and spontaneous rupture of the biceps tendon can lead to significant pain relief. Therefore some surgeons advocate biceps tenotomy when performing a cuff repair.

The results of surgical repair of rotator cuff tears are generally good but depend on the age of the patient and the size and age of the tear. Pain relief is usually achieved, but recovery of strength is less predictable and restoration of joint motion may depend on the amount of postoperative stiffness that develops. A major predictor of outcome following repair is the degree of rotator cuff muscle atrophy and fatty infiltration, which can be assessed preoperatively with CT or MRI.³¹ Therefore, a number of factors must be taken into account when deciding whether to proceed to surgery, including the patient's age and occupation, the size and type of tear (repair of lamination and complex tears can be difficult), and the degree of tendon retraction and muscle atrophy. Surgery should be delayed in patients with associated capsulitis, and capsular release may be required beforehand. Full-thickness tears of the subscapularis are best repaired early because delayed closure may not be possible once the torn tendon has retracted. With large or massive retracted tears, latissimus dorsi or pectoralis major muscle transfer may be required to close the defect and improve function, but other surgical options include simple débridement and decompression or partial repair with a residual defect remaining. However, for many of these patients the best option is total shoulder arthroplasty with a reverse prosthesis if the symptoms and loss of function warrant intervention.

OTHER PERIARTICULAR DISORDERS

Bicipital tendinitis

Pathology

The tendon of the long head of the biceps may be involved at several sites: at its attachment to the superior glenoid labrum, which may be injured in a fall or throwing action (SLAP lesion³²); as it runs across the glenohumeral joint (intraarticular), where it is stabilized by a pulley system made up of

the coracohumeral ligament, SGHL, and fibers of the supraspinatus and subscapularis tendons; or as it runs in the bicipital groove (extraarticular). The transverse humeral ligament stabilizes the tendon in the bicipital groove, and if this mechanism is disrupted, subluxation or dislocation of the tendon can result. This tends to occur as the arm is rotated in the abducted position. The tendon can become inflamed, thickened, and fibrotic in chronic cases, and it has been shown that bicipital groove anatomy correlates with biceps tendon disease.³³ In an older patient, attenuation and thinning of the tendon and eventual rupture may occur. The latter is almost always indicative of underlying rotator cuff degeneration because the bicipital tendon appears to become stressed in its attempt to act as a humeral head depressor in cases of rotator cuff incompetence. In addition, the presence of a complete rotator cuff tear exposes the intraarticular portion of the bicipital tendon to the overlying acromion and further impingement.

Clinical features

Though diagnosed frequently, bicipital tendinitis does not often develop in isolation and usually occurs in association with rotator cuff tendinopathy or impingement or with glenohumeral instability. Primary involvement of the tendon is seen as an overuse injury in sports such as weightlifting, where repetitive stress is placed on the tendon, or after prolonged and repetitive carrying (e.g., of small children). The bicipital tendon acts as a secondary stabilizer of the humeral head, and the translational movement seen with glenohumeral laxity can place increased stress on the tendon and thereby lead to tendinitis. As with rotator cuff tendinopathy, a young patient with bicipital tendinitis should be assessed for instability. With chronic impingement or rotator cuff degeneration, the biceps tendon may become fibrotic and attenuated and eventually rupture. Acute ruptures are also seen in young powerlifters.

Pain is generally felt over the anterior aspect of the shoulder and frequently radiates to the biceps muscle, and there is tenderness over the tendon as it runs in the bicipital groove. Pain is felt with overhead activities and often with shoulder extension and elbow flexion. Examination may reveal features of impingement, rotator cuff tendinopathy, and instability, all of which are important in the etiology of bicipital tendinitis. Pain may be reproduced with resisted elbow flexion, supination, and shoulder flexion, and various provocation tests have been described, although none appears to be consistently positive. Passive shoulder extension stretches the biceps and may be painful. Rupture of the tendon is characterized by bunching up of the lateral muscle belly of the biceps, which is best seen with resisted elbow flexion and supination.

Acute rupture of the transverse humeral ligament can result in subluxation or dislocation of the tendon. This can cause symptoms similar to bicipital tendinitis, and the patient usually complains of catching and a clicking sensation at the shoulder. Clinical examination may demonstrate subluxation of the tendon, which is felt as the arm is passively moved through internal and external rotation while in the 90-degree abducted position. Medial dislocation of the tendon is generally associated with tears of the subscapularis tendon.

Investigation

Special radiographic views demonstrate the bicipital groove and allow assessment of its depth and the presence of any hypertrophic spurring. Filling of the synovial extension around the tendon is seen on arthrography and may be reduced in cases of chronic fibrosis. The tendon and any surrounding fluid can be seen well with US (Fig. 73.11), and this assists in the diagnosis of tears, both partial and complete, as well as tendinitis. It can also be used to demonstrate subluxation or dislocation of the tendon. MRI or arthroscopy allows visualization of the intraarticular portion of the tendon and its labral attachment (Fig. 73.12).

Management

It is necessary to establish whether the tendinitis is primary or secondary because failure to address any underlying rotator cuff pathology or instability will lead to recurrence of symptoms. The principles of management are rest, physical modalities, and NSAIDs as required. Low-power laser therapy has been reported to have a beneficial effect, although this has been disputed.³⁴ Corticosteroid injection is helpful in chronic cases, but care should be taken to not inject the tendon itself. An intraarticular injection or injection into the tendon sheath may be given, but both are best done under US guidance. Because most cases of bicipital tendinitis are secondary, they usually resolve as the primary condition is treated. The primary cases caused by lifting or other activities may respond to rest and antiinflammatory measures. Surgery can be considered in chronic, resistant cases and may involve subacromial decompression in cases of impingement or tenodesis when there is chronic thickening of the tendon in the groove. Rupture of the

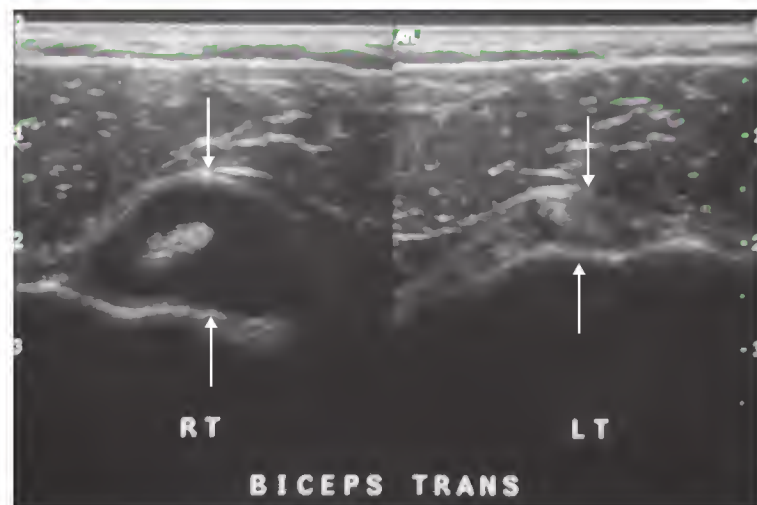


Fig. 73.11 Ultrasound of bicipital tendinitis. A transverse image shows a large effusion (arrows) in the long head of the biceps tendon sheath.



Fig. 73.12 SLAP (superior labrum anterior to posterior) type 2 lesion. A nonarthrographic coronal proton density magnetic resonance image demonstrates a tear (arrow) at the base of the superior labrum involving the biceps anchor.

tendon is normally treated conservatively except in occasional young patients in whom upper arm strength is critical to their sport or profession. Usually, weakness following this injury is not significant. Subluxation of the tendon is often treated conservatively, although surgery is occasionally necessary, and medial subluxation or dislocation of the tendon out of the groove generally indicates the presence of a tear in the subscapularis tendon, which may not be apparent on US.

Any conservative program must include range-of-motion exercises, stretches, and once the symptoms have settled, a graduated eccentric and concentric biceps and rotator cuff strengthening program while ensuring that any instability or scapular dyskinesis is addressed.

Subacromial bursitis

In most cases, inflammation of the bursa arises as part of the impingement process and coexists with an underlying rotator cuff tendinopathy. This bursitis is therefore a reactive phenomenon. In chronic cases the bursa becomes thickened and fibrotic and surgical excision or débridement may

be necessary. Treatment of rotator cuff tendinopathy is directed at reducing inflammation in the subacromial bursa, as well as reducing impingement.

Acute traumatic bursitis in the form of hemorrhage and edema can occur as a result of a fall on or a direct blow to the point of the shoulder. Pain on abduction is present, but differentiation from rotator cuff tendinopathy is possible on the basis of increased tenderness and fluid in the subacromial space. A period of rest combined with simple measures such as the application of ice usually allows resumption of normal activities, but persistent impingement occasionally develops and require further treatment.

Capsulitis

Definition

Capsulitis of the shoulder remains a condition both difficult to define and universally awkward to manage. Many labels have been given to the situation in which painful restriction of shoulder movement is apparently of soft tissue origin, including frozen shoulder, peri arthritis or pericapsulitis of the shoulder, adhesive capsulitis, and adherent or obliterative bursitis. There has been an attempt to classify patients with a painful stiff shoulder according to the presence or absence of capsular joint restriction as seen with arthrography.³⁵ Perhaps incorrectly, the term “frozen shoulder” is applied to many conditions in which restriction of movement is largely due to pain from an underlying condition, such as rotator cuff tendinopathy, rather than caused by the classic global restriction of glenohumeral joint motion seen with true adhesive capsulitis.

Primary capsulitis of the shoulder can be defined as a condition of unknown etiology in which glenohumeral movement is painfully restricted in all planes of motion, both active and passive, in the absence of joint degeneration sufficient to explain such restriction. A similar condition known as secondary capsulitis exists when the condition is associated with a clearly defined clinical disorder or precipitating event.

Pathology

The etiology of adhesive capsulitis is not known. There is some evidence of its association with a number of conditions, including diabetes mellitus, thyroid disease, hyperlipidemia, pulmonary disorders such as tuberculosis or carcinoma, cardiac disease or surgery, cerebrovascular accident, and particularly shoulder trauma. The evidence for such associations, however, is generally unconvincing. Dupuytren disease is often seen in association with adhesive capsulitis, and it has been suggested that the two conditions may have similar biochemical and histologic characteristics.³⁶ Following traction or hyperabduction injuries to the shoulder, a mixed clinical picture of capsulitis and cervicobrachialgia may develop, thus further complicating diagnosis and treatment.

Capsulitis is more prevalent in patients with diabetes (prevalence of 10% to 20%), usually occurs at a younger age, and is often associated with a prolonged duration of diabetes, insulin dependence, the development of limited joint mobility syndrome, and widespread microvascular disease. Bilateral involvement is also more common in diabetes. The links between diabetes and capsulitis may revolve around microvascular disease, abnormalities in collagen repair, or predisposition to infection.³⁷ An association between capsulitis and thyroid disease and pulmonary conditions has been noted but provides little information regarding its pathogenesis. Histologic studies have failed to demonstrate the presence of inflammatory cell infiltrates, granulomas, or vasculitis in the joint capsule or synovium. Also, nothing has been found to implicate infection, crystal arthropathy, or trauma.

Histologic studies of the joint capsule early in the disease are difficult to perform, and the heterogeneity of patients loosely labeled as having capsulitis makes study of this condition problematic. Lundberg noted an increase in fibrous tissue, fibroblast number, and vascularity with no change in the synovial lining and no inflammatory cell infiltrate.³⁸ Bunker and Anthony reported that fibroblasts and myofibroblasts lay down a dense type III collagen matrix in the shoulder joint capsule that leads to joint contracture.³⁹ Cytokine, MMP, and MMP inhibitor abnormalities have been reported, and it has been proposed that increased production of growth factors is the central precursor to capsular fibrosis.⁴⁰ Several studies have looked at a variety of immunologic factors, but no immunologic disturbance has been demonstrated.³⁷

Clinical features

Estimation of the prevalence of adhesive capsulitis is difficult because of variation in the populations studied and the diagnostic criteria used, but it appears to be approximately 2% to 3% in those without diabetes. Onset in those younger than 40 years is rare, with the mean age at onset being in the sixth decade. Women are affected more often than men. Involvement of the contralateral shoulder occurs in 6% to 17% of patients over the subsequent

5 years.³⁷ It is commonly stated that recurrence in the same shoulder does not take place. Patients frequently relate a history of minor shoulder strain or injury before the onset of symptoms, but whether this represents a true strain of the shoulder or simply the earliest awareness of pain is unclear.

The natural history of adhesive capsulitis has been described by various authors, and it appears that there are three phases in its development and progression. The shoulder moves from being simply painful to being painful and stiff and eventually to being less painful but profoundly stiff. This last stage appears to be self-limited, and recovery is gradual and spontaneous. These phases have been termed *painful*, *adhesive*, and *resolution*. The duration of each phase in the overall condition varies considerably, but approximate durations are 3 to 8 months for the painful phase, 4 to 6 months for the adhesive phase, and 1 to 3 years for the resolution phase. The extent of recovery is variable, with quoted figures of 33% to 61% of patients having a clinically detectable limitation of shoulder movement, and although many remain asymptomatic, 7% to 15% of patients may have a persistent functional disability.³⁷ The extent to which the duration of the painful and adhesive phases determines the degree of residual disability remains controversial. It does appear that capsulitis in a patient with diabetes runs a more protracted course with marked stiffness and less complete recovery.

Painful phase

This phase is characterized by the insidious onset of symptoms, usually in the form of pain on shoulder movement and background ache in the shoulder, typically in the suprascapular and deltoid regions. Frequently, patients are treated as for rotator cuff tendinopathy and subacromial bursitis, which is often noted on US. As the condition becomes established, the pain increases during rest and at night, the latter becoming quite disturbing and frequently waking the patient in the absence of a history of precipitative movement. Muscle spasm may develop and further limit shoulder movement, which becomes restricted with the increase in pain and stiffness at the shoulder. Toward the end of this phase stiffness becomes a major complaint.

Adhesive phase

Usually after several months the character of the pain alters and becomes less severe. The pain during rest and at night is reduced, but discomfort and more severe pain at the limits of motion persist. Shoulder movement becomes more restricted during this phase, which can lead to periscapular pain because of the increase in scapulothoracic motion.

Resolution phase

Pain is less evident and the dominant symptom is restriction of movement, which is less distressing for the patient now that the pain has eased. Range of motion improves slowly and gradually, although it is frequently incomplete. The onset and rate of recovery are variable and unpredictable.

Clinical examination

The physical signs change as the condition progresses, with pain, often severe, being present in the earlier stages. Differentiation from symptomatic rotator cuff tendinopathy is possible on the basis of global restriction of passive movement rather than simply the loss of abduction and flexion that is seen with chronic rotator cuff conditions. A useful early clinical indicator of developing capsulitis is pain at the limit of passive external rotation of the shoulder with the arm by the side. In the painful phase there is painful restriction of active and passive motion (often mild in the earlier stages). Pain may occur during impingement testing and resisted movement, although this is less common than in rotator cuff tendinopathy. Associated findings are tenderness in the upper trapezius muscle and early scapula hitching in elevation. In some patients the pain can be severe enough to necessitate opioid analgesia, and the clinician may feel the need to exclude other causes such as avascular necrosis or neoplastic disease. Indeed, shoulder tumors may be manifested as capsulitis. In the latter phases the important finding is significant restriction of glenohumeral movement with a compensatory increase in scapulothoracic motion during flexion and abduction. Pain may be present, but there is less discrepancy between active and passive ranges. Disuse atrophy of the rotator cuff and deltoid muscles may exist. Joint line tenderness may be present in the painful phase.

Investigation

The diagnosis is made largely on clinical grounds because few abnormalities are found on investigation. Plain radiographs are not helpful in making the diagnosis except to exclude osteoarthritis, calcific tendinitis, or neoplasm. In a younger patient with clinical features of adhesive capsulitis, avascular necrosis should be suspected and must be excluded before considering intraarticular corticosteroid injections.

Classic features on arthrography are limitation of joint volume with loss of the normal dependent axillary fold or pouch and irregularity of the capsular insertion to the anatomic neck of the humerus. Between 10% and 30% of patients who undergo arthrography have a demonstrable complete tear of the rotator cuff. Other studies have suggested that a significant number of patients with a clinical diagnosis of adhesive capsulitis have normal findings on arthrography.⁴¹ Arthroscopy allows further evaluation of these patients, and different stages of synovitis and contracture have been described.³⁵

Bone scintigraphy may demonstrate increased uptake of isotope in the affected shoulder region, but this appears to have no predictive value in terms of outcome or response to treatment and is therefore of limited diagnostic value.⁴¹ An average reduction in bone mineral content of 50% in the affected humeral head has been demonstrated, although this is also of little diagnostic or therapeutic value. US has been performed and typical findings are biceps sheath effusion, restriction of movement, and subacromial impingement resulting from the capsular contracture, but these features are not diagnostic and patients are often mistakenly treated for impingement. Indeed, failure to respond to treatment and early loss of joint motion should alert the clinician to the possibility of capsulitis developing. MRI may be indicated to exclude other causes of shoulder pain but is not generally required. However, some features on MRI, including signal change and scarring in the rotator interval, as well as hyperintensity and capsular thickening of the axillary pouch, appear to correlate with the clinical stages of adhesive capsulitis⁴² (Fig. 73.13).

Management

Many therapies have been used in an attempt to modify the natural history of capsulitis, but clinical studies of the efficacy of various treatment methods have been compromised by difficulties in patient selection and diagnostic criteria and variability in natural resolution of the condition. The emphasis of treatment in the early stages should be on reduction of pain and minimization of joint restriction. Analgesics and antiinflammatory drugs provide limited relief of pain but do little to alter the course of the disorder. Physiotherapy uses physical modalities to modify pain and reduce protective muscle spasm while attempting to encourage early range-of-motion exercises for maintaining joint mobility. Shoulder immobilization should be discouraged, although in the painful phase the patient tends to minimize shoulder movement.

Few treatments have been shown to consistently affect the rate of recovery or limit the restriction of movement. Intraarticular corticosteroid injections are commonly used and have been shown to reduce pain and disability for upward of 3 months, although no long-term benefit has been demonstrated.⁴³ The addition of supervised physiotherapy appears to provide faster improvement in range of joint motion. Intraarticular injection is best done under US guidance or fluoroscopy, and failure to do so in previous studies may account for the variable response to corticosteroid injection in the past. It still remains a useful and often effective means of relieving pain and hastening recovery. Oral corticosteroids have also been shown to improve pain but not to affect the rate of recovery. Careful use of analgesic or anti-inflammatory drugs with physiotherapy may be of benefit, although this may be due to a reduction in the protective spasm seen in untreated patients.

Hydrodistention of the joint capsule has been used for treatment of the various stages of this condition, usually in conjunction with corticosteroid injection, but it is still unclear whether it offers any additional benefit over corticosteroid injection alone. Manipulation under anesthesia has been used to restore joint motion but may result in rupture of the inferior capsule and possibly the subscapularis tendon at its insertion. Care should be taken when carrying out this procedure, especially in elderly patients, to avoid humeral fracture, shoulder dislocation, or a significant rotator cuff rupture. Aggressive early rehabilitation in the immediate postmanipulation period is needed to maintain joint mobility, and patient cooperation and tolerance of this treatment are essential. Manipulation during the painful phase is not recommended because painful recontraction of the capsule may occur, and such treatment is usually reserved for the adhesive phase once the pain has settled.

Nonoperative treatment is effective in the vast majority of cases, but arthroscopic capsulotomy can be used to treat recalcitrant cases of frozen shoulder.⁴⁴ Some authors do not restrict the use of this treatment to patients who no longer have significant pain and advocate arthroscopic capsular release over manipulation because it allows direct visualization of the joint capsule and therefore poses less risk for tendon rupture. For many patients, however, once the painful phase of their condition has subsided, the prospect of this painful procedure is not appealing. Improvement in range of movement following manipulation or capsulotomy is variable and perhaps dependent on patient selection. Long-term recovery appears to be unchanged, although resolution may be accelerated immediately following manipulation.

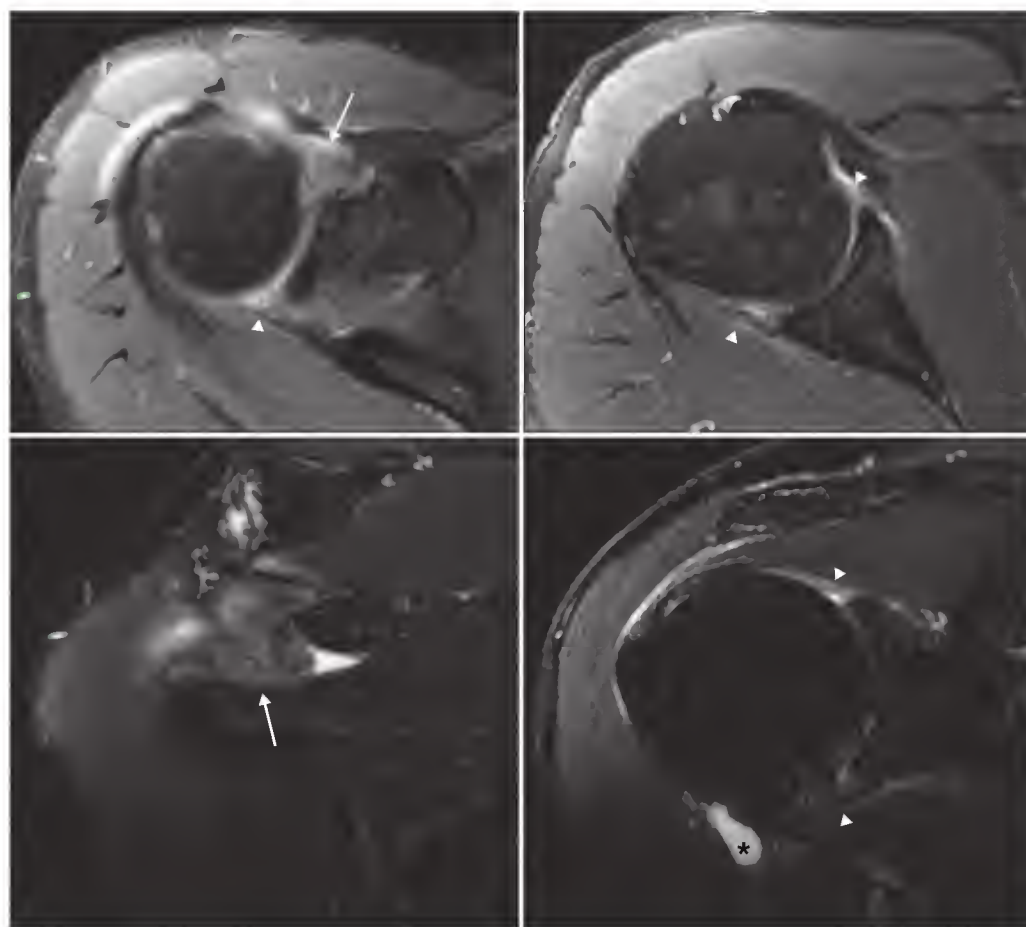


Fig. 73.13 Nonarthrographic magnetic resonance images of capsulitis. Fat-suppressed images show hyperintense capsular and synovial thickening within the rotator interval (arrows) and diffuse hyperintense thickening of the glenohumeral joint capsule (arrowheads) with an accompanying small joint effusion (asterisk).

ACROMIOCLAVICULAR SYNDROMES

Introduction

Pain localized to the acromioclavicular joint is commonly seen as either an acute or a chronic condition. In a younger patient this joint is frequently subjected to trauma as a result of falls or contact sports, which may result in an acute injury and also predispose the joint to further problems such as instability or secondary osteoarthritis. Atraumatic acromioclavicular joint pain is common and may be difficult to distinguish from other causes of shoulder pain. Infection of this joint is rare, but septic arthritis has been described.

Trauma

Disruption of the acromioclavicular joint may be seen in association with fractures of the outer end of the clavicle and often leads to the development of secondary osteoarthritis. More common are injuries to the joint itself, which are graded according to the degree of disruption of the joint capsule and supporting ligaments.⁴⁵ Grade I injury involves a minor sprain of the joint capsule without ligament disruption. Grade II injury involves subluxation of the joint with downward displacement of the acromion relative to the distal end of the clavicle. The inferior acromioclavicular ligaments are stretched, and there is stretching and possibly a partial tear, but not complete rupture, of the coracoclavicular ligaments. In a grade III injury, complete dislocation of the joint occurs through rupture of the coracoclavicular ligaments. Grade III injuries can be further classified (often as grades IV, V, and VI) according to the extent and direction of disruption or perforation of the overlying deltoid fascia or muscle layer by the displaced outer end of the clavicle.

Clinical features

The mechanism of injury usually involves a fall directly onto the point of the shoulder. Pain is localized to the top of the shoulder in the region of the involved joint, which is tender and often swollen. Abduction is limited, both actively and passively, according to the degree of joint disruption. For a minor injury with good preservation of movement, acromioclavicular joint stress tests can be carried out to localize the symptoms. With complete dislocation of the joint a visible step deformity is seen, and examination will determine whether this dislocation can be reduced. This is important in the differentiation of grade III to VI injuries. The patient often describes a feeling of the shoulder having dropped because of downward displacement of the acromion.

Management

For grade I or II injuries, treatment is largely symptomatic and consists of analgesics and provision of a sling for days to weeks depending on the symptoms. Shoulder movements should be encouraged as the pain settles, and functional recovery is excellent.

Controversy exists over the management of grade III injuries. Provided that perforation of the overlying muscle or fascial layer has not occurred, the injury resolves in most patients over a period of 6 to 10 weeks with conservative treatment. Strapping of the joint has no effect on long-term stability and is not indicated in these patients. Surgical stabilization by means of internal fixation is associated with a significant complication and failure rate, but several procedures involving reconstruction of the coracoclavicular ligaments have been shown to be effective, although the long-term results are not demonstrably better than those with nonoperative treatment. Surgical advances have lowered the complication rate and therefore the threshold for considering surgical repair or reconstruction of the acromioclavicular joint, particularly in manual workers or people dependent on overhead function. However, surgery is usually reserved for severe grade III disruptions or situations in which an individual's occupation may be compromised by persistent deformity or instability at that joint. Acute repair should be performed within 2 weeks of the injury or reconstruction will be required.

Late sequelae

Patients may have persistent pain at the acromioclavicular joint. This represents low-grade joint inflammation and may be associated with underlying instability, early development of secondary osteoarthritis, or osteolysis of the distal end of the clavicle. Persistent pain following joint injury may also result from damage to the intraarticular fibrocartilage sustained at the time of injury. Treatment is symptomatic, with antiinflammatory medication or intraarticular injection of corticosteroid for resistant cases. Delayed surgical stabilization may be carried out in those with gross instability, and tears of

the fibrocartilage can be debrided arthroscopically. Long-term treatment is as for osteoarthritis of the joint.

Osteolysis of the clavicle

Osteolysis of the distal end of the clavicle is a condition that may follow an acute injury or repetitive stress involving the shoulder. The symptoms are similar to those of acromioclavicular inflammation, with aching and pain at the limits of flexion and abduction. Radiographic changes typically include resorption of the distal end of the clavicle, often with osteophyte formation, osteoporosis, or tapering. The response to modification of activity and conservative treatment is usually satisfactory, but excision of the distal part of the clavicle may be necessary. Distal clavicular reconstitution may even occur with rest.

Osteoarthritis

Acromioclavicular joint morphology appears to be associated with the development of osteoarthritis, although cadaveric studies have shown that degenerative changes occur in this joint with normal aging after 40 years of age. A previous history of joint injury is common when osteoarthritis of this joint occurs in isolation, but the joint may also be involved as part of generalized osteoarthritis. Acromioclavicular osteoarthritis is common and frequently asymptomatic.

Clinical features

Pain and tenderness are localized to the joint, which is often prominent because of osteophyte formation. Pain is felt on full abduction or horizontal adduction and can also be reproduced with adduction of the extended arm. Crepitus is frequently localized to the joint. It is important to note that osteoarthritis of the joint is often seen in association with rotator cuff degeneration and that inferior osteophytes at the acromioclavicular joint may contribute to the development of a rotator cuff tear. Clinical features of both conditions frequently coexist, especially in an older patient.

Investigation

Osteoarthritis can be diagnosed with plain radiography. Traction or weight-bearing views can be taken to demonstrate joint instability.

Management

Initial management consists of local modalities and the use of analgesic or antiinflammatory drugs. An exercise program should be prescribed to restore normal scapulohumeral rhythm, glenohumeral range of motion, and deltoid and rotator cuff strength once the symptoms have settled. Intraarticular corticosteroid injection usually provides relief of symptoms but often needs to be repeated. Cases resistant to conservative treatment may require surgery, which consists of excision arthroplasty of the joint while ensuring that instability is minimized. Careful assessment of rotator cuff function is important, and in the presence of a significant tear, rotator cuff repair or acromioplasty may be indicated. Excision arthroplasty may also be indicated in a younger patient with chronic symptoms, whether caused by degenerative change, osteolysis, or instability.

CALCIFIC TENDINITIS

The prevalence of radiologically detectable calcification in the rotator cuff tendons is reported to be 2.7% to 7.5%; it occurs in both symptomatic and asymptomatic shoulders.⁴⁶ Calcific tendinitis commonly involves the supraspinatus tendon and has been reported to be more frequent in women and sedentary individuals. Bosworth⁴⁷ estimated that symptoms develop in 35% to 45% of individuals with calcification seen on radiography. Frequently bilateral, it usually develops between the ages of 40 and 60 years but can occur as an acute condition in a younger patient. Patients may have chronic symptoms of catching pain with movement as a result of impingement.

Acute calcific tendinitis has a quite different manifestation, with acute severe pain limiting passive or active shoulder movement almost completely and exquisite point tenderness and occasionally erythema being present over the involved tendon. The onset of symptoms can be rapid with no history of injury or overuse, and this occurs during the resorptive phase of calcification.

Patients can therefore be divided into two groups: those with an acute onset of severe pain and limitation of movement, often in the absence of any previous shoulder symptoms, and those who have more chronic catching pain associated with movement and features of subacromial impingement.

Pathophysiology

It has been argued by various authors that calcification occurs as part of a degenerative process involving the rotator cuff tendons, largely because it is rarely seen in people before the fourth decade. Also, complete cuff tears have been found in 21% of patients with calcific tendinitis.⁴⁸ Histologic studies have confirmed that calcification occurs following tendon fibrosis and subsequent necrosis. Uhthoff and Sarkar⁴⁶ proposed a model for the pathogenesis of calcific tendinitis based on its clinical findings as a self-healing condition in which the calcific process is actively mediated by cells in a viable environment. They classified the disease into three stages: precalcific, calcific, and postcalcific. In the precalcific stage it is thought that fibrocartilaginous transformation takes place in the avascular, or “critical,” zone of the supraspinatus tendon. In the calcific stage, calcium crystals are deposited in matrix vehicles and form large deposits (known as the formative phase). After a variable period of inactivity (resting period), the calcium is spontaneously resorbed by means of peripheral vascularization and phagocytosis of the deposit (resorptive phase). Following removal of the calcium the space is filled with granulation tissue (postcalcific stage). Occasionally, a deposit can rupture into the overlying subacromial bursa. An association between this condition and HLA-A1 has been reported.⁴⁶

Investigation

A plain radiograph will identify and localize the calcific deposit to a particular tendon, generally the supraspinatus. In the formative phase of calcification the deposit is well defined and homogeneously dense. In the resorptive phase, usually manifested as the acute condition, the deposit is less well defined and irregular and has a fluffy, less dense appearance (Fig. 73.14). However, the type and size of the deposit do not correlate with the severity of symptoms.⁴⁹ Cortical erosion develops in patients in whom the deposit is in contact with bone, and some authors think that there is a subset of patients with osteolytic lesions of the tuberosities in whom the disease runs a more protracted course.⁵⁰ Degenerative rotator cuff disease and arthropathy may have radiologically detectable calcification, but this is usually associated with other features of these conditions, and the areas of calcification are generally small, stippled, and close to the tendon insertion at the greater tuberosity.

Laboratory investigation does not usually reveal any abnormality in calcium or phosphate metabolism. There is no associated leukocytosis, raised erythrocyte sedimentation rate, or change in serum alkaline phosphatase activity.

Management

Asymptomatic patients require no specific treatment, and spontaneous healing occurs in a significant number of patients. In those with chronic symptoms, conservative management consists of mobility and strengthening exercises of the glenohumeral joint, correction of any scapular dyskinesis, physical modalities, and NSAIDs for relief of symptoms if required. A subacromial injection of corticosteroid can be given to those with clear-cut features of impingement and inflammation but should be repeated only with caution. ESWT has been reported to be effective in selected patients. In the acute stages, treatment should include resting the arm in a sling, analgesics,

antiinflammatory medication, and local application of ice. Needling and attempted aspiration of the deposit under US control may result in reduction of pain, and needling may be followed by lavage. Subacromial injection of lidocaine should be done for temporary relief of pain. Injection of corticosteroid may inhibit the resorption of calcium by reducing vascular proliferation and macrophage activity, although it is often administered following needling. Conservative treatment is usually effective in acute cases, but surgical intervention is indicated when nonoperative management of the chronic condition has failed and there are persistent features of impingement. The deposit can be removed arthroscopically and may be followed by resection of the coracoacromial ligament and anterior acromioplasty, although some evidence suggests that these additional procedures are unnecessary and may be associated with a poorer outcome.

GLENOHUMERAL INSTABILITY AND INTERNAL IMPINGEMENT

Glenohumeral instability is a major cause of symptoms and pathology around the shoulder joint. The more traditional orthopedic model of shoulder dislocation, whether acute or recurrent, has been expanded to encompass the more subtle but equally important subluxations and occult instabilities that can play an important role in the development of shoulder pain, especially in a young active population. Glenohumeral instability can be classified according to the etiology, direction, type, and circumstance of the instability, although in reality this represents a spectrum of disorders ranging from traumatic unidirectional dislocation with a Bankart lesion (TUBS) to the atraumatic multidirectional instability resulting from bilateral glenohumeral laxity (AMBRI).⁵¹ Symptomatic subluxation or instability often results in a painful shoulder with the features of rotator cuff or bicipital tendinitis, but a careful history and examination coupled with a high index of suspicion in a young adult should confirm the presence of instability. Patients with instability may have symptoms of a labral tear such as painful clicking and catching. A ganglion cyst arising from the posterior glenoid labrum in patients with underlying posterior instability may lead to compression of the suprascapular nerve at the spinoglenoid notch, which causes such patients to occasionally have significant weakness in external rotation (Fig. 73.15).

In a throwing athlete, adaptive changes such as stretching of the anterior capsule and contraction of the posterior capsule provide an increased range of external rotation and reduced internal rotation, which allows higher throwing velocity. There is also evidence of adaptive change in the humerus and glenoid (increased retroversion)⁵² giving rise to asymmetric rotation between the dominant and nondominant shoulder. As a result of such changes or in athletes with occult instability, increased glenohumeral rotation and angulation, and anterior translation of the humeral head, the undersurface of the posterosuperior aspect of the rotator cuff impinges against the posterosuperior glenoid rim. This is known as internal impingement⁵³ or posterosuperior impingement, but there is considerable debate whether it results from anterior instability or simply an increase in the range of external rotation. A number of potential pathologic sites of pain exist, namely, the rotator cuff, capsule, labrum, glenoid, and greater tuberosity, and differentiation between internal impingement and symptoms of instability can be difficult. It is important to distinguish between internal and subacromial (external) impingement because the etiology, treatment, and rehabilitation differ considerably in the two conditions.

Management of tendinitis in a young patient with instability should be directed at resolution of the symptoms, restoration of normal flexibility and scapular control, correction of faulty technique in athletes, and then strengthening of the dynamic stabilizers of the shoulder joint, notably the rotator cuff muscles. Correction of any muscle imbalance about the shoulder girdle is important (i.e., weakness of the serratus anterior). Arthroscopy has an important role in the treatment of symptomatic instability, even to the extent of carrying out stabilization procedures on the biceps anchor or glenoid labrum, as well as formal reconstruction. In patients with chronic or recurrent instability, surgical stabilization is often required.

PRINCIPLES OF REHABILITATION

Effective rehabilitation of shoulder disorders requires a good understanding of the functional anatomy and biomechanical properties of the shoulder girdle. Pathologies cannot be treated in isolation because of the complex relationship between the cervicothoracic spine, thoracic cage, scapula, and glenohumeral joint. The clinician and physical therapist need to understand this relationship when designing an exercise program for restoring normal



Fig. 73.14 Calcific tendinitis: formative phase (top arrow) and resorptive phase (bottom arrow).

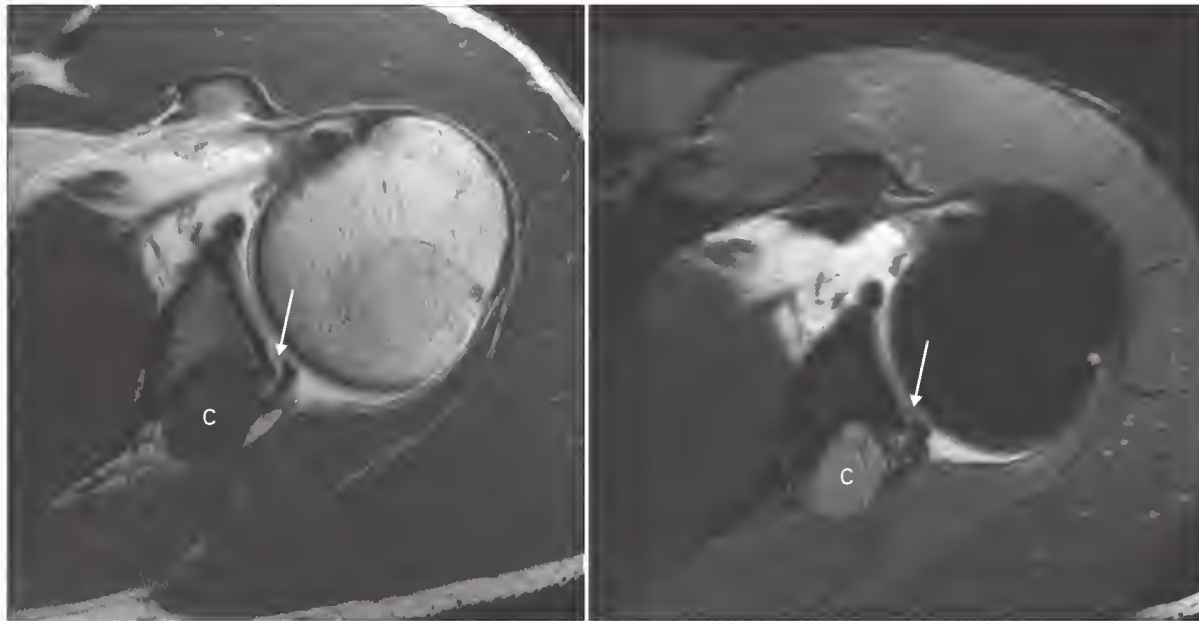


Fig. 73.15 Magnetic resonance image showing a ganglion cyst (C) arising from a tear in the posterior glenoid labrum (arrows).

shoulder kinematics. A simple range-of-motion and strengthening exercise program will not suffice, especially for conditions in which scapulothoracic and scapulohumeral rhythm has been disturbed, and in a significant number of patients with shoulder pain it is this scapular dysfunction that has precipitated or aggravated the underlying pathology. Rehabilitation of the

shoulder in an athlete can be complex because the high demands placed on the shoulder lead to muscle fatigue, which in turn can result in a breakdown in shoulder kinematics. Advances in the treatment of shoulder pain in athletes have improved our overall management of shoulder disorders.

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74

The elbow

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- The elbow is a complex hinge joint that is essential for positioning and full use of the hand.
- Relevant anatomy includes the radiohumeral and ulnohumeral hinge, the connecting proximal radioulnar joint, the radial head, the medial and lateral epicondyles, the ulnar nerve groove, the muscles spanning the elbow, and the olecranon bursa.
- As causes of elbow symptoms, soft tissue lesions such as lateral epicondylitis and olecranon bursitis are far more frequent than joint disease.
- Diagnosis of elbow conditions is largely based on characteristics of the pain, location of the swelling, presence of point tenderness, and the results of passive, active, and resisted motion.

FUNCTIONAL ANATOMY

Bony components

The elbow is accurately classified as a trocho-ginglymus joint because it is a hinged joint that also facilitates rotation (pronation/supination) about a trochlea, or pulley. Flexion and rotation at the elbow bring the hands into view and provide a steady but adjustable base for the hands to maximize use of the highly mobile fingers and opposable thumb. It is a compound synovial joint composed of articulation between the ulnar notch and trochlea of the humerus and between the radial head and humeral capitellum (Fig. 74.1). In continuity with these structures is the proximal radioulnar joint.¹

Humerus

Distally, the humerus expands to form a modified condyle, widest transversely, that consists of articular and nonarticular parts. The capitellum on the lateral aspect is curved, forms less than half a sphere, and contributes anterior and inferior surfaces. A shallow groove separates the capitellum from the medial trochlea, which has anterior, inferior, and posterior surfaces. The medial flange is larger and thus the medial margin projects inferiorly, which results in the plane of the joint being tilted inferomedially. This is the main determinant of the angulation between the long axis of the radius and ulna in an extended supinated position. Medial and lateral bony projections of the lower humerus form the epicondyles, which along with the olecranon, coronoid, and radial fossae, make up the nonarticular part of the condyle. The fossae accept the relevant parts of the ulna and radius during extremes of movement. Above the larger medial and less prominent lateral epicondyle formed by flaring of the distal end of the humerus are the supracondylar ridges. The medial ridge provides a groove for the ulnar nerve as it crosses the elbow and enters the forearm.

Radius and ulna

Proximally, the radius has a head, neck, and tuberosity. The head is discoid, with a shallow cup for the humeral capitellum and an articular periphery that is deepest medially where it contacts the ulnar radial notch. Distal to this is the constriction of the neck, which leads medially to the bony prominence of the tuberosity. The large proximal ulnar segment has large olecranon and coronoid processes, with large trochlear and smaller radial notches to articulate with the humerus and radius. The articulation between the deep trochlear notch and humeral trochlea makes the elbow joint one of

the most congruous and inherently stable. The ulnohumeral and radiohumeral joints provide approximately 50% of the joint's stability, with the rest provided by soft tissues.

Soft tissue components

Ligaments

Varus-valgus stability of the elbow is largely due to the collateral ligaments (Fig. 74.2).² The medial (ulnar) collateral ligament has anterior, posterior, and inferior (oblique) parts. It forms a triangular band with its apex attached around the medial epicondyle and extends in a fan-shaped fashion to insert into a proximal tubercle on the medial coronoid margin (anteriorly) and the medial margin of the olecranon (posteriorly). The anterior portion is the most important elbow stabilizer. The lateral (radial) collateral ligament is attached low on the lateral epicondyle and extends to the annular ligament. Its superficial fibers are blended with those of the attachment of the supinator and extensor carpi radialis brevis.

The strong annular ligament encircles the radial head and holds it against the radial notch of the ulna. It attaches to the edge of the notch anteriorly and on a ridge at or just behind the edge posteriorly. The proximal annular border is continuous with the cubital capsule, except posteriorly, where the capsule passes deep to it at the radial notch. The distal annular border attaches loosely to the radial neck after passing over a synovial reflection. Posterior to the ligament are the anconeus and interosseous recurrent artery. At the point where the ligament is in contact with the radial head internally, it is lined with a thin layer of cartilage, but distally it is covered by a reflected fold of synovium on the radial neck. Recently, mechanoreceptors have been found in the elbow ligaments, thus suggesting that they provide significant sensory function to the elbow joint, as well as being its major mechanical restraints.³

Articular capsule

The elbow has a thin articular capsule. Anteriorly it is broad and attaches proximally to the front of the humerus, medial epicondyle (above the coronoid), and radial fossa (in continuity on its sides with the collateral ligaments), and distally it attaches to the edge of the ulna, coronoid process, and annular ligament. It receives fibers from the brachialis. Posteriorly it attaches to the humerus behind the capitellum, goes around the olecranon fossa (except inferiorly) and the back of the medial epicondyle, and extends to the superior and lateral margins of the olecranon. Laterally it is continuous with the superior radioulnar joint capsule deep to the annular ligament. The anconeus and triceps are related to it posteriorly.

Synovium

The synovial membrane extends from the articular margins of the humerus, lines the articular components of the joint, and descends below the border of the annular ligament. Sometimes the synovial lining of the joint is irregular in the coronoid process on flexion, usually adjacent to the medial collateral ligament, but otherwise it is smooth. Four fat pads are located between the synovium and capsule.

Muscles

The brachialis lies in front of the elbow and triceps with the anconeus behind. The supinator and common extensor tendon of the extensor digitorum communis and extensor digitorum brevis border the joint laterally, and the common flexor tendon and flexor carpi ulnaris border it medially (Fig. 74.3). The biceps tendon passes anterior to brachialis on its way to insertion into the radial tuberosity. The common superficial flexor tendon is attached to the medial epicondyle, and the common superficial extensor tendon is attached to the lateral epicondyle, both outside the joint capsule.

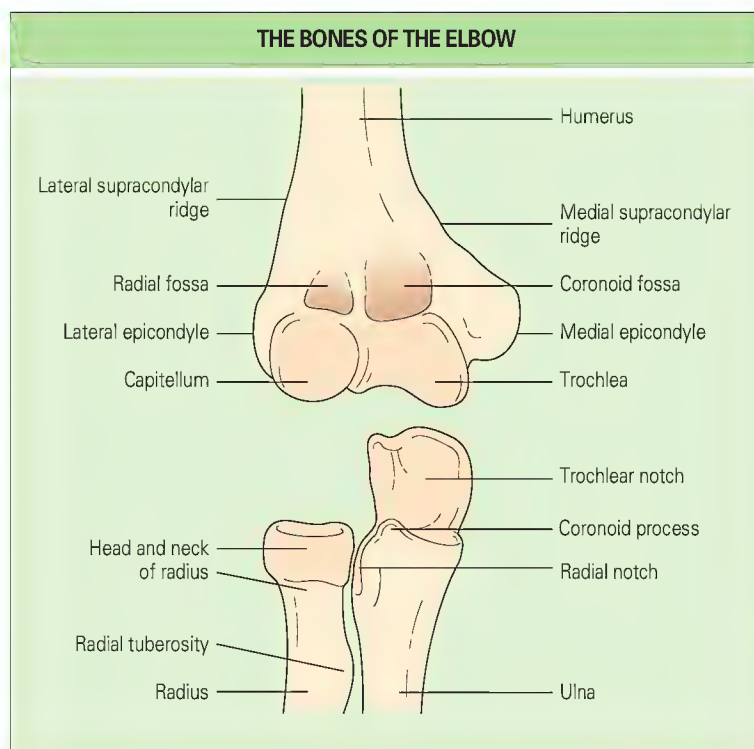


Fig. 74.1 Expanded view of the elbow joint showing the bony features.

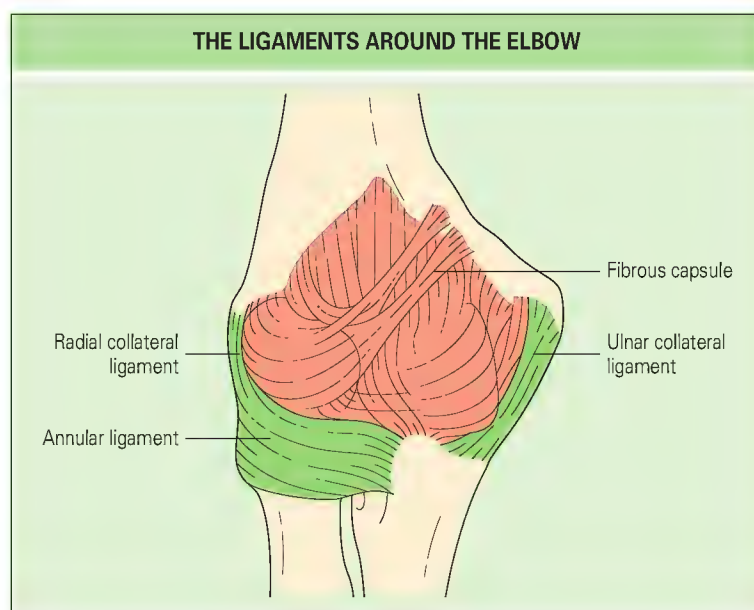


Fig. 74.2 Anterior view of the elbow joint showing the ligaments and capsule.

The anconeus attaches to the posterior lateral epicondyle. Above the medial epicondyle on the supracondylar ridge is attached the humeral head of the pronator teres, and the lateral supracondylar ridge provides attachment to the extensor carpi radialis longus. The triceps passes posterior to the elbow joint and inserts into the olecranon.

Bursae

The main bursa around the elbow is the superficial olecranon bursa, which separates the olecranon from the overlying skin. It forms in late childhood.⁴

Movement

Elbow movements arise from the cubital hinge joint, which traverses around 150 degrees, and the proximal radioulnar joint. Pronation (75 to 80 degrees) and supination (85 to 90 degrees) are achievable, provided that both the

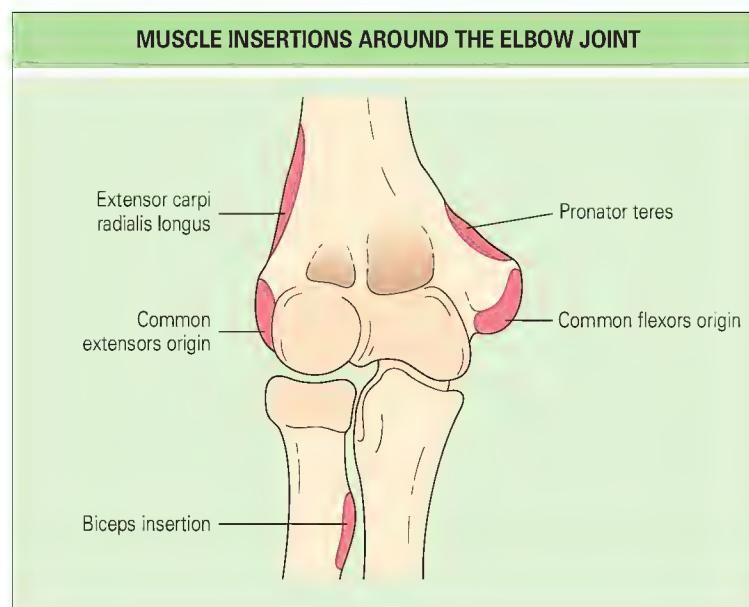


Fig. 74.3 Anterior view of the elbow joint showing the muscle insertions.

proximal and distal radioulnar joints are intact.⁵ The shape of the trochlea causes valgus positioning of the forearm in extension (typically 10 to 15 degrees but more in women), or the “carrying angle.” In flexion, the forearm is positioned in varus to facilitate hand-to-mouth movement.

Neurovascular relationships

The arterial supply to the elbow joint comes from numerous periarticular anastomoses supplied mainly by the brachial artery. The articular nerves are derived principally from the radial and musculocutaneous nerves, but the median, ulnar, and sometimes the anterior interosseous nerves contribute. The nerves follow the blood supply and probably contain vasomotor fibers, as well as pain and proprioception afferents. The brachial artery traverses the joint anteriorly, just medial to the biceps tendon in the antecubital space. The musculocutaneous nerve innervates the biceps and the brachialis above the elbow and terminates distally as the lateral cutaneous nerve of the forearm. The median nerve courses anterior to the joint capsule and medial to the biceps tendon and brachial artery. The radial nerve passes anterior to the lateral epicondyle and descends beneath the brachialis and brachioradialis muscles. The ulnar nerve traverses the elbow in the ulnar groove behind the medial epicondyle.

CLINICAL EVALUATION

History

Evaluation of the elbow must be preceded by a precise history to direct the subsequent examination. Symptoms include pain, loss of movement, weakness, clicking, or locking. Pain may be sharply localized, typical of an extraarticular pathologic process, or may be deep or poorly localizable by the patient (typically referred pain). The functional interplay between the elbow, shoulder, and wrist means that examination of all these joints is usually necessary.

Physical examination

Examination must include a comparison of the right and left arms (Table 74.1).

Inspection

Inspection can be very helpful because much of the elbow joint is subcutaneous and alterations in soft tissue or bony anatomy can readily be visualized. The elbow should be viewed in the extended, supinated position from the front to assess the carrying angle, which can be increased in some congenital conditions, such as Turner syndrome, and may be altered by fractures around the elbow. Synovial proliferation and effusion produce fullness around the lateral infracondylar recess, and the swelling caused by an effusion may reduce or fluctuate with the application of pressure. Radial head

TABLE 74.1**Examination of the elbow**

Inspection	Swelling—joint, bursa Deformity Carrying angle
Palpation	Synovium Joint line epicondyles/soft tissues Ulnar nerve
Movement	Active Passive Resisted
Other	Upper limb neurologic examination Neck and shoulder

pathology (e.g., old fracture) may cause hard bony swelling. Posteriorly, swelling of the subcutaneous olecranon bursa may be detected, and in rheumatoid arthritis, nodules often develop and extend distally along the border of the ulna. Occasionally, ulnar neuritis may result in enlargement of the ulnar nerve, which is detected medially.

Palpation

Palpation should include the lateral and medial epicondyles and the olecranon tip. Tenderness over the lateral epicondyle is typical of lateral epicondylitis. The radial head is palpated by applying gentle pressure over the radiocapitellar joint and is assessed during pronation and supination movements. Loose bodies may be detected in the infracondylar recess. Medially, the ulnar nerve may be palpated to detect thickening, and assessment with the elbow in flexion and extension detects ulnar nerve subluxation. The nerve may be displaced anteriorly during flexion, sometimes with an obvious snap, and be associated with ulnar nerve paresthesia. Posteriorly, the tip of the olecranon and the olecranon fossa above can be felt if the elbow is not in full extension. Flexion to around 15 degrees also enables assessment of the collateral ligaments, which may be palpated. Varus stress with the humerus in full internal rotation and valgus stress in full external rotation test for lateral and medial instability, respectively, but abnormality is often subtle and requires experience to detect.

Movement

Movement should be assessed actively and passively, including flexion, extension, and rotation. Most frequently, a reduced range of movement is due to pain. After injury, elbow joint extension is both the first movement to be lost and the last to recover. The full range of normal flexion/extension is greater than that needed for everyday activity, so patients may be unaware of a small fixed flexion deformity. Forcibly moving the joint beyond the pain-free range helps identify the predominant cause of the restriction. In extension, posterior pain indicates a posterior impingement problem, whereas anterior pain is indicative of tightness of the anterior capsule. The reverse is true for loss of flexion. Early in arthritis, flexion and extension are limited, but rotational movements are often spared. Motion is best assessed with the elbow flexed to 90 degrees and held to the side of the body, with supination often being greater than 85 degrees and a little less for pronation.

Pain should be sought on resisted active movements, particularly when there is no major intraarticular pathologic process. These movements are carried out with the elbow held at 90 degrees. Flexion and supination strength is normally greater than extension and pronation. Passive, but not resisted movements producing pain indicate an intraarticular pathologic process, whereas pain on resisted movement alone is indicative of a musculotendinous pathologic process associated with that movement. To complete the assessment, resisted flexion and extension of the wrist must be performed. Elbow assessment is not complete until neurologic examination has been performed, with particular attention paid to structures supplied by the C5, C6, and C7 nerve roots; the biceps jerk (C5), brachioradialis reflex (C6), and triceps jerk (C7) should be assessed as well.

Differential diagnosis of elbow pain

Pain felt at the elbow may be due to either local pathology or referred pain from the neck or shoulder (Table 74.2). In the case of cervical spine lesions, the pain is often associated with frank neurologic symptoms. Although referred pain is usually part of more generalized arm pain symptoms, it may

TABLE 74.2**Differential diagnosis of elbow pain**

Local	
Articular	Arthritis, osteochondritis, loose bodies, subluxation
Periarticular	Lateral and medial epicondylitis, olecranon bursitis, ligamentous lesions, entrapment neuropathy
Referred	Cervical and shoulder disease

be localized. Examination of the neck and shoulder is therefore important when assessing elbow pain. Intrathoracic pathologic processes can give rise to arm pain but are rarely localized to the elbow.

True elbow pain may be related to joint disease (osteoarthritis, rheumatoid arthritis, gout) but is more commonly due to lesions of the soft periarticular tissues. These causes can usually be distinguished by the history and appropriate examination. Traumatic effusions can occur and the joint may be involved by a fracture of the bones, with minor fractures sometimes being missed until an effusion develops. A traumatic/overuse form of osteochondritis of the radial head can occur in some throwing sports, especially in adolescents. The joint may be affected by loose bodies and synovial osteochondromatosis. Traumatic partial subluxation of the radial head through the annular ligament occurs in children, particularly those with hypermobility.

Investigations

Plain anteroposterior and lateral radiographs are useful in assessing bone and joint pathologic processes. Further investigation by arthroscopy⁶ is very useful, but magnetic resonance imaging (MRI) is often a preferable, noninvasive alternative. MRI and MR arthrography are better than computed tomographic arthrography, although the latter technique is better for assessing the cartilage of the elbow.⁷ High-resolution ultrasonography is a less costly alternative and is particularly useful for assessment of periarticular soft tissues,⁸ especially with the development of color (power) Doppler imaging, which allows detection of abnormalities in blood flow and new vessel formation (angiogenesis), in addition to standard gray-scale ultrasonography. Ultrasonography is very dependent on operator skill, although the precision of the latest equipment is enabling some clinicians to use it as an office investigation.

SOFT TISSUE ELBOW LESIONS

The principal soft tissue lesions of the elbow are lateral epicondylitis (“tennis elbow”), medial epicondylitis (“golfer’s elbow”), and olecranon bursitis. Both epicondylar and radioulnar bursitis have been reported but are rare and produce vague symptoms around the elbow and swelling.

Olecranon bursitis

The principal bursitis at the elbow is olecranon bursitis. The condition is most commonly seen in younger men and is often related to recurrent elbow trauma sustained either at work (e.g., automobile mechanics, miners) or during leisure activities (throwing darts, gymnastics, gardening). Frequently, no obvious precipitating cause of olecranon bursitis is found. It occurs rarely in childhood for developmental reasons.⁴

Etiology

The olecranon bursa is a subcutaneous synovial pouch located on the extensor aspect of the elbow. Because of its superficial position with little soft tissue padding, it is vulnerable to trauma by friction or a blow and to infection through abrasions, puncture wounds, or cellulitis. Olecranon bursitis occurs when the bursa swells because of trauma, inflammation, or infection (Fig. 74.4). Such swelling occurs easily and is readily visible. The swelling may be the result of fluid accumulation but may also be due to synovial tissue hypertrophy or fibrosis. In addition to trauma, the bursa may be involved in crystal arthropathies (gout or, rarely, calcium pyrophosphate arthritis) or in generalized inflammatory arthritis, especially rheumatoid arthritis. Swelling of the olecranon bursa may be seen in association with rheumatoid nodules on the ulnar border of the forearm (Fig. 74.5). Rheumatoid nodules may form within the bursa, but intrabursal nodules may also form as a consequence of traumatic fibrosis or gouty tophi.

Clinical aspects

Olecranon bursitis can be classified clinically into three general categories (Table 74.3):

- Traumatic (or idiopathic) noninflammatory
- Aseptic inflammatory
- Septic inflammatory

Appropriate therapy depends on the category, which must be determined quickly via the history, examination, and when appropriate, bursal aspiration. The main diagnostic challenge is to distinguish septic from nonseptic inflammatory bursitis because septic bursitis has the greatest potential for morbidity. Clinicians must also be aware of the potential for rapid change in the nature of the bursitis, that is, a change from nonseptic to septic. This possibility should be considered at each follow-up visit.

Specific enquiry about occupation, duration of symptoms, and possible trauma or skin injury is important. Information on other causes of bursitis, such as rheumatoid arthritis, gout, or uremia, should be sought. Diabetes or conditions associated with immunosuppression can increase the risk for sepsis. During physical examination the size and turgor of the bursa should be noted (as well as change in size at follow-up visits). Warmth and

erythema of the bursa or skin along with the presence of nodules or lymphadenopathy provide important clues. An effusion in the adjacent elbow joint may occur, especially with inflammatory arthritis. Evidence of trauma, particularly with skin breakage, should be sought. General physical status should be assessed, especially the presence of fever. Key features in the differential diagnosis are provided in Table 74.3.

With traumatic or idiopathic olecranon bursitis, the pain is usually localized and typically does not occur on passive or resisted movement. It is generally provoked by leaning on the elbow or flexion with a constriction around the elbow such as a coat sleeve. Tenderness should be sought about the tip of the olecranon and will be present, sometimes with palpable thickening of the bursal wall, even in the absence of significant effusion; the area is usually very sensitive to pressure. Septic olecranon bursitis occurs less frequently but should not be missed. In general, it occurs after an abrasion or may be associated with an initial cellulitis of the skin. Septic olecranon bursitis can be differentiated from acute arthritis by gentle passive extension, which is unimpaired.⁹

When inflammation or infection is suspected, percutaneous diagnostic aspiration of the bursa is indicated. Aspiration both reduces symptoms and allows assessment of the fluid. Along with gross visualization of blood staining or turbidity of the fluid, a white cell count and differential and Gram



Fig. 74.4 A case of olecranon bursitis in early rheumatoid arthritis.



Fig. 74.5 A case of olecranon bursitis in later rheumatoid arthritis. A rheumatoid nodule is also shown.

TABLE 74.3
Differential diagnosis of olecranon bursitis

	Traumatic noninflammatory	Aseptic inflammatory (e.g., rheumatoid arthritis)	Crystals	Uremia	Septic Inflammatory
Clinical symptoms					
Trauma	+++	+	+	0/+	+++
Tenderness	+	+	++	+	+++
Skin breakage	+	0	0	0	+++
Clinical signs					
Fever	0	0	0	0	++
Warmth	+	+	++	+	+++
Erythema	+	+	++	+	+++
Cellulitis	0	0	+	+	+++
Lymphadenopathy	0	0/+	0/+	0	++
Edema	0/+	0/+	0/+	0	++
Bursal fluid					
Color	C, S	H, C, S	S, H	S	S, H, P
White blood cells per mm ³	50-10,000 (mean, 1100)	1000-60,000 (mean, 3000)	1000-20,000 (mean, 2900)	1200	350-450,000 (mean, 75,000)
Gram stain	Negative	Negative	Negative	Negative	Positive (70%)
Crystals	Negative	Rare cholesterol	Monosodium urate or pyrophosphate	Rare	Negative
Culture	Negative	Negative	Negative	Negative	Positive

Differential diagnosis: 0, usually absent; +, rare; ++, occasional; +++, common. Bursal fluid color: C, clear; H, hemorrhagic; P, purulent; S, serosanguineous.

stain with culture of the fluid should be undertaken to exclude infection. Polarized light microscopy should be performed for detection of crystals. Elbow radiographs are rarely necessary and should be obtained only to exclude traumatic fracture or preexisting joint injury. Ultrasonography can be used to define the characteristics of the bursitis and may assist in needle placement for aspiration and injection in some cases. MRI provides even greater soft tissue definition but cannot reliably distinguish septic from nonseptic bursitis.

Management

Noninflammatory, traumatic (or idiopathic) bursitis usually responds to simple conservative therapy, including rest, elbow protection, and treatment with antiinflammatory drugs. Padded elbow support may help prevent further trauma and skin abrasion. Percutaneous needle aspiration should be considered in patients with significant symptoms. The aspiration itself reduces symptoms, and in addition, a compressive elastic bandage may be used to prevent recurrence of swelling. If infection has been excluded satisfactorily by culture, local corticosteroid injection may be performed, which is effective in speeding recovery.¹⁰ However, it can lead to complications (infection, skin atrophy, chronic pain) and should be used only sparingly for traumatic bursitis. In inflammatory olecranon bursitis related to rheumatoid arthritis or crystalline arthropathy, intrabursal corticosteroid injection is useful. In such cases it should be preceded by aspiration and investigation to exclude infection. An injection of 20 mg methylprednisolone acetate generally leads to rapid recovery.

The finding of infection requires appropriate antibiotic therapy and repeated aspiration as necessary. *Staphylococcus aureus* is the most frequent organism, with group A α -hemolytic streptococci and *Streptococcus epidermidis* being found less commonly.^{9,11} Rarely, *Haemophilus influenzae* and *Pseudomonas* species may be the cause. In immunocompromised patients (malignancy, human immunodeficiency virus [HIV]-positive status, or systemic corticosteroid therapy), specific cultures for atypical organisms, including mycobacteria, fungi, or anaerobic bacteria, should be considered.

Patients who fail to respond to outpatient therapy or who have more severe infection at the outset need to be hospitalized for intravenous antibiotic therapy. This category includes patients with high fever, chills, prolonged duration of symptoms, and cellulitis. Hospitalization also needs to be considered for those with complicating medical conditions (diabetes, uremia, rheumatoid arthritis) and immunosuppression.

Repeated aspiration of the infected bursa is essential and may initially need to be carried out on a daily basis. It can be done percutaneously or, if necessary, with placement of a suction-irrigation system. Cell counts and repeated culture should be performed to monitor response to therapy. Patients initially requiring intravenous antibiotic therapy can be switched to oral medication as soon as the signs and symptoms show consistent improvement. In general, antibiotic therapy should be continued for 10 to 14 days, although some evidence indicates that patients commencing treatment within a week of onset actually require only half this duration to sterilize the bursa.

Surgical drainage or bursectomy is occasionally needed for the management of olecranon bursitis. If repeated traumatic bursitis occurs, surgical removal of the bursa should be considered, either arthroscopically or by open resection. Persistent aseptic inflammatory bursitis may necessitate open resection. Bursectomy may be required for septic bursitis if the acute infection fails to resolve or if after repeated infection a fibrotic, chronically inflamed bursa is left.¹²

Lateral epicondylitis

Epidemiology

Used synonymously with the term *tennis elbow*, this condition is one of the most common specific upper limb disorders. The first description is attributed to Runge in 1873,¹³ but the name “tennis elbow” is derived from Morris’s description of “lawn tennis arm” in *The Lancet* in 1882.¹⁴ Prevalence rates of 0.7% to 2.5%^{15,16} have been reported, with higher rates in manual workers, particularly those performing repetitive bending and straightening of the elbow.¹⁷ Racket sports may be a risk factor, but this has been poorly evaluated, and less than 5% of cases in clinical practice are due to such sports.¹⁸ Nonetheless, the majority of cases do not occur in manual workers, and many cannot describe any specific precipitating factors.¹⁹ Symptoms may be brought on by overuse, and hence lateral epicondylitis is more often seen in the active middle-aged population than in the less active elderly population. In manual workers, relative overuse of the wrist and finger extensors may precipitate or exacerbate the condition, and the dominant arm is most often affected. Sometimes there may be bilateral involvement,

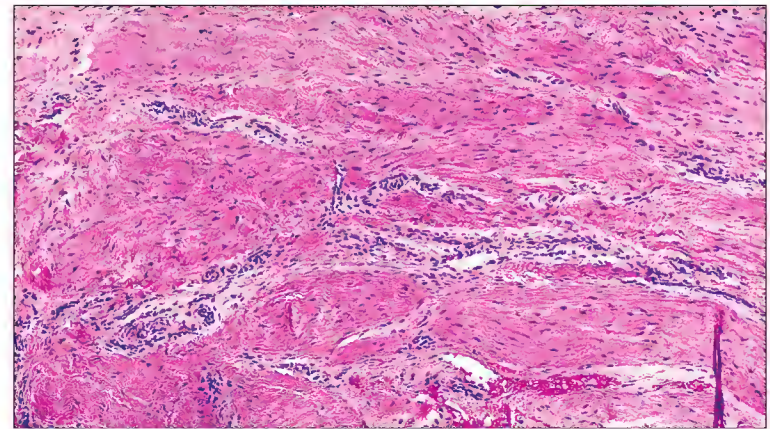


Fig. 74.6 Angiofibroblastic hyperplasia.

either as a result of increased stress placed on the unaffected arm or from a general tendency of some individuals to incur soft tissue lesions.^{17,19}

Etiopathology

More than 25 causes of the condition have been suggested,¹⁹ and this reflects use of the diagnosis nonspecifically for lateral elbow pain. Pathologic material for study is relatively rare because most cases do not come to surgery. Reported operative findings in relatively few chronic cases have included periostitis,¹³ infection,²⁰ radiohumeral joint disease,²¹ radial nerve entrapment,²² and a lesion of the orbicular (annular) ligament.²³ It is thought, however, that the majority of cases are due to a musculotendinous lesion of the common extensor tendon at the attachment to the lateral epicondyle or nearby, especially the portion derived from the extensor carpi radialis brevis.¹⁷ The anatomic location of the extensor carpi radialis brevis makes the undersurface vulnerable to contact and abrasion against the lateral edge of the capitulum with the elbow in motion.²⁴

Originally thought to be an inflammatory lesion, no histologic evidence of inflammation has been found in biopsy material. The reported changes found are consistent with degeneration and attempted repair. Such changes include cystic and fibrinoid degeneration, round cell infiltration, immature fibrous tissue, hyaline degeneration, and vascular plus fibroblastic proliferation (“angiofibroblastic tendinosis”; Fig 74.6), sometimes with calcific debris.^{16,17,25,26} Some cases show a chronic traction effect. The angiogenesis as part of the process is consistent with the vascular changes seen on color (power) Doppler imaging.^{8,27} The changes reported are similar to those seen in the rotator cuff with advancing age, in which tendon vascular factors are thought to be important.²⁸ Some evidence indicates that neurogenic changes of the enthesis may be part of the pathophysiology.²⁹ Ischemic stress may be part of the mechanism because the tenoperiosteal junction (enthesis) and nearby tendon are relatively avascular (the blood supply is a watershed of that derived from muscle and bone) and working muscle takes up the blood supply at the expense of tendon. Lateral epicondylitis is rare in those younger than 30 years, suggesting that aging effects are important and alterations occur in the enthesis in adulthood, including changes in collagen content, reduction in cells and ground substance, and an increase in lipids, which may predispose to injury.³⁰ Other possible factors, including tendon elasticity, have yet to be elucidated. Basic science biochemical investigation of tendon turnover in relation to age and disease may, in the future, lead to further insight into the pathophysiology and possibly novel therapies.

Clinical findings

Lateral epicondylitis usually arises slowly and seemingly spontaneously, with few patients recalling a blow or acute traumatic strain. Pain localizes to the lateral epicondyle but may spread proximally or distally. Grip is impaired because of pain, which may result in restricted daily activities. Tenderness over the epicondyle is usual, although maximum tenderness is sometimes found nearby.²³ The other cardinal sign is an increase in pain on resisting wrist dorsiflexion with the elbow in extension (Fig. 74.7). Symptoms may also be precipitated by extending the elbow with the wrist flexed (Fig. 74.8) and by resisted middle finger extension. Resisted supination may also be painful. Range of movement of the elbow is generally normal, but a few degrees of extension may be lost in severe or chronic cases.

Differential diagnosis

It is important to exclude other conditions producing elbow pain, especially that referred from the cervical spine or shoulder or arthritis of the elbow.

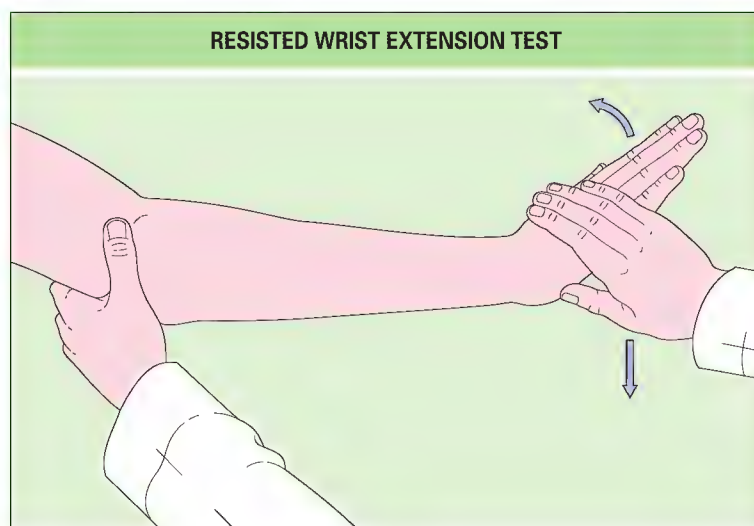


Fig. 74.7 Resisted wrist extension test.

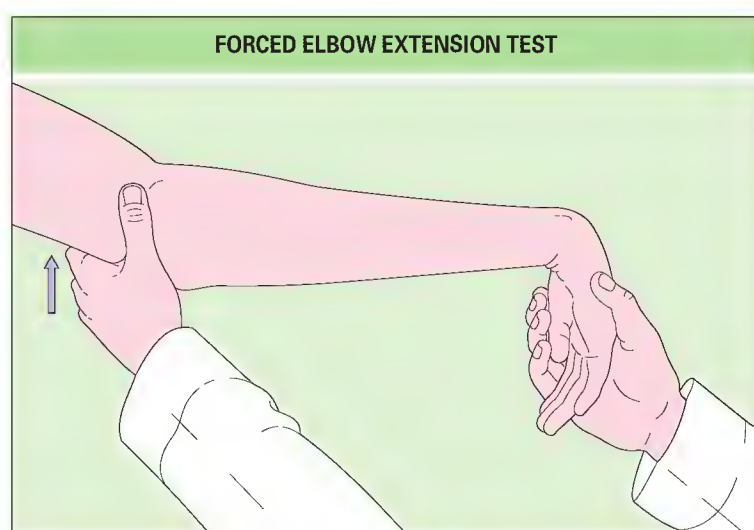


Fig. 74.8 Forced elbow extension test.

Nerve entrapment around the elbow may produce diagnostic confusion. Radial tunnel syndrome or compression of the posterior interosseous nerve²² can provoke lateral elbow and upper forearm pain. It can be the cause of apparent lateral epicondylitis that is unresponsive to conservative treatment but is thought to be a rare cause of resistant cases. These entrapments have been found to be due to compressive lesions caused by abnormal fibrous bands in front of the radial head, a sharp tendinous origin of the extensor carpi radialis brevis, or a radial recurrent fan of vessels. More rarely, a lipoma or ganglion has been found. Compression of the posterior interosseous nerve may occur at the point where it passes through the supinator muscle just below the elbow joint. A well-defined arcade of Fröhse is present in 30% of subjects³¹ and makes a compression neuropathy more likely. Diffuse pain, symptoms distal to the lateral epicondyle, and the presence of muscle weakness may be useful distinguishing features.

Investigations

Investigations are not usually required, but radiographs of the elbow may be helpful in excluding joint disease and may show lateral soft tissue calcification. Electromyography may be helpful in excluding nerve entrapment. Quantitative assessment of severity and response to treatment is difficult, but grading pain, tenderness, and pain on resisted wrist extension can be helpful, and lifting graded weights and grip strength measurement aid objectivity.³² A truly objective measure is infrared thermography of the affected elbow, which shows a discrete localized area of increased heat near the lateral epicondyle in 98% of affected elbows (Fig. 74.9). Analysis of the gradient across the abnormal area reveals a correlation with clinical severity. Lack of general availability of this technique has restricted its use to research. MRI can be used to identify tissue abnormalities before surgery in resistant cases, but the changes identified do not positively correlate with

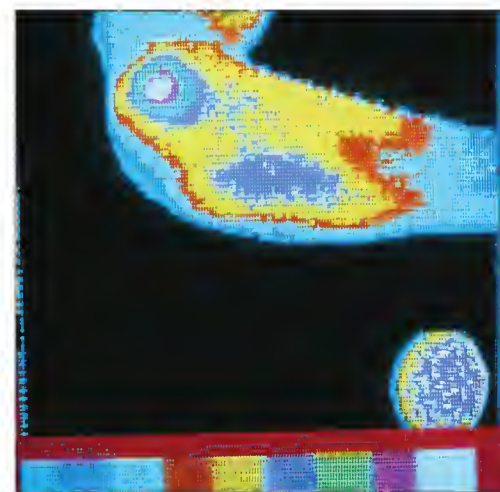


Fig. 74.9 Lateral epicondylitis. Infrared thermography in a patient with lateral epicondylitis shows a localized "hot spot"

TABLE 74.4
Management of lateral epicondylitis

		Evidence grade
Early/mild	Rest, splinting, ¹ NSAID ²	A/B ¹ , A ² (short-term)
Established	Local corticosteroid injection	A (short term)
	Physical therapy	A (weak)
Resistant	Manipulation?	B/C
	Surgery—lateral release	B/C

NSAID, nonsteroidal antiinflammatory drug.

symptoms.³³ High-resolution ultrasonography, especially with color (power) Doppler, is being used increasingly to assess the tissue lesion at an earlier stage and can be of assistance in guiding treatment, including therapeutic injections, and assessing response. In the future the technique may help in predicting resistant cases that will require surgical intervention.^{8,27}

Management

More than 40 treatment regimens for lateral epicondylitis ranging from extremes of "prolonged observation" to x-ray therapy have been described in the literature. Reduced activity may relieve the symptoms in some cases, especially early and in conjunction with splinting (Table 74.4). Though used widely, a systematic review of orthotic devices found that no definite conclusion could be drawn on their effectiveness.³⁴ Oral nonsteroidal antiinflammatory drugs (NSAIDs) or NSAID gels are often used. They have some benefit but have been evaluated only in the short term.³⁵

Numerous physical modalities of treatment of lateral epicondylitis have been tried, but the efficacy of most remains unproven. Lack of evidence may relate to the lack of high-quality trials rather than lack of efficacy. Studies of ultrasound therapy have yielded conflicting results.³⁶ Benefit has not been shown for low-level laser light therapy, possibly because optimal doses and wavelengths were not used.³⁷ Extracorporeal shock wave therapy (lithotripsy) has been suggested for persistent cases, but its efficacy has not been confirmed by controlled studies.³⁸ The reason for this, despite its benefit in some other tendinopathies, is uncertain but may relate to the relative rarity of tendon calcification in this type of tendinopathy. Acupuncture has also been used for treatment but has thus far been shown to have only short-term benefit.³⁹ Evidence accumulated in recent years has suggested that the best physical modality of treatment is an eccentric exercise program.⁴⁰ Various forms have been advocated, either using apparatus or in the form of a simple home exercise program.

Local injections of corticosteroids have been used widely for many years. They produce a rapid response in up to 90% of subjects, albeit often with transient increased pain. Good benefit is achieved for 6 weeks, but as a consequence of a significant relapse rate, long-term benefit is often no better than that with noninvasive approaches to management.^{41,42} Whether this is true failure of the corticosteroid or rapid improvement in pain leading to increased activity too soon is unknown. Some evidence suggests that those

who relapse have a worse long-term prognosis than when just a wait-and-see modified approach is used.^{36,41} These factors, coupled with mounting evidence that the pathology is not inflammatory, have led to increasing consensus that local corticosteroid injections should generally be avoided and that they should be used mainly when a rapid response is important, such as job retention, and then only after suitable counseling about the risks and benefits.

In recent years a number of other treatment modalities have been proposed. Topical nitric oxide delivered via a glyceryl trinitrate patch appears to be beneficial but it has to be applied daily for up to 6 months, and vasodilatation side effects (headache and dizziness/hypotension) can be a problem.⁴³ Autologous platelet-rich plasma injections have been used, but in its 2009 review of this procedure, the National Institute for Health and Clinical Excellence concluded that the evidence available was inadequate for the procedure to be recommended.⁴⁴ Since then, a recent high-quality randomized controlled trial has shown superior long-term benefit over local corticosteroid injections after 2 years of follow-up,⁴⁵ but it is currently unclear whether this technique is better than conservative management, and it is expensive. Similar concerns exist with regard to other treatments, including dry needling, prolotherapy, and injection of autologous blood stem cells or autologous tenocytes. In addition, there is uncertainty about the added value of guiding such injections to the injured tendon tissues with ultrasonography.

Botulinum toxin A injection into the origin of the extensor forearm muscles to temporarily partially paralyze the muscles, particularly the extensor digitorum longus, has been used with the aim of interrupting the repetitive microtrauma, albeit at the expense of some weakness. However, the results have been conflicting. A recent randomized placebo-controlled trial of periarticular hyaluronate gel injection, more commonly used intraarticularly for osteoarthritis, has shown benefit.⁴⁶ Preliminary study of injection of the matrix metalloproteinase inhibitor aprotinin to treat tendinopathy at other anatomic sites has shown some promise but has yet to be used for lateral epicondylitis.⁴⁷

One difficulty with assessment of treatments is that the natural history of lateral epicondylitis is thought to be resolution in around 80% of cases after about 1 year. Treatments are aiming at achieving recovery sooner, but there is concern that failure of some treatments or relapse after improvement may adversely affect outcomes and be worse than a wait-and-see approach.⁴¹ Up to 20% of patients are resistant to conservative management, but we cannot currently reliably identify these patients in the early stages.

Role of surgery

Surgery is usually offered for the approximately 10% of patients failing to respond to conservative measures and should be suggested only after at least 12 months of conservative treatment. The value of manipulation as a means of avoiding surgery is controversial. No evidence-based consensus has been reached on the best surgical management.⁴⁸ Although elbow arthroscopy is becoming more widespread, most published data relate to open procedures involving either resection or débridement of damaged tissue and tendon repair, with or without decortication or drilling of the lateral epicondyle.^{17,25} Alternatively, surgery can involve “lateral release” by division of the origin of the common extensor tendon. Proponents of both approaches claim benefit in up to 90% of cases. The latter approach may be more cost-effective because it can be carried out as a simple percutaneous procedure with a local anesthetic and thus may be done as ambulatory surgery or even as an office procedure.^{48,49} A randomized controlled study comparing standard open débridement and repair surgery with percutaneous “lateral release” reported that recovery and return to work were significantly quicker after the simpler technique.⁵⁰ Arthroscopic release, though more technically challenging and time-consuming, has been shown in a comparative study to be as good as the standard open technique, but with quicker return to work.⁵¹ Also, advocates of arthroscopy point to the fact that the joint can be examined at the same time and may reveal abnormalities contributing to the symptoms and allow their correction. It is generally agreed that extensive lateral release plus resection of the proximal third of the annular ligament is best avoided because of the risk for subsequent elbow instability.

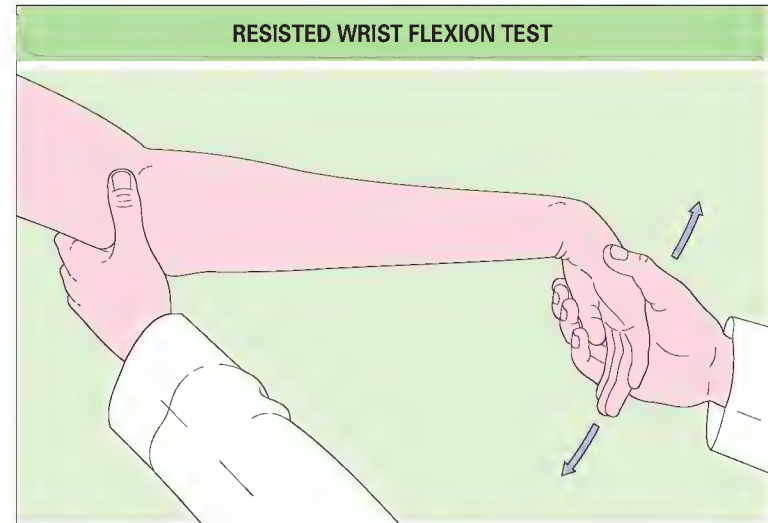


Fig. 74.10 Resisted wrist flexion test.

Prognosis

Lateral epicondylitis is said to improve with time, along with modification of activities. Minor discomfort may persist for several years, and manual workers are at particular risk for recurrence on resumption of the activity that initially induced the pain.¹⁹ Treatment is aimed mainly at settling the condition more quickly, but risk versus benefit, along with cost, has to be considered carefully. Most treatments described for lateral epicondylitis, conservative or operative, are not supported by robust scientific evidence. Until greater proof is available, clinicians need to be guided by the existing evidence, a pragmatic, if subjective viewpoint, and clinical experience.

Medial epicondylitis

Otherwise known as “golfer’s elbow,” this condition is less common than lateral epicondylitis, with a prevalence estimated to be 0.6% in men and 1.1% in women and a peak in middle age.¹⁶ It is a lesion of the common flexor tendon at the medial epicondyle. As with “tennis elbow,” a sporting cause is relatively rare. The condition may cause pain and tenderness slightly less well localized to the medial epicondyle, often felt a little distal to the flexor origin. Pain on resisted wrist flexion with the elbow in extension is the most reliable sign (Fig. 74.10), although rarely, flexion of the fingers rather than the wrist best elicits symptoms. The pathology and management are essentially the same as for lateral epicondylitis, but few data are available on response to treatment of medial epicondylitis.

Other disorders of the elbow

Biceps tendinitis is characterized by local pain and tenderness in the region of the bicipital tuberosity of the radius together with pain on resisted flexion and supination. Pain on resisted flexion alone indicates the rarer brachialis muscle lesion, a condition associated with pain and tenderness that is less well localized and found behind the biceps tendon. Though uncommon, such a tear is particularly prone to the development of myositis ossificans, which in the early phases produces a warm, firm mass that can be mistaken for a tumor. Pain on resisted supination alone is said to indicate a supinator lesion, but this very rarely, if ever occurs and pain would be felt farther down the forearm. It is unusual to have a lesion at the site of the triceps insertion into the olecranon (triceps tendinitis); instead, these lesions occur higher in the arm at the musculotendinous junction. Ligamentous lesions do not usually occur in isolation and are most often associated with traumatic joint synovitis or effusion, if not frank joint derangement or fracture. Medially, a ligamentous lesion may form at least part of the elbow injury caused by some throwing sports, such as javelin, and may, if an overuse injury, need to be distinguished from medial epicondylitis.

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75

The wrist and hand

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- Pain or loss of function in the wrist and hand may originate in the bones and joints, periarticular soft tissues, or peripheral neurovascular structures or may be referred from the cervical spine, thoracic outlet, shoulder, or elbow.
- Precise diagnosis depends on a meticulous history, a thorough physical examination, and appropriately selected diagnostic studies.

INTRODUCTION

The hand is the main tactile sensory organ and is uniquely designed for fine motor activities. Any deviation from the normal architecture or limitation from a painful condition may lead to disability. Understanding this anatomy in detail will help in diagnosis and treatment (Figs. 75.1 to 75.4).¹⁻⁷ The focus of this chapter is on common localized disorders of the hand and wrist.

CLINICAL EVALUATION

History

The evaluation should begin with a complete history—the start of symptoms; their location, nature, and duration; and factors that aggravate or alleviate them. Frequently, chronic conditions have simply worsened over time, and the patient may relate a history of repetitive or strenuous activity that has become more painful or difficult.

Physical examination

The examination should include observation of resting posture and inspection for the presence of any swelling, deformity, ecchymosis, atrophy, or skin and nail changes.^{2,5,6} Understanding the surface anatomy of the hand and wrist is important in evaluating injuries (Fig. 75.5).

Resting posture

At normal rest the metacarpophalangeal (MCP) joints are flexed 45 to 70 degrees, and each of the interphalangeal (IP) joints are slightly flexed up to 10 degrees.⁸ Rheumatoid arthritis (RA) and other chronic inflammatory diseases can cause volar subluxation of the carpus, carpal collapse, and radial deviation of the carpus. Chronic arthritis of the distal radioulnar joint may result in instability with dorsal subluxation of the ulnar head, which displays a “piano key” movement on downward pressure.⁴

Swelling and deformity

The fingers and thumb may demonstrate swelling and deformity of the joints, clubbing, subcutaneous nodules, gouty tophi, Heberden (distal IP [DIP] joint) or Bouchard (proximal IP [PIP] joint) nodes, sclerodactyly, telangiectasia, ischemic digital ulcers, pitting of the skin, nail fold abnormalities, periungual erythema, or psoriatic skin and nail lesions.^{4,5} Swelling secondary to MCP synovitis may obliterate the normal concavity seen between the metacarpal heads. Digital flexor tenosynovitis produces diffuse swelling (sausage finger) with tenderness over the volar aspect of the finger along the tendon sheath. MCP joint deformities include ulnar drift, volar subluxation, and flexion deformities. RA is a disease that affects the soft tissues (ligaments and tendons) of the hand as much as the bones. As a

category, these deformities all arise from alterations in the delicate balance between extensors and flexors acting on the phalanges. A boutonnière deformity is flexion of the PIP joint and hyperextension of the DIP joint (Fig. 75.6a). A swan neck deformity describes hyperextension of the PIP joint and flexion of the DIP joint (see Fig. 75.6b). A Z-shaped deformity of the thumb (commonly seen in RA) involves flexion of the MCP joint and hyperextension of the IP joint (see Fig. 75.6c).⁴ Telescoped shortening of the digits, produced by partial resorption of the phalanges with loss of the articulations secondary to psoriatic arthritis, RA (arthritis mutilans), or inflammatory arthritic conditions, may demonstrate concentric wrinkling of the skin (opera-glass hand).⁴

Differential diagnosis of joint swelling

It is important to distinguish between joint effusion and tenosynovial inflammation from a localized mass. Patients with tenosynovitis have more passive than active range of motion. Arthritis of a joint generally produces a diffuse circumferential swelling, whereas extensor tenosynovitis is usually characterized by a longitudinal or oval dorsal swelling localized to the region of the tendon sheath at the wrist level. When the fingers are actively extended, the distal margin of the swelling moves proximally and folds in, like a sheet being tucked under a mattress (“tuck” sign).^{2,4} Tenosynovitis of the common flexor tendons will be manifested as swelling on the volar aspect of the wrist just proximal to the carpal tunnel (volar “hot dog” sign).⁴ The wrist is also a relatively common site for benign masses; ganglions may mimic the just-mentioned inflammatory processes (Fig. 75.7).

General examination

Dryness or cracking of the fingertips can indicate nerve injury. Normal capillary refill takes less than 2 seconds. The Allen test evaluates the vascular arches of the hand. Sensory function of the fingertips is evaluated by light touch and two-point discrimination with a custom-bent paper clip or calipers. Normal two-point discrimination is less than 5 mm.⁹

Palpation can often localize a specific region with an underlying pathologic process. The wrist is best examined in slight flexion by palpating the dorsal surface of the wrist with the thumbs while supporting the wrist with the fingers of both hands.^{2,3} This technique can gently identify and often distinguish an effusion, inflamed tenosynovium, or another dorsal wrist pathologic process. A similar technique is suited to the carpometacarpal (CMC) and MCP joints as well, where thick volar skin, subcutaneous tissue, and flexor tendons may make volar palpation less helpful. Dorsal fluctuance may indicate an effusion: pressure from one hand on one side of the joint will produce a fluid wave that will be transmitted to the second hand placed on the opposite side of the joint.⁴

The PIP and DIP joints are palpated for nodules, tenderness, capsular irregularities, or effusion by placing the thumbs and forefingers of both hands on opposite sides of the joint.³ Although synovitis and other inflammatory processes may cause tenderness, the dorsal knuckle pads demonstrate nontender, thickened skin localized to the dorsal surface of the PIP joints.⁴

Tendon nodules usually occur at the level of the metacarpal heads opposite the A1 pulleys, just proximal to the MCP flexion creases in the palm. These nodules can be palpated in the palm while the patient slowly flexes and extends the affected finger, which may result in a “triggering” sensation.

Range of motion

Active motion should be assessed before passive manipulation. Lack of ability to flex or extend across a joint or malalignment with motion may indicate either underlying tendon disruption or displacement or joint subluxation or dislocation. As the digits are flexed, the fingertips should point

BONES AND JOINTS OF THE WRIST AND HAND

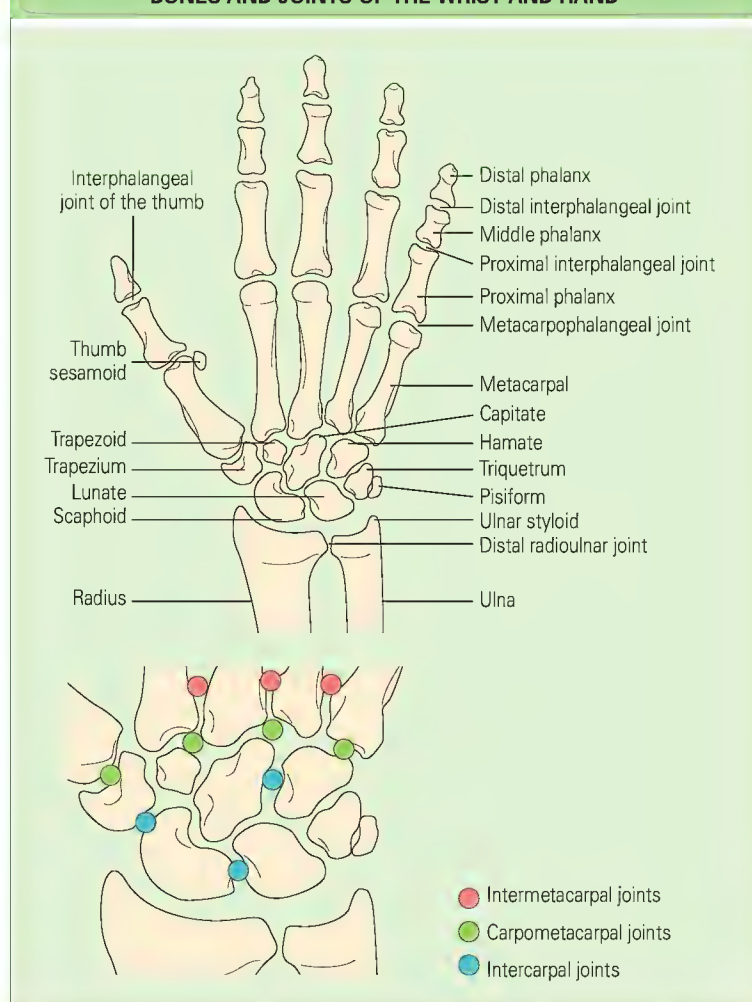


Fig. 75.1 Bones of the wrist and hand. (Used with permission from Fam AG. *The wrist and hand*. In: Hochberg M, Silman A, Smolen JS, et al, editors. *Rheumatology*. 3rd ed. St. Louis: Mosby; 2003, p. 641-50.)

toward the scaphoid. The distal nail tips should be rotationally aligned when the fingers are in a partially flexed position.

Wrist motion should be assessed for flexion, extension, pronation, supination, and radial and ulnar deviation. The normal range is 65 to 80 degrees of flexion, 55 to 75 degrees of extension, 30 to 45 degrees of ulnar deviation, and 15 to 25 degrees of radial deviation.¹⁰ The intercarpal joints and radiocarpal joint allow wrist flexion and extension. Pronation and supination of the hand and forearm occur at the proximal and distal radioulnar joints. Full composite digital flexion should allow the fingertips to touch the palm opposite the MCP joints at the level of the distal palmar crease (see Fig. 75.5). Motion at the thumb CMC joint is variable within the population. The sum of thumb CMC, MCP, and IP motion is about 180 degrees in most healthy people, but the proportion of motion at each joint is distributed differently such that some people have stiffer CMC joints but looser MCP and IP joints or vice versa. Disease may change these proportions. Patients with arthritis of the thumb CMC joint may compensate for lost CMC motion by hyperextending the thumb MCP joint to preserve the span of the first web space for encompassing large objects.

Strength testing should include resisted motion across each joint. Resisted DIP flexion will test the strength of the flexor digitorum profundus, and testing individual digits for resisted PIP flexion while maintaining the other digits extended will evaluate function of the flexor digitorum superficialis. Isolated extension across the MCP, PIP, and DIP joints is important in patients with rheumatic disease to separate extrinsic and intrinsic extensor capabilities.

Stability of the MCP joint is evaluated by flexing it to 90 degrees to place the radial and ulnar collateral ligaments on stretch and then attempting lateral motion while stabilizing the metacarpal joint. The stability of the radial and ulnar collateral ligaments of the PIP and DIP joints can be assessed by applying lateral stress with the joint at 0 and 30 degrees of flexion.

FLEXOR TENDON SHEATHS OF THE WRIST AND FINGERS

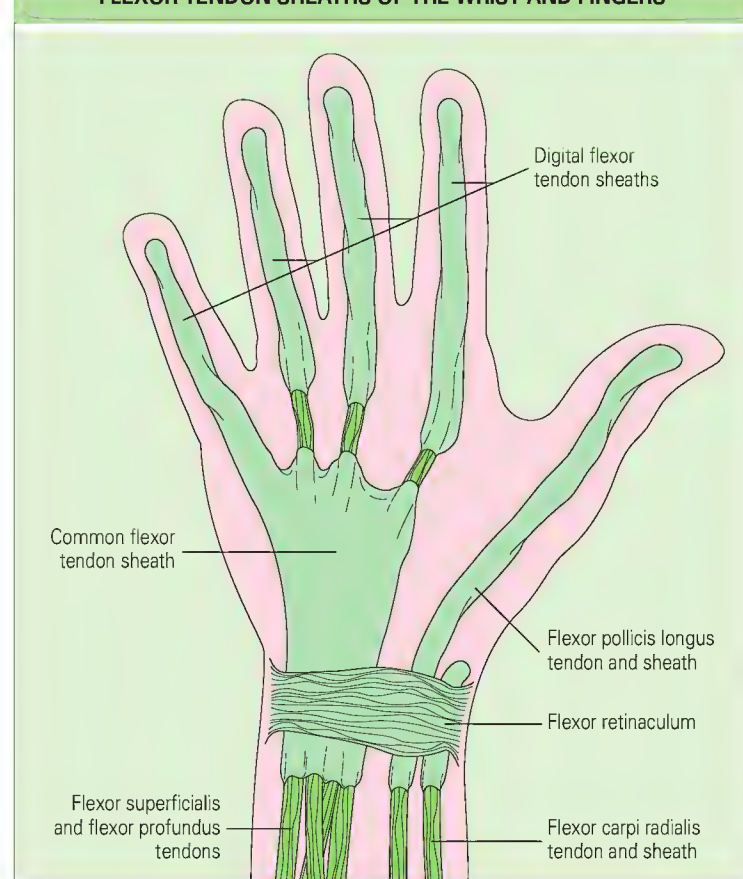


Fig. 75.2 Flexor tendon sheaths of the wrist and fingers. (Used with permission from Fam AG. *The wrist and hand*. In: Hochberg M, Silman A, Smolen JS, et al, editors. *Rheumatology*. 3rd ed. St. Louis: Mosby; 2003, p. 641-50.)

TENDON INSERTIONS OF THE FINGER

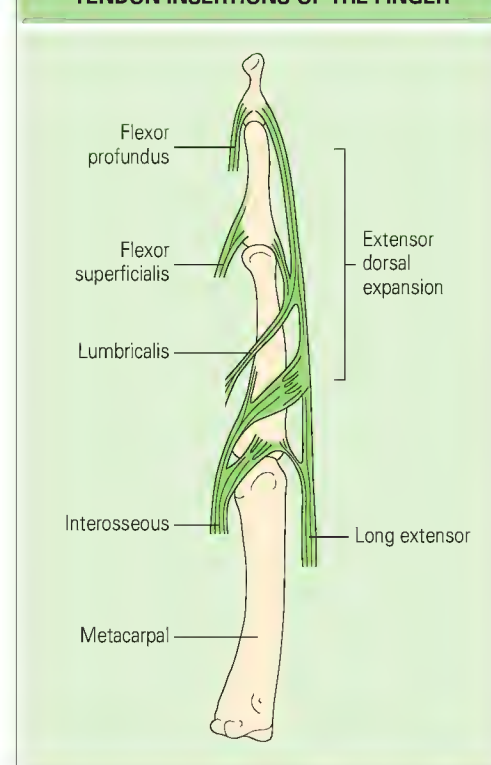


Fig. 75.3 Tendon insertions of the finger. (Used with permission from Fam AG. *The wrist and hand*. In: Hochberg M, Silman A, Smolen JS, et al, editors. *Rheumatology*. 3rd ed. St. Louis: Mosby; 2003, p. 641-50.)

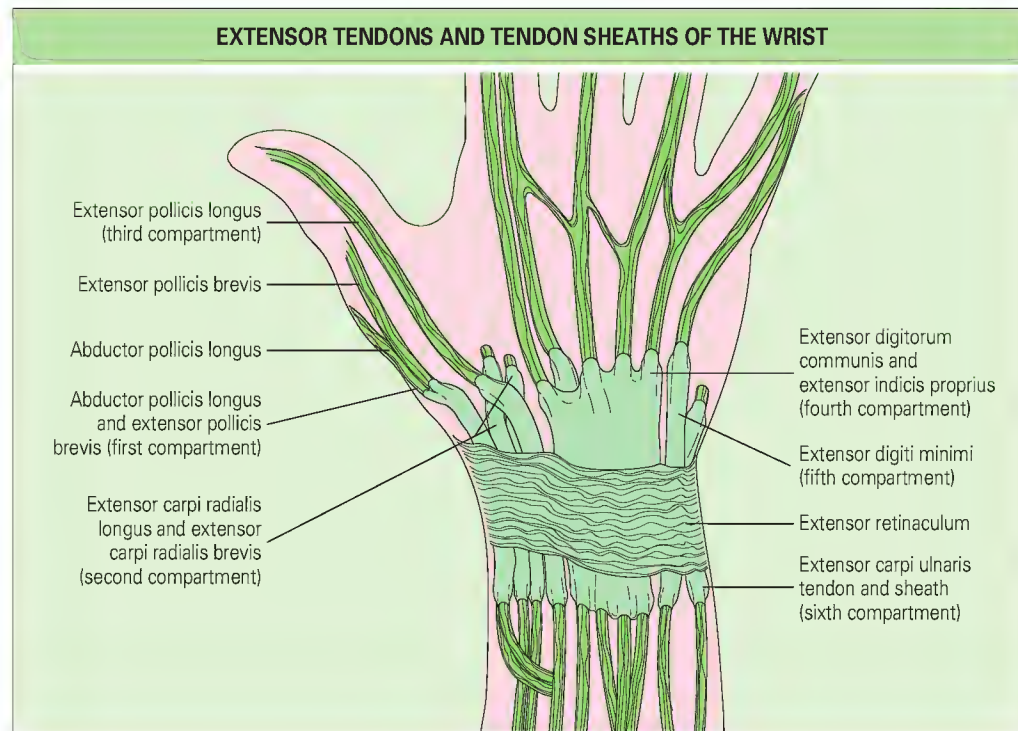


Fig. 75.4 Extensor tendons and tendon sheaths of the wrist. (Used with permission from Fam AG. *The wrist and hand*. In: Hochberg M, Silman A, Smolen JS, et al, editors. *Rheumatology*. 3rd ed. St. Louis: Mosby; 2003, p. 641-50.)

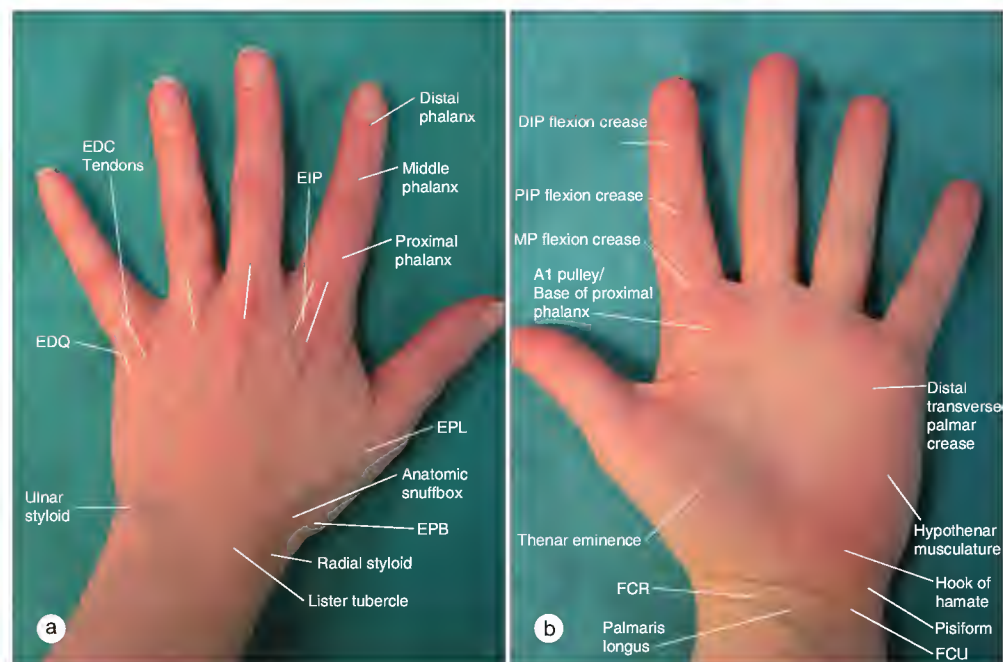


Fig. 75.5 Surface anatomy of the dorsal (a) and volar (b) surfaces of the wrist and hand. DIP, distal interphalangeal; EDC, extensor digitorum communis; EDQ, extensor digiti quinti; EIP, extensor indicis proprius; EPB, extensor pollicis brevis; EPL, extensor pollicis longus; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; MP, metacarpophalangeal; PIP, proximal interphalangeal. (Used with permission from Earp BE, Waters PM. *The wrist and hand*. In: Frontera WR, Micheli LJ, Herring SA, Silver JK, editors. *Clinical sports medicine—medical and rehabilitation aspects*. Philadelphia: Saunders; 2006.)

Differential diagnosis of wrist and hand pain

Pain and functional disability in the wrist and hand are common symptoms that can be caused by a wide range of underlying conditions, including pathologic processes of the bones and joints of the wrist and hand, periarticular soft tissues, tendons, and peripheral neurovascular structures, or may be referred from the more proximal structures of the cervical spine, thoracic outlet, shoulder, or elbow. Table 75.1 details many disorders of the wrist and hand based on the site of origin of symptoms and the primary location. Precise diagnosis rests on a thorough history and physical examination and a few rationally selected diagnostic studies.

SPECIFIC DISORDERS OF THE WRIST AND HAND

Tenosynovitis

As the extrinsic tendons cross the wrist, they provide both power and dexterity to the hand. Each tendon passes through a tendon sheath, which is lined by an inner (visceral) synovial layer that adheres closely to the tendon and an outer (parietal) synovium that covers the inside of the fibrous tendon sheath.⁴ The visceral and parietal synovial sheaths are attached by the



Fig. 75.6 Deformities of the fingers and thumb. (a) Boutonnière deformity. (b) Swan neck deformity. (c) Z-shaped deformity of the thumb. (Used with permission from Fam AG. *The wrist and hand*. In: Hochberg M, Silman A, Smolen JS, et al, editors. *Rheumatology*. 3rd ed. St. Louis: Mosby; 2003, p. 641-50.)



Fig. 75.7 Dorsal wrist ganglion.

mesotendon, through which pass vessels and nerves to the tendon. The mesotendon may be less substantial in some tendon sheaths and be represented only by threads or vinculae.¹¹ With aging, tendons become less elastic and less able to tolerate stress without injury.⁴

Stenosing tenosynovitis is usually an idiopathic condition that results from inflammatory changes, including fibrosis and thickening of the tendon sheath and “fibrillar creep” of the tendon in which the fibers become edematous and bunched.^{11,12} The result is that tendon gliding is impaired and the patient may experience “catching,” “triggering,” or “locking” on either side of the retinacular ligament or pulley. Tenosynovitis is uncommonly related to a single traumatic event.

Patients with tenosynovitis most frequently describe symptoms of discomfort along the tendon, stiffness or lack of motion of the digit, and swelling. On examination, tenderness will be present along the affected tendon longitudinally and crepitus may be palpated, especially with motion. Provocative testing includes placing the tendon under tension, either by resisted muscular contraction or by passive stretching, which will result in an exacerbation of the symptoms.

de Quervain tenosynovitis, intersection syndrome, and trigger finger/thumb are all common conditions caused by “primary” tenosynovitis unrelated to an underlying medical condition.

Secondary causes of tenosynovitis are less common and include RA, systemic lupus erythematosus, scleroderma, psoriatic arthritis, reactive arthritis, infection (bacterial, mycobacterial, fungal, and viral), microcrystalline disease (gout and calcium pyrophosphate and hydroxyapatite or calcific tenosynovitis), amyloid deposition, sarcoidosis, and pigmented villonodular tenosynovitis.⁴

de Quervain syndrome

de Quervain syndrome describes tenosynovitis of the first dorsal compartment tendons: the abductor pollicis longus (APL) and the extensor pollicis brevis (EPB) (see Fig. 75.4). It is most common in women between 30 and 50 years of age^{4,11,13,14} and may occur in association with rheumatoid, psoriatic, or other inflammatory arthritis conditions, localized trauma, and pregnancy or during the postpartum period.^{15,16} Repetitive activity that involves active thumb flexion while radially and ulnarly deviating the wrist may result in inflammation and subsequent thickening and stenosis of the tendon sheath as it passes over the radial styloid beneath the extensor retinaculum.¹⁷ This may lead to significant radial-sided wrist pain with focal swelling and tenderness and crepitus 1 to 2 cm proximal to the radial styloid over these tendons (Fig. 75.8).¹³ In the Finklestein test the thumb is flexed into the palm and then the wrist is gently ulnarly deviated to reproduce the focal discomfort.¹⁸

Symptoms of de Quervain tenosynovitis may be similar to those of osteoarthritis of the first CMC joint or intersection syndrome.

Patients with mild symptoms may be treated by activity modification, rest, use of a long opponens splint with the IP joint free, and antiinflammatory medication.¹⁹ With more severe or persistent pain, corticosteroid injection may be beneficial and can result in complete and lasting relief in about 70% of patients.²⁰⁻²² If conservative management fails to alleviate the symptoms, surgical release of the first dorsal compartment may be appropriate.²¹ Up to 76% of patients have more than one slip of the APL tendon and 60% have a dividing septum in the compartment, which should be released if identified at surgery.²³

Intersection syndrome

Intersection syndrome occurs at the “intersection” where the APL and EPB cross over the extensor carpi radialis longus and brevis approximately 4 cm proximal to the wrist joint.^{24,25} It results from the frequent repetitive wrist

TABLE 75.1

Differential diagnosis of wrist and hand pain

Articular	
Arthritis of the wrist, MCP, PIP, and/or DIP as a result of	Trauma, hypermobility, sprain RA (wrist, MCP, PIP joints) Osteoarthritis (first CMC, PIP, and DIP joints) Other forms of arthritis: gout, psoriatic arthritis, infection Joint neoplasm
Periarticular	
Subcutaneous	RA nodules, gouty tophi, painful subcutaneous calcific nodules in scleroderma, glomus tumor of the nail bed
Palmar fascia	Dupuytren contracture
Tendon sheath	Wrist extensor tenosynovitis, including de Quervain tenosynovitis and extensor carpi radialis tenosynovitis Wrist volar flexor tenosynovitis (including carpal tunnel syndrome) Thumb flexor tenosynovitis (trigger or snapping thumb) Finger flexor tenosynovitis (trigger finger) Pigmented villonodular tenosynovitis (giant cell tumor of the tendon sheath)
Acute calcific periarthritis	Wrist, MCP, and rarely the PIP and DIP joints
Ganglion	
Osseous	
Bone lesions	Fractures, neoplasm, infection, osteonecrosis, including Kienböck disease (lunate) and Preiser disease (scaphoid)
Neurologic	
Nerve entrapment syndromes	
Median nerve	Carpal tunnel syndrome (at the wrist) Pronator teres syndrome (at the pronator teres) Anterior interosseous nerve syndrome
Ulnar nerve	Cubital tunnel syndrome (at the elbow) Guyon canal (at the wrist)
Posterior interosseous nerve syndrome	Radial nerve palsy (spiral groove syndrome)
Lower brachial plexus	Thoracic outlet syndrome, Pancoast tumor
Cervical nerve roots	Herniated cervical disk, tumors
Spinal cord lesion	
Spinal tumors, syringomyelia	
Vascular	
Vasoplastic disorders with Raynaud phenomenon	Scleroderma, occupational vibration syndrome, etc.
Small- or large-vessel vasculitis	With digital ischemia, ischemic ulcers, e.g., systemic lupus erythematosus, RA, and Takayasu arthritis
Referred pain	
Cervical spine disorders	Shoulder-hand syndrome and causalgia
Reflex sympathetic dystrophy syndrome	
Cardiac	Angina pectoris

CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis.

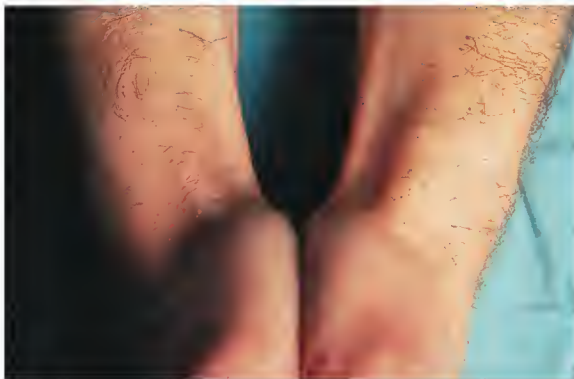


Fig. 75.8 de Quervain tenosynovitis of the wrist. (Used with permission from Fam AG. *The wrist and hand*. In: Hochberg M, Silman A, Smolen JS, et al, editors. *Rheumatology*. 3rd ed. St. Louis: Mosby; 2003, p. 641-50.)

movements most commonly seen in athletes (rowers, canoeists, weight lifters)⁴ and is associated with localized tenderness and swelling and palpable or audible crepitus with wrist flexion and extension. Most patients respond well to splinting, rest, antiinflammatory agents, and possibly an injection. Surgical release of the tendon sheaths of both compartments can be performed in refractory cases.²⁵

Trigger finger/thumb (stenosing digital tenosynovitis)

Trigger finger/thumb is one of the most common causes of pain and disability in the hand and occurs more frequently in patients with RA, diabetes mellitus, gout, and other conditions associated with connective tissue disorders.²⁶ The disorder is commonly limited to one digit but may be seen in multiple digits over time.

Tenosynovitis leads to fibrosis with constriction of the first annular pulley (A1) that overlies the MCP joint.²⁷⁻²⁹ A tendon nodule may develop and can be felt as a palpable mass in the palm that moves with the tendon as the digit flexes and extends. The nodule or tendon sheath constriction interferes mechanically with normal tendon gliding. Intermittent locking of the digit in flexion may also occur and is most frequently

noted on awakening. Over time, not moving the joint can lead to flexion deformity.⁴

Early management may consist of modification of hand activities, heat therapy, gentle exercises, and antiinflammatory medications as required.^{27,28} Extension splinting of the affected digit at night prevents the painful locking of the digit most often found in the morning.

Sometimes, trigger finger or thumb may resolve spontaneously. Corticosteroid injection is often curative, with success rates of up to 85%.^{26,30,31} Insulin-dependent diabetes has been identified as a significant independent predictor of failure of relief from an injection alone.³² If corticosteroid injection fails, surgical release of the A1 pulley is indicated.^{29,33}

Ganglions of the wrist and hand

Ganglions are cystic masses arising from a nearby joint capsule, tendon, or tendon sheath. They are the most common soft tissue tumor in the hand (50% to 75% of all masses), and they commonly occur in women in their 20s and 30s.⁴ Ganglions are lined with synovial tissue and contain a clear, gelatinous fluid. They are typically thin walled and may be unilocular or multilocular. Some may be quite large; others are occult and seen only on magnetic resonance imaging (see Fig. 75.7).

Ganglion cysts most commonly arise on the dorsal surface of the wrist (60% to 70%) and can typically be traced by their stalk to the capsule overlying the scapholunate ligament.³⁴ The second most common location is the volar radiocarpal joint (20%).⁴ Ganglions also arise as cysts of the tendon sheath from the A1 pulley, as mucinous cysts related to DIP joint arthrosis, or along any of the extensor and flexor tendons.

Ganglions are typically painless, well-circumscribed swellings on the dorsum of the wrist. They may cause mild to moderate discomfort when performing activities such as push-ups or other motions that load the wrist in an extended position. Most patients seek treatment because of the appearance of the ganglion rather than its functional limitation. They may note that the mass has changed in size over time—becoming larger for a while and then regressing. The mass may be palpably firm or soft, depending on how tense the cyst is when examined. Patients with symptoms of ulnar or median nerve compression should be evaluated closely because a space-occupying mass such as a ganglion in the canal of Guyon or the carpal tunnel can elicit these symptoms.^{35,36}

Radiographs of the affected region may demonstrate soft tissue swelling, but ultrasonography or magnetic resonance imaging may be required to better delineate the ganglion and trace its origin back to a joint capsule or tendon sheath or to detect intraosseous ganglions.³⁵

Histologically, a ganglion consists of compressed collagen fibers partially lined by fibroblast-like cells, similar to synovium.³⁵ Typically, minimal inflammatory tissue is present. The stalk of the ganglion may take quite a circuitous path as it connects from the joint or tendon sheath to the main body of the cyst. The liquid inside a cyst is a clear, viscous, gelatinous-type fluid containing high levels of hyaluronic acid, glucosamine, albumin, and globulin.⁴

The etiology of ganglion cysts is poorly understood. Although most patients cannot recall a specific traumatic event, it is thought that mild repetitive trauma may thin or tear the joint capsule or tendon sheath and allow the egress of fluid into a subcutaneous location. Arthrography has shown that intraarticular fluid will enter the cyst, but cystograms typically show that the cystic fluid does not reenter the joint, thus indicating that the stalk must include a type of one-way valve.³⁷ The valvular mechanism may explain why aspiration or simple excision of the ganglion without removal of the stalk can result in a recurrence rate of 50%.³⁸

Treatment of dorsal wrist ganglions begins with reassuring the patient that the condition does not require treatment unless it is causing difficulty. Home remedies such as hitting the cyst with a large book are not recommended. Ganglion cysts may change size over time and can disappear spontaneously. Aspiration may lead to complete resolution, but as noted earlier, recurrence is quite common. Aspiration of cysts in some areas may be less of an indication because of the risk of damaging neurovascular structures. Surgery is indicated when symptomatic ganglions fail to respond to more conservative methods. After surgical excision, including eradication of the capsular stalk, the rate of recurrence is less than 5%.³⁸ Wrist ganglions have also been treated successfully by arthroscopic elimination of the stalk from within the joint.³⁹

Carpal tunnel syndrome

Carpal tunnel syndrome is usually associated with burning or tingling sensations or numbness (or both) over the volar aspect of the radial three digits. Pain at night and difficulty sleeping are commonly noted.

Uncommon in the young, carpal tunnel syndrome is most often an idiopathic disease of aging. Pressure on the nerve is increased as it passes through the relatively restrictive carpal tunnel along with nine flexor tendons. Any swelling in this area as a result of tenosynovitis, fluid retention, trauma, or arthritis may decrease the space available for the nerve and can cause symptoms. Pregnancy, thyroid disease, rheumatoid and other inflammatory arthritic conditions, and diabetes are also associated with carpal tunnel syndrome.

On physical examination, patients may have decreased two-point discrimination in the median nerve distribution and, in later stages, weakness of the thenar musculature. Testing of the abductor pollicis brevis by resisted palmar abduction is important. Many patients may not be able to exactly articulate or distinguish the regions of sensory deficit, and some will have objectively decreased two-point discrimination in the ulnar two digits as well, possibly related to increased pressure in the canal of Guyon related to the underlying carpal tunnel syndrome. Tenosynovitis of the digital flexors may be noted especially in the inflammatory arthropathies. Provocative testing includes elicitation of the Tinel sign (distally radiating altered sensibility with percussion of the median nerve just radial to the palmaris longus at the level of the volar wrist crease) and performance of the Phalen test (reproduction of symptoms with the wrist held in gravity-assisted flexion with the elbows extended for 60 seconds) and Durkin test (reproduction of symptoms with pressure applied continuously over the carpal tunnel). Atrophy is a late finding associated with long-standing compression. Many patients respond to nonoperative management consisting of modification of activity, nighttime splints, antiinflammatory medications, and possibly corticosteroid injection. If such treatment fails, nerve conduction testing should be undertaken to confirm the diagnosis. Surgical release of the carpal tunnel may be indicated for relief of symptoms and to prevent further nerve damage. Surgery is the definitive treatment in older patients with chronic numbness, muscle weakness, and symptoms lasting for longer than 6 to 12 months. In patients with comorbid conditions such as mucopolysaccharidoses, dysplasias, endocrine disorders, inflammatory conditions, and connective tissue abnormalities, a surgical procedure is more commonly necessary for treatment.⁴⁰

Dupuytren disease

Dupuytren disease or contracture is a usually painless hereditary condition in which the palmar fascia (aponeurosis) becomes markedly thickened. It may cause small lumps or nodules to form deep to the skin at the base of the digits or in the palm, and pitting of the skin may be noted.^{41,42} The ring finger is most commonly affected, followed by the small and long fingers. Bilateral disease is not uncommon. The myofibroblast is the cell type associated with this condition. Contraction of myofibroblasts in the palmar fascia leads to the early nodular findings. The skin may become involved through local invasion by fibroblastic cells, which results in pitting (Fig. 75.9). Despite being called “local invasion,” Dupuytren disease is noncancerous. In some patients the disorder may never progress from the nodular stage and thus may not require further medical treatment. In most patients, increasing thickening with extension into the digits will develop gradually over a period of months to many years and lead to restriction of motion and flexion contracture. The tendons and joints are not involved with the Dupuytren tissue.

Many patients will not notice or complain of the condition until bands or cords have formed that gradually contract and cause the affected digits to become flexed toward the palm. Most patients will seek medical assistance when they are unable to flatten their hand against a tabletop or other smooth surface or when it becomes difficult to put their hand into a pocket or glove (see Fig. 75.9).

The cause of Dupuytren contracture is not well understood, and no definitive cure is available.^{41,42} It is seen most frequently in white patients of northern European descent. Men are affected seven times more often than women, and it is rarely seen in patients younger than 40 years.⁴ Patients can frequently identify another family member who has had similar findings, thus indicating an autosomal dominant condition with variable penetrance. Trauma has not been proved to be an associated cause.^{41,42}

A more severe and aggressive form of the condition called “Dupuytren diathesis” can affect other parts of the body, including the soles of the feet, the popliteal fascia, the knuckle pads, and the penis. Symptoms frequently develop in these patients at an earlier age.

Treatment depends on how much contracture exists, how rapidly the contracture is progressing, and the functional disability that the patient is experiencing. With mild disease, local application of heat, stretching exercises, and use of protective gloves may be helpful.^{4,41,42} Splinting does not appear to alter progression of the disease. In patients with a painful nodule,



Fig. 75.9 Dupuytren contracture of the ring finger. (a) Pitting of the skin and a longitudinal cord causing flexion of the metacarpophalangeal (MCP) joint can be seen. (b) A contracture/flexion deformity at the MCP joint keeps this patient from flattening his hand against a flat surface.

intralesional corticosteroid injections may provide symptomatic aid.⁴¹⁻⁴³ For patients with progressive deformity or a static contracture greater than 30 degrees at the MCP or PIP joints or those with functional impairment, treatment is indicated. The standard of care remains limited or total surgical palmar fasciectomy with or without skin grafting.⁴⁴ A newer alternative treatment—injection of *Clostridium* collagenase into the cords to weaken them and allow corrective manipulation—has been shown to be equally effective.⁴³ Despite successful treatment with collagenase or surgical

excision, the risk for recurrence in the same digits or new formation of disease in other digits is significant. This risk is increased in younger patients with aggressive bilateral disease, in those with a strong family history, and in patients with fibrotic lesions elsewhere in their body.⁴⁴ Sometimes the disease has progressed to the point that the MCP or PIP joint capsules have become significantly contracted, and in such cases, full digital extension may not be possible without extensive joint release and neurovascular risk.

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76

The hip

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- Hip pain is a common symptom with diverse causes, but most cases can be diagnosed with a careful history, a thorough physical examination, and appropriate radiologic evaluation.
- Even though radiographs often lag behind actual pathologic changes, most intraarticular hip disorders can be effectively diagnosed radiographically, and standard hip and pelvis views should be obtained routinely.
- The role of magnetic resonance imaging in the diagnosis of hip pathology is evolving and becoming increasingly reliable.
- Hip pain in a young, active individual should raise a high index of suspicion for labral pathology.
- The differential diagnosis of unexplained hip pain should include osteonecrosis, even in lieu of apparent risk factors.
- Hip dysplasia describes bony dysmorphisms that affect either component of the hip joint as a result of developmental anomalies and lead to decreased coverage of the femoral head.
- The concept of femoroacetabular impingement describes the situation of mechanical conflict between a morphologically abnormal proximal femur and acetabular rim.

FUNCTIONAL ANATOMY

Bony structures

The hip joint is a ball-and-socket synovial joint in which the head of the femur articulates with the cup-shaped acetabulum (Figs. 76.1 and 76.2). Despite the resulting degree of stability, the hip joint possesses multiaxial mobility in the sagittal, transverse (rotational), and frontal planes, with the greatest freedom sagittally. The motion required for performing activities of daily living is flexion of at least 120 degrees, abduction of 20 degrees, and rotation of 20 degrees, although sporting activities often necessitate greater range of motion.

The acetabular cup is approximately 45 degrees abducted and 15 degrees anteverted and encompasses the femoral head. This bony socket is deepened by the fibrocartilaginous labrum, which augments femoral coverage circumferentially around the perimeter of the acetabulum except at its base, where it continues as the transverse acetabular ligament. The articular cartilage surface of the acetabulum resembles a horseshoe, the central cavity of which is occupied by the pulvinar, a fat pad covered by synovium. The concave opening, or acetabular fossa, lies inferomedially and gives rise to the ligamentum teres, which inserts at the fovea capitis, a small divot in the medial femoral head. Although the fovea itself is devoid of cartilage, the remaining articulating two thirds of the femoral head possesses cartilage varying in thickness from 3 mm in the posterosuperior segment to 1 mm peripherally, which reflects varying degrees of weight-bearing demand (Fig. 76.3).

The anatomy of the proximal end of the femur is composed of the head/neck and intertrochanteric segments. In most hips the center of the femoral head lies at the level of the tip of the greater trochanter, the bony prominence where the gluteal muscles insert laterally. The smaller lesser trochanter is situated medially and serves as insertion point for the hip flexors (iliopsoas). The head/neck segment lies about 15 degrees anteverted in relationship to the shaft of the femur. The normal neck-shaft angle is between 125 and 140 degrees. *Coxa valga* is the term referred to when this

angle increases above this range and *coxa vara* when the angle decreases below this range (Fig. 76.4).

Joint capsule

Contributing to the stability of the hip joint is the strong and dense fibrous capsule. It attaches around the periphery of the acetabulum just outside the labrum and inferiorly along the transverse acetabular ligament. On the femur, the capsule inserts along the intertrochanteric line anteriorly and continues posteriorly just proximal to the intertrochanteric crest, which results in more than 95% of the femoral neck being intracapsular. The capsule is strengthened by three prominent reinforcements: the iliofemoral, the pubofemoral, and the ischiofemoral ligaments. The iliofemoral ligament, also referred to as the Y ligament of Bigelow, is the strongest and most important. It resembles an inverted letter Y and originates at the anterior inferior iliac spine, with its diverging fibers fanning out over the anterior aspect of the hip joint to insert distally along the intertrochanteric line. This ligament prevents excessive extension and helps maintain an erect posture since it is taut in extension and relaxed in flexion. These ligaments all coil and tighten in extension, thus making this the position of maximum stability for the hip joint.

Hip musculature

The hip joint and its surrounding musculature function to meet the requirements of efficient walking. To accomplish this, the hip girdle must maintain stability of the weight-bearing limb despite changes in limb and body position as it propels the body forward. The origins and insertions of the surrounding hip musculature are shown in Figures 76.1 and 76.2. The primary hip flexors are the iliopsoas, rectus femoris, and sartorius. The gluteus maximus and the hamstring muscles (long head of the biceps femoris, semimembranosus, and semitendinosus) are the primary hip extensors. Abduction of the hip joint is accomplished by the gluteus medius and gluteus minimus. The adductor group consists of the adductor longus, adductor magnus, adductor brevis, gracilis, and pectineus. The short external rotators, which extend across the posterior aspect of the hip capsule, include the obturator internus and externus, the superior and inferior gemelli, the quadratus femoris, and the piriformis muscles. The hip has no primary internal rotators, but many muscles do so secondarily, such as the anterior fibers of the gluteus medius.

Bursae

Along with the many muscles groups surrounding the hip joint, several prominent bursae facilitate gliding of soft tissues over areas of potential friction. Since they are lined with synovial tissue, they may be affected by any of the inflammatory diseases that can involve the hip joint, such as rheumatoid arthritis and infectious or crystal-induced synovitis. Most commonly, however, bursitis and tendonitis around the hip are induced by trauma or repetitive microtrauma.

The trochanteric bursa lies between the gluteus maximus and the posterior lateral aspect of the greater trochanter, the iliopsoas bursa lies anteriorly between the hip capsule and the iliopsoas tendon, and the ischiogluteal bursa lies posteriorly between the gluteus maximus and the ischial tuberosity.

Blood supply

Although the hip joint itself is well perfused, the tenuous vascular anatomy of the femoral head makes it highly susceptible to avascular necrosis as a

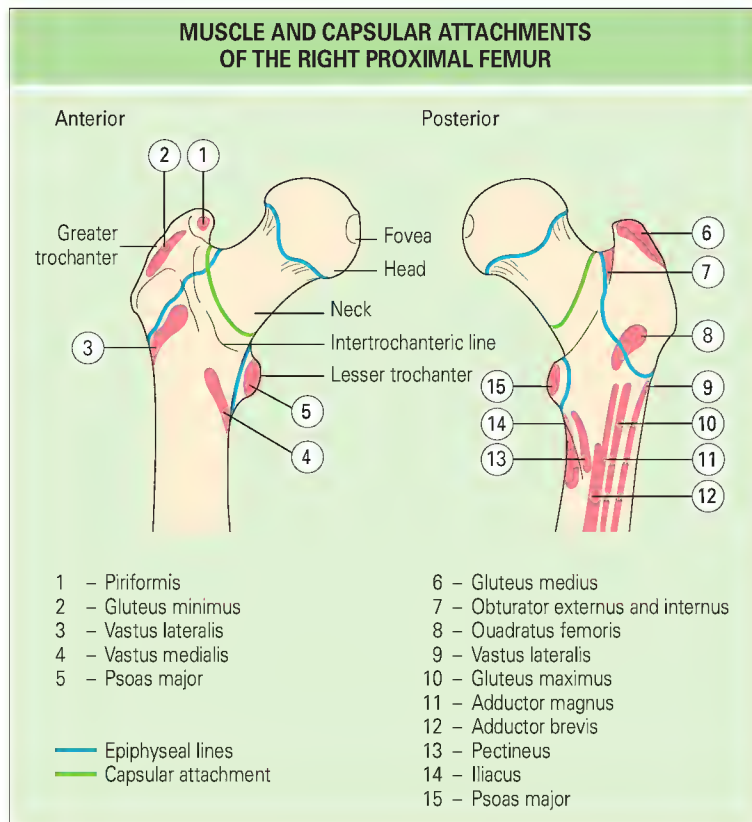


Fig. 76.1 Muscular and capsular attachments of the proximal end of the right femur. Anterior and posterior views of the proximal end of the right femur show the attachments of the muscles and hip capsule.

result of injury, dislocation, or fracture of the femoral neck. The femoral head is supplied by the terminal ascending branches of the medial femoral circumflex artery, a branch of the profunda femoris artery.^{2,3} These small, delicate branches run along the posterior superior aspect of the neck and perforate the femoral head near its base. In developing children, the metaphyseal and epiphyseal blood supplies are separate until physeal closure.³

CLINICAL EVALUATION

Hip pain is a common symptom with diverse causes, but most cases can be diagnosed with a careful history, a thorough physical examination, and appropriate radiologic evaluation.

History

Elucidating the characteristics of the pain is paramount, including the location, severity, and frequency of the pain. Onset, alleviating or aggravating factors, and radiation of the pain up or down the leg should also be noted.

Location of the pain

In the general sense, “hip pain” is often considered to include locations from the lower part of the back, pelvic girdle, and proximal aspect of the thigh. A classification of hip pain based on the tissues primarily involved in specific disorders is outlined in [Box 76.1](#). Of these, osteoarthritis of the hip, trochanteric bursitis, and spinal disorders account for the vast majority of conditions seen in clinical practice. True intraarticular hip pathology will most often cause groin pain plus occasional radiation to the knee, with the pain being referred along the continuation of the obturator and femoral nerves via their respective sensory articular branches in the hip capsule. Radiation to the anterior, medial, or lateral aspect of the thigh is quite common. The most frequent cause of lateral pain is generally related to trochanteric bursitis. Lumbar pathology most often refers pain to the posterior aspect of the hip area, and radicular symptoms usually radiate pain posteriorly along the buttock and below the knee. Posterior hip and buttock pain can also be referred from the sacroiliac joints. If associated with an insidious onset and severe morning stiffness that is relieved by activity, the diagnosis of sacroiliitis is usually considered. In cases in which the history

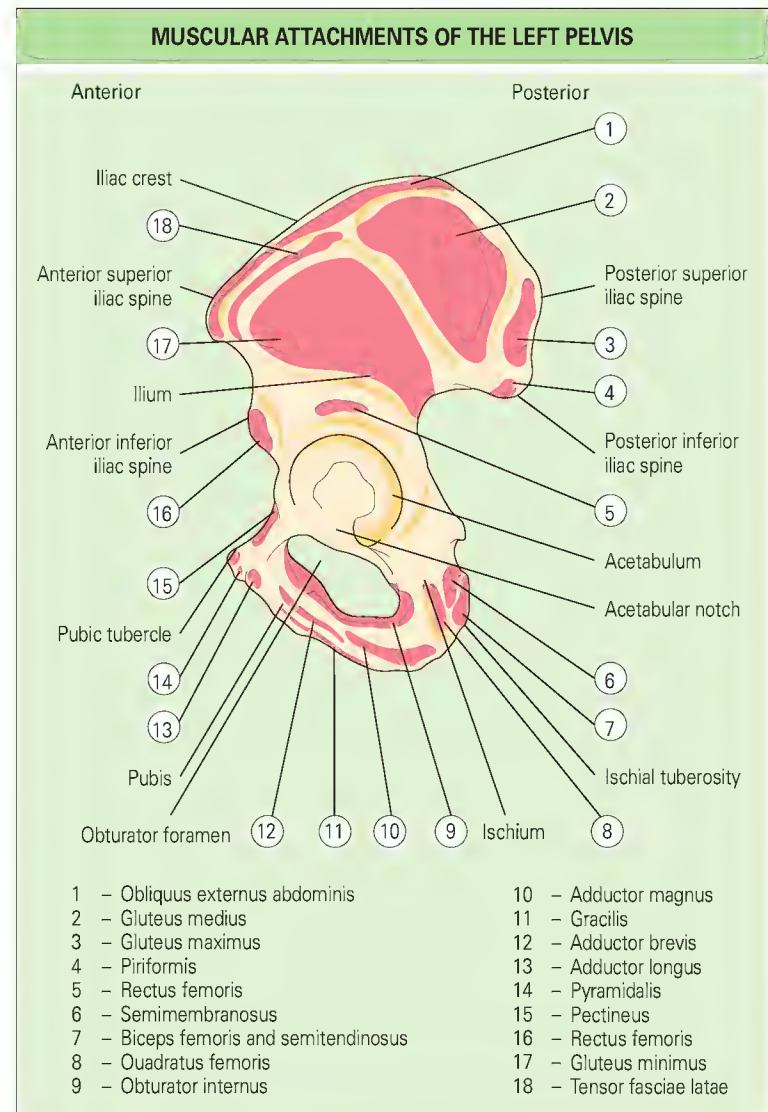


Fig. 76.2 Muscular attachments of the left pelvis—lateral view.



Fig. 76.3 Variations in thickness of the acetabular and femoral head cartilage.

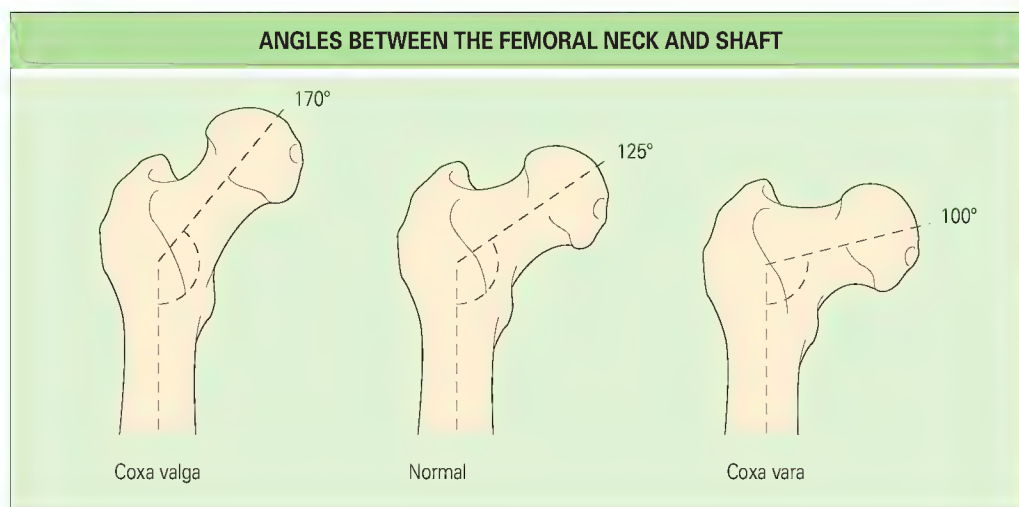


Fig. 76.4 Neck-shaft angle of the proximal end of the femur.

BOX 76.1 DIFFERENTIAL DIAGNOSIS OF HIP PAIN

Articular

Inflammatory joint disease
 Rheumatoid arthritis
 Spondyloarthritis
 Polymyalgia rheumatica
 Degenerative joint disease
 Primary osteoarthritis
 Secondary osteoarthritis
 Metabolic joint disease
 Gout
 Pseudogout
 Ochronosis
 Hemochromatosis
 Wilson disease
 Acromegaly
 Femoroacetabular impingement
 Acetabular labral tear
 Infections
 Tumors
 Benign
 Pigmented villonodular sclerosis
 Osteochondromatosis
 Malignant
 Synovial sarcoma
 Synovial metastasis
 Hemarthrosis
 In children
 Toxic synovitis
 Juvenile chronic arthritis

Periarticular

Bursitis
 Trochanteric
 Iliopsoas
 Ischiogluteal
 Tendinitis
 Trochanteric
 Adductor
 Acute calcific peri arthritis
 Heterotopic ossification

Osseous

Bone lesions
 Fractures, neoplasms
 Infection
 Osteonecrosis of the femoral head
 Paget disease
 Metabolic bone disease
 Stress fracture
 Transient osteoporosis
 In children
 Congenital dislocation of the hip
 Acetabular dysplasia
 Coxa vara
 Slipped capital femoral epiphysis
 Legg-Calvé-Perthes disease
 Rickets

Neurologic

Entrapment neuropathies
 Lateral femoral cutaneous nerve
 (meralgia paresthetica)
 Lumbar nerve root compression
 L2, L3, and L4

Vascular

Atherosclerosis of aorta iliac vessels

Referred pain

Thoracolumbar spine
 Intraabdominal structures
 Retroperitoneal structures

patient's recreational and occupational functions should be discussed, and any alterations in these activities should be sought. Previous treatments, including forms of self-treatment, physical therapy, and medications, along with responses to these modalities, must also be explored.

The onset and character of the pain are worth noting in an effort to distinguish pain at rest, which indicates an underlying, more advanced degenerative process, from mechanical activity-related pain, which suggests soft tissue injury or early degenerative disease.

Further questioning to characterize the alleviating or aggravating factors can help differentiate certain disorders. Degenerative joint arthropathy is usually exacerbated by activity and subsides with rest. If the pain persists with rest, an infectious or inflammatory process should be suspected. Prolonged morning stiffness relieved by activity is typical of an inflammatory arthropathy. Pain aggravated by lying on the affected side is highly suggestive of trochanteric bursitis, whereas buttock pain aggravated by sitting suggests ischiogluteal bursitis. Posterior buttock pain with radiation can be associated with lumbar pathology if symptoms arise with the spine in an upright or extended position, if flexion or leaning forward alleviates the pain, and if the symptoms do not immediately resolve with rest. A vascular etiology should be suspected if the pain is aggravated with any muscular activity and relieved within minutes of rest. A careful history may reveal previous catheterization or other trauma to the femoral vessels.

General enquiry

The history should also include questions about childhood hip disorders (sepsis, developmental dysplasia, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis), previous problems or injuries involving the hip, and previous treatment or surgery. A history of a recent increase in activity should be questioned to rule out stress or overuse injuries. Significant medical factors potentially relating to hip pathology should be sought. Such factors include a previous history of trauma, corticosteroid use, alcohol use, coagulopathies, immune-mediated or inflammatory disorders, and malignancies. This information can provide insight into conditions such as avascular necrosis, pathologic fracture, or the inflammatory arthritides.

Examination

Apart from a detailed examination of the hip, a thorough physical examination requires detailed assessment of the relevant neurologic, muscular, and vascular systems. Neurologic examination, in addition to manual muscle testing, should include assessment of normal sensation to light touch and palpation. Vital signs, including temperature, should be recorded because septic arthritis should be ruled out in patients with hip pain and fever.

Gait examination

Inspection is the first tenet of a thorough physical examination and begins with watching the patient walk into the examination room. The physician should evaluate patients' gait, how they rise from a chair, what type of posture they assume, and how much disability they exhibit. Gait analysis is a complex science; nonetheless, a physician evaluating hip disorders should be able to assess and classify slight, moderate, and severe limps. The normal walking cycle has two phases: the weight-bearing stance phase, which begins with heel strike and ends with toe-off, and the non-weight-bearing swing phase between toe-off and heel strike. During the stance phase the

and physical examination are inconclusive in distinguishing the source of pain, therapeutic corticosteroid injections into the lumbar epidural space or the sacroiliac joint can be helpful in differentiating lumbar pathology, sacroiliitis, and hip pain.

Assessing characteristics and impact

The severity of the pain is best assessed in terms of the patient's ability to perform functional activities such as getting in and out of a car, climbing stairs, taking care of foot hygiene, or sitting comfortably in low chairs. The

hip joint loads three times the patient's body weight, and the length of time spent in single-leg stance by the patient will provide insight into what type of limp is present.

General inspection

The patient should be standing up and adequately disrobed for a proper examination. Note any atrophy or asymmetry and previous surgical scars. Assess for pelvic obliquity by placing a finger above both iliac crests and checking whether they are level. Pelvic obliquity suggests a discrepancy in leg length or a contracture of the hip causing compensatory obliquity. The resting posture of the hip that causes the least pressure within the joint is the flexed, abducted, and externally rotated posture. Patients with acute synovitis or inflammatory effusions may be resting in this position to help splint the pain.

Palpation

Palpation should begin in the standing position as well because this makes it easier to feel all bony landmarks, including the iliac crest, greater trochanter, ischial tuberosity, pubic symphysis, posterior superior iliac spine, and anterior superior iliac spine. Tenderness in some of these areas is suggestive of certain pathologies. Pain with palpation over the greater trochanter is very probably consistent with bursitis, and pain over the pubic symphysis can signal osteitis pubis or athletic pubalgia.

Range of motion

The supine position is best to assess passive and active range of motion of the hip, both of which should be tested in all planes: flexion, extension, adduction, abduction, external rotation, and internal rotation. In the general population normal range of motion is considerably variable, so the examiner should always measure both sides for comparison⁴ while keeping in mind that the comparison side can also exhibit pathology with bilateral disease. Normal flexion should be between 100 and 135 degrees. Similarly, extension of the hip should be from 0 to between 15 and 30 degrees. Abduction and adduction testing is done with the patient supine, and stabilization of the pelvis must be performed to record accurate values. During testing the patient's pelvis should be level and balanced, and no pelvic motion should take place. Normal hip abduction should achieve 40 degrees and adduction 30 degrees from neutral. Rotational motions of the hip are best measured with the hip flexed but also can be done with the hip extended by using the logroll maneuver, which is less sensitive but more specific when assessing for intraarticular pathology. From the neutral position, internal rotation is normally between 30 and 40 degrees. External rotation is usually greater, between 40 and 60 degrees. The first motions that typically diminish in patients with hip arthrosis are internal rotation and abduction. An increase in internal rotation greater than normal is generally indicative of rotational deformities about the proximal end of the femur, such as seen with increased femoral anteversion and dysplasia.

Special tests

Patrick test (FABER test)

The Patrick test is helpful in detecting limited hip motion and distinguishing hip pain from sacroiliac disease. The test is sometimes referred to by the acronym FABER, derived from the initial letters of the movements that it evaluates (*flexion, abduction, external rotation*) (Fig. 76.5).

With the patient lying supine, the knee and hip are flexed to 90 degrees and the foot of the examined extremity is placed on top of the opposite knee ("figure 4" position). The thigh is then slowly abducted fully and externally rotated toward the examining table. The presence of groin pain, spasm, or limitation of movement is suggestive of hip pathology. The Patrick test can also be used to stress the sacroiliac joints. To do so, one hand is placed on the abducted knee and the other on the opposite anterior superior iliac spine. Pain localized to the back when sudden pressure is applied simultaneously on each of these points suggests sacroiliac pathology.⁵

Thomas test

The Thomas test quantifies flexion contracture of the hip by stabilizing the pelvis and eliminating compensatory lumbar lordosis. With the patient lying supine, the thigh opposite the side to be tested is fully flexed on the abdomen to flatten the spine and stabilize the pelvis. This leg is then held in position and the examined limb allowed to extend to neutral. Failure of the hip under observation to lie flat on the examining table allows easy measurement of the degree of fixed flexion (Fig. 76.6).

Stinchfield test

This test is performed in the supine position with the knee extended. The patient is asked to actively elevate the leg while gentle manual resistance is

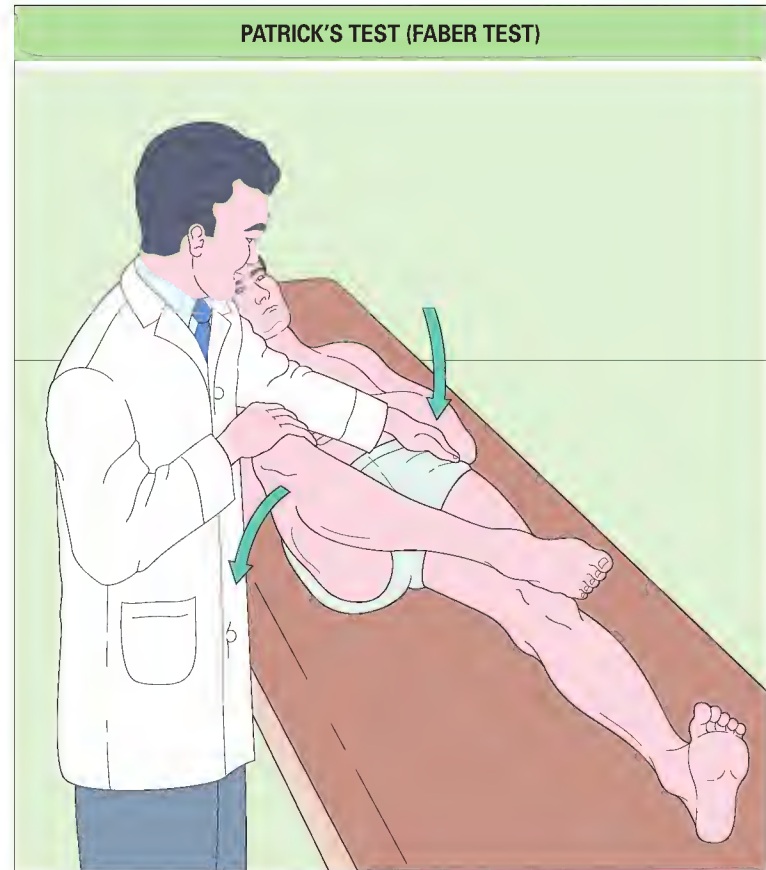


Fig. 76.5 To perform the Patrick test (FABER test), the contralateral iliac crest is stabilized with downward pressure while lowering the ipsilateral flexed, abducted, and rotated leg. Groin pain suggests hip pathology, whereas posterior pain suggests sacroiliac disease.

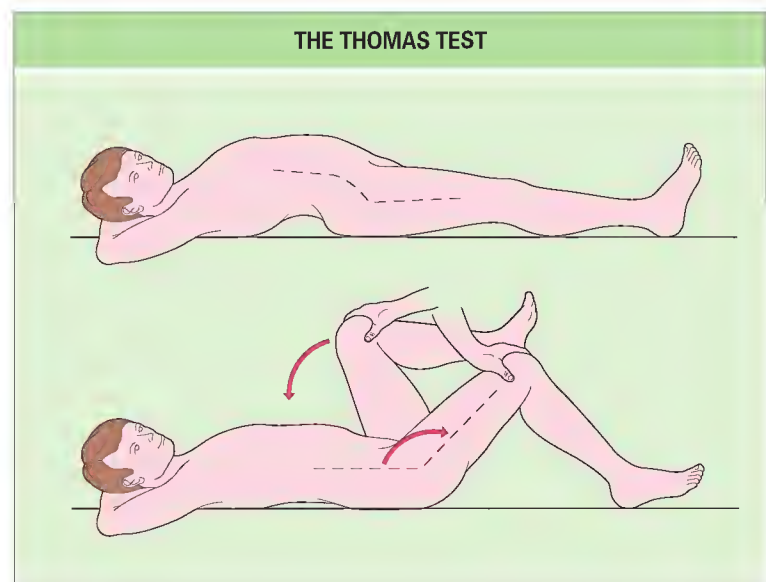


Fig. 76.6 A flexion deformity of the hip is masked by increased lumbar lordosis (top). With the Thomas test, flexion of the contralateral hip flattens the lordosis and reveals the flexion deformity of the hip (bottom).

applied by the examiner. A positive response suggesting hip pathology would be reproduction of pain in the groin, thigh, buttock, and occasionally the knee, a typical pattern related to the sensory innervation of the hip. Back pain suggests a spinal cause.

Apprehension tests

These set of dynamic maneuvers are provocative tests that evaluate for the presence of labral pathology. With the patient lying supine on the examination table, the examiner moves the hip from a flexed, externally rotated and

abducted position to an extended, internally rotated and adducted position. This set of motions tests for anterior labral pathology, and reversing the maneuver will test for posterior pathology. The presence of labral pathology will usually produce a painful click or a searing sensation in the groin or deep anterolateral symptoms.⁶ This should be compared with the contralateral side because such tests may cause minor discomfort even in a healthy hip.

Leg length measurement

Measurements of leg length are best performed with the patient lying supine and the legs fully extended and placed 15 to 20 cm apart. Measurements are made for both true and apparent leg length inequality. True leg length measurements are made between fixed bony landmarks, from the anterior superior iliac spine to the middle of the lateral and medial malleoli. Apparent leg length inequality is measured from a fixed point in the center of the body, usually the umbilicus, to the middle of the medial and lateral malleoli. Standing radiographs of the pelvis can be used to detect leg-length discrepancy as well. In the absence of contracture and pelvic obliquity, a difference in the height of the femoral heads indicates leg length inequality.⁷ A difference in length between the two legs of 1 cm or less is not generally clinically significant. An apparent (or functional) leg-length discrepancy on inspection may result from a pelvic tilt secondary to scoliosis or contractures of the hip (Fig. 76.7). In these situations, measurements from the umbilicus will show an apparent shortening of the leg on the side with the higher pelvis. However, when measured from the anterior superior iliac spine, the legs will have the same length.

True leg-length discrepancy can be due to various congenital or acquired disorders. The most common of these disorders include congenital dislocation of the hip, acetabular dysplasia, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and congenital coxa vara. Leg-length discrepancy is associated with an increased incidence of trochanteric bursitis on the longer leg, which is typically held in adduction under a tilted pelvis. This results in decreased covering of the femoral head by the acetabulum. The increased localized stress on the remaining weight-bearing area of the femoral head may contribute to the development of osteoarthritis.⁸

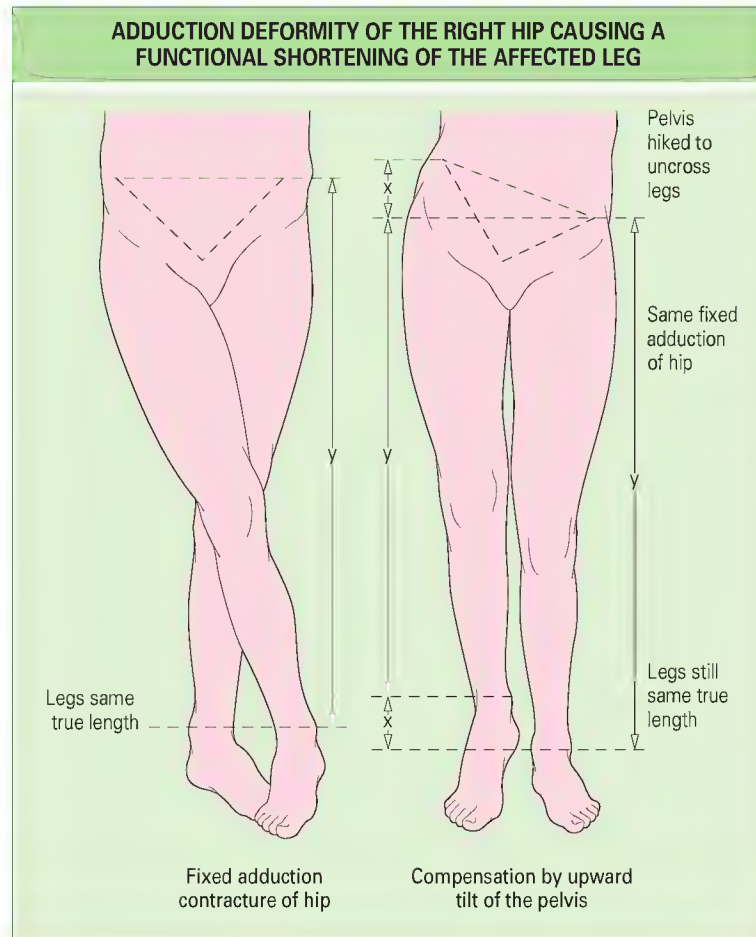


Fig. 76-7 Functional shortening of the affected leg may be due to adduction deformity of the right hip.

RADIOGRAPHIC EVALUATION

Plain radiographs

Most intraarticular hip disorders can be effectively diagnosed radiographically. Thus, complete evaluation of a patient with hip pain should include an anteroposterior view of the pelvis and either true cross-table or frog-leg lateral views of the hip. Obtaining a pelvis view that includes both the right and left hips makes a built-in comparison readily available (Fig. 76.8). The clinician should use these radiographs to assess for fractures, leg-length discrepancy, extent of degenerative or inflammatory arthropathy, evidence of dysplasia or other deformities, and the occurrence of abnormal calcification or ossification as seen with calcific bursitis or sacroiliitis, respectively. Although plain radiographs cannot be used to diagnose fluid in the hip joint, labral pathology, chondral defects, unmineralized loose bodies, or tendon disorders, they may provide clues to sources of referred pain such as ureteral stones, lumbar pathology, or severe calcific vascular disease.

Other imaging

Depending on what is learned from these initial radiographs, further imaging studies may be warranted. If the clinician is concerned about fluid in the hip joint, ultrasound evaluation is most efficient and cost-effective in determining the amount of fluid and the possible need for joint aspiration. Bone scans can be useful for evaluation of bone metabolism and osseous pathology such as occult femoral neck fractures. However, magnetic resonance imaging (MRI) has been shown to be more cost-effective when evaluating for occult femoral neck fractures because of earlier detection.⁹ The role of MRI in the diagnosis of hip pathology is evolving and becoming increasingly reliable with the development of specialized protocols and high-resolution scanners using bigger magnets. Although cost is an issue, MRI is most valuable in assessing for the presence of avascular necrosis of the femoral head, but it can also be used for detecting fluid in the hip joint or extraarticular soft tissue abnormalities. The addition of gadolinium-enhanced arthrography has increased sensitivity in detecting intraarticular pathology such as articular cartilage delamination or fragmentation and labral changes, including hypertrophy, tears, and associated paralabral cyst formation (Fig. 76.9).

Role of imaging in clinical practice

Even though radiographs often lag behind actual pathologic changes and are unimpressive in the early stages of disease, they will usually show characteristic changes over time, and the diagnosis should pose little difficulty. For instance, it is easy to diagnose Paget disease of the femur and hip joint (abnormal bone remodeling showing coarsened trabeculae, a blastic appearance, and remodeled cortices). Similarly, primary hip osteoarthritis is readily diagnosed in the presence of subchondral sclerosis, marginal osteophytes, and superolateral joint space narrowing. The same applies to late stages of

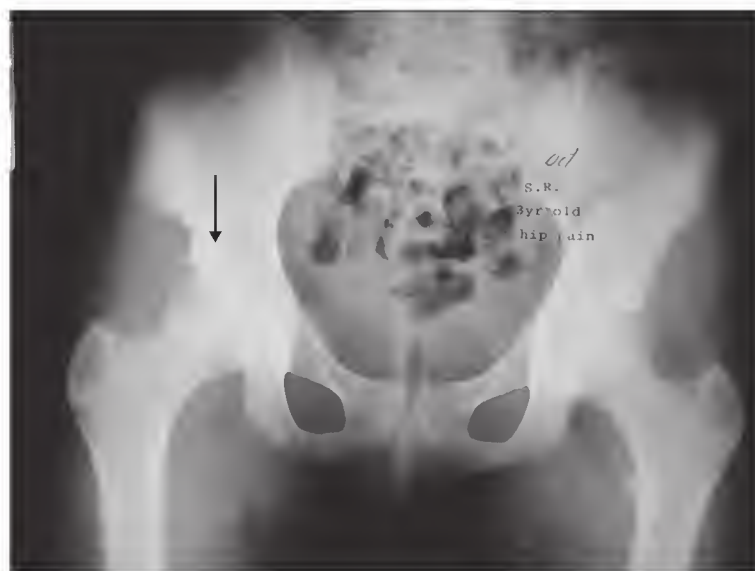


Fig. 76-8 Anteroposterior view of the pelvis demonstrating right hip dysplasia (arrow) and a normal contralateral hip. This view allows a built-in comparison.

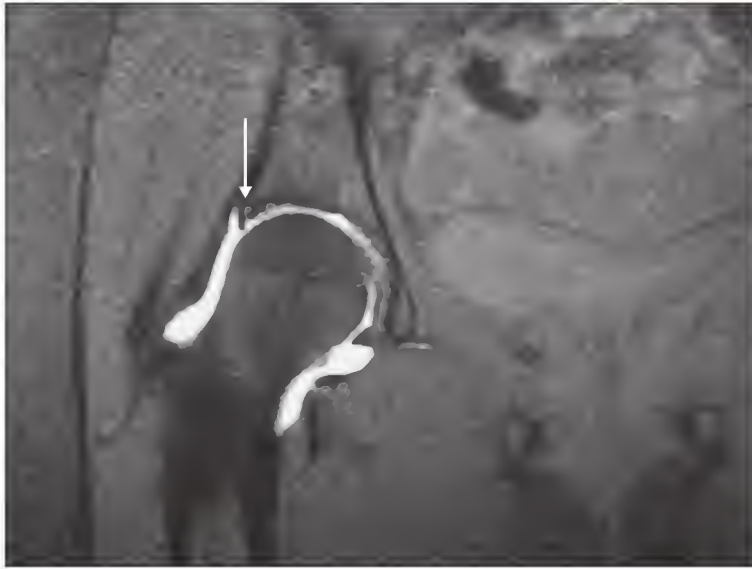


Fig. 76-9 Magnetic resonance arthrogram of the hip demonstrating slight effusion and a superior labral tear (arrow).

osteonecrosis when flattening of the femoral head has occurred or to chondrocalcinosis when calcific deposits are visible in hyaline cartilage or the acetabular labrum. Inflammatory arthritis may be suspected when subchondral erosions, osteopenia, and minimal joint space narrowing without osteophytes or sclerosis are present. In other more difficult cases the radiographic findings are abnormal but are not characteristic of a specific disorder. Bone pathology may be suspected by the presence of localized or diffuse osteopenia or sclerosis of the femoral head, neck, or acetabulum. Diagnosis and management are even less obvious when patients have hip pain and normal radiographic findings. In these circumstances, further diagnostic modalities should be guided by a careful history and physical examination. Clinical suspicion of early osteonecrosis may require MRI for confirmation. An arthrogram may be helpful in documenting chondromatosis, synovial tumors, and labral tears, as well as local thinning, cystic changes, delamination, or fragmentation of cartilage in the weight-bearing areas of an early osteoarthritic joint. Suspicion of chronic septic or crystal-induced synovitis would require joint aspiration for analysis of synovial fluid. Limitation of hip movements in all directions in a diabetic patient suggests adhesive capsulitis of the hip joint. The presence of systemic symptoms, such as fatigue, fever, weight loss, or worsening of pain at night, suggests infection or malignancy.

SPECIFIC HIP DISORDERS

Hip disorders that occur as part of a generalized rheumatologic problem such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis are covered elsewhere in this volume. This chapter focuses on other hip- and hip area-specific conditions.

Hip dysplasia

Hip dysplasia describes bony dysmorphisms that affect either component of the hip joint as a result of developmental anomalies and lead to decreased coverage of the femoral head (see Fig. 76.8).¹⁰ Excessive vertical slope of the acetabulum with valgus angulation of the femoral neck is generally considered a hallmark of classic dysplasia and can be associated with excessive anteversion or retroversion of the acetabulum. The femoral head is commonly aspherical and situated laterally in the acetabulum, thus making the labrum part of the weight-bearing surface of the acetabulum.¹¹ The vertical center edge (CE) angle of Wiberg can be determined from an anteroposterior radiograph to assess the amount of femoral head coverage. The CE angle is measured between a line connecting the lateral edge to the center of the femoral head and a vertical line extending from the center of the head. A normal CE angle is greater than 25 degrees, whereas it is less than 20 degrees in a dysplastic hip. Values between 20 and 25 should be considered borderline dysplastic. Likewise, a vertical center anterior angle can be derived from a false profile lateral view to measure sagittal version and assess anterior coverage of the head.¹⁰ Labral tears are a common feature in hips with subtle or severe dysplasia.¹¹ Thus, any patient



Fig. 76-10 Lateral view of the left hip demonstrating bony buildup (arrow) with loss of sphericity at the femoral head-neck junction.

with a known labral tear should be evaluated carefully for underlying hip dysplasia.

Femoroacetabular impingement

The concept of femoroacetabular impingement (FAI) describes the situation of mechanical conflict between a morphologically abnormal proximal end of the femur and acetabular rim. Repetitive abutment, especially during terminal flexion and internal rotation, leads to cumulative damage to the labrum and subsequently delamination or ulceration of the articular cartilage overlying the adjacent acetabular rim.¹²

Subtypes

Two types of FAI are recognized and defined by their etiology. In cam-type FAI, the primary site of malformation is the femur, whereas in the pincer type, it is the acetabular component that is dysmorphic. The cam type is characterized by an increased radius of the neck-head junction with loss of sphericity, either primarily because of lack of head offset or as a result of bony buildup secondary to pincer-type FAI. Repetitive trauma to the labrum from impingement by the neck segment in flexion and internal rotation results in damage to cartilage and ultimately labral-osseous separation, mostly in the anterior-superior region. Conditions associated with the development of cam-type impingement include femoral neck retroversion and a history of slipped capital femoral epiphysis or Legg-Calvé-Perthes disease.¹³ Pincer-type FAI results from lack of acetabular clearance, which leads to linear contact between the anterior acetabular rim and head-neck junction. The resulting relative overcoverage of the femoral head causes increased impaction and ultimately failure of the labrum and, with subsequent rim ossification, worsening overcoverage and abutment, which can lead to kissing lesions on the femoral neck. Associated conditions include coxa profunda, protrusion, acetabular retroversion, and a history of acetabular fracture.¹² Demographically, cam impingement typically occurs in young athletic males with labral tears, whereas pincer impingement is more common in middle-aged active woman and usually has a more benign course.

Clinical features

Typically, patients will experience intermittent, progressive activity-related groin pain with occasional mechanical symptoms. Pain in the position of impingement (flexion, internal rotation, adduction), especially after prolonged sitting, is commonly present.

Findings on physical examination include decreased motion in internal rotation and adduction in flexion. The impingement maneuver is part of the apprehension test and is performed by internally rotating and then adducting and flexing the patient's hip to 90 degrees. This causes a shearing force at the labrum or chondral surface and reproduces the symptoms.⁶

Imaging

Radiographic evidence is usually subtle, but close scrutiny may reveal bony prominence of the femoral head-neck segment (Fig. 76.10), as well as

flattening and reduced offset of the anterolateral neck (pistol grip deformity). Rim ossification/os acetabuli and herniation pits can also be assessed and allow evaluation of the status of the acetabular cartilage at the impingement site.¹² Suspicion for FAI with inconclusive screening radiographs should be followed by special lateral views or three-dimensional tomography with surface rendering, which is usually accurate in diagnosing the underlying pathology.

Treatment

Over the last decade, hip arthroscopy has advanced to a common diagnostic and therapeutic modality. Even though arthroscopy has helped better define the periarticular and intraarticular pathoanatomy of hip disease, indications for its use are still evolving.¹⁴ Therapeutic use has advanced from simple débridement of the affected soft tissues or osteoplasty of a hyperplastic femoral neck or hypertrophic acetabular lip to arthroscopic repair of labral tears and articular cartilage repair procedures. In addition, surgical hip dislocation is increasingly being used to address morphologic contributors to FAI of the nondysplastic hip and to allow advanced restorative options in addressing osteoarticular lesions.¹⁵

Periarticular soft tissue problems

Several problems of the hip are related to the soft tissue structures around the joint and its surrounding muscles. Though relatively common, many of these problems are poorly defined, misdiagnosed, or both.¹⁶

Bursitis

Trochanteric bursitis

Trochanteric bursitis is the most common cause of pain about the hip region. Patients with trochanteric bursitis have deep, aching pain sometimes associated with a burning sensation on the lateral aspect of the hip and thigh that increases with activity and can be associated with a limp.¹⁷ Typically, the pain decreases at rest, although it is frequently worse at night, especially when the patient is lying on the affected side. Tenderness can be elicited by palpation of the area around the greater trochanter. The trochanteric bursa is not usually palpable unless it is distended or inflamed. Resisted abduction of the hip when the patient is lying on the opposite side may accentuate the discomfort. Hip range of motion is usually preserved, but in severe cases the discomfort can limit motion. Slight irregularities of the greater trochanter or peritrochanteric calcifications of the bursa are sometimes seen on plain radiographs. The course of trochanteric bursitis is varied: an acute phase may last several days, followed by gradual abatement of the symptoms, although low-grade discomfort may persist for weeks or months.

Treatment includes rest, as well as physical therapy for abductor and iliotibial band conditioning and stretching. Nonsteroidal antiinflammatory drugs (NSAIDs) can be used, but the results are often mixed. Infiltration of a local anesthetic and a long-acting corticosteroid preparation has been shown to be helpful in confirming the diagnosis and bringing long-term relief.^{16,17} It is considered by many to be the most effective treatment modality. Various surgical procedures, including bursectomy, have been proposed for refractory cases, but these are rarely needed.

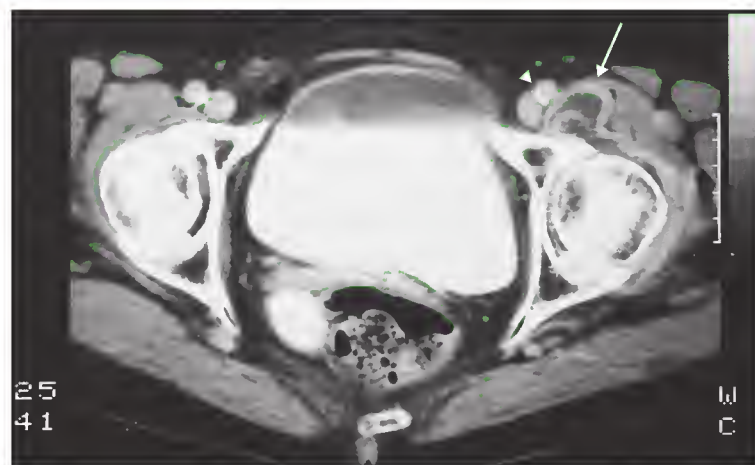


Fig. 76-11 A computed tomography scan of a patient with rheumatoid arthritis shows an enlarged fluid-filled iliopsoas bursa (arrow) communicating with the hip joint and displacing the neurovascular bundle (arrowhead). (With permission from Letourneau L, Dessureault M, Carette S. Rheumatoid iliopsoas bursitis presenting as unilateral femoral nerve palsy. *J Rheumatol* 1991;18:462-3.)

Iliopsoas bursitis

The iliopsoas bursa may communicate with the hip joint in approximately 15% of adults. Thus, iliopsoas bursitis can be manifested in association with a variety of hip disorders, including osteoarthritis, rheumatoid arthritis, synovial chondromatosis, pigmented villonodular synovitis, osteonecrosis, and septic arthritis.¹⁸ The direction and degree of bursal enlargement will dictate the symptoms, and patients may have a painful inguinal mass, groin pain, varicosities secondary to femoral vein compression, or paresthesias secondary to femoral nerve compression.^{19,20} Computed tomography has been proposed as the best diagnostic test to document iliopsoas bursitis (Fig. 76.11). Treatment with bursography and the instillation of corticosteroids is an effective diagnostic and therapeutic modality. Occasionally, the symptoms persist after nonoperative measures such as physical therapy and NSAIDs. In these cases, surgical excision of the bursa is sometimes necessary.

Ischiogluteal bursitis

Ischiogluteal bursitis is most commonly seen in patients engaged in jobs that require long periods of sitting²¹ and thus is also known as “weaver’s bottom.” Patients complain of exquisite pain over the ischia that is aggravated by sitting and lying. Local tenderness on palpation of the ischial tuberosity is always found. Use of an 8- to 10-cm-thick rubber cushion with holes to accommodate the ischial prominences may alleviate the symptoms. Trunk and knee-to-chest stretching exercises while lying on the cushion should also be encouraged. Local injection of corticosteroid may be used in refractory cases, but the sciatic nerve, which passes just lateral to the bursa, must be avoided.

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77

The knee

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- The knee is a complex diarthrodial joint that forms a highly modified hinge between the distal end of the femur and proximal end of the tibia.
- Knee stability is provided by the osseous anatomy, four major ligaments (the anterior and posterior cruciate and medial and lateral collateral ligaments), the medial and lateral menisci, and the adjacent musculature, which together provide static and dynamic stability for the joint. Several bursae are distributed around the knee where soft tissues move against bony prominences or in fascial planes.
- Knee pain may arise from the joint itself or from periarticular tissues such as tendons and bursae, or it may be referred from distant sites such as the hip or femur.
- Accurate diagnosis of knee conditions can usually be made on the basis of findings on the history and physical examination. Standard investigations include synovial fluid analysis, conventional radiography, magnetic resonance imaging, and arthroscopy.

SKELETAL ANATOMY

The knee is a large synovial joint formed between the articulation of the distal end of the femur, proximal end of the tibia, and the patella. Three separate compartments are recognized in the knee: medial tibiofemoral, lateral tibiofemoral, and patellofemoral (Fig. 77.1). The knee joint functions as a modified hinge joint that allows flexion and extension, together with some limited rotation.

Distal femur

The distal end of the femur has an asymmetric bicondylar shape, with a larger medial femoral condyle and a smaller, more rounded lateral femoral condyle. The patella articulates with the trochlear groove on the distal end of the femur, and the extension of this region forms the intercondylar notch, which contains the femoral origins of the anterior cruciate ligament (ACL, posterolateral) and the posterior cruciate ligament (PCL, anteromedial).

Proximal tibial plateau

The medial and lateral tibiofemoral compartments are formed by the articulation of the distal end of the femur with the convex articular surface of the lateral tibial plateau and the concave surface of the medial tibial plateau. The medial condyle is concave and longer in the anteroposterior plane to accommodate the medial femoral condyle. They are separated by the tibial spines, which are closely related to the insertion of the ACL.

Patella

The patellofemoral joint is formed by the articulation of the trochlea and patella. The patella is the largest sesamoid bone in the body, and it engages the trochlea when the knee is flexed more than 30 degrees. It increases the lever arm available to the quadriceps muscle in extending the knee, thereby leading to large forces acting across this compartment. To accommodate these high loads, the patellar articular cartilage is specially adapted such that it reaches up to 7 mm in depth, thicker than any other articular cartilage in the body.

SOFT TISSUE ANATOMY

The bones of the knee joint are connected together by five major ligamentous structures: the medial collateral ligament (MCL), lateral collateral ligament (LCL), ACL, PCL, and the posterior capsule (Figs. 77.2 and 77.3). The fixed attachments of the ligaments, which interact with the shapes of the articular surfaces, guide the motion of the knee driven by muscle activity.

Ligaments

The MCL is a broad flat ligament with superficial and deep layers. The superficial layer arises from the medial epicondyle and inserts over a broad area of the medial aspect of the proximal end of the tibia; it extends approximately 8 cm distally, below the joint line. The deep layer originates with the superficial layer and inserts into the medial meniscus just above the joint line. The LCL is smaller and more rounded in cross section, arises from the lateral femoral condyle, and inserts into the fibular head. These collateral ligaments provide varus and valgus stability to the knee joint.

The ACL and PCL lie within the center of the knee and form a four-bar linkage system. They act together to control anteroposterior and rotational movement within the knee. Both ligaments are intraarticular but extrasynovial and consist of two bundles. The bundles spiral around each other and insert on the anteromedial aspect of the tibia; they work synergistically to resist excessive anterior translation and internal rotation of the tibia relative to the femur.

The posterior capsule is augmented on the lateral side of the knee by the following structures: the popliteus tendon, the arcuate ligament, the popliteofibular ligament, the biceps femoris tendon, and the LCL. This constellation of soft tissue structures forms the “posterolateral” corner and helps control mainly rotation of the knee.

Menisci

The medial and lateral menisci are load-sharing crescentic disks of fibrocartilage that lie interposed between the femur and tibia. They act primarily to distribute load in the tibiofemoral compartment and thereby reduce contact stress, but in addition they help stabilize the joint. In cross section the menisci are triangular, thickest at the periphery and thinning on their inner concave aspect. Collagen fibers are aligned within the menisci to absorb hoop stress and dissipate compressive loads. The menisci are attached to the tibial surface at the intercondylar eminences. In addition, the semicircular medial meniscus is closely attached to the medial capsule and collateral ligaments by coronary ligaments. The smaller lateral meniscus forms a nearly complete circle and has a looser peripheral attachment, including a hiatus in the posterolateral capsule through which the popliteus tendon enters the knee.

The peripheral third of both menisci are vascularized through capsular attachments, thus offering potential for the structures to heal after injury. In contrast, the central third of the menisci, known as the “white zone,” is avascular and has minimal healing potential. Between the peripheral and white zones lies an intermediate zone, which has more limited healing potential.

Muscles and tendons

The primary extensor of the knee is the quadriceps, which consists of four muscles, namely, the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius. These muscles join together distally to form the quadriceps tendon, which inserts into the superior pole of the patella. Fibrous

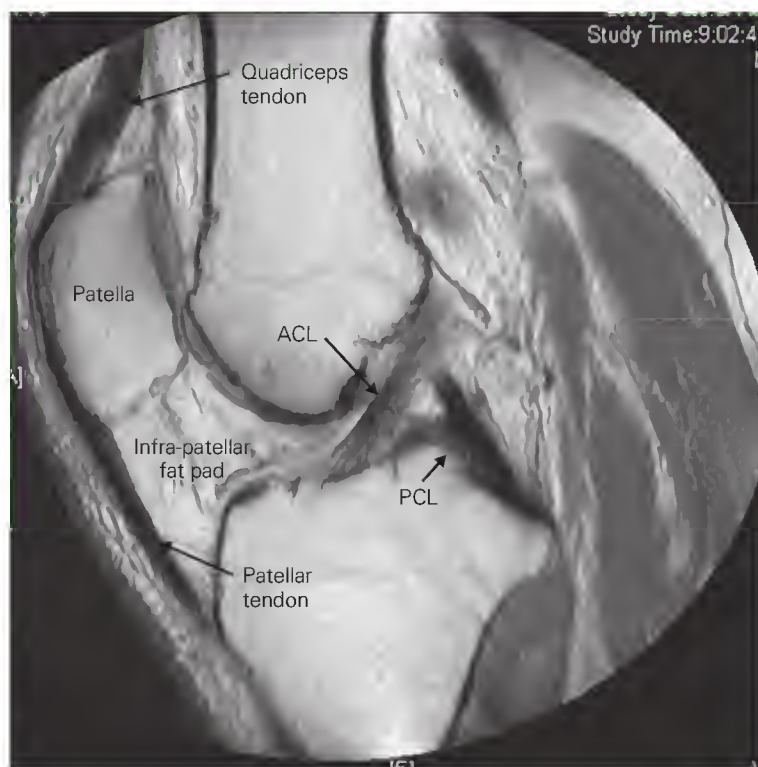


Fig. 77.1 Sagittal section of the knee joint. ACL, anterior cruciate ligament; PCL, posterior cruciate ligament.

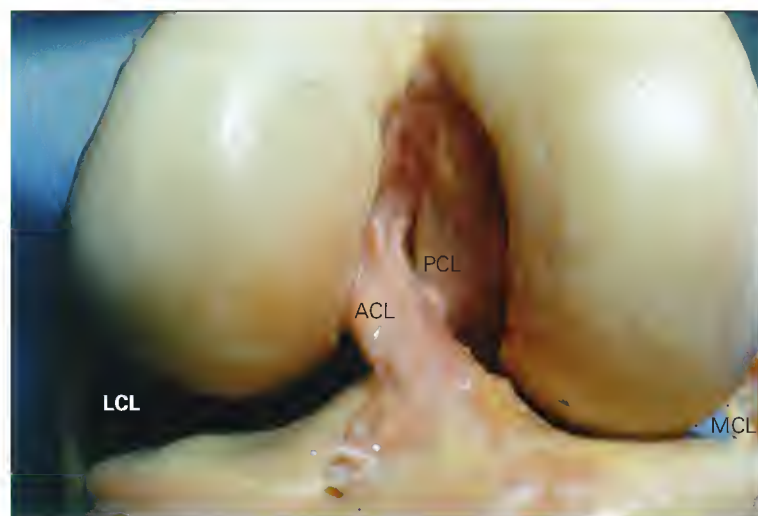


Fig. 77.2 Gross appearance of a right knee. ACL, anterior cruciate ligament; LCL, lateral collateral ligament; PCL, posterior cruciate ligament.

expansions from the vastus medialis and lateralis insert obliquely into the sides of the patella and form the medial and lateral patellar retinacula. The distal fibers of the vastus medialis, the vastus medialis obliquus (VMO), insert on the medial border of the patella and are the principal dynamic restraint to excessive lateral patellar subluxation. The hamstrings are the principal flexors of the knee. The semimembranosus and semitendinosus are located on the posteromedial and the biceps femoris on the posterolateral side of the knee. In addition to providing a degree of rotational stability, the hamstrings act as accessory stabilizers in the coronal and sagittal planes.

The iliotibial band (ITB) is a thickening of the fascia lata on the lateral aspect of the thigh. Proximally, the ITB is in continuity with the tensor fasciae latae muscle; distally, it inserts into the lateral femoral epicondyle and on Gerdy's tubercle. The ITB helps stabilize the lateral side of the knee and can act as an accessory extensor or flexor of the knee, depending on its position relative to the center of rotation of the knee.

Extensor mechanism

The extensor mechanism consists of the quadriceps tendon, the patellar tendon, and the patella. The Q angle is subtended by a line drawn from the

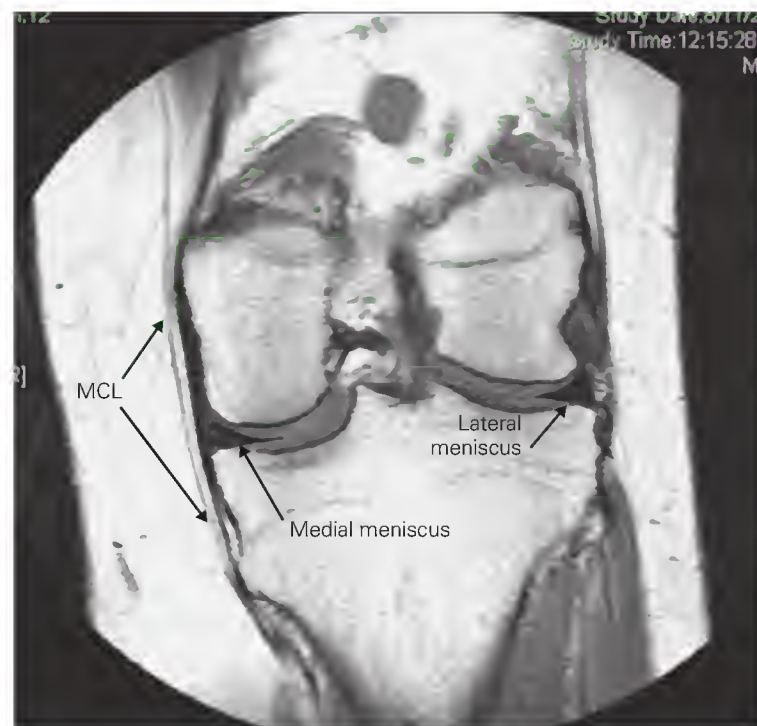


Fig. 77.3 Coronal magnetic resonance image demonstrating the medial collateral ligament (MCL) and menisci ligaments.

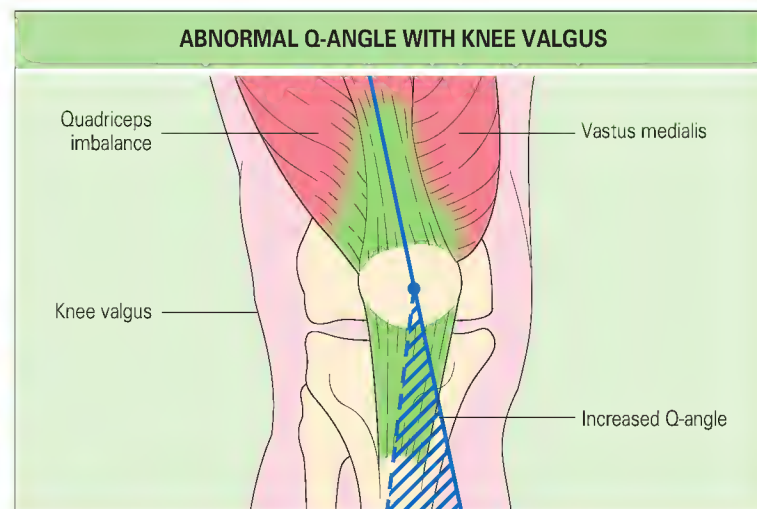


Fig. 77.4 Anatomic diagram of the quadriceps musculature with onlay of the Q angle.

anterior superior iliac spine to the center of the patella and another line drawn from the center of the patella to the tibial tubercle (Fig. 77.4). A normal knee Q angle measures approximately 13 degrees in men and 18 degrees in women, and an angle exceeding 20 degrees is abnormal. A high Q angle reflects a large unbalanced force vector tending to pull the patella laterally.

HISTORY, EXAMINATION, AND INVESTIGATION

History

The history of a patient's knee problem is a critical part of the assessment. Pain is the most common cause of referral to secondary care, and it is necessary to determine its nature. It should be established whether there is a continuous ache (e.g., arthritis) or a more intermittent mechanical component of the problem (e.g., meniscal tear). Closer review of the problem may identify a history of a new or long-established injury. Locking, catching, or giving way can occur. Patients may localize the pain to specific areas of the knee, although referred pain within the joint can be misleading in locating

pathology. Pain may also be referred from lumbar spine pathology or the hip joint. Previous medical history, including other joint disease and the patient's family history, can also offer critical information.

Examination

Examination of the knee should be performed by following the principles of look, feel, and move.

Observation

The knee examination begins with gaining adequate exposure of the knee, together with the joint above and below. Initially, alignment during standing should be noted, with the knee normally found in 4 to 7 degrees of valgus. Tibia vara is a common normal variant, but excessive varus or valgus alignment may reflect underlying knee pathology. The patient's gait and use of walking aids are then observed to look for typical patterns of gait that indicate knee pathology: antalgic, stiff knee and varus thrust. While standing, inspection of the soft tissues around the knee may reveal erythema, swelling, or scars. The patient is then further inspected on an examination couch. The quadriceps muscle is inspected, with a check for reduction in muscle bulk in comparison to the contralateral thigh. Muscle wasting is a key indicator of knee pathology.

Palpation

The integrity of the extensor mechanism is then assessed by asking the patient to actively straighten the knee against gravity. The ITB functions as an accessory knee extensor with the knee in an extended position and can hide significant disruption of the extensor mechanism. Active knee extension from a flexed starting position must therefore be assessed.

Active extension of the knee also allows assessment of patellofemoral crepitus and tracking. With one hand resting lightly on the patella, the knee is extended and flexed to ascertain patellofemoral crepitus. Patellar tracking is movement of the patella over the distal end of the femur and refers to engagement and articulation of patella within and out of the trochlear groove. In patients with a high Q angle or other causes of lateral patellar subluxation, the patella may translate laterally during the terminal 30 degrees of knee extension, which causes a "J" sign.

With the patient positioned supine the knee is examined for evidence of swelling or effusion. Subtle joint effusions may be detected by the "bulge test," in which fluid is milked into the suprapatellar pouch from the medial gutter with one hand and then the lateral side of the knee gently stroked in a proximal to distal direction to observe a bulge appear in the medial sulcus. Moderate-sized effusions may be detected by the "ballotement test," in which the examiner presses the patella down onto an extended knee while milking the suprapatellar pouch empty of fluid.

Palpation of the knee for tenderness should include the patella, quadriceps and patellar tendons, tibial tubercle, femoral epicondyles, collateral ligaments, hamstrings, pes anserinus, and ITB. Tenderness, swelling, or ecchymosis along these structures may indicate traumatic injury or rupture. The medial and lateral joint lines should be palpated for tenderness, and if present, provocative tests for meniscal pathology should be performed. Various tests have been described, but the principle is to elicit tenderness with rotatory movements of the tibia while the knee is taken through a range of motion. The popliteal fossa should be palpated to identify the popliteal pulse and any masses. A pulsatile and expansile mass in the popliteal fossa may indicate the presence of a popliteal aneurysm. In this scenario a bruit is heard on auscultation, and the mass should be further evaluated with an ultrasound scan.

Range of motion

Range of knee motion should be assessed next and comparison made between passive and active range. A normal knee moves within the range of 0 to 135 degrees, although considerable variation occurs. Up to 10 degrees of recurvatum (hyperextension), especially in younger patients, can be considered normal. Fixed flexion in which patients cannot fully extend the knee should be assessed. An extensor lag exists if asymmetry between active and passive extension of the knee is noted. This occurs after damage to or weakness of the extensor mechanism. The Q angle (see earlier) may be assessed with the patient supine and the knee flexed 15 degrees by identifying the anterior superior iliac spine, patella, and the tibial tubercle. The angle subtended by these lines is measured and recorded.

Ligamentous stability

Ligament abnormalities can be identified by performing a series of provocative tests that demonstrate inherent instability in the knee.



Fig. 77.5 Lachman test for anterior cruciate ligament injury.

The collateral ligaments are tested with the patient supine. A valgus force is applied across the knee with the knee initially in extension to test the MCL, medial capsule, posteromedial corner, and PCL. The test is repeated at 20 degrees of flexion to isolate the MCL and posteromedial capsule. If no endpoint is reached during the valgus stress, the MCL is deficient, but a firm endpoint suggests a strain or partial tear. A similar test on the LCL is performed by applying a varus force across the knee.

The ACL can be assessed with three tests. The Lachman test is the most reliable test for outpatient examination and has a high positive predictive value for detecting ACL injury. In the supine position the knee is flexed to 20 degrees. The examiner stabilizes the patient's thigh with one hand and grasps the proximal end of the tibia just below the joint line with the other hand. The femur is fixed with one hand by the examiner above the knee and an anterior translation stress is then applied across the knee by drawing the tibia forward with the other hand (Fig. 77.5). Laxity is recorded if abnormal translation is noted. The anterior drawer test is performed with the knee flexed 90 degrees. The examiner grasps the proximal end of the tibia with both hands and applies firm anterior translation stress while trying to detect abnormal anterior translation. With both these tests, hamstring activity can create a false-negative result. The pivot shift test is considered the "gold" standard test of ACL function. The examiner uses a combination of internal rotation and valgus stress applied across the knee during the range of movement from 0 to 40 degrees. A positive test produces a palpable clunk as the knee reduces from a subluxed position.

The PCL is assessed with the knees flexed to 90 and the heels placed together. The position of the tibial tubercles in the coronal plane is compared between knees, with discrepancy signaling PCL injury in the knee or the more posteriorly positioned tuberosity. This is known as a positive posterior sag test. Laxity in the PCL can then be confirmed by translating the tibia anteriorly relative to a fixed femur to reduce the sag. A positive posterior drawer test restores the tibia to the sagged position with posterior translation (Fig. 77.6).

Damage to the posterolateral corner can be identified by using the "dial test." With the patient supine and the knees initially flexed to 30 degrees, an external rotation stress is exerted (dialed) across the knee. A difference of greater than 10 degrees of rotational laxity is considered significant. The test is repeated with the knees flexed 90 degrees. Increased rotational laxity at 30 degrees but not at 90 degrees suggests an isolated injury to the posterolateral corner. However, laxity at both 30 and 90 degrees indicates combined disruption of the PCL and posterolateral corner (Fig. 77.7).

Patellofemoral joint stability

Patellar instability is assessed with the patella apprehension test. With the patient supine and the knee extended, a lateralizing force is applied to the patella while the knee is flexed from 0 to 20 degrees. A positive test is recorded when the patient is apprehensive of the action, usually stating that it makes the knee feel unstable.

Investigations

Radiologic investigation of a patient with a knee problem starts with weight-bearing anteroposterior, lateral, and skyline plain radiographs. Long-leg



Fig. 77.6 Posterior drawer test for tears of the posterior cruciate ligament.



Fig. 77.7 Dial test.

alignment films aid in assessment of the mechanical axis of the lower limb and are essential when considering reconstruction or osteotomy around the knee. Ultrasound scans are useful when investigating masses or tendon injuries, and the ability to perform this imaging test dynamically makes it valuable in patients with partial tendon ruptures. Computed tomography (CT) is excellent for assessing osseous anatomy, and three-dimensional CT reconstructions are increasingly being used in preoperative planning for treatment of intraarticular fractures. Magnetic resonance imaging (MRI) is the modality of choice for more detailed assessment of the knee. Any intraarticular pathology involving the soft tissues, bone marrow, ligaments, menisci, and articular cartilage can be detected with great accuracy.

SPECIFIC DISORDERS OF THE KNEE

Clinical problems within the knee joint can be considered in chronologic terms, with certain diagnoses being associated with specific patient age

groups (Table 77.1). Features of the clinical manifestation, investigation, and treatment of common knee conditions are summarized in the following sections.

Infancy and early childhood

Knee pain in an infant or toddler is uncommon but usually highly significant. A clear history may be difficult to establish, but painful swelling or limping must be investigated with some urgency to establish the cause, start treatment, and avoid disturbances in future growth. Infection must be considered, together with referred hip or spine pain. Subtle fractures may not be seen on radiographs, and nonaccidental injury must be excluded.

Referred hip pain

Hip pathology may produce ipsilateral knee pain as a result of the common sensory innervation of both regions by the obturator nerve. Common diagnoses such as Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, transient synovitis, and septic arthritis may all be manifested in this manner. A careful history and examination of the hip are critical in making these diagnoses. Investigations play an important role, including blood tests¹ and imaging techniques.

Septic arthritis

Septic arthritis represents a surgical emergency in all age groups of patients, but the consequences of chondrolysis and secondary growth disturbance are particularly important for young patients. The etiology is usually hematogenous spread. Patients have pain, swelling, reduced movement, and systemic signs of infection. A dramatic increase in pain on passive joint movement is the key examination finding for septic arthritis. Joint aspiration, under ultrasound guidance if necessary, is mandatory, with samples sent for microbiologic investigation, including microscopy and culture. If the diagnosis is confirmed on investigation or strong clinical suspicion exists despite normal results of investigations, the joint should be washed out in the operating room via arthroscopic or open débridement and irrigation. Repeated surgical washouts may be required. Appropriate antibiotics, guided by culture sensitivity studies, are required for an extended period until the joint settles.

Osteomyelitis

Acute hematogenous osteomyelitis is the most common type of bone infection. It is usually seen in children and is more common in boys. The infection generally occurs in areas of high metabolic activity and commonly affects the distal femoral and proximal tibial metaphyses. Only 60% of patients are febrile on initial evaluation, but they typically have pain and local tenderness with raised inflammatory markers. Findings on plain radiographs are frequently normal, and changes such as periosteal reaction and bony destruction may take 2 weeks or longer to appear. MRI is the gold standard imaging technique and reveals early inflammatory change in bone marrow and soft tissues with hypointense signal on T1-weighted images and increased signal on T2-weighted series. Correct and timely diagnosis is crucial because delay and inappropriate treatment can result in the devastating complications of growth arrest and angular deformity. Antibiotic therapy is often sufficient for uncomplicated osteomyelitis, although surgery may be required in those with concurrent septic arthritis or abscess formation. The aim of surgery is to drain the abscess cavity and remove all nonviable and necrotic tissue.

Discoid meniscus

A discoid meniscus is a congenital anomaly of the knee found in 3% of the population (Fig. 77.8). It typically affects the lateral meniscus and may be found bilaterally in 20% of cases.² It results when the lateral meniscus does not differentiate into a semilunar shape and instead forms a thick wafer of fibrocartilaginous tissue. The anomaly in itself is asymptomatic; however, a tear in the meniscus can result in pain and mechanical symptoms in the affected knee. Discoid lateral menisci are classified as complete or incomplete (determined by coverage of the tibial plateau) and by Wrisberg type (determined by the presence or absence of the normal posterior meniscotibial attachment). Discoid menisci are more prone to tears because of the thickness of the meniscus, its diminished vascular blood supply, and in some instances, weak capsular attachment. Symptomatic tears may be treated by arthroscopic débridement and saucerization, but if the meniscus is unstable, it should be stabilized before partial meniscectomy.^{3,4}

Malignancy and hematologic conditions

Malignancies can first be manifested as arthritis caused by malignant cell infiltration of structures surrounding the joint. Patients are typically ill and may have difficulty using the affected limb. One or many joints can be

■ TABLE 77.1

Common causes of knee pain in different age groups

Age group	Intraarticular	Periarticular	Cause referred
Childhood (2-10 yr)	Juvenile chronic arthritis Osteochondritis dissecans Septic arthritis Torn discoid lateral meniscus	Osteomyelitis	Perthes disease Transient synovitis of the hip Septic hip arthritis Slipped capital femoral epiphysis
Adolescence (10-18 yr)	Osteochondritis dissecans Torn meniscus Anterior knee pain syndrome Patellar malalignment	Osgood-Schlatter disease Sinding-Larsen-Johansson syndrome Osteomyelitis Tumors	Slipped capital femoral epiphysis
Early adulthood (18-30 yr)	Torn meniscus Instability Anterior knee pain syndrome Inflammatory conditions	Overuse syndromes Bursitis	Rare
Adulthood (30-50 yr)	Degenerate meniscal tears Early degeneration after injury or meniscectomy Inflammatory arthropathies	Bursitis Tendinitis	Degenerative hip disease secondary to hip dysplasia or injury Lumbar herniated disk
Older age (>50 yr)	Osteoarthritis Inflammatory arthropathies	Bursitis Tendinitis	Osteoarthritis of the hip Lumbar spondylosis, stenosis

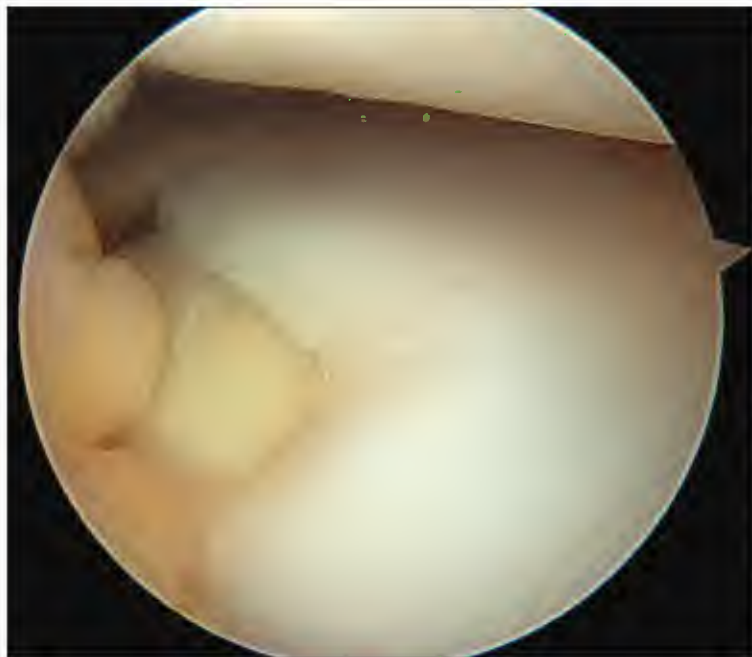


Fig. 77.8 Arthroscopic view of a discoid meniscus.

affected. Pathologic fractures associated with benign or malignant lesions may give rise to sudden disability and severe pain. A complete blood cell count, erythrocyte sedimentation rate, and radiographs are often the first step in making a diagnosis. Hematologic conditions can cause limb pain around the knee. Hemophilia is most commonly manifested as joint swelling secondary to hemorrhage. Knee hemarthrosis is most common, followed by elbow hemarthrosis. Children with sickle cell anemia may experience knee pain in the context of vasoocclusive sickle cell crises.

Inflammatory disease of the knee

Inflammatory conditions include juvenile rheumatoid arthritis (JRA) and pediatric spondyloarthritis. School-aged children and adolescents are most affected by polyarticular-onset JRA and type II pauciarticular arthritis. JRA has a wide spectrum of severity of symptoms ranging from mild pain and swelling with minimal limitation in activity to deforming and incapacitating symptoms. Long-term medical treatment may be required, depending on the type and severity of the arthritis. Early diagnosis and intervention are important to allow normal growth and development. Juvenile-onset spondyloarthritis (JSPAs) often affect boys at approximately 10 years of age and occur

at an estimated rate of 2 per 100,000 in the United States. JSPAs include the gastrointestinal-associated arthropathies, reactive arthritis, and psoriatic arthritis. JSPA may be manifested as an isolated arthritis, enthesitis, tendonitis, or dactylitis or as a clinical syndrome called seronegative enthesopathy and arthropathy. In the majority of children these syndromes will evolve into ankylosing spondylitis or another form of spondyloarthritis over the subsequent decades. These children will often have an asymmetric arthritis commonly involving the knee, midtarsal joint, and ankle. Spondyloarthritis should be suspected in those with a history of enthesitis affecting the Achilles tendon or insertion site of the plantar fascia to the os calcis.

Adolescence

Osgood-Schlatter disease

Osgood-Schlatter disease is a traction apophysitis of the tibial tubercle.^{5,6} It typically occurs during the adolescent growth spurt and is more common in boys. It results from repetitive tensile stress exerted by the pull of the quadriceps muscle, magnified by the patellar mechanism, on the insertion of the patella tendon into tibial tubercle apophysis. Patients classically report anterior knee pain that is exacerbated by jumping activities. Examination may reveal swelling or a prominent tubercle with localized tenderness. Pain is elicited with direct pressure and resisted knee extension. Plain radiographs frequently have normal findings in the early stages, but osseous fragments may be visible on lateral radiographs within the distal insertion of the patellar tendon in chronic cases (Fig. 77.9). Osgood-Schlatter disease is usually self-limited, with resolution of the symptoms after skeletal maturity. Treatment is therefore generally nonoperative and consists of modification of activity and physiotherapy with a focus on strengthening exercises and stretching of the quadriceps, hamstrings, and ITB. Occasionally, immobilization in a removable splint is required. One in 10 patients may eventually experience pain as an adult because of formation of a separate ossicle. Surgery is rarely necessary, but it may be indicated when osteochondral fragments cause persistent pain with kneeling.⁷

Sinding-Larsen-Johansson disease

Sinding-Larsen-Johansson disease is another traction apophysitis, similar to Osgood-Schlatter disease, that involves the distal pole of the patella.⁸ Pain and tenderness are felt at the distal pole of the patella, and the symptoms are aggravated by running, jumping, and kneeling. The natural history and treatment are similar to those described for Osgood-Schlatter disease.

Osteochondritis dissecans

Osteochondritis dissecans (OCD) is avascular necrosis of the subchondral bone with partial or complete separation of the bony fragment. Boys are affected three times more commonly than girls, with the peak incidence occurring in the second decade of life. OCD is generally unilateral, and the knee joint is by far the most commonly affected site. Within the knee, 80% of the lesions occur in the lateral border of the medial femoral condyle. Less common areas of involvement are the posterior aspect of the lateral femoral

condyle, the trochlea, and the patella. The exact cause is not fully understood but is thought to be multifactorial, with genetic predisposition, mechanical stress, and repetitive trauma contributing to development of the lesion. There is commonly a history of participation in sports with patients complaining of vague knee pain and swelling. Mechanical symptoms such as locking may be present when an osteochondral fragment is unstable or loose. Physical examination reveals an effusion with local tenderness over the OCD lesion. Plain knee radiographs are useful in delineating the OCD lesion or identifying osteochondral loose bodies. The tunnel view is especially good for detecting classic OCD lesions on the lateral aspect of the medial femoral condyle (Fig. 77.10). CT is helpful in identifying the precise

osseous extent of the lesion, but to assess the integrity of the overlying hyaline cartilage and to differentiate stable from unstable lesions, MRI, especially MR arthrography, is essential (Fig. 77.11).⁹

Treatment of OCD depends on the age of the patient and the severity of the lesion (Table 77.2, Fig. 77.12). Skeletally immature patients with stage 1 or 2 lesions have a favorable prognosis for spontaneous healing. Symptomatic patients are treated by limitation of activities, protected weight bearing, and gentle physiotherapy because motion of the knee joint contributes to nourishment of the cartilage. The prognosis is less favorable in skeletally mature patients, and conservative measures often fail to result in healing. The principles of operative management are maintenance of



Fig. 77.9 Osgood-Schlatter disease. Loose ossicles are present in the patellar tendon.

TABLE 77.2

Classification of osteochondritis dissecans (based on severity and arthroscopic appearance)

Classification	Appearance
Stage 1	Softening and irregularity of the articular cartilage without fissuring
Stage 2	Nondisplaced but breach of the articular cartilage
Stage 3	Displaced but attached <i>in situ</i> by intact fibrocartilage
Stage 4	Completely displaced osteochondral fragment



Fig. 77.10 Notch radiograph showing a lesion in the medial femoral condyle. An osteochondral defect developed in a 17-year-old with a defect over the weight-bearing area of the lateral femoral condyle.



Fig. 77.11 Radiograph (a) and magnetic resonance image (b) of an osteochondritis dissecans lesion.



Fig. 77.12 Arthroscopic view of an osteochondritis dissecans lesion in the medial femoral condyle.

articular congruity and removal of loose fragments. Stable lesions are treated by arthroscopic débridement and retrograde drilling to stimulate fibrocartilage formation. Unstable lesions require removal of small loose bodies and fixation of larger unstable osteochondral fragments with cannulated screws or bioabsorbable devices.

A variety of surgical techniques have been developed to address the difficult problem of large cartilage defects in young patients.¹⁰ Procedures such as microfracture and abrasion, in which the bony bed of the defect is débrided and drilled, are designed to stimulate fibrocartilage production by provoking an inflammatory reaction by local marrow cells. The resulting fibrocartilage lacks the tensile properties of hyaline cartilage, and it degenerates over time.¹¹ Osteochondral allograft or autograft transfer procedures involve harvesting osteochondral plugs from non-weight-bearing joint surfaces and reimplanting the plugs into an osteochondral defect in a weight-bearing area. Although good results have been demonstrated with this technique, the area that can be grafted is limited by the availability of donor site cartilage and by donor site morbidity. When allograft is used, a small risk for disease transmission is recognized.

A more recent development in cartilage repair surgery is autologous cartilage implantation (ACI). In this technique, the patient first undergoes diagnostic knee arthroscopy in which the size and location of the osteochondral defect are noted and a small, full-thickness sample of articular cartilage is harvested. From this sample, chondrocytes are isolated and cultured *ex vivo*. At least 6 weeks later, the patient returns to the operating room and cultured chondrocytes are implanted into the cartilage defect and sealed there with a periosteal patch or membrane via sutures or fibrin glue (Fig. 77.13). Encouraging outcomes have resulted from this procedure, and histologic evaluation shows stable repair tissue.¹²

Anterior cruciate ligament rupture

Isolated ACL ruptures are occurring with increasing frequency in children because of greater high-level sports participation. The controversy surrounding its management in skeletally immature patients has attracted much interest and debate in the literature over recent decades. The mechanism of injury and clinical features are similar to those in adults. ACL reconstruction in adults typically involves techniques for drilling bony tunnels, which if used in children would violate the physal plate. Traditionally, this has been thought to carry a potentially serious risk for growth disturbance.¹³ For this reason, extraphyseal methods of reconstruction have been developed for use in young children who require surgical stabilization to return to sports. Children who have no specific sports requirement and are not disabled by ACL laxity have historically been managed conservatively until skeletal maturity. There is now sufficient evidence to support the safe use of conventional transphyseal techniques in skeletally immature patients without any significant risk for growth abnormality.¹⁴⁻¹⁶

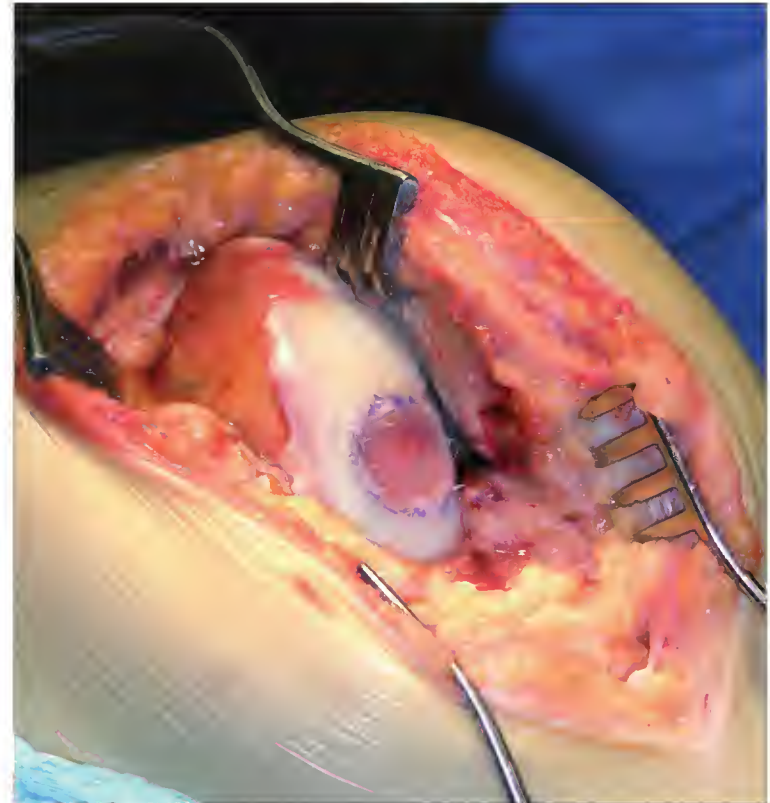


Fig. 77.13 Autologous chondrocyte implantation for medial femoral condyle lesion.

TABLE 77.3
Classification of chondromalacia patellae

Classification	Appearance
Stage 1	Softening and swelling of the articular cartilage
Stage 2	Deep fissures extending to subchondral bone
Stage 3	Fibrillation of the articular surface
Stage 4	Loss of articular cartilage with exposed subchondral bone

Adults

Anterior knee pain

Anterior knee pain can be caused by a wide range of conditions, including chondromalacia patellae, patellofemoral maltracking, and medial plica syndrome. A careful history should be obtained to establish the exact site of pain, as well as any exacerbating and relieving factors.¹⁷

Chondromalacia patellae

Chondromalacia patellae is sometimes referred to as patellofemoral syndrome¹⁸ and represents pathologic softening and fragmentation of the articular cartilage of the patella as a result of impact loading and excessive shear stress (Table 77.3). Patients with this condition commonly have anterior knee pain, especially on descending stairs and with prolonged sitting. Physical examination often reveals significant patellofemoral crepitation and retropatellar tenderness. In idiopathic cases the mainstay of treatment is physiotherapy with isometric quadriceps exercises and hamstring stretches. Patients with pain and mechanical symptoms may benefit from an arthroscopic procedure to remove any unstable chondral fragments. When associated patellofemoral malalignment is present, the underlying abnormality should be addressed to relieve the symptoms.

Patellofemoral maltracking, subluxation, and dislocation

Stability of the patellofemoral joint is derived partly from the osseous anatomy and partly from the muscles and ligaments around the patella. Instability often results from an imbalance between the medial and lateral forces acting on the patella and may be exacerbated by patella alta because a higher patella engages into the trochlear groove at a later point in the knee flexion arc.¹⁹ Static instability is associated with an abnormally high Q angle,

and dynamic instability may result from weakness of the VMO or contracture of the lateral retinaculum and ITB.

Patellofemoral instability may be characterized by patellar subluxation or dislocation. Patellar subluxations often reduce spontaneously and tend to be recurrent. Acute patellar dislocations may result from a direct blow to the knee and usually require medical assistance for reduction. The patella is always dislocated laterally, along with damage and tearing of the medial retinaculum. If the patella has spontaneously reduced, only swelling and tenderness may be noted over the torn medial retinaculum. Acute dislocation may be associated with an osteochondral fracture of the lateral femoral condyle or medial facet of the patella. In cases of recurrent dislocations, an underlying soft tissue or osseous abnormality is almost always present. The patient may have generalized ligamentous hyperlaxity, an abnormally high Q angle, patella alta, or a shallow trochlear groove. Chronic patellofemoral maltracking can cause a spectrum of symptoms ranging from pain to instability. Excessive lateral stress on the articular cartilage can result in anterior knee pain and, in the longer term, can cause arthritis. Patients may also complain of episodes of the knee “giving way” because of lateral subluxation of the patella. Physical examination may demonstrate a “J” sign, tight lateral retinacular structures, and a positive apprehension test.

Plain knee radiographs in patients with patellofemoral maltracking may reveal lateral placement of the patella, patella alta, hypoplasia of the distal femoral trochlea, or incongruity of the patellofemoral osseous anatomy. Patella alta is recognized on the lateral view by comparing the length of the patella with the length of the patellar tendon. The average ratio is approximately 1:1 (Fig. 77.14).¹⁹ Skyline views of the patellofemoral joint, taken with the knee flexed 30 degrees, may show the patella to be tilted laterally and translated toward the lateral femoral condyle (Fig. 77.15). Sclerosis may be seen in the subchondral bone of the lateral facet and is indicative of arthrosis from stress concentrated across the articulation. MRI can be particularly useful in assessing the integrity of the patellofemoral articular cartilage and measuring the tibial tuberosity–trochlear groove distance.

Treatment of patellofemoral maltracking varies according to the severity of symptoms. With an acute dislocation (Fig. 77.16) the patella must be reduced and the patient subsequently managed by mobilization as tolerated and physiotherapy for strengthening of the VMO and stretching of the ITB.



Fig. 77.14 Lateral knee radiograph with measurement of the Insall-Salvati ratio.

The decision-making process for operative intervention is complex; however, surgery is usually indicated for recalcitrant recurrent dislocations, for which the aim is to address the underlying abnormality and reduce the patient's risk for further chondral injury. Several surgical techniques have been described, including repair or reconstruction of the medial patellofemoral ligament, VMO advancement, lateral retinacular release, and tibial tubercle osteotomy.²⁰

Traumatic ligamentous injuries

Ligamentous injuries are common in young athletes. A ligament sprain is an injury in which the fibers are stretched or torn. In a first-degree sprain, the fibers are torn but function is unimpaired. In a second-degree sprain, more fibers are torn, along with stretching of the ligament, which causes abnormal joint laxity. A third-degree sprain involves complete ligament rupture with marked instability.²¹ The degree of instability after ligament injury is assessed by specific provocative maneuvers and quantified by using a three-point scale: I+ laxity is up to 5 mm, II+ is 5 to 10 mm, and III+ is 10 to 15 mm.

Anterior cruciate ligament injuries

ACL injuries are common in athletes engaging in sports requiring cutting, twisting, or jumping. Injuries are significantly more common in women, with female athletes being eight times more likely than male athletes to sustain ACL injuries.²² Potential risk factors include an increased Q angle, femoral anteversion, genu valgum, external tibial torsion, femoral intercondylar notch shape and size, ACL thickness, hormonal influences, and training techniques.

The classic history of an ACL injury involves a noncontact deceleration, jumping, or a pivoting action. It can also be caused by direct trauma such as a valgus force onto a flexed knee or hyperextension of an internally rotated tibia.²³ Patients typically describe a twisting injury with a backward fall and a palpable “pop” followed by knee pain and swelling. Resumption of activity is not usually possible, and walking is often difficult. The Lachman test is the most sensitive test for anterior tibial displacement and has 95% sensitivity. Radiographic studies may be useful but the findings are often normal. They may reveal a fracture of the tibial eminence—indicating avulsion of the tibial attachment of the ACL, or a Segond fracture (Fig. 77.17)—an avulsion fracture of the lateral capsule that is pathognomonic for ACL rupture.²⁴ MRI is the most useful diagnostic modality with a reported accuracy of greater than 95%. It is also a valuable screening tool for associated chondral and meniscal injuries. The overall incidence of meniscal tears in ACL injuries is reported to be as high as 70%, with the lateral meniscus more commonly being torn in the initial incident.²⁵ The risk for meniscal injury is somewhat static in the first few months following ACL rupture, but in the context of functional instability in an ACL-deficient knee, risk increases significantly with time after the initial injury.²⁶

Treatment of ACL injuries is patient specific and depends on the symptoms and the desired level of activity of the patient. Nonoperative treatment may be an appropriate option for a low-demand patient or one who is willing to make lifestyle changes and avoid activities that cause recurrent instability, and it should include an aggressive rehabilitation program and counseling about activity levels. However, in young patients, those with a desire to return to high-level sports, or patients with recurrent rotational instability, reconstruction of the ligament is recommended. Surgery involves secure fixation of the graft within bony tunnels in the femur and the proximal end of the tibia. The choice of graft is often surgeon dependent and includes synthetic graft, allograft, or autograft, with the patella and hamstring tendons being the two most commonly used grafts. Surgery is carried out once the knee is pain free and full range of motion is restored to allow immediate rehabilitation postoperatively.^{27,28} The success of surgery is largely dependent on the position of the tunnels and patient compliance with postoperative physiotherapy.



Fig. 77.15 Skyline radiograph showing lateral subluxation of the patella.

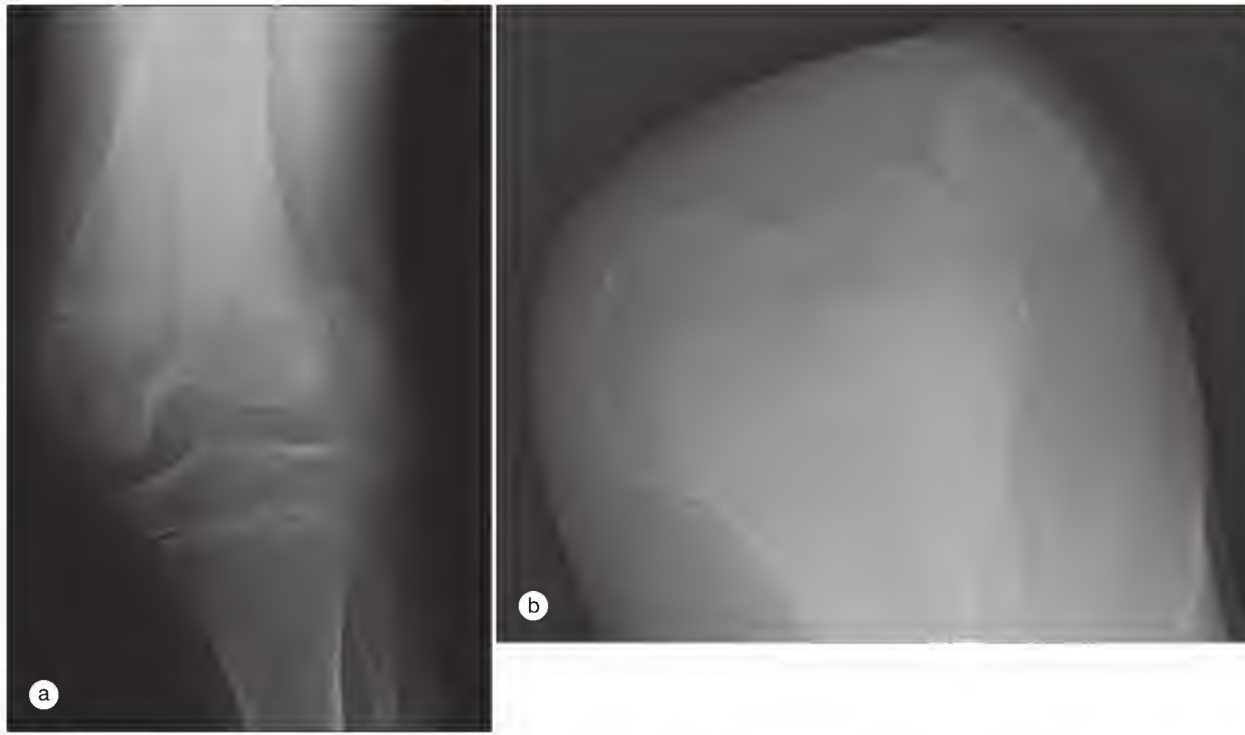


Fig. 77.16 Anteroposterior (a) and skyline (b) radiographs showing patellar dislocation.

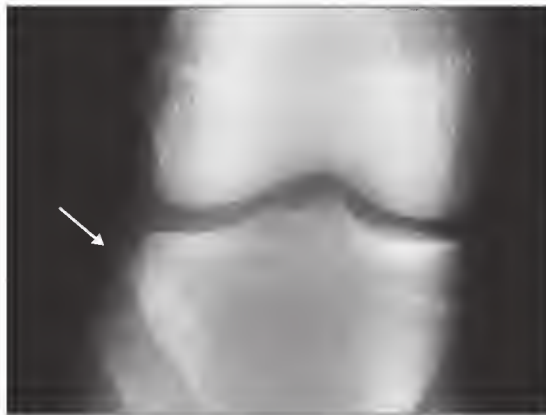


Fig. 77.17 Anteroposterior radiograph of a Second fracture. The figure shows a flake of bone (arrow) and avulsion of the anterolateral capsule in the region of the Gerdy tubercle, frequently associated with rupture of the anterior cruciate ligament.

Posterior cruciate ligament injuries

PCL injuries occur much less commonly than ACL injuries, primarily because of the larger size of the PCL, which makes it biomechanically twice as strong as the ACL.²⁹ Typically, the injury occurs as a result of a direct impact against the anterior aspect of a flexed knee or a hyperextension injury resulting in an isolated avulsion or a combined ligament injury. Physical examination may reveal a contusion over the anterior aspect of the tibia with posterior tibial sag and a positive posterior drawer test result. An avulsion fracture of the tibial insertion of the PCL is sometimes visible on a lateral knee radiograph, although the findings on plain radiographs are often normal and the gold standard imaging modality is MRI (Fig. 77.18). Isolated rupture of the PCL does not usually result in significant functional knee instability unless other structures, especially the posterolateral corner, have also been damaged.^{30,31} Nonoperative treatment of isolated PCL injuries consists of short-term immobilization and protected weight bearing, followed by quadriceps-strengthening and range-of-motion exercises.

Medial collateral ligament injuries

The MCL is the major static stabilizer of the medial side of the knee joint. The vast majority of injuries to the MCL result from a valgus force, although an external rotational force sometimes leads to rupture of the posterior oblique ligament (POL) and posterior fibers of the MCL.³² Findings on

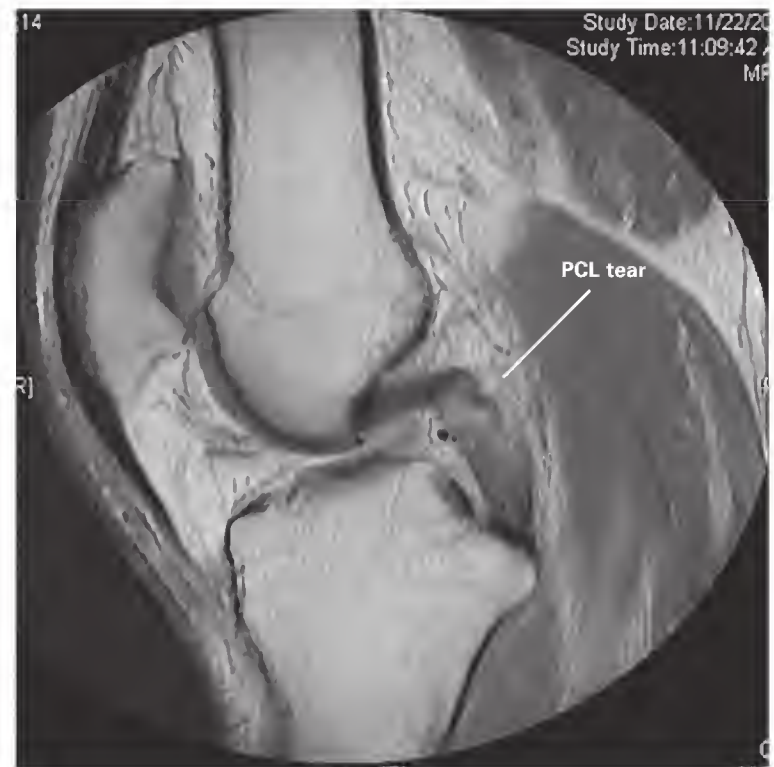


Fig. 77.18 Magnetic resonance image showing rupture of the posterior cruciate ligament (PCL).

physical examination include swelling, bruising, and tenderness along the course of the ligament. The knee must be examined in 20 to 30 degrees of flexion to isolate the MCL, as well as in full extension to determine whether other supporting structures such as the POL are injured, which signifies a much more extensive injury. Low-grade MCL tears are treated conservatively in a hinged knee brace to allow protected range of motion, followed by progressive physiotherapy.³³ There is a growing tendency to surgically repair high-grade MCL tears because nonoperative management of these injuries often results in an unsatisfactory outcome. Pellegrini-Stieda disease is an infrequent chronic sequela of an MCL injury in which a patient has persistent pain over the MCL femoral origin as a result of local calcification.



Fig. 77.19 Radiograph of a patient with Pellegrini-Stieda disease showing calcification of the insertion of the medial collateral ligament.

The area is tender to palpation, and pain is elicited on stressing of the ligament. Radiographs reveal characteristic calcification at the ligament insertion (Fig. 77.19). Treatment consists of rest and nonsteroidal antiinflammatory drugs (NSAIDs) because the condition is usually self-limited. Occasionally, targeted corticosteroid injection helps ameliorate the symptoms.

Lateral collateral ligament injuries

The LCL is the least commonly injured knee ligament in isolation. It is part of the posterolateral ligament complex of the knee, which also includes the lateral capsule, arcuate ligament, popliteofibular ligament, and popliteus tendon. Injury to the posterolateral structures frequently occurs in combination with injury to the cruciate ligaments and may represent a reduced knee dislocation. The mechanism of injury is typically a direct blow to the antero-medial aspect of an extended knee. In isolated LCL injury, the ligament usually ruptures at its fibular insertion, or it may avulse off the fibular styloid. Because of its close proximity to the common peroneal nerve, with severe injuries there is often some distal sensory and motor disturbance. Isolated low-grade injuries may be treated conservatively, but high-grade or combined injuries should be acutely reconstructed surgically.

Bursitis

Bursitis is inflammation of a synovial-lined bursa and may result from direct trauma, recurrent minor injury, infection, or crystal deposition diseases. The most frequent site of knee bursitis is the prepatellar bursa, which usually covers the lower half of the patella and the upper half of the patellar tendon. It can become chronically inflamed in those whose occupation involves much kneeling, thus giving rise to the eponym “housemaid’s knee.” Symptoms include erythema, swelling, and tenderness over the patella. Treatment of prepatellar bursitis depends on the underlying etiology but, as a general rule, involves rest, avoidance of kneeling, and systemic antiinflammatories. Occasionally, a large bursitis may be aspirated, and in cases of infective bursitis, parental followed by a course of oral antibiotics is often required. Surgical management is rarely indicated, although recalcitrant bursitis may necessitate open bursectomy.

Patellar tendonitis

Patellar tendonitis, also called “jumper’s knee,” is an overuse syndrome that occurs not uncommonly in young people participating in repetitive jumping sports such as volleyball and basketball. Chronic overloading of the tendon results in microtears, fraying, and focal degeneration of the deep fibers of the patellar tendon, especially near the insertion at the inferior pole of the patella.³⁴ Histologic evaluation reveals mucoid degeneration and fibroid necrosis. In older patients the superior pole of the patella may be affected



Fig. 77.20 Magnetic resonance image showing patellar tendonitis with high signal at the inferior pole of the patellar tendon.

by analogous quadriceps tendonitis. Symptoms include sharp localized pain at the apex of the patella exacerbated by activities that load the extensor mechanism. Findings on routine knee radiographs are usually normal, and MRI is the investigation of choice to confirm the diagnosis (Fig. 77.20). The tendon is weakened by this inflammatory response; however, tensile strength can recover if progressive stress is imposed on the tendon. The mainstay of treatment is therefore nonoperative management consisting of modification of activities, physiotherapy concentrating on eccentric loading exercises, and NSAIDs. A variety of braces and straps that stabilize the patella may be added to the physical therapy program. Surgery is reserved for recalcitrant cases; the degenerative tissue is excised to decompress the tendon, with a phased return to activities.

Iliotibial band syndrome

ITB syndrome is an overuse syndrome and the most common etiology of lateral knee pain in runners.³⁵ Several causes have been suggested, and the friction theory of repetitive ITB motion against the lateral femoral epicondyle during knee flexion and extension is most widely accepted.³⁶ Anatomic factors that biomechanically predispose patients to this condition include excessive genu varum, internal tibial torsion, planovalgus, and hip abductor weakness. Patients typically localize pain to the region of the distal ITB between the lateral femoral condyle and Gerdy’s tubercle and characteristically report worsening symptoms when running downhill or lengthening their stride. The mainstay of treatment is nonoperative: activity modification, NSAIDs, and physiotherapy for specific stretching exercises focused on the ITB, tensor fasciae latae, and gluteus medius. Injection of local anesthetic and steroid can aid in the diagnosis of ITB syndrome and may provide relief of pain in acute exacerbations. Surgery is reserved for recalcitrant cases that fail to improve with at least 6 months of conservative treatment.

Popliteal cysts

A popliteal cyst is a synovial fluid-filled mass located in the popliteal fossa. It is also referred to as a Baker cyst, who described it in 1877.³⁷ Popliteal cysts are generally considered to be distention of the bursa located beneath the medial head of the gastrocnemius muscle. This bursa directly communicates with the knee joint, and excess synovial fluid is forced into it via a one-way valve phenomena during knee flexion. Any underlying knee pathology causing accumulation of synovial fluid can result in the formation of a popliteal cyst, and degenerative joint disease is the most common cause of such cysts. Small cysts are frequently asymptomatic; however, patients



Fig. 77.21 Synovial chondromatosis.

TABLE 77.4

Milgram classification⁴¹

Phase 1 (early)	Active intrasynovial disease without loose bodies
Phase 2 (transitional)	Transitional lesions with OC nodules in the synovial membrane and OC bodies lying free in the joint cavity
Phase 3 (late)	Multiple free OC bodies with quiescent intrasynovial disease

OC, osteochondromatosis.

with larger cysts may have achy knee pain and a palpable posterior knee mass. Popliteal cysts, as with other synovial cysts, may enlarge or regress gradually over time, or they may rupture acutely. Plain radiography may confirm the underlying cause, and the mass is best evaluated with ultrasound or MRI. The differential diagnosis of a popliteal mass includes popliteal artery aneurysm, lipoma, nerve sheath tumor, and sarcoma. Treatment in adults is initially tailored to address the cause of the knee effusion.³⁸ Ultrasound-guided aspiration and corticosteroid injection may be performed to reduce synovial fluid volume and production. Surgery is indicated only in very rare cases when the cyst remains symptomatic and consists of cyst decompression and ablation of the communicating channel between the joint and cyst cavity, often via an open procedure.

Synovial chondromatosis

Synovial chondromatosis is a rare synovial proliferative disease of unknown origin.³⁹ It is characterized by cartilaginous metaplasia of the intimal layer of the synovial membrane of joints, tendons, and bursae (Fig. 77.21). The condition is most often seen in middle-aged men but has been reported in children and teenagers. The knee joint is most commonly affected, and involvement is typically monoarticular. Patients generally have pain and swelling⁴⁰ in the early stages, but multiple loose bodies can result in locking of the knee. In later stages of the disease, knee range of motion may be decreased, with calcified lesions clearly visible on plain radiographs. Knee stiffness may be caused by thickened metaplastic synovium and may portend a poor prognosis if severe. Treatment of symptomatic synovial chondromatosis involves arthroscopic removal of symptomatic loose bodies. In the first and second phases of disease (Table 77.4),⁴¹ active synovium should be excised. Recurrence is treated by repeated arthroscopic débridement.

Pigmented villonodular synovitis

Pigmented villonodular synovitis (PVNS), a rare, benign proliferative process, involves the synovial tissue, mainly of large joints. It was thought to be of a reactive inflammatory origin but is now regarded as a tumor of periarticular tissue. The knee is the most commonly affected joint. There is often a long history and delay in diagnosis. Patients typically complain of an intermittently painful knee and may have a history of recurrent atraumatic knee hemarthrosis with no underlying bleeding disorder. Aspiration of brown synovial fluid in the absence of recent trauma is characteristic and may often be the first indication of the disease. MRI is the mainstay for



Fig. 77.22 Magnetic resonance image of a knee with pigmented villonodular synovitis showing bony erosion.

imaging of PVNS and has a characteristic appearance because of the presence of hemosiderin (Fig. 77.22). The lesions have predominantly low signal intensity on T1- and T2-weighted images with marked enhancement on T1-weighted, contrast-enhanced studies. Treatment of PVNS depends on the extent and location (intraarticular or extraarticular) of the disease. Localized intraarticular PVNS may be successfully treated arthroscopically, but for diffuse PVNS, open synovectomy is now recommended to allow access to the posterior joint, collateral ligaments, and cruciate ligaments. Radiosynovectomy, or intraarticular injection of radioactive colloid, can be used as local adjuvant treatment following synovectomy. Radiation therapy can also be used as primary treatment of unresectable disease or as local adjuvant treatment.^{42,43}

Meniscal injuries

The menisci are the most commonly injured structure within the knee joint. In young adults, meniscal tears usually result from an acute traumatic or sports-related event and, in older patients, as part of a degenerative process. Meniscal injuries are also associated with chronic ligamentous instability. Tears are most frequently located in the midportion and posterior horn, with a higher proportion involving the medial meniscus. Patients typically have pain and swelling, and there may be mechanical symptoms of catching or locking. A locked knee will exhibit a springy block to extension, with pain occurring on forced extension. With an acute event it is crucial to establish the time interval during which the swelling developed. Effusion developing within 1 hour of injury signifies a hemarthrosis, which may result from peripheral tears involving the vascularized red zone, or signals a concomitant osteochondral fracture or a ligament rupture, most commonly the ACL. Plain radiographic findings are generally normal unless an associated osseous injury is present. MRI is the study of choice to confirm a meniscal tear, with diagnostic accuracy being greater than 90% (Fig. 77.23).⁴⁴ Treatment of meniscal tears depends on a multitude of factors, including age of the patient; pattern, size, and vascularity of the tear; general condition of the joint; and associated ligamentous injuries. The aim of treatment should be to preserve meniscal tissue wherever possible. Conservative management may therefore be appropriate for low-demand patients, chronic tears in a degenerative joint, radial tears smaller than 5 mm in length, partial-thickness tears, or stable longitudinal tears in the red zone.⁴⁵

In young patients with symptomatic tears, surgical intervention is indicated. When feasible, meniscal repair should be done in an attempt to maintain meniscal integrity and prevent the long-term degenerative changes that occur after meniscectomy. When meniscal repair cannot be done or is

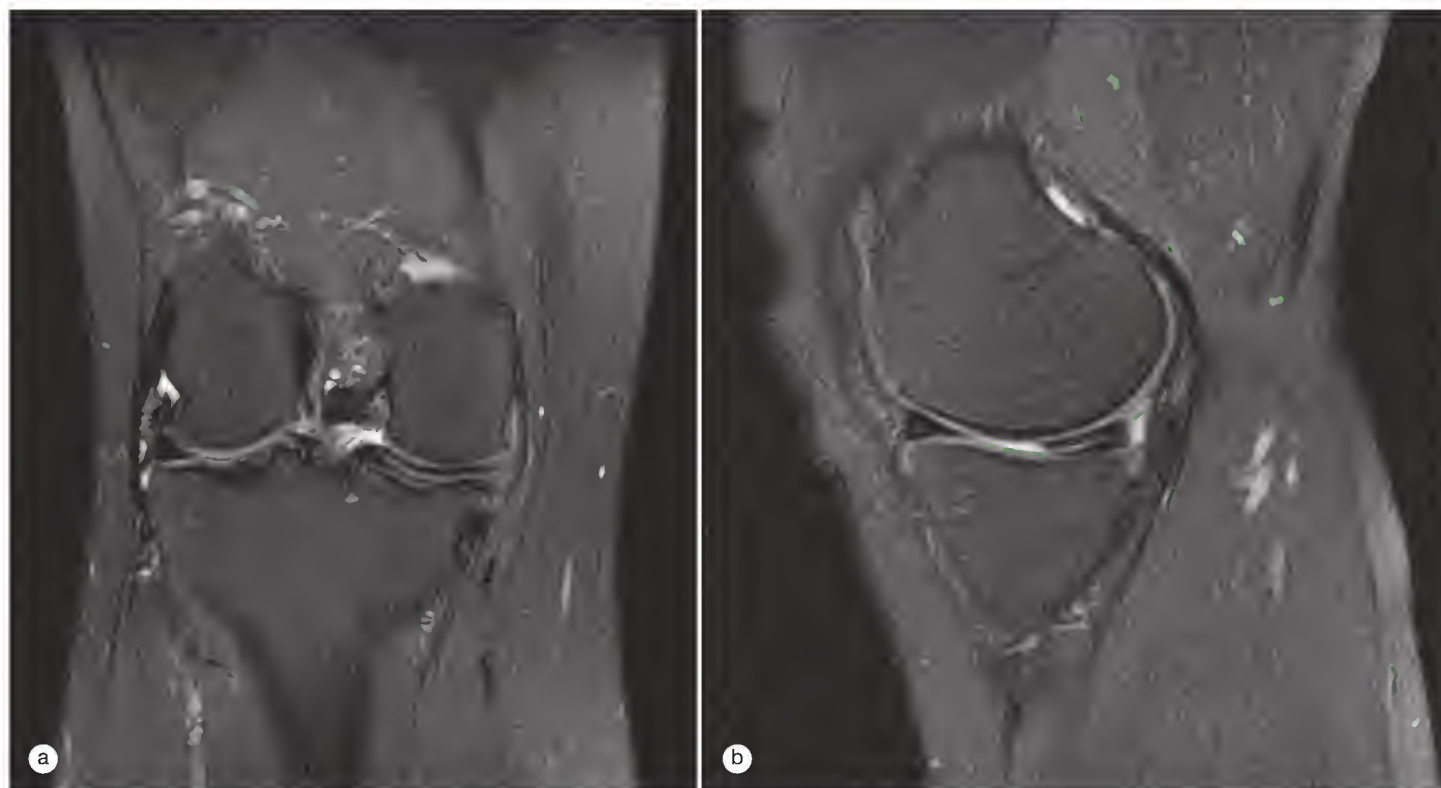


Fig. 77.23 Magnetic resonance images of a degenerative medial meniscus tear in the coronal (a) and sagittal (b) views.

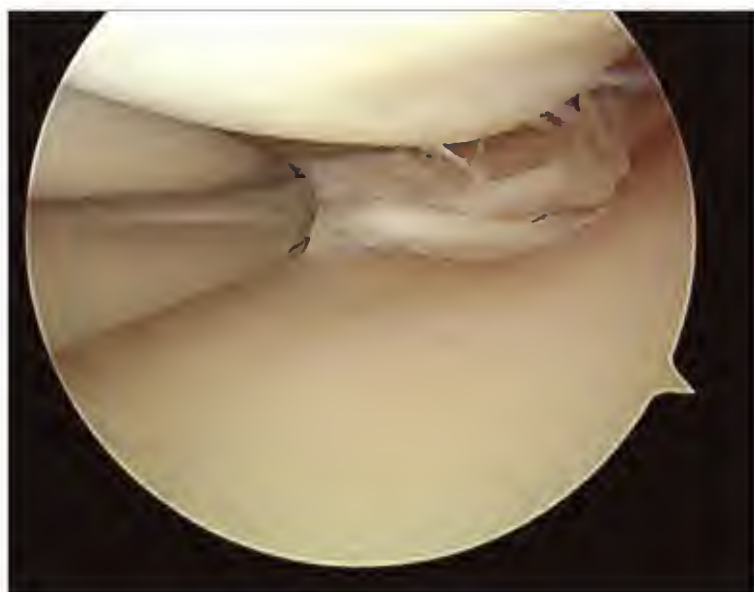


Fig. 77.24 Arthroscopic partial medial meniscectomy.

contraindicated, partial meniscectomy may be considered (Fig. 77.24), with the goal of retaining as much viable meniscal tissue as possible. Successful repair has been reported in more than 80% of cases in conjunction with ACL reconstruction, although success rates are lower for isolated repairs. Complications related to repair include neurologic injury, postoperative loss of motion, recurrence of the tear, and infection. Meniscal allograft transplantation may provide a treatment option when meniscus salvage is not possible or when total meniscectomy has previously been performed.

Extensor mechanism injuries

The extensor apparatus comprises the quadriceps tendon, the patella, and the patellar tendon. Disruption of this mechanism is one of the most common injuries in the elderly population. The injury often results from a simple fall in which the quadriceps muscle contracts forcefully and eccentrically against a flexed knee. Patients have an acutely painful, swollen knee



Fig. 77.25 Magnetic resonance image showing patellar tendon rupture.

with an inability to actively extend the knee. It should be noted that an intact straight leg raise does not exclude this injury because the ITB acts as an accessory extensor when the knee is fully extended. It is therefore important to assess active knee extension from a flexed position. Examination may reveal a palpable defect in the ruptured tendon. Lateral radiographs of the knee may demonstrate a fracture of the patella or patella alta when the patellar tendon is ruptured. MRI can be used (Fig. 77.25) in cases in which the diagnosis is uncertain; however, the investigation of choice is ultrasound, which is cheap and more readily available and allows dynamic assessment of the tendon. Treatment of complete rupture of the quadriceps



Fig. 77.26 Anteroposterior radiographs of total knee replacement (a) and unicompartmental knee replacement (b).

or patellar tendon consists of surgery to repair the extensor mechanism and physiotherapy for rehabilitation and restoration of function.

Isolated cartilage defects

The natural history of cartilage lesions in the knee is still unknown. Even though some lesions may be asymptomatic initially, it is widely held that they lead to degenerative arthritis of the knee over time. Treatment of these lesions is therefore important to prevent the development of osteoarthritis. Several surgical techniques have been used for the treatment of these lesions, with microfracture and ACI having the most favorable outcomes.⁴⁶ Microfracture is ideally suited for small, well-contained Outerbridge grade III/IV defects and has been reported to improve functional outcomes in more than 70% of patients. ACI is recommended for patients with larger or multiple defects and is intended to produce durable repair tissue that functions in a manner similar to hyaline cartilage. The future of biologic regenerative techniques for the treatment of articular cartilage defects in the knee is promising.

Osteoarthritis

Primary osteoarthritis is associated with aging and the “wear and tear” of life. It is a disease process and not part of the normal aging process. Secondary osteoarthritis, in contrast, tends to develop after a specific event, such as an infection or trauma. Any insult that alters the alignment, stability, or osseous congruence of the knee joint will accelerate the development of degenerative joint disease. It is therefore imperative to achieve anatomic

reduction of intraarticular fractures and the correct rotation and alignment of diaphyseal fractures and to restore ligamentous stability in the knee joint to minimize the risk for secondary osteoarthritis.

Medical or nonoperative management of osteoarthritis consists of a reduction in body weight by the use of regular low-impact aerobic exercise, physiotherapy, walking aids, and analgesia to control pain. Surgical management of knee osteoarthritis can be broadly divided into joint-preserving and joint-replacing (arthroplasty) procedures. Joint preservation procedures such as high tibial osteotomy aim to redistribute the weight-bearing forces to “offload” the degenerative compartment by realigning the mechanical axis of the lower limb. Ten-year survivorship rates with this type of intervention have been reported to be higher than 70%.⁴⁷

Knee arthroplasty, such as partial (unicompartment) or total knee replacement (TKA), is indicated for severe disability resulting from pain and deformity and should be considered only after adequate trials of conservative therapy (Fig. 77.26). The majority of patients undergoing knee arthroplasty achieve marked pain relief and improvement of function, although a small percentage continue to have pain, stiffness, or instability. In patients in whom osteoarthritis is isolated to one compartment, unicompartmental knee replacement (UKA) may be considered in those with an intact ACL, correctable deformity, and flexion greater than 90 degrees. UKA is technically a more challenging procedure but has gained popularity in carefully selected cases because of its distinct advantages over TKA, which include lower perioperative morbidity and blood loss, preservation of bone stock, more normal knee kinematics, and accelerated patient recovery.⁴⁸⁻⁵⁰

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78

The ankle and foot

■ ANTHONY C. REDMOND

- Problems affecting the foot and ankle are common in rheumatology practice but are often neglected.
- Foot problems require consideration of local mechanical demands as well as systemic disease processes.
- A simple but comprehensive clinical assessment of the ankle and foot can be performed in around 1 minute.
- Many rheumatologic problems affecting the ankle and foot can be self-managed by the patient.
- Foot problems can be complex in people with systemic rheumatologic disorders and often require onward referral and/or appropriate multidisciplinary care.

INTRODUCTION

Recent years have seen some significant advances in the care of foot and ankle problems. In this chapter the manifestations of foot abnormalities are covered for the major rheumatologic disorders: rheumatoid arthritis, osteoarthritis, the seronegative arthritides, connective tissue disease, crystal diseases, and miscellaneous conditions including hypermobility syndrome. The principles of assessing and treating foot and ankle problems in rheumatology are covered, along with the relevant specific approaches.

EPIDEMIOLOGY OF FOOT AND ANKLE PROBLEMS

Approximately 10% of all adults report significant foot pain at any given time, and the number increases with age so that half of individuals older than age 50 have foot pain.^{1,2} Foot problems are also five times more common in females than in males. When ankle and foot problems are present there is the potential for significant impact because the involvement of such important weight-bearing structures leads to compromise of daily activities.^{3,4} Furthermore, foot problems rarely occur in isolation and are often found in conjunction with other musculoskeletal problems such as hip or knee pain.⁵ Despite the high prevalence of foot symptoms in patients coming to rheumatology clinics, foot and ankle problems are relatively neglected. Time constraints are often blamed, and poor training or limited confidence in the clinical examination of foot problems may contribute.⁶ However, the prevalence of foot problems in rheumatology is high enough that an explicit question about foot problems, and (when relevant) a basic screening examination, should be considered an integral part of every patient encounter in rheumatology practice.

**ANATOMY OF THE ANKLE AND FOOT****EXAMINATION OF THE FOOT AND ANKLE**

A basic ankle and foot screen need take no more than 1 minute per foot provided it is performed by an assessor with the requisite knowledge, training, and practice. A good starting point for lower limb assessment is the

Regional Examination of the Musculoskeletal System (REMS).⁶ For a more detailed foot examination, the author and colleagues have described extensively a Leeds foot assessment protocol that is a comprehensive assessment of foot problems based on the widely used approach of history→observation→examination. A detailed development of this approach can be found elsewhere.⁷

In routine practice, the most logical overview of foot and ankle involvement is provided by a simple assessment of the patient walking, followed by observation of the legs and feet with the patient standing still, followed by observations with the patient seated or lying supine (i.e., not weight bearing). It is helpful to observe the transition between non-weight bearing and weight bearing to note any changes that occur as the limb accepts weight.

Once the examination moves on to the specific exploration of ankle and foot abnormalities, it is useful to conduct a systematic observation of the overall foot shape and palpation of the relevant joint margins (ankle, subtalar, midfoot joints, and metatarsophalangeal [MTP] joints), soft tissue structures, and insertions to isolate inflamed or damaged tissues. Active movement of the ankle is evaluated, with assessment of the direction, range, and quality of motion and noting of any related pain. Finally, the assessment is completed with clinician-mediated passive motions of the ankle, subtalar, midfoot, and forefoot joints, with pain and the direction, range, and quality of movement again noted. Using a 1-minute protocol it is possible to identify the soft tissue structures involved, differentiate ankle involvement from subtalar disease, identify midfoot disease, and isolate and quantify forefoot joint involvement.

IMAGING

Traditionally, the most widely used imaging modality has been plain radiography, although it is limited to the assessment of existing bony anatomy and joint damage. Foot radiographs can be taken either non-weight bearing—the norm in most centers—or, increasingly, with the patient bearing weight. When available, weight-bearing radiographs better represent the foot in its functional state and allow monitoring of postural change over time.

Other imaging modalities useful in the assessment of foot and ankle problems are magnetic resonance imaging (MRI), ultrasonography, computed tomography, and scintigraphy.⁸ These modalities are used less often than plain radiography because of cost and access but can provide useful diagnostic information, particularly about the soft tissues (Table 78.1). Scintigraphy, which was used widely in the past in the diagnosis of foot stress fractures, has largely been superseded by MRI, although expertise in interpretation of MRI imaging of the complex anatomy of the foot may not be available in all units. Ultrasonography can be very useful in imaging foot problems and is used increasingly in rheumatology. The high resolution afforded by ultrasonography can be useful in identifying precisely which tissues are associated with presenting symptoms. Features such as power Doppler also enable differentiation between active inflammation and non-inflammatory or mechanical disorders.⁸

OTHER ASSESSMENTS

Recent advances in the technologies available to quantify foot function in health and disease have made diagnosis of the various systems increasingly feasible. Using affordable hand-held Doppler ultrasonography or photoplethysmography units, vascular pathologic conditions can be quantified accurately, and neurologic status can be assessed using monofilaments or



The ankle is a simple mortise that articulates with the talus inferiorly. The motion of the ankle is almost entirely plantar flexion/dorsiflexion. Conversely, the foot is a complex structure consisting of 26 bones (Fig. e78.1) and more than 30 articulations. For simplicity the foot can be simplified into three interrelated functional units: the hindfoot/ankle (consisting of the ankle, talus, and calcaneus), the midfoot (talus/navicular/cuneiforms and cuboid), and the forefoot (metatarsals and associated digits). The main roles of the foot and ankle are to provide a stable platform for locomotion and to facilitate progression of the leg over the fixed foot. The functional units of the foot are interrelated, and so the stability of the distal regions (i.e., the midfoot and forefoot) is affected by the regions proximal to them and vice versa. During normal locomotion the healthy foot goes through a repeated cycle of pronation and supination. In early stance physiologic pronation facilitates adaptation to uneven surfaces and shock absorption, and a subsequent period of resupination provides a more rigid lever for propulsion and a resulting conservation of energy. In association with some conditions, the pronation/supination cycle may be impaired; this results in overpronation (foot flattening), which leads to instability and excessive weight bearing in the medial structures, or oversupination (often seen as a cavus/cavoid foot type), which leads to excessive rigidity and poor shock absorption combined with a lateral deviation in the path of the center of mass. Change in the load distribution can lead to localized increases in pressures under the forefoot (and to a lesser extent the midfoot and hindfoot), causing joint pain, soft tissue change such as bursitis, or skin change such as clavus (corn) or hyperkeratosis (callus) formation. These are all common secondary features of rheumatologic conditions.

Ankle

The ankle is a hinge joint composed of the distal end of the tibia and fibula and the talar dome (Fig. e78.2). The talus is stabilized in the mortise by the medial and lateral malleoli. The strength of the ankle joint is augmented by the deltoid ligament medially and three ligaments laterally: the posterior talofibular, calcaneofibular, and anterior talofibular ligaments, which are

often injured in ankle sprains. Syndesmotic ligaments stabilize the fibula to the tibia, permitting a few degrees of rotation and a few millimeters of translation.

Tendons passing around the ankle are held in place by a series of extensor and flexor retinacula (Figs. e78.3 and e78.4). Within a few centimeters of the retinacula the tendons are invested in a synovial sheath, which can become inflamed and lead to tenosynovitis. The tendons pass around the ankle, along with a neurovascular bundle, in three compartments; the anterior, the posteromedial, and the posterolateral. Several mnemonics have been developed to help clinicians recall the relative positions of the anatomic structures within the compartments. For the anterior compartment, from medial to lateral, a useful mnemonic is *Tom Hates Dick*, representing the tibialis anterior, extensor hallucis longus, and extensor digitorum longus (Fig. e78.5). Extensor tendons cross the anterior aspect of the ankle extending from the anterior compartment of the leg distally to their insertion on the foot. The extensor tendons tibialis anterior, extensor hallucis, and extensor digitorum longus are stabilized by a superior and an inferior retinaculum, and their main function is to dorsiflex the ankle and toes.

In the posteromedial compartment the mnemonic *Tom, Dick and (A Very Nervous) Harry* applies representing, from the medial malleolus to the Achilles tendon, the tibialis posterior, flexor digitorum longus, (posterior tibial artery, tibial vein, tibial nerve), and flexor hallucis longus. Hugging the medial malleolus, the posterior tibial tendon is the most medial and anterior, followed in the posterior direction by the flexor digitorum longus, posterior tibial artery and veins, posterior tibial nerve, and flexor hallucis longus (FHL) (see Fig. e78.3). The low-lying muscle of the FHL is closely apposed to the posterior tibia, and its tendon runs in a tight sheath directly behind the talus and between the posterior lateral and posterior medial tubercles. The relationship is so close that often subtalar or ankle synovitis tracks along the FHL tendon sheath. The flexor retinaculum, the “roof” of the tarsal tunnel, encases the posterior medial tendons and is anchored from the medial malleolus to the calcaneus. The posterior tibial tendon, perhaps the most structurally critical of the medial tendons, provides support for a neutral heel position, prevents arch collapse secondary to gravity (the main result being flatfoot acquired in adulthood), provides critical push off during ambulation, and controls inversion of the subtalar joint through its insertion on the navicular.

The peroneus longus and brevis are located in the lateral compartment of the lower leg, and their tendons travel posterior to the fibular and lateral malleolus (see Figs. e78.2 and e78.5). They are found in a single tenosynovial sheath and are also stabilized by the superior and inferior retinacula. Their primary role is as evertor stabilizers of the foot and ankle.

On the posterior aspect of the ankle, the gastrocnemius and soleus tendon complex (Achilles tendon) inserts into the posterior surface of the calcaneus (see Fig. e78.3). There is no specific tenosynovial sheath encasing



Fig. e78.1 Bony anatomy showing forefoot, midfoot, and hindfoot regions.

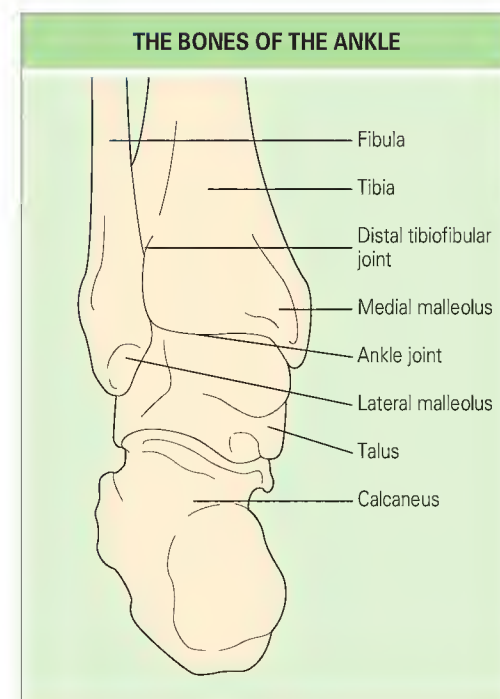


Fig. e78.2 Ankle anatomy including talocrural and subtalar joints.

TENDONS AND TENDON SHEATHS OF THE ANTERIOR (EXTENSOR) AND PERONEAL COMPARTMENTS OF THE ANKLE

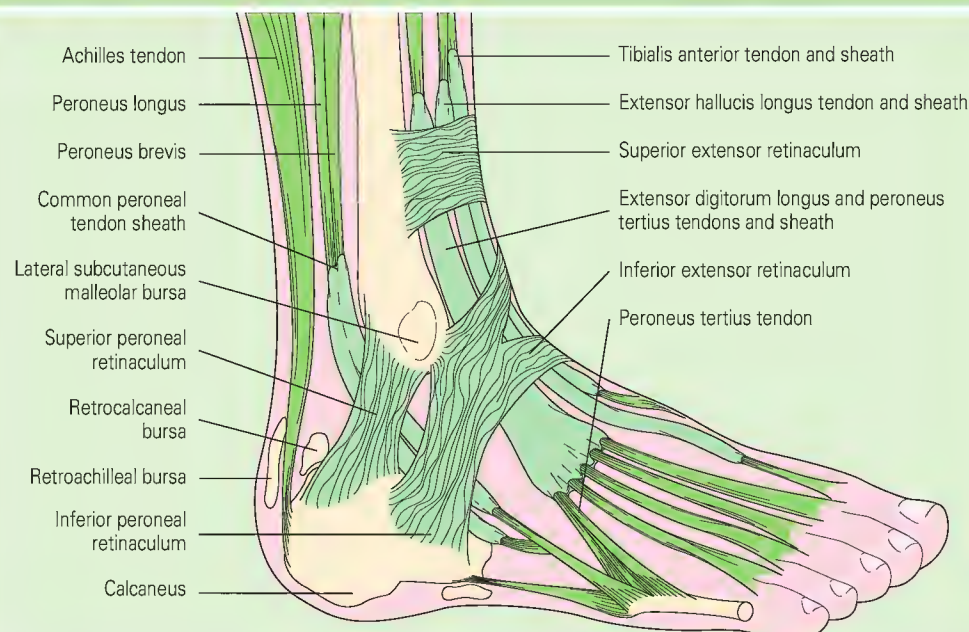


Fig. e78.3 Soft tissue anatomy of the lateral ankle.

TENDONS AND TENDON SHEATHS OF THE MEDIAL COMPARTMENT OF THE ANKLE

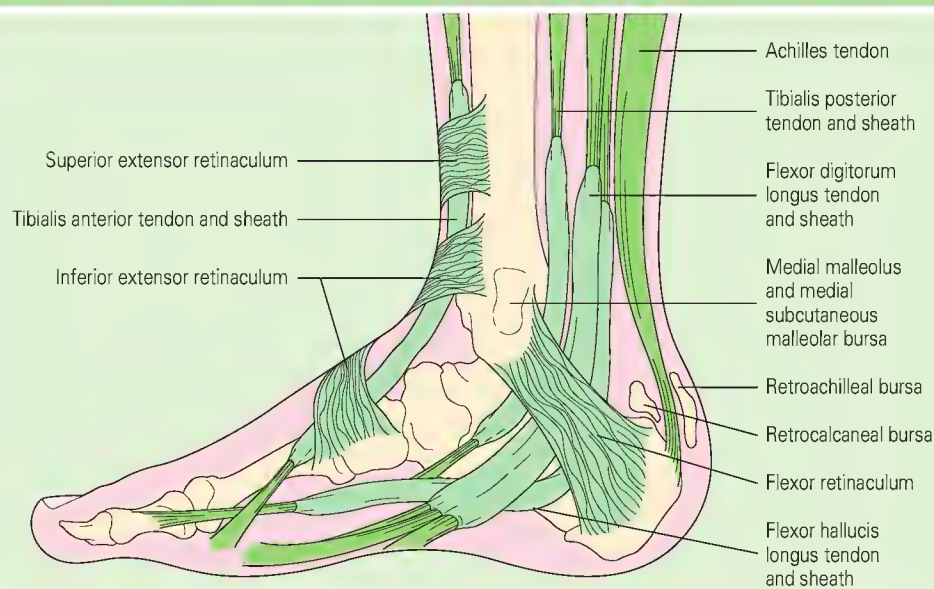


Fig. e78.4 Soft tissue anatomy of the medial ankle.

the Achilles tendon, but it is surrounded by a paratenon as well as superficial and deep bursae. The deep retrocalcaneal bursa is found between the Achilles tendon insertion and the posterior calcaneus and serves to decrease friction between the tendon and bone. The superficial (retro-achilleal) bursa is the adventitial bursa, which is located between the skin and the paratenon to provide protection (Fig. e78.6). The gastrocnemius-soleus complex through the Achilles tendon provides powerful plantar flexion, resistance to gravity during standing, transition from a seated position to upright, forward propulsion of the legs during gait, stair climbing, and jumping. The movements of the ankle include dorsiflexion and plantar flexion with the axis of movement generated approximately between the tips of the malleoli. Normal passive range of motion of the ankle is 10 to 25 degrees of dorsiflexion and 40 to 50 degrees of plantar flexion.

Foot

As noted earlier, the foot can be divided into three functional units: hindfoot, midfoot, and forefoot (see Fig. e78.1). The main articulation of the hindfoot is the subtalar joint (talus and calcaneus), which is a complex three-facet joint responsible for inversion/eversion and pronation/supination of the foot. The talus sits on the calcaneus on the superior surface of the sustentaculum tali, which provides stability and a point of routing for the posteromedial soft tissues. The normal passive motion of the hindfoot is 20 to 30 degrees of total excursion, usually with more inversion than eversion available.

The midfoot bones consist of the navicular, cuboid, and three cuneiforms and functionally include the talonavicular, calcaneocuboid and tarsometatarsal (TMT) joints (see Fig. e78.1). These joints permit plantar flexion/

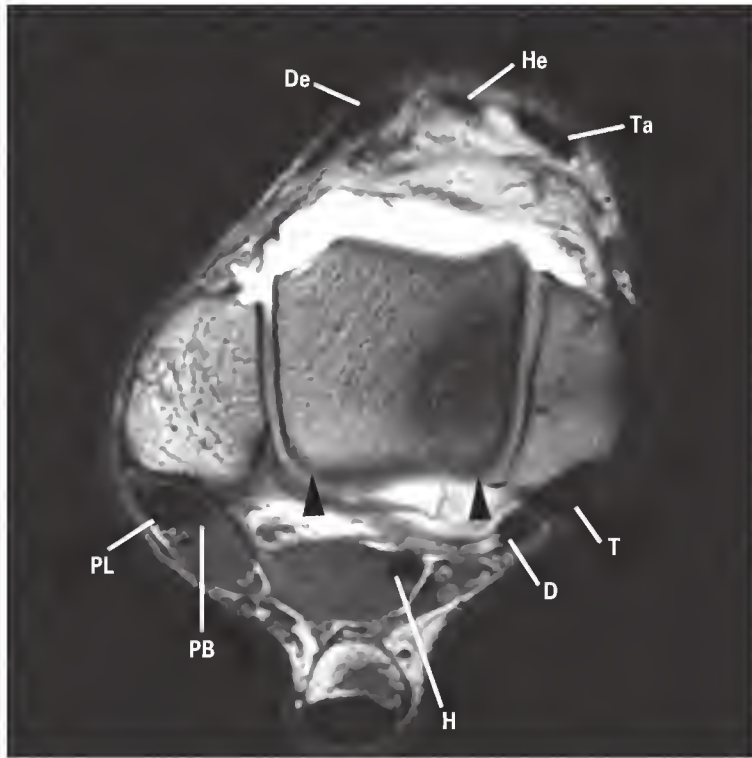
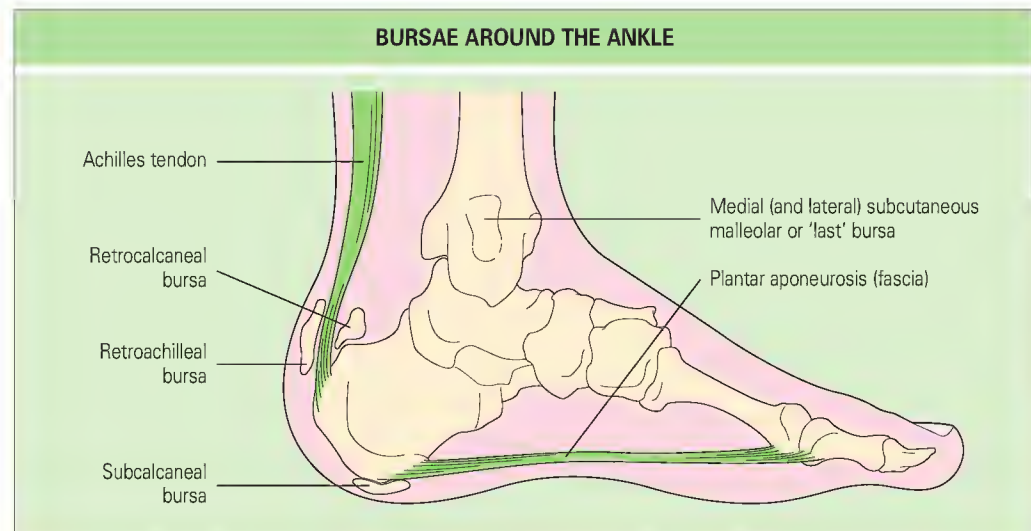


Fig. e78.5 Tendons around the ankle. D, flexor digitorum longus; De, extensor digitorum longus; H, extensor hallucis longus; P, tibialis posterior; PB, peroneus brevis; PL, peroneus longus; Ta, tibialis anterior. (From Conaghan PG, O'Connor P, Isenberg D, editors. *Musculoskeletal imaging*. Oxford specialist handbooks in radiology. Oxford: Oxford University Press; 2010. With permission.)

dorsiflexion and rotation and serve functionally as a limited composite ball-and-socket joint, allowing adjustments to uneven terrain and dynamic distribution of forces in the midfoot during normal walking.

The forefoot extends from distal to the TMT joints and includes the metatarsals and phalanges (see Fig. e78.1). Each metatarsophalangeal (MTP) joint has its own synovially lined capsule, supported by medial and lateral collateral and plantar ligaments. Forefoot motion includes dorsiflexion and plantar flexion as well as pronation and supination as influenced by the hindfoot. The first MTP joint accommodates 70 to 80 degrees of dorsiflexion and 40 to 50 degrees of plantar flexion. Approximately 30 degrees of dorsiflexion is required for normal walking. The interphalangeal joints in the toes are hinge joints that allow plantar flexion and dorsiflexion. These joints are flexed by the FHL and flexor digitorum longus muscles through their plantar tendon insertions and extended through the extensor hallucis longus and extensor digitorum longus through their dorsal insertions.

Fig. e78.6 Bursae around the ankle.



■ TABLE 78.1

Differential diagnosis of ankle and foot pain

Anterior ankle	Anterior impingement Ankle arthritis/synovitis Osteochondral defect/lesion (cartilage injury) Loose body within the joint Talar avascular necrosis Talar stress fracture Tenosynovitis of the extensor hallucis longus, extensor digitorum longus Deep (central) or superficial (anterolateral) peroneal nerve injury Saphenous (anteromedial) nerve injury
Posterior ankle	Os trigonum (accessory ossicle involving the posterior lateral tubercle of the talus) Posterior impingement Retrocalcaneal bursitis Achilles tendinopathy Flexor hallucis longus tendinopathy or stenosis
Posterolateral ankle	Peroneal tendinopathy Subfibular impingement due to flatfoot and impingement Fibular stress fracture Sural nerve injury Lateral ligament injury (sprain)
Posteromedial ankle	Posterior tibial tendinopathy Flexor digitorum longus/flexor hallucis longus tendinopathy Tibial stress fracture Medial malleolar stress fracture Tarsal tunnel syndrome Tibial nerve injury Deltoid ligament injury
Heel	Achilles insertional tendinopathy Inflammatory enthesitis Plantar fasciitis Haglund disease (pump bump) Calcaneal stress fracture
Hindfoot	Subtalar, talonavicular, or calcaneocuboid arthritis/synovitis Posterior tibial tendon dysfunction/tendinopathy (medial) or peroneal tendon dysfunction (lateral) Occult fracture of talus, calcaneus cuboid, or navicular Accessory navicular
Midfoot	Insertional tendinopathy (peroneal, posterior tibial, tibialis anterior) Arthritis/synovitis (navicular-cuneiform, cuneiform-metatarsal, cuboid-metatarsal) Navicular stress fracture Spring ligament strain
Forefoot	
First ray, first MTP joint, hallux	Arthritis/synovitis MTP (hallux limitus/rigidus) and IP joints Hallux valgus Hallux varus Sesamoiditis Gouty monoarthritis
Second to fifth rays, MTP joints, lesser toes	Arthritis/synovitis (MTP, proximal and distal IP joints) Lesser toe deformities (hammer and claw toes) Metatarsalgia MTP instability MTP dislocations Morton neuroma (interdigital neuralgia) Stress fracture of the metatarsals Bunionette (fifth metatarsal phalangeal deviation) Rheumatoid nodules Bursitis (intermetatarsal or adventitious) Ulcer Infection

IP, interphalangeal; MTP, metatarsophalangeal.

BOX 78.1 OTTAWA RULES FOR REFERRAL FOR RADIOGRAPHY IN THE PRESENCE OF ANKLE SPRAIN

Radiographic investigation is required if there is pain in the malleolar zone and any one of the following is present:

- Bone tenderness along the distal 6 cm of the posterior edge of the tibia or tip of the medial malleolus, *or*
- Bone tenderness along the distal 6 cm of the posterior edge of the fibula or tip of the lateral malleolus, *or*
- An inability to bear weight both immediately and at the clinic for four steps.

vibration perception meters. Assessment of musculoskeletal function has also improved enormously, and technologies exist that can quantify activity profiles, overall functional ability, the motions and forces occurring in specific joints, and the forces and pressures underneath the feet. Most of these technologies are expensive and time consuming to use, however, and although they are common in research settings they offer less advantage in day-to-day clinical practice over keen observation and clinical experience.

LOCAL ANKLE AND FOOT PROBLEMS

Ankle sprains

Acute ankle injuries rarely are encountered in rheumatology practice, but care must be taken to ensure that severe soft tissue injuries and fractures are recognized. The most common site of ankle sprain is the lateral ankle. The Ottawa ankle rules for requiring radiography are a useful triage tool (Box 78.1).

Chronic ankle instability after a severe ankle sprain can lead to osteochondral defects in the articular surface of the talus and the tibia. If ankle pain becomes chronic following sprain injury, then ligament rupture, osteochondral lesions, or avulsion injury (at the base of the fifth metatarsal) should be considered. In these cases further imaging diagnostics are required. Nonsurgical treatment of chronic ankle instability requires strengthening the peroneal muscles and improving proprioception. Bracing or taping can help, particularly when used during activities in which there is a risk of further ankle sprain. If there is no response to nonsurgical treatments, referral for surgical evaluation with a view to stabilization may be necessary.

Impingement syndromes

Anterior ankle impingement is most often associated with repeated dorsiflexion (common in ballet and ball sports) and direct microtrauma (particularly seen in soccer players during kicking), which causes damage at the anteromedial margins of the articular cartilage. Anterior tibiotalar spurs create a bony mass (Fig. 78.1) that leads to the clinical features of anterior ankle pain and a reported feeling of blocking of dorsiflexion. Lateral-view conventional radiographs can explore the presence and extent of osseous spurs, which occur at the anterior and medial articular margins. Conservative management is often of limited help, and surgical or arthroscopic resection of the osseous spurs may be required.

Anterolateral impingement can develop secondarily to a relatively minor injury if ongoing functional instability leads to further soft tissue hemorrhage, synovial scarring, and hypertrophy. Anterolateral ankle pain will be provoked by supination or pronation of the foot. If the abnormality is focal, then symptomatic relief can be obtained with steroid injections into the thickened capsule or nodules combined with physical therapies.

Posterior impingement develops in response to repeated or forced ankle plantar flexion and compression of tissues between the posterior calcaneus and tibia (Fig. 78.2). The lateral talar process or an os trigonum (an unsupplied secondary ossification center) can also increase the degree of soft tissue compression with or without stress reaction in the bone itself. The soft tissues compressed include the Kager fat pad, the tibiotalar joint capsule, and local ligaments. Posterior impingement is typically chronic and of insidious onset, affecting athletes who regularly undergo forced plantar flexion. Symptoms include posterior ankle pain exacerbated by either dorsiflexion or plantar flexion, and on examination there is posterior tibiotalar joint tenderness not involving the Achilles tendon. Conventional radiographs can demonstrate minor bony changes, but the same findings are often seen in asymptomatic individuals. MRI is preferred because it can define bone marrow edema, fracture lines, or active bony impingement.

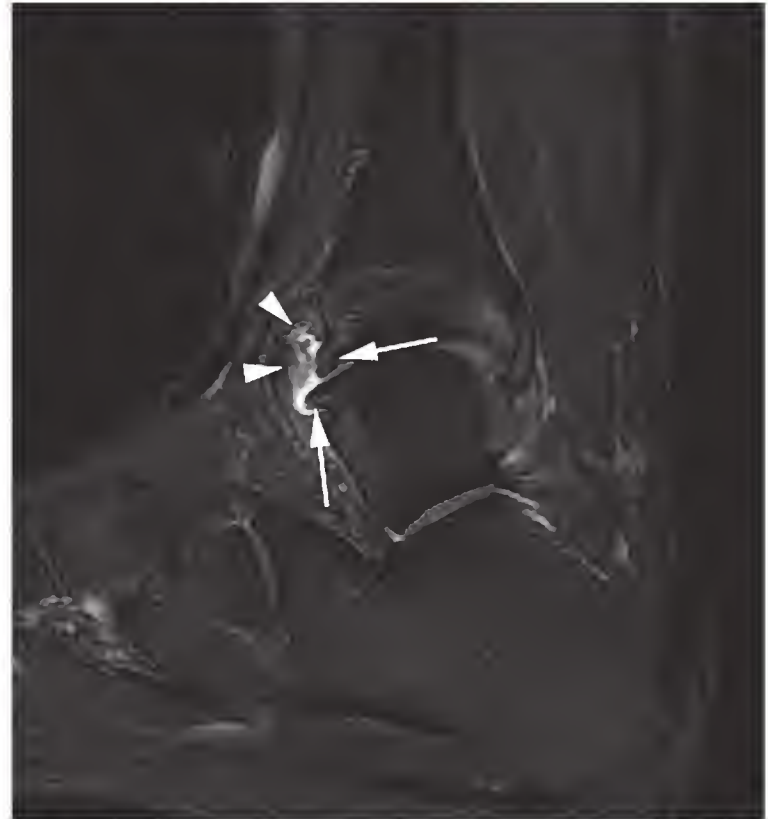


Fig. 78.1 Sagittal T2-weighted magnetic resonance image showing anterior tibiotalar spurs (white arrows) and synovitis (arrowheads). (From Conaghan PG, O'Connor P, Isenberg D, editors. *Musculoskeletal imaging. Oxford specialist handbooks in radiology*. Oxford: Oxford University Press; 2010. With permission.)

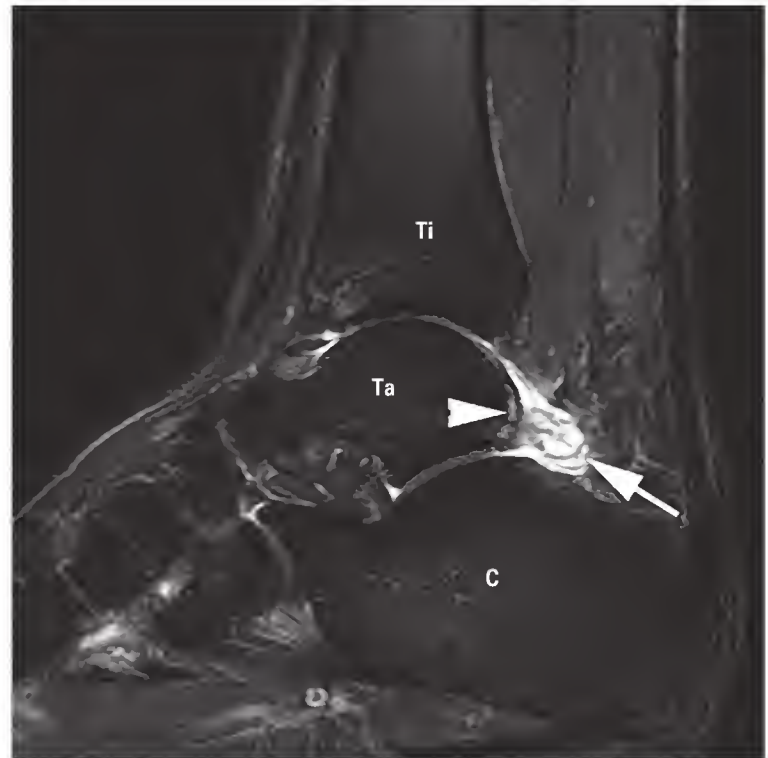


Fig. 78.2 Sagittal T2-weighted magnetic resonance image showing posterior synovitis (arrow) and posterior talar edema (arrowhead). C, calcaneus; Ta, talus; Ti, tibia. (From Conaghan PG, O'Connor P, Isenberg D, editors. *Musculoskeletal imaging. Oxford specialist handbooks in radiology*. Oxford: Oxford University Press; 2010. With permission.)

Achilles tendinopathy

The Achilles tendon can be affected by traumatic or degenerative damage, typically at the myotendinous junction or the insertion into the calcaneus. Note that the Achilles tendon has no synovial sheath, so tenosynovitis cannot occur. Risk factors for chronic Achilles tendinosis include previous injury and older age, and the tendon can be damaged by repetitive micro-trauma or an acute injury. Full-thickness tears are obvious on clinical examination and require immediate surgical intervention. A partial tear or pathologic thickening of the tendon can occur in the substance, proximal to the insertion where the blood supply is poorest. A fusiform swelling may be palpable and can be confirmed by MRI or ultrasonography (Fig. 78.3). Conservative treatment of Achilles tendinopathy is difficult and somewhat controversial. The treatment algorithm proposed by Alfredson and Cook,⁹ involving heel drop stretches, glyceryl trinitrate patches, and sclerosing treatments, may offer some advance over traditional approaches.

Tibialis posterior tendon dysfunction and acquired adult flatfoot

Tibialis posterior dysfunction (TPD) is a progressive tendinopathy of the tendon of the tibialis posterior muscle that can result in an acquired flatfoot in older adults. Initial symptoms are pain and swelling in the medial ankle, and sometimes there is concern over the changing shape of the foot as the arch flattens. As the pathologic process progresses the foot acquires a marked and progressively valgus position. A useful diagnostic test is to ask the patient to stand on tiptoe using only the affected side. In the presence of

tibialis posterior dysfunction, this is not possible unless the patient is counterbalanced by the contralateral limb. Diagnosis can be confirmed with ultrasonography or MRI, and early, conservative treatment employs various combinations of orthoses, supportive footwear, ankle taping, and bracing to offload the tendon and support the midfoot. Surgical treatment includes tendon transfer if the tendon has adequate structural integrity, combined with hindfoot osteotomy. In severe cases reconstruction and arthrodesis of the hindfoot is required.

Flatfeet (pes planus) and high arched feet (pes cavus)

The range of naturally occurring foot postures comprises a continuum from cavoid (or highly arched), through obviously normal, to flat (or planus). At the extremes of this continuum are features that are clearly pathologic (such as the frank cavus foot of inherited neuropathy or the planovalgus foot of established rheumatoid arthritis). Between these extremes, however, although that abnormal foot posture can increase mechanical loads on local structures and so may predispose to mechanical foot pain, care must be exercised to avoid medicalizing normal variants. There is insufficient evidence to support active intervention in most cases of asymptomatic flatfoot, and therapy should be directed at the combination of any presenting symptoms and the underlying biomechanics. Mechanical therapies can include footwear modifications, foot orthoses, taping, splints, and braces. The goal of most mechanically mediated treatments for the mobile flatfoot is to limit excessive mobility of affected joints and to promote stability. Conversely, treatment for the rigid cavoid foot is aimed at improving shock absorbency and stretching any tight soft tissues. Useful treatment approaches for cavoid feet include cushioning insoles, change in footwear, and stretching exercises.

Nerve entrapments

Rheumatology patients present with symptoms of nerve entrapment because of the complex anatomy and high prevalence of osteophytes and altered bony structures in this group. The most common nerve entrapment syndrome in the foot is so-called Morton neuroma, which is not a true neuroma but a fibrotic enlargement of the perineurium that affects the plantar digital nerve just proximal to the metatarsal heads. It is usually seen in the third and fourth metatarsal space but can occur in any of the intermetatarsal spaces.

The typical clinical presentation is of pain, numbness, or tingling in the affected interdigital cleft and the associated toes that may radiate proximally or onto the plantar aspect of the forefoot. Tight footwear and high-heeled shoes exacerbate the symptoms, and the clinical diagnosis can be aided by squeezing the forefoot across the metatarsals while exerting a pressure between the MTP joints of the affected area to reproduce symptoms. A Mulder click, which can be elicited by lateral compression, was considered diagnostic although the click can be elicited in normal feet. Differentiation of Morton neuroma and intermetatarsal bursitis can be made readily with ultrasonography or MRI. Treatment may include advice to adopt wider-fitting shoes, use of orthoses, local steroid injection, or oral nonsteroidal antiinflammatory drugs (NSAIDs). Surgery may be required in severe cases.

Tarsal tunnel syndrome is the other significant nerve entrapment found in rheumatology practice and involves the tibial nerve, which is compressed as it passes around the posterior medial aspect of the ankle. Tarsal tunnel syndrome may be caused by compression arising from tendinopathy or tenosynovitis or may be secondary to a severe valgus position of the ankle, such as can occur in rheumatoid arthritis. The symptoms include numbness, tingling, and pain in the arch area, which can radiate to the plantar surface and medial aspect of the ankle. Clinical diagnosis can be made by percussion to elicit the Tinel sign. When local inflammation underlies the compression, local injection of steroid may be helpful. When the cause is a valgus heel position, short-term reduction of symptoms can sometimes be achieved by splinting, taping, or orthoses; otherwise, surgical intervention may be required.

Heel pain

Some 10% of people will experience an episode of plantar heel pain at some point in their lives, and heel pain is more common in rheumatology patients. Plantar fasciitis is the most common underlying pathologic condition, characterized by thickening of the plantar fascia at the enthesis of the calcaneal tubercle and in some cases extending along the fascia (Fig. 78.4). The characteristic symptom is pain on the plantar surface of the heel (sometimes extending into the medial arch) during activity or on initial weight bearing.



Fig. 78.3 Sonograms of Achilles tendon showing (a) normal structure and (b) fusiform swelling indicating tendinopathy (with power Doppler ultrasonographic evidence of increased vascularity). (From Conaghan PG, O'Connor P, Isenberg D, editors. *Musculoskeletal imaging*. Oxford specialist handbooks in radiology. Oxford: Oxford University Press; 2010. With permission.)

Ultrasonography can be useful in confirming the presence of fascial thickening. Many cases are self-limiting, and in any case self-care is the best initial option. Recommending change of footwear and encouraging weight loss is often helpful, and physical therapies such as stretches can provide additional benefit. There is some evidence of efficacy for taping¹⁰ and the use of contoured foot orthoses.¹¹ There is also evidence for the short-term benefit of injection with a corticosteroid, although the injections are painful and the long-term benefits unclear.¹²

Posterior heel pain can be caused by Achilles tendon enthesitis, which is common in seronegative arthropathies, or by bursitis in one of two sites. The retrocalcaneal bursa is an anatomic bursa that lies deep to the Achilles tendon, and the Achilles bursa is an adventitious bursa that is superficial to the tendon insertion but is not always present. The Achilles bursa is especially prone to mechanical irritation from footwear. Bursitis arising in the deeper, retrocalcaneal bursa is more often associated with inflammatory disease such as rheumatoid arthritis. MRI or ultrasonography is diagnostic.

Treatment of local, mechanical bursitis centers on physical therapies and use of NSAIDs. Modification of footwear can help prevent further irritation. Bursitis associated with inflammatory disease usually responds to corticosteroid injection.

Midfoot pain

Plantar midfoot pain usually originates in the soft tissues and is part of the presentation of plantar fasciitis and related conditions. Dorsal midfoot pain of insidious onset more commonly implies degenerative change¹³ or bony damage such as mechanical stress reactions. There is currently little evidence of benefit of any specific treatment approaches for midfoot osteoarthritis, and NSAID use plus mechanical therapies are the best available option.

Stress reactions and stress fractures can arise at sites of high mechanical demand. The navicular and the metatarsals are the most common sites of stress fracture, although diagnosis can be difficult because the fractures often are not visible on plain radiographs, especially in the early stages. A stress reaction or fracture is characterized by diffuse pain in the midfoot, with exacerbation on activity and increase in intensity and localization of pain. The onset usually follows an increase in activity levels such as sports participation (e.g., distance running) or long walks, although stress reactions can be precipitated by relatively normal levels of activity in patients with poor bone stock.

Any fracture is usually preceded by profound bony edema. Scintigraphy has traditionally been used to identify early stress reaction and MRI is also highly sensitive to stress fractures. Treatment is with local offloading and systemic antiresorptive agents.

Forefoot pain

In the absence of systemic disease, most forefoot pain is relatively benign and associated with local mechanical demands. High pressures can occur

under the plantar MTP joints when clawing or subluxation of the toes or loss of fat pad protection inhibits the normal distribution of loads. There may be musculoskeletal discomfort and associated thickening of the skin, (hyperkeratosis/callus and clavus/corn formation). Some common causes of pain in the forefoot have been described previously (e.g., Morton neuroma), and although intermetatarsal bursitis is a common manifestation of inflammatory arthritis it can also be seen in otherwise healthy individuals.

RHEUMATOID ARTHRITIS

The ankle joint is affected in only 10% to 20% of people with rheumatoid arthritis (RA), but because of the many synovial structures in the foot, about 80% to 90% of people with RA have foot involvement.¹⁴ The foot is involved even in early disease,¹⁵ and the initial onset of RA is noted in the foot almost as frequently as in the hands. The forefoot is affected in more than three quarters of people with RA and the hindfoot (subtalar joint) is involved in around two thirds of those with longstanding RA.¹⁶ The prevalence and impact of foot problems is closely related to disease duration,¹⁴ and overall foot-related impact arises from a combination of factors, including pain, inflammation, and altered mechanics. Foot involvement contributes to difficulty in walking in about three quarters of people with RA and is the main or only cause of walking impairment in one quarter.¹⁴

Articular damage is driven mainly by synovitis but in the ankle and foot this is compounded by the mechanical stress of weight bearing. In the longer term irreversible changes occur in the anatomic structures, including valgus deformity of the heel, forefoot changes, flattening of the arch (Fig. 78.5), and typical forefoot hallux valgus-type presentation¹⁷ (Fig. 78.6). Although better disease-modifying antirheumatic drug protocols and early intervention have improved the prognosis, not all patients do well, even in the postbiologic era.

Ankle involvement is almost always preceded by subtalar joint involvement and may be a consequence of altered hindfoot alignment associated with long-standing subtalar disease.¹⁸ Subtalar joint disease is accompanied by pain on walking on uneven ground and swelling posterior to the medial malleolus or in the sinus tarsi.¹⁹ Over time, synovitis and mechanical loads lead the hindfoot to function in a progressively more valgus position.²⁰ The deformities are largely reducible initially, and in this phase functional foot orthoses have been shown to restore normal function and to slow the progression of fixed deformity.²¹ If the deformities are uncorrected, bony adaptation occurs and the changes become irreversible. In the presence of significant deformity, use of adaptive footwear might be necessary.

In the severely valgus rheumatoid foot, synovitis and compression of tissues of the medial hindfoot can lead to tarsal tunnel syndrome as described earlier. Other soft tissue manifestations include retrocalcaneal bursitis, nodules over areas of mechanical irritation, and tenosynovitis of long flexor and extensor tendon sheaths leading sometimes to the development of

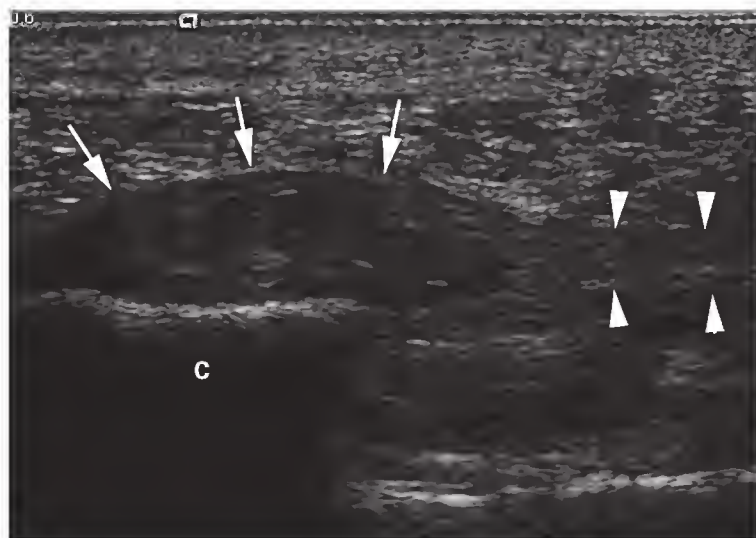


Fig. 78.4 Marked thickening of fascia (arrows) at calcaneus (C) with more normal structure distally (arrowheads).



Fig. 78.5 Planovalgus deformity.



Fig. 78.6 Plain radiograph showing the characteristic hallux valgus-type changes in a foot with rheumatoid arthritis.

intrasubstance tears and degeneration. In tendons subject to high mechanical demands, such as the tendon of the tibialis posterior, this can occasionally result in complete rupture of the tendon. Varus deformities of the hindfoot are rare, occurring in fewer than 1 in 30 people with RA.²² The joints of the midfoot are often affected, with the talonavicular joint and tarsometatarsal joints affected in 15% to 30% of cases. Diffuse joint degenerative change may be evident, but the characteristic erosions seen in the forefoot are rare.

In the forefoot, severe synovitis can result in a typical “daylight” sign in which neighboring toes are separated by the soft tissue mass. Persisting synovial inflammation causes stretching and weakening of the joint capsule and loss of integrity of the stabilizing structures in the forefoot.²³ The hallux valgus-type deformity of RA is severe, often resulting in subluxation of the first MTP joint. The second, third, and fourth toes develop a hammer toe deformity and exhibit lateral drift, whereas the fifth toe drifts toward the midline, coming to lie over or under the fourth. In cases in which forefoot deformity is severe the lesser digits no longer contribute to weight bearing, and when this is combined with anterior displacement and atrophy of the plantar fat pads, significantly increased pressure under the MTP joints can result.²⁴ Intermetatarsal bursae protrude onto the plantar surface or prominent adventitious bursae can develop under the metatarsal heads, and these prominences can be overlaid with hyperkeratosis (Fig. 78.7). Bursitis at this site is painful, and localized areas of skin ulceration are not uncommon. Patients often describe a sensation of “walking on pebbles.”

The evidence of benefit for most treatments relating to the foot in RA is not especially strong, although some countries have been able to formulate guiding principles. There is some evidence that use of contoured functional foot orthoses reduces foot pain and improves function in people with RA,²⁵ although a subsequent review of the use of foot orthoses in patients with RA indicated a lack of consensus on the precise types of orthoses likely to perform best.²⁶



Fig. 78.7 Prominent intermetatarsal bursae with overlying hyperkeratosis. (From Frowen P, O'Donnell M, Burrow D, Lorimer G, editors. *Neale's disorders of the foot*, 8th ed. Churchill Livingstone, Edinburgh; 2010. With permission.)

Provision of therapeutic footwear has been shown to provide symptom relief and improvement in function in patients with RA. Traditionally, therapeutic footwear was made to measure, but the high costs and poor patient satisfaction have led to a change in approach.²⁷ Off-the-shelf shoes have been shown to provide significant improvements in pain, quality of life, and gait parameters.²⁷ There is evidence of similar levels of satisfaction with custom-made and off-the-shelf shoes in people with RA. In one Dutch study about one third of RA patients had been provided with therapeutic footwear, some 80% of which were in daily use.²⁸

Soft flexible uppers made of soft leathers or stretchable textile can reduce the pressure on deformed toes, and the demand for painful motion in the forefoot joints during walking can be addressed by the provision of shoes with a rocker sole. If patients experience difficulties with shoe fastenings, standard laces can be changed for elastic laces in existing shoes or other fastenings such as Velcro or elastic can be considered.

Soft tissue presentations such as prominent bursae or nodules can respond well to the use of pressure-relieving insoles and padding. Plantar callosities that build up over metatarsal heads can benefit from a similar approach. Scalpel débridement of hyperkeratosis appears ineffective if used in isolation, however, and should be combined with other interventions to prevent recurrence of symptoms.²⁹

Most surgical procedures are performed relatively late in the disease process and include tarsal tunnel decompression and ankle, subtalar, or talonavicular arthrodesis as well as a range-of-forefoot procedures.³⁰ Subtalar arthrodesis can be required following rupture of the tendon of the tibialis posterior if tendon repair is not possible and the region is mechanically unstable.¹⁹ The end-stage procedure is triple arthrodesis with corrective wedge osteotomies to restore alignment (Fig. 78.8). In the forefoot, excision arthroplasty is a part of most procedures, and the metatarsal heads, the proximal third of the phalanges, or both are usually excised. All lesser MTP joints are usually operated on simultaneously because more selective approaches tend to have poorer long-term results in people with RA.³¹ Modern variations, including techniques involving interposition of the plantar plate and preservation of the metatarsal head, are gradually supplanting the more traditional approaches.³²

JUVENILE IDIOPATHIC ARTHRITIS

In the polyarticular form of juvenile idiopathic arthritis, the foot is involved in about two thirds of cases,³³ predominantly at the hindfoot. When the ossification centers are involved, there may be an effect on the growing bones leading to deformity and brachydactyly. Pes planus or pes cavus deformities are common, as is the hallux valgus-type deformity also described previously in adult RA. In juveniles affected by enthesitis-related arthritis and psoriatic arthritis the clinical picture is similar to that seen in adult seronegative disease. The hindfoot and interphalangeal joints are affected, and there is enthesitis at the insertion of the Achilles tendon and plantar fascia. Ongoing inflammation in midfoot and hindfoot joints may lead to ankylosis. Attention should be given to the feet in juvenile idiopathic arthritis because deformity occurs quickly. Children are usually compliant with the use of in-shoe orthoses, but regular review is required.



Fig. 78.8 Triple arthrodesis of subtalar, talonavicular, and calcaneocuboid joints.

OSTEOARTHRITIS

The ankle and foot have not generally been considered an important anatomic region in osteoarthritis (OA). The ankle is remarkably resistant to OA for a weight-bearing joint,³⁴ and presentations of OA in the feet are often trivial relative to OA in the hips and knees. When the ankle joint does develop OA it is usually a consequence of major trauma such as complex ankle fracture, repeated minor trauma such as chronic ankle instability, or inflammatory arthritis. There are no good data about foot OA because of lack of consistency in definitions and resulting poor case ascertainment in studies. The use of radiologic definitions is associated with higher estimates of prevalence overall, whereas the use of clinical definitions yield variable rates. A standardized radiographic atlas and classification system for foot joint OA has been developed in recent years, which should improve the quality of data.³⁵ Subclinical OA has been reported in half of first MTP joints in older people.³⁶ Beyond the first MTP joint, foot OA arises as a consequence of mechanical damage, trauma, or systemic disease, and studies using the new radiographic atlas have highlighted a much higher prevalence of OA than previously thought¹³ in regions such as the midfoot (Fig. 78.9). Importantly, foot OA usually presents in combination with pain in other joints such as knees, back, hands, and hips, which increases the impact.⁵

The most obvious presentation of OA in the foot is in the first MTP joint, where the degenerative change presents as limitation, fixation, or deformity of the hallux joint (known as *hallux limitus*, *hallux rigidus*, or *hallux valgus*). Periarticular osteophyte causes thickening of the joint, sometimes with an overlying bursa. OA in the foot is a predictor of health care service use, with the presence of foot OA doubling the risk of reliance on health services.³⁷ Treatments for OA of the foot are of variable efficacy, however. NSAIDs and acetaminophen are cornerstones, and weight loss and low-impact exercise are of known benefit.³⁸ Local therapies are directed at abnormal biomechanics or symptoms. The use of contoured foot orthoses can stabilize foot joints and act through offloading the forefoot and heel regions, and so may help some patients. Shock-absorbing insoles or footwear can also provide symptom relief. Accommodative padding may reduce pressure over bony prominences. Footwear adaptations such as rocker-bottom shoes lessen the movement in degenerate joints and aid sagittal plane motion. Intraarticular steroid injections may relieve symptoms,³⁹ although in practice the effect rarely lasts longer than 2 to 4 weeks. When surgical intervention is required it usually provides the definitive solution, and arthrodesis, replacement, or excision arthroplasty reduces pain significantly. Surgery of the first MTP joint is undertaken widely, and the use of more sophisticated, joint-sparing procedures have improved outcomes considerably in the past two decades.



Fig. 78.9 Midfoot osteoarthritis. (From Frowen P, O'Donnell M, Burrow D, Lorimer G, editors. *Neale's disorders of the foot*, 8th ed. Churchill Livingstone, Edinburgh; 2010. With permission.)

Surgery is required less often for the subtalar joint, ankle joint, and midfoot. Ankle joint surgery includes many variants of arthroscopic and open approaches. Unless there is advanced degeneration and deformity, arthrodesis of the ankle is considered a salvage procedure because of the significant physical demands on this joint.⁴⁰ Pantalar and triple arthrodeses are similarly regarded as salvage procedures.

Ankle and foot joint replacements have performed poorly relative to hip and knee replacements. Initial optimism from early experiments with total ankle replacement arthroplasty was followed by poor medium- and long-term results, and the technique fell from favor.⁴¹ Ongoing refinements have led to some resurgence in interest in ankle replacements, and the use of third-generation mobile bearings appears to be associated with better functional outcomes and lower failure rates,⁴² although ankle replacements do not yet approach the life span of replacements of large joints. Surgical joint distraction using external Ilizarov fixation is another experimental technique undergoing trials in the hope of inducing cartilage regeneration, and there have been some encouraging early results in severe ankle arthritis.⁴⁰

PSORIATIC ARTHRITIS AND SERONEGATIVE DISEASES

Relatively little clinical research has been carried out on the involvement of the foot and ankle in the seronegative diseases. Psoriatic arthritis (PsA) is the major form of spondyloarthritis affecting the feet, and most of the clinical studies relate to PsA. The underlying pathologic process in most of the seronegative disease is enthesitis, typically at the insertion of the Achilles tendon and origin of the plantar fascia and the multiple entheses of flexor and extensor tendons in the digits. Isolated recurrent or bilateral Achilles enthesitis should suggest a diagnosis of spondyloarthritis. In early PsA, the prevalences of plantar fasciitis and Achilles insertional enthesitis have been reported as 12% and 6%, respectively,⁴³ and hindfoot enthesitis is the defining feature in reactive arthritis. Dactylitis is the classic presenting feature of PsA in the foot, with involvement of the skin and nails usual but not universal. The presence of dactylitis is associated with more severe disease, including arthritis mutilans. Plain radiography may show typical changes such as erosion of the terminal phalangeal tufts, juxtaarticular and enthesal new bone formation, periostitis, and severe osteolysis.

The extent of articular involvement ranges from monoarthritis to a destructive erosive polyarthritis.⁴⁴ Hindfoot deformity manifesting as pes planovalgus has been reported in two thirds of established cases of PsA,⁴⁵ and forefoot involvement is even more common in established disease, with more than 90% of people with long-standing PsA having hallux valgus and claw toes.

Intraarticular steroid injections may be used to treat persistent monoarthritis or oligoarthritis, and steroids can be used with good effect at the insertions of the peroneals, the extensor and flexor tendons, and the plantar

fascia. The use of steroids around the insertion of the Achilles tendon is discouraged because of the risk of rupture. There is currently no specific evidence to support the use of special footwear and orthoses in PsA, although it is reasonable to conclude that the inflammatory and mechanical factors that affect the feet in PsA generally should be addressed in much the same way as in RA.

CONNECTIVE TISSUE DISEASES

The two most relevant connective tissue diseases (CTDs) are lupus and systemic sclerosis (SSc or scleroderma), both of which are characterized by vascular features that are found in the feet of 90% or so of individuals with CTDs. Raynaud phenomenon is almost universal, and telangiectasia and purpura are common. Severe vasculopathy in the form of vasculitis and ulceration occur in some 10% to 20% of people with CTDs, in the hands and to a slightly lesser extent in the feet.⁴⁶ Among the CTDs, SSc often gives rise to the most significant foot problems and is the focus of the rest of this section.

The initial presentation in SSc is often Raynaud phenomenon accompanied by edema of the hands or feet (Fig. 78.10). Over time the skin, particularly in the extremities, thickens and tightens. Flexion contractures compromise function, and localized calcinotic lesions may develop on the digits or other areas of mechanical stress. Involvement of the foot in SSc is less common and less severe than involvement of the hands, although the foot is affected in about 75% of patients with progressive SSc.⁴⁷ Articular synovitis does occur in SSc but in large joints more than in the foot. Any inflammatory arthropathy in the feet is usually nonerosive, although tendinopathy can sometimes be seen, especially in the Achilles tendon.

Onycholysis and pitting of the nails may be observed similar to that encountered in psoriasis. Splinter hemorrhages may also be seen in the nail beds, reflecting the vascular involvement. The effects of local vasculitis are exacerbated by concomitant large-vessel disease leading to gangrene and increased risk of amputation.⁴⁸ Vasculitic ulcers associated with SSc are often very painful, and the healing process can take many months, usually occurring through necrosis and fibrosis rather than granulation and reepithelialization.

The consequences in the feet are not well described, and although SSc has been reported to lead to difficulties with shoe fitting,⁴⁹ the precise extent of the impact is not well studied. Nevertheless, it appears sensible that patients with SSc undergo regular foot checks and have access to foot health services.

CRYSTAL ARTHROPATHIES

Acute gout presents classically in the first MTP joint (Fig. 78.11), although any of the joints of the foot may be affected. The acute gouty presentation

is of a hot, swollen joint that is exquisitely tender with a history of rapid onset. When foot joints are affected, the pain is severe enough to prevent weight bearing, but acute episodes typically settle in 10 to 14 days.

Systemic symptoms such as fever may occur, and levels of inflammatory markers such as C-reactive protein may be significantly elevated. Serum urate level may be normal in an acute attack, and an elevated serum urate level either during or after an episode is not diagnostic of gout. Infective monoarthritis can be excluded by testing of fluid aspirated from the affected joint.

Chronic (tophaceous) gout (Fig. 78.12) usually occurs insidiously and can involve the large or small joints. The chronic form is likely to be associated with radiologic abnormalities such as periarticular erosions and is arguably more worrisome than the more obvious acute attacks. Gouty tophi can develop in periarticular anatomic structures and in tendons such as the Achilles tendon. Tophaceous gout is associated with progressive deformity and impairment of function. Treatment is systemic, with the manifestations in the feet being most important for recognition of chronic uncontrolled disease.

HYPERMOBILITY SYNDROME

People with joint hypermobility have greater foot impairment than matched controls, and the severity of symptoms correlates with the severity of systemic hypermobility.⁵⁰ Treatments are aimed at improving mechanical



Fig. 78.11 Acute gout in the first metatarsophalangeal joint. (From Frowen P, O'Donnell M, Burrow D, Lorimer G, editors. *Neale's disorders of the foot*. 8th ed. Churchill Livingstone, Edinburgh; 2010. With permission.)



Fig. 78.10 Raynaud phenomenon and diffuse edema in scleroderma. (From Watts RA, Conaghan PG, Denton C, et al, editors. 4th ed. *Oxford textbook of rheumatology*, Oxford, Oxford University Press; 2013. With permission.)



Fig. 78.12 Chronic tophaceous gout. (From Frowen P, O'Donnell M, Burrow D, Lorimer G, editors. *Neale's disorders of the foot*. 8th ed. Churchill Livingstone, Edinburgh; 2010. With permission.)

stability, although there is minimal formal evidence regarding efficacy. Pilates-type approaches seem helpful and building muscle strength may be advantageous. Gentle stretching can also be useful because people with hypermobile joints often have pathologic tightness of surrounding muscles and tendons. Footwear advice usually helps, and some people with mechanical foot pain benefit from the use of foot orthoses, which control joint function and stabilize specific foot joints.

ACKNOWLEDGMENTS

The author would like to acknowledge the contributions of Dr. Pamela G. Allen and Dr. Lew C. Schon, who were the authors of this chapter in the previous edition, and colleagues Dr. Philip Helliwell, Dr. Heidi Siddle, and Dr. Philip Robinson, who have contributed previously to some of the materials on which this chapter is based.

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79

The temporomandibular joint

■ SHARON M. GORDON ■ JENNIFER FRANGOS ■ GARY WARBURTON

- The temporomandibular joint is covered with fibrocartilage rather than hyaline cartilage.
- Temporomandibular joint pain is common and occurs more frequently in women than in men.
- Management is generally multimodal and multidisciplinary.

BACKGROUND: EPIDEMIOLOGY AND CLASSIFICATION

Temporomandibular joint disorder (TMJD) is classified as a musculoskeletal disorder and is a major cause of chronic pain in the craniofacial region, second only to headache.¹ It is estimated that more than 5.3 million U.S. adults seek treatment annually.² The annual incidence of TMJD is 2%, with women being at higher risk than men.³ Approximately 20% of patients will progress to a persistent pain state.⁴ Although the current literature lacks universal staging criteria, most sources concur on the categories listed in Box 79.1. Importantly, more than one of these categories can occur together.

FUNCTIONAL ANATOMY

The temporomandibular joint (TMJ) is a diarthrodial synovial joint with both rotational and translational movement. It is unique in that its surfaces are covered with fibrocartilage rather than hyaline cartilage, which allows greater repair capacity and less susceptibility to degeneration. The meniscus or disk is bilaminar, also composed of fibrocartilage, and devoid of blood vessels or nerves. However, the intervening tissue is very vascular and well innervated. The meniscus and retrodiscal tissue separate the joint into superior and inferior compartments. Three functional ligaments (collateral, capsular, and temporomandibular) and two accessory ligaments

(sphenomandibular and stylomandibular) provide support for the joint. The muscles of mastication move the joint, offset loading, and maintain the condyles within the fossa. Innervation is provided by the mandibular branch of the trigeminal nerve: the auriculotemporal, masseteric, and deep temporal branches. The blood supply is derived from three branches of the external carotid artery: the superficial temporal, middle meningeal, and internal maxillary arteries. The fluid produced by the synovial lining provides nutrients to the nonvascularized meniscus. It thought that hypoxic reperfusion produces free radicals and inflammatory mediators that lead to breakdown of the lubrication system.^{5,6}

DIAGNOSIS: HISTORY AND EXAMINATION

A thorough history and physical examination are key to identifying the primary source of dysfunction, thereby helping determine treatment (Box 79.2). Pain and range of motion should be evaluated with an analog score at each visit to document improving or worsening symptoms. The quality, location, timing, and exacerbating or relieving factors should also be identified. Clinical examination includes palpation of the muscles of mastication and notation of any pain or spasms (Fig. 79.1). Pain on joint palpation and on loading of the TMJ, as well as palpable and audible joint sounds, should be recorded. Signs of parafunction such as tongue scalloping, tooth wear, and buccal ridging may be noted. A diagnostic auriculotemporal nerve block with a local anesthetic such as 3% mepivacaine may be valuable in differentiating arthrogenous pain from that attributable to other sources. Appropriate imaging should be obtained, such as magnetic resonance imaging to visualize the meniscus or computed tomography to visualize the bony elements (Fig. 79.2).

MANAGEMENT

Therapies for TMJD can be divided into two major categories: nonsurgical and surgical. Goals of management include reduction or resolution of pain and inflammation, improved function and range of motion, and reduction of joint-loading force. As a chronic pain condition with a multifactorial nature, management should likewise be multimodal.

Nonsurgical management

The majority of patients can be managed nonsurgically.⁷ Physical and psychological approaches are generally used in combination and include occlusal appliances, physical therapy, behavioral modification, and pharmacologic adjuvants. As can be seen in Table 79.1, some drugs have been studied specifically for TMJD pain. Pharmacologic management should be based on the same principles that apply to other chronic conditions: demonstrated efficacy, acceptable adverse effect profile, and safety when given for prolonged periods. In addition, a broad range of other conditions can coexist with TMJD, and such conditions need to be taken into account when considering treatment because they may modify safety or effectiveness.

BOX 79.1 CLASSIFICATION OF TEMPOROMANDIBULAR JOINT DISORDER**Myofascial pain disorder and dysfunction**

Most common, primarily of muscular origin
 Characterized by myogenous pain and limited mandibular function
 May be associated with parafunctional habits, stress, anxiety, depression, or trauma
 Internal displacement of the temporomandibular joint (disk displacement)
 Reducing or nonreducing (closed lock) with joint sounds and deviation with opening
 Most common is anteromedial displacement of the disk
 Results in mechanical interference leading to moderate to severe restriction in range of motion

Systemic diseases (arthritis such as rheumatoid arthritis, psoriatic arthritis, osteoarthritis)

Affect the joint through inflammation or degenerative processes
 May result in condylar remodeling and degenerative joint disease
 May also be related to infectious processes triggering joint inflammation

Congenital and developmental diseases (including trauma and neoplasms)

Hemifacial microsomia or condylar hyperplasia
 Infection
 Ankylosis

BOX 79.2 COMMON DIFFERENTIAL DIAGNOSES

Trigeminal neuralgia, particularly atypical trigeminal neuralgia
 Atypical facial pain, such as atypical odontalgia
 Odontogenic infection, particularly in the molar region
 Sinus or ear infection
 Salivary gland dysfunction, particularly the parotid gland



Fig. 79.1 Clinical examination of the muscles of mastication, the temporomandibular joint, and range of mandibular motion.

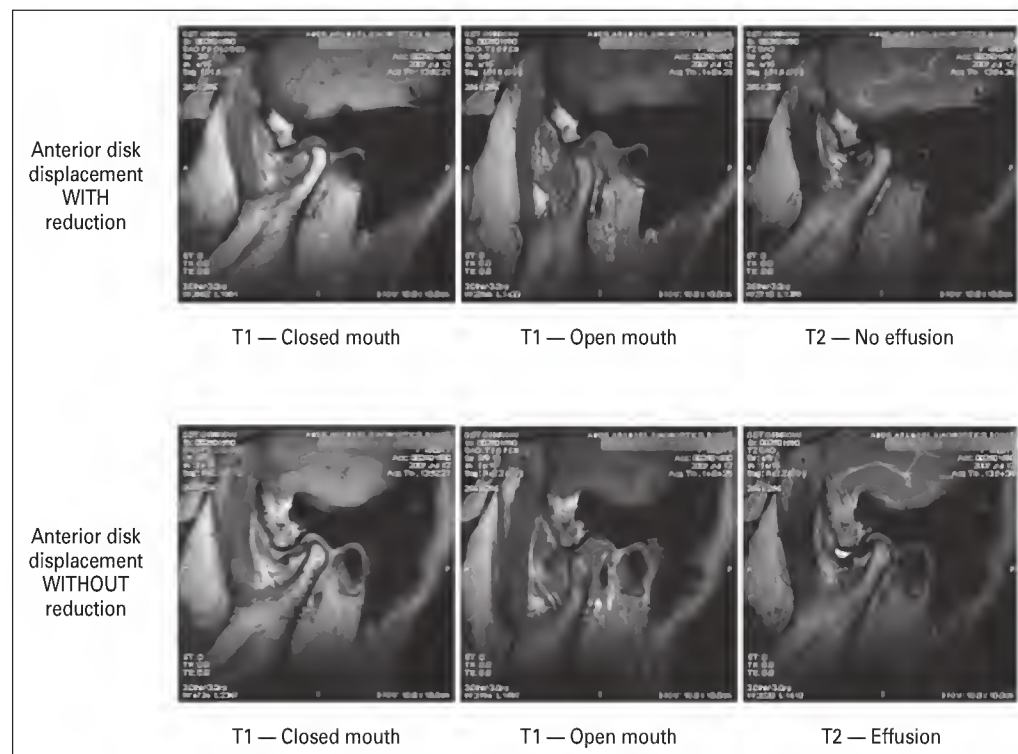


Fig. 79.2 Magnetic resonance images depicting disk displacement.

■ **TABLE 79.1**
Hierarchical evidence for nonsurgical pharmacologic management

Drug class	Examples
Nonsteroidal antiinflammatory drugs	Piroxicam, diclofenac, ibuprofen, celecoxib, naproxen
Muscle relaxants and benzodiazepines	Clonazepam, cyclobenzaprine, orphenadrine, and meprobamate but not carisoprodol, alprazolam, or triazolam
Antidepressants/epileptics	Amitriptyline, gabapentin
Immune-modifying drugs	Infliximab with or without methotrexate, glucosamine, chondroitin sulfate
Topically applied agents	Capsaicin cream; topical and oral diclofenac equally effective

Level of evidence at the I or II level; drug class omitted if no published trials are available.

Surgical management

A small proportion of patients are considered surgical candidates. Surgical options range from arthrocentesis, arthroscopic surgery, and modified condylotomy to total joint replacement. Absolute indications for surgical intervention are pathology, trauma, and ankylosis, whereas relative indications include those refractory to nonsurgical management only when the TMJ is directly involved. Minimally invasive measures or injections of local anesthetic, steroid, hyaluronic acid or other viscosupplementation, or botulinum toxin type A (Botox) may be useful.⁸⁻¹⁰

SUMMARY

The symptoms of TMJD may be enhanced by the mechanisms of pain amplification. Recent evidence has linked TMJD to other chronic pain disorders such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and others. Therefore, it is important for practitioners to have an understanding of TMJD as a coexisting or contributory condition.

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80

Fibromyalgia and related syndromes

■ DANIEL J. CLAUW

- Fibromyalgia can be considered both a discrete illness and a construct to help explain when and why many individuals with chronic pain centralize their pain.
- When individuals with any chronic pain state centralize their pain, they are less likely to respond to treatments (e.g., injections, surgery, opioids) that work better for acute or peripheral pain.
- Nonpharmacologic therapies can be extremely helpful for patients with fibromyalgia or centralized pain and are often underused in clinical practice.

INTRODUCTION

Clinical practitioners commonly see patients with pain and other somatic symptoms that they cannot adequately explain based on the degree of damage or inflammation noted in peripheral tissues. In fact, this may be among the most common predicaments for which individuals seek medical attention. Typically an evaluation is performed looking for a cause of the pain.

If no cause is found, these individuals are often given a diagnostic label that merely connotes that the patient has chronic pain in a region of the body, without an underlying mechanistic cause (e.g., chronic low back pain, headache, temporomandibular joint disorder). In other cases, the label given alludes to an underlying pathologic abnormality that may or may not be responsible for the individual's pain (e.g., endometriosis, facet syndrome). In the worst case scenario, these patients are told that there is nothing wrong with them, advised that the disorder is "all in their head," and given a label such as "somatizer" without being offered any treatment.

Fibromyalgia (FM) is merely the current term for chronic widespread musculoskeletal pain for which no alternative cause can be identified. Gastroenterologists often see the very same patients and focus on their gastroenterologic complaints, and often use the terms *functional gastrointestinal disorder*, *irritable bowel syndrome* (IBS), *nonulcer dyspepsia*, or *esophageal dysmotility* to explain the patients' symptoms. Neurologists see these patients for their headaches and/or unexplained facial pain, urologists for pelvic pain and urinary symptoms (and use labels such as *interstitial cystitis*, *chronic prostatitis*, *vulvodynia*, and *vulvar vestibulitis*), dentists for temporomandibular joint syndrome, and so on.

Until recently these unexplained pain syndromes perplexed researchers, clinicians, and patients. However, the following is now clear:

- Individuals sometimes have only one of these idiopathic pain syndromes over the course of their lifetime. But more often, individuals with one of these entities, and their family members, are likely to have several of these conditions.¹ This is not surprising because recent studies have shown that a variety of chronic pain conditions are very familial, and specific genetic polymorphisms that increase or decrease pain processing are rapidly being identified. Many terms have been used to describe these coaggregating syndromes and symptoms, including *functional somatic syndromes*, *somatization disorders*, *allied spectrum conditions*, *chronic multisymptom illnesses*, *medically unexplained symptoms*, among others (Fig. 80.1).
- Some of these individuals have comorbid psychiatric conditions, but at any given time, most do not. A number of different types of studies make it clear that these pain syndromes are clearly different and

separable from depression and anxiety, and have strong genetic underpinnings.

- Women are more likely to have these disorders than men (approximately 1.5 times as likely) but the sex difference is more pronounced in FM than in other chronic pain conditions because of the unintended consequences of requiring the presence of a certain number of tender points in the 1990 American College of Rheumatology (ACR) criteria. Also, clinical samples (especially for tertiary care) tend to overrepresent females compared with population-based samples.
- A hallmark of these conditions (e.g., FM, IBS, headache, temporomandibular disorder) is that individuals display diffuse hyperalgesia (increased pain to normally painful stimuli) and/or allodynia (pain to normally nonpainful stimuli). This suggests that these individuals have a fundamental problem with augmented pain or sensory processing (i.e., an increased gain setting) in the central nervous system (CNS) rather than a pathologic abnormality confined to the region of the body where the person is currently experiencing pain. These findings of centralization of pain can be corroborated by the presence of these same phenomena on functional neuroimaging studies and appear to be due in part to imbalances in levels of neurotransmitters that affect pain and sensory transmission. Because of this, CNS-mediated symptoms other than pain (fatigue, memory difficulties, sleep and mood disorders) are frequent comorbidities.
- Similar types of therapies are efficacious for all of these conditions, including both pharmacologic treatments (e.g., drugs that raise levels of antinociceptive neurotransmitters such as serotonin and norepinephrine, or lower levels of pronociceptive neurotransmitters such as glutamate and substance P) and nonpharmacologic treatments (e.g., exercise, cognitive behavioral therapy). The shared neurotransmitter hypothesis regarding the pathogenesis of these conditions suggests that because these neurotransmitters that control pain sensitivity are also known (in different and overlapping brain regions) to control sleep, level of alertness, memory, and mood, then when a patient receives a drug of the correct class of such centrally acting analgesics, the patient typically experiences improvement in many different symptoms other than just pain. The problem is that few people respond well to any single class of drug.
- Conversely, individuals with these conditions typically do not respond well when given therapies that are effective for acute pain or pain caused by damage to or inflammation of tissues (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], opioids, injections, surgical procedures).

Even if a practitioner has a problem with considering FM as a discrete disorder, it is very important that he or she understand the diagnostic and therapeutic importance of centralization of pain, as exemplified by a typical FM patient. When a patient with any *rheumatic disorder* develops evidence of centralization of pain, it is likely that treatments that work well for acute pain or pain primarily due to nociceptive input (NSAIDs, opioids, antiinflammatory drugs, immunosuppressives, disease-modifying antirheumatic drugs, injections, surgical procedures) will be less effective.

HISTORICAL PERSPECTIVE

Although the term *fibromyalgia* is relatively new, this condition has been described in the medical literature for centuries. Sir William Gowers coined the term *fibrositis* in 1904. During the next half century, fibrositis (as it was then called) was considered by some to be a common cause of muscular pain, by others to be a manifestation of "tension" or "psychogenic rheumatism," and by the rheumatology community in general to be a nonentity.

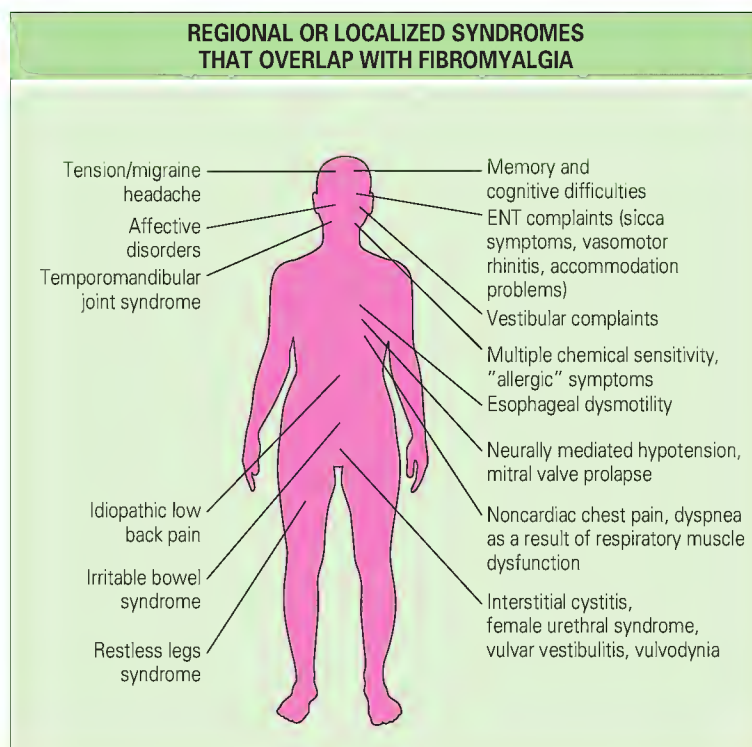


Fig. 80.1 Regional or localized syndromes that overlap with fibromyalgia in prevalence, mechanisms, and treatment. ENT, ear, nose, and throat.

The current concept of FM was established by Smythe and Moldofsky² in the mid-1970s. The name change reflected the increasing evidence that there was no “-itis” (inflammation) in the connective tissues of individuals with this condition, but instead “-algia” (pain). These authors characterized the most common tender points (regions of extreme tenderness in these individuals) and reported that patients with FM had disturbances in deep and restorative sleep and that selective stage 4 interruptions induced the symptoms of FM.³ Yunus and associates⁴ then reported on the major clinical manifestations of patients with FM seen in rheumatology clinics.

The next advance in FM was the development of the ACR criteria for FM, which were published in 1990.⁵ These classification criteria require that an individual have both a history of chronic widespread pain (CWP) and the presence of 11 or more of a possible 18 tender points on examination. These ACR classification criteria were intended for research use to standardize definitions of FM. In this regard, the criteria have been extremely valuable. Unfortunately, many practitioners use these criteria in routine clinical practice to diagnose FM in individual patients, and this unintended use has led to many of the current misconceptions regarding FM, which are discussed later.

The finding of diffusely increased tenderness, as well as the failure to find inflammation in the muscles or other tissues of FM patients, caused the name of this entity to be changed from *fibrositis* to *fibromyalgia*, as noted earlier. The diffuse nature of the pain and tenderness also led many groups of investigators to begin to explore CNS mechanisms to explain the underlying pathogenesis of these disorders.^{6,7} In fact, major advances in understanding individual syndromes within this spectrum occurred only after investigators concluded that this was not a condition caused by peripheral damage or inflammation and began to explore central, neural mechanisms of these diseases.

EPIDEMIOLOGY

Chronic widespread pain

Epidemiologic studies of CWP, the historical component of the ACR criteria for FM, have been extremely instructive. CWP is typically operationalized as pain above and below the waist, involving the left and right sides of the body, and also involving the axial skeleton. Population-based studies of CWP suggest that 5% to 15% of the population has this symptom at any given time.⁸ Chronic regional pain is found in 20% to 25% of the population. Both chronic widespread and chronic regional pain occur about 1.5 times more commonly in women than in men.

Fibromyalgia

As noted earlier, the 1990 ACR criteria for FM require that an individual have both a history of CWP and the presence of 11 or more of 18 possible tender points on examination. Tender points are represented by nine paired predefined regions of the body, often over musculoskeletal insertions. If an individual reports pain when a given region is palpated with 4 kg of pressure, it is considered to be a positive finding of a tender point. Between 25% and 50% of individuals who have CWP also have 11 or more tender points and thus meet the criteria for FM. The prevalence of FM is just as high in rural or nonindustrialized societies as it is in countries such as the United States.

In 2010 and 2011, alternative criteria for FM were established that did not require performing a tender point count.^{9,10} These new criteria are aligned with a more contemporary view of the “pain centralization phenotype” which acknowledges that the most discriminating features of FM and other centralized pain states are multifocal pain (i.e., involving many areas of the body rather than just a few) combined with other comorbid symptoms such as fatigue, memory difficulties, and sleep and mood disturbances.^{11,12}

Significance of tender points

At the time the 1990 ACR criteria were first published, it was thought that there might be some unique significance to the locations of tender points. In fact, the term *control points* was coined to describe areas of the body that should not be tender in FM, and individuals were assumed to have a psychological cause of their pain if they experienced tenderness in these regions. Since then, we have learned that the tenderness in FM extends throughout the entire body. Thus, relative to the pain threshold that a normal non-FM patient would experience at the same points, control regions of the body such as the thumbnail and forehead are just as tender as FM tender points. Thus, to assess tenderness in clinical practice, practitioners can apply pressure wherever they wish, and as long as they perform this examination with the same pressure in a series of patients, they can get a good sense of the overall pain threshold of any individual patient.

The tender point requirement in the 1990 ACR criteria not only misrepresents the nature of the tenderness in this condition (i.e., local rather than widespread) but also strongly influences the demographic and psychological characteristics of FM as defined by these criteria. Women are only 1.5 times more likely than men to experience CWP but are 10 times more likely than men to have 11 or more tender points. Because of this, women are approximately 10 times more likely to meet the 1990 ACR criteria for FM than men. Most of the men in the population who have CWP but are not tender enough to meet the criteria for FM likely have the same underlying problem as the women who meet the ACR criteria for FM.

Another unintended consequence of requiring both CWP and the presence of at least 11 tender points for a diagnosis of FM is that many individuals with FM have high levels of distress. Wolfe has described tender points as a “sedimentation rate for distress” because of population-based studies showing that tender points are more common in distressed individuals.¹³ Distress is usually considered as a combination of somatic symptoms and symptoms of anxiety and/or depression. Until recently, many assumed that because *tender points* were associated with distress, *tenderness* (an individual's sensitivity to mechanical pressure) was associated with distress. However, evidence suggests that this latter association is probably due to the standard tender point technique, which consists of applying steadily increasing pressure until 4 kg is reached. In this situation, individuals who are anxious or expectant have a tendency to “bail out” and report tenderness. More sophisticated measures of tenderness apply stimuli in a random, unpredictable fashion, and the results of these tests are much less influenced by psychological status; results of these tests of pain threshold are similarly abnormal in FM.¹⁴ But because tender points are associated with high levels of distress, requiring the presence of 11 or more tender points to diagnose FM in someone with CWP increases the likelihood that these individuals will be female and/or distressed, compared with individuals with CWP and fewer than 11 tender points.

In fact, population-based studies suggest that the primary symptom of FM—CWP—is only modestly associated with distress, and distress is only weakly associated with the subsequent development of CWP.¹⁵ There are far more psychologically “normal” individuals who develop CWP than distressed or depressed people that do, and most individuals with CWP do not have or subsequently develop distress or depression. Other symptoms such as poor sleep¹⁶ are better predictors of who in the population without pain will subsequently develop pain than is psychological distress.

In summary, although many clinicians uniquely associate FM with women who display high levels of distress, much of this is an artifact of the 1990 ACR criteria requiring the presence of 11 tender points, as well as the

fact that most studies of FM have used clinical samples from tertiary care centers. When all these biases are eliminated by examining CWP in population-based studies, a clearer picture of FM can be gleaned, and CWP becomes much like chronic musculoskeletal pain in any other region of the body.

ETIOLOGY

Genetic factors

Research has indicated a strong familial component to the development of FM, as well as most other chronic pain states.¹⁷ First-degree relatives of individuals with FM display an eightfold greater risk of developing FM than those in the general population.¹ These studies also show that family members of individuals with FM are much more tender than the family members of control subjects, regardless of whether they have pain or not. Family members of FM patients are also much more likely to have IBS, temporomandibular disorder, headaches, and a host of other regional pain syndromes.¹⁸ This familial and personal coaggregation of conditions that include FM was originally collectively termed *affective spectrum disorder* and more recently has been called *central sensitivity syndromes* and *chronic multisymptom illnesses*. In population-based studies, the key symptoms that often coaggregate besides pain are fatigue, memory difficulties, and mood disturbances.

Recent twin studies have been particularly helpful in establishing that these somatic syndromes strongly coaggregate with each other, are strongly genetic, and are clearly separable from anxiety and depression.^{19,20} These studies also suggest that approximately half of the risk of developing these conditions is due to genetic factors and half to environmental factors.

Recent studies have begun to identify specific genetic polymorphisms that are associated with a higher risk of developing FM. To date, the serotonin 5-HT_{2A} receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor, and catechol O-methyltransferase polymorphisms have all been noted to be seen in higher frequency in FM patients in several studies, although, as often occurs, these findings are not seen in all cohorts studied.^{21,22} It is noteworthy that most of the polymorphisms identified to date involve the metabolism or transport of neurotransmitters that are known to increase or decrease pain or sensory responsiveness and/or play a critical role in activity of the human inflammatory or stress responses. It is likely that there are scores of genetic polymorphisms and haplotypes that in part determine an individual's set point for pain and sensory processing and in part establish their subsequent risk of developing chronic pain.

Environmental factors

As with most illnesses that may have a genetic underpinning, environmental factors may play a prominent role in triggering the development of FM and related conditions. Environmental stressors temporally associated with the development of either FM or chronic fatigue syndrome include physical trauma (especially involving the trunk); certain infections such as hepatitis C, Epstein-Barr virus infection, parvovirus infection, and Lyme disease; and emotional stress.^{23,24} Of note, each of these stressors leads to CWP or FM in only approximately 5% to 10% of individuals who are exposed; the overwhelming majority of individuals who experience these same infections or other stressful events regain their baseline state of health.

FM also occurs quite commonly in individuals who initially have an autoimmune or other disorder associated with ongoing peripheral nociceptive input, which can then drive the centralization of pain.¹² At least 20% of individuals with rheumatoid arthritis, systemic lupus erythematosus, and osteoarthritis meet categorical (i.e., yes or no) criteria for FM, and there is now emerging evidence that these individuals have centralized their pain and thus have some of the same underlying CNS pain amplification mechanisms operative as those with FM.²⁵ The proportion of individuals who have centralized their pain appears to be higher yet in cohorts of individuals with lifelong ongoing peripheral nociceptive input, such as individuals with Ehlers-Danlos syndrome or sickle cell disease.

PATHOGENESIS

Role of stressors

Once FM develops, the mechanisms responsible for ongoing symptom expression are likely complex and multifactorial. Because disparate stressors

can trigger the development of these conditions, the human stress response has been closely examined for a causative role. In humans, daily hassles and personally relevant stressors seem to be more capable of causing symptoms than major catastrophic events that do not personally impact the individual. Two studies performed in the United States just before and after the terrorist attacks of 9/11 illustrate this latter point. In one study performed by Raphael and colleagues,^{25a} no difference in pain complaints or other somatic symptoms was seen in residents of New York and New Jersey who had been surveyed before 9/11 and then were surveyed immediately following the terrorist attacks on the World Trade Center. In another study^{25b} performed in the Washington, DC, region (near the Pentagon—the other site of attack) during the same time period, patients with FM had no worsening of pain or other somatic symptoms following the attack, compared to just before the attack.

To complete this vicious circle, these changes in baseline function of the stress response (i.e., of the autonomic and neuroendocrine systems, see later) that may occur following a stressor earlier in life have been shown to predict which symptom-free individuals without chronic pain or other somatic symptoms are more likely to develop these somatic symptoms. This has been noted both in population-based studies and in experiments in which healthy young adults are deprived of regular sleep or exercise.^{8,26}

This theoretical link between stress, changes in stress-axis activity, and subsequent susceptibility to development of somatic symptoms or syndromes is also supported by studies showing that patients with FM and related conditions may be more likely than nonaffected individuals to have experienced physical or sexual abuse in childhood.²⁷ Twin studies have recently supported a link between posttraumatic stress disorder (PTSD) and CWP.²⁸ Just as a lack of or cessation of exercise following trauma seems to be associated with a higher likelihood of developing pain or other somatic symptoms, a recent study of Israeli war veterans with PTSD showed that those who exercised regularly were much less likely to develop CWP or FM.

Role of neuroendocrine abnormalities

Because of this link between exposure to stressors and the subsequent development of FM, the human stress systems have been extensively studied in this condition. These studies have generally shown alterations of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system in FM and related conditions.^{29,30} Although these studies often note either hypoactivity or hyperactivity of both the HPA axis and sympathetic nervous system in individuals with FM and related conditions, the precise abnormality varies from study to study. Moreover, these studies find abnormal HPA or autonomic function in only a very small percentage of patients, and there is tremendous overlap between patients and control subjects in any of these studies.

The inconsistency of these findings should not be surprising, because nearly all of these studies were cross-sectional studies which assumed that if HPA and/or autonomic dysfunction was found in FM, it must have *caused* the pain and other symptoms. Data now suggest a much more complicated picture. As noted earlier, there are better data suggesting that especially HPA abnormalities might represent a diathesis or be *due to* the pain or early life stress, rather than causing it.³¹ The picture is a very complicated one, with good evidence for a role of “sympathetic overdrive” (especially at night) in a subset of FM patients but not in others.^{32,33} It is likely that some of these neurobiologic alterations are shared with other syndromes that are known to be associated with HPA and/or autonomic function such as depression or PTSD. In fact, this has led some who have superficially reviewed the neurobiologic data regarding FM to conclude erroneously that this condition shares many biologic underpinnings with depression.³⁴

Augmented pain and sensory processing as a hallmark of fibromyalgia and related syndromes

Once FM is established, by far the most consistently detected objective abnormalities involve pain and sensory processing systems. Because FM is defined in part by tenderness, considerable work has been performed exploring the potential reason for this phenomenon. The results of two decades of psychophysical pain testing in FM have been very instructive.³⁵

One of the earliest findings in this regard was that the tenderness in FM is not confined to tender points but instead extends throughout the entire body. Theoretically, such diffuse tenderness could be due primarily to either psychological factors (e.g., hypervigilance, in which individuals are too attentive to their surroundings) or neurobiologic factors (e.g., the plethora of factors that can lead to temporary or permanent amplification of sensory input).

Early studies typically used dolorimetry to assess pressure pain threshold and concluded that tenderness was in large part related to psychological factors, because these measures of pain threshold were correlated with levels of distress. Also, nuances such as the rate of increase of stimulus pressure, control of pressure by the operator versus by the patient, and patient distress have been shown to influence pain threshold when it is measured in this manner. To minimize the biases associated with ascending measures of pressure pain threshold (i.e., those in which the individual knows that the pressure will be predictably increased). These studies showed the following: (1) The measures of pressure pain threshold that used random administration of pressures were not influenced by levels of distress of the individual, whereas tender point count and dolorimetry examinations were. (2) FM patients were much more sensitive to pressure even when these more sophisticated paradigms were used. (3) FM patients were not any more expectant or hypervigilant than controls. (4) Pressure pain thresholds at any four points in the body are highly correlated with the average tenderness at all 18 tender points and 4 control points (the thumbnail and forehead).

Heat, cold, and electrical stimuli

Not only is heightened sensitivity to pressure noted in FM, but other types of stimuli applied to the skin are also judged as more painful or noxious by these patients. FM patients also display a decreased threshold to heat, cold, and electrical stimuli.

Responses to other sensory stimuli

Gerster and colleagues^{35a} were the first to demonstrate that FM patients also display a low noxious threshold to auditory tones, and this finding was subsequently replicated. However, both of these studies used ascending measures of auditory threshold, so these findings could theoretically be due to expectancy or hypervigilance. A more recent study by Geisser and colleagues³⁶ used an identical random staircase paradigm to test FM patients' unpleasantness threshold for the loudness of auditory tones and for pressure. This study found that FM patients displayed low unpleasantness thresholds for both types of stimuli, and the correlation between the results of auditory and pressure pain threshold testing suggested that some of this was due to shared variance and some was unique to one stimulus or the other. Results of this study (and many others) do not support the view that generalized hypervigilance is responsible for these phenomena. The notion that FM and related syndromes might represent biologic amplification of all sensory stimuli gains significant support from functional imaging studies which suggest that the insula is the most consistently hyperactive region (see later). This region has been noted to play a critical role in sensory integration, with the posterior insula serving a purer sensory role and the anterior insula being associated with the emotional processing of sensations.³⁷

Specific mechanisms that may lead to a low pain threshold in fibromyalgia

Two different specific pathogenic mechanisms in FM have been identified using experimental pain testing: (1) an absence of descending analgesic activity, and (2) increased wind-up or temporal summation.

Attenuated diffuse noxious inhibitory control in fibromyalgia

In healthy humans and laboratory animals, application of an intense painful stimulus produces generalized whole-body analgesia. This analgesic effect, originally termed *diffuse noxious inhibitory control* (DNIC) and more recently *conditioned pain modulation*, has been consistently observed to be attenuated or absent in groups of FM patients compared with healthy controls.³⁸ This phenomenon has similarly been noted in a number of other chronic pain states, especially those closely associated with FM. Attenuated DNIC is not found in all patients with FM or chronic pain but is considerably more common in these patients than in control subjects.

The DNIC response in humans is thought to be mediated partly by descending opioidergic pathways and in part by descending serotonergic-noradrenergic pathways. In FM, the accumulating data suggest that endogenous opioidergic activity is normal or even increased (see later).³⁹ Studies directly measuring autonomic function and descending analgesic activity in both FM and IBS support the contention that dysautonomia (and thus the catecholaminergic systems) may be closely tied.⁴⁰ Moreover, positron emission tomography data show that baseline μ -opioid receptor binding is decreased in multiple pain-processing regions in the brains of FM patients, which is consistent with (but not proof of) the hypothesis that there is increased release of endogenous μ -opioid ligands in FM leading to high baseline occupancy of the receptors, rather than a deficiency of endogenous opioid release, that might in part be responsible for decreased DNIC. The biochemical and imaging findings suggesting increased activity of

endogenous opioidergic systems in FM are consistent with the anecdotal experience that opioids are generally ineffective analgesics in patients with FM and related conditions. There is even emerging evidence that blocking endogenous opioid release with the use of low-dose naltrexone might be an effective treatment strategy in some FM patients.⁴¹

In contrast, studies have suggested that there is decreased endogenous serotonergic and noradrenergic activity in FM. Studies have shown that levels of the principal metabolite of norepinephrine, 3-methoxy-4-hydroxyphenethylene, are lower in the cerebrospinal fluid (CSF) of FM patients. Similarly, patients with FM have been shown to have reduced serum levels of serotonin and its precursor, tryptophan, as well as reduced levels of the principal serotonin metabolite, 5-HIAA, in their CSF. The best evidence that low levels of these neurotransmitters is involved in the pathogenesis of FM comes from clinical trials in which nearly any compound that simultaneously raises both serotonin and norepinephrine levels (serotonin-norepinephrine reuptake inhibitors [SNRIs] such as tricyclics, duloxetine, milnacipran, tramadol) has been shown to be efficacious in treating FM and related conditions. A recent study by Yarnitsky and colleagues⁴² showed that individuals with neuropathic pain who had decreased DNIC/conditioned pain modulation at baseline were most likely to respond to duloxetine, which affirms what has been suspected for some time—that drugs with SNRI effects are likely working in part by restoring DNIC. In fact, a number of therapies used to treat FM or centralization of pain, including exercise and many complementary and alternative therapies, might be working in part by restoring descending analgesic activity.

Increased wind-up in fibromyalgia

Early experimental pain-testing studies also suggested that some individuals with FM may have evidence of wind-up, indicative of central sensitization.⁴³ More recent studies suggest that this does not occur as commonly in FM as diffuse hyperalgesia or decreased DNIC, but nonetheless it may help to further characterize patients.⁴⁴ In animal models this finding is associated with increased glutamatergic and excitatory amino acid and substance P hyperactivity.

Although experimental pain testing cannot yet identify individuals with increased glutamatergic or substance P activity contributing to FM pathogenesis, there is ample evidence that increased levels of these neurotransmitters are playing some role in FM. Four independent studies have shown that patients with FM have approximately threefold higher concentrations of substance P in the CSF compared with normal controls.⁴⁵ Other chronic pain syndromes, such as osteoarthritis of the hip and chronic low back pain, are also associated with elevated substance P levels, although chronic fatigue syndrome (which is not defined on the basis of pain) is not. Interestingly, once elevated, substance P levels do not appear to change dramatically and do not rise in response to acute painful stimuli. Thus, high substance P levels appear to be a biologic marker for the presence of chronic pain, and substance P antagonists were widely tested and then abandoned as analgesics.

There is better evidence that increased glutamatergic activity plays some role in the pathogenesis (and treatment) of FM. Glutamate is a major excitatory neurotransmitter in the CNS, and CSF levels of glutamate are twice as high in FM patients than in controls.⁴⁶ Not only are CSF glutamate levels elevated, but several recent studies using proton magnetic resonance spectroscopy demonstrated that the glutamate levels in FM patients are also elevated in key pain-processing areas of the brain such as the insula and change in response to changes in both clinical and experimental pain when patients are successfully treated.⁴⁷ A new imaging study by Harris suggests that the drug pregabalin is acting in FM in part by decreasing glutamatergic activity in the insula and thus decreasing functional connectivity between the default mode network and insula.⁴⁸ In this study individuals with the highest levels of glutamate in the insula before treatment were the ones most likely to respond to pregabalin. There is also evidence that subsets of patients respond to drugs known to be N-methyl-D-aspartate (NMDA) receptor antagonists, which suggests that glutamatergic activity is increased; unfortunately, these drugs, such as ketamine or dextromethorphan, are generally not well tolerated and thus not often practical for clinical use.

Nerve growth factor is another pronociceptive neurotransmitter that has been evaluated in FM and shown to be increased. Nerve growth factor antibodies currently are in clinical trials and are being shown to be very effective analgesics, although there have been safety issues. It is unclear if these drugs would work in FM because they would not generally enter the CNS, but they could affect centralization by reducing peripheral drive to centralization mechanisms (Fig. 80.2).

Thus a number of lines of evidence suggest that FM is a state of heightened pain or sensory processing and that this might occur because of high levels of neurotransmitters that increase pain transmission and/or low levels of neurotransmitters that decrease pain transmission (see Fig 80.2).

NEUROTRANSMITTERS THAT ARE KNOWN TO PLAY EITHER FACILITATORY OR INHIBITORY ROLES IN THE CENTRAL NERVOUS SYSTEM

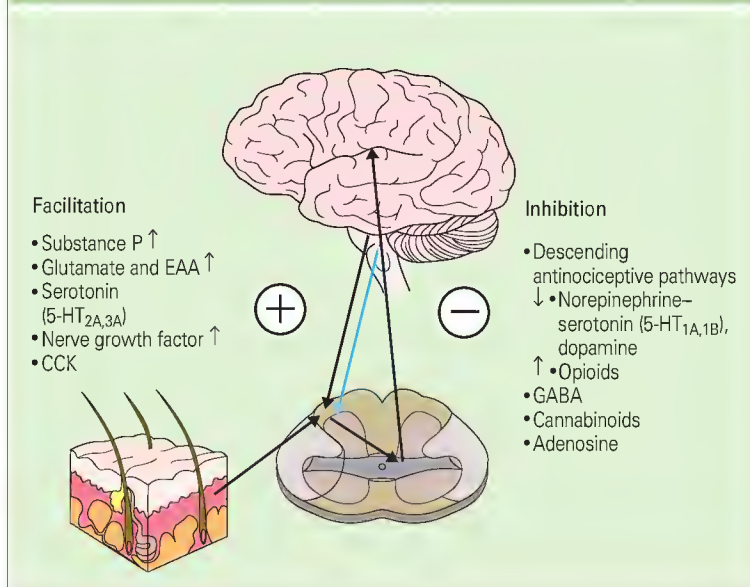


Fig. 80.2 Neurotransmitters known to have either a facilitatory role (indicated in red, and generally increasing pain transmission in the spinal cord) or an inhibitory role (indicated in blue, and decreasing pain transmission) in the central nervous system. The arrows indicate the direction of the abnormality that has been identified in fibromyalgia (FM) and show that the only neurotransmitter system studied in FM that has not been found to be abnormal in a direction that would cause hyperalgesia/allodynia is the opioidergic system; that may explain why this class of drugs is not very effective in FM.

Abnormalities on functional and chemical neuroimaging

Functional neural imaging enables investigators to visualize how the brain processes the sensory experience of pain. The primary modes of functional imaging that have been used in FM include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and proton magnetic resonance spectroscopy (H-MRS).

fMRI is a noninvasive brain imaging technique that relies on changes in the relative concentration of oxygenated to deoxygenated hemoglobin within the brain. In response to neural activity, oxygenated blood flow is increased within the local brain area. Unlike SPECT and PET, which can measure baseline levels of blood flow, the fMRI BOLD signal originates from a difference between experimental conditions and does not assess baseline blood flow. Typically in FM and other pain states, individuals are administered an experimental pain stimulus, and the neuronal activation associated with this stimulus during the “on” condition is subtracted from the neuronal activation pattern seen during the “off” condition (often light touch).

The first study to use fMRI in FM patients was performed by Gracely and coworkers.⁴⁹ In this and other subsequent confirmatory studies, FM patients were shown to have greater amounts of neuronal activation in pain-processing regions of the brain than control subjects when they were given the same amount of pressure stimuli (Fig. 80.3). These findings were entirely consistent with the left shift in stimulus-response function noted with experimental pain testing and has been established in normal healthy individuals who span the entire continuum of pain thresholds. These and subsequent studies, which have generally reproduced these findings, suggest that FM patients have an increased gain or “volume setting” in brain pain-processing systems.

fMRI has also proved useful in determining how comorbid psychological factors influence pain processing in FM. For example, a study by Giesecke and colleagues⁵⁰ explored the relationship between depression and enhanced evoked pain sensations in 30 patients with FM. The authors found that the anterior insula and amygdala activations were correlated with depressive

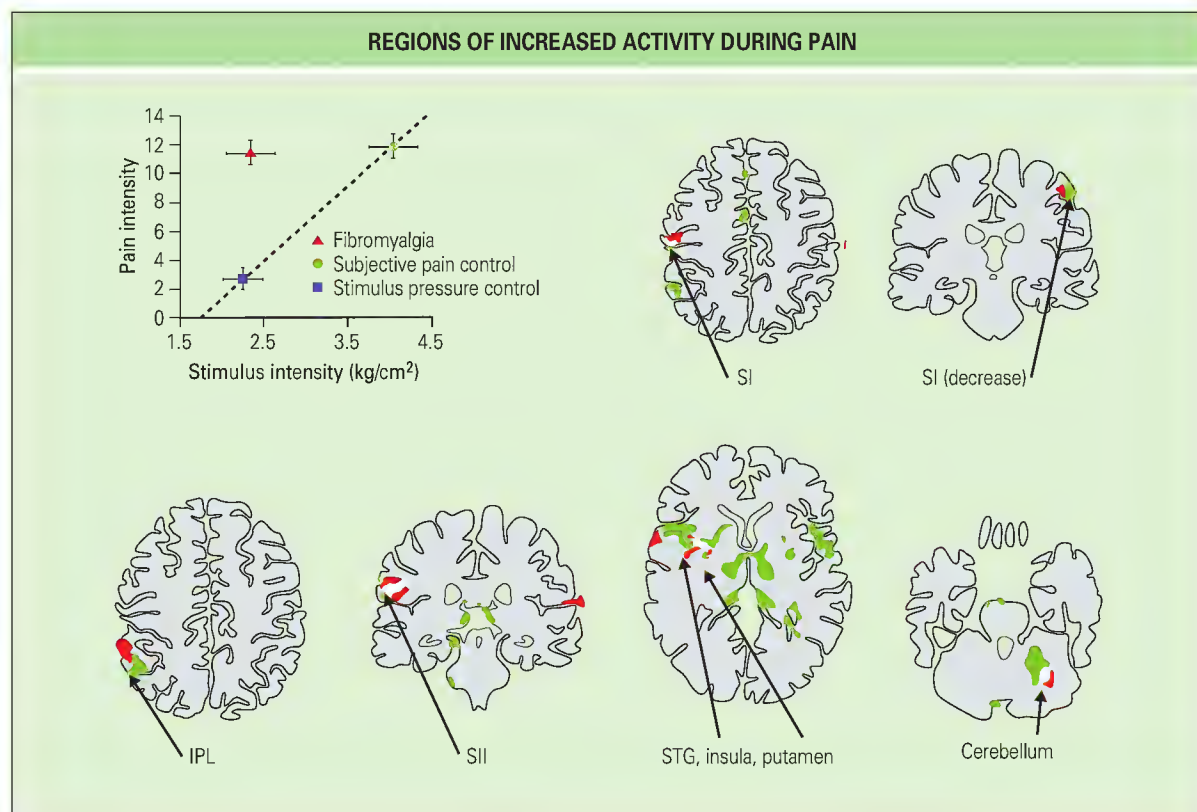


Fig. 80.3 In top left graph, individuals with fibromyalgia (red) given a low-pressure stimulus have levels of pain and neuronal activation in areas of the brain known to be involved in pain processing (tips of arrows) that are similar to those of control subjects (green) given a stimulus with nearly twice as much pressure. Control subjects (blue) given the same low-pressure stimulus that causes pain in fibromyalgia patients rated their pain as 2 out of 20 instead of 12 out of 20 and have no neuronal activation with this amount of pressure. IPL, inferior parietal lobule; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; STG, superior temporal gyrus.

symptoms, consistent with these medial and prefrontal brain regions' being involved in affective or motivational aspects of pain processing (and being more closely related to unpleasantness than to the sensory intensity of pain). However, the degree of neuronal activation in more lateral structures generally thought to be involved in the sensory processing of pain (i.e., where the pain is localized and how intense it is) were not associated with levels of depressive symptoms or the presence or absence of major depression. These data are consistent with a plethora of evidence in the pain field indicating that there are different regions of the brain responsible for pain processing devoted to sensory intensity and to affective aspects of pain sensation, and suggest that the former and latter are largely independent of each other.

A more recent advance is the use of fMRI to look at the extent to which brain regions are connected to each other (i.e., simultaneously activated or deactivated). This analysis can be applied to fMRI data acquired either when individuals are resting (resting state analysis) or when they are performing a task. The advantage of resting state analysis is that it does not require giving the participant a stimulus, and thus it potentially provides a window into measurement of brain changes associated with chronic, ongoing spontaneous pain. Another advantage is that there are many known neural networks that subserve different functions in the human brain, so the extent to which these networks are either intact or somehow disrupted by chronic pain can be examined. Napadow and Harris⁵¹ have used this technique to demonstrate that individuals with FM show increased connectivity between the default mode network (a network active when the brain is resting and not performing any specific task) and the insula—a known pronociceptive region of the brain. Furthermore, in these studies the degree of increased connectivity was related to the intensity of ongoing, spontaneous pain. A different group has shown that during a painful stimulus, connectivity is *decreased* between key antinociceptive regions (e.g., the brainstem—the origin of descending analgesic pathways) and a region they had previously identified to be a potential source of dysfunctional pain inhibition in FM.⁵² Thus these measures of connectivity hold considerable promise as potential biomarkers for pain intensity or mechanism, especially if they can be accurately and reliably measured using techniques such as electroencephalography that are more practical for use at the point of care.

PET has been used in several studies in FM. Wood and colleagues⁵³ used PET to show that attenuated dopaminergic activity may be playing a role in pain transmission in FM, and Harris and colleagues⁵⁴ showed evidence of decreased μ -opioid receptor availability (possibly due to increased release of endogenous μ -opioids) in FM.

In addition to the aforementioned use of *H-MRS* to show elevated glutamate levels, this technique has also been used by Harris and colleagues⁵⁵ to show that the levels of γ -aminobutyric acid (GABA), an inhibitory neurotransmitter, are decreased in the insula in individuals with FM.

Other serologic and biochemical abnormalities

Although these conditions all were originally thought to be autoimmune or inflammatory diseases and then later felt not to be, recent findings are leading to a reconsideration of whether subtle inflammatory changes may be responsible for some of the symptoms seen. Immunologic cascades have a role in the maintenance of central sensitivity and chronic pain, which is enhanced through release of proinflammatory cytokines by CNS glial cells; thus the traditional concept of inflammatory versus noninflammatory pain may gradually become less dichotomous. As may be expected in any complex biologic system, a delicate mechanism of checks and balances is at work in the spinal transmission of pain. Multiple inhibitory transmitters act at the spinal level to reduce the volume of pain transmission. Serotonin, norepinephrine, enkephalins, dopamine, and GABA are among the better-known players in this balance.

The amino acid tryptophan and the cytokines interleukin-8 (IL-8) and IL-6 have been shown to be different in FM patients compared with control subjects in several studies, but none has been evaluated in longitudinal studies.⁵⁶ Increased IL-8 level has been perhaps the most consistently demonstrated serum/plasma abnormality. Moreover, IL-8 level has been shown to correlate with symptoms and not to be associated with depressed FM. IL-8 levels are closely tied to autonomic function, and the findings of these increased levels could be due to the dysautonomia seen in FM and related conditions. Serum IL-6 level has also been shown to be elevated in FM in several studies. Low levels of tryptophan, a precursor for serotonin, have been found in two of three studies by three different groups.

Structural or peripheral abnormalities in fibromyalgia

Although a few studies have found mild abnormalities in the *skeletal muscles* of FM patients, these findings have been inconsistent and may be due to

deconditioning rather than the illness itself. Studies suggest that the tenderness in FM is not at all confined just to the muscle, so in aggregate most investigators have concluded that primary muscle disease is not a likely cause of the pain associated with FM.

Newer studies, however, are suggesting that the small fibers of peripheral nerves may be abnormal (e.g., decreased number, increased tortuosity) in some individuals with FM. Caro and colleagues⁵⁷ have published a series of studies suggesting that a subset of FM patients may have a mildly inflammatory small fiber neuropathy. Other groups have also identified evidence of a small fiber neuropathy in the skin in subsets of FM patients, but the meaning of this finding is not clear, because this same finding has been noted in many other chronic pain states.⁵⁸

Somewhat more concerning are the plethora of studies suggesting that there may be structural abnormalities of the brain in individuals with FM, which are aligned with other studies in the pain field suggesting that chronic pain may be a neurodegenerative disorder. There are now several groups that have used either voxel-based morphometry or diffuse tensor imaging to identify abnormalities in brain structure in individuals with FM, although the largest such study suggested that some of these abnormalities may be due to frequently comorbid psychiatric conditions that are known to demonstrate the same changes.⁵⁹ Regardless, these subtle changes in size and shape of cortical and subcortical areas in chronic pain states are allowing us to learn more about neuroplasticity in chronic pain, and the latter term is probably much more accurate than *neurodegeneration*, because these areas are known to increase in size following therapy.

Thus, if there are structural abnormalities or damage to tissues in FM, the most evidence for this is in neural tissues, rather than in the regions of the body where individuals with this condition experience pain. Furthermore, studies suggest that maintenance of central augmentation to some extent requires persistent noxious peripheral input, even in syndromes such as IBS and FM, which are characterized by the absence of well-defined, localized, pain-causing lesions. In fact, a recent study of FM patients with comorbid myofascial pain or regional joint pain showed that peripheral trigger point injections and hydroelectrophoresis aimed at reducing these peripheral pain generators ameliorated FM pain and increased pain thresholds at sites distant from the therapeutic interventions, which provides further evidence that painful peripheral stimuli contribute to the perpetuation of central augmentation processes.⁶⁰

Sleep and fibromyalgia

Because early studies by Moldofsky showed that sleep deprivation can lead to FM-like symptoms (these studies have subsequently been replicated) and more recent epidemiologic studies show that poor sleep is a very strong predictor of subsequent pain, there has been extensive work in FM to better understand the role of poor sleep in the pathogenesis of FM. However, the electroencephalographic abnormalities that were noted and initially thought to be a marker for FM, so-called alpha intrusions, have subsequently been found to be present in normal individuals and individuals with other conditions. More recent studies have used polysomnography to identify findings that occur more commonly in FM, including fewer sleep spindles, an increase in cyclic alternating pattern rate, upper airway resistance syndrome, and/or poor sleep efficiency, but other studies have found very little differences in sleep characteristics in FM patients and control subjects.^{61,62} At present, it is known that poor sleep can contribute to FM symptoms and that making sleep better is an important therapeutic target, but there is no evidence that there is any specific sleep abnormality causing FM.

Behavioral and psychological factors

In addition to neurobiologic mechanisms, behavioral and psychological factors also play a role in symptom expression in many patients with FM and other chronic pain. The rate of psychiatric comorbidity in patients with FM may be as high as 30% to 60% in tertiary care settings, and the lifetime rate of psychiatric disorders may be even higher.⁶³ Depression and anxiety disorders are the most commonly seen. However, these rates may be artificially elevated by virtue of the fact that most of these studies have been performed in tertiary care centers. Individuals who meet ACR criteria for FM who are identified in the general population do not have this high a rate of identifiable psychiatric conditions.

As already noted, population-based studies have demonstrated that the relationship between pain and distress is complex and that distress is both a cause and a consequence of pain. In this latter instance, a typical pattern is that, as a result of pain and other symptoms of FM, individuals begin to function less well in their various roles. They may have difficulties

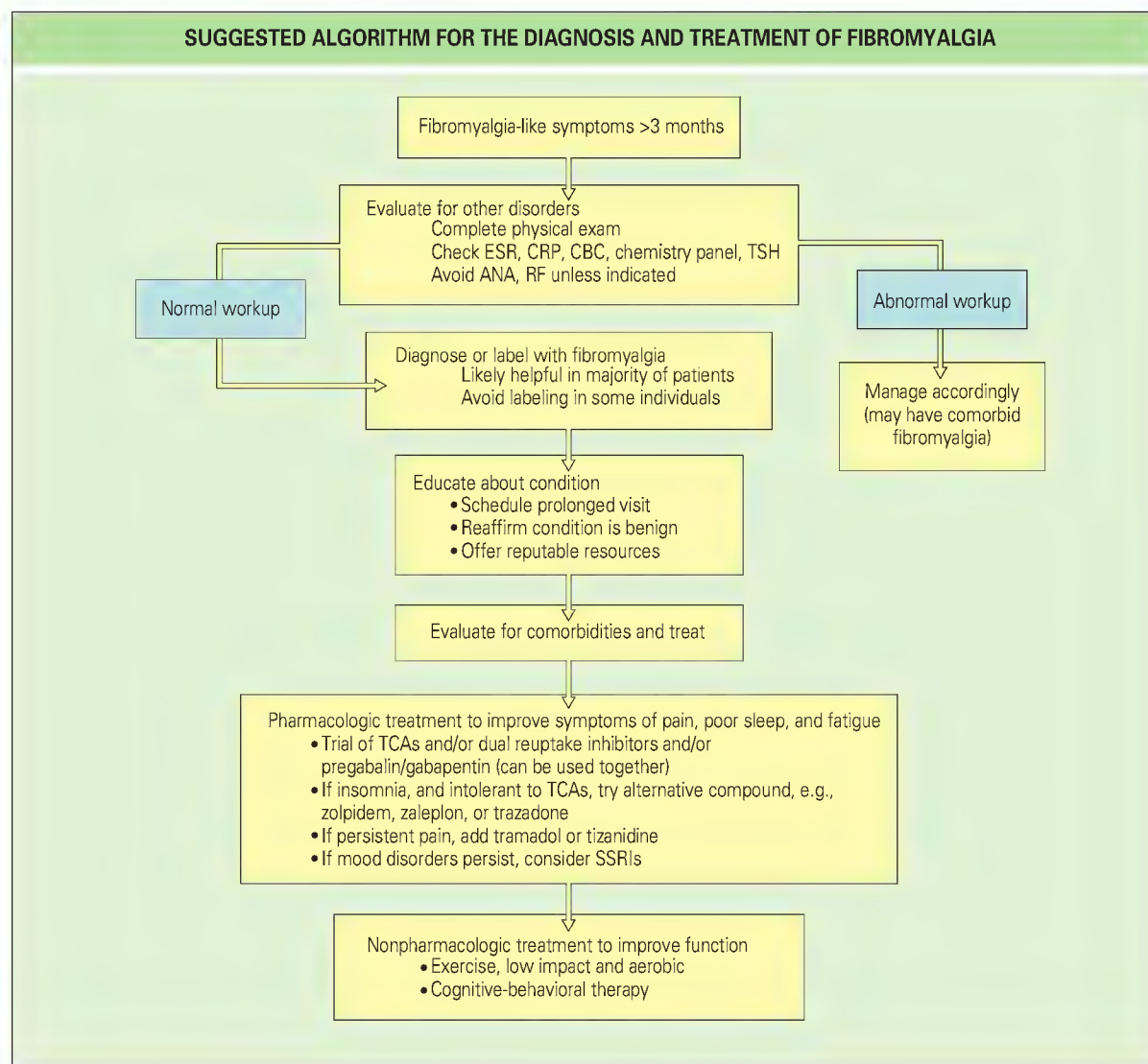


Fig. 80.4 Suggested algorithm for the diagnosis and treatment of fibromyalgia. ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; TSH, thyroid-stimulating hormone.

with spouses, children, and work inside or outside the home, which exacerbate symptoms and lead to maladaptive illness behaviors. These include isolation, cessation of pleasurable activities, reductions in activity and exercise, and so on. In the worst cases, patients become involved with disability and compensation systems that almost ensure that they will not improve.

The complex interaction of biologic, behavioral, psychological, and behavioral mechanisms is not, however, unique to FM. Nonbiologic factors play a prominent role in symptom expression in all rheumatic diseases. In fact, in conditions like rheumatoid arthritis and osteoarthritis, nonbiologic factors such as level of formal education, coping strategies, and socioeconomic variables account for more of the variance in pain report and disability than biologic factors such as joint space width or sedimentation rate.⁶⁴

Because of the biopsychosocial nature of FM, several groups have attempted to identify subgroups of individuals with this condition who may have different presentations or respond differentially to treatment. One of the important emerging notions in this field is that in addition to patients with what are often considered the negative contributions of psychological factors, there are also subgroups of patients who are very resilient. Therapeutic attempts to instill positive psychological and cognitive characteristics may actually buffer neurobiologic factors leading to pain and other symptoms in FM. Increasingly, studies in FM and the broader pain field are also suggesting that a subset of chronic pain patients who might require particularly increased psychological attention are those with significant early life trauma. These individuals may be more refractory to other types of treatments and may need additional therapy aimed at identifying and working through these issues, even using nonintensive techniques such as journaling or emotional disclosure.⁶⁵

EVALUATION OF INDIVIDUALS WITH CHRONIC WIDESPREAD PAIN

The evaluation of an individual with chronic pain is a complex process (Fig. 80.4). Unlike with most other medical problems, simply arriving at a diagnosis is typically insufficient to guide treatment. This is because within any given pain diagnosis, there is tremendous heterogeneity with respect to the underlying causes and contributors to symptoms, and the most effective treatments. In particular, individuals with chronic pain can have greater or lesser peripheral nociceptive contributions (e.g., tissue damage, inflammation) and central nonnociceptive contributions (e.g., pain amplification, psychological factors) to their pain (Box 80.1). Therefore the differential diagnosis of chronic pain involves identifying which of these factors are present in which individuals, so that the appropriate pharmacologic, procedural, and psychological therapies can be administered.

Careful musculoskeletal history taking and examination remain the most important diagnostic tool for musculoskeletal pain. In other fields of medicine, advances in diagnostic testing have largely rendered a physical examination obsolete. However, in musculoskeletal medicine, technology confuses as much as it helps. For example, a high proportion of the healthy, asymptomatic population tests positive for antinuclear antibody or rheumatoid factor, or has abnormal findings on imaging studies. Worse yet, these diagnostic tests cannot tell the practitioner how severe the pain is, because there is typically a significant discordance between the results of laboratory or imaging studies and the severity of pain and other symptoms that the individual is experiencing.

Therefore the musculoskeletal history taking and examination must allow the clinician to arrive at the diagnosis (or, at worst, a very narrow

BOX 80.1 MECHANISTIC CHARACTERIZATION OF PAIN

Peripheral (nociceptive)	Neuropathic	Centralized
Primarily due to inflammation or mechanical damage in periphery	Due to damage or entrapment of peripheral nerves	Primarily due to central disturbance in pain processing
Responds to nonsteroidal antiinflammatory drugs, opioids	Responds to both peripheral and central pharmacologic therapy	Tricyclic, neuroactive compounds most effective
Responds to procedures	Examples: ■ Diabetic painful peripheral neuropathy	Behavioral factors more prominent
Behavioral factors minor	■ Postherpetic neuralgia	Examples
Examples: ■ Osteoarthritis		■ Fibromyalgia
■ Rheumatoid arthritis		■ Irritable bowel syndrome
■ Cancer pain		■ Tension headache
		■ Idiopathic low back pain

differential diagnosis), and then, if necessary, further diagnostic testing should be used to confirm these findings.

DIAGNOSIS

The ACR criteria for FM were never intended to be used as strict diagnostic criteria for application in clinical practice. Many individuals who clearly have FM do not have pain throughout their entire body or do not have 11 tender points. Moreover, pain and tenderness occur across a continuum in the population, and it is impossible to know where to draw the line between an individual with symptoms and someone with an illness.

For this and many other reasons, the alternative 2010 FM criteria may represent a preferred manner of diagnosing or thinking about FM.^{9,10} The survey version of these criteria consists entirely of patient self-report and can be administered on a single piece of paper. There is a body map with 19 areas and well as a symptom survey that asks about the presence and severity of fatigue, sleep disturbances, memory difficulties, and mood problems. When used as a dichotomous measure with a variety of cut points, this tool will identify roughly the same group of individuals as the old criteria (except many more males will be included).^{9,10} However, when FM is considered more as a physiologic construct to determine where on the continuum of pain sensitivity an individual lies, then this tool can be used as a continuous measure (i.e., to determine the degree of “fibromyalgia-ness” or the degree to which pain is centralized) that can be helpful in the diagnosis and treatment of virtually any patient with a rheumatic disorder who is experiencing pain.

History Pain

In clinical practice, one should suspect FM in individuals with multifocal pain that cannot be fully explained on the basis of damage or inflammation in those regions of the body. In most cases, musculoskeletal pain is the most prominent feature, but because pain pathways throughout the body are amplified, pain can be perceived anywhere. Thus chronic headaches, sore throats, chest pain, abdominal pain, and pelvic pain are very common in individuals with FM, and patients with chronic regional pain in any of these locations are more likely to have FM. It is especially helpful to take a lifetime history of chronic pain. Individuals with conditions such as FM nearly always begin having chronic pain in various regions of their body early in life (e.g., dysmenorrhea, functional abdominal pain, growing pains), and this continues throughout their life. What often looks to one subspecialist like a new episode of pain in the region of the body that is that practitioner's purview is in fact one in a series of chronic pain conditions that have occurred over the lifetime of the individual.⁶⁶

Because pain is a defining feature of FM, it is helpful to focus on the features of the pain that can help distinguish it from other disorders. The pain of FM is typically diffuse or multifocal, often waxes and wanes, and is frequently migratory. These characteristics of central pain are quite different from those of peripheral pain, in which both the location and severity of pain are typically more constant. Patients may complain of discomfort when they are touched or when wearing tight clothing and may experience dysesthesias or paresthesias that accompany the pain. For this latter reason

self-report measures such as the PainDETECT questionnaire that assess both the character and spatial extent of pain have been shown to be helpful in differentiating pain of neural origin (such as that of FM) from pain due to peripheral nociceptive input.

Nonpain symptoms

Aside from the pain, a number of seemingly nonrelated symptoms may develop and persist. These include fatigue, sleep difficulties, weakness, problems with attention or memory, unexplainable weight fluctuations, and heat and cold intolerance. “Allergies” are reported much more commonly in FM patients, although these excess symptoms are better considered sensory hypersensitivities than true immunoglobulin E-mediated immunologic reactions. These patients are also more prone to nonallergic rhinitis, sinus and nasal congestion, and lower respiratory tract symptoms, all of which again may be attributable primarily to neural mechanisms. Distortions in hearing, vision, and vestibular symptoms are often reported, as are sicca symptoms (sometimes so prominent that these individuals will overlap with those with Sjögren syndrome).

“Functional disorders” involving visceral organs have long been noted to be more common in FM. These include noncardiac chest pain, heartburn, and palpitations, and the frequent comorbidity of IBS. Thus there are reports of increased echocardiographic signs of mitral valve prolapse and esophageal dysmotility, and reduced static inspiratory and expiratory pressure on pulmonary function tests. The latter might be explained by pain in respiratory muscles. Syncope and hypotension are symptoms that may occur in FM, and in some cases are accompanied by neurally mediated hypotension or postural orthostatic tachycardia. Pelvic complaints are common, including not only pain but also urinary frequency and urgency. In females the frequent comorbid diagnoses are dysmenorrhea, interstitial cystitis or painful bladder syndrome, endometriosis, and vulvar vestibulitis/vulvodynia, whereas in males similar symptoms are sometimes diagnosed as chronic or nonbacterial prostatitis.

Physical examination and laboratory investigations

Critical information can be gleaned from the history and physical examination findings that can further help identify individuals with FM or centralized pain. It might seem a leap to move from experimental pain testing, brain imaging, and genetic studies of centralized pain states to a better understanding of the diagnosis and treatment of any chronic pain, but in reality this is not such a stretch. Much of the same information obtainable via these sophisticated research methods can also be gained (albeit less precisely) by taking a history and performing a physical examination.

For example, individuals with centralized pain states very often demonstrate an altered noxious threshold (the point at which a sensory experience such as pressure, heat, or sounds become bothersome) for virtually every type of sensory stimulus.⁶⁷ This can be easily understood by patients and clinicians alike when the phenomenon is likened to an increased volume control in the brain for any sensory stimulus. Because of this, individuals with FM or other centralized pain states often note that they find noises, odors, and bright lights very bothersome, and this sensory sensitivity likely even explains many of the visceral symptoms these individuals experience (e.g., indigestion, heartburn, abdominal pain, urinary urgency and frequency). These are often noted on a review of systems. Sometimes merely highlighting this physiologic understanding of sensory augmentation can be extremely helpful to patients because they are less concerned that something is wrong when they develop new symptoms that follow this same pattern—symptoms that before would often trigger a frustrating search for the cause of the pain.

Also, although pain threshold testing is not available in routine clinical practice, there are many ways that a clinician can assess for overall pain sensitivity. For examples, individuals with FM are more sensitive to the inflation of a blood pressure cuff.⁶⁸ Another way to assess overall pain threshold while also obtaining other valuable diagnostic information is to assess pain thresholds in the hands and arms of all patients with chronic pain. A rapid examination performed by applying firm pressure over several interphalangeal joints of each hand, also over the adjacent phalanges, and then caudally to include firm palpation of the muscles of the forearm, including the lateral epicondyle region, is one way to assess overall pain threshold as well as get additional diagnostic information about the patient. If the individual is tender in many of these areas, or in just the muscles of the forearm, he or she is likely diffusely tender (i.e., has a low central pain threshold). However, if the individual is tender only over the interphalangeal joints and not the other regions, and especially if there is any swelling over these joints, the practitioner should be more concerned about a systemic autoimmune disorder (e.g., rheumatoid arthritis, lupus).

Alternatively, sometimes individuals are tender only over the phalanges, and in these instances one might suspect a metabolic bone disease or condition causing periostitis (e.g., hypothyroidism, hyperparathyroidism).

Laboratory testing is generally not useful except for the purpose of differential diagnosis. One factor that can help guide the intensity of the diagnostic workup is the length of time the patient has had symptoms. If the patient's symptoms have persisted for several years, minimal testing is required, whereas a more aggressive strategy should be employed for acute or subacute onset of symptoms. Simple testing should be limited to complete blood count and routine serum chemistry panels, along with thyroid-stimulating hormone level and erythrocyte sedimentation rate and/or C-reactive protein level.

Serologic studies such as antinuclear antibody and rheumatoid factor assays should generally be avoided unless there are historical features not seen in FM or abnormalities on physical examination.

Aside from the many comorbid conditions already discussed, FM may present similarly to a number of disorders or concurrently with other disorders that may confuse the diagnosis. Hypothyroidism and polymyalgia rheumatica can be differentiated from FM by results of thyroid-stimulating hormone level and erythrocyte sedimentation rate. Sleep apnea, Chiari malformation, celiac sprue, and hepatitis C also simulate FM and tend to present more often in men than women.

TREATMENT

Progress in the understanding of FM has led to more therapeutic options for patients with this condition. Investigators are examining the utility of newer medications as well as nonpharmacologic interventions in controlled trials. It is important to use symptom-based pharmacologic therapy together with nonpharmacologic therapies because medications typically target symptoms, whereas nonpharmacologic treatments target dysfunction and functional decline (Fig. 80.5).⁶⁹

Diagnostic labeling

Once a physician rules out other potential disorders, an important and at times controversial step in the management of FM is asserting the diagnosis. Despite some assumptions that being labeled with FM may adversely affect patients, many studies have now suggested that this is not typically the case, in part because individuals stop looking for the cause of their pain and therefore see fewer subspecialists and undergo less diagnostic testing once they are diagnosed with FM.⁷⁰ Nonetheless, in certain select individuals, such as adolescents or young adults or overtly anxious persons, the preferred route may still be to avoid a label. Regardless, confirmation of the diagnosis ideally should be coupled with patient education, an intervention shown to be effective in randomized controlled trials.

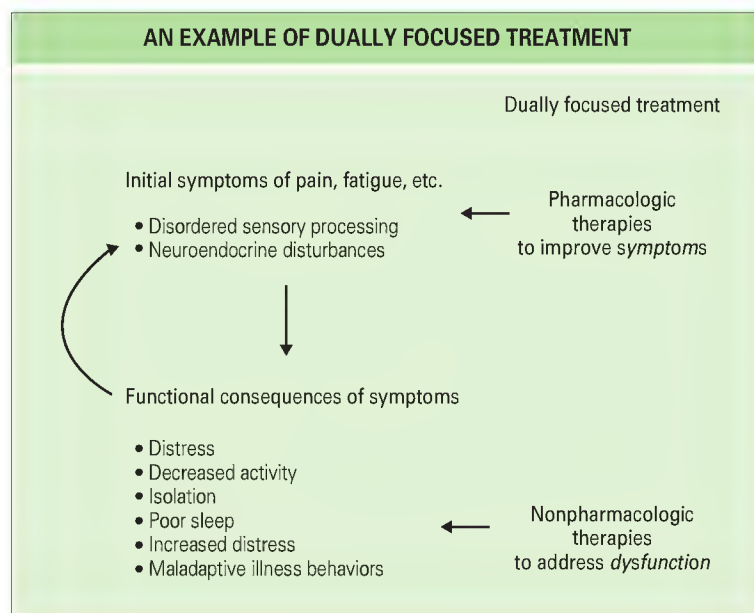


Fig. 80.5 An example of dually focused treatment.

Pharmacologic therapy

The majority of clinical trials in FM have examined the use of antidepressants of one class or another. Trials studying the oldest class of agents, tricyclic antidepressants (TCAs), are most abundant, although several recent studies have focused on selective serotonin reuptake inhibitors and atypical antidepressants, a class that includes dual reuptake inhibitors and monoamine oxidase inhibitors.

Tricyclic antidepressants

The most frequently studied pharmacologic therapy for FM is low doses of tricyclic compounds. Most TCAs increase the concentration of serotonin and/or norepinephrine (noradrenaline) by directly blocking their respective reuptake. The effectiveness of TCAs, particularly amitriptyline and cyclobenzaprine, in treating the symptoms of pain, poor sleep, and fatigue associated with FM is supported by several randomized controlled trials.⁷¹ Tolerability is a problem but can be improved by beginning at very low nighttime doses (e.g., 10 mg of amitriptyline or 5–10 mg of cyclobenzaprine), giving the dose a few hours before bedtime, and very slowly escalating the dose. Very-low-dose cyclobenzaprine has recently been shown to be quite effective in a subset of individuals with FM who have a specific sleep architecture, and seemingly causes fewer adverse effects than seen in some of the earlier studies using higher dosages.⁷²

Serotonin and norepinephrine reuptake inhibitors

Because of their better adverse effect profile, a newer class of antidepressants—the selective serotonin reuptake inhibitors (SSRIs)—is frequently used in FM. The SSRIs fluoxetine, citalopram, and paroxetine have all been evaluated in randomized placebo-controlled trials.⁷³ In general, the results of studies of SSRIs in FM have paralleled the experience in other pain conditions. The newer highly selective serotonin reuptake inhibitors such as citalopram seem to be less efficacious than the older SSRIs, which have some noradrenergic activity at higher dosages.⁷⁴

Because TCAs and high dosages of certain SSRIs such as fluoxetine and sertraline that have the most balanced reuptake inhibition are the most effective analgesics, many have concluded that dual-receptor inhibitors such as serotonin-norepinephrine and norepinephrine-serotonin reuptake inhibitors (SNRIs and NSRIs) may be of more benefit than pure serotonergic drugs.⁷⁴ These drugs are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both serotonin and norepinephrine but are differ from TCAs in being generally devoid of significant activity in other receptor systems. This selectivity results in diminished adverse effects and enhanced tolerability. Some data are available for venlafaxine, the first available SNRI, to support its use in the management of neuropathic pain, but studies in FM have yielded conflicting results.

Two newer SNRIs, duloxetine and milnacipran, have undergone recent multicenter trials and were shown to be effective in terms of a number of outcome variables; both are now approved in the United States for the treatment of FM.^{75,76} These drugs seem roughly comparable in overall efficacy profile, with studies generally noting modest improvement (although not reaching statistical significance in all studies) in domains such as pain, overall improvement, physical functioning, level of fatigue, and degree of reported physical impairment. For both compounds these effects seemed to be independent of the drug's effect on mood, which suggests that the analgesic and other positive effects of this class of drugs in FM is not simply due to their antidepressant effects. Both of these drugs are better tolerated if taken with food; patients should be warned about likely initial nausea, counseled that this typically resolves in a week or so, and told to discontinue the drug if the nausea persists. The maximum approved dosage of duloxetine is 60 mg/day, but it was studied in trials at doses of up to 120 mg and shown to be safe. Similarly, the initial dose of milnacipran is 100 mg/day, but some patients benefit from increasing the dose as high as 200 mg. Hypertension is more likely to be a problem with milnacipran because it appears to be more noradrenergic; for the same reason it might be slightly more likely to help with symptoms such as fatigue.

Esreboxetine, a selective norepinephrine reuptake inhibitor, was also tested and shown to be efficacious in treatment of FM.⁷⁷ This finding adds to emerging evidence suggesting that norepinephrine reuptake activity may be much more important than serotonergic reuptake for analgesic effects.

Other drugs acting on the central nervous system

Some antiepileptic drugs have been shown to be effective in the treatment of various chronic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy. Pregabalin and gabapentin have the same mechanism of action and bind to the $\alpha_2\delta$ subunit of calcium channels, and both are approved for the treatment of neuropathic pain as well as several

other indications. Several studies have shown the efficacy of pregabalin against pain, sleep disturbances, and fatigue compared with placebo in FM; as a result pregabalin was the first drug approved in the United States for use in this condition.⁷⁸ Gabapentin has been shown to have very similar efficacy and adverse effect profile in FM. The tolerability of these drugs can be dramatically enhanced by beginning at a low dose, and giving either two thirds of the dose or the entire dose at bedtime. The maximal approved dosage of pregabalin is 450 mg/day, but in trials it was studied at dosages as high as 600 mg/day and was shown to be safe and efficacious. The dosage of gabapentin needed for analgesic effect is often 1800 to 2400 mg/day. Another antiepileptic compound, clonazepam, has demonstrated efficacy in treating temporomandibular disorder and associated jaw pain; it is also useful in the treatment of restless leg syndrome and may be of value in FM.

Sedative-hypnotic compounds are widely used by FM patients. A handful of studies has been published on the use of certain nonbenzodiazepine hypnotics such as zopiclone and zolpidem in FM. These reports have suggested that these agents can improve the sleep and perhaps the fatigue level of FM patients, although they had no significant effects on pain.

On the other hand, γ -hydroxybutyrate (also known as *sodium oxybate*), a precursor of GABA with powerful sedative properties, was recently shown to be quite efficacious in improving fatigue, pain, and sleep architecture in patients with FM.⁷⁹ Note, however, that this agent is a scheduled substance due to its abuse potential and was not approved by the U.S. Food and Drug Administration (FDA) because of safety concerns. Nonetheless, these studies along with the H-MRS findings showing low GABA suggest that other less toxic GABA agonists may have an important role in treating FM.

Cannabinoids are another class of drugs in which there is renewed interest for treatment of chronic pain states. There have been two randomized controlled trials examining the use of synthetic cannabinoids in FM (both using nabilone), and both studies concluded that the drug was efficacious (in one study for improvement of both pain and sleep, in the other study at a lower dose just for sleep improvement).⁸⁰ This is not surprising because there is increased recognition that this class of drugs may have utility in treating pain of neural origin.

Pramipexole is a dopamine agonist indicated for Parkinson disease that has shown utility in the treatment of periodic leg movement disorder. One study suggested that this compound may improve both pain and sleep in FM patients, but these results have not been replicated with this or other dopamine agonists. Because of this, this class of drug may be best reserved for individuals with other indications, such as concurrent restless legs syndrome.

Tizanidine is a centrally acting α_2 -adrenergic agonist approved by the FDA for the treatment of muscle spasticity associated with multiple sclerosis and stroke. Literature suggests that this agent is a useful adjunct in treating several chronic pain conditions, including chronic daily headaches and low back pain. A randomized controlled trial examining the use of this drug in FM showed significant improvements in several parameters including sleep and pain, and treatment with tizanidine resulted in a reduction in substance P levels in the CSF of patients with FM.

Analgesics

There have been no adequate randomized, controlled clinical trials examining the use of opiates in FM, and most in the field (including the author) have not found this class of compounds to be effective in anecdotal experience. Tramadol is a compound that has some opioid activity (weak μ agonist activity) combined with serotonin-norepinephrine reuptake inhibition. This compound does appear to be somewhat efficacious in the management of FM, as both an isolated compound and in fixed-dose combination with acetaminophen.

In addition to the previously cited mechanistic studies suggesting why opioids might not be effective in FM (i.e., PET evidence of decrease opioid receptor availability, and high CSF levels of endorphins), recent functional and chemical imaging studies by the same group suggest an even more important potential problem. In these studies there is evidence that the native state of FM may be akin to that of opioid-induced hyperalgesia, in that the regions with the lowest receptor occupancy are the most hyperalgesic. Thus it is possible that in at least a subset of individuals, opioids may make the hyperalgesia worse rather than better. This notion is also supported by previously cited clinical studies suggesting that opioid antagonists may be effective in FM. If opioids are used in patients with refractory FM, it is possible that those opioids with mixed opioid antagonist effects (e.g., buprenorphine), norepinephrine reuptake inhibition (tapentadol), or NMDA receptor blockade (methadone) might be better than pure μ agonists, but this is entirely conjecture.

A large number of FM patients use NSAIDs and acetaminophen. Although numerous studies have failed to confirm their effectiveness as analgesics in FM, there is limited evidence that patients may experience enhanced analgesia when treated with combinations of NSAIDs and other agents. This phenomenon may be a result of the presence of concurrent peripheral pain conditions (due to damage or inflammation of tissues, e.g., osteoarthritis, rheumatoid arthritis) and/or worsening of central pain by these comorbid peripheral pain generators.

Neurostimulatory therapies

A variety of neurostimulatory therapies can be effective in treating musculoskeletal pain. For some time, transcutaneous electrical nerve stimulation (TENS) has been used to treat musculoskeletal pain. Conventional TENS (C-TENS) is given at a high stimulation frequency and low intensity. Pain relief is immediate, but short-lived, when it occurs. Acupuncture-like TENS (often abbreviated *AI-TENS*) is given at a lower frequency and higher intensity (which is sometimes uncomfortable), and when it works generally has a longer-lasting effect than C-TENS. These neurostimulatory therapies would be expected to be most helpful for pain of peripheral/nociceptive origin.

A new set of neurostimulatory therapies is emerging that would be expected to be more effective for centralized pain, because these therapies all aim to stimulate the CNS and, in doing so, modulate CNS pain transmission. Many such therapies have been developed and tested, with many showing some efficacy in treating several pain states. These include noninvasive techniques such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct-current stimulation (tDCS), and newer ways of noninvasively stimulating brain structures. Although the studies to date using these therapies have yielded somewhat inconsistent results, a trend is emerging suggesting that these treatments might be most effective in centralized rather than purely peripheral pain states, and with stimulation parameters that enable signals to travel into deeper cortical tissues than occurs with typical delivery of rTMS and tDCS. Other more invasive techniques, such as spinal cord stimulation, deep brain stimulation, and vagal nerve stimulation, have also shown promise in patients with more refractory pain states.

Other nonpharmacologic therapies

The two best-studied nonpharmacologic therapies are cognitive-behavioral therapy and exercise. Both of these therapies have been shown to be efficacious in the treatment of FM as well as a plethora of other medical conditions.^{69,81} Both of these treatments can lead to sustained improvements (i.e., longer than 1 year) and are very effective when an individual complies with the therapeutic regimen.

Complementary and alternative therapies have been explored by patients managing their own illness as well as by health care providers. As with other diseases, there are few controlled trials to advocate their general use. Trigger point injections, chiropractic manipulation, acupuncture, and myofascial release therapy are among the more commonly used modalities and achieve varying levels of success.

Sham-controlled trials of acupuncture in FM have generally showed no difference between active and sham treatments, but recent work in the acupuncture field suggests that there might be no such thing as an inert sham acupuncture site. A comparison group receiving usual care was not included in these studies in FM, and when this has been done in studies of other chronic pain conditions the effect of acupuncture typically exceeds that of usual care. The use of tai chi in FM has also been studied in several randomized controlled trials and appears to be effective in some individuals.

PROGNOSIS

The prognosis of FM depends largely on where the individual falls on a continuum. At one end of the continuum are individuals in the population with CWP or individuals with FM who are seen in primary care, and the prognosis in these individuals is reasonably good. On the other end are individuals with FM seen in tertiary care settings, who do quite poorly. In this latter group, studies have found little change in symptoms over time, and no significant change in health satisfaction, symptoms, or functional disability.

With regard to function in FM, studies have reported varying disability rates ranging from 9% to 44%. Disability has been most strongly associated with functional and work status, pain, mood disturbances, coping ability, depression, pending litigation, and educational background.

SUMMARY

Much has been learned about chronic pain by studying FM. FM is now viewed as the prototypical central pain syndrome, occurring primarily because of spinal and supraspinal mechanisms involved in pain transmission, rather than because of peripheral inflammation or damage, or nerve damage. The same mechanisms that lead to centrally mediated pain also lead to other somatic symptoms such as fatigue and insomnia, likely because similar neurotransmitter imbalances can also cause these symptoms. Because of this, any patient with chronic pain, especially widespread multifocal pain that is accompanied by other somatic symptoms and syndromes, should be considered as possibly having comorbid FM or an element of FM (see Fig. 80.4).

Wolfe and coworkers¹³ have clearly demonstrated that FM is *both* a discrete illness (i.e., in an individual with FM) *and* the end of a continuum

of pain processing. Wolf has performed seminal work in showing that the degree of fibromyalgia-ness in an individual with any rheumatic disorder (including individuals with osteoarthritis, rheumatoid arthritis, regional pain syndromes, etc.), as measured by his Symptom Inventory, is closely correlated with the individual's level of pain and/or disability, even if the person does have a peripheral cause for the pain. The Symptom Inventory (or other measures of the current or lifetime level of somatic symptoms or somatization) is a very good measure of whether an individual has an illness on this spectrum or an element of central sensitivity, regardless of the presence or absence of a peripheral cause for the pain. A better understanding of the underlying mechanisms and most effective treatment for this spectrum of illness is critical to rheumatologists because, as Wolfe has taught us, many patients with rheumatic disorders have a little, or a lot, of fibromyalgia-ness.

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81

Entrapment neuropathies and compartment syndromes

■ BANSARI GUJAR ■ RAYMOND H. FLORES

- An entrapment neuropathy results from increased pressure on a nerve as it passes through an enclosed space.
- Knowledge of the anatomy of each potential site of entrapment is essential for an understanding of the clinical manifestations of these syndromes.
- Conservative measures such as splinting, nonsteroidal antiinflammatory drugs, and local corticosteroid injections usually suffice when the symptoms are mild and of short duration. Surgical procedures to decompress the nerve are indicated for more severe cases.

INTRODUCTION

Entrapment neuropathy results from increased pressure on a nerve as it passes through an enclosed space. Nerves are most vulnerable as they traverse a fibroosseous canal because of disproportionate contents and capacity. Familiarity with the anatomy of each site is essential to completely understand the manifestations of each syndrome.

The signs and symptoms that accompany nerve entrapment may at times be subtle and easily confused with those of rheumatic disorders. In addition, rheumatic diseases that manifest synovitis or tenosynovitis are capable of causing compression neuropathy. Because entrapment neuropathies produce focal neurologic deficits, other conditions that can exhibit similar patterns (e.g., vasculitis, radiculopathy, reflex sympathetic dystrophy) must be included in the differential diagnosis.

Neural entrapment can occur at many sites (Table 81.1). This chapter focuses on the compressive neuropathies most often encountered in clinical practice.

THORACIC OUTLET SYNDROME

Thoracic outlet syndrome (TOS) results from compression of one or more of the neurovascular elements that pass through the superior thoracic aperture. Neurogenic entrapment accounts for the majority of the symptoms. In those relatively rare cases with clear-cut involvement of the brachial plexus, the disorder is referred to as true neurogenic TOS. Nonspecific or disputed TOS refers to patients with more poorly defined pain syndromes.¹

Anatomy

The thoracic outlet consists of several narrow channels through which the subclavian vessels and the lower trunk of the brachial plexus (eighth cervical and first thoracic fibers) pass from the thoracocervical region to the axilla (Fig. 81.1). The first area of narrowing and potential entrapment is between the scalenus anterior and medius muscles as they attach to the first rib. Next is the costoclavicular space, which is bordered by the clavicle anteriorly, the first rib posteromedially, and the superior margin of the scapula posterolaterally. Finally, the neurovascular bundle travels under the coracoid process and beneath the pectoralis minor tendon.

Etiology

Because the thoracic outlet has three well-defined areas of narrowing, traditional teaching has ascribed specific clinical syndromes to each area. Thus,

a fairly rigid classification has evolved that includes the anterior scalene, costoclavicular, and hyperabduction syndromes. However, it is more likely that anatomic abnormalities and trauma involving the shoulder girdle region have a far more pivotal role in causing this syndrome.

Cervical ribs, some incomplete with fibrous attachments to the first rib, are an anomaly often associated with true neurogenic TOS. Some have suggested that too much significance has been placed on this finding because cervical ribs may be noted on up to 0.5% of routine radiographs. Furthermore, abnormal anatomy of the thoracic outlet—and in particular the presence of fibrous bands—is a common finding in the general population.² The congenital bands may arise from a cervical rib or from the transverse process of the seventh cervical vertebra, or they may be associated with the scalene muscles. These cervical bands and certain scalene muscle abnormalities appear to play an important part in the pathogenesis of neurogenic TOS.³

Clinical features

Paresthesias are common and follow the ulnar nerve distribution along the medial aspect of the arm and forearm and then distally to the fourth and fifth fingers. Aching pain radiating to the neck, shoulder, and arm is a frequent complaint and is often more diffuse than the paresthesias. Carrying heavy objects, persistent abduction of the shoulder, and work that requires overhead use of the arms may exacerbate these symptoms. TOS is also more likely to occur in individuals with poor posture and drooping shoulders.

Signs of motor weakness, if they appear, usually follow the sensory complaints. Patients may describe a feeling of weakness or clumsiness when using the hand. Wasting of the thenar, hypothenar, and intrinsic muscles of the hand is indicative of true neuropathic TOS.

A small number of patients have vasomotor disturbances, which may take the form of coldness, blanching, or cyanosis. In more extreme cases, trophic changes and even infarction of tissues at the fingertips may appear.⁴

Diagnosis

The most useful diagnostic approach to TOS is a careful physical examination, which may reveal tenderness over the brachial plexus, sensory deficits, motor weakness, or signs of muscle atrophy. Certain clinical stress tests have traditionally been used to diagnose TOS. The Adson, costoclavicular, and hyperabduction maneuvers (Figs. 81.2 to 81.4) are used. However, because these maneuvers are positive in the majority of normal individuals (a reduction in the radial pulse), they have diagnostic utility only when the patient's sensory symptoms are reproduced.

A radiograph of the cervicothoracic region may reveal a cervical rib or an elongated transverse process of C7, a clue to the presence of a fibrous band. The anatomy of the thoracic outlet can be well visualized with magnetic resonance imaging (MRI). Functional imaging can now be obtained with open-magnet MRI.⁵ With this technology one can assess compression of the brachial plexus by measuring the distance between the clavicle and first rib while the arm is in abduction.

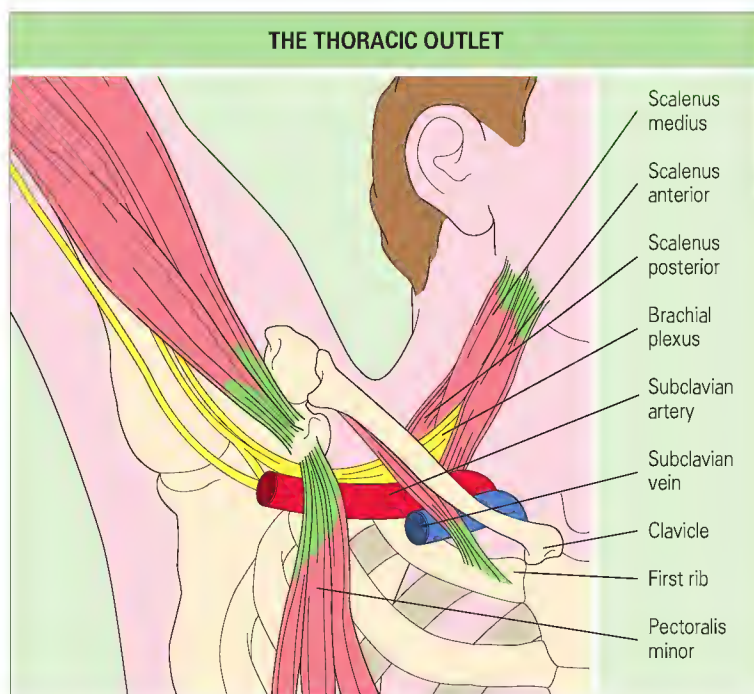
Nerve conduction studies may be helpful in diagnosing true TOS but may not be revealing in disputed TOS. The differential diagnosis of disputed TOS should include other cervical lesions (tumors, disk disease, spondylosis) and reflex sympathetic dystrophy; in patients with vascular signs, other disorders of vessels should be considered (e.g., vasculitis and atherosclerosis).

Treatment

Initial management is conservative, especially when the symptoms are subjective, and consists of appropriate exercises designed to improve posture

TABLE 81.1 Peripheral entrapment neuropathies

	Nerve	Location/syndrome
Upper extremity and thorax	Brachial plexus	Thoracic outlet
	Dorsal scapular	Scalenus medius
	Suprascapular	Scapular notch
	Musculocutaneous	Elbow
	Radial	Posterior interosseous nerve syndrome
	Median	
	At elbow	Ligament of Struthers
	At forearm	Pronator teres
	At wrist	Carpal tunnel syndrome
	Anterior interosseous	Forearm
	Ulnar	
	At elbow	Cubital tunnel syndrome
	At wrist	Ulnar tunnel syndrome
Lower extremity	Obturator	Pelvis
	Sciatic	Piriformis syndrome
	Ilioinguinal	Lower part of abdomen
	Lateral femoral cutaneous	Meralgia paresthetica
	Femoral	Hip
	Peroneal	Fibular tunnel
	Saphenous	Hunter canal
	Sural	Lower part of leg
	Posterior tibial	Tarsal tunnel syndrome
	Interdigital plantar	Morton metatarsalgia

**Fig. 81.1** The three narrow channels of the outlet include the scalene triangle, the costoclavicular passage, and the pectoralis minor attachment at the coracoid process.

by strengthening the rhomboid and trapezius muscles. Avoidance of hyperabduction is important, and patients may have to consider changing occupation if their job requires prolonged use of their arms above the head.

It must be remembered, however, that carpal tunnel syndrome (CTS) may be manifested as pain radiating to the shoulder region and thus may be confused with TOS.⁶ Accordingly, distal nerve entrapment should be excluded before definitive therapy for TOS is considered.

Careful screening of patients is crucial before surgery since a large number of treatment failures have been reported in patients with the common or disputed forms of neurogenic TOS and because the brachial plexus is at risk for injury during surgery. Indications for surgery include true neurogenic TOS as evidenced by abnormal results on nerve conduction studies, intrinsic hand muscle atrophy, and the presence of a fibrous band or cervical rib, intermittent fleeting paresthesias replaced by continuous

**Fig. 81.2** The Adson maneuver. The patient inhales deeply, extends the neck fully, and turns the head to the side being examined. This tests for compression in the scalene triangle and is positive if the radial pulse diminishes and the patient's symptoms are reproduced.**Fig. 81.3** The costoclavicular maneuver. The patient takes an exaggerated military position of attention with the shoulders thrust backward and downward. A decreased radial pulse and reproduction of symptoms suggest neurovascular compression between the clavicle and first rib.

sensory loss, incapacitating pain, or worsening circulatory impairment (if present).³

Because it is often difficult to define the exact anatomic area of compression preoperatively, success rates of particular surgical procedures are, not surprisingly, quite variable. The transaxillary approach with first rib resection has many proponents. This method is useful for costoclavicular compression. Others prefer supraclavicular exploration with division of the scalenus anterior muscle and resection of the first rib.⁷ In either case, the surgeon must also search for constricting fibrous bands.

ULNAR NERVE COMPRESSION SYNDROMES

Cubital tunnel syndrome

Compression neuropathy of the ulnar nerve as it traverses the elbow has long been recognized as a complication of local trauma, particularly



Fig. 81.4 The hyperabduction maneuver. The patient lifts the hands above the head with the elbows somewhat flexed and extending out laterally from the body. This maneuver tests compression by the pectoralis minor at the coracoid process.

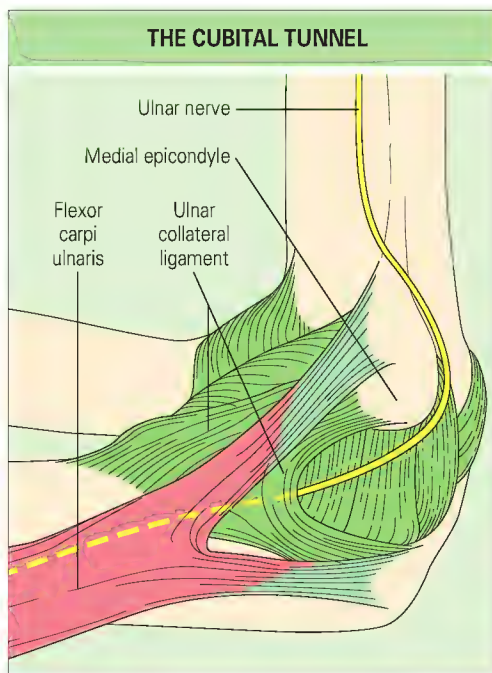


Fig. 81.5 The fibroosseous canal is formed by the medial epicondyle, the ulnar collateral ligament, and the flexor carpi ulnaris muscle. Elbow flexion decreases the volume of the channel.

fractures of the humerus. Only in recent years has the concept of constriction of the nerve in a fibroosseous tunnel been suggested.⁸

Anatomy

The osseous portion of the cubital tunnel is formed anteriorly by the medial epicondyle, laterally by the fibrous portion of the ulnohumeral ligaments, and posteromedially by the aponeurosis of the two heads of the flexor carpi ulnaris (Fig. 81.5). The size of the tunnel is reduced when the elbow is placed in flexion.

Etiology

Factors contributing to cubital tunnel syndrome include trauma, chronic pressure over the ulnar groove by occupational stress or unusual positioning of the elbow, synovitis, or osteophytes causing compression.

Clinical features

Paresthesias are noted in the distribution of the ulnar nerve, and in many instances the neuropathy is bilateral. The symptoms are often aggravated by prolonged use of the elbow in a flexed position. The Tinel sign may be positive over the ulnar groove, and pain may be provoked by placing pressure directly on the nerve, which may be noticeably swollen. A majority of patients will demonstrate atrophy of the intrinsic muscles and weakness in pinch and grasp. Wasting of the hypothenar muscles and slight clawing of the fourth and fifth fingers may be noted. A positive Wartenberg sign indicates weakness in adduction of the fifth finger.

Diagnosis

Consideration must be given to compression of the ulnar nerve at other locations, including the cervical spine, thoracic outlet, and Guyon canal (see later). Also, cubital tunnel syndrome must be differentiated from tardy ulnar palsy, in which neuropathy develops years after an injury.

Radiographs may be helpful in defining the cubital tunnel area and may reveal lesions such as osteophytes, which may impinge on the nerve. Electrodiagnostic studies are useful in establishing the site of ulnar compression and in monitoring recovery after treatment. The readily accessible location of the entrapment area allows direct testing of sensory and motor conduction across the cubital tunnel. High-resolution ultrasonography and MRI can accurately demonstrate ulnar nerve thickening as a result of entrapment.^{9,10}

Treatment

When the symptoms are primarily sensory and motor weakness is not marked, avoidance of prolonged elbow flexion may be sufficient. Compression resulting from inflammatory lesions, such as rheumatoid synovitis, may respond to local injection of corticosteroid along the ulnar groove while paying particular attention to avoid direct contact of the needle with the nerve.

In more advanced cases of cubital tunnel syndrome, a number of surgical procedures to decompress the nerve have been used, including simple release of the flexor carpi ulnaris aponeurosis, medial epicondylectomy, and anterior transposition of the nerve, the last being the most demanding operation. Simple decompression of the ulnar nerve is as effective as transposition and has fewer complications.¹¹ Because reinnervation of the nerve occurs slowly, in severe cases postsurgical recovery may take up to a year after a decompression procedure.

Ulnar tunnel syndrome

Ulnar tunnel syndrome results from entrapment of the ulnar nerve in the canal of Guyon at the wrist.¹² Many factors that affect the carpal tunnel can also influence the ulnar tunnel, which is in close proximity; at times, both areas are simultaneously involved.

Anatomy

The ulnar tunnel is bounded on the sides by the hook of the hamate and the pisiform bone. Above and below the tunnel are the volar and transverse carpal ligaments, respectively (Fig. 81.6). Inside the tunnel the ulnar nerve divides into sensory and motor branches.

Etiology

The most common cause of nerve compression in the canal of Guyon is a ganglion. Aberrant muscles, Dupuytren disease, rheumatoid arthritis (RA), and osteoarthritis may also cause impingement. Chronic trauma from the use of certain tools and occupations that require blows to the palm also predispose to ulnar tunnel syndrome.

Clinical features

When compression of the nerve occurs in the proximal portion of the ulnar tunnel, the patient will have combined sensory and motor deficits, hypoesthesia in the hypothenar region and fourth and fifth fingers (Fig. 81.7), and weakness of the intrinsic muscles of the hand. More distal lesions may be manifested as either motor or sensory impairment.

Diagnosis

Electrodiagnostic studies are helpful in determining the site of entrapment and in defining which branches are involved. Ulnar tunnel syndrome must be differentiated from TOS and CTS.

Treatment

If conservative measures such as avoidance of trauma to the palm do not result in improvement, surgical decompression may be necessary. When

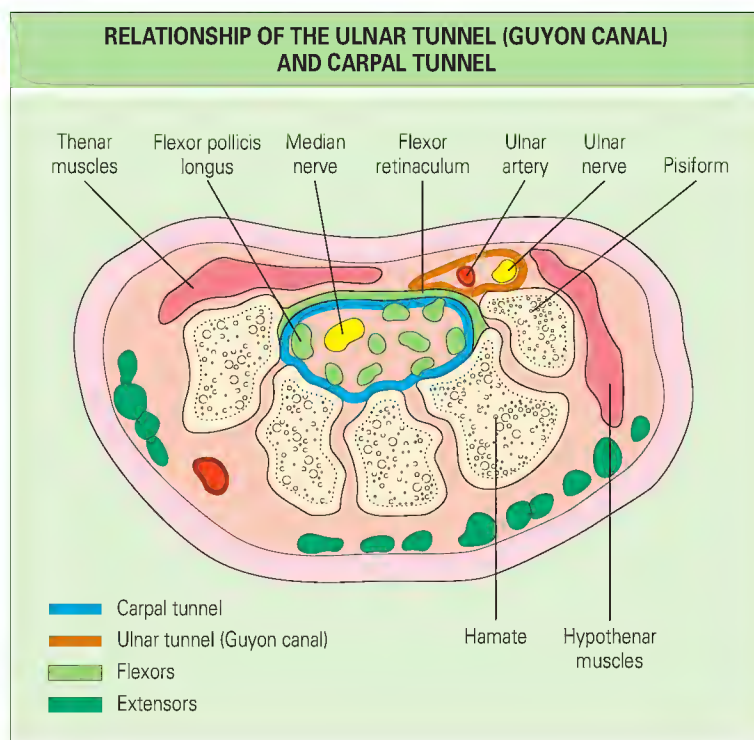


Fig. 81.6 Because of the close relationship of the ulnar tunnel to the carpal tunnel, pathologic processes affecting one may simultaneously affect the other.

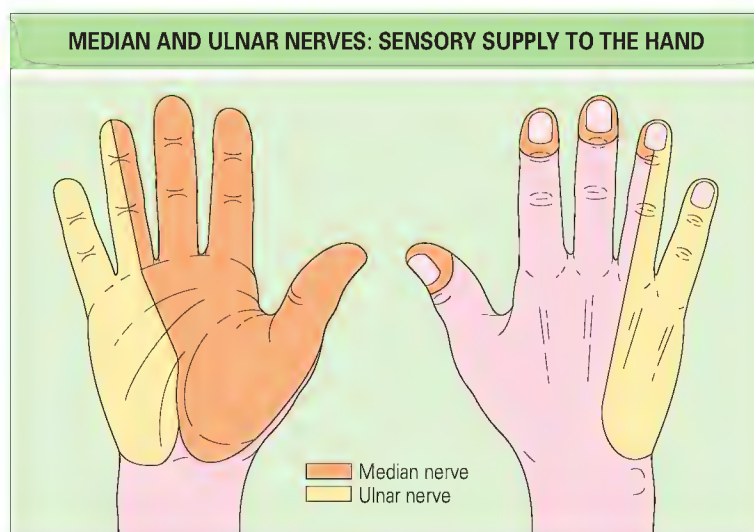


Fig. 81.7 The radial three digits and half of the ring finger are supplied by sensory branches of the median nerve. The fifth finger and half of the ring finger are supplied by sensory branches of the ulnar nerve.

entrapment is caused by ganglions, synovitis, or fibrosis, the offending tissue is excised.

MEDIAN NERVE COMPRESSION SYNDROMES (FOREARM ENTRAPMENT)

Anterior interosseous nerve syndrome

The anterior interosseous nerve (AIN) is a purely motor branch of the median nerve (Fig. 81.8). It innervates the pronator quadratus, the flexor pollicis longus, and the flexor digitorum profundus to the index finger. The nerve branches off from the median nerve about 6 cm below the lateral epicondyle. Entrapment may result from compression by aberrant or accessory muscles or fibrous bands beneath the pronator teres or by pressure from an enlarged bicipital bursa.

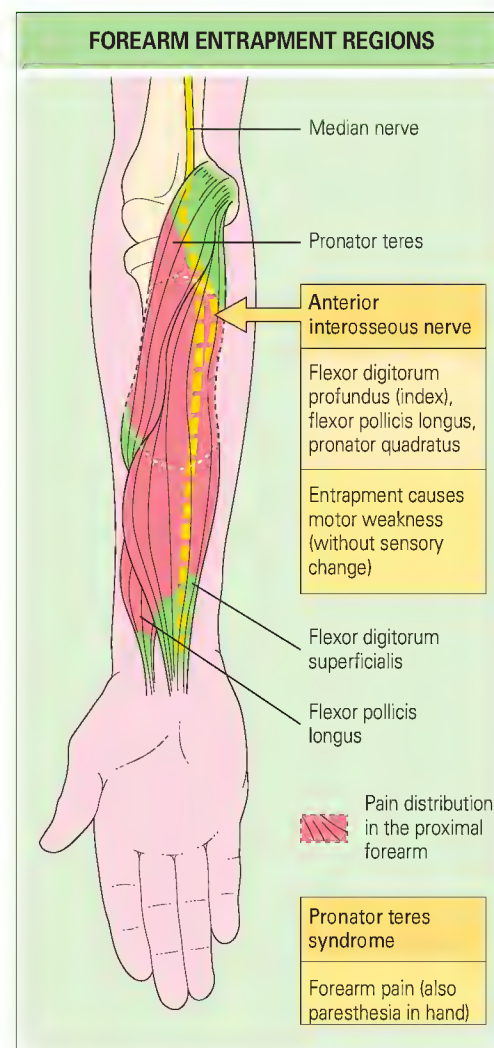


Fig. 81.8 The median nerve may be compressed at several locations in the forearm, most commonly as it traverses the pronator teres muscle. The anterior interosseous branch of the median nerve is solely motor; thus entrapment produces no sensory deficit.

Because the AIN does not have any sensory fibers, the patient has no sensory complaints and experiences only motor weakness. The typical pattern is loss of distal flexion of the thumb and index finger, which produces a characteristic pinch sign (Fig. 81.9). The pronator quadratus is tested with the elbow fully flexed. Resistance to forced supination of the forearm is decreased. The patient may also note a dull, aching pain in the volar aspect of the proximal part of the forearm.

Confirmation of AIN entrapment depends on electromyography (EMG) of the forearm muscles. Findings on MRI include increased signal intensity on T2-weighted or short tau inversion recovery sequences or atrophy of the innervated muscles (or both). The differential diagnosis for this syndrome should include rupture of the flexor pollicis longus tendon, which may occur with RA, and more proximal lesions such as brachial neuritis.

Because AIN syndrome improves with time in most patients, initial management is conservative unless the condition has been induced by a wound. The patient is advised to avoid repetitive forearm motion (pronation-supination). If the weakness does not resolve after 2 or 3 months, surgery is usually recommended.¹³

Pronator teres syndrome

The median nerve can become entrapped in the forearm at several potential sites (see Fig. 81.8). It may occur at the lacertus fibrosus, at the proximal edge of the flexor digitorum superficialis, or most commonly, by the pronator teres muscle itself or fibrous bands at the superficial head of this muscle.

The most consistent symptom in pronator teres syndrome is aching pain in the proximal part of the forearm, which often begins insidiously. The pain may be exacerbated by activities that require intensive use of the elbow, including pronation and grasping. Paresthesias are common and follow the median nerve distribution into the hand (see Fig. 81.7). Because the sensory



Fig. 81.9 Anterior interosseous nerve paralysis. The hand on the left demonstrates loss of function of the flexor pollicis longus and flexor digitorum profundus muscles, which results in a characteristic flattened pinch pattern.

findings are similar to those of CTS, the two conditions may be confused. However, unlike CTS, nocturnal paresthesias are less frequent in pronator teres syndrome.

Physical examination may reveal local tenderness on palpation over the pronator teres muscle. In addition, percussion in this area may elicit a positive Tinel sign with radiation of pain into the hand. A provocation test that may reproduce the pain involves pronation of the forearm and flexion of the wrist performed against resistance. Some thenar atrophy may be noted, but profound muscle weakness is rare.

In a study by Hartz and colleagues,¹⁴ electrophysiologic testing was often inconclusive and could not be relied on to exclude pronator teres syndrome. The differential diagnosis of pronator teres syndrome should include CTS and more proximal nerve lesions at the cervical spine or thoracic outlet. However, with thoracic outlet lesions the pain usually radiates into the ulnar rather than radial portion of the hand. There are few reports of effective imaging in this syndrome.

For some patients, sufficient treatment may be avoidance of provocative activities. Surgical decompression is performed when the symptoms become chronic.

CARPAL TUNNEL SYNDROME

CTS is the most common entrapment neuropathy. The syndrome has gained increased recognition in recent years because of the prominent attention that it has received in certain industrial settings, and it is now one of the most commonly reported occupational illnesses.

Anatomy

The carpal tunnel is bounded on its dorsal and lateral surfaces by the carpal bones and their connecting ligaments and on the volar or anterior aspect by the transverse carpal ligament (Fig. 81.10). Nine flexor tendons and the median nerve pass through the tunnel. The median nerve may become entrapped in two ways: pressure may be exerted on the nerve as a result of reduced capacity of the carpal tunnel, as occurs with swelling or lesions of surrounding tissues, or as a result of an increase in volume of the contents of the tunnel, an example being flexor tenosynovitis. Increased intracarpal canal pressure in patients with CTS has been confirmed by use of a wick catheter measuring device.¹⁵

Etiology

CTS has many causes (Table 81.2), but in some patients an underlying disease process cannot be identified and the designation “idiopathic CTS” is used. Because of increased awareness of certain occupational risk factors and the availability of sophisticated diagnostic techniques, an attributable cause of CTS can now often be found.

CTS is noted most commonly in persons whose occupations require substantial use of the hands. Workers who spend long hours using a keyboard, musicians who keep the wrist in a flexed position, and meat cutters are all especially susceptible to the development of CTS.

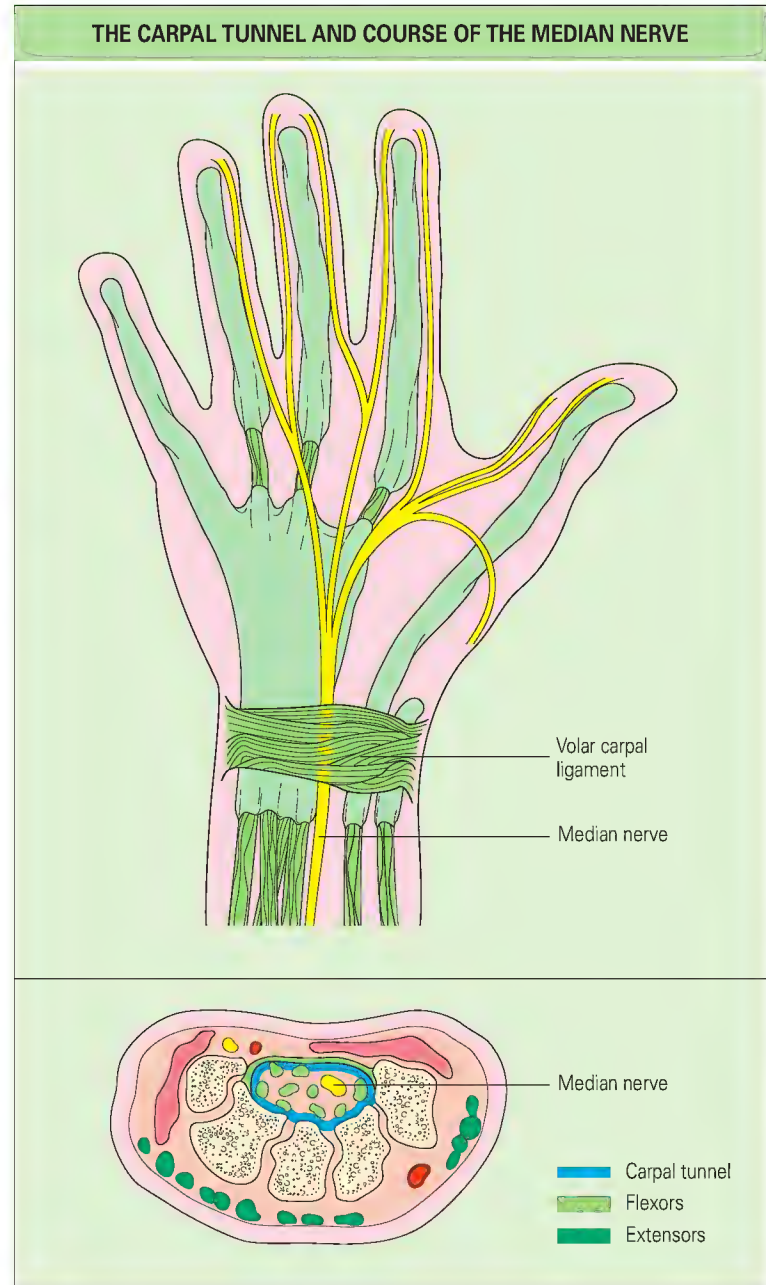


Fig. 81.10 The space for the median nerve and flexor tendons is very confined. The median nerve courses under the region occupied by the palmaris longus and flexor carpi radialis tendons.

Crystal-induced rheumatic disorders have been known to cause CTS. In the case of gout, tophaceous deposits or tenosynovitis may result in nerve entrapment. CTS is reported as a complication of several connective tissue diseases, including systemic sclerosis, polymyositis, polymyalgia rheumatica, and most commonly, RA. Indeed, prolonged median nerve sensory conduction velocities have been noted in up to 50% of all RA patients tested.¹⁶ Generally, CTS is a result of rheumatoid flexor tenosynovitis. When the symptoms are mild, it may be difficult to differentiate the muscle atrophy noted in CTS from that associated with severe rheumatoid disease.

Uremia also predisposes patients to entrapment neuropathy. CTS is particularly common in hemodialysis patients,¹⁷ and in many of these cases it is the result of β_2 -microglobulin amyloid deposition. A number of metabolic and endocrine diseases may have CTS as one of their manifestations, including diabetes, myxedema, mucopolysaccharidosis, and acromegaly.

Infections involving the carpal bones or flexor tendons at the wrist may result in CTS. Such infections include chronic granulomatous infections caused by *Coccidioides*, *Histoplasma*, *Mycobacterium tuberculosis*, and atypical mycobacteria.

Familial occurrence of CTS has also been reported. In one family the mean age at onset of CTS was 24 years, and flexor tenosynovitis was the dominant finding.¹⁸ The onset of symptoms in familial CTS may even occur in early childhood.

■ **TABLE 81.2** Conditions associated with carpal tunnel syndrome

Space-occupying lesions	Ganglion
	Hemangioma
	Osteoid osteoma
	Thickened transverse carpal ligament (familial)
	Anomalous muscles
Connective tissue disease	Tenosynovitis (nonspecific)
	Rheumatoid arthritis
	Osteoarthritis
	Progressive systemic sclerosis
	Polymyositis
Crystal-induced rheumatic disease	Polymyalgia rheumatica
	Gout
	Calcium pyrophosphate dihydrate disease
	Hydroxyapatite disease
Occupational disease (repetitive motion disorders)	Meat cutters
	Musicians
	Keyboard workers
Metabolic and endocrine disease	Diabetes
	Thyroid (myxedema)
	Acromegaly
	Mucopolysaccharidosis
Infection	Osteomyelitis (carpal bones)
	Tenosynovitis
	Tuberculosis
	Atypical mycobacterial infection
	Histoplasmosis
Iatrogenic	Coccidioidomycosis
	Hematoma
	Phlebitis
Miscellaneous conditions	Use of aromatase inhibitors
	Pregnancy
	Amyloidosis
	Dialysis
	Fractures

All varieties of amyloidosis—primary, secondary, hereditary, and associated with myeloma—may cause CTS. Lambird and Hartmann¹⁹ have shown that the transverse carpal ligament may appear grossly normal at the time of surgery and that if histologic stains for amyloid are not performed, the diagnosis of hereditary amyloidosis may be missed.

The development of CTS in pregnancy has been well documented. It has been attributed, by some, to fluid retention. In one series, 21% of pregnant women described paresthesias or hypoesthesia quite typical of CTS.²⁰ In the majority of patients, symptoms begin in the third trimester, usually resolve spontaneously after delivery, and do not require surgery.

A number of local space-occupying lesions may impinge on the contents of the carpal tunnel, including ganglions, hemangiomas, osteoid osteomas, and lipomas, as well as an anomalous median artery. Anomalous muscles may also compromise the carpal tunnel space. Most often this is caused by abnormalities of the palmaris longus, an extremely variable muscle that inserts on the transverse carpal ligament.²¹

Clinical features

Because the median nerve supplies sensory branches to the radial three fingers and half of the ring finger, these digits may have sensory loss with CTS (see Fig. 81.7). Typically, patients complain of burning, pins-and-needles sensations, numbness, and tingling in the fingers (Table 81.3). When questioned about the location of the paresthesias, many will indicate that the entire hand is involved. Only after careful examination does it become clear that the sensory abnormalities are limited to the area of the median nerve distribution.

In some cases pain may not follow the usual pattern of radiation in the median nerve distribution of the hand. Silver and colleagues²² found that 34% of patients with CTS also had signs of ulnar nerve compression. Proximal pain, often with a dull or aching quality, is also a common feature of CTS.⁶ Pain may radiate to the antecubital region or to the lateral shoulder area. Although the possibility of more proximal entrapment should be kept

■ **TABLE 81.3** Symptoms and signs of carpal tunnel syndrome

Symptom or sign	Percentage of patients*
Median paresthesias	100
Nocturnal paresthesias	71
Proximal extension of pain	38
Tinel sign	
Positive	55
Negative	29
Unknown	17
Phalen test	
Positive	53
Negative	23
Unknown	24
Sensation on sensory examination	
Decreased	28
Normal	36
Unknown	36
Thenar muscle strength	
Decreased	18
Normal	42
Unknown	41
Thenar muscle bulk	
Wasted	18
Normal	31
Unknown	50

*Data from 1016 patients.

Data from Spinner RJ, Bachman JW, Amadio PC. The many faces of carpal tunnel syndrome. *Maya Clin Prac* 1989;64:829-36.

in mind, the majority of patients experience improvement of symptoms after nerve decompression at the carpal tunnel.

Patients frequently complain of interruption of sleep because of paresthesias and often note that they shake their hands or run them under warm water to improve their symptoms.

Activities that result in persistent or repeated flexion or extension of the wrists are more likely to intensify the symptoms. Some patients report that they are more likely to drop objects, which they attribute to hand weakness. However, these individuals rarely have profound weakness on grip testing, and it is more likely that the problem stems from sensory deficit at the fingertips.

Tests

Testing for the Tinel sign consists of tapping lightly over the median nerve, and it is positive if the patient perceives paresthesia that radiates distally. Its diagnostic value depends largely on how the test is conducted. Mossman and Blau²³ found that to be effective, percussion must be performed with the patient's wrist in extension so that the carpal tunnel is compressed. They also noted that percussion with a fingertip or small neurology hammer is less effective than percussion with a broad-headed hammer, which can be used to percuss over the entire transverse carpal ligament and somewhat more proximally. The wrist flexion (Phalen) test is performed by having patients hold their wrists in extreme but unforced flexion for 1 minute. It is positive if the paresthesias are reproduced. As with the Tinel sign, the wrist flexion test is not invariably positive for CTS, but when it is, it helps substantiate the diagnosis.

Another provocative test for CTS is the carpal compression test, in which pressure is applied directly over the carpal tunnel and the underlying median nerve. Opinions are conflicting on whether it is more sensitive or specific than the Tinel or Phalen test. When compared with the "gold standard" of electrophysiologic testing, the carpal compression test appears to have only marginal predictive value.²⁴

To determine motor loss, the strength of the thenar muscles should be tested. The easiest muscle to test is the abductor pollicis brevis. With the thumb first adducted toward the fifth finger, the patient is asked to abduct against resistance to the distal phalanx. The opponens pollicis muscle is tested by having the patient touch the tip of the thumb to the tip of the fifth finger, and then the examiner attempts to break the pinch. Inspection of the hand may reveal atrophy of the thenar muscles (Fig. 81.11).



Fig. 81.11 Thenar muscle atrophy. Chronic entrapment of the median nerve in the carpal tunnel or more proximally may produce thenar atrophy.

Diagnosis

Diagnosis of CTS is based on the patient's history and clinical examination, but imaging and electrodiagnostic studies may be useful in confirming the diagnostic impression. Conventional radiographs using a carpal tunnel projection can help delineate the soft tissues and carpal bones. Increasingly, ultrasonography has been found to be very effective in diagnosing CTS.²⁵ Typically, it reveals swelling of the median nerve in the proximal end of the tunnel and flattening more distally. Some have even suggested that it should be the study of first choice, even before electrodiagnostic testing.²⁶ However, the anatomy of the carpal tunnel, thickening of the flexor tendon sheaths, or the presence of space-occupying lesions or aberrant muscle can be better visualized with MRI.²⁷

The most important electrodiagnostic study is measurement of sensory nerve conduction velocity (NCV) across the carpal tunnel. Slowed NCV, along with prolongation of distal motor latency, lends support to the diagnosis of CTS.

In about 15% of the population, fibers from the median nerve travel via the ulnar nerve to the thenar muscles: the Martin Gruber anastomosis. It is important to recognize this entity because it may result in sparing of the thenar muscles in patients with CTS. A clue to the presence of this anatomic variation is the finding of normal proximal latency but prolonged distal latency.

The differential diagnosis of CTS must include median nerve entrapment proximal to the carpal tunnel.⁴ As noted earlier, compression of the median nerve near the elbow, as found in pronator teres syndrome, may yield similar sensory findings.

Treatment

Specific treatment of CTS depends, to a large degree, on whether a cause of the entrapment can be identified. Conservative measures may suffice when the symptoms are of short duration. EMG repeated over time may help the clinician determine the correct therapeutic approach. Patients with progressive increases in distal motor latency times should be considered for surgery.

Splinting

Splinting is a simple and cost-effective modality that if successful in relieving the symptoms, helps confirm the diagnosis of CTS. Because wrist motion often worsens CTS, splinting is an important treatment element. A volar wrist splint that keeps the wrist in a neutral position is particularly helpful during the night, when the wrist often falls into a position of flexion. Splinting alone may be sufficient to relieve CTS, primarily in cases in which the symptoms are of recent onset.

Local injection of corticosteroid

Injection of corticosteroid into the carpal tunnel is another effective treatment in individuals whose disease is of shorter duration and who have no significant muscle wasting. The best response to injection occurs in patients whose symptoms have been present for less than 1 year and who have no significant muscle atrophy or weakness. A recent randomized, controlled trial that compared local corticosteroid injection with surgical decompression found that over the short term, injection provided better relief and was equal to surgery in alleviating symptoms at 1 year.²⁸

Before injection is attempted, certain landmarks should be identified, including the tendons of the palmaris longus and flexor carpi radialis

muscles. This is most easily accomplished by asking the patient to flex against resistance. Injection can be facilitated if the wrist is placed in slight extension. The needle is inserted ulnar (medial) to the palmaris longus tendon and proximal to the wrist crease. If the patient notes median nerve paresthesia during the injection, the needle should be withdrawn and repositioned to avoid injury to the nerve. Frequent injections are proscribed because of the danger of tendon rupture. Evidence for the use of ultrasound-guided techniques for injection of the carpal tunnel is increasing.^{29,30}

Nonsteroidal antiinflammatory drugs and other agents

The use of nonsteroidal antiinflammatory drugs (NSAIDs) is generally limited to patients with an underlying inflammatory lesion, such as tenosynovitis. Oral corticosteroids also appear to be an effective treatment of mild to moderate CTS.

Surgery

Surgical release of the transverse carpal ligament is the definitive treatment of more severe cases of CTS. Surgery is indicated when the response to conservative measures is inadequate, in patients with progressive or persistent neurologic changes, or when muscle atrophy is present. In patients with marked tenosynovitis, such as occurs with RA or granulomatous disease, simple decompression of the carpal tunnel may not be sufficient; additional tenosynovectomy with lysis of adhesions may be necessary. Furthermore, when infiltrating processes are present, such as amyloid deposits attached to tendons, the more complicated procedure of tenolysis may be necessary. Because tuberculosis and fungal infections are sometimes a cause of CTS, appropriate cultures and histologic studies should be undertaken at the time of surgery, particularly if tenosynovitis is noted. The traditional surgical approach of ligament sectioning via a palmar incision is increasingly being replaced by endoscopic release. However, this is controversial among hand surgeons because of the lack of strong evidence supporting this newer technique.³¹ Though equally effective, it must be performed with great care to avoid injury to the superficial palmar arterial arch or to the median or ulnar nerves.³²

Failure of surgery to relieve the symptoms is often the result of incomplete release of the ligament. Postoperative improvement depends in part on the severity of the initial nerve deficit. Although most patients' symptoms are ameliorated by surgery, individuals whose occupations require repetitive motion may need to be retrained for less hand-intensive work.

RADIAL NERVE COMPRESSION SYNDROME

Posterior interosseous nerve syndrome

Posterior interosseous nerve (PIN) syndrome is a well-recognized, but uncommon entity caused by compression of the radial nerve. The most common site of compression is at the level of the supinator muscle.³³

Anatomy

The radial nerve comes off the posterior branch of the brachial plexus (C5 through C8, T1), and it branches proximal to the lateral epicondyle into a superficial sensory branch and a deep motor branch. The deep motor branch pierces the supinator muscle and courses along the dorsal aspect of the interosseous membrane. The deep motor branch is called the *posterior interosseous nerve*.

Etiology

PIN syndrome can be caused by intrinsic as well as extrinsic lesions. Trauma, inflammatory processes such as RA, and space-occupying lesions may be causative.³⁴

Clinical features

Patients with PIN syndrome usually complain of forearm pain. Other patients describe weakness of the extensor muscles. If entrapment occurs at the level of the supinator, the radial wrist extensors innervated at this level will be spared because they branch off proximal to the PIN. Complete sparing of the extensor carpi radialis longus and frequent sparing of the extensor carpi radialis brevis occurs because they, too, branch off proximal to the PIN. As a result, the ulnar wrist extensors and the extensors of the metacarpophalangeal joints will be compromised. With attempted wrist extension, the wrist deviates radially in PIN syndrome. Because the extensor muscles of the fingers are affected, it is difficult to maintain the fingers in extension. PIN syndrome is not associated with any reflex or sensory loss.

PIRIFORMIS MUSCLE AND SCIATIC NERVE, POSTERIOR VIEWS

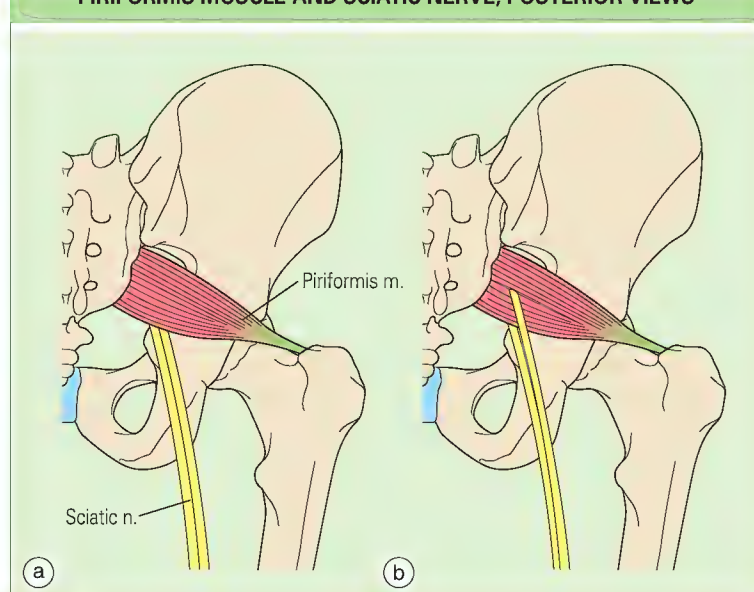


Fig. 81.12 The piriformis muscle arises from the anterior surface of the sacrum and the gluteal surface of the ilium and crosses the greater sciatic foramen to insert onto the superior border of the greater trochanter. (a) In most instances the sciatic nerve passes along the anterior surface of the piriformis muscle and exits the pelvis below the piriformis muscle while passing posteriorly along its inferior border. (b) In some individuals a portion of the sciatic nerve passes through the piriformis muscle. Other anatomic variants have been described.

Diagnosis

The differential diagnosis of PIN syndrome includes lateral epicondylitis and other chronic pain syndromes in the region of the elbow and forearm. Other diagnoses to consider in patients with wristdrop and fingerdrop include a central lesion or one in the posterior cord of the brachial plexus. Electrodiagnostic and imaging studies are useful in confirming the diagnosis of PIN syndrome and differentiating it from other causes.^{35,36}

Treatment

Treatment of PIN syndrome usually consists of conservative measures. Modalities such as splinting can be used. In patients whose symptoms do not resolve with conservative management, surgery is an option. PIN syndrome that results from compression by a tumor should be treated surgically.

PIRIFORMIS SYNDROME

Piriformis syndrome results from compression of the sciatic nerve by the piriformis muscle. This syndrome, though relatively uncommon and underdiagnosed, nevertheless accounts for a discrete portion of patients with buttock and sciatic-type pain.

Anatomy

As the sciatic nerve passes through the greater sciatic foramen, it is in close proximity to the piriformis muscle (Fig. 81.12). The muscle originates from the anterior surface of the sacrum and the gluteal surface of the ilium. After passing through the sciatic foramen, it inserts on the medial aspect of the greater trochanter. Usually, the sciatic nerve passes below the piriformis muscle, but in some cases a segment of the nerve or the entire nerve passes through the muscle.

Etiology

The leading cause of piriformis syndrome is thought to be trauma to the gluteal region with resultant inflammation and spasm of the muscle. This in turn leads to irritation of the sciatic nerve. When the nerve or a portion of the nerve passes through the muscle, nerve compression can occur with stretching of the muscle on internal hip rotation.

Clinical features

Typically, patients with piriformis syndrome complain of pain in the buttock region with radiation to the posterior aspect of the thigh. However, discomfort and paresthesias may occur along the entire course of the sciatic nerve. Pain may be induced by prolonged sitting or by stooping and lifting.

On physical examination, pain may be elicited by applying direct pressure over the gluteal region. Also, piriformis muscle tenderness or spasm may be noted on rectal or pelvic examination. Maneuvers that internally rotate, flex, and adduct the hip often cause aggravation of the pain because such motion stretches the piriformis muscle. With the patient seated, resisted abduction of the hip (the Pace sign) may also elicit pain.

Diagnosis

Included in the differential diagnosis of piriformis syndrome are conditions that result in sciatic nerve irritation, such as a herniated lumbar disk, spinal stenosis, or a pelvic lesion, but it is unusual for patients with piriformis syndrome to have neurologic defects. Thus, the diagnosis is often one of exclusion.

MRI is useful in detecting changes in the piriformis muscle and in defining its relationship to the sciatic nerve.³⁶ It is also a means of excluding mass lesions in the pelvic area, as well as spinal stenosis and disk herniation.

Treatment

Initial management of piriformis syndrome consists of conservative measures, including physical therapy, analgesics, and NSAIDs. Injection of corticosteroid or botulinum toxin directly into the piriformis muscle appears to benefit some patients.³⁷ Patients who do not respond to conservative therapy may be candidates for surgical intervention. The piriformis is released from its insertion on the femur to allow reattachment in a shortened position.³⁸

MERALGIA PARESTHETICA

The term *meralgia* has its roots in the Greek words for thigh (*meros*) and a painful condition (*algia*). Meralgia paresthetica is caused by entrapment of the lateral femoral cutaneous nerve. One of the earliest descriptions of this entity was by Sigmund Freud, who related the typical symptoms of meralgia paresthetica that he experienced.³⁹ Although meralgia paresthetica occurs primarily in adults, children may be affected, and there is often a significant delay in diagnosis.⁴⁰

Anatomy

The lateral femoral cutaneous nerve is entirely sensory and arises from the second and third lumbar roots. It proceeds from the lateral border of the psoas muscle, along the ilium, and passes under or through the lateral aspect of the inguinal ligament just medial to the anterior superior iliac spine, the most common site of entrapment (Fig. 81.13). The nerve travels down the anterior aspect of the thigh, where it divides into anterior and posterior branches. These branches supply sensation to the anterolateral portion of the thigh.

Etiology

Direct pressure from belts and other tight-fitting garments may contribute to entrapment of the nerve as it passes under the inguinal ligament. Workers who support heavy bundles on their thigh are also at risk. Several clinical conditions have been associated with the development of meralgia paresthetica, including obesity, pregnancy, diabetes, ascites, and trauma to the thigh or inguinal region. The neuropathy may also occur as a consequence of direct injury to the nerve during surgery in the pelvic region (e.g., appendectomy, inguinal herniorrhaphy, iliac bone procurement, bariatric surgery).

Clinical features

Patients with meralgia paresthetica typically complain of burning pain and dysesthesia in the sensory distribution of the nerve. However, a smaller area of sensory deficit is common. The patient may volunteer that certain positions seem to exacerbate the discomfort, such as sitting with the legs crossed, prolonged standing, or extending the leg posteriorly.

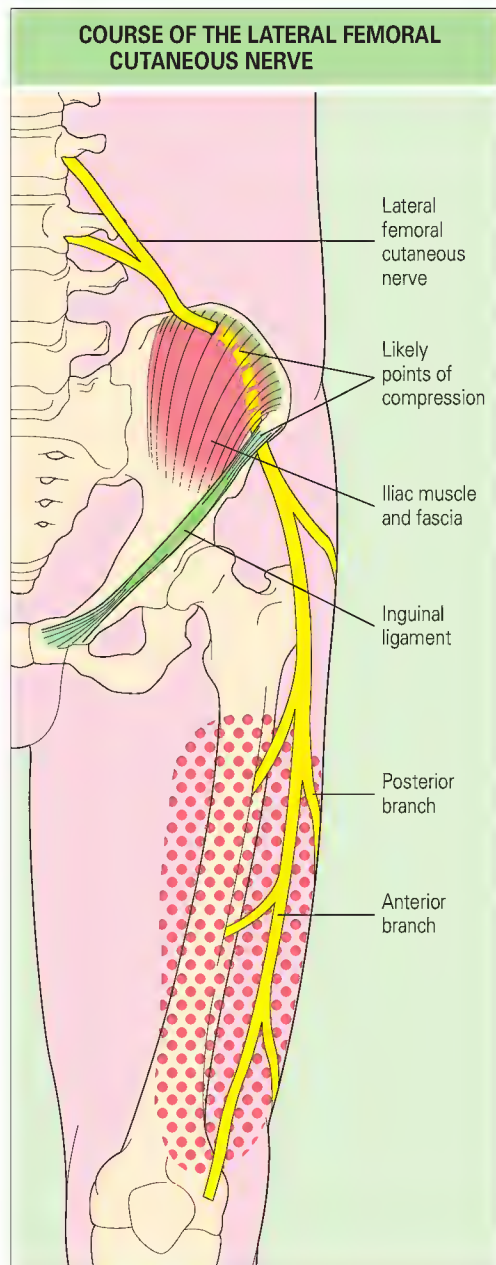


Fig. 81.13 The potential for entrapment of the lateral femoral cutaneous nerve can be seen by its course just under the inguinal ligament and medial to the anterior superior iliac spine.

Diagnosis

In the differential diagnosis of meralgia paresthetica it is important to consider the possibility that radiculopathy of the L2 or L3 nerve roots or spinal stenosis may be causing the symptoms. Some patients will report direct tenderness over the inguinal ligament.

Electrodiagnosis using superficial electrodes to measure NCV may be useful in confirming the diagnosis. Nerve block may also affirm the diagnosis in addition to offering pain relief.

Treatment

Because meralgia paresthetica is often self-limited, conservative measures should be used, possibly including weight reduction, elimination of occupational trauma, and avoidance of external mechanical pressure over the inguinal ligament. Local injection of anesthetic and corticosteroid may be useful, as may be NSAIDs.

If meralgia paresthetica becomes chronic and the pain unremitting, surgical decompression (neurolysis) or transection of the nerve may be considered.⁴¹ When it is of spinal origin, epidural corticosteroid injection may be helpful.

PERONEAL NERVE ENTRAPMENT

Anatomy

The common peroneal nerve (also known as the common fibular nerve) is derived from the dorsal branches of the fourth and fifth lumbar and the first and second sacral nerves. It descends obliquely along the lateral side of the popliteal fossa to the head of the fibula, close to the medial margin of the biceps femoris muscle. It lies between the tendon of the biceps femoris and the lateral head of the gastrocnemius muscle, winds around the neck of the fibula between the peroneus longus and the bone, and divides beneath the muscle into the superficial peroneal nerve and the deep peroneal nerve. It innervates the peroneus longus, peroneus brevis, and the short head of the biceps femoris muscle.

Etiology and clinical features

Compression of the common peroneal nerve occurs most commonly just below the knee as the nerve wraps around the lateral aspect of the fibula. It is usually caused by external pressure on the nerve, as during prolonged periods of lying down such as after surgery or prolonged hospitalization. Crossing the legs, squatting, and leg casts can also cause compression at this site. Occasionally, injury can occur in the popliteal fossa secondary to compression from a Baker cyst. Lipomas and ganglion cysts can also be factors in causing compressive symptoms. Several recent case series have looked at the relationship between significant weight loss and peroneal neuropathies in populations with cancer or anorexia nervosa and after bariatric surgery.⁴²⁻⁴⁴ Typically, patients have footdrop or a high-stepping gait to compensate for the inability to dorsiflex the affected foot. Patients may also complain of paresthesias and occasionally sensory loss over the dorsum of the foot and lateral aspect of the shin. The deep peroneal nerve can be injured in the region of the ankle as a result of a tight-fitting rim or strap from a shoe. Patients generally complain of pain in the region with minimal weakness and sensory disturbance involving only the web space between digits 1 and 2.

Diagnosis

On physical examination, patients are often unable to dorsiflex and evert the foot. Sensory disturbance is confined to the dorsum of the foot, including the web space between digits 1 and 2, and the lateral aspect of the shin. Reflexes are normal. EMG and NCV studies are very useful for identifying peroneal neuropathy at the fibular neck; conduction block may be identified on peroneal motor studies. Increasingly, ultrasound and MRI are being used as the imaging modalities of choice for peroneal neuropathies.⁴⁵⁻⁴⁷

Treatment

In patients with a peroneal neuropathy at the fibular neck, measures that reduce pressure, such as extra cushioning while sleeping and avoidance of crossing the legs during the day, are usually sufficient to alleviate the symptoms. An ankle-foot orthosis splint to keep the foot dorsiflexed should be used until active movement has recovered. Physical therapy consisting of active and passive range-of-motion exercises, as well as walking, is an important conservative measure. Surgical decompression can be considered for patients who do not recover on their own with the aforementioned measures.

TARSAL TUNNEL SYNDROME

Tarsal tunnel syndrome undoubtedly occurs more frequent than suggested by the isolated reports in the literature.⁴⁸ It is often mistaken for other disorders of the foot, and clinicians are less likely to include this entrapment neuropathy in the differential diagnosis of foot pain (see Chapter 78).

Anatomy

The tarsal tunnel is a fibroosseous canal formed by the flexor retinaculum (lacinate ligament) as it extends from the medial malleolus down onto the calcaneus (Fig. 81.14). The posterior tibial nerve passes through the tunnel along with vascular structures, tendons of the flexor hallucis longus, and the flexor digitorum longus muscle. Along its course the tibial nerve gives off calcaneal branches and then lateral and medial plantar branches (see Fig. 81.14). The calcaneal branches are solely sensory, but the plantar nerves have mixed motor and sensory function. Because the narrowest aspect of

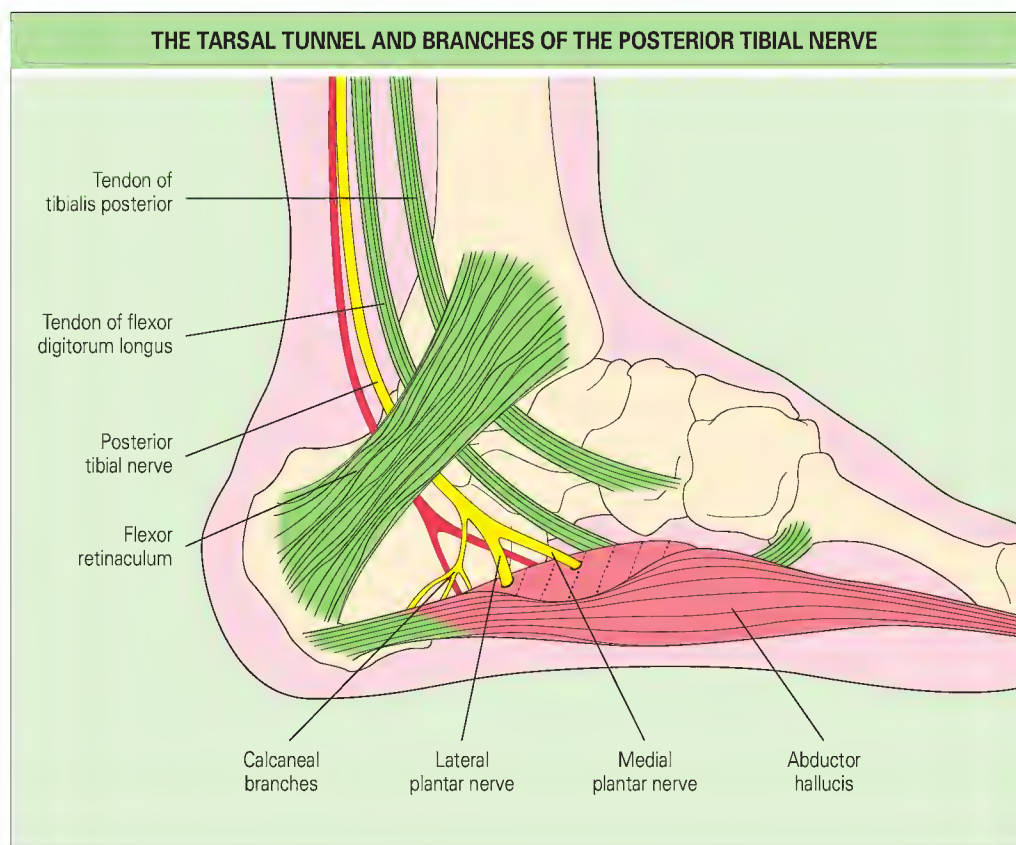


Fig. 81.14 Entrapment of branches of the posterior tibial nerve occurs under the flexor retinaculum, which attaches to the medial malleolus. Because the posterior tibial nerve has calcaneal and medial and lateral plantar branches, symptoms of entrapment will depend on which branches are affected.

the tunnel is the distal or anteroinferior portion, the plantar nerve branches are most likely to be entrapped at this location.

Etiology

A number of abnormalities have been reported to cause tarsal tunnel syndrome, including bone deformity after fractures, pressure from casts, hypertrophy of the lacinate ligament or the abductor hallucis muscle, flexor tenosynovitis, synovial cysts, ganglion cysts, and diabetes mellitus. The proliferative synovitis accompanying RA is also causative.

Clinical features

The signs and symptoms of tarsal tunnel syndrome depend on the level of stenosis and consequently on which branches of the posterior tibial nerve are involved. The patient usually complains of burning pain or paresthesias in the toes, sole, or heel of the foot. As with CTS, pain may awaken the patient at night and may move in a retrograde fashion to the calf. Relief may be obtained by walking. Commonly, direct palpation over the nerve posterior to the medial malleolus elicits tenderness, and a fusiform swelling may be present in this region. Other findings can include a positive Tinel sign over the tarsal tunnel, vasomotor changes, and weakness of toe flexion and the intrinsic muscles of the foot.

Diagnosis

The differential diagnosis for tarsal tunnel syndrome includes arthritis of the tarsal bones, plantar fasciitis, vascular insufficiency, and systemic peripheral neuropathy. Tarsal tunnel syndrome may also be confused with lumbosacral nerve root radiculopathy. Another differential condition, particularly in runners, is hypertrophy of the abductor hallucis muscle; however, in this case, compression of the plantar nerve occurs distal to the lacinate ligament.

Electrodiagnostic studies are useful in confirming the diagnosis of tarsal tunnel syndrome. NCV is often diminished, and there may be abnormalities in distal motor latencies. Prolonged distal motor latencies of the plantar nerves may occur in 25% of patients with RA. MRI is the best method for demonstrating the anatomy of the tarsal tunnel and thus for detecting space-occupying lesions.

Treatment

A number of conservative therapies have been used for tarsal tunnel syndrome, including local injection of corticosteroid, NSAIDs, and orthotics, none of which have consistently been effective. The standard treatment is surgical decompression, which gives excellent results in the majority of patients.⁴⁹ If the patient's symptoms are the result of pressure on the nerve from the abductor hallucis muscle, release of the muscle at its origin is performed rather than sectioning of the flexor retinaculum.

MORTON METATARSALGIA (MORTON NEUROMA, INTERDIGITAL NEURITIS)

Entrapment neuropathy of the interdigital plantar nerves occurs most commonly in the web space between the third and fourth toes, but it may also affect other interspaces. Chronic irritation of the nerve may lead to the development of a neuroma (see Chapter 78).

Anatomy

The medial and lateral plantar nerves of the foot divide into digital nerves in the web spaces between the toes. These interdigital nerves lie on the plantar side of the transverse metatarsal ligament (Fig. 81.15). Between the metatarsal joints are bursae that project distally and are close to the neurovascular bundle.

Etiology

Because the interdigital nerves are on the plantar side of the transverse metatarsal ligament, entrapment as a result of compression between the metatarsal heads, as originally proposed by Morton, is highly unlikely. It is more probable that the taut ligament itself is the cause of the entrapment. In addition, there is evidence that the intermetatarsal bursae may also impinge on the nerve directly or, when inflamed, cause metatarsalgia. Wearing tight-fitting or high-heeled shoes also tends to aggravate the condition, which may explain why women are affected more often.

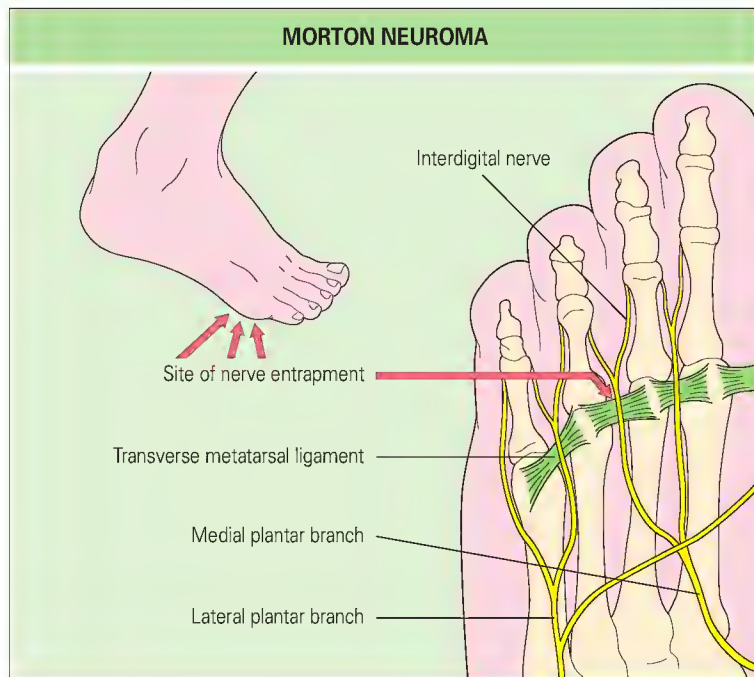


Fig. 81.15 On the plantar surface of the foot the interdigital nerve is compressed below the transverse metatarsal ligament and not between the metatarsal heads (plantar view).

Clinical features

Typically, patients complain of an aching or burning pain that radiates from the web space distally to the affected toes. Activities such as jogging or long periods of standing may worsen the metatarsalgia, as does walking on hard surfaces. Direct pressure applied over the interspace between the metatarsal bones often elicits tenderness, and occasionally a painful nodule may be palpated.

Diagnosis

Morton metatarsalgia must be differentiated from inflammatory conditions affecting the forefoot. RA may be manifested as metatarsalgia, but in most cases examination reveals synovitis, and neuritic pain is uncommon. Conventional radiographs are of little value in diagnosing Morton neuroma but may demonstrate other causes of forefoot pain such as exostosis or fracture. Ultrasonography can identify neuromas, which appear as ovoid, hypoechoic lesions. MRI is very effective in identifying and localizing neuromas. Interestingly, lesions consistent with neuroma may be found in 33% of asymptomatic individuals.⁵⁰

Treatment

Initial treatment should include conservative measures such as padding the metatarsal area and the use of broad-toed shoes. Benefit has also been reported to be derived from injection of local anesthetic and corticosteroids.

When conservative treatment fails, the traditional approach has been surgical resection of the neuroma. The clear drawback with this procedure is that the patient is left with a sensory deficit. Another strategy is release of the transverse metatarsal ligament and epineural neurolysis of the interdigital nerve.⁵¹ This method avoids neurectomy while decompressing the nerve.

COMPARTMENT SYNDROMES

Compartment syndromes can be defined as an increase in tissue pressure within a confined space or muscle compartment that compromises the local circulation and neurologic function.

Acute compartment syndrome

Acute compartment syndrome is a surgical emergency that can result from a direct blow to the muscle, from the trauma associated with a fracture, or from prolonged pressure over a muscle compartment. It also occurs rarely

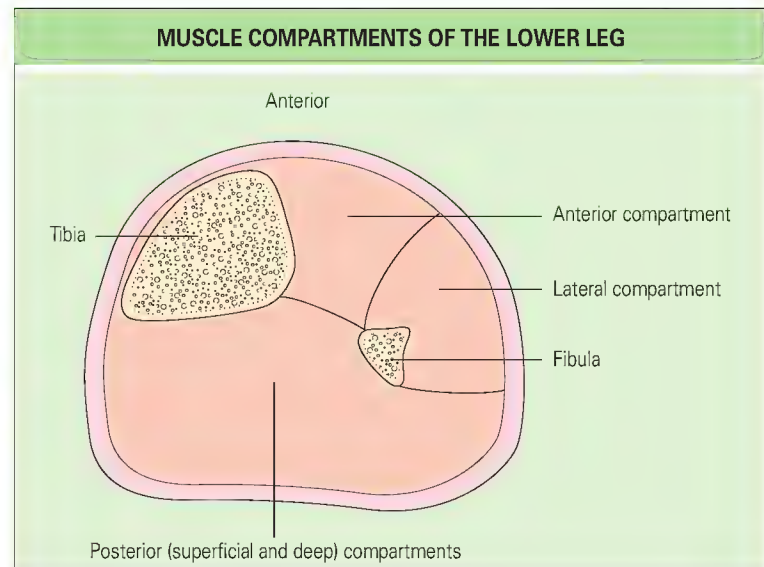


Fig. 81.16 The muscles of the leg are contained within four compartments separated by deep transverse fascia.

after prolonged exertion. Acute compartment syndromes can lead to rapid and complete muscle necrosis as a result of vascular compromise. Early surgical decompression of the compartment may allow restoration of circulation to the muscle and preserve function. The clinical diagnosis of acute compartment syndrome should be suspected in patients who have pain that is out of proportion to the injury or a history of injury, swelling and firmness of the muscle compartment, and pain on passive stretch. Later in the evolution of acute compartment syndrome, signs of decreased perfusion develop, including decreased pulses, reduced capillary refill, and skin pallor. Neurologic symptoms may also appear.

Chronic compartment syndrome

This is the typical form seen in athletes and is characterized by return to normal function between episodes of exercise-induced pain. It most commonly occurs in the lower part of the leg.

The muscles of the leg are contained within four compartments separated by deep transverse fasciae (Fig. 81.16). The athlete describes aching or cramping of the leg, roughly in the distribution of the involved compartment. The period from commencement of exercise to the onset of symptoms is variable and depends on the type and intensity of exercise but is usually within 10 to 30 minutes. Return to normal is also variable, within minutes in most cases, but in more severe cases complete resolution can occasionally take hours. Neurologic symptoms may occur because of ischemia of nerves, particularly in anterior tibial syndrome.

No diagnostic signs occur during rest, which makes the diagnosis difficult and dependent on a good history. However, fascial defects may be found with MRI in up to 40% of patients. After sufficient exercise, tenderness and fullness will be noted in the muscle compartment involved, most commonly the anterolateral compartment.

Slit catheter measurement of intracompartmental pressure before and after exercise can be used to select patients suitable for surgical decompression, provided that it is performed in a specialized center with reliable standardization.⁵² However, the significance of a mild elevation in pressure in some patients remains controversial. It is likely that MRI will prove to be of increasing importance in diagnosis, along with the development of more sophisticated imaging techniques involving biochemical shifts or pH changes.⁵³

Compartment syndrome of the forearm is much less common but may particularly be seen in weight lifters and rowers. The deep fascia of the forearm encloses both the flexor and extensor muscles, which are separated by the radius, ulna, and interosseus membrane. The deep flexor compartment of the forearm is the more common site of involvement.

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82

Complex regional pain syndrome

■ RACHEL GORODKIN

DEFINITION

- *Complex regional pain syndrome* (CRPS) is a pain disorder that can develop after injury to a limb.
- There are no diagnostic tests for CRPS; the diagnosis is made on the basis of specific symptoms and signs.

CLINICAL FEATURES

- There is usually a preceding noxious event or period of immobilization, although in 10% of cases there is no clear precipitating event.
- The most characteristic feature is spontaneous pain, which usually begins in an extremity and then extends proximally and is disproportionate to the initiating event.
- Edema, vasomotor abnormalities (color and temperature), sudomotor abnormalities (changes in sweating), and motor and trophic changes are common but variable features.
- Radiographs of the affected extremity may show patchy osteoporosis, which is most marked in the juxtaarticular region.

HISTORY AND TERMINOLOGY

In 1864, Mitchell and colleagues¹ described what we now recognize as complex regional pain syndrome (CRPS) when reporting the complications of peripheral nerve injuries caused by gunshot wounds sustained by soldiers during the American Civil War. The old term *reflex sympathetic dystrophy* was first used by Evans in the mid-1940s.² Since then, many terms, some of which are listed in [Box 82.1](#), have been used to describe the painful swelling of an extremity that is usually associated with a preceding injury. This multiplicity of terms has been confusing, and in recent years considerable effort has been invested in clarifying the definition and terminology for this condition, with the descriptive term *complex regional pain syndrome* coming into usage in 1995.³

CRPS type I (*without* preceding nerve injury) equates to what was previously termed *reflex sympathetic dystrophy*, and CRPS type II (*with* preceding nerve injury, usually traumatic) is what was previously termed *causalgia*. Therefore the problems that Mitchell and colleagues described in soldiers would now more accurately be called *CRPS type II*. Although the distinction between the two subtypes can be made, there is currently no evidence that it affects outcome.

DIAGNOSIS AND CLINICAL FEATURES

CRPS is primarily a clinical diagnosis and is often difficult to make. The current diagnostic criteria are known as the *Budapest criteria*⁴ ([Box 82.2](#)) and rely purely on symptoms and signs, so the clinician needs to be familiar with these. In addition to varying among patients, clinical features vary within an individual patient over time. Almost invariably, it is an extremity that is affected. Hand and wrist, knee, or foot and ankle are most commonly involved, although an entire limb can become affected, as shown in [Fig. 82.1](#). Usually only one limb is affected, but the condition may be bilateral or another limb may become affected at a later date.⁵

Both symptoms and signs are grouped under four headings, which are considered in turn: sensory, vasomotor, sudomotor/edema, and motor/trophic. These features are summarized in [Table 82.1](#).

Sensory

The most characteristic feature of CRPS is severe, persistent pain, which often has a burning quality. The pain is different in character from that of the injury that precipitated the CRPS and, although usually beginning in the extremity, frequently extends proximally in a nondermatomal pattern. On examination, the affected site is diffusely tender, often with allodynia and hyperalgesia. These are separate phenomena: *allodynia* is pain that is provoked by a stimulus that is not normally painful, whereas *hyperalgesia* is an exaggerated response to a painful stimulus. *Hyperpathia* is also observed in patients with CRPS (especially those with later disease) and can be defined as an increased response to a repetitive stimulus. It is being increasingly recognized that patients with CRPS may also experience disturbances in body perception.⁶

Vasomotor

The patient may complain of changes in skin color or temperature in the affected extremity, which are revealed on clinical examination by comparison with the unaffected side. A temperature difference of at least 1°C is counted as significant and coincides with the minimum that can easily be picked up by clinical examination. Typically, the affected limb is initially warm and red and may then become mottled and intermittently warm and cool before becoming more permanently cold and cyanotic. However, not all patients pass through these three phases (see later). It has been suggested that patients who report early coldness are at high risk of going on to develop severe, late-stage disease, with infection, ulcers, chronic edema, dystonia, and myoclonus.⁷

Sudomotor/edema

Swelling of the affected extremity is common, especially in the early phase ([Fig. 82.2](#)), and may be associated with increased or reduced sweating.

Motor/trophic

The patient may describe inability to initiate movement, weakness (although this is difficult to assess in the presence of severe pain), tremor, or muscle spasms. Sometimes there are dystonic features.⁸ Hair growth and nail changes are commonly seen, and the skin may become atrophic and shiny. Contractures can occur in late-stage disease ([Fig. 82.3](#)).

EPIDEMIOLOGY

There is little accurate data on either the incidence or prevalence of CRPS. However, it is clear that minor forms are not rare. Some investigators have reported, in prospective studies, a cumulative incidence of around 30% after Colles or tibial fractures,⁹ although others reported an incidence as low as 1%.¹⁰ Fortunately, only a minority of patients progress to late-stage disease (see later). A recent study in the Netherlands estimated the overall incidence rate to be 26.2 per 100,000 person-years, with the highest incidence in the 61- to 70-year age group.¹¹ However, CRPS can occur in persons of any age and is well recognized in children.¹² It has been reported more frequently in women than in men with a ratio of 3.5:1.^{11,13,14}

BOX 82.1 TERMS USED IN THE DEFINITION OF COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) type I (the preferred term)
 Causalgia (now CRPS type II)
 Reflex sympathetic dystrophy (RSD)
 Sudeck atrophy
 Shoulder-hand syndrome
 Algodystrophy
 Algoneurodystrophy
 Posttraumatic dystrophy
 Posttraumatic osteoporosis
 Painful osteoporosis
 Transient osteoporosis

Some terms are listed that are or have been used to describe what is now considered under the definition of CRPS.

BOX 82.2 CRITERIA FOR THE DIAGNOSIS OF COMPLEX REGIONAL PAIN SYNDROME TYPE I

1. Continuing pain disproportionate to the inciting event
2. At least one sign in two or more categories
3. At least one symptom in three or more categories
4. No other condition present that could explain the symptoms and signs

Categories

- A. **Sensory:** allodynia, hyperalgesia, hyperesthesia (symptom only)
 B. **Vasomotor:** temperature asymmetry (at least 1°C), skin color asymmetry, skin color changes
 C. **Sudomotor/edema:** edema, changes or asymmetry in sweating
 D. **Motor/trophic:** decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nails, skin)

Adapted from Harden RN, Bruhl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med* 2007;8:326-31.



Fig. 82.1 Complex regional pain syndrome affecting the lower limb, which shows marked swelling and color change. (Reproduced with permission from Salford Royal NHS Foundation Trust.)

Triggers

A variety of triggers can precipitate CRPS (Table 82.2). The most common causes are peripheral trauma (fracture or soft tissue injury) and orthopedic surgery. CRPS can also develop after central nervous system or spinal disorders and rarely after visceral lesions such as myocardial infarction. Up to 10% of patients have no identifiable causative event.^{13,14} Immobilizing a limb (for any reason) is likely to be a significant predisposing factor: in one large study, 47% of subjects had undergone a period of limb immobilization before diagnosis.¹³

Personality traits

Patients with CRPS are often extremely distressed by their pain, and it has been suggested that certain personality traits are associated with CRPS, but there is no convincing evidence to support this hypothesis.¹⁵ It seems likely that the pain behavior that undoubtedly develops in a proportion of patients is a consequence of, rather than a predisposing factor for, their CRPS.

TABLE 82.1**Clinical features of complex regional pain syndrome**

Sensory	Pain, often burning, extending beyond the area of the original injury Allodynia Hyperalgesia/hyperpathia Disturbed body perception
Vasomotor	Color change* Temperature change*
Sudomotor/edema	Edema Increased sweating
Motor/trophic	Weakness/inability to initiate movement Tremor Muscle spasms Dystonic features Contractures Skin, hair, and nail changes

*Compared with the unaffected side.



Fig. 82.2 Early complex regional pain syndrome of the left hand and wrist, which show edema. (Reproduced with permission from Salford Royal NHS Foundation Trust.)

NATURAL HISTORY

The clinical course of CRPS has been divided into three stages. Although there is some doubt as to the clinical usefulness of this subdivision, it may be of help when considering studies of pathophysiology and treatment. The three stages are as follows:

Fig. 82.3 Complex regional pain syndrome (CRPS) of the ankle and foot. (a) Well-established CRPS of the right ankle and foot, showing contracture. (b) The extent of deformity associated with CRPS is well demonstrated radiographically. The affected foot is osteoporotic. (Reproduced with permission from Salford Royal NHS Foundation Trust.)



TABLE 82.2
Typical triggering events for complex regional pain syndrome

Trauma	Wrist fractures Tibial fractures Soft tissue injuries
Surgery	Carpal tunnel decompression Arthroscopy Lumbar spine surgery
Central nervous system or spinal disorders	Head injury Hemiplegia
Visceral lesions	Myocardial infarction

Stage 1: acute. The limb may be either warm or cool, with edema.¹³
Stage 2: dystrophic. The limb becomes cooler, and either mottled or cyanotic, with early dystrophic changes of the skin and nails.
Stage 3: atrophic. During this stage, the pain spreads proximally (in some patients the limb may become less painful) and there are irreversible atrophic changes and contracture. In some patients ankylosis can occur.

The duration of each of these three stages is highly variable, and patients may exhibit features of more than one stage simultaneously.¹⁶ Many patients never progress beyond stage 1.
The vast majority of patients with CRPS experience a single episode, with only 2% experiencing a relapse.¹³

DIFFERENTIAL DIAGNOSIS

The differential diagnosis, at least in the early stages of CRPS, is that of the causes of a tender, often swollen limb. Inflammatory arthritis, cellulitis, osteomyelitis, deep vein thrombosis, malignancy, and fracture might all be suspected, but careful history taking should point to the diagnosis, especially when there is a history of a prior trauma. Neuropathic pain disorders also enter into the differential diagnosis. Chronic vascular insufficiency and thoracic outlet syndrome must be considered in the differential diagnosis of late-stage CRPS.

INVESTIGATIONS

There is no diagnostic test for CRPS. However, certain investigations may give supportive evidence. Blood tests should all yield normal results.



Fig. 82.4 Complex regional pain syndrome of the wrist seen (a) at the time of the initial injury and (b) after 3 months, with patchy osteoporosis apparent. (Reproduced with permission from Central Manchester University Hospitals NHS Foundation Trust.)

Plain radiography

The characteristic radiographic findings of CRPS are well described. The typical appearance is of patchy osteoporosis of the affected extremity. This is most marked in the juxtaarticular region (Fig. 82.4) but can be more diffuse.¹⁷ Soft tissue swelling is often present, at least in early disease. The joint space is usually preserved, although in patients who progress to late-stage disease there may be loss of joint space and ankylosis.

Isotope bone scanning

Traditionally, isotope bone scanning (especially three-phase imaging) was considered useful in the diagnosis of CRPS to seek asymmetry between affected and nonaffected limbs, although the actual abnormality depends on disease stage. Thus there is increased uptake in early disease (Fig. 82.5) and reduced uptake in later disease.¹⁸ However, there has been some skepticism as to the true usefulness of isotope bone scanning,¹⁴ and many specialist units rarely use it.

Magnetic resonance imaging

Appearances on magnetic resonance imaging tend to be nonspecific and include soft tissue changes and bone marrow edema.¹⁹ At present, magnetic resonance imaging is not considered part of the routine diagnostic evaluation of CRPS but is often useful if the diagnosis is uncertain.

Other investigations

A number of other investigations have been used primarily on a research basis. These include measurement of surface temperature using thermography (Fig. 82.6),²⁰ quantitative sweat testing (using the quantitative

sudomotor axon reflex test), quantitative sensory testing (testing small fiber function), sympathetic skin response (which measures skin conductance),²¹ and psychological tests.

PATHOLOGIC FEATURES

The pathologic features of CRPS are not well described, which reflects the reluctance to subject affected limbs to biopsy for fear of exacerbating the clinical problem. A pathologic study of skeletal muscle and peripheral nerve tissue from lower limb amputations from eight patients revealed muscle changes consisting of type I fiber atrophy, an increase in lipofuscin (suggestive of free radical-mediated injury), and capillary abnormalities, with thickening or duplication of the basement membrane.²² There were no consistent abnormalities in peripheral nerves. The authors postulated that a microangiopathy was central to pathophysiology. In contrast to the lack of tissues from deeper structures, there is a relative wealth of data from skin biopsies. The largest study looked at biopsy specimens from 43 patients but found no difference in epidermal nerve fiber density or sweat gland nerve fiber density between patients and control subjects.²³

PATHOPHYSIOLOGY

The pathophysiology of CRPS is not fully understood. It is unknown why some patients, after only a minor injury, go on to develop CRPS, whereas most make an uncomplicated recovery. Many different theories have been suggested.^{16,21,24-28} It seems most likely that both peripheral and central mechanisms are involved, interacting to maintain a vicious cycle of events, the end result of which is the persisting pain of CRPS with its accompanying vasomotor, sudomotor, and trophic changes. Inflammatory changes and microcirculatory dysfunction, possibly resulting in oxidant stress, have also been proposed as important mechanisms of tissue injury, as has immune dysfunction. It seems probable that these different aspects of pathophysiology are all interrelated (Fig. 82.7).

Peripheral mechanisms

Peripheral nerve damage

It is likely that trauma to type C nerve fibers and A δ afferents is an initiating event in the CRPS process, and at least some patients go on to demonstrate sensitization of their C or A δ nociceptors in the context of thermal and mechanical hyperalgesia.¹⁶ Although localized small fiber nerve damage precipitated by trauma would fit many of the features of CRPS, this is not consistently borne out in skin biopsy studies.²³

Sympathetic dysregulation

It was originally thought that abnormality of the sympathetic nervous system was a key component in the pathogenesis of CRPS. Although this is no longer generally accepted, there is no doubt that a select group of patients have an element of sympathetically maintained pain,²⁴ as demonstrated by their response to sympathetic blockade.



Fig. 82.5 Isotope bone scan showing diffuse increased uptake in the distal tibia, talus, and navicular in a patient with complex regional pain syndrome of the left ankle and foot. (Reproduced with permission from Salford Royal NHS Foundation Trust.)

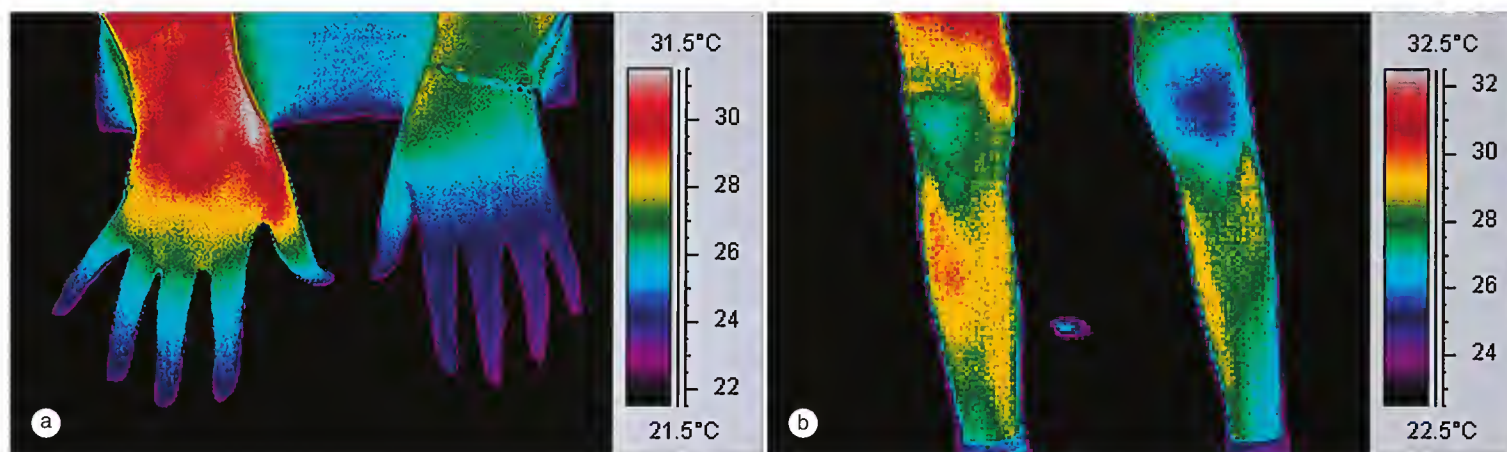


Fig. 82.6 Thermographic images. (a) A patient with complex regional pain syndrome (CRPS) of the left hand (same patient as in Fig. 82.2). The affected hand is cooler: the temperature difference between the dorsum of the left hand and the dorsum of the right hand is 3.4°C. (b) A patient with CRPS of the left knee. The affected knee is cooler: the temperature difference between the left and right knees is 1.9°C. (Reproduced with permission from Salford Royal NHS Foundation Trust.)

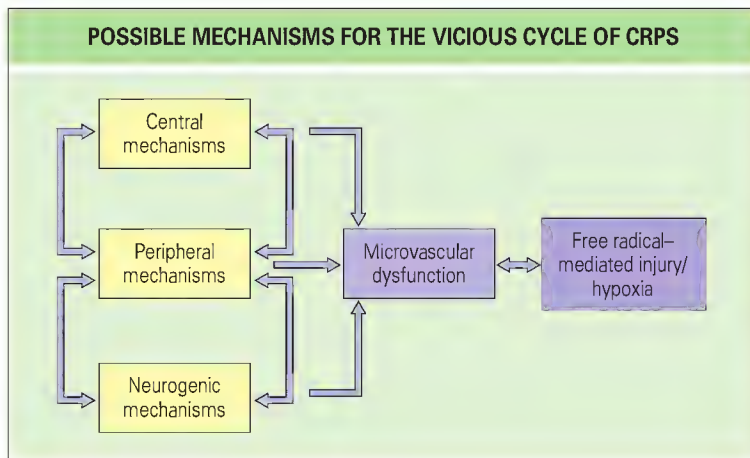


Fig. 82.7 Central, peripheral, and neurogenic mechanisms have been proposed for complex regional pain syndrome (CRPS).

Sympathetic activity may activate both mechanoreceptors and nociceptors and could therefore contribute to the vicious cycle involving central mechanisms (see later). α -Adrenoreceptors may be overexpressed in hyperalgesic skin of patients with CRPS and may then be activated through sympathetic discharge.²⁴ Some patients experience pain relief from α -adrenergic blockade with intravenous phentolamine, but the situation is complex, with several studies suggesting a reduction in sympathetic efferent activity leading to supersensitivity to catecholamines.^{29,30} Despite these pointers toward a role for the sympathetic nervous system, a systematic review of clinical trials using regional guanethidine sympathetic blocks found no effect,³¹ and the current consensus is that sympathetic dysregulation plays only a minor role in the pathophysiology of CRPS.

Neurogenic inflammation

There is considerable evidence to suggest that neurogenic inflammation contributes to the pathogenesis of CRPS.²⁶ This might explain why some of the early clinical features of CRPS are inflammatory.¹³ Release from afferent nerve fibers of vasoactive peptides, including substance P and calcitonin gene-related peptide, causes vasodilation with increased vascular permeability and protein leakage, and also increases the excitability of primary sensory nerve fibers, which leads to changes in the dorsal horn.

Microvascular dysfunction

It is not known whether the vascular changes in CRPS drive the disease process by causing hypoxia and free radical-mediated damage or whether they are secondary. A number of investigators have confirmed microvascular dysfunction in CRPS,^{29,30} and hypoxia has been directly demonstrated in CRPS-affected limbs.³² Relevant to this is that vitamin C, a powerful antioxidant, may prevent the development of CRPS,³³ and free radical scavengers may have a beneficial effect in the treatment of CRPS.³⁴

Central mechanisms

Central sensitization

It has been suggested that, in CRPS, an initial activation of nociceptors leads to alteration of central information processes, resulting in central sensitization. This disordered processing of nociceptor impulses may be the most important mechanism of persisting pain in late-stage CRPS—activation of low-threshold mechanoreceptors is interpreted as noxious and so causes allodynia. A role for the *N*-methyl-D-aspartate (NMDA) receptor has been suggested¹⁶ and is borne out by recent trials looking at the use of intravenous ketamine (an NMDA antagonist).³⁵ Inhibitory neurons using γ -aminobutyric acid (GABAergic) may also play a part, as indicated by improvement in dystonia in response to baclofen (a GABA receptor agonist).³⁶

Cortical reorganization

There is increasing interest in the role that abnormal cortical processing plays in CRPS, with motor and sensory cortical reorganization demonstrated via various techniques including magnetoencephalography and functional magnetic resonance imaging.²⁷ Graded motor imagery³⁷ (thought-based exercises designed to train the brain) and mirror therapy³⁸ (physical exercises using a mirror to hide the affected limb and visually trick the brain into seeing two normally functioning limbs) have both been demonstrated

TABLE 82.3

Approaches to the treatment of complex regional pain syndrome

Prevention	Early mobilization Vitamin C
Physiotherapy	Desensitization techniques Mirror therapy Graded motor imagery Transcutaneous electrical nerve stimulation Acupuncture
Drug treatment	Possibly effective (although no large-scale studies) Bisphosphonates Free radical scavengers (dimethyl sulfoxide [topical] and <i>N</i> -acetylcysteine) Ketamine (intravenous) Insufficient evidence for effectiveness Analgesics (including paracetamol, nonsteroidal antiinflammatory drugs, and opioids) Anticonvulsants Antidepressants Baclofen (oral and intrathecal) Botulinum toxin (intramuscular) Calcitonin Calcium channel blockers Capsaicin Corticosteroids Lidocaine 5% plasters
Spinal cord stimulation	
Surgery (very rarely indicated)	Surgical sympathectomy Amputation

to be helpful, although the mechanism by which they exert their effect is unclear.

Other mechanisms

Autoimmunity

Antineuronal antibodies have been found in patients with CRPS, and infusion of patient immunoglobulin into mice produces abnormal behavior. There has been recent interest in the effect of a single infusion of low-dose (0.5 g/kg) intravenous immunoglobulin. Pain relief has been demonstrated in a subgroup of patients, but the numbers tested remain very small at present.²⁸

Genetics

Various HLA associations have been tested for, but there has been no overall consensus on a single area of interest.

Summary

Our current state of knowledge regarding the pathophysiology of CRPS can be summed up as follows: the condition is most likely initiated by a peripheral injury causing subclinical nerve damage and neurogenic inflammation, and possibly also altering immune system function. Initial changes are mediated by nociceptive A δ and C fibers, leading to sensitization and release of inflammatory neuropeptides at the dorsal horn ganglion and abnormal connections with the sympathetic nervous system, potentially resulting in sympathetically maintained pain. Dysfunction within the spinal cord can extend to adjacent levels and can cross the midline, leading to spread within a limb and contralateral symptoms. Later changes include long-term alterations in neuropeptide production, abnormalities of both excitatory and inhibitory spinal and supraspinal pathways, and motor and sensory cortical reorganization. Both early and late changes cause abnormalities of blood flow, which may themselves be responsible for some of the features of CRPS.

MANAGEMENT

There are a number of treatment options in CRPS, which are summarized in Table 82.3.

Although many patients with mild forms of CRPS may experience spontaneous improvement, those who progress to a late stage with atrophy and

contracture are very unlikely to recover. These patients are left with pain and major functional disability. Therefore early diagnosis is a key principle of management.

In addition to being a condition that is difficult to diagnose and treat, CRPS is difficult to study because of its heterogeneity, the problems in definition referred to earlier, a lack of outcome measures,³⁹ and the incomplete understanding of its pathophysiology. As a result, until very recently there have been very few controlled clinical trials,^{40,41} and those that do exist tend to be in small numbers of patients, with subjective endpoints. Many of the recommendations about treatment (including those considered here) are based on anecdotal observations or small series of patients.

The treatment of CRPS should be multidisciplinary. Many of the patients demonstrate marked pain behavior, and their distress may be compounded by the fact that, before diagnosis, their pain was thought to be “nonorganic.” Patient education and an approach based on a biopsychosocial model of pain management are integral to treatment. Although there are no randomized controlled trials of cognitive-behavioral therapy in CRPS, it is appropriate to refer patients for psychological input if they appear distressed or are slow to improve. Medications and interventions are discussed later, but given the overall lack of CRPS-specific evidence, drugs given are usually those with support for their use in patients with other types of neuropathic pain.

Prevention

Ideally, the development of CRPS should be prevented by early mobilization of patients with predisposing conditions and careful attention to surgical technique. A recent study of 300 patients undergoing surgery for Dupuytren contracture suggested that anesthetic technique was also likely to influence outcome.⁴² As stated earlier, it has been suggested that vitamin C (500 mg/day), a powerful antioxidant, may prevent the development of CRPS,³⁸ the rationale being that oxidant stress contributes to pathophysiology. Although potentially very exciting, this observation requires confirmation in further studies.

There is very little evidence regarding secondary prevention in patients with CRPS who need to undergo surgery. A common sense approach is to try and defer surgery until the CRPS symptoms are well controlled.

Physiotherapy and occupational therapy

Physiotherapy alone may correct mild cases of CRPS. In more advanced disease, severe pain is a barrier to rehabilitation, and physiotherapy is used in parallel with medical and psychological approaches. In a randomized trial in patients with upper limb CRPS, both physiotherapy and occupational therapy conferred benefit in terms of pain reduction and functional improvement.⁴³ An algorithm for therapy, with an emphasis on the rehabilitative aspects, has been put forward by Stanton-Hicks and coworkers.⁴⁴ Mirror therapy is now relatively widely used because it is a very simple and safe technique to apply, although it is most effective if implemented very early in the course of the condition.⁴⁵ Graded motor imagery has also been increasingly used, but it requires a significant time commitment from the patient, and unpublished clinical audits from several centers have not been able to reproduce the degree of effectiveness seen in Moseley's original paper.³⁷

Physiotherapists may also try modalities such as transcutaneous nerve stimulation and acupuncture, but there are no good-quality studies as yet to support their use.

Drug treatment

A very large number of drugs have been suggested for the treatment of CRPS (see Table 82.3), but, to reemphasize what was stated earlier, few have been shown to be effective in randomized clinical trials. Even when good-quality trials have been carried out, the numbers of patients are almost invariably small.^{40,41} Usually the first-line pharmacologic intervention is with analgesics and nonsteroidal antiinflammatory drugs. Because most patients have a significant element of neuropathic pain, a reasonable next step is to

commence neuropathic analgesics such as tricyclic antidepressants and anti-epileptics. However, there are no CRPS-specific trials to back up this recommendation, and the little evidence there is suggests that gabapentin is not effective at a dose of 1800 mg/day.⁴⁶

Several papers have been published on the use of bisphosphonates reporting generally positive results. For example, alendronate has been shown to reduce pain and improve function,^{45,47} but dosages used have varied widely, ranging from 35 mg per week to 40 mg daily.

Ketamine at subanesthetic doses blocks NMDA receptors and therefore reduces the excitatory effect of glutamate on the central nervous system; benefit has been reported in two small randomized, controlled trials,^{35,48} but most regimens require a 5- to 10-day hospital admission for relatively short periods of relief.

Lidocaine 5% patches show promise,⁴⁹ if only for the way they protect allodynic skin from contact with clothing. Small studies have also shown benefit from early use of corticosteroids and use of antioxidant agents such as *N*-acetylcysteine and dimethylsulfoxide.³⁴

Sympathetic blockade

In the past, sympathetic blockade has been recommended as a treatment for CRPS, and a good response to this treatment has been considered an aid to diagnosis. However, guanethidine regional blockade has been shown to be ineffective in meta-analyses,³¹ and this procedure is falling out of use, although it may continue to be a helpful intervention in a small subgroup of patients. Local anesthetic sympathetic blockades are also ineffective.⁵⁰

Other treatments

Spinal cord stimulation has been shown to be effective in reducing pain (but not in improving function) in patients with well-established CRPS, although its effectiveness decreases over time.⁵¹ Because the procedure is not without risk, patients must be carefully selected.

A small proportion of patients come to surgical treatment. Rarely, surgical sympathectomy has been advocated if a patient gains benefit from temporary sympathetic blocks. Amputation is not recommended for pain alone, because phantom limb pain at the amputation stump may result, but it may be indicated, for example, if a limb is persistently infected.

Future therapies

Recent years have seen a huge expansion in research interest in CRPS, with the result that better classification criteria (lack of which was a major stumbling block to earlier research) and better outcome measures are being developed, which will facilitate clinical trials of new treatments.³⁹ Development of new therapies will, in turn, be directed by advances in understanding of pathophysiology and may include vasoactive, antioxidant, and immunomodulatory treatments in addition to different forms of analgesia such as NMDA antagonists.

CONCLUSION

CRPS remains a condition that is difficult to diagnose, to treat, and to study. However, it is a major source of pain and disability in that subgroup of patients who go on to develop severe, late disease. The rheumatologist's task is to maintain a high index of suspicion of CRPS in a patient with a painful extremity and to institute treatment, including mobilization, early in an attempt to prevent progression to late disease. Ideally, patients with CRPS should be cared for by an experienced multidisciplinary team.

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RHEUMATOID ARTHRITIS AND
OTHER SYNOVIAL DISORDERS

83

Classification and epidemiology
of rheumatoid arthritis

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- Rheumatoid arthritis (RA) has an annual incidence of approximately 0.4 per 1000 in females and 0.2 per 1000 in males; recent evidence indicates that the incidence may be rising.
- A prevalence of 0.4% to 1% is reported in diverse populations worldwide with evidence for geographic variation.
- Cigarette smoking remains the strongest environmental risk factor for RA; other lifestyle factors and exposures such as alcohol use may be inversely associated with RA.
- Childhood and current low socioeconomic status are associated with increased risk of RA.
- Hormonal and reproductive factors contribute to the female predominance in RA; parity, breastfeeding, and exogenous hormones are modifiers of RA risk in women.

CLASSIFICATION OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) typically manifests clinically as symmetric inflammation of the small joints in the hands and feet. However, few patients are textbook cases, and studying the disease requires a uniform definition with high sensitivity and specificity that is valid across institutions and countries as well as over time. The 2010 RA classification criteria, developed collaboratively by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), are the current standard for disease classification.¹ These new criteria replaced the 1987 ACR classification criteria, which up until recently were the gold standard for case definition in the majority of RA clinical studies.² It is important that rheumatologists remain acquainted with the 1987 criteria because many of the epidemiologic studies used this criteria set until 2010.

The 1987 ACR criteria for the classification of RA, designed for application in clinical research studies only and not for diagnosis, were developed from data for individuals diagnosed with RA by their rheumatologists (mean duration of symptoms, 7.7 years).² Members of the classification committee employed expert opinion and consensus to determine the final seven clinical characteristics they believed were important in determining RA status. Validation studies conducted in the outpatient clinics confirmed that the criteria were an accurate method of classifying RA with a sensitivity in the range of 77% to 95% and specificity in the range of 85% to 98%.³ Due to the nature of the training cohort from which the criteria were developed, the criteria perform best at distinguishing individuals with long-duration and active RA from individuals with other arthritides.

The 2010 update in the RA classification criteria (Table 83.1) reflects advancements in the diagnosis and treatment of RA since 1987. Antibodies to citrullinated proteins (ACPs) were found to be a more specific biomarker for early RA than rheumatoid factor (RF) (specificity of ACPs ranged from 94% to 100% compared with 23% to 96% for RF) with

sensitivity comparable to that of RF.^{4,5} Of equal import, more recent studies have demonstrated that early aggressive treatment of RA can halt or slow the progression of synovitis and bone erosions, decreasing disease-related disability and increasing the rate of remission.⁶⁻⁸ This led to strong interest in detecting the disease earlier in the clinical setting and identifying patients with early disease for research studies. However, the 1987 ACR criteria did not perform as well in classifying early RA (in studies, defined as the presence of arthritis symptoms for 4 weeks to 2 years) as in identifying longer-duration RA. The presence of ACPs was not part of the 1987 ACR criteria, and other criteria, such as joint erosions and rheumatoid nodules, are not often found in early RA and are outcomes rheumatologists seek to prevent.

The goal of the 2010 ACR/EULAR criteria was to create a method for RA classification *de novo* using rigorous methodology by employing both a data-driven and a consensus-driven approach. These criteria were designed primarily for RA classification for research studies, but in contrast to the 1987 ACR criteria can also be used for diagnosis. Development of the 2010 ACR/EULAR criteria occurred in three phases. Phase 1 used data from nine early arthritis cohorts across Europe and Canada to identify important domains and clinical variables that define RA. Phase 2 engaged an international panel of expert clinicians to score abstracted real-life clinical cases for probability of RA. Information from their scoring was used to extract the clinical information deemed important for ruling in or out RA. The final phase incorporated information from both the data-driven and the consensus-driven segments to determine the specific clinical factors to be included in the 2010 RA classification criteria (see Table 83.1). The notable differences between the 2010 and 1987 criteria are the following: First, synovitis was redefined as active synovitis in at least one joint that cannot be better explained by another diagnosis. Second, positivity for ACPs and abnormal levels of the inflammatory markers erythrocyte sedimentation rate and C-reactive protein level were added as criteria, whereas morning stiffness, rheumatoid nodules, and erosions or periarticular osteopenia on radiographs were removed. Thus far, validation studies have demonstrated that the 2010 criteria perform well, classifying RA patients earlier in the course of the disease than the 1987 criteria with comparable sensitivity and specificity.^{9,10}

DISEASE OCCURRENCE

Determining the precise incidence and prevalence of RA can be challenging. An ideal of study of RA incidence would include continual surveillance of a stable population over time. Because of the low incidence of the disease, only a few studies have been conducted with adequate sample size and follow-up to provide statistically precise estimates. An ideal study of prevalence should include all past and inactive cases of a disease in a population (and hence provide a measure of lifetime cumulative prevalence). RA is a disease that after onset can follow varying clinical courses, including progression, stable disease with or without flares, or remission. For a study to recognize remitted disease requires the use of criteria specifically designed for this purpose. It is often difficult to establish the extent to which remitted disease has been included in published reports.

TABLE 83.1
2010 ACR/EULAR criteria for rheumatoid arthritis (RA)

Target population (those who should be tested): Patients	
1. who have at least 1 joint with definite clinical synovitis (swelling) ^a	
2. whose synovitis is not better explained by another disease ^b	
Classification criteria for RA (score-based algorithm: add score of categories A to D; a score of $\geq 6/10$ is needed to classify a patient as having definite RA) ^c	
A. Joint involvement^d	Score
1 large joint ^e	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints) ^f	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint) ^g	5
B. Serologic results (at least 1 test result is needed for classification)^h	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)ⁱ	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms^j	
<6 wk	0
≥ 6 wk	1

^aThe criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with long-standing disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

^bDifferential diagnoses vary among patients with different presentations but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

^cAlthough patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

^dJoint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement. "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

^e"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

^fIn this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (temporomandibular, acromioclavicular, sternoclavicular, etc.).

^g"Negative" refers to international unit (IU) values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; "low-positive" refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay. Where RF information is available only as positive or negative, a positive result should be scored as low-positive for RF.

^hNormal/abnormal is determined by local laboratory standards.

ⁱ"Duration of symptoms" refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; RF, rheumatoid factor.

From Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569-81, Table 3.

Direct comparisons of published data of RA occurrence are problematic because of the need to take into account differences in the sensitivity and specificity of criteria sets used at the time of the study, such as the 1958 American Rheumatism Association (ARA) criteria, the 1987 ACR criteria, and now the 2010 ACR/EULAR criteria. There is now evidence that the severity of RA may be declining and the disease may be entering remission earlier after treatment.¹¹ Hence older prevalence estimates may be less relevant to the contemporary pattern of disease occurrence.

Incidence

Since a number of methods have been used to classify RA, incidence and prevalence rates are not directly comparable across studies. Overall,

incidence rates are higher in northern Europe and North America than in southern Europe (Table 83.2) based on a review of studies using the 1987 ACR criteria.¹² The median observed incidence was 29 cases per 100,000 (range, 24 to 36), in northern Europe, 38 (range, 31 to 45) in North America, and 16.5 (range, 9 to 24) in southern Europe.¹²

Prevalence

There have been a number of contemporary studies of the prevalence of RA based on large-scale cross-sectional population samples. Estimates using the 1987 ACR criteria conducted in various populations worldwide are listed in Table 83.3.¹² Because the 2010 RA criteria were recently published, there are no studies to date using the most recent criteria. Estimates using past criteria sets are listed in Table 83.4. Most studies show a female-male excess of between 2:1 and 3:1. In all studies, age-specific prevalence rates increase with age.

In the United States, the lifetime risk of RA, interpreted as the percentage of individuals who develop RA at any age, is 3.6% for women and 1.7% for men.¹³ These estimates were determined based on incidence rates in a population-based RA cohort in Rochester, Minnesota, from 1997 to 2007 and age- and sex-specific mortality rates for the United States for the year 2000.

Geographic variation

Overall, the majority of estimates of RA prevalence worldwide based on 1987 ACR criteria range between 0.4% and 1% (see Tables 83.3 and 83.4). Northern Europe and North America had higher prevalence rates than the rest of the world, ranging from 0.4% to 1%. Southern Europe had lower prevalence rates, ranging from 0.3% to 0.7%. The two studies from the Middle East suggest that prevalence rates in that region are similar to the rate in the northern countries. Prevalence rates in Africa and Asia tended to be lower, with the majority ranging between 0.2% and 0.3%, with higher rates in urban areas. Particularly high prevalence rates of RA have been found in certain Native American groups, including the Pima, Yakima, and Chippewa. This excess is not seen in other Native Americans, such as the Blackfoot and Haida.

Time trends

Two studies that used the 1987 ACR criteria examined trends in the incidence of RA since 1995 and reported an increase in this period, particularly in women, in the United States and Denmark.^{14,15} However, more data are needed to determine whether this represents a true increase in the overall incidence of RA. This increase follows decades of decline in the incidence in RA reported by several studies. In the Pima Indian population, the incidence of RA was observed to have halved in both males and females in the 25 years between 1965 and 1990.¹⁶ Data from a study in the United States in which similar methods of case ascertainment have been in place for 40 years confirm a decline in incidence from 0.61 per 1000 in 1955-1964 to 0.33 per 1000 in 1985-1994.¹⁷ The decrease was greatest in females. The declining incidence was also seen through successive birth cohorts. Updated RA incidence data from a population in the United States show a striking cyclical variation in the rate from year to year, which suggests the possibility of specific risk factors acting at different points in time (Fig. 83.1).

The severity of RA may also be declining over time. In an analysis of the features of disease severity in successive birth cohorts of patients, one study showed that there was a peak in erosive, seropositive, and nodular disease in individuals diagnosed with RA in the 1960s but a decline in the severity of disease in subsequent generations.¹⁸ A decline in prevalence of RF seropositivity has also been reported among younger birth cohorts in the Pima Indian population.¹⁹ However, this trend has not been seen in U.S. data,¹⁷ which show no evidence that the proportion of patients with RF seropositivity or erosive change has diminished over time. The mortality from RA also remained constant over the 40-year period of observation.

ENVIRONMENTAL FACTORS

Lifestyle factors

Cigarette smoking, a modifiable risk factor, remains the strongest known environmental risk factor for RA.^{20,21} Since this association was first discovered over a decade ago, subsequent studies have elucidated the nature of this association.²² We now know that smoking is most strongly associated with ACPA-positive and RF-positive RA.^{23,24} The risk of RA increases with

TABLE 83.2

Incidence rates of rheumatoid arthritis worldwide in studies based on the 1987 ACR criteria

Study	Population/country	Incidence (cases per 1000 inhabitants)		
		Female	Male	Total
Doran et al (2002) ¹⁷	United States	0.6	0.3	0.5
Savolainen et al (2003) ⁹³	Finland	0.5	0.3	0.4
Chan et al (1993) ⁹⁴	United States	0.5	0.2	0.3
Kaipiainen-Seppanen et al (2006) ⁹⁵	Finland	0.4	0.2	0.3
Riise et al (2000) ⁹⁶	Norway	0.4	0.2	0.3
Uhlig et al (1998) ⁹⁷	Norway	0.4	0.1	0.3
Drosos et al (1997) ⁹⁸	Greece	0.4	0.1	0.2
Symmons et al (1994) ⁹⁹	England	0.3	0.1	0.2
Soderlin et al (2002) ¹⁰⁰	Sweden	0.3	0.2	0.2
Guillemin et al (1994) ¹⁰¹	France	0.1	0.1	0.1

ACR, American College of Rheumatology.

Adapted from Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 2006;36:182-8.

TABLE 83.3

Prevalence estimates of rheumatoid arthritis (RA) worldwide in studies based on the 1987 ACR criteria

Study	Population/country	Prevalence of definite RA (%)		
		Female	Male	Combined
Asia				
Lau et al (1993) ¹⁰²	China			0.4
Dai et al (2003) ¹⁰³	China	0.4	0.1	0.3
European and North American white				
Symmons et al (2002) ⁵¹	England	1.1	0.4	0.9
Hakala et al (1993) ⁵³	Finland	1.0	0.6	0.8
Guillemin et al (2005) ¹⁰⁴	France	0.5	0.1	0.3
Saraux et al (1999) ¹⁰⁵	France	0.8	0.2	0.5
Andrianakos et al (2003) ¹⁰⁶	Greece	1.9		0.7
Drosos et al (1997) ⁹⁸	Greece	0.5	0.2	0.4
Power et al (1999) ¹⁰⁷	Ireland			0.5
Cimmino et al (1998) ¹⁰⁸	Italy	0.5	0.1	0.3
Kvien et al (1997) ¹⁰⁹	Norway	0.7	0.2	0.4
Riise et al (2000) ⁹⁶	Norway	0.7	0.2	0.4
Carmona et al (2002) ¹¹⁰	Spain	0.8	0.2	0.5
Simonsson et al (1999) ¹¹¹	Sweden	2.0-7.4		0.5
Myasoedova et al (2010) ¹⁴	United States	1.4	0.7	1.1
Stojanovic et al (1998) ¹¹²	Yugoslavia	0.3	0.1	0.2
Middle East				
Akar et al (2004) ¹¹³	Turkey	0.7	0.2	0.4
South America				
Spindler et al (2002) ¹¹⁴	Argentina	0.3	0.1	0.2

ACR, American College of Rheumatology.

Adapted from Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum* 2006;36:182-8.

the intensity (packs per day) and duration of cigarette use.^{25,26} An individual's risk can remain elevated for up to 20 years after smoking cessation²⁵; however, it does decrease with time since quitting.²¹ Among blacks, the increased risk of RA associated with smoking was found to be limited to heavy smokers (defined as 10 pack-years or longer) in one cohort.²⁷ The population excess risk due to smoking is estimated to be 35%.^{25,28}

Carrying RA risk alleles in the human leukocyte antigen shared epitope (HLA-SE), the strongest genetic risk factor for RA, modifies the risk of RA in smokers, which suggests a gene-environment interaction.^{29,30} Studies show gene-environment interaction in analyses of ever smokers compared with never smokers in predicting seropositive (ACPA+ or RF+) RA, with

stronger interactions in analyses comparing never or light smokers with heavier smokers (10 pack-years or more), which suggests a dose response for smoking.^{25,31,32} This gene-environment interaction between smoking, the shared epitope, and increased risk of ACPA+ RA forms a potential model for the cause of RA.²⁹ Smoking increases the proportion of citrulline-positive cells in the lungs (demonstrated to occur by analysis of bronchoalveolar lavage fluid in smokers and absent in nonsmokers). Individuals with the shared epitope may be genetically predisposed to develop ACPAs, which places them at higher risk of developing RA.

There is evidence suggesting that other genes may also have significant interactions with cigarette smoke to increase risk for RA.³² These include

TABLE 83.4

Prevalence estimates of rheumatoid arthritis (RA) worldwide in populations not represented in Table 83.3 for which information on 1987 ACR criteria was unavailable

Study	Population/country	Prevalence of definite RA (%)		
		Female	Male	Combined
Africa				
Moolenburgh et al (1986) ¹¹⁵	Lesotho	0.4	0	0.3
Silman et al (1993) ¹¹⁶	Nigeria	0	0	0
Beighton et al (1975) ⁶⁹	Rural South Africa	0.1		
Solomon et al (1975) ⁷⁰	Urban South Africa	1.4	0	0.9
Asia				
Shichikawa et al (1981) ¹¹⁷	Japan	0.3		
Darmawan et al (1993) ¹¹⁸	Rural Indonesia			0.2
Darmawan et al (1993) ¹¹⁸	Urban Indonesia			0.3
Chou et al (1994) ⁷¹	Rural Taiwan	0.4	0.2	0.3
Chou et al (1994) ⁷¹	Urban Taiwan	1.2	0.6	0.9
Minh Hoa et al (2003) ¹¹⁹	Urban Vietnam			0.3
Europe				
Sorensen (1973) ¹²⁰	Denmark	1.2	0.3	0.8
Middle East				
Al-Rawi et al (1978) ¹²¹	Iraq			1
Pountain (1991) ¹²²	Oman			0.8
Native American				
Oen et al (1986) ¹²³	Inuit Eskimos, Canada	1.8		
Boyer et al (1998) ¹²⁴	Inupiat, Alaska	2.3	0.6	1.4
Jacobsson et al (1994) ¹⁶	Pima Indians, USA	3.1	1	
Boyer et al (1991) ¹²⁵	Southeast Alaska Natives	3.5	1.3	2.4
Boyer et al (1998) ¹²⁴	Yupik, Alaska	1	0.1	0.6

ACR, American College of Rheumatology.

ACR, American College of Rheumatology.

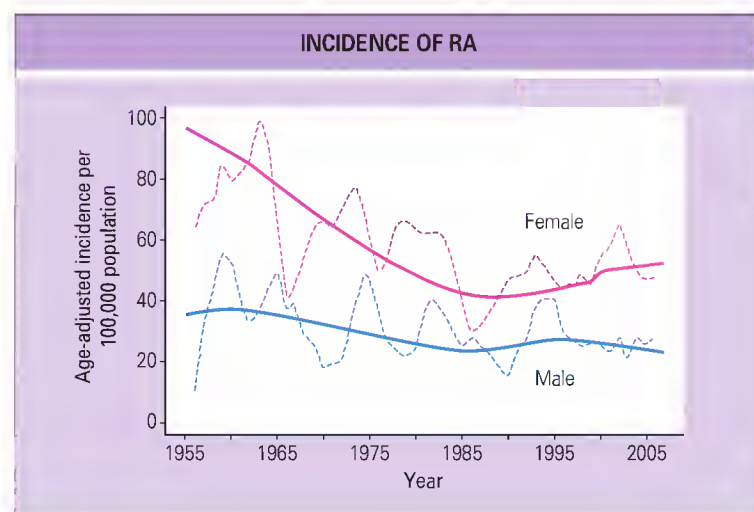


Fig. 83.1 Annual incidence of rheumatoid arthritis (RA) per 1000 population in Rochester, Minnesota, between 1955 and 2007. (From Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. *Arthritis Rheum* 2010;62:1576-82, Fig. 1.)

specific polymorphisms of genes encoding enzymes that detoxify carcinogens, glutathione S-transferase genes and the heme oxygenase 1 gene (HMOX1) among whites.^{33,34} Among blacks, an interaction between heavy smoking and the N-acetyltransferase 2 (NAT2) loci was observed.³⁵

Alcohol consumption may also lower the risk of developing RA, particularly ACPA+ RA.²⁴ A dose-dependent effect was also observed whereby individuals with the highest consumption (five or more drinks or 80 g ethanol per week) had a decreased risk of RA on the order of 40% to 50% compared to those with low to no consumption (less than 0.5 g ethanol per

week).³⁶ Coffee consumption has also been implicated as a risk factor for seropositive RA in longitudinal data from Finland,²² as has consumption of decaffeinated coffee in the United States³⁷; however, neither of these associations was replicated in a subsequent study.³⁸

The evidence linking obesity to increased risk of RA is conflicting. Obesity, defined as a body mass index of 30 or higher, was found to be associated with RA risk in population-based case-control studies with odds ratios ranging from 1.4 to 3.7.^{39,40} However, no association was observed in follow-up studies with prospective cohort designs.^{41,42} The most recent study conducted using a population-based case-control design found an association between individuals with a body mass index of 30 or higher and RA risk (odds ratio, 1.6; 95% confidence interval, 1.0 to 3.3) in ACPA+ women only.⁴³ This association was not observed in men with RA or ACPA+ women.

Nutrition

Studies of dietary influences on risk of RA have also produced conflicting results. Consumption of olive oil and fish oil has been reported to protect against the risk of developing RA; however, this association could not be confirmed in a prospective cohort study.⁴⁴ High protein and red meat intake was found to increase the risk of inflammatory arthropathy,⁴⁵ but a subsequent study showed no association with protein, iron, or red meat consumption and the risk of developing RA.⁴⁶

Vitamin D is an important modulator of the inflammatory response through the vitamin D receptor⁴⁷ in addition to playing a role in bone and mineral homeostasis. Lower intake of vitamin D was associated with an increased risk of RA in one study,⁴⁸ but no association was observed in another prospective study.⁴⁹ In a study assessing vitamin D levels before RA diagnosis, there was no difference in vitamin D levels measured at 1 year, 2 years, or 5 or more years before diagnosis.⁵⁰ Diets high in vitamin C were associated with a reduced risk of inflammatory polyarthritis in the United Kingdom⁵¹; however, an antioxidant protective effect was not observed in a large prospective cohort study based in the United States.⁵² There is also some evidence that copper and selenium deficiency are linked with RA.⁵³

Medications

The hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) have modest antiinflammatory effects in both RA cases and patients without rheumatic disease.^{54,55} Recent studies suggest that statin use may also reduce risk of RA by approximately 40% in individuals with hyperlipidemia.^{56,57}

Infectious agents

Classic epidemiologic evidence of an infectious cause for RA has not been forthcoming. Incident cases of RA do not cluster in space or time.⁵⁸ Concordant monozygotic twins, sibling pairs, and spouse couples show very little similarity in the timing of disease onset. Overcrowding as assessed by sibship size also has not been found to be a risk factor.

Potential associations with infectious agents have been observed, although the data are often conflicting. Increased titers of antibodies to the Epstein-Barr virus (EBV) have been demonstrated in RA patients after diagnosis. Titers were also shown to be increased before disease onset in a small group of patients in one longitudinal study⁵⁹; however, a subsequent longitudinal study found no difference in EBV titers in pre-RA cases and controls.⁶⁰ Antibodies to human parvovirus B19 were also found to be increased in females with RA in one case-control study.⁶¹ In general, it is conceivable that increased autoantibody concentrations may be a reflection of the disease process rather than infection prior to onset of disease. Serologic data have yielded no conclusive evidence of association with a number of other putative infectious triggers, including *Proteus*, cytomegalovirus, retroviruses, mycoplasma, and mycobacteria.⁶²

Socioeconomic status and occupation

The data regarding the association between socioeconomic status and RA are varied. The most recent studies demonstrate an inverse association between socioeconomic status measured by education and occupational class and risk of RA.⁶³ Furthermore, this risk was strongly associated with RF+ RA and not RF- RA in a Finnish cohort.⁶⁴ There was a twofold lower risk of RA in individuals with the longest education compared with those with the lowest level of education. These results concur with those of a previous population-based study in Sweden in which the risk of RA in subjects without university degrees was 40% higher than in those with university degrees. In subjects whose occupation required manual labor, the risk was 20% higher than in nonmanual workers.⁶⁵ Among the occupational exposures related to increased risk of RA are exposure to silica dust and mineral oil.^{65,66} These associations were not seen in a study conducted in the United Kingdom.⁶⁷ Furthermore, low socioeconomic status during childhood, which was based on measures such as level of food insecurity, household income of parents, and young maternal age, was found to be significantly associated with risk of RA.⁶⁸

Urban and industrialized environments

A more general association between RA and urban industrialized environments has been suggested. The influence of urbanization on increased risk of RA is suggested in studies of RA prevalence in urban environments compared with rural environments in both South Africa^{69,70} and Taiwan.⁷¹ However, this association is not seen in all population groups. With the development of reliable methods of studying geographic location, there is evidence that location of residence is associated with differential risk of RA in the US. Women living in the northeastern US had the overall highest risk compared to other regions of the country^{72,73} and exposure to traffic pollution is associated with an increased risk for RA.⁷⁴

HOST FACTORS

Reproductive and endocrine factors

The greater incidence of RA among females, which is most apparent before menopause, suggests an influence of reproductive and hormonal factors. Epidemiologic interest has focused on the influence of pregnancy itself, on risk factors such as breastfeeding in the postpartum period, and on the contribution of endogenous and exogenous hormones.

Nulliparity has been suggested as a risk factor for RA from the results of several case-control studies. However, the association is inconsistent and has not been confirmed in two prospective cohort studies.^{75,76} It is difficult to determine whether any putative association with nulliparity reflects an increased risk of infertility before the development of RA or a protective effect of pregnancy itself. The observations that the frequency of RA is no greater in unmarried than in married women and that family size is similar for patients with RA and for controls suggest that pregnancy does not have a protective influence overall.⁷⁷

Pregnancy may also influence the timing of disease onset. One study showed that the risk of new-onset RA is reduced during pregnancy itself but is increased in the 12 months after delivery.⁷⁸ Another study observed that the risk of RA was related to time since the last birth. The lowest risk of RA was among women who were 1 to 5 years postpartum (relative risk, 0.27; 95% confidence interval, 0.11 to 0.67), with this risk reduction decreasing with increasing time since last birth.⁷⁹

Breastfeeding is also associated with a decreased risk of RA. One prospective study based in the United States observed that breastfeeding for longer than 12 months was associated with decreased risk of RA and that the risk decreases with increasing duration of breastfeeding.⁸⁰ A subsequent case-control study in Sweden confirmed this association.⁸¹ These findings are contrary to those of a previous case-control study, which observed that in the first 12 months after pregnancy, breastfeeding after the first pregnancy increased the risk of RA fivefold.⁸²

The importance of the timing of pregnancy to the onset and severity of RA suggests a contribution from hormonal factors. Early menopause (age 45 years or younger) was associated with an increased risk of subsequent development of RA, even after adjustment for other risk factors such as smoking, level of education, and duration of breastfeeding.⁸³ Androgen deficiency is also thought to play a role in RA risk. The finding that androgen concentrations are lower than expected before the onset of disease in females suggests a possible causal link.⁸⁴ However, another study failed to confirm this association.⁸⁵

Exogenous hormones have also been studied extensively. Overall, the studies of association between oral contraceptive pill use and risk of RA have been conflicting, with two separate analyses reaching opposite conclusions.^{86,87} One study suggested an inverse association for oral contraceptives used in the 1960s when estrogen doses were higher than the current formulations.⁸⁸ There have been fewer studies of the effect of hormone replacement on RA, and a similarly conflicting picture has emerged.

Birth weight

In a case-control study in Sweden, higher weight at birth (more than 4 kg) was found to be associated with as high as a threefold increased risk of RA.⁸⁹ This finding was confirmed by a subsequent study in the United States which showed that babies weighing more than 4.5 kg at birth had a twofold higher risk of developing RA compared with babies who were 3.2 to 3.9 kg at birth.⁹⁰ Although the pathophysiology behind this association is unknown, it is hypothesized that the common pathologic process in the two conditions is hypothalamic-pituitary axis dysfunction, which is associated with both RA and high birth weight.^{91,92}

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84

Preclinical features of rheumatoid arthritis

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- Autoimmune diseases including rheumatoid arthritis (RA) typically begin with a prolonged asymptomatic period characterized by the presence of circulating disease-specific autoantibodies.
- RA is characterized by an increase in the number of epitopes recognized by anti-citrullinated protein antibodies as the point of appearance of clinically apparent disease approaches.
- RA is also characterized by an increase in levels of cytokines and chemokines as the onset of clinical disease nears.
- As clinical disease nears, RA-related autoantibodies increase their avidity and the G0 carbohydrate content of immunoglobulin G increases.
- The preclinical state in RA is characterized by the presence of asymptomatic small-airway disease that may play a key role in initiation of the disease.
- Other mucosal tissues, including periodontium, gut, and genitourinary tract, may also be sites of inflammation and/or dysbiosis in preclinical RA.
- Further studies of the natural history of RA are necessary to deepen the understanding of the initiation and propagation of disease.
- Ultimately, well-planned clinical trials in individuals at high risk of future development of RA are necessary to reach the goal of RA prevention.

INTRODUCTION

Definition and primary conceptual underpinnings of preclinical disease in autoimmunity

Traditionally, the field of rheumatology has considered the onset of autoimmune diseases to be the time point when clinically apparent disease occurs. With regard to rheumatoid arthritis (RA), that point would be the first onset of detectable joint discomfort or swelling. However, more recently it has been learned through the efforts of many investigators around the world that there is a prolonged period of highly specific RA-related autoantibody positivity in patients that occurs for several years before the onset of clinically apparent disease (reviewed by Deane and colleagues¹). Therefore new thinking is required about the disease, as well as a new lexicon that incorporates the emerging understanding of the natural history of RA.² One way to envision the current understanding of the natural history of seropositive RA is shown in [Figure 84.1](#).

This autoantibody-positive but asymptomatic period of time is now operationally defined as the *preclinical* period. How asymptomatic an individual is during this period is uncertain, though, because some investigators have included presentations such as “palindromic rheumatism” or “arthralgia” that evolve into classifiable RA as part of the preclinical period.³ Nevertheless, as discussed later, much of the research being performed involves individuals who exhibit a pattern of autoantibodies and biomarkers that indicates that they are at high risk of the *future* development of clinically apparent disease but have not yet transitioned to that period and are indeed asymptomatic. It is understood that a substantial proportion of these individuals will at some point in the future be given a confirmed diagnosis of RA based on either the 1987 American College of Rheumatology (ACR) criteria⁴ and/or the 2010 ACR/European League Against Rheumatism (EULAR) criteria.⁵

Importantly, the finding that preclinical asymptomatic disease evolves into clinically apparent disease only after a prolonged period of highly specific autoantibody positivity is not limited to RA. For example, similar

progression has been observed in the natural history of other autoimmune diseases, including systemic lupus erythematosus,⁶ type 1 diabetes mellitus,⁷ celiac disease,⁸ and Hashimoto thyroiditis.⁹ However, what is remarkable about RA, as compared with diseases such as type 1 diabetes mellitus and thyroiditis—in which the assumption has been that the presence of disease-specific autoantibodies is evidence of ongoing inflammation and organ-specific damage, for instance, in beta cells of the islets—is that the preclinical period is apparently not characterized by detectable arthritis histologically, even in patients who have arthralgia alone without arthritis.¹⁰

Seropositive versus seronegative rheumatoid arthritis

RA is characterized by two major subsets of disease: seropositive and seronegative (reviewed by Fuchs and Sergent¹¹). The discovery of new RA-related autoantibodies such as anti-carbamylated protein antibodies¹² in individuals who lack other RA-related autoantibodies, including rheumatoid factor and anti-cyclic citrullinated peptide antibodies, is decreasing the proportion of seronegative individuals; nevertheless, the seronegative subset is still found. Based on comparative studies of epidemiology and genetic associations, though, it is very likely that the pathogenesis of the two forms of disease is immunologically distinct.^{13,14}

Currently, because of the lack of autoantibody biomarkers, it is not possible to perform effective and informative prospective studies of the natural history of seronegative RA. In addition, many of the inflammation-related biomarkers that one typically sees in seropositive RA are not present at high levels in the preclinical period of seronegative disease.¹⁵ Because of this situation, this chapter primarily focuses on the natural history of seropositive RA.

NATURAL HISTORY OF RHEUMATOID ARTHRITIS

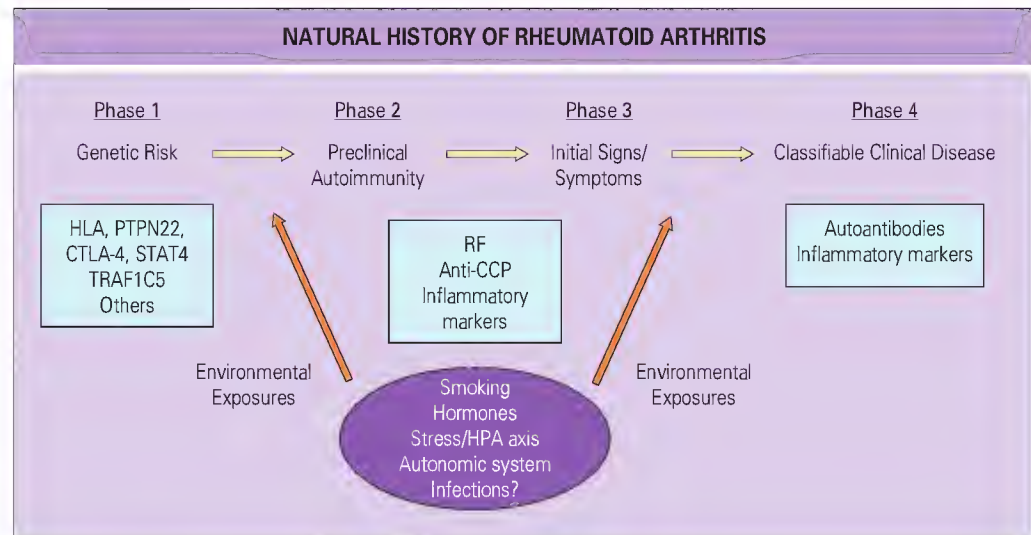
Autoantibodies precede the onset of clinically apparent disease

Importantly, based on a large number of studies performed in the United States, Canada, and Europe using different methodologies and types of retrospective cohorts, it is now known that levels of RA-related autoantibodies are elevated in asymptomatic individuals for up to 5 to 10 years before the development of clinically apparent signs and symptoms of RA.¹⁵⁻²³ As the onset of clinically apparent disease nears, the levels of these autoantibodies rise,¹⁵ and other features described later change. One notable characteristic of this pattern is that the relative duration of RA-related autoantibody positivity in the preclinical period exhibits an age dependence, with older individuals transitioning more slowly to clinically apparent disease than younger individuals.²⁴

Several types of autoantibodies have been detected and characterized in the preclinical period of RA. One type is rheumatoid factor (RF): autoantibodies that react primarily with the Fc domain of immunoglobulin G (IgG; reviewed in Schrohenloher and coworkers²⁵). Importantly, IgM, IgG, and IgA RF isotypes can all be readily measured; this is relevant because each RF test measures a unique population of autoantibodies that share the capacity to react with the Fc domain but differ in their isotypes as well as other physicochemical properties and are thus considered to be the products of related but immunologically distinct processes.²⁶

The second form of RA-related autoantibodies that has been studied is anti-citrullinated protein antibodies (ACPAs; reviewed in Girbal-Neuhauser and colleagues²⁷ and Schellekens and colleagues^{28,29}), for which the primary commercially available test is an enzyme-linked immunosorbent assay

Fig. 84.1 Development of seropositive rheumatoid arthritis (RA) through the initial phase of genetic risk, followed by the asymptomatic development of RA-related autoantibodies. The detail around the transition to early symptoms in the absence of identifiable synovitis is less well understood, but at some point patients develop synovitis and fulfill either 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) or 1987 ACR classification criteria. Many epidemiologic factors as noted appear to contribute to the development of the disease, although the phases to which each contributes are uncertain. Anti-CCP, anti-cyclic citrullinated peptide; HPA, hypothalamic-pituitary-adrenal; RF, rheumatoid factor.



BOX 84.1 AUTOANTIBODY CHARACTERISTICS IN THE TRANSITION FROM PRECLINICAL RHEUMATOID ARTHRITIS (RA) TO CLASSIFIED DISEASE

Identified changes in autoantibodies associated with the onset of clinically apparent disease

Increase in levels of anti-cyclic citrullinated peptide (anti-CCP) antibodies
Epitope expansion to additional peptides of anti-citrullinated protein antibodies
Increase in G0 content of immunoglobulin G (IgG) and anti-CCP antibodies
Increase in avidity of anti-CCP antibodies

Potential changes that could increase pathogenicity of RA-related autoantibodies

Ability to fix complement
Ability to engage activating Fc receptors
Development of IgE isotype antibodies

(ELISA) with a cyclic citrullinated peptide (CCP) antigen base of unknown composition. Detection of anti-CCP antibodies by ELISA was originally described as demonstrating a sensitivity of 60% to 70% and a specificity of 98%.^{29,30} More recent studies have modulated the specificity as more diseases have been evaluated and variations of the ACPA evaluation have evolved (reviewed in Demoruelle and Deane³¹). In addition, anti-CCP antibodies have been found in patients with RF-negative RA, and they are associated with the eventual diagnosis of RA in patients who clinically show undifferentiated polyarthritis at presentation.²⁸⁻³⁰

Reactivity to specific citrullinated peptides beyond that identified by standard CCP testing has also been evaluated using both bead-based arrays³² and the ELISA method.³³ Use of a peptide-based Luminex technology to detect elevations in a range of peptide-specific ACPAs has been found to be more sensitive than CCP testing alone for predicting the future development of clinically apparent RA and maintains specificity equivalent to that of anti-CCP testing; this method also detects increases in both the levels and the number of recognized epitopes as the time of clinical presentation approaches.³⁴ ELISA-based methods can also be used to detect elevations of ACPAs in the preclinical period.³³

In seronegative RA, although these individuals did not demonstrate a substantial number of ACPAs, there was evidence of increasing levels of systemic cytokines as the disease onset approached.³⁴ Thus there are some similarities in the biomarker evolution in seronegative RA, although the pattern is much less pronounced.

Modifications and other pathogenic features of autoantibodies evolve as clinical disease onset approaches

In addition to antigen reactivity, isotype, epitope spreading, and levels, there are other key features of autoantibodies that underlie their pathogenicity (Box 84.1). One feature of particular importance to RA is the specific carbohydrate content of IgG, defined as G0, G1, and G2 content. It has been known for several decades that G0 content is increased in individuals with clinically apparent RA, which is important because this type of antibody is considered to be more pathogenic due to its ability to more efficiently interact with Fc receptors and the lectin pathway of

complement.³⁵ Elevations of G0 carbohydrates were found to increase substantially as the time of onset of clinically apparent disease neared.³⁶

Another important characteristic of autoantibodies is the avidity of the mixture for self-antigen. In this regard, using ELISA assays it has been found that ACPAs with intermediate but not high avidity are associated with clinically active disease.³⁷ In addition, when avidity in the preclinical period was assessed, it was found that avidity increased from the preclinical stage to the stage of clinically apparent disease, which suggests that some threshold of avidity needs to be reached for transition from an asymptomatic state to clinically apparent disease.³⁸

What is yet unknown, although under study, is how other features, such as the presence of IgE ACPAs as previously described in patients with established RA³⁹; ACPA complement-activating potential for the classical, alternative, or lectin pathways⁴⁰; and Fc receptor engagement and cellular activation⁴¹ evolve over time in the transition from preclinical to clinical disease.

Other proinflammatory biomarkers increase as clinical disease onset approaches

In addition to changes in levels and other characteristics of RA-related autoantibodies as the time of clinical onset appears, changes in a number of other biomarkers have been shown to occur (Box 84.2). One is the number of cytokines and chemokines that are present in the peripheral blood, which has been shown to increase in an age-dependent manner.¹⁵ Another example is general measures of inflammation such as C-reactive protein. Importantly, there is no canonical pattern of cytokines that evolves in the preclinical period, which suggests that RA can develop through several pathways.^{15,42} Notably, even in first-degree family members of individuals with RA, elevations of certain cytokines are found both in association with elevations of autoantibodies⁴³ and even in the absence of autoantibodies.⁴⁴ This latter finding suggests that there may be genetically based alterations in specific inflammatory pathways that contribute to the risk of RA. Thus these biomarkers serve as measures of risk or impending clinical disease onset but have not yet been highly informative with regard to specific pathogenic processes.

EPIDEMIOLOGY OF PRECLINICAL RHEUMATOID ARTHRITIS

Environmental factors associated with rheumatoid arthritis that may operate in the preclinical period

Cross-sectional and retrospective analyses have identified many potential environmental factors that could play important roles in modifying either susceptibility to RA or disease severity (reviewed in Karlson and Deane⁴⁵). An important exposure that has received substantial recent attention is smoking.^{13,14,46} In addition, environmental lung exposure to silica-containing dust has been linked to the development of disease as well as to the presence of RF in individuals without RA,^{47,48} and a closer residence to a major road as a proxy for exposure to elevated air pollution is associated with an increased risk of RA.⁴⁹

A compelling case for environmental exposures' modifying risk or triggering disease can also be made for infection with certain bacteria and

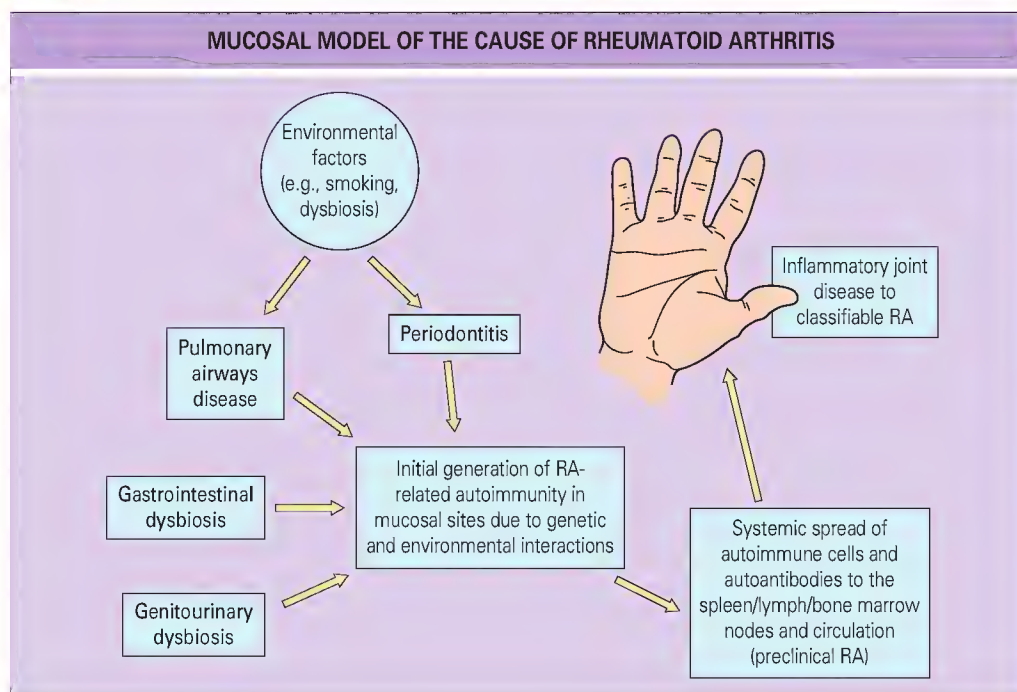


Fig. 84.2 In this pathogenic scheme, inflammation at one or more mucosal sites in individuals leads to the initial break in tolerance to self-antigens. The common pathogenic mechanism that ties these sites together is systemic spread of the anti-citrullinated protein antibody response and eventual targeting of the joint that is enabled by even transient local inflammation.⁸⁰ RA, rheumatoid arthritis.

BOX 84.2 ELEVATED PRECLINICAL CYTOKINE/CHEMOKINE AND INFLAMMATION-RELATED BIOMARKERS

High-sensitivity C-reactive protein
 Interleukin-1 α
 Interleukin-1 β
 Interleukin-1 receptor antagonist
 Interleukin-2
 Interleukin-4
 Interleukin-5
 Interleukin-6
 Interleukin-7
 Interleukin-8
 Interleukin-9
 Interleukin-10
 Interleukin-12p70
 Interleukin-13
 Interleukin-15
 Interleukin-17
 Eotaxin
 Fibroblast growth factor–basic
 Granulocyte colony-stimulating factor
 Granulocyte-macrophage colony-stimulating factor
 Interferon- γ
 Interferon-inducible protein 10
 Monocyte chemoattractant protein-1
 Macrophage inflammatory protein-1 α
 Macrophage inflammatory protein-1 β
 Tumor necrosis factor- α
 Vascular endothelial growth factor
 Soluble tumor necrosis factor receptor 1

viruses. Organisms studied include Epstein-Barr virus,^{50,51} parvovirus B19,⁵² and *Escherichia coli* expressing the dnaJ heat shock protein.⁵³ Substantial evidence also exists in patients with active RA for enhanced reactivity against several bacteria of gut origin, as well as for an increased rate of infection with specific organisms such as *Proteus mirabilis*.⁵⁴ In addition, levels of IgA reactivity against *P. mirabilis*, *E. coli*, *Campylobacter jejuni*, *Salmonella typhimurium*, *Salmonella enteritidis*, *Yersinia enterocolitica*, and *Klebsiella pneumoniae* have all been reported to be increased in individuals with RA compared with control subjects,⁵⁵ which suggests a relationship between RA and changes in gut permeability, specific or general levels of mucosal infection, or alterations of the normally noninflammatory mucosal milieu.

Recent studies have also suggested that the relative levels of specific organisms found in the largely unculturable microbiome is substantially different in patients with early RA at disease onset compared with control

subjects⁵⁶ and that specific changes in the oral microbiome are found.⁵⁷ In addition, individuals at higher risk of the future development of RA exhibit increased levels of antibodies to *Porphyromonas gingivalis* in the serum.⁵⁸ Finally, mycoplasma species have also been proposed to play important roles as environmental triggers of RA.⁵⁹ One way to integrate the findings of pulmonary, oral, and gut microbiome changes into the pathogenesis of RA is illustrated in Figure 84.2.

In addition to risk factors for disease, protective factors reported for RA include oral contraceptive pill use,⁶⁰⁻⁶² successful pregnancy,^{63,64} and dietary components including increased consumption of ω -3 fatty acids in fish and fish oils⁶⁵ and ω -9 fatty acids in olive oil. In addition, low levels of the serum antioxidants α -tocopherol and β -carotene have been proposed to increase disease risk.⁶⁶

Finally, although these associations are present in individuals with clinically active and long-standing RA, the stage at which factors that are associated with increased risk of RA impact the development of autoimmunity and clinically apparent disease is unknown. However, based on available data, it appears that smoking increases risk of the early-stage development of RA-related autoantibodies, whereas oral contraceptive exposure decreases the risk.⁶⁷ Further studies are needed to understand exactly when in the course of RA development these factors may act to trigger or promote disease.

Pulmonary disease in the preclinical period

Substantial prior data suggest that the lung is an important organ that is commonly affected in patients with RA (reviewed in Klareskog and associates¹³ and Demoruelle and Deane³¹). In addition, recent studies have demonstrated that individuals who are at increased risk of the future development of RA by virtue of asymptomatic elevations of ACPAs and/or RFs also exhibit an increased prevalence of airway disease, even in the absence of smoking, which suggests that other potential causes of local inflammation are driving these changes.⁶⁸ Furthermore, ACPA elevations can be found in individuals who have clinically apparent lung disease initially in the absence of inflammatory arthritis and who later progress to clinically apparent articular RA.^{69,70} In total, these findings suggest that the lung could be a site of initial generation of RA-related autoimmunity in a proportion of individuals who develop RA, an assertion supported by studies in patients with established RA which have demonstrated that the airways can be a site of generation of RA-related autoantibodies.⁷¹

THERAPEUTIC APPROACHES TO THE PRECLINICAL PERIOD OF RHEUMATOID ARTHRITIS

The existence of a prolonged stage of preclinical RA (see Fig. 84.1) suggests that if one can identify individuals in this phase and predict the onset of

clinically apparent RA with sufficient accuracy, the next logical step is to determine whether one can prevent the onset of disease.⁷² Certainly previous studies have strongly supported the concept that the earlier the treatment, the better the long-term outcome (reviewed in Demoruelle and Deane⁷³). One expectation is that extending treatment into the preclinical period with the goal of prevention will provide even more benefit.

Prediction of the timing of onset of clinically apparent disease

The major limitation to the development of therapeutic strategies in the preclinical period is the relative lack of understanding of the timing of the onset of clinically apparent disease in individuals positive for high-risk RA-related autoantibodies. Several approaches are being undertaken to identify predictive patterns, and these use two parallel methods. The first is to assess the extent of expansion of epitopes recognized by ACPAs, which is also reflected in the levels of anti-CCP antibodies.³⁴ The other is to evaluate the number and levels of increases in peripheral cytokines and chemokines in the sera of individuals who also exhibit high-risk RA-related autoantibodies¹⁵ (Fig. 84.3). Finally, other combinations of biomarkers are envisioned as being potentially informative in this manner.¹

Risk factor modification

Eliminating in the preclinical phase of RA development factors that may trigger or propagate RA-related autoimmunity may be an effective approach to prevent or modulate clinically apparent disease. In particular, given the importance of the association between smoking and the risk of the development of seropositive RA in individuals with the proper HLA-DRB1 genetic background,^{13,14} it is logical to ask what would be the population-based effect of an intervention to decrease smoking. That question has been addressed by a modeling study conducted in the Swedish population, which estimated that smoking potentially was responsible for up to 35% of cases of ACPA-positive RA and up to 55% of cases of ACPA-positive RA in

individuals with two copies of HLA-DRB1 alleles containing the shared epitope.⁷⁴ Whether smoking provides a similar effect in other populations is uncertain.⁷⁵ In addition, it is not certain what would be the effects of smoking cessation in those who have already developed RA-related autoantibodies and other biomarkers, especially if smoking acts to trigger initial autoimmunity but other factors lead to propagation of RA to clinically apparent disease. Notably, however, in retrospective studies approximately 20 years are required after smoking cessation to diminish the elevated risk of RA development.⁷⁶ Certainly further work is necessary to identify risk factors for RA that impact autoimmunity in the preclinical period of disease development so that mitigation of these factors, including smoking, can be evaluated as prevention strategies for RA.

Approved drug therapies as potential prevention approaches

Recent clinical trials in patients with classifiable RA have focused increasingly on treating patients at earlier and earlier time points following the onset of clinically apparent disease, with almost universally improved long-term clinical outcomes. Thus it is not unreasonable to expect that the use of therapeutics in this period would at a minimum improve long-term outcomes beyond traditional approaches, even if the treatment did not prevent the onset of clinically apparent disease.

In this light, potential approaches to the prevention of clinical onset of signs and symptoms of RA start with the use of traditional small-molecule drugs such as methotrexate or hydroxychloroquine. Beyond this, the use of biologic therapies, especially ones that are predicted to affect ACPA antigen-specific tolerance or responses, are also candidates for consideration.

Additionally, other pharmacologic agents may impact autoimmunity and therefore may be considered in preventive approaches for RA. Candidates include the statins, the use of which in two population-based studies suggested a modest decrease in risk of RA.^{77,78}

Antigen-specific tolerance approaches

Murine studies have been conducted in which the administration of citrullinated filaggrin peptide using a tolerizing approach was successful in diminishing the subsequent development of arthritis and ACPA epitope spreading.⁷⁹ Given these results, if one were to understand what antigens are driving evolution of disease, the development of tolerizing regimens is possible. In this area of human investigation, therefore, research efforts are being focused on determining the “original sin,” that is, the antigen(s) to which tolerance is initially broken, as well as defining the range of ACPA epitopes that are recognized in the preclinical period.

Clinical trial endpoints

With regard to potential trial endpoints, ultimately prevention of the onset of clinically apparent inflammatory arthritis is the goal. However, short of that, other potential endpoints that may be realized in a time frame more applicable to a clinical trial (e.g., 2 to 3 years) include either biomarker-related endpoints such as alterations and improvements in the rate or level of ACPA epitope spreading, or changes in the levels of biomarkers such as cytokines, chemokines, or C-reactive protein.

Treatment of the underlying causal mechanisms of disease

Finally, it is important to include the possibility of using radically different approaches that are directed at the causal mechanisms of disease. Examples of such approaches are treatment of periodontitis, modulation of pulmonary inflammation, and treatment focused on repairing a causal dysbiosis.

CONCLUSION

In summary, RA appears to develop in a series of stages, with a preclinical period present for a substantial time before the onset of clinically apparent inflammatory arthritis. The preclinical stage of RA is characterized by the evolution of multiple autoimmune and inflammatory processes that are measured by a number of specific biomarkers. These biomarkers can also be used to predict both the likelihood and timing of future inflammatory arthritis, although additional studies to refine existing prediction models are needed. Multiple genetic, environmental, and lifestyle factors may play a role in the initiation and propagation of RA-related autoimmunity. Importantly, established and emerging data have led to the concept that RA may

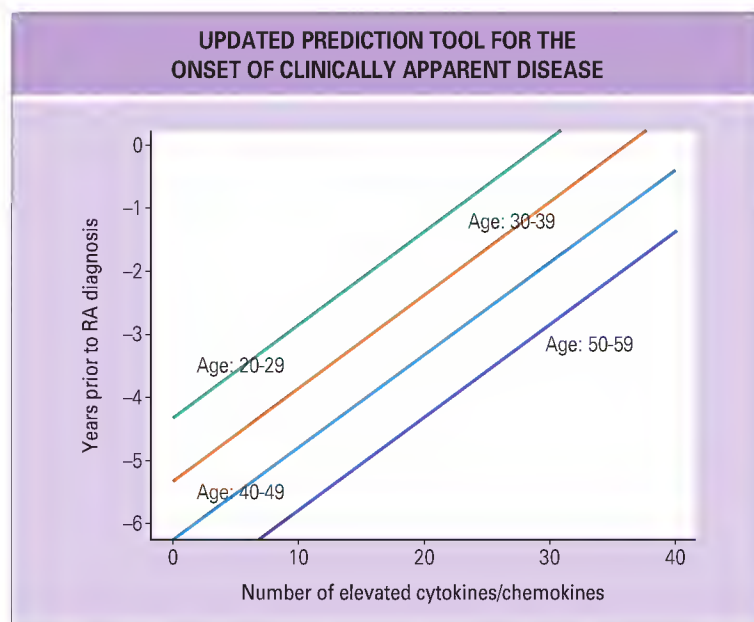


Fig. 84.3 This model was developed as a two-step approach to predict the timing of onset of future rheumatoid arthritis (RA), using blood samples obtained before a diagnosis of RA from members of the United States armed forces. The first step was to select individuals whose blood samples were positive for RA-related autoantibodies highly predictive (>96% specific) for future RA (antibodies to citrullinated peptide antigens and/or two or more rheumatoid factor isotypes). The second step was to test for 48 cytokines and chemokines, with a cutoff for each marker established in healthy controls. An increase cytokine/chemokine count is predictive of a shorter time to diagnosis of RA in an age-dependent fashion. For example, in an individual who was 25 years old at the time of testing, positive results for 30 cytokines/chemokines indicates <1 year until diagnosis of RA; however, in a 55-year-old, that same cytokine/chemokine count indicates ~3 years until diagnosis. In a real-time fashion, this model can be used to predict both the likelihood and timing of future RA in a currently asymptomatic individual.

be a preventable disease. To reach this goal, further natural history studies of RA development are needed to understand key mechanistic aspects of the development of disease. Furthermore, methods to identify individuals in the general population who are at high risk of RA need to be established. Ultimately, all of the aforementioned factors need to be distilled into

well-planned clinical trials in individuals who are at high risk of future RA to prevent clinically apparent disease, with such trials using either established pharmacologic agents or other interventions that are firmly rooted in a mechanistic understanding of RA development and that achieve a balance between risk and benefit.

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85

Clinical features of rheumatoid arthritis

■ RICHARD D. BRASINGTON, JR.

- Morning stiffness and swelling in the wrists and proximal interphalangeal and metacarpophalangeal joints are the typical features of rheumatoid arthritis (RA).
- Early diagnosis of RA is critical, but many cases of “early arthritis” are not RA.
- The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA provide a framework for accurate diagnosis of early RA.
- Anti-citrullinated peptide antibodies occur earlier than rheumatoid factor and are more specific for RA.
- Aggressive early administration of disease-modifying antirheumatic drugs is critical to a good outcome.

INTRODUCTION

Rheumatoid arthritis (RA) is the paradigm of a systemic autoimmune disease characterized by inflammatory polyarthritis. The hallmark of RA is symmetric synovial proliferation and tenderness in multiple joints, particularly the small joints of the hands and feet. Most patients experience joint stiffness or gelling for more than an hour in the morning. The blood of approximately 80% of patients with RA contains rheumatoid factor (RF), an immunoglobulin that binds the Fc region of the IgG molecule, anti-citrullinated peptide antibodies (ACPAs), or both RF and ACPAs. Rheumatoid nodules are seen in about 20% of patients. Thus, an individual with a several-week history of symmetric swelling and tenderness of the small joints of the hands, morning stiffness, and positive RF or ACPA probably has RA.

These clinical features are reflected in the 1987 criteria for the classification of RA developed by the American College of Rheumatology (ACR) (Box 85.1).¹ The criteria were developed for classification of patients with RA for inclusion in research studies, not to make the clinical diagnosis of RA. Though quite specific for the diagnosis, these criteria have significant limitations because our understanding of and approach to RA have changed dramatically since 1987. The 2010 RA classification criteria (discussed in more detail in Chapter 83), developed by a joint working group from the ACR and the European League Against Rheumatism (EULAR), provide a mechanism for the diagnosis of RA before the development of erosive joint disease and persistence of symptoms.² The 2010 criteria apply to patients with definite synovitis for which there is no better explanation than RA. The criteria include the number and distribution of joints with synovitis (but no longer symmetry of involvement), duration of symptoms, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and RF and ACPA. Table 85.1 lists the criteria and explains their application.

Perhaps the most important concept in our contemporary approach to RA is the recognition that prognosis and outcome are improved when disease-modifying antirheumatic drug (DMARD) therapy is started within a few weeks or months of disease onset. We now believe that it is critical to identify RA within a few weeks or months of its onset because immediate institution of DMARD therapy results in better outcomes than when administration of DMARDs is delayed for even several months. It is well established that erosive damage can be seen on radiographs of the hands and feet early in the course of RA. Progression of radiographic damage occurs to a lesser degree in patients receiving early therapy than in those for whom therapy is delayed. Because there appears to be a general correlation between

radiographic damage and disability over time, it is hypothesized that preventing radiographic damage will reduce the extent of disability over the years.³ Patients have a greater likelihood of attaining remission with early treatment. Thus it is axiomatic that the diagnosis of RA be made as soon as possible so that DMARD treatment can be started without delay.

CLINICAL EVALUATION

History

The patient's history is typically strongly suggestive of the development of inflammatory arthritis. Commonly, patients will have polyarthritis of the small joints of the hands, but monoarticular involvement can occur initially. The development of joint symptoms may occur almost overnight, or they may evolve slowly over a period of several months. RF and ACPAs have been found in up to half of patients with RA as long as 5 years before the development of clinical disease, thus suggesting the insidious development of disease over time.⁴ Stiffness or gelling in the joints is present on arising and often takes several hours to abate. An inability to “wring out a washcloth” is common, as is the need to hold a coffee cup with both hands. Patients will typically report soft tissue swelling over the knuckles and describe markedly reduced grip strength. Discomfort in the feet is generally most prominent in the metatarsal area; patients may complain of the sensation of having a “stone in my shoe.” Profound fatigue often accompanies the joint complaints, and anorexia and mild weight loss may occur. Typically, patients with RA do not have rash, fever, headache, visual disturbance, or pleuropericardial symptoms at initial evaluation.

Pain in the joints is universal in patients with RA. The pattern of joint involvement in RA is quite typical in most cases. Affected joints include the proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, shoulder, hip, knee, ankle, and metatarsophalangeal (MTP) joints. However, the quality of the pain may vary depending on the type of joint involvement. For example, the pain associated with chronic inflammatory synovial proliferation may be experienced as a dull ache with little fluctuation in intensity. By contrast, the mechanical pain associated with bone and cartilage damage in the knee or hip, in the absence of inflammation, may be more sharp and acute and be associated with activity and relieved with rest.

Patients with musculoskeletal distress commonly complain of joint “swelling,” even in the absence of detectable abnormality on physical examination. However, patients with RA will probably notice swelling in their hands, particularly the MCP joints. Rings may need to be resized or cut off the swollen finger. “Trigger finger” secondary to flexor tenosynovitis may occur.

Examination and clinical features of specific joints

The key to recognition of the physical findings in RA is the ability to recognize the manifestations of synovial proliferation. Unlike normal synovial lining, which is only one or two cell layers thick, in RA the synovium proliferates out of control. As it grows thicker and covers a greater surface area, the rheumatoid *pannus* (Latin for “cloth”) becomes palpable between the patient's skin and the underlying bone and cartilage. This proliferating synovium has a “doughy” or “squishy” feel on palpation, quite distinct from bony enlargement or synovial fluid. This finding is often referred to as “synovitis”; however, the classic inflammatory signs of heat and redness are usually absent, and external examination cannot determine the functional characteristics of the enlarged synovial tissue. Some prefer to use the term *synovial thickening* to describe palpable synovial proliferation. Because *synovitis* is the most commonly used term, palpable synovial tissue will

BOX 85.1 1987 CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

The clinical criteria must have been observed by a physician and have been present for at least 6 weeks. At least four of the seven criteria are required for the diagnosis of rheumatoid arthritis (RA). Individuals can be classified as having or not having RA (no RA). New criteria were developed in 2010.

- Morning stiffness lasting at least 1 hour
- Swelling in three or more joints
- Swelling in hand joints
- Symmetric joint swelling
- Erosions on radiographs of the hands
- Rheumatoid nodules
- Positive rheumatoid factor

TABLE 85.1

2010 ACR/EULAR classification criteria for RA*

	Score
Joint involvement	
1 large joint†	0
2-10 large joints	1
1-3 small joints‡	2
4-10 small joints	3
>10 joints (at least 1 small joint)	5
Serology	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
<6 wk	0
≥6 wk	1

*The target population should have at least one joint with definite synovitis that is not better explained by another diagnosis. A score of 6 of 10 or greater is needed for classification of definite RA.

†Large joints: shoulders, elbows, hips, knees, and ankles.

‡Small joints: second to fifth metacarpophalangeal (MCP), proximal interphalangeal (PIP), thumb interphalangeal, and wrists.

ACPA, anti-citrullinated peptide antibody; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor.

Adapted from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria. *Arthritis Rheum* 2010;62:2569-81.

subsequently be referred to as synovitis in recognition of the fact that acute inflammation is not necessarily present.

Rheumatoid nodules are quite specific for RA and occur in about 20% of patients, generally those with more severe disease and high-titer RF. It is uncommon for nodules to be present within the first year. A nodule is a mass of inflammatory tissue with a central focus of necrosis, presumably the consequence of vascular inflammation, surrounded by chronic inflammatory cells. Nodules occur over extensor surfaces and joints, at sites of chronic mechanical irritation (elbow, toe, and heel), and in subcutaneous tissue of the fingers. Nodule formation sometimes progresses during methotrexate treatment. Rheumatoid nodules may be confused with gouty tophi, so aspiration for crystals or biopsy is sometimes necessary.

In the hands the MCP and PIP joints are almost always involved (Fig. 85.1), and typically the index and long fingers are more involved than the others. A “four-point” technique in which the examiner uses both index fingers and thumbs is preferred for palpating the small joints of the hands (Fig. 85.2). With the patient’s hand in pronation, the examiner palpates the dorsal and volar aspect of the MCP and PIP joints (Fig. 85.3). Particular attention should be paid to the second MCP joint because synovitis may be especially prominent there. The joint line between the distal metacarpal and proximal phalanx, which is easy to palpate in a normal joint, becomes effaced by the synovitis. The “valleys” between the MCP joints are filled in by synovitis. PIP joint synovitis is more easily recognized by lateral



Fig. 85.1 The hand in early rheumatoid arthritis (RA). The right hand shows swelling of the metacarpophalangeal and proximal interphalangeal (PIP) joints. Swelling of the PIP joints is typical of RA and associated with morning stiffness, difficulty making a fist, reduced grip strength, and tenderness of the affected joints. The left hand showed similar changes. (Reproduced with permission from Dieppe P, Bacon PA, Bamji AN, Watt I. *Slide atlas of clinical rheumatology: the clinical evaluation of rheumatic diseases*. London: Gower Medical; 1982.)



Fig. 85.2 “Four-point” technique for palpating the small joints of the hands. (From Lawry G. *The general musculoskeletal examination*. Iowa City, Iowa: University of Iowa Press; 2002.)

palpation of the joint. In RA, involvement is clearly localized to the PIP joint, unlike the dactylitis (“sausage” digit) of spondyloarthritis. The distal interphalangeal (DIP) joints are rarely involved in RA, perhaps because they have less synovium than the MCP and PIP joints. Rheumatoid nodules may occur on the extensor aspect of the fingers.

Flexor tenosynovitis is common and may lead to “trigger finger.” The flexor tendons for the fingers pass through the A1 pulley near the palmar surface of the MCP joint. Thickening or nodularity may prevent the flexor tendon from sliding smoothly through the pulley and result in a snapping sensation with flexion and extension or result in just flexion, as though pulling the trigger of a gun. Frequently, a palpable nodularity of the tendon can be felt by palpating this area with the index finger as the patient flexes and extends the finger.

Signs of late disease with irreversible damage include “swan neck” and “boutonnière” deformities and subluxation of the MCP joints with “ulnar drift” (Fig. 85.4), often accompanied by atrophy of the intrinsic muscles of the hand. The boutonnière deformity entails flexion of the PIP joint and extension of the DIP joint (see Fig. 85.4). As the central extensor tendon is damaged by tenosynovitis, the PIP joint ruptures through it dorsally, thereby

resulting in lateral and volar displacement of the lateral bands of the tendon. Paradoxically, the lateral bands of the central extensor tendons now function as flexors of the PIP joint, and with tendon shortening, hyperextension of the DIP joint develops. By contrast, the swan neck deformity is basically the opposite of the boutonnière deformity, with hyperextension of the PIP joint



Fig. 85.3 Palpation of the dorsal and volar aspects of the metacarpophalangeal and proximal interphalangeal joints to detect synovial proliferation. (From Lawry G. *The general musculoskeletal examination*. Iowa City, Iowa: University of Iowa Press; 2002.)

and flexion of the DIP joint (see Fig. 85.4). The lateral bands of the central extensor tendon sublux dorsally as the PIP joint herniates in a volar direction. Alternatively, the DIP joint can rupture dorsally through the central extensor tendon (like the PIP joint in the boutonnière deformity). In either case, progressive shortening of the tendon maintains DIP flexion and PIP extension. Early in the course, both the boutonnière and swan neck deformities may be reducible. However, as the disease progresses and the tendons shorten, fixed joint contractures develop.

The thumb can be affected by several deformities. Arguably, the most common has been described as the flail interphalangeal (IP) joint (Fig. 85.5), in which case the patient loses the ability to flex that joint. This results in significant functional impairment because of loss of pinch strength, with the patient pinching the index finger against the proximal phalanx. Surgical fixation of the IP joint in flexion may be required to maintain function. A boutonnière deformity of the thumb develops secondary to MCP synovitis and results in MCP joint flexion and IP joint hyperextension. (Imagine the boutonnière deformity described earlier moved back one joint proximally.) The equivalent swan neck deformity of the thumb develops with dislocation of the first carpometacarpal joint, MCP hyperextension, and IP flexion.

At the wrist, synovial proliferation occurs around the ulnar styloid (see Fig. 85.5), and as the disease progresses, laxity of the radioulnar ligament gives rise to the “piano key” sign as the ulnar styloid moves up and down in response to dorsal pressure from the examiner’s thumb. Carpal tunnel syndrome from compression of the median nerve is quite common and often responds to treatment of the disease. Subluxation of the wrist can result in severe disease (Fig. 85.6). Tenosynovitis of the extensor carpi ulnaris and extensor digitorum communis sheaths in the dorsal aspect of the wrist produces a characteristic pattern that is virtually unique to RA (Fig. 85.7); the tubular swelling of the common extensor tendon sheath ends abruptly just distal to the wrist joint. This often obscures swelling on the dorsum of the wrist (radiocarpal) joint itself. Damage from chronic tenosynovial inflammation and friction from the extensor tendons of the third, fourth,

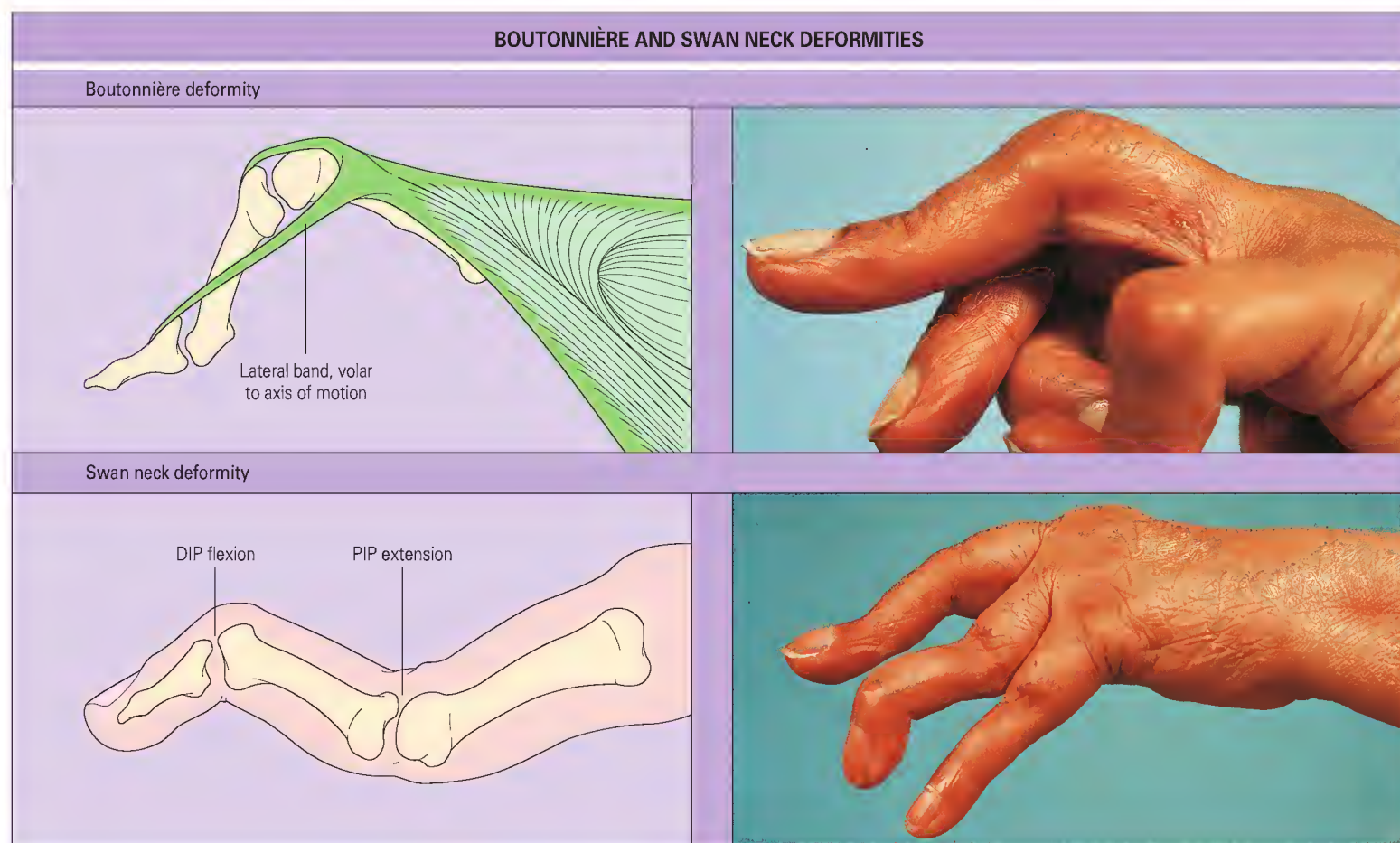


Fig. 85.4 The boutonnière deformity—flexion of the proximal interphalangeal (PIP) joint and hyperextension of the distal interphalangeal (DIP) joint—results from relaxation of the central slip with “buttonholing” of the PIP joint between the lateral bands. The swan neck deformity—flexion of the metacarpophalangeal (MCP) joint, hyperextension of the PIP joint, and flexion of the DIP joint—may be mobile, snapping, or fixed. Its pathogenesis may be related primarily to PIP or MCP involvement. Combinations of MCP and PIP involvement are less frequent. (Adapted with permission from Hastings DE, Welsh RP. *Surgical reconstruction of the rheumatoid hand*. Toronto: Orthopaedic Medical Management Corporation; 1979.)



Fig. 85.5 Hyperextension of the interphalangeal joint of the right hand illustrates a “flail thumb.” Note also subluxation of the right fifth metacarpophalangeal joint, the prominent ulnar styloid, and ulnar drift. (From *Clinical Slide Collection on the Rheumatic Diseases*, American College of Rheumatology.)



Fig. 85.6 Subluxation of the wrist in severe disease associated with extensor tenosynovitis and extensor tendon rupture. (From *Clinical Slide Collection on the Rheumatic Diseases*, American College of Rheumatology.)



Fig. 85.7 Tenosynovial swelling as a result of tenosynovitis—the “tuck” sign. Tenosynovial swelling overlies the metacarpals of the right hand. Bulging becomes accentuated with full extension of all the fingers of the hand. Persistent tenosynovitis over the dorsum of the wrist may lead to extensor tendon erosion and rupture, particularly of the tendons of the fourth and fifth fingers.

and fifth fingers crossing the jagged and eroded ulnar styloid can lead to tendon rupture with an inability to actively extend those fingers (see Fig. 85.7).

Three characteristic findings occur at the elbow. Synovitis may be palpated between the lateral epicondyle and the olecranon prominence. The radiohumeral joint is just distal to the lateral epicondyle. Swelling of the olecranon bursa often occurs in more severe disease and tends to be bilateral. In fact, bilateral olecranon bursal swelling occurs only in RA, gout, and pseudogout. Finally, the olecranon and extensor surface of the proximal end of the ulna are very common sites for rheumatoid nodules.

Shoulder involvement typically produces significant limitation of motion in all planes. Visible effusion of the glenohumeral joint is unusual but can produce a “shoulder pad” sign. On examination the patient will elevate the scapula to improve range of motion for abduction and elevation. Shoulder pain is often referred to the proximal deltoid region. Evidence of impingement of the supraspinatus and biceps tendons is frequently present. Because of ongoing synovitis, rupture (either partial or complete) of the rotator cuff group of muscles may occur. Tenderness and swelling may also be seen at the sternoclavicular joint.

Spine involvement in RA is limited mostly to the cervical spine, particularly the upper portion. On examination one notices decreased range of motion in all planes. The most critical involvement occurs at the atlantoaxial joint, where the ring of C1 pivots on the odontoid peg of C2 (Fig. 85.8). The transverse ligament of the axis courses around the posterior portion of the odontoid, which prevents subluxation of C1 on C2. Tenosynovitis here can decrease the space available for the upper cervical cord as it passes through the bony spinal canal posterior to the odontoid. This can also lead to laxity of the transverse ligament or erosion of the odontoid, in which case the ring of C1 can move forward on neck flexion (atlantoaxial subluxation) and reduce the diameter of the spinal canal and compress the upper cervical cord (Fig. 85.9). Cranial settling describes caudal migration of the cranium on the spinal column, which results in movement of the odontoid into the foramen magnum, where it compresses vital structures (Fig. 85.10). Subaxial subluxation represents unstable movement of one vertebral body on another below C1-C2. Vertebral artery compromise can also occur as a result of these structural defects.

Significant cervical spine involvement can have protean clinical manifestations, including headache, neck pain, a sensation that the head might fall off, paresthesias, weakness, transient ischemic attacks, and bowel and bladder sphincter impairment. The development of any of these symptoms in a patient with severe RA calls for immediate neurologic examination. Magnetic resonance imaging provides the best information on anatomic derangements in the area.

The hip is frequently affected in RA, and progressive disease can lead to severe secondary osteoarthritis requiring total joint replacement. Pain from the hip joint itself is experienced in the groin and medial aspect of the thigh, sometimes with radiation to the buttock. Pain over the greater trochanter, which most patients refer to as the “hip,” is more likely due to bursitis. The Patrick test (also known by the acronym FABER for flexion, abduction, external rotation) puts the hip through passive motion in all major planes and produces groin pain in the presence of true hip disorders. In later

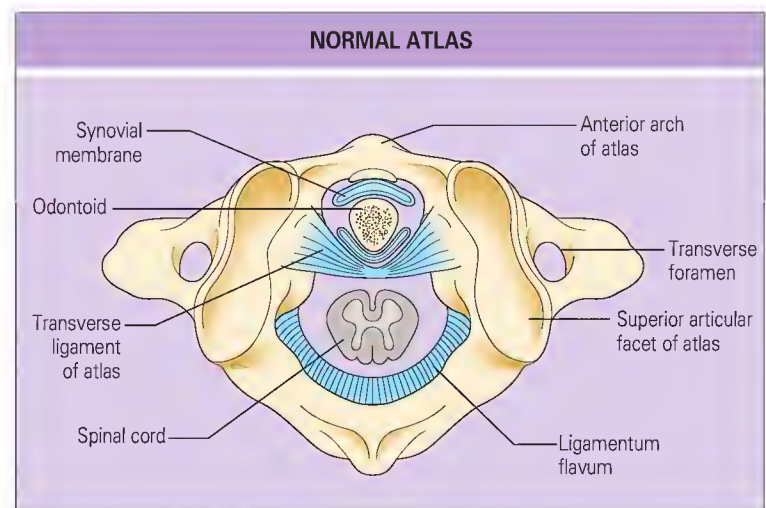


Fig. 85.8 Relationship between the peg of the odontoid and the arch of C1. (From *Clinical Slide Collection on the Rheumatic Diseases*, American College of Rheumatology.)

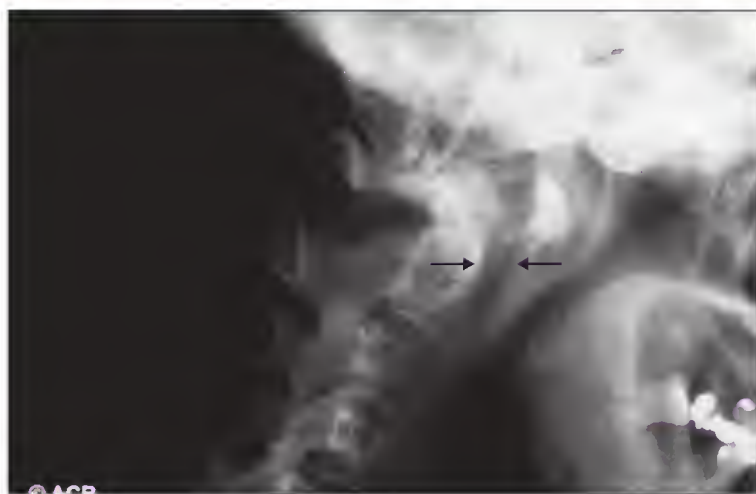


Fig. 85.9 This radiograph of a rheumatoid cervical spine in flexion demonstrates atlantoaxial subluxation as the arch of C1 slides forward (arrows). (From *Clinical Slide Collection on the Rheumatic Diseases*, American College of Rheumatology.)

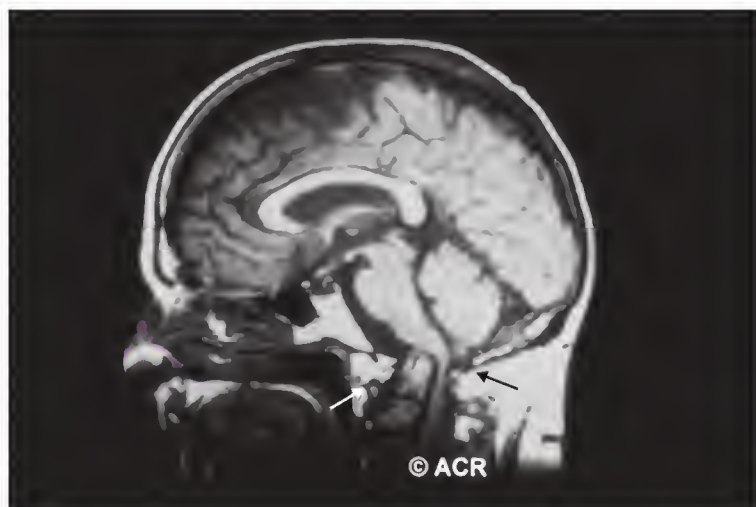


Fig. 85.10 Cranial settling occurs when the cranium migrates caudally onto the odontoid, which impinges on the brain stem above the foramen magnum. The odontoid should not extend much above a line drawn between the white and black arrows. (From *Clinical Slide Collection on the Rheumatic Diseases*, American College of Rheumatology.)

disease it is essential to distinguish symptoms of ongoing synovitis from mechanical pain related to joint damage. Sudden development of hip pain suggests avascular necrosis or fracture in patients taking corticosteroids long-term.

Rheumatoid involvement of the knee joints is easy to detect by physical examination and is often a good indicator of disease activity. Anterior swelling is detectable by the “bulge” sign, in which the examiner strokes the medial part of the knee to move the synovial fluid cephalad and then presses on the lateral aspect of the knee to produce a visible fluid wave, or “bulge,” on the medial part of the knee. With a large tense effusion it may be impossible to move enough fluid to produce a bulge, in which case ballottement of the patella with the index finger produces downward movement of the patella in the fluid. Distention of the posterior compartment of the knee capsule produces a tense Baker cyst in the popliteal region. Rupture of such a popliteal cyst can produce swelling, heat, and pain in the posterior part of the calf, similar to deep venous thrombosis. A hemorrhagic “crescent” sign below the malleoli (Fig. 85.11) may result. Musculoskeletal ultrasound examination can be useful in detecting a popliteal cyst before rupture. Progressive synovitis can lead to loss of articular cartilage, secondary osteoarthritis, and the need for total knee arthroplasty. Examination of synovial fluid can be very helpful in distinguishing between persistent disease activity and mechanical damage. In chronic disease, quadriceps atrophy and flexion contracture are common.



Fig. 85.11 Acute synovial rupture. An effusion in the right knee developed in a 51-year-old man with rheumatoid arthritis of 3 years' duration after an evening of square dancing. Two days later he noted progressive pain and swelling in his right calf. (a) Six days later, bluish discoloration developed on both sides of his ankle. (b) A few weeks later, after more dancing, he noted posterior thigh pain and swelling that soon became associated with purple discoloration on the posterior aspect of his right thigh.

The ankle is another large weight-bearing joint in which active RA can be directly visualized. The capsule of the tibiotalar joint distends anteriorly and effaces the normal contour of the tibialis anterior tendon. The joint line itself can be palpated between that tendon and the medial malleolus, where synovial proliferation can be identified. Progressive damage to the tibiotalar, subtalar, and talonavicular joints can result in ankle and midfoot pronation and loss of the transverse arch and produce mechanical symptoms that can be quite challenging to manage. Tendinitis of the posterior tibialis develops posterior and medial to the medial malleolus. In the same area the posterior tibial nerve can be compressed in the tarsal tunnel, thereby leading to paresthesias on the sole of the foot. “Pump bumps” and rheumatoid nodules commonly develop at the site of shoe friction on the posterior aspect of the heel.

The forefoot is an area of major rheumatoid involvement. Early in disease, examination will reveal tenderness on palpation of the individual MTP joint or on squeezing the forefoot. Swelling can be seen in the dorsum of the foot just proximal to the toes. As the disease progresses, the metatarsals sublux on the plantar aspect of the proximal phalanges and displace the soft tissue fat pads that normally underlie the metatarsal heads. Furthermore, the forefoot broadens and the transverse arch of the forefoot disappears, and thus the patient's metatarsal heads are now directly bearing the weight of the entire body. Calluses develop under the metatarsal heads, and in advanced cases of RA, ulcerations occur at this location. Hammertoes (resembling piano key hammers) develop from increased tension on the flexor tendons secondary to subluxation of the MTP joint.

DIAGNOSIS

RA is a clinical diagnosis for which no single physical finding or laboratory test result is pathognomonic. A broad differential diagnosis must be considered in patients with joint pain and swelling (see Table 85.1). As a practical matter, a patient older than 18 years who has symmetric joint pain, swelling in the hands and feet, and morning stiffness is likely to have RA, especially if RF or ACPA is positive. Its early manifestations can be quite similar to several other conditions, which must be excluded, so one must be cautious to avoid overdiagnosis of RA. On the other hand, early diagnosis is critical so that appropriate treatment can be initiated and irreversible damage does not occur. The 2010 RA classification criteria are very helpful in this regard. Some data suggest that definitive treatment should be started within 3 months of the onset of disease. Therein lies the advantage of the 2010 ACR/EULAR classification criteria for contemporary clinicians: they provide diagnostic support for recognition of early RA, which allows physicians to make a definitive diagnosis without delay and thus to make a decision to administer DMARD therapy timely and before joint destruction occurs.

The ACR/EULAR criteria provide a useful starting point for one to become familiar with the key clinical features of RA (see Chapter 83). The ability to recognize early synovitis in the joints of the hands and feet is critical (see Fig. 85.1). Radiographs of the hands and feet are sometimes diagnostic at initial evaluation, and musculoskeletal ultrasound and magnetic resonance imaging can detect early evidence of synovitis and erosions not seen on radiographs (see Chapter 88), although the aim today is to prevent joint damage from occurring. RF and ACPA tests are readily available and positive in about 80% of patients with RA. However, RF may be negative early in RA, and positive RF may be seen with many other conditions, especially hepatitis C infection.

Differential diagnosis

A number of disorders can closely resemble RA and must be considered and excluded when a diagnosis of RA is being made (see Table 85.1).

NATURAL HISTORY

Disease onset

The clinical course of RA follows an onset of disease that may be abrupt and acute, gradual and insidious, or subacute between these extremes. A gradual onset is most common (at least 50% of cases), whereas a sudden onset is much less common (10% to 25%). RA begins predominantly as an articular disease, and one or many joints may be affected. It may also start as an extraarticular or nonarticular manifestation, such as local bursitis, tenosynovitis, or carpal tunnel syndrome, or as a systemic manifestation with diffuse polyarthralgia or polymyalgia. Although the onset of RA is predominantly articular, it is frequently associated with a variety of extraarticular features, including generalized weakness, anorexia, weight loss, or fever. In some cases, fatigue alone or diffuse nonspecific aching with other extraarticular features such as pulmonary disease may herald—by weeks or months—the onset of polyarthritis.

Patterns of onset

Gradual onset

The most common early finding is a gradual or insidious onset in which small peripheral joints such as the wrist, MCP, PIP, ankle, or MTP joints are affected. It is defined as one that the patient can date only to the nearest month. It is usually symmetric, with considerable morning stiffness, difficulty making a fist, and poor grip strength. The morning stiffness may last minutes to hours.

Slow, monoarticular onset

Less common is a slow monoarticular process affecting larger joints such as shoulders or knees. The symptoms may remain confined to one or two joints but frequently spread over the ensuing days and weeks additively to affect the wrists, fingers, ankles, or feet in widespread fashion.

Abrupt, acute polyarthritis

Less frequently, RA is manifested as an abrupt acute polyarthritis of the shoulders, elbows, wrists, fingers, hips, knees, ankles, and feet, with intense joint pain, diffuse swelling, and limitation leading to incapacitation. A sudden onset is defined as one for which the patient can give a specific date.

This type of onset may affect patients at any age but has particular significance in the elderly.

Acute monoarthritis

Acute monoarthritis of the knee, shoulder, or hip can present a picture suggesting a septic, pseudogout, or gouty process, although this finding is rare. Joint pain more severe than that found in RA is characteristic of pseudogout or gout, which may resemble or even complicate RA. The results of synovial fluid analysis should settle any diagnostic confusion in such cases. An acute monoarticular manifestation may proceed to more widespread involvement with any of the preceding patterns.

Tenosynovitis or bursitis may also be associated with monoarthritis or polyarthritis and subcutaneous nodules over extensor surfaces such as the elbow, sacrum, or Achilles tendon.

Local extraarticular features

As noted, bursitis and tenosynovitis may be associated with RA. Sometimes, however, the earliest manifestation of RA may be median nerve compression (carpal tunnel syndrome) secondary to volar wrist tenosynovitis. Similarly, other local extraarticular features may be the initial feature.

Systemic extraarticular features

Elderly patients, in particular, may have polyarthralgia and polymyalgia affecting the neck and shoulders or the hips and knees and profound fatigue. Although these features, especially in association with fever and a high ESR lasting several weeks, suggest a diagnosis of polymyalgia rheumatica, this picture may be a forerunner of full-blown RA.

Patterns of progression

No matter what the type of onset or signs and symptoms, the patient's subsequent progress may follow several different patterns. It may be a course that is brief and self-limited, episodic (palindromic) or prolonged and progressive, or something intermediate. Severity may vary from mild to intense. Attacks may be prolonged and smoldering or prolonged and progressive.

With continuing disease activity, the patient's daily activities and functional capacity are affected to a greater or lesser extent. Although disability is usually proportional to the amount of painful joint involvement, men who do hard physical work sometimes have progressive joint dysfunction and disability without much pain. The physical ability of patients who have this "neuropathic" picture may dwindle insidiously before work becomes impaired or daily activities decline and the seriousness of the situation becomes apparent. This highlights the importance of careful evaluation and reevaluation of the patient's condition. For this reason, good records are essential for documenting the patient's progress and response to treatment.

Clinical course—morbidity and mortality

Studies of the natural history of RA could provide insight into outcome variables and prognosis. Understanding the prognosis helps in better evaluating the psychosocial and compensation implications for estimating work disability in RA. It is worthwhile considering whether the type of disease onset and patterns of features previously outlined can be used to predict the subsequent course of RA.

Acute-onset pattern

In a series of 102 cases of early adult RA, Fleming and associates⁵ reported that 11 patients with a sudden disease onset showed, after 5 years, a better functional outcome than did 69 patients with a slow onset of disease. However, in a later series of 100 patients, Jacoby and coworkers⁶ observed that after an 11-year follow-up, there was no difference in functional class regardless of whether onset of the disease was acute, subacute, or gradual. In the past, patients with an acute onset as a result of a reactive or viral polyarthritis may have been misdiagnosed as having RA. Another explanation for a better outcome in patients with an acute onset is that they are more likely to seek prompt medical attention. The favorable course of mild, transient, or self-limited RA, however, has not attracted much attention because rheumatologists are concerned mostly with progressive RA.

Gradual-onset pattern

In the report by Fleming and associates,⁵ a worse prognosis was found in patients with disease that was gradual in onset and associated with involvement of large joints (e.g., shoulders, elbows, wrists, knees), in addition to involvement of the first and second MTP joints. In the series of Jacoby and coworkers⁶, the type of onset was not predictive of functional status after

TABLE 85.2

Self-report questionnaire for rheumatoid arthritis

Please check (✓) the ONE best answer for your abilities				
At this moment, are you able to	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dress yourself, including tying shoelaces and doing buttons?				
Get in and out of bed?				
Lift a full cup or glass to your mouth?				
Walk outdoors on flat ground?				
Wash and dry your entire body?				
Bend down to pick up clothing from the floor?				
Turn regular faucets (taps) on and off?				
Get in and out of a car?				
<i>The questionnaire is used to make a quantitative assessment of the functional capacity of the patient to carry out tasks of daily living.¹⁰</i>				

11 years; moreover, in a later Finnish study of 235 patients with RA, radiographically evident damage after 7 years was the same whether the onset had been acute, subacute, or gradual.⁷

Assessment of disease activity

A critical component of providing care to patients with RA is accurate assessment of disease activity and the extent to which the patient's daily functioning is impaired. To some degree this is intuitive and readily evident from the history and physical examination at each visit. However, more quantitative outcome measures are available and can be applied at selected outpatient visits.

Recording a tender joint count (TJC) and swollen joint count (SJC) is simple and straightforward. Controversy exists regarding the ideal number of joints to be counted: 28, 44, 66, or more. The 28-joint count (PIP, MCP, wrist, elbow, shoulder, and knee joints) can be accomplished quickly and efficiently in the office setting,⁸ although some argue that the 44-joint count is more representative of the patient's clinical situation. Assuming that the same examiner performs the count on each visit, it is an accurate and reproducible record of the patient's status. Another objective and quantifiable tool is measurement of an acute-phase reactant, either ESR or CRP. The ESR can easily be determined in the outpatient setting by office staff, whereas CRP is a more complex measurement. A more subjective method is use of a 100-mm visual analog scale (VAS) by the patient or health care provider (or both). Patients can indicate a VAS measurement for pain, global assessment of arthritis activity, or general sense of health. The most common VAS performed by physicians is global assessment of arthritis activity.

Two composite scores have been used extensively and validated: the EULAR Disease Activity Score (DAS) and the ACR Core Data Set. Although both are used to measure outcome in clinical trials of medications for the treatment of RA, the DAS28 is readily adaptable to repeated visits in the outpatient setting. The DAS28 is a discrete variable calculated from the TJC and SJC for 28 joints, the ESR or CRP, and the patient's VAS for general health. A rather complicated calculation that includes logarithmic transformation produces a discrete numeric value between 0 and 10.⁹ A DAS is available online⁸ to easily generate this number. Some investigators have proposed making specific treatment decisions at each visit based on escalating medication treatment to achieve a DAS below a certain threshold level indicating "remission." Further details on disease activity and outcome assessment are provided in Chapter 96.

The Health Assessment Questionnaire (HAQ) has become an established outcome measure that is easily self-administered by the patient in a short amount of time.¹⁰ Originally developed at Stanford University, the HAQ has undergone many iterations, each of which has its proponents. In its simplest form, the questionnaire addresses the patient's ability to perform activities of daily living in eight domains (Table 85.2), for example, getting in and out of bed, bending down to pick up clothing from the floor, and so on. The patient indicates the level of difficulty in performing each activity, and each answer receives a certain score based on where it falls on the continuum (0 = "without any difficulty" to 3 = "unable to do"), and the highest value for each of the eight domains is indicated. These eight values are totalled and divided by 8 to yield an HAQ score. As the score increases, so does the level of disability. HAQ scores can be compared from visit to visit, with a change of 0.22 representing a significant difference. Early in the

disease the HAQ score tends to reflect disease activity, whereas later in the disease it tends to indicate level of disability.

Regular application of such outcome measures allows the clinician to make a quantitative determination of how the patient is doing, which can be especially valuable when assessing a patient's response to a change in treatment. In some situations, documentation of response to treatment is required by health insurance providers as a condition for continuing to provide expensive medications such as monoclonal antibodies or recombinant fusion proteins.

PROGNOSIS

It is critically important for the clinician to make the best possible assessment of prognosis for an individual patient with RA. Despite consensus that all patients with RA should receive DMARDs, the choice of medications individually or in combination for a particular patient depends greatly on the clinician's judgment of the severity of the illness and the likelihood that joint destruction will occur. There is evidence from several trials that some patients have a better outcome if a combination regimen is started immediately as opposed to an approach in which individual agents are added sequentially,^{11,12} and there is strong support for trying to achieve "tight control" in the treatment of RA.¹³ A recent study showed no difference in efficacy between stepping up from methotrexate monotherapy to combination DMARDs versus starting with a combination of methotrexate and a tumor necrosis factor (TNF) antagonist,¹⁴ whereas another study suggested that immediate institution of anti-TNF therapy was superior to combination oral DMARDs.¹⁵ Approaches to treatment are in rapid evolution, and it is unlikely that there will be agreement regarding a single best algorithm for choosing therapeutic agents in the foreseeable future. Nonetheless, prediction of prognosis at the time of diagnosis or when assuming care is essential.

The literature on prognostic factors for RA is voluminous, and no clear consensus has been reached regarding which factor or combination of factors is most important. Several factors reported to influence prognosis are discussed below.

A recent study from France attempted to correlate HAQ scores with subsequent radiographic features.¹⁶ The authors found, as did other studies, that the HAQ score at baseline is an excellent predictor of outcome. Furthermore, the HAQ score has also been shown to predict the risk for future loss of productivity in RA patients.¹⁷

Radiographic damage at onset has been shown to be an important predictor of clinical outcome and radiographic progression. Gossec and colleagues¹⁸ found that a Sharp score (van der Heijde modification) of lower than 4 points at baseline was predictive of remission (DAS28 <1.6) 3 and 5 years later. Not surprisingly, radiographic erosions at baseline are predictive of further radiographic damage 2 to 3 years later.

Acute-phase reactants also have predictive value regarding the development of radiographic damage over time. The ESR at the start of the study was the best predictor of radiographic outcome in the first 5 years in a Swedish study,¹⁹ and the prognostic value of ESR has been demonstrated in other studies. Likewise, baseline CRP is predictive of subsequent radiographic damage.²⁰ Finally, serologic markers may predict prognosis. The presence of RF has consistently been associated with radiographic

progression. Data are emerging that the presence of ACPAs is an independent predictor of radiographic damage.²⁰

In summary, the clinician has a number of readily available tools that can be useful in predicting the prognosis of patients with RA several years later: ESR, CRP, RF, ACPA, HAQ, and baseline radiographs of the hands and

feet. Although it is not possible at present to assign the relative importance of these factors in combination because the presence of each of them has negative implications on prognosis, the presence or absence of these factors can help the clinician make a rational assessment when making treatment decisions for individual patients.

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86

Extraarticular features of rheumatoid arthritis and systemic involvement

■ CARL TURESSON ■ ERIC L. MATTESSON

- Rheumatoid arthritis may be associated with inflammation in extraarticular organs.
- Features of systemic involvement in rheumatoid arthritis include constitutional symptoms, distinct organ manifestations, and severe multiorgan disease.
- Systemic features may be associated with a poor prognosis, especially vasculitis and rheumatoid lung disease.

INTRODUCTION

Constitutional features of rheumatoid arthritis (RA), such as fatigue and weight loss, may occur early in the course of the disease and predominate and overshadow the joint manifestations.

At times, inflammation may extend beyond the joints (Table 86.1). Overall, these systemic manifestations occur equally in men and women and may appear at any age.¹

Extraarticular disease manifestations (except for laboratory abnormalities) occur in about 40% of patients at some time during the course of their disease.¹ The incidence of severe extraarticular disease (vasculitis, vasculitis-related neuropathy, pericarditis, pleuritis, glomerulonephritis, scleritis/episcleritis, Felty syndrome) has been estimated to be 1 per 100 person-years in well-defined RA populations.^{1,2} In recent years a decrease in the incidence of rheumatoid vasculitis¹ and perhaps extraarticular manifestations in general has been observed (see Table 86.1).¹

The systemic inflammatory process is a major predictor of mortality in patients with RA. Extraarticular disease confers a mortality risk ratio five times that in patients without these manifestations, even after comorbid conditions such as heart and lung disease, malignancy, and dementia are accounted for.¹ Some extraarticular disease manifestations, especially vasculitis, pericarditis, pleuritis, amyloidosis, and Felty syndrome, are associated with a diminished life span in comparison to patients without extraarticular disease^{1,3} (Fig. 86.1). The mortality associated with extraarticular disease appears to have diminished somewhat in recent years.¹ Smoking,⁴ the presence of rheumatoid factor and circulating antibodies against citrullinated proteins, and RA-associated HLA-DRB1*04 genes^{5,6} predict extraarticular disease. Other genetic markers, such as HLA-C*03 and genes regulating killer immunoglobulin-like receptor expression on T-cell subsets, may have a particular impact on the risk for vasculitis.^{7,8} Probably because of interactions between these and other risk factors, extraarticular manifestations tend to cluster in individual patients.⁹

The nature of the specific organ involved and the severity of the involvement guide treatment of the extraarticular manifestations of RA. Frequently, therapeutic strategies designed to control joint involvement, including disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids, are effective in treating systemic disease. Although glucocorticosteroids are the mainstay of treatment of systemic disease, cytotoxic agents such as cyclophosphamide are sometimes needed for severe disease, including organ-threatening eye disease and systemic vasculitis.¹⁰ Anti-tumor necrosis factor (TNF) antagonists, B cell-depleting therapies, and other specific immunomodulating agents may be particularly useful in managing these manifestations,¹¹ although extraarticular manifestations sometimes also develop in patients treated with TNF blockers and other biologics.

SKIN DISEASE

Subcutaneous nodules develop mainly in RA patients who are rheumatoid factor positive and rarely in seronegative patients. Patients with rheumatoid nodules early in the course of RA are at an increased risk for the development of severe extraarticular manifestations. Rheumatoid nodulosis (numerous, widespread nodules) occasionally occurs as a separate condition, usually in men, with a low-grade and sometimes barely detectable synovitis.¹²

Nodules develop most commonly on pressure areas, including the elbows, finger joints, ischial and sacral prominences, occipital scalp, and Achilles tendon. Rheumatoid nodules are firm and frequently adherent to the underlying periosteum (Fig. 86.2). Histologic evaluation reveals focal central fibrinoid necrosis with surrounding fibroblasts (Fig. 86.3), which is thought to occur as a result of small-vessel vasculitis. Microchimerism is frequently present in the nodules of patients with RA and may serve as an allogeneic stimulus or target.¹³

Subcutaneous nodules may regress during treatment with disease-modifying drugs, usually as the RA improves. Paradoxically, methotrexate may increase nodules, particularly over finger tendons (Fig. e86.1), despite improvement in the overall disease activity.

Other skin lesions include neutrophilic dermatoses such as Sweet syndrome (Fig. 86.4) and pyoderma gangrenosum. Skin ulcers may be the result of vasculitis or Felty syndrome (see later), venous or arterial insufficiency, and neutrophilic infiltration.

HEMATOLOGIC ABNORMALITIES

The cause of anemia in individuals with RA is multifactorial. Reduced erythropoietin and a blunted response to erythropoietin also contribute to the anemia of RA. Additional factors include increased phagocytosis of red blood cells in the spleen and even by the synovium.

The degree of anemia in RA usually correlates with disease activity, particularly the degree of articular inflammation. It is commonly normochromic and normocytic. The anemia caused by rheumatoid inflammation can improve with therapy that treats the disease successfully. Administration of erythropoietin to RA patients improves red blood cell counts.¹⁴

Thrombocytosis is a frequent finding in active RA. The degree of thrombocytosis may correlate with the number of joints involved with active synovitis and may be associated with extraarticular features. Thrombocytopenia is rare in RA, except when related to drug treatment or Felty syndrome.

Lymphadenopathy is frequent in active RA. Histologic examination usually reveals benign follicular hyperplasia. Patients with RA, however, have a higher risk for malignant non-Hodgkin lymphoma than the general population does.¹⁵ High disease activity¹⁶ and concomitant Sjögren syndrome¹⁷ may confer increased risk for lymphoma.

FELTY SYNDROME

Felty syndrome is defined as RA in combination with splenomegaly and leukopenia. The syndrome characteristically occurs in patients with longstanding, seropositive, nodular, deforming RA. In white patients, the major histocompatibility locus associations with Felty syndrome are the result of





Fig. e86.1 Rheumatoid nodules in a patient with long-standing rheumatoid arthritis treated with low-dose methotrexate weekly.

TABLE 86.1

Extraarticular disease manifestations in a community-based sample of patients with rheumatoid arthritis 1995–2007

Extraarticular manifestation	10-Year cumulative incidence (%)
Pericarditis	2.6
Pleuritis	1.9
Major cutaneous vasculitis	0.6
Vasculitis-related neuropathy	0.2
Felty syndrome	0.5
Scleritis	0
Episcleritis	0.7
Glomerulonephritis	0
Amyloidosis	0
Secondary Sjögren syndrome	9.6
Pulmonary fibrosis	5.0
Bronchiolitis obliterans	0.7
Subcutaneous rheumatoid nodules	31.2

Data from Myasaeova E, Crowson CS, Turesson C, et al. Incidence and mortality of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, 1995–2007: a population-based study. *J Rheumatol* 2011;38:983–9.

SURVIVAL OF PATIENTS WITH EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

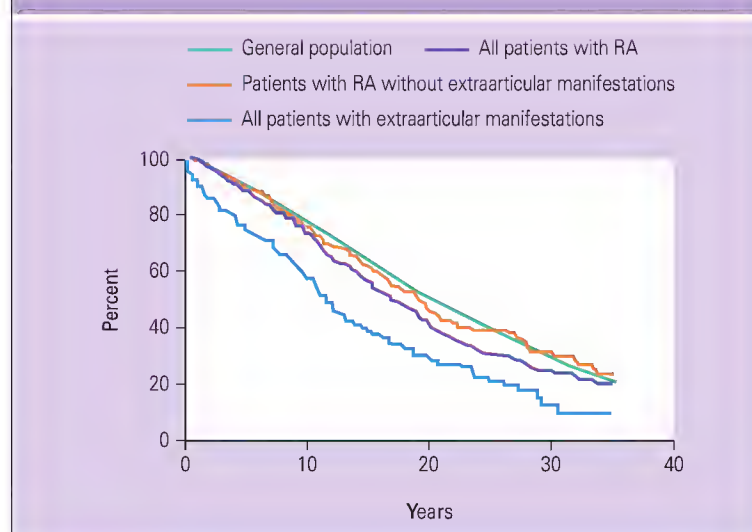


Fig. 86.1 Increased mortality in patients with extraarticular manifestations of rheumatoid arthritis. Curves illustrate survival by disease subset.

linkage disequilibrium with HLA-DRB1*0401.¹⁸ Some patients have no active synovitis at the time that Felty syndrome develops. Many of these patients have indolent lower extremity ulcerations (Fig. 86.5), hyperpigmentation, and antinuclear antibodies.

Bacterial infections are common in Felty syndrome and correlate with a polymorphonuclear leukocyte count lower than $100/\text{mm}^3$, and they account for substantial mortality in this condition. Other factors associated with an increased incidence of infections are skin ulcers, the dose of glucocorticosteroid, hypocomplementemia, and high levels of immune complexes. Bone marrow is usually normal or hyperplastic. In some patients, however, bone marrow does not respond appropriately to the degree of leukopenia, perhaps because of inhibitors induced by proinflammatory cytokines that suppress myelopoiesis.¹⁹ Thrombocytopenia also occurs in Felty syndrome.

Treatment strategies for Felty syndrome may include methotrexate,²⁰ parenteral gold²¹ (grade C), glucocorticoids, granulocyte colony-stimulating factor, and splenectomy.

Risk for the development of lymphoproliferative and other malignancies is increased in patients with RA, particularly in those with Felty syndrome.¹⁵



Fig. 86.2 Gross anatomic specimen of a rheumatoid nodule. The yellow tissue is caused by fibrinoid necrosis.

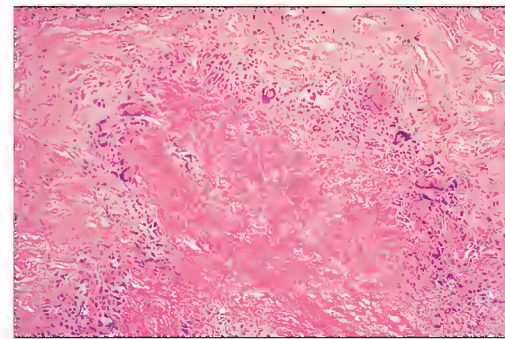


Fig. 86.3 Rheumatoid nodule with granulomatous transformation. Prominent central fibrinoid necrosis is present along with surrounding palisading histiocytes and an outer layer of chronic fibrosing connective tissue with inflammatory cells, including lymphocytes and fibroblasts (hematoxylin-eosin; original magnification $\times 450$).



Fig. 86.4 Neutrophilic dermatosis (Sweet syndrome) in a patient with multiple erythematous plaques and pustules.



Fig. 86.5 Indolent and recurrent lower extremity ulcer in a typical midshaft location in a person with Feltz syndrome.

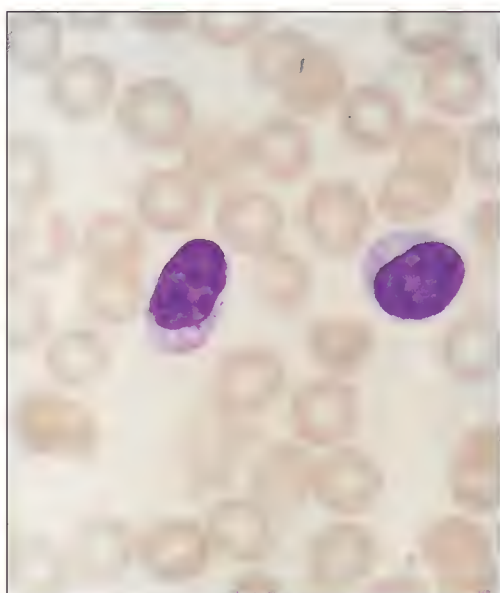


Fig. 86.6 Large granular lymphocytes.

A variant of Feltz syndrome has been described in which patients have neutropenia and an increase in the number of large granular lymphocytes in blood and bone marrow²² (Fig. 86.6). The large granular lymphocytes in these patients represent *in-vivo* activated cytotoxic T cells, and clonality is present. However, rapidly progressive malignancy with decreased survival is unusual.

HEPATIC ABNORMALITIES

Active RA may be associated with an increase in liver function abnormalities, which may parallel the anemia, thrombocytosis, and increased erythrocyte sedimentation rate. With control of the rheumatoid inflammation, the liver function abnormalities return to normal.

Liver involvement, including hepatomegaly, may be present in up to 65% of patients with Feltz syndrome.²³ Histologic abnormalities may even be present when liver function test results are normal. The liver pathology varies from portal fibrosis and abnormal lobular architecture to nodular regenerative hyperplasia. Portal hypertension, esophageal varices, and variceal bleeding can develop in these patients.



Fig. 86.7 Pleural effusion and rheumatoid nodule in a person with rheumatoid arthritis. Changes associated with diffuse interstitial fibrosis are also present.

PULMONARY INVOLVEMENT

Pulmonary involvement in RA occurs frequently, although it is not always recognized clinically.²⁴ Men are affected more often than women. In autopsy studies, involvement of the pleura is reported in up to 50% of individuals with RA but detected clinically in only about 7% to 10% of such cases.^{1,25} Rheumatoid pleural effusions are usually exudates with mixed cell counts, high lactate dehydrogenase concentrations, and high protein concentrations (>4 g/L). The presence of multinucleated giant cells is highly specific for rheumatoid pleuritis, but such cells are seen in less than 50% of these cases. Glucose concentrations are often lower than 25 mg/dL (1.4 mmol/L).

Parenchymal pulmonary nodules (Fig. 86.7) are generally asymptomatic and found in seropositive RA patients with widespread synovitis and, usually, nodules elsewhere. The pulmonary nodules tend to be peripheral in location and can measure less than 1 cm or up to 6 to 8 cm in diameter. They can cavitate and cause pleural effusions and bronchopleural fistulas. Pathologic examination of the nodules reveals a central necrotic zone surrounded by a cellular area of proliferating fibroblasts. The differential diagnosis of pulmonary rheumatoid nodules includes neoplasms, tuberculosis, and fungal infections. In the case of a solitary rheumatoid nodule in the lung, excisional biopsy may be necessary to confirm the diagnosis. Treatment of the underlying rheumatoid disease frequently results in improvement in the pulmonary nodules.

Pulmonary nodulosis and pneumoconiosis in patients with RA (Caplan syndrome) is characterized by several nodules greater than 1 cm in diameter scattered throughout the peripheral lung field (Fig. e86.2). Caplan syndrome is seen in individuals with extensive exposure to coal dust, although exposure to silica and asbestos may also lead to pulmonary nodulosis in these patients.

In patients with RA, interstitial lung disease (ILD) generally takes the form of nonspecific interstitial pneumonitis or usual interstitial pneumonitis (Fig. 86.8). The lifetime risk for the development of symptomatic ILD in a community-based population of patients with RA was found to be 7.7%, which is nine times higher than the risk for ILD in the general population.²⁵ Patients with RA-associated ILD have a three times higher risk for death than do patients without ILD, with median survival after a diagnosis of ILD being 2.6 years. The most common radiographic finding is bilateral basilar interstitial abnormalities, which are often asymmetric. Initially, these abnormalities may appear as patchy alveolar infiltrates; with progressive disease a more reticulonodular pattern is seen. High-resolution computed tomography (CT) and open lung biopsy are considered the “gold standard” methods for diagnosing ILD. The clinical features and course of pulmonary fibrosis in RA have been reported to be similar to those of idiopathic pulmonary fibrosis, but response to immunosuppression may be better if the



Fig. e86.2 Caplan syndrome.

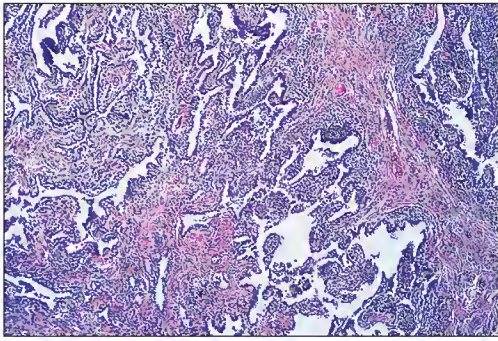


Fig. 86.8 Usual interstitial pneumonitis in an 83-year-old man with a 23-year history of rheumatoid arthritis.



Fig. 86.9 Diffuse interstitial pneumonitis with sclerosing alveolitis. Lymphocytes are prominent (hematoxylin-eosin stain; original magnification $\times 150$.)

pulmonary fibrosis occurs in the context of RA or other collagen diseases.²⁶

Rheumatoid ILD is seen more frequently in men than in women, particularly in those who have long-standing nodular, seropositive disease and in patients who smoke. The histologic findings and results of bronchoalveolar lavage can be variable and range from lymphocytic alveolitis to neutrophilic inflammation. Features on routine histologic examination of lung biopsy specimens are nonspecific and include an inflammatory infiltrate with lymphocytes, plasma cells, and histiocytes (Fig. 86.9). B cells and CD4⁺ T cells may be more abundant in the lung tissue of patients with RA-associated ILD than in patients with idiopathic ILD (Fig. e86.3).^{27,28} The greater density of T and B cells observed in RA-related ILD has been linked to high levels of circulating anti-cyclic citrullinated peptide antibodies.²⁹ Tumor necrosis factor (TNF) inhibitors may have a negative effect on RA-associated interstitial pneumonitis in some cases,³⁰ possibly because of the direct antifibrotic properties of TNF.³¹ RA-associated interstitial pneumonitis needs to be distinguished from methotrexate-induced toxicity, which usually has a subacute onset with rapidly progressive respiratory symptoms, less radiographic evidence of fibrosis, and a histologic pattern dominated by eosinophilia and type II pneumocyte hyperplasia.

Cryptogenic obstructive pneumonia (COP) in patients with RA generally responds to glucocorticosteroid treatment and often has a good prognosis. Obliterative or constrictive bronchiolitis responds poorly to treatment and has a worse prognosis. Patients have shortness of breath and a nonproductive cough, but unlike COP, there is not usually any fever or other constitutional symptoms.



Fig. 86.10 Laryngeal edema with cricoarytenoid arthritis on direct laryngoscopy. Black arrow, left arytenoid; black arrowhead, right arytenoid; white arrowhead, left vocal cord; white arrowhead, right vocal cord. (Courtesy Dr. Yuki Nanke.)

Obstructive lung disease is more common in patients with RA than in age-matched controls; it occurs in 9.6% of patients with RA and 6.2% of controls.³² High-resolution lung CT reveals that up to 50% of patients with RA have bronchiectasis and bronchiolectasis,³³ possibly because of increased susceptibility to airway infection, obstructive airway disease, and genetic predisposition.

Upper airway obstruction in RA can also be caused by inflammation of the cricoarytenoid joint. Symptoms include sore throat, hoarseness, dysphagia, pain with speech, pain radiating to the ears, foreign body sensation in the throat, and difficulty with inspiration. Laryngoscopy and CT are the most sensitive methods for evaluating cricoarytenoid arthritis (Fig. 86.10).

CARDIAC DISEASE

RA may lead to cardiac and noncardiac vascular disease^{3,34} through mechanisms of chronic inflammation, vasculitis, nodule formation, amyloidosis, serositis, valvulitis, and fibrosis. Though usually asymptomatic, pericarditis is the most common cardiac manifestation of RA and is found on random electrocardiographic evaluation and autopsy studies in 50% of individuals.³⁵ Analysis of pericardial fluid reveals changes similar to those found in rheumatoid pleural effusions. Symptomatic patients with mild disease generally respond to glucocorticosteroids; pericardiocentesis, intrapericardial glucocorticoid administration, and even pericardiectomy may sometimes be required for management³⁶ (Figs. 86.11, 86.12, and e86.4).

Nonspecific myocarditis is usually asymptomatic and rarely affects cardiac size or function. Congestive heart failure may be more frequent than is clinically evident in RA, and left ventricular diastolic function is more often impaired than in those without RA despite normal left ventricular systolic function.³⁷ Valvular lesions, aortic root abnormalities, and coronary arteritis can also occur (Fig. 86.13).

RA itself is an independent risk factor for coronary artery disease,³⁸ and patients with severe extraarticular disease have a particularly increased risk for cardiovascular death.³ It has been suggested that coronary artery disease may be associated with clonal expansion of CD4⁺CD28null T cells,³⁹ which has also been seen in patients with RA, particularly in those with vasculitis. It has been proposed that atherosclerosis should be regarded as an extraarticular feature of RA.³⁸ Biomarkers of inflammation predict cardiovascular events in the general population,⁴⁰ and vascular disease is more likely to develop in patients with RA and a persistently elevated erythrocyte sedimentation rate.³ Successful DMARD therapy with methotrexate⁴¹

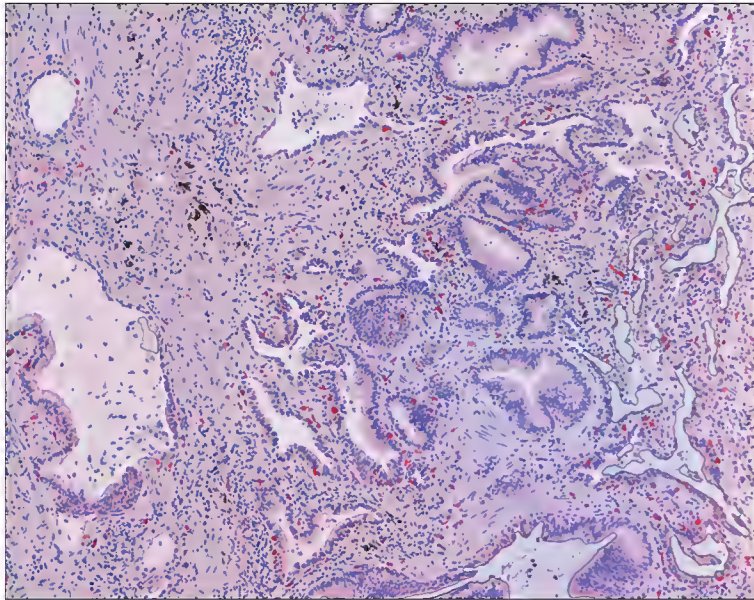


Fig. e86.3 Interstitial pneumonitis with CD4+ T cells (red stain) in a patient with rheumatoid arthritis (original magnification $\times 100$).

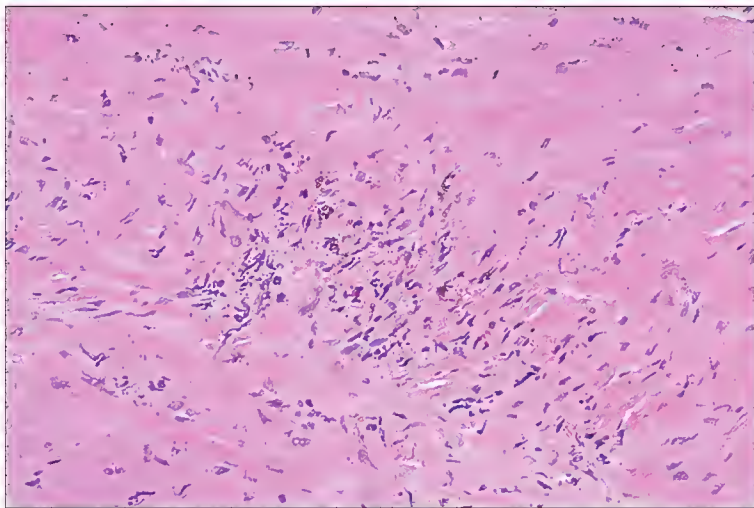


Fig. e86.4 Rheumatoid pericarditis (same patient as in Fig. 86.11). Marked noncalcific dense fibrosis, moderate nongranulomatous lymphoplasmacytic infiltrate, and hemosiderin pigment are present (hematoxylin-eosin stain; original magnification $\times 400$).



Fig. 86.11 Magnetic resonance image of constrictive pericarditis in rheumatoid arthritis. The dense white infiltrate between the pericardium and gray myocardium is pericardial fluid.

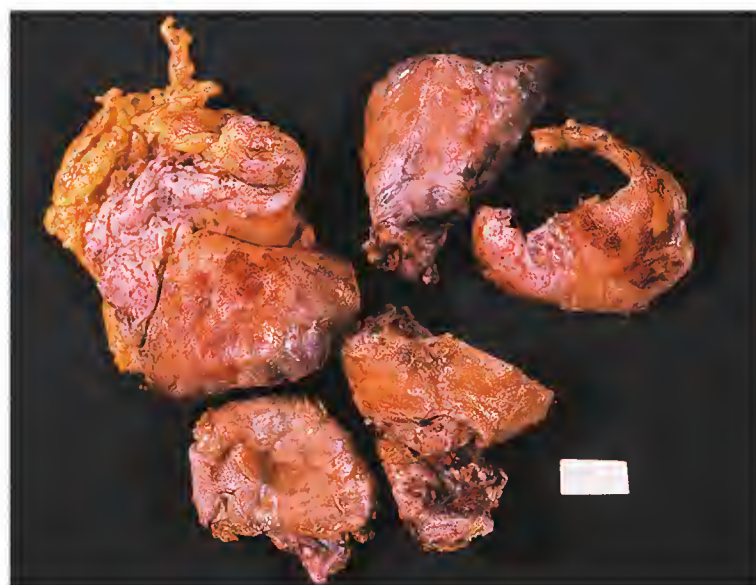


Fig. 86.12 Gross anatomic specimen obtained at radical pericardiectomy showing constrictive pericarditis. The fibrotic pericardium is massively thickened, with a diameter of up to 0.5 cm; the outer layer of the pericardium is covered with fat at the top.

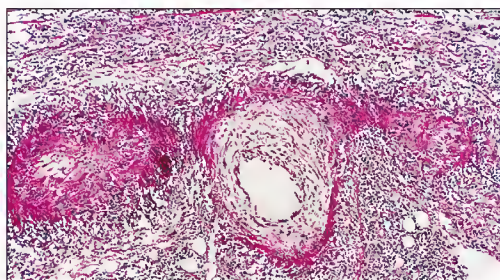


Fig. 86.13 Coronary arteritis. Two arteries are seen. A dense inflammatory infiltrate is present in the adventitia, with some intimal luminal narrowing and destruction of the media of one artery (hematoxylin-eosin stain; original magnification ×250).



Fig. 86.14 Episcleritis usually occurs in the setting of active rheumatoid arthritis and is associated with the sudden onset of redness and eye pain.

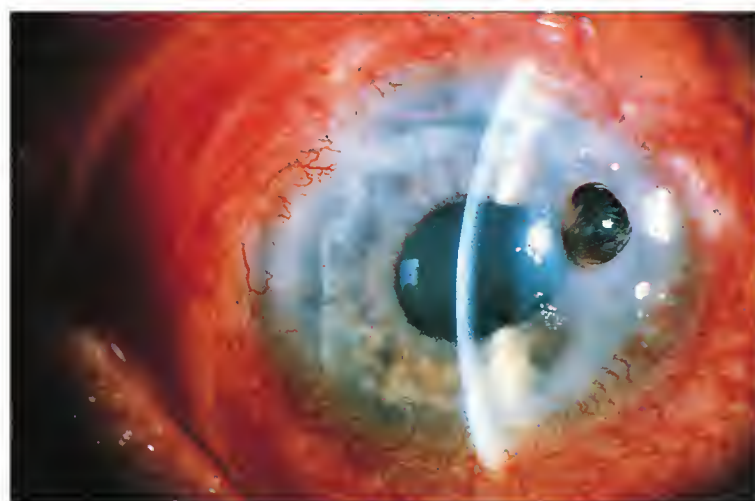


Fig. 86.15 Scleromalacia in a patient with rheumatoid arthritis.

or TNF blockers⁴² may substantially reduce the risk for cardiovascular comorbidity.

OCULAR INVOLVEMENT

The most common ocular involvement in RA is keratoconjunctivitis sicca, which affects at least 10% of patients. The severity of the symptoms may not correlate with the severity of the arthritis.

Episcleritis usually correlates with the activity of RA (Fig. 86.14). This process, which may be either nodular or diffuse, develops acutely and causes eye redness and pain; only rarely does it cause changes in visual acuity. Scleritis is less common than episcleritis but is correlated with vasculitis, long-standing arthritis, and active joint inflammation. Untreated scleritis may progress to scleromalacia (Fig. 86.15). Episcleritis or scleritis is sometimes seen in patients whose polyarthritis has responded well to treatment.

Other unusual ocular findings in RA include uveitis, episcleral nodulosis, ulcerative keratitis ("corneal melt," which may be central [Fig. e86.5] or peripheral [Fig. 86.16]), and corneal filamentary keratitis (Fig. 86.17). Peripheral ulcerative keratitis develops as an extension of scleral inflammation, is sometimes bilateral, and may occur in the absence of scleritis. These conditions are associated with increased mortality and poor visual outcomes.⁴³ Treatment may include topical or systemic cytotoxic or glucocorticosteroid therapy, anticytokine agents, or both. Lesions resembling vasculitis may be seen in the limbal part of the cornea, and conditions such as scleritis and ulcerative keratitis can herald impending vasculitis.⁴³ The most common fundus lesions are caused by posterior scleritis; exudative retinal detachment and disc and macular edema may also be found in association with RA.



Fig. e86.5 Central keratolysis and corneal perforation. This is an example of how corneal collagen can degrade in the absence of corneal inflammation in patients with rheumatoid arthritis.

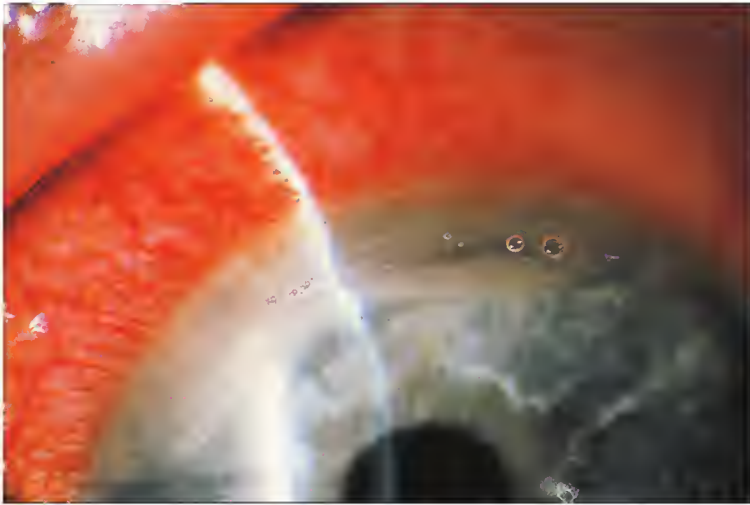


Fig. 86.16 Marginal corneal melt (ulcer) with inflammation.



Fig. 86.17 Corneal filamentary keratitis with early corneal stromal activity near the limbus at the 8 o'clock position and 9:30. Filamentary keratitis concentric to the limbus can be a precursor of marginal corneal ulceration in rheumatoid arthritis.

Other uncommon ocular complications of RA include Brown syndrome, which is defined as diplopia on upward and inward gaze and is thought to be the result of inflammation and thickening of the superior tendons and optic neuritis.

NEUROLOGIC IMPAIRMENT

Peripheral entrapment neuropathy, which tends to occur when the nerve is compressed by the inflamed synovium against a fixed structure, and atlantoaxial subluxation may cause neurologic impairment in patients with RA. Atlantoaxial subluxation caused by erosion of the odontoid process or the transverse ligament of C1 may allow the odontoid process to slip posteriorly and cause cervical myelopathy (Fig. 86.18). Basilar invagination with upward impingement of the odontoid process into the foramen magnum can also result in cord compression (Fig. 86.19). The presence of cord compression is indicated by a positive Babinski sign, hyperreflexia, and weakness. Surgical stabilization may be required.

Peripheral neuropathy manifested as diffuse sensorimotor neuropathy or mononeuritis multiplex occurs in a small subset of patients with RA. The underlying mechanism is small-vessel vasculitis with ischemic neuropathy.

Involvement of the central nervous system in RA is rare. A diffuse, granulomatous pachymeningitis with fever and headache occurs rarely (Figs. 86.20 and e86.6), and vasculitis and amyloidosis may occasionally involve the dura or choroid plexus in patients with long-standing RA.



Fig. 86.18 Plain film of the cervical spine showing erosion of the odontoid.

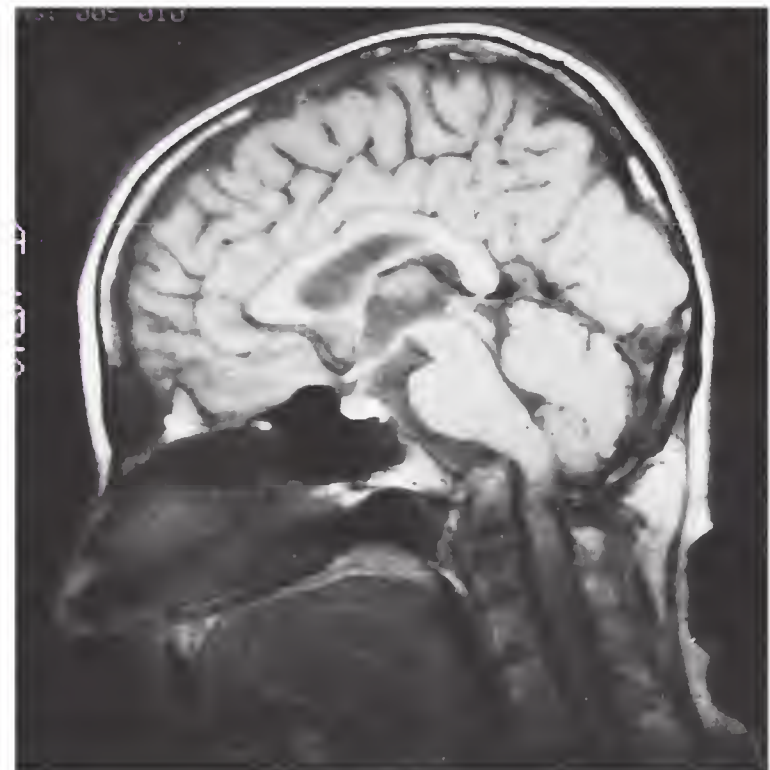


Fig. 86.19 Magnetic resonance image of the cervical spine showing basilar invagination.

MUSCULAR INVOLVEMENT

Muscle weakness in RA is usually due to muscle atrophy secondary to joint inflammation. Nutritional problems, medication, and neurologic dysfunction may contribute. A rare inflammatory myopathy with patchy lymphocytic and plasma cell infiltration in muscle fibers that results in some fiber degeneration has been described. RA may coexist with idiopathic inflammatory myopathy without other signs of systemic disease.

RENAL ABNORMALITIES

Patients with RA are at higher risk for all causes of chronic kidney disease (CKD).⁴⁴ Inflammation and concomitant cardiovascular disease, as well as



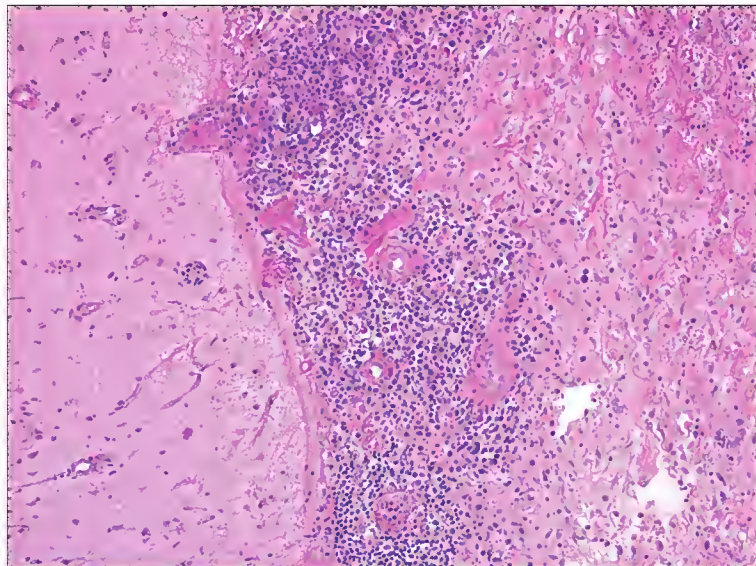


Fig. e86.6 Rheumatoid arthritis–associated meningitis (same patient as in Fig. 86.20) with necrotizing granulomatous meningitis. Cultures were negative and the patient improved after immunosuppressive treatment (hematoxylin-eosin stain, original magnification $\times 200$).

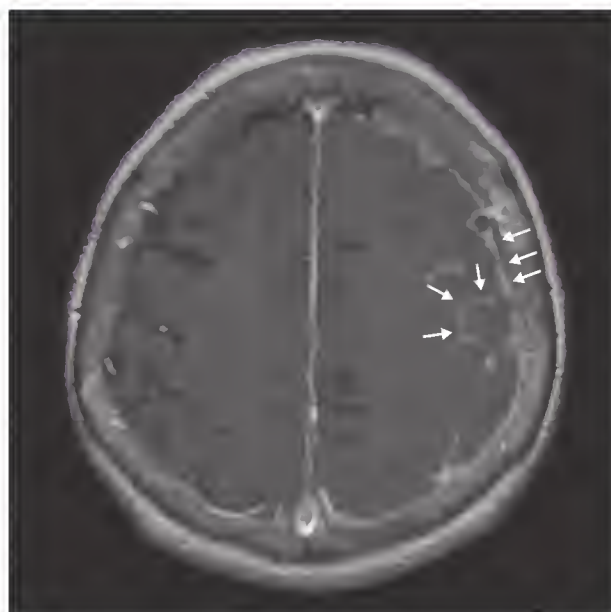


Fig. 86.20 Rheumatoid arthritis–associated meningitis in a patient with headache and fever. Magnetic resonance imaging shows abnormal leptomeningeal enhancement, especially of the left parietal and frontal lobes and temporal dura (arrows).

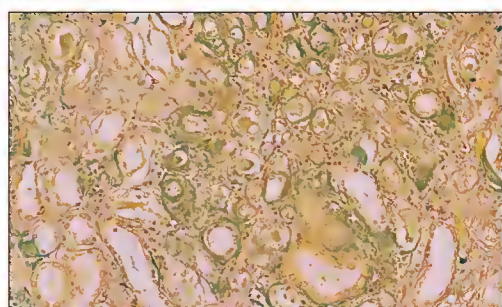


Fig. 86.21 Renal amyloidosis in rheumatoid arthritis (secondary amyloidosis). Diffuse amyloid deposition is present throughout the renal parenchyma, with deposition in blood vessel walls. Amyloid deposits are green (sulfated Alcian blue; original magnification ×400).

medications, play a role in RA-associated CKD. Low-grade membranous nephropathy, glomerulitis, vasculitis, and nephrotic syndrome as a result of secondary reactive amyloidosis have all been described. In patients with RA who undergo kidney biopsy, the most common histopathologic finding is mesangial glomerulonephritis, and amyloidosis is the most common finding in patients with nephrotic syndrome.⁴⁵ Perinuclear antineutrophil cytoplasmic antibody has been found in about 20% of patients with RA and renal diseases of various cause and may be an independent predictor of nephropathy, even in the absence of systemic vasculitis.⁴⁶ Mesangioproliferative glomerulonephritis is considered a sign of systemic organ involvement in patients with RA.

AMYLOIDOSIS

Amyloidosis may rarely complicate long-standing RA. Reports of its occurrence vary widely, but more recent population studies indicate that clinical visceral amyloidosis is detected in 0.7% of patients with RA.¹ In patients with active RA, serum amyloid A protein concentrations are increased as a result of stimulation by increased cytokine production.

Virtually every organ system may be involved in secondary amyloidosis. The diagnosis is confirmed by biopsy of involved tissue (Fig. 86.21). The presence of secondary amyloidosis in patients with RA portends a poor outcome: 4-year survival rates of about 58% are reported.⁴⁷ Cytotoxic drugs may improve the prognosis, but progressive organ failure often occurs despite aggressive treatment.

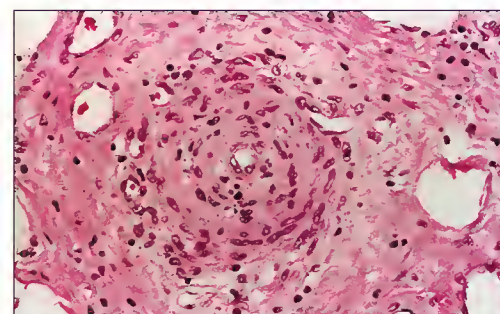


Fig. 86.22 Artery with intimal proliferation and luminal occlusion (hematoxylin-eosin stain; original magnification ×312).



Fig. 86.23 Nail fold infarcts in a patient with rheumatoid arthritis.

RHEUMATOID VASCULITIS

Small-vessel vasculitis is intimately associated with many of the clinical manifestations seen in RA. Subclinical vasculitis is probably common in patients with seropositive RA, and immune deposits have been demonstrated in clinically uninvolved skin and labial salivary glands.⁴⁸

Systemic endothelial activation has been suggested in patients with severe extraarticular disease, even in the absence of overt signs of vasculitis.⁴⁹ Inflammation of small and medium-sized arteries in the extremities, peripheral nerves, and occasionally other organs may complicate RA. The frequency of HLA-DRB1 alleles and particularly B1*0401 homozygotes is greater in patients with rheumatoid vasculitis than in those with uncomplicated RA.^{5,6}

Study of involved vessels from patients with rheumatoid vasculitis reveals a pathologic picture and distribution similar to that seen in polyarteritis, but renal involvement is rare. Early lesions show fibrinoid necrosis of the vessel wall with an inflammatory cell infiltrate. Chronic changes such as arterial wall fibrosis, occlusion, and recanalization may be seen (Fig. 86.22). The acute arterial lesions are immune complex mediated, as indicated by the involved arteries (Fig. e86.7). Immune deposits are not detected in the more chronic lesions; rather, fibrinogen is found (Fig. e86.8).

Systemic vasculitis is uncommon in RA but often occurs in rheumatoid patients with long-standing disease of more than 10 years' duration. Rheumatoid synovitis may not be active when features of the systemic vasculitis are present. Small-vessel vasculitis commonly involves the skin and causes nail fold infarcts (Fig. 86.23), digital gangrene (Fig. 86.24), and leg ulcers. The rapid, progressive, and widespread appearance of new areas of involvement, including clinical cutaneous vasculitis and multiple neuropathies, is indicative of systemic arterial disease and portends a worse outcome.⁵⁰

Treatment of rheumatoid vasculitis must be individualized. In patients with progressive widespread systemic vasculitis involving peripheral nerves, digits, viscera, or the central nervous system, the inflammation must be treated and the resulting vasculopathy anticipated. High doses of prednisone may be needed initially to control the inflammation. Two controlled trials

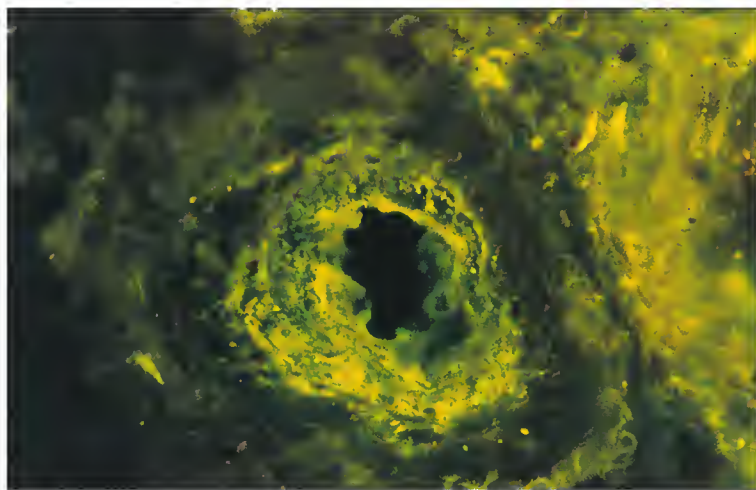


Fig. e86.7 Immunoglobulin M in an artery with fibrinoid necrosis (IgM by immunofluorescence; original magnification $\times 312$).

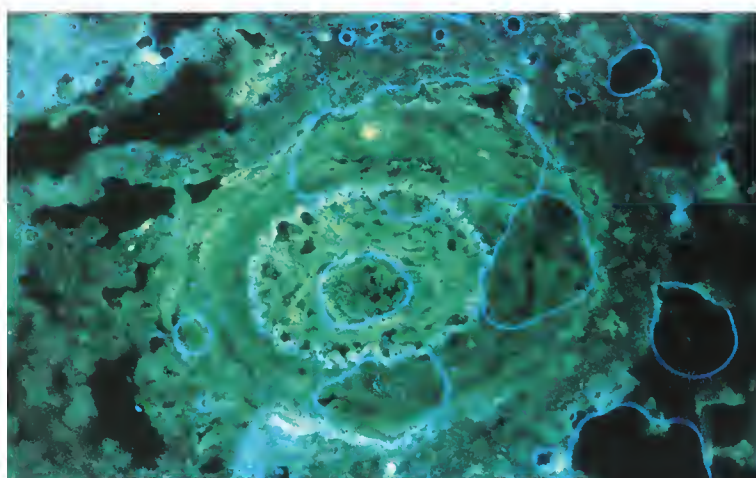


Fig. e86.8 Fibrinogen in an artery with intimal proliferation (fibrinogen by immunofluorescence; original magnification $\times 312$).



Fig. 86.24 Digital tip and proximal infarcts and mononeuritis multiplex with bilateral footdrop in a patient with rheumatoid vasculitis.

have demonstrated that pulsed⁵¹ or continuous⁵² cyclophosphamide leads to greater clinical benefit than more conservative treatment regimens do in patients with systemic vasculitis (grade B). Even though TNF inhibitors may be useful in the management of vasculitis, they have also been associated with cutaneous small-vessel and systemic vasculitis.^{52,53} Anti-B cell therapy is emerging as effective treatment of rheumatoid vasculitis, either as primary therapy or in patients refractory to cyclophosphamide (grade C).⁵⁴ Low-dose aspirin as an antiplatelet agent should also be considered, and prostacyclin infusions may be helpful in patients with threatening peripheral gangrene. Patients with vasculitis and other forms of severe extraarticular involvement are at an increased risk for cardiovascular events and severe infections and should be monitored adequately for such complications. Preventive measures such as statin therapy should be considered in patients with high cardiovascular risk because patients with RA may benefit from both the antiinflammatory and lipid-lowering effects of statins.⁵⁵

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87

Adult-onset Still disease

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- Adult-onset Still disease is an uncommon autoimmune inflammatory disease most often seen in young adults.
- Clinical findings consist of a combination of systemic manifestations (mostly spiking fever, evanescent rash, and lymphadenopathy) and joint symptoms ranging from arthralgia to aggressive arthritis.
- No specific diagnostic test is available; the clinical diagnosis is based on pattern recognition and exclusion of other diseases.
- The outcome is unfavorable in a third of patients, in whom chronic arthritis develops.
- Therapeutic decisions should be based on the extent and severity of organ involvement. Nonsteroidal antiinflammatory drugs, glucocorticoids, methotrexate, and biologic therapies are good options. There is a lack of clinical trials on adult-onset Still disease.

INTRODUCTION

In 1897 George Frederic Still first reported 22 cases of chronic seronegative polyarthritis in children with periods of fever, lymphadenopathy, and splenomegaly, as well as pericardial adhesions¹; this disease is currently known as the systemic subset of juvenile idiopathic arthritis (JIA) and has the accepted eponym of Still disease. The term *adult-onset Still disease* (AOSD), or Still disease in adults, was introduced by Eric Bywaters in 1971, who described 14 cases of an illness starting in adult life that resembled Still disease.² Currently, systemic JIA and AOSD are considered the same entity.

EPIDEMIOLOGY

AOSD is a rare disease, and at this time there is no consensus on its incidence and prevalence in different populations. It occurs worldwide and affects women slightly more than men, as well as younger people, with three quarters of patients reporting onset of the disease between 16 and 35 years of age.³ However, patients older than 70 years have been reported. The annual incidence estimated in retrospective European studies is 0.1 to 0.4 per 100,000 inhabitants.⁴⁻⁶ Additional data on the epidemiology of AOSD are needed.

ETIOPATHOPHYSIOLOGY

The etiology of AOSD is currently unknown. Interplay among several factors contributing to the mechanism of the disease has been speculated. The hypothesis that AOSD may be a reactive syndrome in which various infectious agents may act as disease triggers in a genetically predisposed host has been classically accepted. More recently, it has been suggested that alterations in cytokine production have an important pathophysiologic role in AOSD.

Genetic predisposition

Although HLA antigens have been associated with susceptibility to AOSD (HLA class II types DRB1*15 and DRB1*12 in Korea)⁷ and clinical prognosis (HLA class I types B35 with self-limited disease and DR2 and DR5 with a chronic course in Japan),⁸ other studies have not confirmed these findings.⁹ Therefore, studies conferring genetic associations with the disease and disease patterns are inconclusive.

Infectious component

Some viral syndromes closely resemble the clinical findings in patients with AOSD, and a temporal relationship between disease onset and viral or bacterial syndromes has been described. Many viruses have been reported to interact with the genetic background of the host (parvovirus B19, rubella virus, mumps, echovirus 7, human herpes virus 6, parainfluenza virus, Epstein-Barr virus, cytomegalovirus, coxsackievirus B4, adenovirus), as well as some bacterial infections (*Chlamydia pneumonia*, *Yersinia enterocolitica*, *Brucella abortus*, and *Borrelia burgdorferi*),¹⁰ but no proof of an infectious etiology has yet been established.

Immune dysregulation

Currently, it is thought that the immune response is dysregulated in patients with AOSD. On one hand, innate immunity with macrophage and neutrophil activation possibly under the effects of the proinflammatory interleukin-18 (IL-18) has been implicated.¹¹ On the other hand, adaptive immunity with a predominance of type 1 helper T-cell (Th1) responses as indicated by increased levels of interferon- γ , tumor necrosis factor- α (TNF- α), and IL-2 has been associated with disease activity.¹² Moreover, the role of Th17 responses is emerging in the pathogenesis of AOSD, and levels of Th17-related cytokines, including IL-1 β , IL-6, IL-17, IL-18, IL-21, and IL-23, are elevated.¹³

CLINICAL FEATURES

The typical features of AOSD consists of a triad of symptoms that include high spiking fevers, evanescent rash, and arthritis or arthralgia. Not all three symptoms need be present at disease onset, and atypical findings may occur; therefore, the pleiotropic manifestation often leads to delays in diagnosis and treatment. In general, a shared constellation of clinical features can be found in most cohort studies reported over the past 7 years from various parts of the world (Table 87.1).¹⁴⁻²⁹

Fever

High fever (temperature $>39^{\circ}\text{C}$) was the initial symptom in more than 95% of patients with AOSD in the largest retrospective studies. Actually, fever of unknown origin is one of the most frequent reasons for patients with new-onset AOSD to seek help, and it is the final diagnosis in about 5% of these patients.¹⁵

The classic fever pattern is one to two daily fever spikes exceeding 39°C , most often occurring late during the day (afternoon or evening) and receding spontaneously within hours. However, continuous fever or early morning spikes are seen in up to 20% of cases.³⁰ Symptoms that occasionally precede the fever and should raise suspicion for AOSD include sore throat, seen in up to 80% of patients, as well as constitutional symptoms such as anorexia, myalgia or arthralgia, fatigue, and weight loss.

Arthritis

Musculoskeletal pain is present in virtually all patients with AOSD at onset and often worsens during periods of fever; such pain includes myalgia (13% to 70%), arthralgia (80% to 100%), and arthritis (18% to 100%). Initially, the arthritis may be mild, transient, and oligoarticular. These manifestations may evolve over a period of months into a more severe, destructive symmetric polyarthritis. Joints affected most frequently are the knees, wrists, and ankles, although involvement of the elbow, shoulder, proximal and distal interphalangeal, metacarpophalangeal, metatarsophalangeal,

TABLE 87.1

Frequency (%) of clinical disease manifestations at initial evaluation in recent series of adult-onset still disease

Country	Baxevasanos ¹⁴	Chen ¹⁵	Laskari ¹⁶	Riera ¹⁷	Kong ¹⁸	Franchini ¹⁹	Zeng ²⁰	Lee ²¹	Mitamura ²²	Cagatay ²³	Mehrpoor ²⁴	Singh ²⁵	Uppal ²⁶	Pay ²⁷	Evensen ⁶	Appenzeller ²⁸	Crispin ²⁹
Year	Greece	China	Greece	Spain	China	Italy	China	Korea	Japan	Turkey	Iran	India	Kuwait	Turkey	Norway	Brazil	Mexico
No. in cohort	22	61	25	41	104	66	61	71	34	84	28	14	28	95	13	16	26
Age (yr)	32	30	32	38	33	37	38	40	41	33	25	30	28	27	34	31	29
Female (%)	32	52	48	61	66	58	74	88	65	70	75	36	79	53	20	46	42
Fever (>39°C)	100	100	96	100	100	95	100	100	94	95	100	100	100	99	100	100	100
Arthralgia	91	80	88	98	NA	100	NA	85	91	96	92	NA	100	100	NA	69	92
Arthritis	18	NA	60	88	90	79	82	NA	41	69	60	100	64	85	69	100	88
Rash	73	79	64	93	95	79	89	84	91	60	85	57	85	82	77	100	54
Lymphadenopathy	73	52	56	41	66	54	53	68	58	33	57	71	61	37	62	50	54
Hepatosplenomegaly	NA	NA	44	NA	44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hepatomegaly	NA	21	NA	22	NA	41	13	30	27	38	NA	57	35	45	23	81	38
Splenomegaly	NA	64	NA	17	NA	38	38	37	64	29	32	57	57	42	23	31	46
Serositis	NA	NA	20	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	23	NA	19
Pleuritis	NA	11	NA	15	NA	18	18	15	9	10	NA	7	17	22	NA	6	19
Pericarditis	NA	10	NA	12	NA	14	25	14	9	12	28	14	3	8	NA	13	19
Myalgia	NA	36	NA	NA	NA	70	28	70	50	13	NA	NA	NA	70	NA	50	61
Sore throat	73	84	56	90	78	58	72	57	85	65	93	36	57	66	62	56	65
Inclusion criteria	Yama	Yama	Yama	Yama	Yama	Yama	Yama	Yama	Yama	Cush	Yama	Yama	Yama	Yama	Yama	Cush	Expert

NA, not available; Yama, Yamaguchi.

temporomandibular, and hip joints has been described as well (Table 87.2). Synovial fluid shows mild to moderate inflammation in most patients. The histopathology is nonspecific and includes chronic synovitis with slight cell proliferation in the synovial lining layers, variable degrees of vascular engorgement, and moderate infiltrates with mononuclear cells.^{30,31}

Early radiographic findings are usually nonspecific and consist of periarticular osteopenia and slight joint space narrowing. Carpal involvement with selective carpometacarpal and intercarpal space narrowing and focal erosive alterations leading to bone ankylosis has been suggested to be a differential diagnostic characteristic between AOSD and rheumatoid arthritis (RA)³² (Fig. 87-1). Severe involvement of the hip joint leading to bilateral hip destruction has also been reported (Fig. 87.2).

■ TABLE 87.2

Frequency (%) of joint involvement in series of adult-onset Still disease

	Chen ¹⁵ (N = 61)	Riera ¹⁷ (N = 1)	Franchini ¹⁹ (N = 66)	Cagatay ²³ (N = 84)	Pay ²⁷ (N = 95)
Knee	74	61	65	51	56
Wrist	31	63	56	43	67
Ankle	33	32	52	39	39
Shoulder	26	27	27	13	15
Elbow	47	22	19	19	28
PIP	20	20	37	21	18
MCP	18	27	29	21	22
MTP	16	5	12	11	6
Hip	15	20	12	4	2
DIP	7	2	19	1	1
TMJ	2	2	8	NA	3

DIP, distal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; NA, not available; PIP, proximal interphalangeal; TMJ, temporomandibular joint.

Myalgia is generalized and more often appears with exacerbations of fever. Inflammatory myopathy is found rarely, although a number of case reports have described an increase in muscle enzymes, but electromyography and muscle biopsy have not generally been suggestive of myositis.

Rash

The typical rash is an evanescent, salmon-pink, macular or maculopapular eruption that tends to occur with the fever (Fig. 87-3). The rash involves predominantly the trunk and extremities, but the palms, soles, and occasionally the face can also be involved. The Koebner phenomenon may be present in 30% to 60% of patients.^{28,33} Skin biopsy specimens are not diagnostic and show slight inflammatory infiltrates of polymorphonuclear and mononuclear cells in the upper dermis.³⁴ Even though the histopathology is nonspecific, skin biopsy can be important in differentiating this disorder from vasculitis, Sweet syndrome, and other conditions. Atypical skin lesions that have been associated with AOSD include urticaria and persistent pruritic papules and plaques, which show a distinctive distribution of dyskeratotic keratinocytes in the cornified layers, as well as in the epidermis.³⁴

Other frequent findings

Sore throat is common at initial evaluation (55% to 90%) and frequently recurs during a disease flare.³⁵ Examination shows severe, nonsuppurative pharyngitis with negative bacterial cultures.

Lymphadenopathy is detected in 33% to 73% of patients, with the cervical chain being most commonly involved. Splenomegaly may also be present (17% to 64%). The precise relationship between lymphadenopathy and other reticuloendothelial system manifestations such as hepatomegaly or splenomegaly is unclear; its combined presence with constitutional symptoms could lead to diagnostic confusion with lymphoma and even lymph node biopsy. Histopathologic evaluation shows a benign reactive hyperplasia with plasma cells and polymorphonuclear cell infiltration.^{30,31}

Liver abnormalities, predominantly hepatomegaly and abnormalities in liver biochemistry, are present in approximately 20% to 90% of patients. Fulminant hepatic failure requiring liver transplantation is extremely rare.



Fig. 87.1 (a and b) Radiographs of the wrists of a patient with adult-onset Still disease showing narrowing of the carpometacarpal and intercarpal spaces and focal erosive alterations that have led to bone ankylosis in the left wrist.

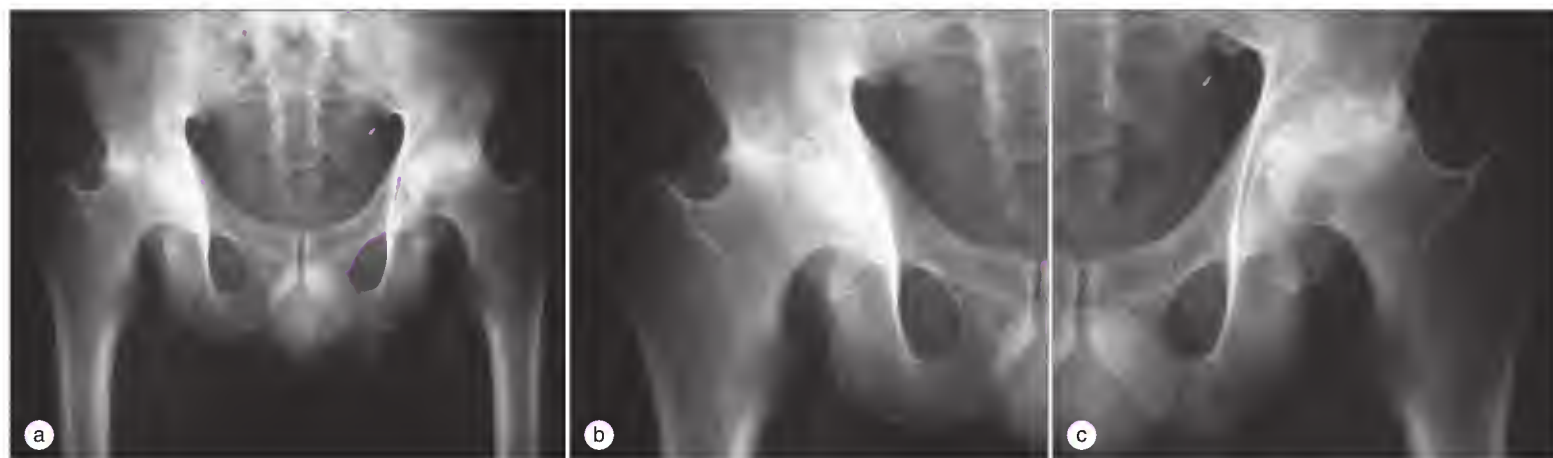


Fig. 87.2 (a to c) Radiographs of the pelvis showing the typical hip involvement leading to joint destruction.

Fig. 87.3 Example of the typical salmon-pink maculopapular rash affecting the extremities (a) and in more detail (b).



Pericarditis, pleural effusions, and transient pulmonary infiltrates have also been observed in patients with AOSD. Affected patients may complain of cough, pleuritic pain, or mild dyspnea. However, severe interstitial lung disease has been described, and some patients progress to acute respiratory distress syndrome.

Infrequent findings

Over the years, less common findings have been described: myocarditis and cardiac tamponade, aseptic meningitis and encephalitis, seizures, cranial neural palsies, uveitis, interstitial nephritis, collapsing glomerulopathy, renal amyloidosis, and macrophage activation syndrome.

Laboratory findings

The characteristic laboratory findings of AOSD are not pathognomonic, but its presence plus the clinical manifestations should help clinicians establish the diagnosis.

The laboratory profile of the disease is a reflection of the systemic inflammation and cytokine cascade present. The erythrocyte sedimentation rate and C-reactive protein are almost invariably elevated.³⁰ These are typically accompanied by leukocytosis (white blood cell count $>10,000/\text{mm}^3$) with a predominance of neutrophils ($>80\%$), normocytic normochromic anemia (typically the anemia of chronic disease), and thrombocytosis (Table 87.3). These hematologic abnormalities may sometimes reach extreme levels and mimic primary hematologic disease. Bone marrow examination has been reported to show hyperplasia of granulocytic precursors in all patients and hypercellularity and hemophagocytosis in some.³⁶

Abnormal liver enzymes (aspartate aminotransferase, alanine aminotransferase, and γ -glutamyltransferase) can be seen in up to 75% of patients,^{30,37} are more frequent in patients with hepatomegaly, and may show a hepatocellular, cholestatic, or mixed pattern. Abnormal liver function is thought to be part of the inflammatory process of the disease itself and tends to normalize with remission of the disease, although concomitant use of potentially hepatotoxic treatments often complicates interpretation.³⁸

Serum ferritin is markedly elevated in as many as 70% of patients.³⁷ The elevations correlate with disease activity and have been suggested to be a serologic marker for monitoring response to treatment.³⁹ Elevated serum ferritin levels, higher than five times the upper limits of normal (40 to 200 ng/mL), may suggest the presence of the disease with 80% sensitivity and 46% specificity; when combined with a decrease in the proportion of glycosylated ferritin ($<20\%$), the specificity rises to 93%.⁴⁰

Absence of antinuclear antibodies and rheumatoid factor is one of the minor Yamaguchi criteria for AOSD.⁴¹ However, a low titer of either occurs in less than 10% of patients without clinical implications and may reflect their presence in the general population. Complement consumption is rare, with C3 levels in general being normal to slightly elevated in the acute

phase. The presence of anti-citrullinated peptide antibodies has been reported in only 1 of 23 patients tested, but there are no data about their role in AOSD.¹⁷

CLASSIFICATION AND DIAGNOSIS

No specific test is available that can be used for the diagnosis of AOSD. Therefore, the diagnosis is based on recognition of the specific disease pattern and exclusion of other causes: infection, malignancy (lymphoma), necrotizing vasculitis, autoinflammatory syndromes, Schnitzler syndrome, and some drug hypersensitivity reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.⁴²

Several criteria sets have been proposed for accurate diagnosis of AOSD^{41,42,43} (Table 87.4). The Japanese criteria (Yamaguchi criteria⁴¹) have the highest sensitivity in patients with a definite diagnosis of AOSD.⁴⁴ The Yamaguchi criteria are hampered by a long list of diseases that must be excluded. The Fautrel criteria, which are more specific, require the not readily available measurement of glycosylated ferritin.⁴⁰

MANAGEMENT

First-line treatment: nonsteroidal antiinflammatory drugs and glucocorticoids

AOSD is not a common disease, and therefore no randomized controlled trials have been performed. Treatment is based on information from observational studies. Therapeutic decisions should be based on the extent and severity of organ involvement.

Nonsteroidal antiinflammatory drugs (NSAIDs) are considered the first-line agents for AOSD. Patients with mild disease may respond. Twenty percent to 25% of patients achieved control with this therapy. No randomized trials have compared different NSAIDs. Aspirin (3 to 4 g daily), ibuprofen (800 mg four times daily), and naproxen (500 mg/twice daily) are selections for initial therapy. Of the NSAIDs, indomethacin (100 to 150 mg/day) seems to be the most effective. It is advisable that liver enzymes be monitored at the onset of therapy. Severe hepatitis has been suggested to be related to treatment with NSAIDs.³⁸

Glucocorticoids are usually required to induce remission of symptoms. Patients with severe symptoms should be treated with glucocorticoids from the outset of therapy. The usual prednisone dose is 0.5 to 1 mg/kg/day. Intravenous pulse methylprednisolone (1000 mg/day times three) is reserved for life-threatening disease such severe hepatic involvement, disseminated intravascular coagulation, cardiac tamponade, and macrophage activation syndrome. No consensus has been reached on a therapeutic tapering scheme

TABLE 87.3

Frequency (%) of laboratory findings at initial evaluation in recent series of adult-onset Still disease

	Baxevasanos ¹⁴ (N = 22)	Chen ¹⁵ (N = 61)	Laskari ¹⁶ (N = 25)	Riera ¹⁷ (N = 41)	Kong ¹⁸ (N = 104)	Franchini ¹⁹ (N = 66)	Zeng ²⁰ (N = 61)	Lee ²¹ (N = 71)	Mitamura ²² (N = 34)	Cagatay ²³ (N = 84)	Mehrpoor ²⁴ (N = 28)	Singh ²⁵ (N = 14)	Uppal ²⁶ (N = 28)	Pay ²⁷ (N = 95)	Evensen ⁶ (N = 13)	Appenzeller ²⁸ (N = 16)	Crispin ²⁹ (N = 26)
Year of cohort	2012	2012	2011	2011	2010	2010	2009	2009	2009	2009	2008	2008	2007	2006	2006	2005	2005
Leukocytes >10 ⁴	91	80	84	93	98	79	84	NA	74	84	92	NA	100	NA	91	100	85
Anemia	NA	18	64	24	69	38	15	NA	33	36	NA	50	54	75	36	62	NA
Thrombocytosis	NA	36	32	NA	77	20	NA	NA	NA	24	NA	71	82	48	46	NA	NA
Abnormal liver enzymes	86	70	60	51	62	79	23	NA	76	54	89	50	14	64	62	50	NA
Hypoalbuminemia	NA	72	NA	NA	NA	65	NA	NA	70	42	NA	NA	NA	42	37	NA	100
Elevated ESR	91	98	96	100	96	100	100	NA	89	94	NA	100	96	94	NA	NA	NA
Elevated CRP	91	100	100	100	92	NA	80	NA	NA	NA	NA	NA	NA	97	NA	NA	NA
Elevated ferritin	95	94	96	86	99	97	80	NA	100	95	71	87	89	89	62	56	NA
RF positive	5	7	4	0	5	0	11	NA	12	NA	4	10	0	NA	0	0	21
ANA positive	5	10	12	0	0	8	11	NA	23	NA	4	0	0	NA	0	0	13

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NA, not available; RF, rheumatoid factor.

once clinical remission is achieved. Slow reduction over a 6- to 12-month period is recommended to maintain response and avoid relapse. Approximately 70% of patients respond to glucocorticoids. Serious side effects are common.^{45,46}

Second-line therapy: immunosuppressants

Methotrexate (MTX; 10 to 20 mg/wk) is used frequently for the treatment of AOSD. It is efficient in controlling AOSD activity and as a glucocorticoid-sparing agent. It is not clear whether MTX can prevent or limit joint damage in the erosive form of AOSD.

Cyclosporine and tacrolimus are reserved for the treatment of macrophage activation syndrome.^{45,46}

Third-line therapy: biologic agents

Biologic agents have been used for the treatment of AOSD, namely, TNF inhibitors, anakinra, tocilizumab, rituximab, and abatacept.

Tumor necrosis factor inhibitors

TNF blockers have been tested in patients with resistant AOSD. The experience is limited to case reports and small case series. The regimen of administration is the same as for RA. Promising results were reported with infliximab and etanercept, but treatment failures and loss of efficacy have also been described. In a retrospective study conducted by French investigators,⁴⁷ among the 15 patients who were treated with infliximab (some patients successively received both infliximab and etanercept), 4 of 15 (27%) and 9 of 15 (60%) achieved complete and partial responses, respectively. In the two remaining patients, infliximab therapy was ineffective. At the time of the survey, 10 of the 15 patients treated with infliximab had discontinued the treatment after a mean treatment duration of 9 months because of lack of efficacy (6 patients) or a side effect (3 patients). In the same study, in the 10 patients who were treated with etanercept, only 1 achieved a complete response and 7 of 10 a partial response. More than 120 patients treated with a TNF- α blocker have been reported in the literature, including those in whom it was ineffective. Switch from one TNF- α blocker to another one may be useful. Infliximab may be more effective than etanercept. Experience with adalimumab is limited.^{45,46}

Anakinra

Data from case series indicate that anakinra can control disease activity in patients with AOSD resistant to treatment with other drugs such as glucocorticoids, MTX, or even TNF blockers. Fitzgerald and colleagues⁴⁸ in a seminal study were the first to use anakinra for AOSD. In this open-label study of four patients with AOSD refractory to MTX and also to etanercept, treatment with anakinra in two patients resulted in rapid and complete resolution of both the systemic and articular manifestations that was sustained during a 6- to 14-month follow-up. Recently, in a series of 15 patients with AOSD, at least 50% improvement was seen in 11 patients (73%) at a mean follow-up of 17 months. Finally, in a recent open, randomized, multicenter study of 24 weeks' duration, 22 patients with AOSD who were taking prednisolone received anakinra (n = 12) or a disease-modifying antirheumatic drug (DMARD) (n = 10). At 8 and 24 weeks, 7 of 12 and 6 of 12 receiving anakinra and 5 of 10 and 2 of 10 receiving a DMARD achieved remission. During an open-label extension of 28 weeks, 7 of 14 patients taking anakinra and 2 of 3 taking a DMARD were in remission.⁴⁹ More than 140 patients with AOSD have been treated with anakinra. Anakinra is well tolerated. In some patients a reduction in anakinra injections was possible.^{45,46}

Tocilizumab

Tocilizumab is a humanized anti-IL-6 receptor antibody that specifically blocks the actions of IL-6, a cytokine that is markedly elevated in active AOSD. Several case reports have shown promising results of tocilizumab for AOSD. Most of the patients were resistant to MTX, corticosteroids, and biologic drugs, including anti-TNF blockers and anakinra. French investigators reported 14 patients (9 women and 5 men, mean age of 38.4 years, disease duration of 13.6 years) with refractory AOSD treated with tocilizumab.⁵⁰ All these patients had persistent active arthritis (14/14) or systemic manifestations (7/14) that were resistant to conventional treatment, including MTX (14/14), anakinra (14/14), and anti-TNF- α drugs (12/14). In most patients tocilizumab was administered at a dose of 8 mg/kg every 4 weeks intravenously (as for RA), but four patients received 8 mg/kg every 2 weeks. Tocilizumab was combined with MTX in eight patients and with leflunomide in two. In most patients, response to tocilizumab was rapid and sustained. More than 40 patients with AOSD have been reported to be treated with tocilizumab.^{45,46}

■ **TABLE 87.4**
Criteria sets proposed to identify patients with adult-onset Still disease

	Cush et al. (1987) ⁴³	Yamaguchi et al. (1992) ⁴¹	Fautrel et al. (2008) ⁴²
Design	Single center, retrospective	Multicenter, retrospective	Single center, retrospective
Data analysis	Descriptive	Discriminatory statistical analysis	Logistic regression analysis
Cohort size	21	90	72
Disease duration	11.8 yr	3.8 yr	2.9 yr
Case definition	Fever ≥39°C and arthralgia/arthritis with any 2 of leukocytosis, JRA, rash, serositis/RES involvement	Clinical diagnosis upheld after case review by expert committee	Patients undergoing ferritin measurement and clinical diagnosis upheld after prolonged observation and case review by one expert
Excluded from analysis	RF >1:80 ANA >1:100	Nondefinite cases after review (n = 56)	Nondefinite cases after review
Comparator group	None	267 definite non-AOSD cases	130 definite non-AOSD cases
Criteria set	Fever ≥39°C and arthralgia/arthritis with any 2 of leukocytosis, JRA, rash, serositis/RES involvement	<i>Major:</i> Fever ≥39°C for >1 wk, arthralgia >2 wk, maculopapular nonpruritic salmon-pink rash, leukocytosis ≥10,000/mm ³ with ≥80% neutrophils <i>Minor:</i> Pharyngitis or sore throat, lymphadenopathy and/or splenomegaly, abnormal aminotransferases, negative rheumatoid factor or ANA assay	<i>Major:</i> Spiking fever ≥39°C, arthralgia, transient erythema, pharyngitis, neutrophils >80%, glycosylated ferritin fraction <20% <i>Minor:</i> Typical rash, leukocytosis ≥10,000/mm ³
Required	As above	At least 5 criteria, including 2 major	Four major criteria or 3 major and 2 minor criteria
Exclusion needed	None	Infections, malignancies, vasculitides	None
Sensitivity for set	Not analyzed	96%	81%
Specificity for set	Not analyzed	92%	98%

ANA, antinuclear antibody; AOSD, adult-onset Still disease; JRA, juvenile rheumatoid arthritis; RES, reticuloendothelial system; RF, rheumatoid factor.

Other biologic agents

Limited evidence suggests that rituximab and abatacept may be effective in treating AOSD refractory to other biological agents. Canakinumab, a fully human monoclonal antibody against IL-1β with a half-life of 26 days, is promising. It is used for the management of cryopyrin-associated autoinflammatory syndromes caused by mutations in the NALP3 inflammasome. It has been used successfully in two patients with AOSD resistant to anakinra. Interestingly enough, canakinumab has been shown to be very effective in children with systemic JIA. Rilonacept (IL-1 Trap molecule, a soluble dimeric fusion protein) is another long-acting inhibitor of IL-1. It has been used successfully in four patients with AOSD.^{45,46}

Treatment strategy for adult-onset Still disease

It is essential to keep in mind that therapeutic decisions should be based on the extent and severity of organ system involvement. The main options are NSAIDs, glucocorticoids, MTX, and biologic agents.

NSAIDs should be the initial therapy in patients with mild disease. Most patients will require treatment with glucocorticoids, especially those with fever, joints symptoms, or internal organ involvement. If glucocorticoids are required, we suggest adding MTX because long-term corticosteroid treatment is the rule. Pulse corticosteroid therapy is reserved for patients with life-threatening disease such as pericardial tamponade, myocarditis, diffuse intravascular coagulation, and macrophage activation syndrome. In patients with refractory disease, biologic agents, especially anakinra and tocilizumab, are promising^{45,46} (Fig. 87.4).

Special issues regarding treatment

Pregnancy

Patients with AOSD are at increased risk for adverse outcomes of pregnancy. An increased rate of preterm birth and intrauterine growth retardation and a possible influence of disease activity on pregnancy outcome have been reported. AOSD may occasionally appear during pregnancy. Treatment with glucocorticoids is mandatory. In a patient known to have AOSD, pregnancy should be planned and treatment with immunosuppressors (MTX) stopped. A combined regimen consisting of glucocorticoids and NSAIDs is advisable. In the case of biologic drugs, it is recommended that they be stopped. Successful pregnancy and breastfeeding have been reported in a pregnant patient treated with anakinra.⁵¹

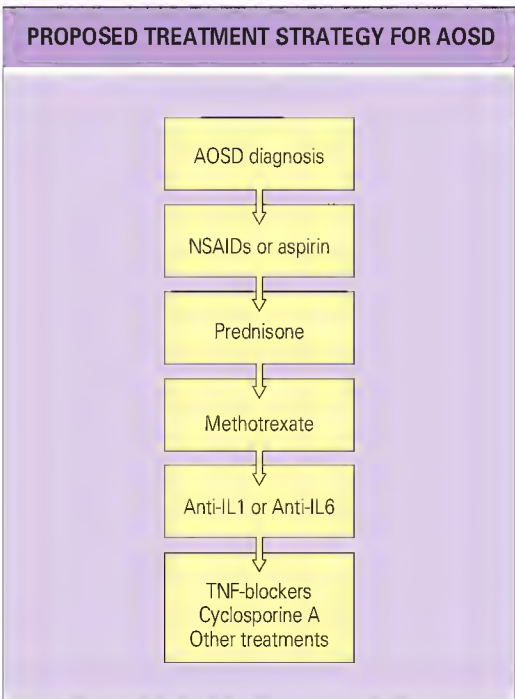


Fig. 87.4 Principal treatment regimens for adult-onset Still disease include NSAIDs, glucocorticoids, MTX, and biologic agents. AOSD, adult-onset Still disease; IL-1, interleukin-1; NSAID, nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

Hip involvement

Hip involvement in patients with AOSD is a dramatic issue. The clinician should dismiss the possibility of osteonecrosis, fracture, and actual hip involvement by arthritis. Rapid diagnosis is required. If confirmed, corticosteroid injections are advisable. If the patient is not taking biologic drugs, this is recommended.

Macrophage activation syndrome

Macrophage activation syndrome could be the initial form of AOSD. However, the appearance of this complication during the diagnostic process or evolution of the disease is most common. Clues to the diagnosis are fever, cytopenia, hypertriglyceridemia, and an increase in ferritin and lactate dehydrogenase. The diagnosis should be confirmed by marrow aspirate or bone marrow biopsy. Treatment consists of pulse glucocorticoids, intravenous immunoglobulins, cyclosporine, and biologic drugs (anakinra or tocilizumab).⁵²

AA amyloidosis

AA amyloidosis may complicate the evolution of AOSD. Very occasionally is AA amyloidosis the initial form of AOSD. The most common sign is proteinuria. The diagnosis should be confirmed by abdominal fat, rectal, or kidney biopsy. Treatment with biologic drugs is recommended to halt the evolution to renal failure.^{53,54}

PROGNOSIS AND FUNCTIONAL OUTCOME

Three main patterns are recognized in the course of AOSD. Approximately a third of patients fall into each pattern:

- Monophasic pattern: patients with the monophasic pattern have a disease course that usually lasts less than 1 year, with complete resolution of symptoms. Weaning from drug treatment may take longer.
- Intermittent pattern: patients have two or more disease flares with complete remission between episodes. Subsequent flares tend to be less severe and of shorter duration than the initial episode.
- Chronic pattern: patients with chronic AOSD have persistently active disease associated with destructive arthritis.

Baseline risk factors for the development of chronic disease and an unfavorable outcome are the occurrence of polyarthritis early in the course of AOSD, hip and shoulder involvement, and the need of glucocorticoid therapy for more than 2 years.

The functional status of patients with AOSD is generally good. In one series of 62 patients, 90% were American College of Rheumatology functional class I. In another series of 41 patients, 90% were also class I or II.^{17,30}

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88

Imaging of rheumatoid arthritis

■ THOMAS J. LEARCH

- Symmetric bilateral rheumatoid arthritis (RA) is commonly seen in the hands and feet, but asymmetric disease is frequently found in large joints.
- Hands and feet show the earliest radiographic changes of RA, which include soft tissue swelling, erosions, and diffuse joint space narrowing.
- Radiographic damage to large joints is seen most frequently in the elbow, shoulder, and knee.
- Sacroiliac joint disease in a patient with RA is relatively insignificant and not common.
- Atlantoaxial subluxation and basilar invagination are frequently present. The lateral cervical spine in flexion is the best way to evaluate patients for atlantoaxial subluxation. Basilar invagination is best appreciated on magnetic resonance imaging and computed tomography.

INTRODUCTION

Diagnostic imaging plays an integral role in the diagnosis and follow-up of patients with articular disorders. Patients with unclear and confusing clinical manifestations may have specific imaging findings that allow more accurate and timely diagnosis. For the rheumatologist, diagnostic imaging aids in the clinical diagnosis of rheumatoid arthritis (RA), provides insight into the severity and extent of joint disease, and helps in monitoring response to treatment regimens.

With the increasing use of disease-modifying antirheumatic agents and biologics early in the course of disease, accurate diagnosis, documentation, and staging of disease with imaging studies have become ever more important. Imaging provides an important tool to aid in the early diagnosis of RA and can also be used to evaluate the extent and severity of disease. Imaging studies provide an objective measure of the anatomic damage that defines the course of the disease and the long-term effects of treatment. Imaging studies help in monitoring disease progression or remission and response to therapeutic interventions. Advances in imaging technologies beyond conventional radiography have been dramatic and offer new insight into diagnosis and progression of disease.

APPROACH TO IMAGING AND GENERAL IMAGING FEATURES

The imaging hallmarks of RA are abnormalities in alignment, periarticular osteoporosis that progresses to generalized osteoporosis, bony erosions, uniform joint space narrowing, and periarticular soft tissue swelling with the formation of synovial cysts and rheumatoid nodules. The distribution of changes is generally bilateral and symmetric, especially in the hands, wrists, and feet, where the earliest changes are seen.

Various imaging modalities can be used to study RA. Each modality has strengths and weaknesses, and some are better than others in visualizing various pathologic processes. A generalized approach to analyzing imaging studies for RA has been suggested by Forrester and Brown,¹ who proposed using the mnemonic “the ABCD’s of arthritis”:

- A—Alignment
- B—Bone mineralization

- C—Cartilage and joint space
- D—Distribution
- S—Soft tissues

Changes in alignment are searched for in all imaging studies but are particularly common in the wrists, hands, feet, and craniocervical junction. Abnormalities in alignment may be reduced and minimized when the patient is positioned for posteroanterior radiographs of the hands, but they should be readily visualized on oblique and lateral views, during which the hands are not flattened on the film cassette. Atlantoaxial subluxation is frequently seen only on flexion radiographs, and therefore lateral views of the cervical spine should be obtained with the patient assuming a flexed spine posture.

Bone mineralization is usually normal in all arthropathies except RA. Diffuse osteoporosis is commonly seen in the aging process and with RA. It can also occur as a side effect of certain medications, such as corticosteroids. Disuse and immobilization likewise lead to osteoporosis. Conventional radiographs underestimate early osteoporosis but are positive in advanced stages. This is frequently a subjective finding. Periarticular demineralization is subjectively evaluated by the presence of decreased radiographic density in the osseous structures surrounding a joint space.

Cartilage and joint spaces have the same radiographic density as soft tissues and are therefore not directly visualized on conventional radiographs. Normal joints have a uniform covering of cartilage on their articular ends that correlates with the space seen between the articular surfaces of adjacent bones. Cartilage thinning is inferred on conventional radiographs by the finding of joint space narrowing. Joint space narrowing in RA is diffuse, unlike that in osteoarthritis, in which narrowing occurs along biomechanical vectors of use. As articular cartilage narrows, erosive changes can be seen. Erosions are an important imaging finding that helps confirm the diagnosis of RA and demonstrate the severity of disease. Erosions initially appear at the edge of the joint where cartilage is thinnest and synovium attaches. This is referred to as the “bare area.” Such erosions are also called marginal erosions.

Distribution of the pathology is an important observation because various arthropathies have characteristic areas of involvement well known to rheumatologists. Symmetric bilateral disease is commonly seen in RA, particularly in the hands and feet. However, asymmetric disease is frequently found in large joints.

Soft tissue changes are easily overlooked on radiographs because the eye is naturally drawn toward the more dense osseous structures. Digital conventional radiographs allow adjustment of the window or level on viewing monitors and have led to improved visualization of joint and bursal swelling and effusions. Symmetric swelling about joints in the hands as a result of a combination of effusion, synovial proliferation, and periarticular soft tissue edema is an early finding on conventional radiography. Advanced imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) can be used to optimally resolve any diagnostic difficulties in soft tissue disease.

IMAGING MODALITIES

Conventional radiography

Conventional radiography has long been the mainstay of imaging. It is inexpensive, easily performed, and readily available. Therefore imaging of articular disorders should start with this modality. Well-performed, high-quality radiographs show osseous and soft tissue changes that document



the severity and extent of disease. They often are sufficient, and no further imaging may be required. Follow-up films allow assessment of disease progression or remission.

Hands and wrists

The hands and wrists are commonly involved in RA. The hands (as well as the feet) show radiographic changes the earliest, and the findings are typical.^{2,3} Therefore these studies are frequently obtained during initial evaluation of the disease. All the joints of the wrist and hand can be assessed with one radiographic study, so in the interest of cost savings, hand films only need be requested. Hand films routinely include the wrist joints.

Soft tissue swelling related to joint effusion, synovitis, and periarticular edema is the earliest radiographic change and can be seen at the proximal interphalangeal and metacarpophalangeal (MCP) joints and at the ulnar styloid (Fig. 88.1). Hyperemia and disuse result in periarticular osteoporosis. Erosions are initially very subtle on conventional radiographs and are seen as irregularity of the white cortical line. Erosions occur earliest about the carpus (usually at the pisiform, triquetrum, and ulnar styloid) and second MCP joint.³ Initially, they may have a dot-dash appearance with subsequent progression to frank defects and irregularity. Bare area erosions at the metacarpal head-neck junction and bases of the phalanges follow. These erosions are more prominent at the radial and volar aspect of the metacarpal head. Inflamed synovial-lined tendons can also lead to erosion. This typically occurs at the ulnar styloid secondary to tenosynovitis of the adjacent extensor carpi ulnaris tendon (Fig. 88.2).

As cartilage destruction continues, diffuse narrowing of affected joints becomes evident on conventional radiographs. This is well visualized at the carpal and MCP joints. Normally, these articulations are uniformly 2 mm wide. Comparison with adjacent or contralateral uninvolved joints or previous studies helps in making this finding more obvious.

Joint ankylosis occurs later in the disease process and typically involves the carpus and rarely the interphalangeal joints.

Abnormalities in alignment are most dramatic in the hands and wrists and tend to be symmetric. They are caused by the abnormal kinetic pull of tendons on damaged joints, which produces unbalanced forces that result in characteristic deformities. The carpus deviates radially and translates toward the ulna. On the posteroanterior view the lunate normally articulates

with the lateral aspect of the radius. When more than half the articular surface of the lunate is medial to the ulnar edge of the distal end of the radius, radial deviation and ulnar translation of the carpus have occurred (Fig. 88.3). Characteristic ulnar deviation and palmar subluxation of the MCP joints, boutonnière and swan neck deformities of the fingers, and Z deformities of the thumb are easily assessed clinically and further documented on conventional radiographs (see Fig. 88.3). Such changes in alignment are also associated with systemic lupus erythematosus and Jaccoud arthropathy; however, joint space narrowing, erosions, and inflammation are much more prominent in RA.

Feet and ankles

The forefoot has been reported to show the earliest radiographic changes in patients with RA.³ The lateral fifth metatarsal head is the first area to show erosion. The medial aspect of the first interphalangeal joint is also involved early (Fig. 88.4). Posteroanterior views are best used to assess for early erosions. Oblique views are not necessary and may be overread by inexperienced viewers because the normal facets of the metatarsal heads, exaggerated on this view, may be falsely interpreted as erosions.

Diffuse joint space narrowing of the ankle and tarsal articulations is seen frequently. Effusions involving the ankle joint and retrocalcaneal bursa effusions are readily appreciated on lateral conventional radiographs (Fig. 88.5). As in the carpus, the tarsal joints may become fused in advanced disease.

Abnormalities in alignment similar to those seen in the hand occur in the forefoot. Fibular deviation of the toes and dorsolateral subluxation or dislocation of the proximal phalanges at the metatarsal head are common. The fifth toe may be relatively spared.

Large joints

In patients with long-term RA, radiographic damage to the large joints is seen most frequently in the elbow, shoulder, and knee, with reported rates of 32%, 31%, and 27%, respectively. This is followed by the subtalar, ankle, and hip joints, with reported rates of 24%, 22%, and 21%, respectively.⁴ In general, the distribution of the arthropathy is bilateral and symmetric, especially in the small joints of the hands and feet. With involvement of large joints, symmetry is less common.



Fig. 88.1 Early rheumatoid arthritis. Mild pancarpal and third through fifth metacarpophalangeal (MCP) joint space narrowing is present. The second MCP joint is not narrowed, but note the soft tissue fullness (arrows) radial to the joint secondary to pannus and joint fluid. Soft tissue fullness is also present near the distal end of the ulna (arrowheads) secondary to tenosynovitis of the extensor carpi ulnaris.



Fig. 88.2 Erosive disease is present at the ulnar styloid and bare areas of the second metacarpophalangeal joint (arrowheads). Note the erosive changes of the radial aspect of the second metacarpal head with interruption of the white cortical line as opposed to the intact third metacarpal head. This is a Korean patient who used acupuncture to treat her rheumatoid arthritis. Note the acupuncture needle tips (arrows) that were left in the patient's soft tissues.



Fig. 88.3 Radial deviation and ulnar translation of the carpus with the majority of the lunate no longer articulating with the radius. Palmar subluxation and ulnar deviation of the metacarpophalangeal joints and a swan neck deformity of the fifth digit are apparent.



Fig. 88.4 Radiograph of the foot demonstrating erosions of the third through fifth metacarpal heads with associated narrowing of the metatarsophalangeal joint space. There is also narrowing of the first interphalangeal joint space with bare area erosions.

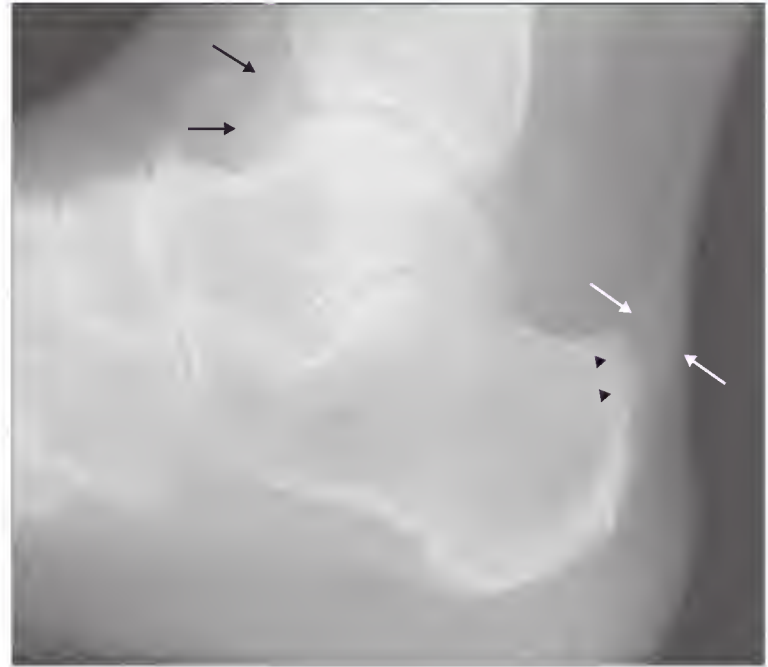


Fig. 88.5 Lateral hindfoot. The Achilles tendon is thickened at the insertion of the calcaneus (white arrows) secondary to retrocalcaneal bursitis. Note the associated erosions and irregularity of the posterior calcaneus (arrowheads). Ankle joint effusion is present (black arrows).

Pelvis and hips

Soft tissue changes about the hip such as joint effusion and greater trochanteric and iliopsoas bursitis are not readily appreciated on conventional radiographs. These findings usually require advanced imaging modalities. The hallmark of RA of the hip on conventional radiographs is diffuse joint space narrowing with erosions of the femoral head and neck (Fig. 88.6). Later in the disease process the erosions may greatly deform and whittle the femoral head. Thinning and erosive disease of the acetabular surface leads to protrusion of the femoral head and acetabulum into the pelvis, a condition called protrusio (Fig. e88.1).

Sacroiliac joint disease in RA is relatively insignificant and not commonly observed on imaging studies. The sacroiliac joints are not generally radiographically abnormal until late in disease, when asymmetric narrowing, erosions (predominantly on the iliac side because its articular cartilage is thinner than in the sacrum), and possibly areas of fusion may be seen.

Knee

This large synovial joint is frequently affected by RA. Early radiographic findings include joint effusion with engorgement of the suprapatellar bursa (seen best on lateral radiographs), pancompartmental joint space narrowing, and bare area erosions (Fig. 88.7). As ligamentous laxity ensues, varus or valgus deformities develop. Later in disease, osteophytosis related to secondary osteoarthritis can be seen. Popliteal cysts are commonly noted on advanced imaging studies but are rarely identified on conventional radiography.

Shoulder

Early in disease, marginal erosions are seen in the rotator cuff attachments at the superolateral aspect of the humeral head, where cartilage is the thinnest—the bare area of this joint. This is followed by diffuse glenohumeral joint space narrowing as loss of cartilage continues (Fig. 88.8). The joint space narrowing may be difficult to appreciate on routine anteroposterior shoulder radiographs because the glenohumeral joint is not in profile. The Grashey view, obtained with the patient in 30 to 40 degrees of posterior oblique positioning of the torso, provides a perpendicular profiled view of the joint and is more sensitive in identifying joint space narrowing. Glenohumeral joint effusions are not detected on conventional radiographs.

In more chronic disease, rotator cuff atrophy and tearing result in superior migration of the humeral head, narrowing of the acromiohumeral distance to less than 7 mm, and eventual mechanical pressure erosion caused by contact of the uncovered humeral head with the undersurface of the acromion. Erosive changes about the acromioclavicular joint occur with later resorption of the distal end of the clavicle (Fig. e88.2).



Fig. e88.1 Advanced disease of both hips. The right femoral head is eroded superiorly, and an acetabular protrusio deformity with marked thinning and a resultant fracture is present. The left hip demonstrates diffuse joint space narrowing with a large subchondral cyst present in the superior acetabulum (arrows).



Fig. e88.2 Advanced erosive disease of the glenohumeral joint. Note the erosive changes involving the distal end of the clavicle. The humerus is high riding secondary to a rotator cuff tear and atrophy. The bones are markedly osteopenic with an insufficiency fracture of the acromial spine (arrows).



Fig. 88.6 Diffuse narrowing of the left hip joint space with small erosions of the femoral head. Note the linear sclerotic area of the pubis (arrows) related to an insufficiency fracture.



Fig. 88.7 Diffuse joint space narrowing involving both medial and lateral compartments bilaterally. Multiple erosions are present at the articular surface and the bare areas of the knee joint.

Elbow

The elbow is frequently involved in RA, and indeed, this is the most common arthritis affecting this joint. Soft tissue changes are the early radiographic findings and include joint effusion with displacement of the anterior and posterior fat pads away from the humerus and soft tissue swelling posterior to the olecranon corresponding to olecranon bursitis. Diffuse joint space narrowing secondary to cartilage loss and articular erosions occurs in both the radiocapitellar and ulnotrochlear compartments (Fig. 88.9). It may become quite severe with marked articular bone loss and subluxation. Other synovium-lined areas about the joint may be involved by synovitis and pannus as well (Fig. 88.10).

Cervical spine

Spinal disease in RA occurs most frequently in the cervical spine, with more than half of all patients with RA experiencing involvement in the course of their disease. Most patients with severe RA will have abnormalities in this area. The most common abnormality is atlantoaxial subluxation, followed by basilar invagination.^{5,6}

The most important radiograph in the cervical spine series is the lateral radiograph with the patient assuming a flexed position. The diagnosis of atlantoaxial subluxation, which is difficult to discern on physical



Fig. 88.8 Diffuse glenohumeral joint space narrowing with multiple erosions (arrows). Note the large erosion just medial to the greater tuberosity (arrowhead). This is the bare area of the shoulder, where the earliest erosions are seen.

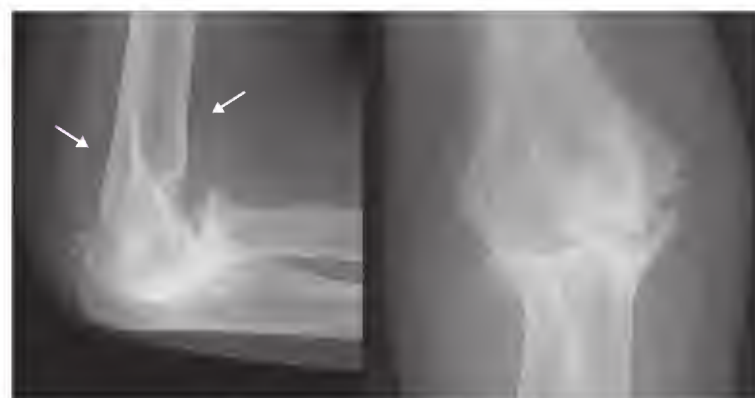


Fig. 88.9 Diffuse elbow joint space narrowing with erosions. The trochlea is much more eroded than the capitulum. Displaced fat pads are present (arrows) secondary to joint effusion.

examination, is made easily with this projection (Fig. 88.11). Normally, the distance between the anterior arch of C1 and anterior aspect of the dens of C2 is less than 3 mm in adults and less than 5 mm in children. Subluxation greater than 8 mm usually requires surgical intervention. The anterior C1-C2 area may be obscured because of cranial settling or basilar invagination. Atlantoaxial subluxation can still be diagnosed by evaluating the posterior cervical line. This is a radiographic line drawn between the spinal lamina of C1, C2, and C3 and should be straight. Anterior subluxation of the C1 lamina reflects the same degree of anterior subluxation of the atlantoaxial articulation (see Fig. 88.11). Mid and lower cervical laxity allows anterior listhesis of the vertebral bodies, which results in a stepladder appearance on the lateral flexed radiograph. The flexed view also permits better visualization of the synovial facet joint surfaces as they open. Fusion of the facet joints may occur at some levels, but multilevel posterior ankylosis is rare in adult-onset RA. Basilar invagination may be diagnosed on conventional radiographs but is best studied with MRI or computed tomography (CT).^{7,8} This allows visualization of the adjacent brain stem and spinal cord, which may be impinged by the dens (Fig. 88.12). Advanced imaging also demonstrates associated pannus and erosions about the dens.

Arthrography

Diagnostic arthrography was previously used to evaluate intraarticular structures, the joint capsule, and surrounding ligaments but has largely been replaced by MRI and ultrasonography. It is rarely used today in the

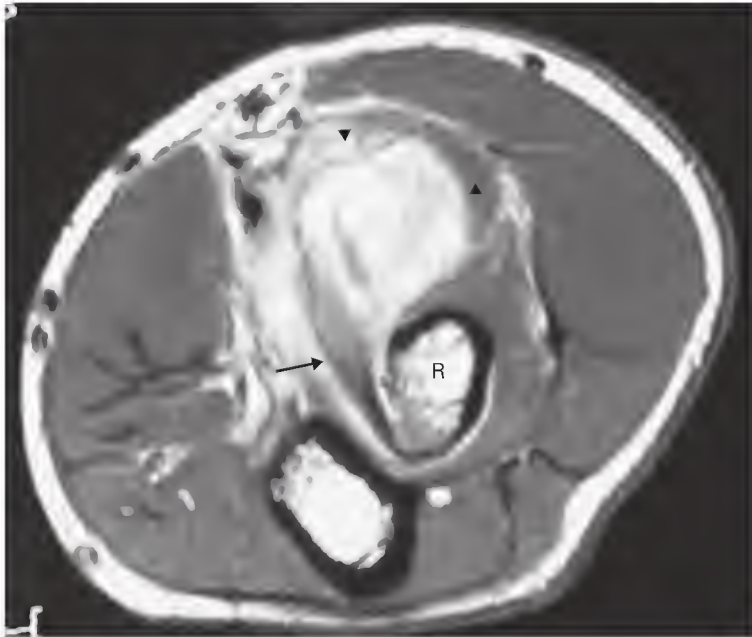


Fig. 88.10 This patient was found to have a mass in her elbow. Axial T1-weighted magnetic resonance imaging with fat saturation after intravenous gadolinium enhancement demonstrates enhancing synovium in the bicipitoradial bursa (arrowheads) where the biceps tendon (arrow) inserts on the radius (R). Conventional radiographs of the hands demonstrated changes consistent with rheumatoid arthritis. This was the patient's initial findings.



Fig. 88.11 Atlantoaxial subluxation. The anterior arch of C1 is displaced 8 mm anterior to the dens. This is confirmed by the abnormal posterior cervical line.

evaluation of patients with RA. Image-guided injection and aspiration of joints, however, still play an important role in the injection of corticosteroids or other medications directly into a specific location and in the diagnosis of rheumatoid joints complicated by infection.

Many of the classic imaging features of RA overlap considerably with septic arthritis, and this differential diagnosis needs to be considered.^{9,10}



Fig. 88.12 A sagittal T2-weighted magnetic resonance image of the craniocervical junction demonstrates basilar invagination with superior migration of the dens through the foramen magnum. The dens is indenting the medulla.

Septic arthritis is usually a monoarticular disease. However, it must be kept in mind that patients with RA are at increased risk for septic arthritis as a result of immune suppression and that previous damage to joints during the course of the disease makes these joints more prone to infection.¹¹ Because septic arthritis is such a catastrophic illness, prompt aspiration of these joints is essential in the evaluation and diagnosis of these patients. Cadaveric joint arthrocentesis studies performed by senior emergency medicine residents have shown success rates of 80% for accurate positioning of needles in various joints.¹² Because imaging guidance is not routinely used by orthopedic, rheumatology, or emergency physicians, radiologists are frequently requested to aspirate or inject joints. By using fluoroscopic or ultrasound guidance, deep, difficult-to-palpate joints such as the hip or shoulder can easily be accessed. During this procedure, contrast medium is injected into the joint to yield additional information on surrounding synovial cyst formation and the presence of sinus tracts (Fig. e88.3). Image guidance offers the distinct advantage of directed needle placement and imaging proof that the sample obtained did indeed come from the joint itself.

Ultrasonography

Ultrasonography is a readily available and relatively low-cost modality that has increasingly gained wide acceptance in the evaluation of patients with RA, particularly in Europe. In experienced hands, ultrasonography can be used to evaluate soft tissue structures and demonstrate fluid collections and muscle and tendon integrity. It is used for evaluation of muscle/tendon subluxations, dislocations, and tears and tenosynovitis. It can be done in real time with patient movement, and the contralateral side can be imaged quickly for comparison. Fluid collections such as abscesses, popliteal and other synovial cysts, bursae, ganglia, and joint effusions are all well imaged (Fig. 88.13). Under direct ultrasound guidance these collections can be aspirated or injected with medication.

Ultrasound beams cannot penetrate bone, so intraosseous lesions and some intraarticular areas cannot be imaged. Ultrasonography, however, has increasingly been used to study articular surface cartilage abnormalities, particularly in the evaluation of early erosive disease, and has higher sensitivity in detecting erosions than conventional radiography does.¹³



Fig. e88.3 Arthrogram of a septic right hip joint demonstrating a sinus tract (arrows) exiting the inferolateral aspect of the thigh.

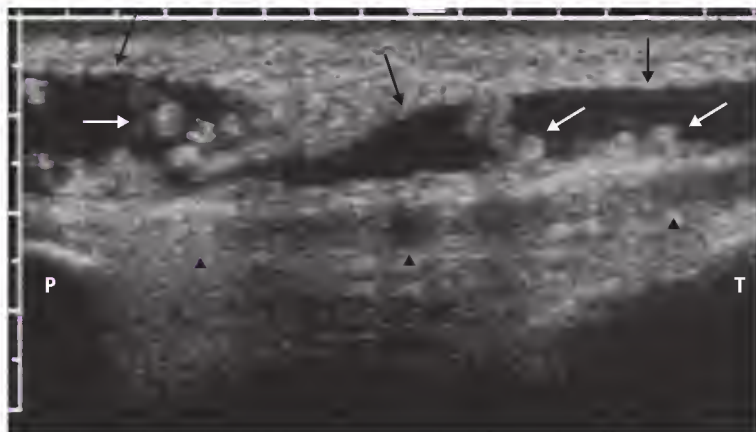


Fig. 88.13 Longitudinal ultrasound image anterior to the knee along the patellar tendon. A large fluid collection (black arrows) is located anterior to the patellar tendon (arrowheads) in the prepatellar and infrapatellar bursae along with areas of synovial hypertrophy (white arrows). P, patella; T, tibial tuberosity.

Ultrasonography has been shown to be highly sensitive in assessing bone destruction and inflammation in finger joints, with high correlation to MRI studies done concurrently.¹⁴ The main limitation of ultrasonography, however, remains the steep learning curve in performance of subspecialized examination protocols. Additionally, many hospitals and imaging facilities, especially in the United States, may not have radiologists familiar with musculoskeletal ultrasonography.

Computed tomography

Since the development of CT in the 1970s, it has been used extensively to image osseous structures. Most imaging was generally performed in the transverse plane, with computer reformatted images in other planes lacking resolution and detail. Imaging of muscle, ligaments, and joint structures was limited and considered insufficient. Imaging of metallic orthopedic hardware and joint replacements caused considerable artifact, thereby limiting the usefulness of CT in many musculoskeletal cases.

However, recent developments in multidetector CT technology and computer-enhanced reformatting of image data have revolutionized this modality and broadened its use. Images are still generally obtained in the transverse plane, but reformatted images in other planes can now be obtained immediately on advanced workstations to allow visualization of structures in any linear or even curvilinear plane. Soft tissue resolution in many areas now rivals that of MRI and ultrasonography. With intraarticular injection of a contrast agent, articular structures such as menisci and cartilage are well demonstrated. Decreased streak artifact from metal now permits detailed imaging of joint arthroplasties and other orthopedic hardware.

CT optimally images osseous structures and can easily detect erosions. It is more sensitive than MRI in the detection of early erosions in the hand.¹⁵ CT is often used in the preoperative evaluation of patients for joint arthroplasty because of its optimal assessment of bone stock, articular surfaces, and version. Postoperative evaluation of hardware positioning and complications is also now possible (Figs. 88.14 and 88.15).¹⁶ CT arthrography (done after injection of a contrast agent into the joint) assesses intraarticular structures and cartilage surfaces.¹⁷ It has been used increasingly in patients who cannot tolerate or have absolute contraindications to MRI.

Magnetic resonance imaging

MRI is unique in its ability to optimally image bone, articular structures, and soft tissues, with the added advantage of not using ionizing radiation. Initially used to evaluate large joints such as the hips, knees, and shoulders, new developments have improved the ability of MRI to resolve smaller joints and structures, thus furthering its application in the diagnosis and evaluation of patients with RA.

MRI is generally well tolerated by all patients except those with claustrophobia, although open scanners and medications have substantially decreased this problem; by the disoriented or confused, who may not tolerate the inherent noise that the scanner produces or may not be able to stay still during sequence acquisitions; or by the morbidly obese, where weight limitations may hinder tabletop movement and positioning. Some relative and absolute contraindications to MRI exist and preclude its use in some patients. All patients are screened before the procedure to determine any



Fig. 88.14 Coronal reformatted computed tomographic image of a patient with a total hip replacement. There is marked wear of the polyethylene cup superiorly, with the femoral head component now in contact with the metal acetabular cup. The interface between the native acetabulum and acetabular cup is markedly widened, which has resulted in a loose, floating prosthetic cup. Protrusio deformity is present.

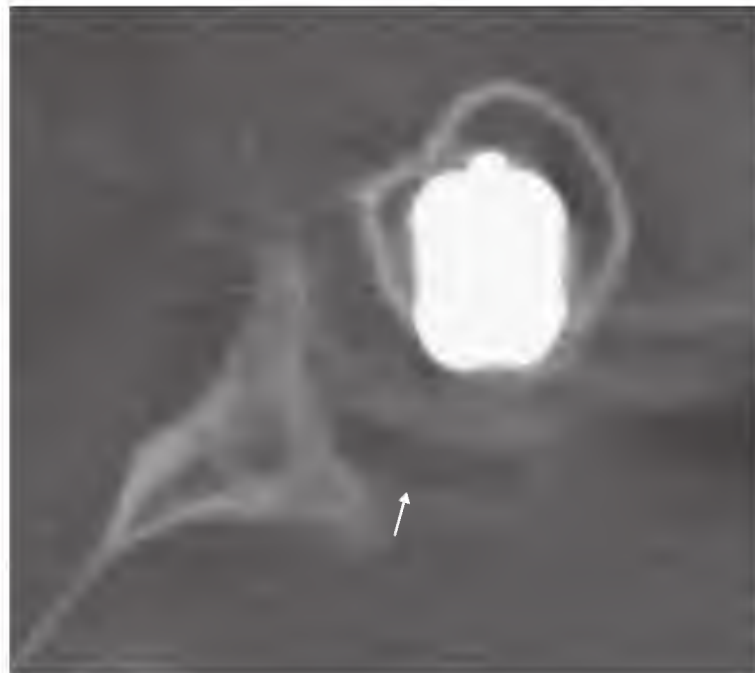


Fig. 88.15 Computed tomographic arthrogram of a total shoulder replacement. Intraarticular contrast medium surrounds the dislocated polyethylene glenoid component (arrow).

potential contraindications. A common misconception is that patients with joint replacements or other orthopedic hardware cannot undergo MRI. In fact, MRI has been used increasingly to evaluate painful or infected arthroplasties, and newer sequences can minimize metallic artifact. If there is any concern that the patient cannot be in a high magnetic field environment,

other imaging strategies such as ultrasonography or CT may be recommended by the radiologist.

MRI has long been advocated for the evaluation of internal joint derangement. To this end, it can superbly image ligaments, tendons, menisci, articular cartilage, synovium, and joint fluid (Figs. 88.16 and 88.17; also see Fig. 88.10).

Structures surrounding articulations such as musculature and the spinal cord are well delineated. MRI is the modality of choice for evaluating the cervicocranial junction for atlantoaxial subluxation and basilar invagination and their effects on the adjacent spinal cord and brain stem (see Fig. 88.12). In patients with symptomatic cervical spine involvement, there is a strong correlation between the development of neurologic dysfunction and MRI identification of atlantoaxial spinal canal stenosis, especially in those with evidence of upper cervical cord or brain stem compression and subaxial myelopathic changes.¹⁸

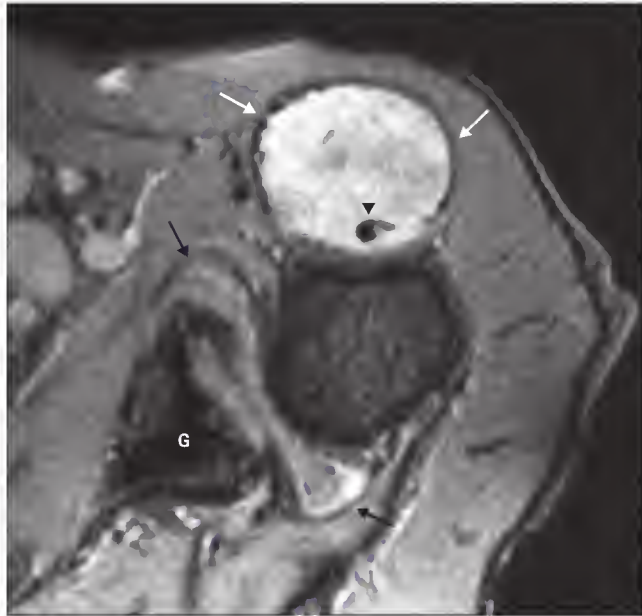


Fig. 88.16 Axial gradient-echo magnetic resonance image of the shoulder in a patient with rheumatoid arthritis complaining of a mass. A large synovial cyst (white arrows) has dissected along the long head of the biceps tendon (arrowhead). Pannus (black arrows) is present in the glenohumeral joint along with marked irregular erosive change of the glenoid (G).

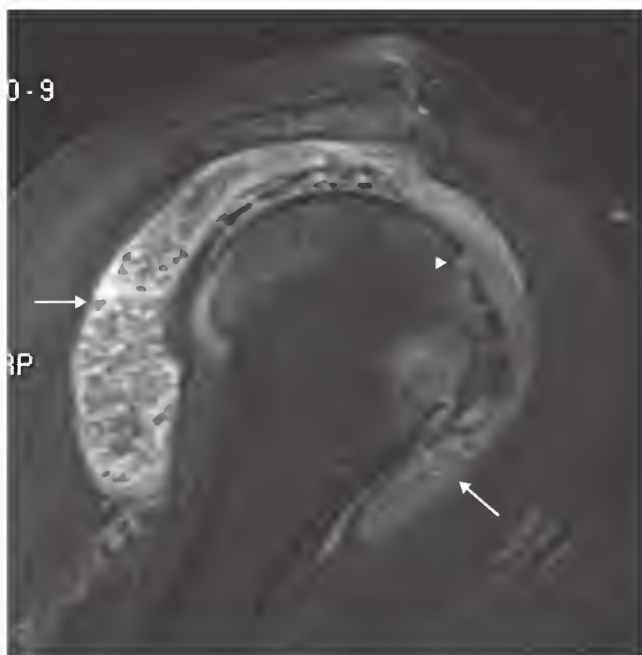


Fig. 88.17 Sagittal fat-saturated proton density-weighted magnetic resonance image of the shoulder demonstrating large chronic subacromial or subdeltoid bursal fluid inflammation and rice body formation (arrows). Erosion (arrowhead) is present in the humeral head.

MRI is also the modality of choice for imaging bone marrow abnormalities. In patients with RA, bone infarction, bone marrow edema adjacent to synovial inflammation, and occult traumatic and insufficiency fractures are all optimally imaged with this modality.

MRI clearly demonstrates early disease before conventional radiography does. Since medical therapy for RA has become increasingly more effective, early diagnosis and assessment of disease activity and joint damage have become ever more important. MRI has also been used to detect early synovitis and to quantify early marginal erosions, joint effusion, and cartilage disease, which are frequently radio-occult (Fig. 88.18).¹⁹ MRI has been shown to detect erosions years before their appearance on conventional radiographs²⁰ and is more sensitive than ultrasonography.²¹

Hence MRI can play an important role in diagnosis, prognosis, and monitoring of the effectiveness of therapies in clinical practice. However, although erosions, synovitis, and tenosynovitis in the hands are frequently encountered in early RA and are well demonstrated by MRI, these findings are not specific. They can also be seen in patients with systemic lupus erythematosus and primary Sjögren syndrome.²²

The main limitation of MRI is expense and availability; however, the modality is now in most hospitals and many outpatient facilities, and its more ubiquitous presence may reduce the cost. Its effectiveness in early diagnosis of disease has led to increasing use at the onset of disease. Cost-saving measures can be used and are advocated by radiologists familiar with early disease. This may include scanning both wrists and hands together in the prayer position with the patient lying on the side and hands above the head. The right hand can be labeled with a dedicated MRI marker to avoid confusion, and simultaneous imaging of both sides can be performed to obtain a “two for one” study.

As good as 1.5-T MRI is, newer high-field-strength (3.0-T) imaging can provide even more detailed resolution of smaller structures. Currently, 3.0-T imaging is becoming increasingly available at the university and community level. These magnets produce more detailed imaging studies, and they are particularly useful in neuroradiology. Although musculoskeletal examinations are generally of higher quality with 3.0-T magnets, which improve evaluation of the extent of bone edema and synovitis and identification of small bone erosions by 14% to 22%, acceptable image quality is still achieved with 1.5 T.²³

As further developments in MRI technology, protocols, and research improve our understanding and ability to image rheumatic diseases, this modality will undoubtedly play an important role in diagnosis, prognosis, and monitoring of the effectiveness of therapies in clinical practice.



Fig. 88.18 Coronal T1-weighted magnetic resonance image of the wrist demonstrating multiple carpal erosions. These erosions were not seen on radiographs.

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89

The contribution of genetic factors to rheumatoid arthritis

■ ROBERT M. PLENCE

- Twin and family studies have confirmed an important contribution of genetic factors to the development of rheumatoid arthritis.
- Genes encoded within HLA-DRB1 from the major histocompatibility complex have provided the most consistent evidence of an effect.
- Recent studies covering the whole genome have suggested a number of other candidate genes.
- The effects of key genes, including HLA-DRB1, are modified by environmental factors, particularly smoking.

INTRODUCTION

This chapter endeavors to summarize the wealth of information that has emerged on the contribution of genetic factors to rheumatoid arthritis (RA). The first associations of genetic factors with RA were described more than 4 decades ago, but the rate of progress in recent years has been exponential. This chapter summarizes the strength of the evidence suggesting a role for genetics in susceptibility to RA. A detailed analysis of the role of both HLA and other loci within the major histocompatibility complex (MHC) is presented. Much of the most recent data has come from studies outside the MHC and is based on emerging powerful technologies. Finally, the evidence for gene-environmental interactions is reviewed briefly.

STRENGTH OF GENETIC CONTRIBUTION

Early evidence for a genetic component in RA was derived from family and twin studies.^{1,2} The risk for RA is 0.5% to 1% in the general population, but a monozygotic twin of a patient with RA has a risk of around 15%.³⁻⁵ Moreover, the relative risk (RR) to the sibling of a proband with RA (known as λ_s) is approximately 5 for RA,⁶⁻⁸ although the number varies depending on the population studied.⁹ A complementary approach for estimating the genetic component is to consider the heritability of a disease, which is the proportion of the variance of the disease that is explained by the inherited genetic variance. Using data on twins, the heritability of RA has been estimated to be about 60%, thus indicating that genetic factors account for a large proportion of the population's liability to the disease.¹⁰ However, this serves as only an estimate because measures of heritability may overestimate the genetic component because of the common environment shared by family members or even underestimate the genetic component because of complex genetic interactions (e.g., gene-gene or gene-environment interactions).

ROLE OF MAJOR HISTOCOMPATIBILITY COMPLEX GENES

In common with many other autoimmune diseases, much genetic research has revolved around genes within the MHC region on chromosome 6. The MHC region is the most gene-dense region in the mammalian genome, and it plays an important role in the immune system, autoimmunity, and reproductive success. In humans, the 3.6-megabase pair (Mb) MHC region contains more than 180 expressed genes, about half of which are of known immunologic function. The genes that have garnered the most attention have been the class II human leukocyte antigen (HLA) genes.

History

Over the past 4 decades, many genetic studies have demonstrated the importance of the MHC region in susceptibility to RA. In 1969 it was noted that lymphocytes from patients with RA were poorly reactive when incubated together in mixed lymphocyte culture (MLC).¹¹ In the early 1970s, weak and variable associations between RA and genes in the HLA class I region were described with the use of serologic reagents. More rapid progress was made, however, when techniques became available for testing HLA class II antigens. The earlier MLCs were further refined in 1976, and an association between RA and MLC type Dw4 was described.¹²⁻¹⁴ Thereafter, a serologically defined marker, HLA-DR4, was found to be associated with RA in white populations in the United States. Combining MLC and serologic techniques distilled the RA association to a few specific alleles, namely, DR4 Dw4, DR4 Dw14.1, DR4 Dw14.2, and DR4 Dw15. These techniques were superseded in the 1990s by various DNA-based techniques that provided much greater precision (Fig. 89.1). It was recognized that the MLC and serologic markers just listed represent alleles that change the amino acid sequence of the HLA-DRB1 gene. These alleles were subsequently renamed HLA-DRB1*0401, *0404, *0408, and *0405, respectively. Overall, it has been estimated that the MHC region accounts for approximately a third of the overall genetic burden of RA.^{7,15}

THE SHARED EPITOPE HYPOTHESIS

With the advent of sophisticated DNA typing for HLA-DRB1 alleles, it was noted that not all HLA-DR4 alleles are associated with RA and that different alleles confer risk for RA in different ethnic populations.¹⁶⁻²⁷ The most common (>5% frequency in the population) HLA-DRB1 susceptibility alleles include *0101, *0401, and *0404 in individuals of European ancestry and *0405 and *0901 in individuals of Asian ancestry; less common alleles include *0102, *0104, *0408, *0413, *0416, *1001, and *1402. The classic shared epitope (SE) alleles may not contribute to risk in African American and Hispanic American RA populations,^{28,29} and other HLA-DRB1 alleles may be associated with protection against RA (DRB1*0103, *0402, *0802, *1302).²⁷ (See Table 89.1 for these and other important allelic associations.)

In 1987 Peter Gregersen and coworkers³⁰ proposed an elegant hypothesis for these complex and diverse associations. They showed that RA risk alleles share similarities in a key sequence of five amino acids at residues 70 to 74 in the third hypervariable region of the HLA-DRB1 gene (⁷⁰QRRRAA⁷⁴, ⁷⁰QRRRAA⁷⁴, ⁷⁰QRRRAA⁷⁴). These residues are important in peptide binding, and thus it is hypothesized that RA-associated alleles bind specific peptides, which in turn facilitates the development of autoreactive T cells. These alleles are now widely known collectively as SE alleles (Fig. 89.2). Of note, the *0901 allele observed in Asian populations does not strictly conform to the SE amino acid sequence motif (⁷⁰RRRAE⁷⁴).

Although SE susceptibility alleles are often considered as a group, the strength of the genetic association with susceptibility to RA differs between the individual DRB1 alleles.³¹ There are at least two classes of SE risk alleles (high and moderate). In general, DRB1*0401 and *0405 alleles exhibit a high level of risk, with an RR of approximately 3. The DRB1*0101, *0404, *0901, and *1001 alleles exhibit a more moderate RR in the range of 1.5.

It is becoming increasingly clear that HLA-DRB1 SE alleles largely influence the development of seropositive RA and, more specifically, anti-cyclic citrullinated peptide (CCP)-positive RA.^{32,33} Collectively, SE alleles have an odds ratio of greater than 5 if patients with anti-CCP+ RA are compared with matched healthy controls. Because these alleles are quite common in the general population (together, an allele frequency of approximately 40% in individuals of European ancestry), the attributable risk in individuals with SE alleles is quite high.

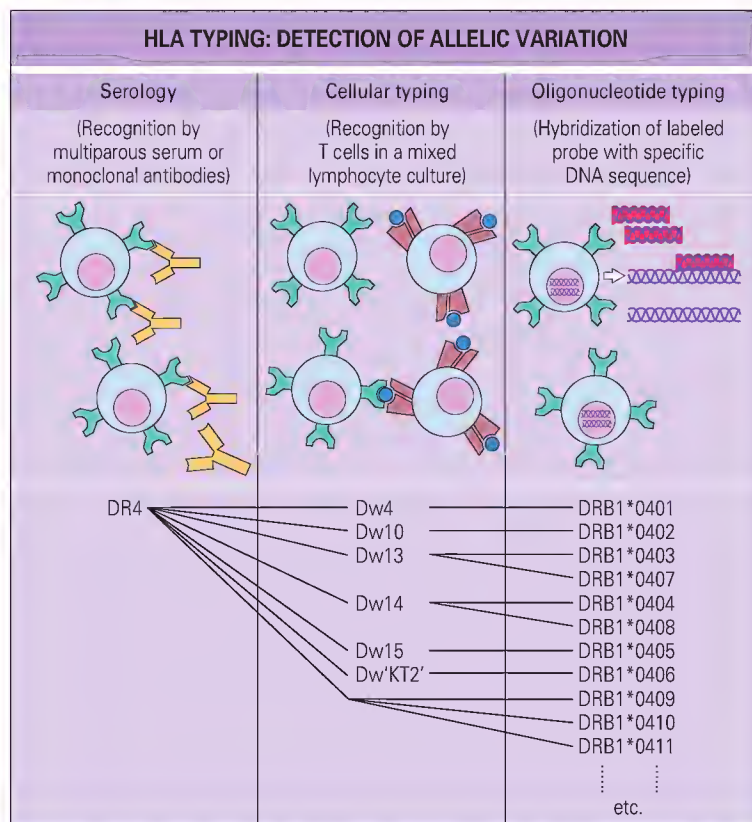


Fig. 89.1 The left panel illustrates HLA typing with sera that recognize alloantigens. These sera often recognize broad antigenic specificities, such as DR4, which are epitopes present on a number of different alleles. Finer discrimination is frequently obtained through cellular typing, as schematized in the second panel. In this case, mixed lymphocyte culture of T cells of unknown HLA type is used to measure proliferation on responder cells of known HLA type. In this way, “subtypes” of DR4 are defined: Dw4, Dw10, Dw14, and others. Currently, most laboratories use oligonucleotide typing, as outlined in the third panel. Based on the known nucleotide sequence of different alleles, synthetic labeled oligonucleotide probes are designed that hybridize specifically to the DNA sequence unique to the gene of interest. In some cases a series of oligonucleotide probes are required to distinguish among the different alleles, and a “matrix” approach can be used. In this way even minor differences among alleles can be recognized; for example, this has led to the identification of more than 20 different DR4+ alleles.

TABLE 89.1
Rheumatoid arthritis: HLA-DRB1 alleles conferring susceptibility

	DRB1 susceptibility allele	Epitope sequence	Prevalence in RA (%)	Relative risk
Whites	*0401 (DR4, Dw4)	LLEQKRAA	50	6
	*0404 (DR4, Dw14)	LLEQRRAA	30	5
	*0101 (DR1, Dw1)	LLEQRRAA	24	1
Japanese	*0405 (DR4, Dw15)	LLEQRRAA	71	3.5
Yakima	*1402 (DR6, Dw16)	LLEQRRAA	83	3.3
Israeli Jews	*0101 (DR1, Dw1)	LLEQRRAA	28	6

Summary of the important HLA-DRB1 alleles conferring susceptibility to RA in different ethnic populations. Their approximate prevalence in patients with rheumatoid arthritis in each population, along with relative risk, is listed. Each of these alleles includes the shared epitope (or a close variation), even though the sequence of the remainder of the DRB1 gene may be quite varied among these alleles.

Biologic function of shared epitope alleles

If the SE is important in predisposing to RA, how might it work? Despite more than 3 decades of research, the answer is not completely clear.

The SE region constitutes a helical domain that forms one side of the antigen-binding site, thus suggesting functional significance and an ability to influence the nature of potentially arthritogenic peptides (Fig. 89.3). In

keeping with the hypothesis, alleles that negatively associate with RA have substitutions of amino acids within the SE that would exert a profound influence on the attributes of any bound antigenic peptide. For example, DRB1*0402 and *0103 alleles have a ⁷⁰DERAA⁷⁴ motif, which would have a marked impact on the peptide-binding properties of the molecule.³⁴ Fascinatingly, canine RA (a spontaneous condition affecting dogs that resembles human RA) is associated with dog MHC DRB1 alleles that also have the QRRAA sequence in the third hypervariable region.³⁵ A study from France suggested that the amino acid sequence RAA at positions 72 to 74 is the key sequence in increasing susceptibility to RA and that this is modulated by amino acids at positions 70 and 71.³⁶

Three predominant biologic models have been proposed to explain this association. Each model centers around the interaction between the T-cell receptor (TCR) and class II MHC molecules (Fig. 89.4).

1. HLA molecules are important in selection and establishment of the antigen-specific T-cell repertoire. Interactions with HLA molecules instruct the T cell to differentiate between self and nonself.^{34,37} T cells that show self-reactivity are deleted or inactivated, whereas others are positively selected to establish a repertoire of cells capable of recognizing foreign antigen in the context of self-MHC. It is possible that the SE assists in some way in the positive selection of autoreactive T cells, with a subsequent breakdown in self-tolerance such that the immune system reacts against the body's own constituent parts.
2. As mentioned, the primary role of HLA molecules is to bind peptide and present it to antigen-specific T cells. The location of the SE in a critical area of the binding site of the HLA-DR molecule would influence the nature and orientation of processed peptides that might bind there and thus exert an impact on the trimolecular complex of the HLA-DR molecule, bound peptide, and TCR. Binding to an arthritogenic peptide (e.g., a processed microbial antigen) might initiate and sustain a pathologic immune response. To date, no peptide has been identified that could be recognized by a T-cell clone in the context of all the HLA-DR molecules that associate with RA. However, some mutated variants of naturally occurring peptides have a pattern close to that needed, which suggests that this model is a possibility.^{34,38,39}
3. In a similar fashion to some of the mechanisms that have been proposed for the association between HLA-B27 and spondyloarthritis, “molecular mimicry” may occur in which similarities between the SE and foreign protein might break self-tolerance and generate autoreactive T-cell clones, which eventually leads to RA. Some amino acid sequences from HLA molecules share homology with those from potentially antigenic proteins derived from infectious agents.⁴⁰

Limitations of the shared epitope hypothesis

However, the veracity of the SE hypothesis has been challenged. A number of observations do not fit comfortably with a straightforward pathogenic association between the SE and RA:

- In all populations that have been studied, a variable but substantial minority of individuals with RA do not possess the SE.^{21,41,42}
- Some ethnic populations do not demonstrate a significant association with SE alleles and risk for RA, such as African Americans,^{43,44} whereas others have shown associations with DR markers that do not possess the SE (e.g., HLA-DR3 in Arabs).⁴⁵
- Not all SEs are the same, with a hierarchy of risk attached to the associations with different HLA-DRB molecules. For example, the *0401 allele shows a much greater association with RA than *0101 does, particularly when *0401 is inherited in combination with *0404 (Table 89.2).⁴⁶⁻⁴⁹
- The *0404 and *0405 alleles have an identical SE sequence (⁷⁰QRRAA⁷⁴) yet have different effect sizes (as measured by the odds ratio [OR]).³¹
- The MHC is an extraordinarily gene-rich area in which other loci in close proximity to the HLA-DRB1 gene might exert an impact on predisposition to disease. This complexity is considered in further detail below.
- If the pathogenic process in RA is a simple presentation of arthritogenic peptide, this would intuitively fit with a dominant mode of inheritance. However, the distribution of the SE genotype fits better with a multiplicative mode of inheritance.^{15,50-52} In keeping with a multiplicative mode of inheritance, concordance rates in siblings sharing two HLA haplotypes are double those of siblings sharing one or no haplotypes.^{53,54} It has been argued that having two copies of the SE could influence the downstream T-cell response through earlier effects in modeling the T-cell repertoire.⁵⁵

COMPARISON OF AMINO ACID SEQUENCES CONFERRING RA SUSCEPTIBILITY									
RA susceptibility DRB1 genes:									
	20		40		60		80		
*0101 (DR1, Dw1)	GDTRPRLWQLKFECHFFNGTERVRLLERCIYNQEEVSFRDSDVGEYRAVTELGRPDAEYWN SQKDLLEQRRRAAVDTYCRHNYGVGESFTVQRR								
*0401 (DR4, Dw4)	E V H		F D YF H Y				K		
*0404 (DR4, Dw14)	E V H		F D YF H Y				V		
*0405 (DR4, Dw15)	E V H		F D YF H Y		S				
*1402 (DR6, Dw16)	E YSTS		F YFH N						
Closely related DRB1 genes not conferring RA susceptibility:									
*0402 (DR4, Dw10)	E V H		F D YF H Y				I DE		V
*0403 (DR4, Dw13)	E V H		F D YF H Y				E		V
*1301 (DR6a)	E YSTS		F D YFH N		F		I DE		V
*1401 (DR6b)	E YSTS		F D YFH F		A H		R E		V
Other more distantly related DRB1 genes not conferring RA susceptibility:									
*1501 (DR2, Dw2)	Q D Y		F H D DL				F D		
*1502 (DR2, Dw12)	Q D Y		F H G N				F D		
*0301 (DR3, Dw3)	E YSTS		Y D YFH N		F		K GR N		V
*0406 (DR4, Dw'KT2')	E V H		F D YF H				E		V
*1101 (DR5, Dw5)	E YSTS		F D YF Y		F E		F D		
*1102 (DR5, Dw'JVM')	E YSTS		F D YF Y		F E		I DE		V
*1201 (DR5, Dw'DB6')	E YSTG Y		HFH LL		F V S		I D		AV
*0701 (DR7, Dw17)	Q G YK		QF LF F		V S		I D GQ		V
*0801 (DR8, Dw8.1)	E YSTG Y		F D YF Y		S		F D L		
*08031 (DR8, Dw8.3)	E YSTG Y		F D YF Y		S		I D L		
*09011 (DR9, Dw23)	Q K D		Y H G N		V S		F R E		V
*1001 (DRw10)	E EV		RVH YA Y				R		

<

Fig. 89.2 Sequences of HLA-DRB1 alleles that do or do not confer susceptibility to rheumatoid arthritis (RA) in different populations. (a) At the top are listed the sequences of the DRB1 alleles known to confer susceptibility to RA, with the shared epitope highlighted. The single-letter amino acid code defined at the bottom of the figure is used. Under these sequences are listed very similar sequences from closely related DRB1 alleles that do not confer susceptibility to RA. The lower portion of part (a) contrasts the sequences of other more distantly related DRB1 alleles that are now known to confer susceptibility to RA. The shared epitope occurs only in susceptibility alleles and does not occur in nonsusceptibility alleles, even when their “background” sequence is very similar or identical to that of the susceptibility alleles. (b) Schematic representation of how the amino acid sequence of the first domain of DRB1 relates to the three-dimensional conformation of the final molecule. Red-highlighted arrows correspond to the clustered hypervariable sequences in the DRB1 regions shown above, thus illustrating that the shared epitope constitutes part of the α-helical “wall” of the antigen-binding groove.

Refining the shared epitope hypothesis—the “binding groove” hypothesis

Given the limitations of the SE hypothesis, additional research has been undertaken to refine the model. A study published in 2012 offered a refined view of the SE hypothesis.⁵⁶ Using genome-wide single-nucleotide polymorphism (SNP) data and a novel computational strategy to impute amino acid polymorphisms in HLA-A, HLA-B, HLA-C, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1 and HLA-DRB1, conditional and haplotype analyses identified three amino acid positions (11, 71, and 74) in HLA-DRB1 and single-amino acid polymorphisms in HLA-B (at position 9) and HLA-DPB1 (at position 9) that could almost completely explain the MHC association. These variants account for about 13% of the overall risk for RA in the populations studied.

Interestingly, all five amino acids are located in the peptide binding grooves of the three different HLA molecules. This has led to the “binding groove” hypothesis because the location of these positions within the peptide binding grooves implies a functional impact on antigenic peptide presentation to T cells, either during early thymic development or during peripheral immune responses. The presence of class I and II MHC alleles implicates both CD8+ cytotoxic and CD4+ helper T cells in the pathogenesis of RA.

MAJOR HISTOCOMPATIBILITY COMPLEX: DISEASE SUSCEPTIBILITY OR SEVERITY?

Irrespective of the limitations of the SE hypothesis, the MHC region demonstrates the strongest association with RA and in different family studies

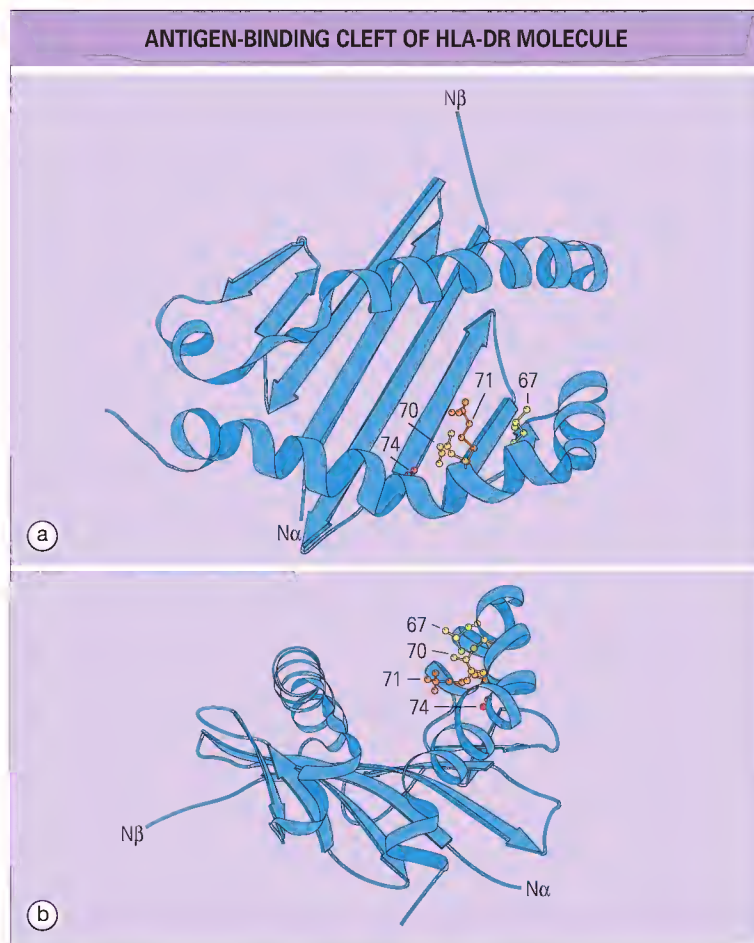


Fig. 89.3 Location of important polymorphic residues with the rheumatoid arthritis-associated “shared epitope.” A ribbon diagram of a DRA/DRB1*0401 molecule is presented and viewed while looking down from above (a) and from the side (b). Amino acids 67, 70, 71, and 74, the residues noted from sequence comparisons and from site-directed mutagenesis analysis to be critical in function of the “shared epitope,” are shown pointing into or out of the peptide-binding groove. Residues pointing into the groove are important in binding peptide, whereas those pointing out of the α -helix are hypothesized to interact directly with the T-cell receptor. Na, Nb, N-terminal residues of the α and β chains.

is the locus that has most consistently demonstrated genetic linkage.^{9,57,58} However, a debate has been generated regarding whether the HLA association is more important in predisposing to RA or in determining disease severity.

For more than 20 years, studies have shown that the HLA-DRB1 alleles are more frequently observed in patients with more severe disease. Clinically, RA is very heterogeneous: some patients have mild, self-limited disease, whereas others have severe multisystem disease. It is entirely plausible that genetic heterogeneity underlies such clinical heterogeneity. Studies in the 1980s suggested that the serologically defined HLA-DR4 association was not observed in community surveys, which presumably represents milder RA.⁵⁹ Conversely, the HLA-DR4 association was very marked in patients with severe articular disease or extraarticular manifestations, such as Felty syndrome.⁶⁰ With the increasing sophistication of molecular typing, it was demonstrated that the SE did not associate with recent-onset inflammatory arthritis.⁶¹ At the opposite end of the clinical spectrum, a meta-analysis of rheumatoid vasculitis⁶² and a review of the extraarticular manifestations of RA⁶³ confirmed the importance of the SE in associating with more severe disease. Multivariate analyses have indicated that presence of the SE predicts erosions at initial diagnosis of RA, as well as an erosive outcome at 3 years.⁶⁴⁻⁶⁷

The question remains: are SE alleles predictive of RA risk or RA severity? Genetic association studies alone may not be able to resolve this question. It could be that more severe disease is more likely to develop in patients with a greater genetic burden of disease, regardless of which alleles predispose to RA. Alternatively, it may be that non-SE genetic factors predispose to risk whereas the SE predisposes to severity. However, all genetic factors

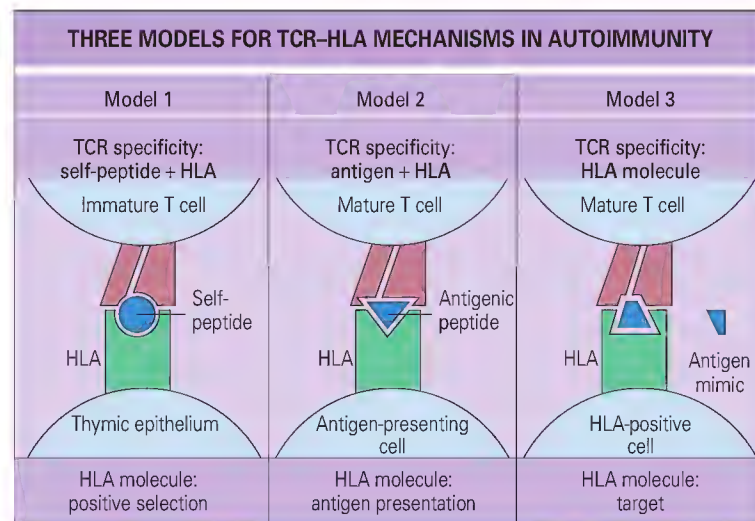


Fig. 89.4 The key role of polymorphic amino acid residues in the HLA molecules associated with disease indicates that intimate contacts between these amino acids and antigenic peptides or the T-cell receptor (TCR), or both, are important genetically regulated triggering events in autoimmunity. In model 1, the polymorphic HLA molecule, in combination with a bound self-peptide, has a key selection role, presumably during the thymic development of maturing T cells. An immature T cell “tests” its receptor specificity before leaving the thymus; suitable recognition and stimulation by the HLA molecule at this point are postulated to lead to maturation and expansion of the T-cell specificity, which in an appropriate context, may be potentially autoreactive. In model 2, a similar recognition event occurs in the peripheral immune system between a mature T cell and an HLA-expressing antigen-presenting cell. The polymorphic determinants on the HLA molecule determine the binding and presentation of the antigenic peptide related to the target tissue, such as the joint. In model 3, T-cell specificity is directed toward the polymorphic amino acid residues of the HLA molecule itself by molecular mimicry. The immune response is postulated to focus on an HLA-positive target by virtue of cross-reaction with an antigen mimic that has successfully bypassed normal tolerance mechanisms and stimulated the reactive T cell. A variation of the mimicry hypothesis that partly reconciles all three models postulates that the polymorphic sequence on the HLA molecule is the primary antigenic target but that it is seen by the TCR as a processed self-peptide, bound and presented by another intact HLA molecule. (Major histocompatibility complex structural models for the figures in this chapter were constructed with molecular homology modeling techniques by Carol DeWeese, Department of Bioengineering, University of Washington School of Medicine.)

TABLE 89.2

Risk estimates for rheumatoid arthritis in white individuals

HLA class II allele	Frequency/10,000 population		Approximate risk ratio
	+RA	No RA	
DRB *0401	50	1800	1 in 35
DRB *0404	25	500	1 in 20
DRB *0101	25	2000	1 in 80
0401 or 0404	65	2300	1 in 35
0401, 0404 or 0101	90	4200	1 in 46
0401 and 0404	15	100	1 in 7
Other	10	5800	1 in 580

These numbers represent the “absolute risk” for the development of clinical rheumatoid arthritis in white individuals. They are based on a disease frequency of 7 to 10 per 1000 population and accordingly represent an upper limit of the predictive value.

Adopted with permission from Nepom G. Prediction of susceptibility to rheumatoid arthritis by HLA genotyping. *Rheum Dis Clin North Am* 1992;18:785-92.

are present throughout the life of a patient and therefore by definition before onset of the disease. As a consequence, susceptibility and severity are inextricably linked.

ROLE OF NON-MAJOR HISTOCOMPATIBILITY COMPLEX GENES

Calculations based on monozygotic twin concordance rates and HLA haplotype sharing in affected sibling pairs indicate that HLA genes contribute approximately 30% of the total genetic risk for RA.^{7,68} This leaves considerable room for other genes outside the HLA region to contribute to risk for RA. It is likely that the remaining genetic risk is distributed among many loci across the human genome, with each locus contributing substantially less than the HLA region to overall RA risk.⁶⁹

Genome-wide linkage scans in rheumatoid arthritis

The human genome is riddled with DNA variants (alleles) that make each of us unique. There are single-base pair variants (also known as SNPs) and structural variants (including duplications and deletions of many kilobases of DNA). These variants are further classified by the frequency with which they are observed in the general population. As a rule of thumb, variants present in more than 5% of chromosomes from the general population are considered “common,” and those present in less than 5% are considered “rare.” Rare variants can be further classified as “low frequency” (found in multiple families but generally with a population frequency of >0.5%) or “private” (segregating in only a single family as a result of a recent *de-novo* mutation).

A fundamental challenge in human genetics has been *how to systematically test human genetic variation to determine its role in human disease*. The ideal genetic study would resequence the entire human genome in a large collection of patients with a disease and controls in which detailed environmental exposure and clinical phenotypic information have been collected. Causal mutations would be recognized by a simple test of association between allele frequency in cases and controls while controlling for potential environmental and clinical confounders. Assuming complete coverage of the human genome, this hypothetical approach would identify all classes of DNA variants (e.g., SNPs, copy number variants) and the entire allele frequency spectrum (e.g., common and rare) in an unbiased manner. Such an approach, however, is impractical because of current limitations in technology and cost constraints.

Initial attempts to scan the human genome used hundreds of microsatellite markers and tests of “linkage” in families. These studies relied on meiotic recombination between a microsatellite marker and an unknown mutation that increases risk for disease. This approach has been very successful in identifying rare, highly penetrant alleles that predispose to mendelian forms of disease. However, this strategy has had limited success in patients with more complex patterns of inheritance, such as RA. Because of the theoretic limitations of linkage scans, researchers in the early 2000s turned their attention to genetic studies of “association.”

Candidate gene association studies in rheumatoid arthritis

An alternative statistical approach to genome-wide linkage was to conduct genome-wide genetic association studies. Instead of mapping disease genes by following transmission in families, association studies compare the frequencies of genetic variants among affected and unaffected individuals. Theoretically, association studies have more power than linkage studies to detect common variants of modest effect size.⁷⁰ Until recently, genetic association studies were limited to candidate genes. This was simply a matter of practicality because it was prohibitively expensive to genotype more than a handful of SNPs in large patient samples. Furthermore, no comprehensive map of common genetic variation was available, and it was unclear how many SNPs would need to be genotyped to test the majority of common human variations.

One solution in the early 2000s was to select biologically plausible candidate genes and test SNPs that were found in and around these genes. A major limitation of this approach was obvious: there are more than 20,000 genes in the human genome, and most candidate gene studies are limited to a small number of candidate genes. A handful of successes were achieved.

PTPN22

One candidate gene association study selected putative functional SNPs from a set of biologic candidate genes. With this approach, a missense SNP

in the intracellular *PTPN22* gene was identified.⁷¹ Outside the MHC region, this gene became the first to be widely replicated in multiple independent collections. The susceptibility allele is a missense variant in which an arginine is changed to tryptophan (R620W). The change results in altered binding of the *PTPN22* protein to an intracellular signaling molecule called Csk, which subsequently alters the threshold of T-cell activation.^{71,72} The magnitude of the genetic effect, as measured by the OR, is substantially less than that for HLA-DRB1*0401 but similar to other SE alleles (*PTPN22* OR ≈ 1.75). Interestingly, this allele is absent in east Asians and thus not associated with susceptibility in Japanese populations.⁷³ *PTPN22* associates only with seropositive RA. There is some evidence that *PTPN22* influences age at onset⁷⁴ and may have a more significant effect in males than in females^{74,75} but no evidence that it influences disease activity or radiographic erosions.^{76,77}

PADI4

PADI4 encodes an enzyme that posttranslationally changes arginine to citrulline and may therefore be important in generating anti-CCP autoantibodies. Based on this hypothesis, a Japanese group tested more than 100 SNPs in the region that contains *PADI4* and a cluster of related genes. In the initial report, a common variant (population allele frequency $\approx 35\%$) was found to increase risk for RA.⁷⁸ Subsequent reports provided support for this allele in individuals of Asian ancestry, with a meta-analysis showing an OR of 1.30 per copy of the risk allele.⁷⁹ The same allele is either not associated or only modestly associated (OR < 1.10) with risk for RA in individuals of European ancestry.^{74,79,80}

CTLA4

CTLA4 is a negative regulator of T-cell activation. Based on this biology, genetic studies in the early 2000s tested SNPs for association with several autoimmune phenotypes. The association between *CTLA4* and susceptibility to autoimmunity was initially confirmed in patients with type 1 diabetes and autoimmune thyroiditis.⁸¹ An allele in the 3' untranslated region of the gene causes a modest increase in risk for disease (OR = 1.2). Several studies extended these findings to RA, for which the magnitude of the genetic effect is reproducible but modest (OR = 1.15).^{74,82} The association is stronger in autoantibody-positive RA patients.

STAT4

Another strategy for choosing candidate genes is to select those that are biologically plausible *and* localized in suggestive regions of linkage. With this strategy, Remmers and colleagues⁸³ studied haplotype-tagging SNPs within 13 candidate genes under a linkage peak on chromosome 2. In a staged design of more than 7500 case-control samples, one SNP was reproducibly associated with risk for RA (OR = 1.20). This result has been replicated by others. *STAT4* plays a critical role in differentiation of T cells into distinct lineages. It is unclear whether the risk allele alters *STAT4* gene expression. There is no known coding variant that disrupts *STAT4* function.

Genome-wide association studies in rheumatoid arthritis

These four successes notwithstanding, the majority of candidate gene association studies have not led to reproducible genetic associations in RA.⁷⁴ Accordingly, a set of resources has been developed to systematically test the majority of common SNPs for their role in disease. The rationale for this approach is rooted in population genetic theory: common SNPs explain much of the genetic diversity in our species. This is a consequence of the historically small size and shared ancestry of the human population.

There are approximately 10 million common SNPs in the human genome, although 90% of these SNPs are highly correlated ($r^2 > 0.80$).^{84,85} As a consequence, not every SNP in the human genome needs to be tested directly in a genetic association study. A subset of “tagging” SNPs can adequately capture the majority of common genetic variations across a locus; this is also known as linkage disequilibrium (LD) mapping. The International Haplotype Map (HapMap) Project has provided a catalog of common SNPs in the human genome,^{84,85} which facilitates LD mapping. The HapMap has genotyped more than 3 million SNPs in four reference groups from a total of 270 individuals.

Genetic studies of common variants can now be conducted across the entire human genome. Such studies, termed genome-wide association studies (GWASs), are feasible because of improved understanding of LD structure across the human genome,^{84,85} technical capacity to genotype hundreds of thousands of SNPs in a cost-effective manner,⁸⁶ and methods of analyzing large data sets.^{87,88} GWASs have a distinct advantage over previous

genetic studies in that they are able to test, in an unbiased manner, the majority of common SNPs across the genome in a single experiment. Implementation of GWASs has greatly expanded the number of true-positive loci (i.e., those that have been replicated consistently in more than one study at a high level of statistical confidence) that are associated with complex traits.⁸⁹

In 2007, three GWASs of RA were published, and two new RA risk loci were identified.⁹⁰⁻⁹² One GWAS was a collaborative effort between groups in North America (NARAC) and Sweden (EIRA).⁹² A total of around 1500 anti-CCP+ RA patients and about 1800 controls were genotyped for more than 300,000 SNPs, followed by replication of the most significant SNPs in an additional approximately 1000 anti-CCP+ RA cases and about 1700 controls. The most significant result outside *PTPN22* and the MHC loci was the *TRAF1-C5* locus. A single SNP on chromosome 9 was strongly associated with susceptibility to anti-CCP+ RA (OR = 1.20). An independent group identified the same DNA variant as part of a candidate gene association study.⁹³

Two other GWASs led to identification of the *TNFAIP3* locus on chromosome 6q23.^{90,91,94} Interestingly, two independent risk alleles were identified, although both were within 5 kb of each other. Both alleles reside approximately 185 kb away from the nearest biologic candidate gene, *TNFAIP3*. The distance of the risk alleles from the nearest candidate gene underscores a limitation of candidate gene association studies: many risk alleles reside some distance from the protein-coding sequence. *TNFAIP3*, also known as A20, is a potent inhibitor of NF- κ B (nuclear factor κ -light chain enhancer of activated B cells) signaling and is required for termination of tumor necrosis factor- α (TNF- α)-induced signals.⁹⁵ TNF- α levels are increased in patients with RA, and inhibition of TNF- α is a potent treatment of severe RA.⁹⁶ Furthermore, mice lacking *Tnfaip3* demonstrate chronic inflammation,⁹⁷ consistent with loss of function of this gene playing a role in autoimmunity. Even though it may be logical to conclude that the RA risk alleles alter expression of *TNFAIP3*, no direct data support this claim. A variety of 6q23/*TNFAIP3* alleles, some of which are different from the RA risk alleles, contribute to risk for other autoimmune diseases.

Follow-up studies of these GWASs have identified more than 50 RA risk loci.⁹⁸⁻¹⁰⁰ Several important observations have emerged: (1) hundreds (if not thousands) of alleles contribute to risk for any given complex disease,^{101,102} (2) each allele has a small effect on risk, and (3) most alleles discovered to date are common in the general population (although this is a biased estimate because only common alleles have been tested by contemporary GWASs).

Other follow-up GWASs have capitalized on the observation that many RA risk loci are associated with other autoimmune diseases. As an example, epidemiologic data suggest an overlap among the risk factors for type 1 diabetes and RA.¹⁰³ Consistent with this observation, a locus on 4q27 containing the *IL2* and *IL21* genes demonstrates a clear association with risk for type 1 diabetes and a highly suggestive association with risk for RA.¹⁰⁴ Approximately half the validated RA risk loci have strong evidence of association for at least one additional autoimmune disease. Frequently, the same allele confers risk for both autoimmune diseases (e.g., 4q27/*IL2-IL21* and risk of RA/type 1 diabetes). In other instances, different alleles at the same locus confer risk for disease (e.g., *TNFAIP3* and risk for RA/psoriasis). Occasionally, the same allele confers risk for one disease and protection against another (e.g., *PTPN22* and risk for RA/protection against Crohn disease).¹⁰⁵

Although GWASs and related approaches have greatly expanded the number of RA risk loci, the non-MHC alleles that have been validated explain less than 5% of the disease variation.⁹⁸ The alleles identified to date are common and of modest effect size. Based on considerations of statistical power, many more RA common risk alleles will be identified in the near future. These discoveries will require continued international collaboration given the large sample sizes needed to achieve statistical significance.

Insight into the pathogenesis of rheumatoid arthritis from non-major histocompatibility complex genetic studies

Despite decades of research, the exact cause of RA is unknown.¹⁰⁶ Without knowing the specific pathways that lead to RA, it is very difficult to develop novel therapies and preventive strategies. Because genetic mutations are inherited before onset of disease, human genetics provides *prima facie* evidence that a pathway is important in pathogenesis. Moreover, because human genetics studies can be done without any specific biologic hypothesis (other than the hypothesis that there are alleles that influence risk for RA), human genetics offers an unbiased search of the human genome.

When considering pathways implicated by genetic studies, there are two important caveats in the way in which risk alleles are often described. First,

the risk locus is frequently assigned a gene name (e.g., *TNFAIP3*) even though there may be no direct evidence that the gene itself has been disrupted by the risk allele. Generally, the most compelling biologic candidate gene from a locus is chosen. Sometimes the choice is clear, as in the case of *TNFAIP3*, in which a knockout mouse model demonstrates severe inflammation, consistent with the phenotype of RA.⁹⁷ Second, the reported risk allele most likely represents a highly correlated proxy for the as-yet unidentified causal allele (i.e., the causal allele has not yet been identified). In other words, for most RA risk loci, the exact causal mutation and the exact causal gene have not yet been determined.

Despite these caveats, recent genetic discoveries have identified pathways that are important in RA pathogenesis. One is the NF- κ B signaling pathway.¹⁰⁷ NF- κ B, a protein complex that acts as a transcription factor, is found in almost all cell types and is involved in a variety of cellular responses to stimuli. Both TNF and CD40 signal through NF- κ B to exert their effects on the immune system. Several of the RA risk loci contain genes that are involved in NF- κ B signaling, including *CD40*, *TRAF1*, *TNFAIP3*, *PRKCQ*, and *TNFRSF14*.

Integration of GWAS data with gene expression and epigenetic data points to the critical role of certain cell types.^{108,109} GWASs implicate the importance of CD4+ T cells in risk for RA. As the list of GWAS hits expands, it is likely that additional pathways and cell types will be identified.

GENE AND ENVIRONMENT INTERACTIONS

With the heritability of RA being approximately 60%,¹⁰ the remainder of the variance in the disease must be accounted for by environmental, nongenetic factors or complex gene-gene/gene-environment interactions. It seems plausible that interactions occur between genetic and environmental factors or that environmental factors function as “triggers” for promoting and driving the disease process.

Smoking is the known environmental risk factor with strongest risk for development of RA. Over the past 20 years, many studies have convincingly shown that smoking increases the risk for RA in both males and females by a factor of approximately 1.5 to 2.0.^{110,111} Most of these studies demonstrate that the increased risk is for the development of autoantibody-positive RA and that the risk is greatest for heavy, current smokers. The risk remains, however, for longer than 10 years following smoking cessation.

Other putative environmental risk factors that have not been as widely replicated as smoking include blood transfusions, obesity, occupational silica and mineral oil exposure, and socioeconomic class.^{112,113} It is interesting that several of these putative environmental factors are inhaled through the lungs. Silica dust and mineral oil exposure, similar to exposure to cigarette smoke, was a risk factor only for seropositive RA. Mineral oil can also act as an adjuvant capable of inducing experimental arthritis in rodent models.

Even though smoking is a clear environmental risk factor and many MHC and non-MHC genes confer risk for RA, the question remains: is there an interaction between environmental and genetic risk factors that departs from an expected model? A challenge in the field is the definition of “expected model.” Given that most genetic risk factors conform to a multiplicative (or log-additive) model, the most conservative estimate is to define “interaction” as departure from a multiplicative model. The best example of a gene-environment interaction that appears to depart from a multiplicative model has been the interaction between cigarette smoking and HLA-DRB1 alleles. A study by Padyukov and colleagues¹¹⁴ using the Swedish EIRA cohort found evidence of an interaction between the presence of the SE and cigarette smoking. When compared with patients who had never smoked and had no copies of the SE, they found ORs of 2.8 in seropositive smokers with SE alleles who had never smoked, 2.4 in current smokers without SE alleles, and 7.5 in current smokers with SE alleles. Smokers carrying two SE alleles displayed an RR for rheumatoid factor-positive RA of 15.7. No influence of smoking or SE alleles was seen for seronegative RA. These data suggest an interaction between smoking, SE alleles, and seropositive RA.

Clearly, additional work is required to elucidate important interactions between genes and the environment. This will be an important area for future investigation and may empower the design of better clinical prediction models or novel gene discovery.

CONCLUSION

There is considerable evidence that genetic factors are important in the predisposition to RA and contribute to the heterogeneity of the broad

spectrum of disease that is currently classified as RA. The contribution of MHC genes and their interactions has yet to be fully elucidated, but recent work indicates that multiple genes within this region influence risk for disease. The SE hypothesis alone does not fully explain the complexity of the MHC contribution to RA, which has led to the refined “binding groove” model. Overall, the MHC contributes approximately a third of the total genetic contribution to RA. Advances in genetic technology have enabled unbiased scans of the human genome, and as a consequence, many non-MHC gene loci have been identified. Interactions between genes and environmental factors may be important, but work in this area is quite preliminary. Potential interactions between exposure to tobacco smoke and HLA and non-HLA genes are the best characterized to date. Clearly, much progress has been made, although substantial work is still needed to fully explain the genetic contribution to RA. Progress in this area is likely to translate into greater understanding of disease pathogenesis and the development of improved diagnostic and therapeutic tools for this chronic and disabling illness.

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Animal models of arthritis

■ WIM B. VAN DEN BERG

- Arthritis may be induced in animals by immunization with cartilage components, by nonspecific immune stimuli, by bacterial or viral components, or by transgenic manipulation.
- Animal models are tools that mimic various aspects but never fully resemble human rheumatoid arthritis.
- Models have a defined onset and are useful for kinetic evaluation of arthritis, cell and mediator involvement, and detailed analysis of joint erosion.
- Animal models serve an important role in the evaluation of antirheumatic treatments and provide direction for novel approaches to treatment such as cytokine inhibition.

INTRODUCTION

Experimental animal models of arthritis have contributed to the understanding of basic mechanisms of joint disease. Marked diversity is seen among the numerous models, with arthritis being induced by the following:

- Immunization with cartilage components
- Injection of nonspecific immune stimuli
- Components of infectious agents
- Immune complexes
- Manipulation of genetic information in transgenic animals

No single animal model of arthritis truly represents the human disease. The wide variety of agents that can induce experimental arthritis with clinical and histopathologic features close to those of human arthritides suggests that disparate etiologic pathways could exist for rheumatoid arthritis (RA). Aspects peculiar to individual models are of value but must be interpreted with caution. Much can be learned from the general validity of mediator involvement and common concepts. Models provide valuable preclinical data for the development of novel treatments, both pharmacologic and biologic, and insight into relevant mechanisms common to both experimental arthritis and RA.

MECHANISMS OF INDUCTION OF EXPERIMENTAL ARTHRITIS

Autoimmunity to cartilage components

Articular cartilage is an intriguing tissue. It is the target of the disease, but it may also function as the trigger by releasing potential autoantigens and trapping exogenous antigens in its avascular matrix. Destructive forms of RA tend to decline when cartilage is fully destroyed, and arthritis also wanes in joints undergoing replacement surgery, both arguments for a crucial role of cartilage in the arthritic process. Classic arthritis models based on cartilage autoimmunity¹ can be induced by immunization with either of the two major components of hyaline cartilage: type II collagen (CII) and aggrecan proteoglycans (PGs). More recently, similar models have been developed in which other, less abundant cartilage components have been identified as potential autoantigens in arthritis.

In principle, any cartilage matrix component can potentially be arthritogenic, provided that it is released in substantial amounts and natural

tolerance is lost. Collagen-induced arthritis (CIA) can be elicited in mice, rats, and primates,^{2,3} whereas PG arthritis has been successfully established only in BALB/c mice.⁴ Both models require induction of a vigorous immune response directed initially against the immunizing (heterologous) cartilage antigen, which subsequently reacts with autologous cartilage antigens. A hypothetical mechanism for the development of CII- and PG-induced experimental arthritides is shown in [Figure 90.1](#).

Susceptible strains of animals immunized with either CII or high-density aggrecan PGs in adjuvant recognize specific epitopes. Autoreactive CD4⁺ T cells respond to either cross-reactive or cryptic epitopes (privileged antigens normally concealed from immune surveillance) and elicit connective tissue antigen-specific Th1 (type 1 helper T cell) and Th17 cells and autoantibodies. Adoptive and passive transfer experiments suggest that both immunologic elements are required for the generation of chronic arthritis, although transient but destructive forms can be elicited with cocktails of anti-CII autoantibodies only. Localization of antibody and reactive cells in synovial joints causes immune-mediated cartilage damage, and the immune response may be perpetuated by the release of cartilage antigens. These damage-associated molecular patterns may also directly activate cells through Toll-like receptors (TLRs), in particular, TLR4.

The pathology of CIA and PG arthritis appears to be similar and includes synovial hypertrophy and hyperplasia, which give rise to pannus formation and severe cartilage erosion. Both models were considered to be driven by Th1 cells, yet interferon- γ (IFN- γ) deficiency makes BALB/c mice more susceptible to CIA but it prevents PG arthritis. More recent insight has indicated a dominant role of Th17 cells in CIA, whereas Th1 cells are crucial in PG arthritis, and a role of Th17 in this model is unmasked only under IFN- γ -deficient conditions. Neutralization of tumor necrosis factor (TNF) was efficacious in early stages of CIA, and interleukin-1 (IL-1) blocking and IL-17 neutralization suppressed both early and fully established arthritis.⁵

Response to nonspecific immunologic stimuli

Injection of nonspecific agents with adjuvant activity (the capacity to elicit an indirect immunologic response) can provoke experimental arthritis in certain species. The classic example is adjuvant-induced arthritis (AA) in the Lewis rat.⁶ The precise contributions of the oil and the mycobacterial components of Freund complete adjuvant in the pathologic pathway of this experimental disease remain unclear, but both may contribute. A bacterium-specific pathogenesis seems likely in AA because conventionally bred rats are generally resistant to AA whereas germfree Fisher or Wistar rats are susceptible. Germfree rats lack early contact with bacteria and therefore tolerization does not occur. This is in striking contrast to suppression of pristane (mineral oil)-induced arthritis in germfree mice, hence implying a different pathogenesis.

Adjuvant- and pristane-induced arthritis

Incomplete Freund adjuvant, which lacks mycobacteria, and the mineral oil pristane, can induce arthritis in susceptible rats and mice, evidence that oil can override natural tolerance.⁷ The arthritogenic consequences appear to ultimately depend on a reaction against either exogenous or autologous antigens. Heat shock proteins may be regulators in AA.⁸ A hypothetical mechanism for the development of AA and pristane-induced arthritis is shown in [Figure 90.2](#). In susceptible strains of animals, macrophages phagocytose nondegradable oil components, become intensely activated, and produce large concentrations of proinflammatory cytokines (IL-1, IL-6, TNF, and IFN- γ). This cytokine-rich environment activates T and B cells. The results of polyclonal activation are apparent in pristane-induced arthritis, in which lymphadenopathy and hypergammaglobulinemia precede the onset of disease.

HYPOTHETICAL MECHANISM FOR THE DEVELOPMENT OF COLLAGEN-INDUCED AND PROTEOGLYCAN-INDUCED EXPERIMENTAL ARTHRITIS

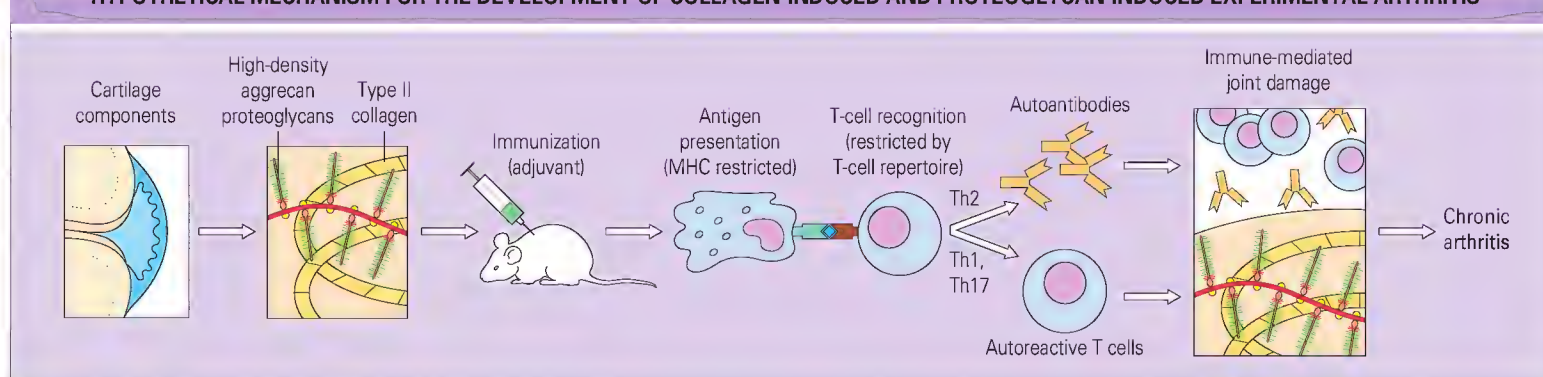


Fig. 90.1 Animals are immunized with type II collagen or high-density aggrecan proteoglycans, and an autoimmune response results when specific epitopes are presented in the context of major histocompatibility complex (MHC) class II antigens and recognized by autoreactive CD4+ T-cell populations. Autoantibodies and T effector cells reactive against cartilage components develop via helper T-cell pathways (Th1, Th17, and Th2) and localize in synovial joints, which causes an immune-mediated inflammatory response. The immune response is perpetuated by the release of cartilage antigens within the damaged joint, and chronic arthritis develops.

HYPOTHETICAL MECHANISM FOR THE DEVELOPMENT OF PRISTANE-INDUCED AND ADJUVANT-INDUCED EXPERIMENTAL ARTHRITIS

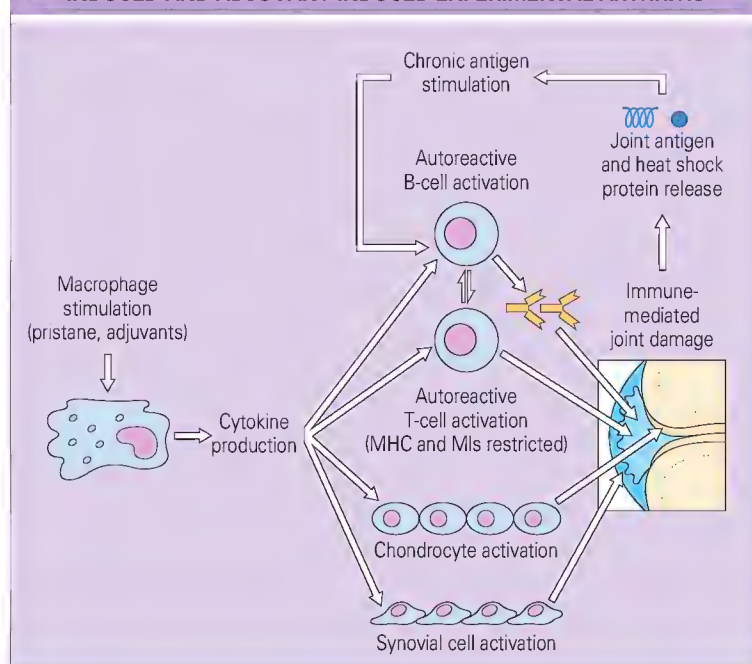


Fig. 90.2 Circulating macrophages become intensely activated by the nondegradable oil components and produce high levels of proinflammatory cytokines (interleukin-1 and interleukin-6, tumor necrosis factor- α , and interferon- α). Genetic regulation governs the presence of autoreactive T cells and B cells, which become activated and clonally expand. Joint-reactive lymphocytes migrate to the joint and induce immune-mediated joint damage. The release of cartilage antigens and heat shock proteins may feed back to the autoreactive lymphocytes and result in chronic immune stimulation. Cytokines may also act directly on both synovial cells and chondrocytes and thereby result in synovial hypertrophy, abnormal expression of major histocompatibility complex (MHC) class II antigens and adhesion molecules, and atypical production of matrix components. Arthritis develops as a result of the chronic nature of the inflammatory stimulation.

Expansion of autoreactive T- and B-cell populations can occur as a consequence of the adjuvant activation process and result in the migration of cells to the joint and subsequent immune-mediated joint damage and production of a spectrum of autoantibodies against cartilage antigens. Disease onset is rapid in AA (2 weeks), often followed by spontaneous remission. Pristane-induced arthritis is slower (months) and characterized by remissions and relapses, with no indication of B-cell involvement at the onset. The pristane model is highly suited to studying genes controlling onset, severity, and chronicity.⁹ The spontaneous remission and lack of

susceptibility to reinduction make AA a suitable model for studies on the regulation of T-cell tolerance. Histopathologic study of AA shows major involvement of bone marrow, bone erosion, extensive bone apposition, and minor direct cartilage damage in the early stages (Table 90.1).^{2-4,6,7,10-24} Indirect cartilage damage occurs later, mainly as a consequence of the loss of underlying bone. The latter may explain the cartilage-protective effect of treatment with osteoprotegerin (OPG), which is a selective inhibitor of the osteoclast activator RANKL (receptor activator of nuclear factor κ B ligand).^{10,25} Combined blocking of TNF and IL-1 is associated with optimal control of arthritis and joint destruction.

Components of infectious agents

The development of arthritis as a consequence of infection is apparent in both natural and induced animal models. Infectious agents may be tropic for the joint as a result of expression of adhesins or other molecules that promote sequestration within synovial tissue. Bacterial cell wall and *Mycoplasma* membrane components may also provide nonspecific immune activation through mitogenic activity. Viral infection of synovial cells may elicit novel cell-surface antigens or abnormal expression of activation antigens and the overproduction of autoantigens. Viral infection may also disrupt immune regulation and increase proinflammatory cytokines and immune activity against normally immunologically privileged components of the joint.

Streptococcal cell wall arthritis

Persistence of antigens from microorganisms within the joint can be critical for the induction of arthritis (Fig. 90.3). Streptococcal cell wall (SCW) arthritis can be induced in Lewis rats¹¹ by the systemic injection of cell wall fragments of group A streptococci, which are highly resistant to biodegradation. A similar disease can be induced with fragments from other bacteria, such as *Lactobacillus casei* or *Eubacterium aerofaciens*. The underlying principle of this model resides in the poor degradability of the fragments, thereby creating a persistent stimulus.

The *Lactobacillus* and *Eubacterium* models are of particular interest for human disease because these bacteria are part of the normal gastrointestinal flora. An enormous load of potential arthritogenic stimuli is continuously present in the normal gastrointestinal tract, fragments may spread in a noninfectious manner to other tissues, and this may provoke arthritis when immunoregulatory control is insufficient.

Within 24 hours of administration of cell wall fragments to rats, acute inflammation develops in peripheral joints, coincident with dissemination of the cell wall fragments in blood vessels of the synovium and subchondral bone marrow. The acute, complement-dependent inflammation subsides over the next week, followed within 2 weeks by a chronic, T cell-dependent erosive polyarthritis involving mainly peripheral joints. Chronic joint inflammation develops only in susceptible strains that are unable to maintain tolerance and therefore display SCW-specific T-cell responses. Lewis rats are highly vulnerable to this arthritis. The mouse strains studied thus far are not susceptible to the single intraperitoneal injection model, and repeated dosing is needed to break tolerance. It is tempting to speculate that similar loss of tolerance may occur in RA patients with age, combined with costimulatory environmental factors.

TABLE 90.1
Models of arthritis

Model	Abbreviation	Species*	Feature	IC	T cell	References
Induced models						
Collagen-induced arthritis	CIA	DBA mouse	CII	+	+	2, 3
Proteoglycan-induced arthritis	PG-A	BALB/c mouse	PG	+	+	4
Adjuvant-induced arthritis	AA	Lewis rat	Autoimmune	–	+	6
Oil-induced arthritis	OIA	DA rat	Autoimmune	–	+	7
Pristane-induced arthritis	PIA	DA rat	Autoimmune	–	+	7, 10
Streptococcal cell wall–induced arthritis	SCW-A	Lewis rat	Persistent bacteria	–	+	11
Flare	SCW	Mouse	T cell–derived IL-17	–	+	12
Antigen-induced arthritis	AIA	Rabbit, mouse	Persistent antigen	+	+	13, 14
Flare	AIA	Mouse	T cell–derived IL-17	–	+	15
Transgenic models						
KRN arthritis	KRN	K/BxN mouse	GPI	+	+	16
TNF transgenic arthritis	TNFtg	Mouse	TNF overexpression	–	–	17, 18
IL-1 transgenic arthritis	IL-1tg	Mouse	IL-1 overexpression	–	–	19
IL-1ra transgenic arthritis	IL-1ra–/–	BALB/c mouse	Autoimmune T cells	±	+	20, 21
HTLV-induced arthritis	HTLV	Mouse	Viral, transgenic	–	+	22
SKG arthritis	SKG	Mouse	T-cell defect	–	+	23
gp130-induced arthritis	gp130	Mouse	STAT3 defect	–	+	24

*Mostly used.

IC, immune complexes; gp130, glycoprotein 130; GPI, glucose-6-phosphate isomerase; IL-1, interleukin; TNF, tumor necrosis factor.

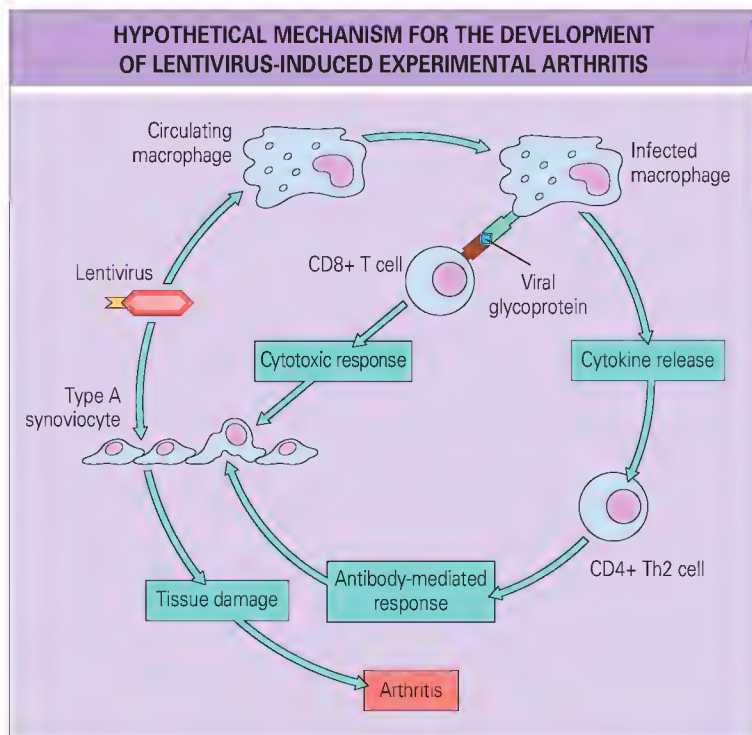


Fig. 90.3 Infection of macrophages and monocytes induces both expression of cell-surface viral antigens and release of cytokines. Macrophage activation appears to promote both CD4+ type 2 helper T-cell (Th2) expansion and the development of activated CD8+ T cells. T-cell cytotoxicity directed against infected type A (macrophage lineage) synovial cells may result in a local inflammatory reaction within the joint, and cartilage may be damaged concomitantly. The increased Th2 activity may contribute to local immune complex formation, which eventually leads to chronic inflammatory activity within the joint and the development of arthritis.

Studies of the involvement of cytokines in SCW arthritis show a combined role of TNF and IL-1, as found in AA.¹² In mice, a chronic relapsing SCW model can be induced by repeated weekly injection of SCW fragments directly into the knee joint, which displays a gradually increasing role of T cell–derived IL-17 and synovial IL-17 receptor-bearing cells with every flare.²⁶

Bacterial DNA can induce arthritis. In particular, the CpG motifs are arthritogenic and substantial amounts can be found in joint tissues.²⁷ Macrophages play a major role in this arthritis through TNF production. However, in comparison to cell wall fragments, the cytokine-inducing capacity of bacterial DNA is weak. Normal joints of individuals contain both bacterial fragments and bacterial CpG (CP61) motifs, and it is conceivable that both factors contribute to arthritis.

Antigen-induced arthritis

Antigen-induced arthritis (AIA) provides a designed model of the development of chronic erosive arthritis that reflects a sustained immune reaction to a persistent trigger in joint tissues, in this case a planted protein antigen. It is elicited by local injection of a high dose of antigen into the knee joint of an animal previously hyperimmunized with that antigen in Freund complete adjuvant. Such a model was first developed by Dumonde and Glynn¹³ in rabbits. In principle, it can be induced in any species, provided that proper immunity to a particular antigen can be mounted. Applications have since been developed in mice, rats, and guinea pigs.

In contrast to the polyarthritis models described thus far, AIA remains confined to the injected joint. Commonly used antigens are ovalbumin, bovine serum albumin (BSA), fibrin, and cationic forms such as methylated BSA. Preimmunization with antigen in complete Freund adjuvant induces strong humoral and cell-mediated immunity. Arthritis is usually induced 3 weeks later by local injection of a large amount of antigen into the knee joint. Initially, an immune complex (IC) type of reaction dominates, followed by T cell–mediated chronic inflammation. In the rabbit, chronicity may last for years. Histopathologic examination shows a granulocyte-rich exudate in the joint space, thickening of the synovial lining layer, and at later stages, a predominantly mononuclear infiltrate in the synovium, which later includes numerous T cells and clusters of plasma cells making antibodies to the inciting antigen, thus implying that retained antigen is still a driving force in chronic arthritis. Intense IC formation is seen in superficial layers of the articular cartilage, which may contribute to localized cartilage destruction. Early loss of PG, followed by pannus formation and cartilage and bone erosion, is a common finding.

Two important principles emerge from this model: first, chronicity occurs only in the presence of sufficient antigen retention in joint tissues, in combination with proper T cell–mediated delayed hypersensitivity; and second, joints contain numerous noncollagenous and avascular collagenous tissue such as cartilage, ligaments, and tendons, which allows prolonged antigen retention by antibody-mediated trapping and charge-mediated binding.^{14,28} Chronicity is caused by the generation of local antigen-specific T-cell hyper-reactivity, which allows flares in response to tiny amounts of antigen.

In rabbits, antibody responses are generally high and allow sufficient IC-mediated trapping of antigen in the joint. Because antibody levels are lower in mice, cationic antigens are needed as suitable arthritogens because of their ability to stick to the negatively charged collagenous structures of the joint and to accumulate IC formation at the surface.²⁸ Of interest, this principle may extend to cationic bacterial or viral components and appears to be of importance in the more recently developed KRN model of arthritis, in which anti-glucose-6-phosphate isomerase (anti-GPI) antibodies stick to GPI antigen trapped at cartilage surfaces.

In AIA in the rabbit and the mouse, elimination of TNF and IL-1 was poorly effective in suppressing joint inflammation, thus pointing to substantial “overkill” by other mediators in this severe onset of arthritis. However, elimination of IL-1 did yield impressive protection against cartilage destruction. The AIA model is most suited to studies of the mechanism of cartilage destruction as induced by a mix of ICs and T-cell reactivity. It is assisted by knowledge of the exact time of onset, accessibility of the knee joint (as compared with the ankles), and the presence of a contralateral control joint. Moreover, the model can be used to evaluate the regulation of local T-cell hyperreactivity against a retained foreign antigen.

Flares of arthritis

In contrast to the chronicity of human RA, most animal models have a relatively short duration of severe and rapidly destructive inflammation. In this respect, models of repeated flares of arthritis, with slower development of lesions, provide a valuable extension.

An arthritic joint bearing retained antigen and a chronic antigen-specific T-cell infiltrate displays a state of local hyperreactivity. This situation is not restricted to retained antigen but also applies to new antigen entering the sensitized joint from the circulation. Flares of smoldering arthritis can be induced with as little as 10 ng of antigen, and T cell–derived IL-17 plays a dominant part in such exacerbations.¹⁵

Similar flare models have been developed in rats and mice with bacterial cell wall constituents. Bacterial fragments may function as an antigen but also directly trigger TLRs, in particular, TLR2. The ensuing reactions are a mixture of T cell– and macrophage/fibroblast-driven processes. In the mouse model of repeated SCW rechallenge, the swelling response of every flare remains dependent on TNF. However, the chronic erosive infiltrate in the synovial tissue that occurs after repeated challenges is dependent on IL-1. Cartilage erosion is absent in IL-1–deficient mice but does occur in TNF-deficient mice. This model is more severe and erosive in DBA mice than in C57Bl mice, erosion is absent in T/B cell–deficient RAG–/– mice, and blocking of IL-17 prevents an erosive phenotype. The repeated-challenge model becomes Th17 dependent, and IL-1 is a major cytokine driving this process of Th17 generation.²⁶

Of note, considerable cross-reactivity occurs between cell walls from different bacterial origins, and flares may result from homologous and heterologous fragments. This may extend to cross-reactive autoantigens from cartilage, which underlines the fact that arthritis can start in response to a particular antigen but may spread to other antigens, including autoantigens.

Recently, TLRs have been identified as recognition sites for bacteria. TLR2 is involved in SCW recognition, whereas TLR4 is triggered by lipopolysaccharide but also by the damaged connective tissue components released in erosive stages. The acute SWC arthritis model is dependent on TLR2, whereas the more chronic rechallenge model loses TLR2 dependence and becomes dependent on TLR4.²⁹ These principles open up a wide range of putative stimuli involved in exacerbations, which simultaneously complicates the search for the driving “antigen” in humans. Flares can be blocked efficiently with a combination of antibodies to TNF, IL-1, and IL-17¹⁵ in particular. Evaluation of the efficacy of TLR blockers is warranted.

Immune complex–induced arthritis

Autoantibodies such as rheumatoid factor and anti-citrullinated peptide antibodies (ACPAs) are a key feature of RA, and the recent success of treatment with an anti-B cell drug (rituximab) enhanced the interest in their pathogenic role. In some of the models discussed earlier such as collagen-

PG-, and antigen-induced arthritis, IC formation at joint tissues is a major element (see Table 90.1). Although excessive IC formation can cause destructive arthritis, chronicity is limited and much promoted by T cells.³⁰ Minute amounts of antigen suffice to stimulate T cells, whereas considerable amounts of ICs are necessary to stimulate the release of inflammatory mediators from phagocytes. It is likely that IC models mimic part of the RA pathology.

Interest is growing in the use of passive IC models, along with the availability of a range of transgenic knockouts, to identify crucial pathways of inflammation and tissue destruction. The advantage of passive systems is the lower dependence on genetic background, thereby avoiding excessive backcrossing to create transgenics in suitable, susceptible mouse strains. Passive transfer of collagen-induced arthritis can be performed with a critical mixture of a number of anti-CII monoclonal antibodies, including complement-binding IgG2a. Sets are now commercially available, with DBA mice routinely recommended as sensitive recipients. Accepted concepts of inflammation pathways include IC-mediated complement activation and Fcγ receptor triggering on phagocytes.

An IC model emerging from the murine AIA model and using the principle of cationic retention is the passive transfer of antilysozyme antibodies to mice by local injection of poly-L-lysine (PLL)-coupled lysozyme into one knee joint. PLL-coupled lysozyme is highly cationic and sufficiently large to be retained in the joint for prolonged periods. Both association with synovial tissue and heavy sticking to cartilage surfaces contribute to the chronicity and cartilage destruction. An intriguing observation is the more chronic and destructive nature of this arthritis in DBA/1j mice than in BALB/c mice,³¹ which seems to be related to high sustained levels of activating Fcγ receptors on the macrophages of DBA/1j mice. The model shows strong dependence on IL-1, whereas TNF blockade was ineffective. FcγRI rather than FcγRIII appears to be crucial in the cartilage damage.³²

A final model to be mentioned here is the passive GPI model, which is addressed following a description of KRN arthritis. Differences between the various IC models lie mainly in the subclasses of antibodies and related complement-binding activity or FcγR-mediated activation of granulocytes, macrophages, and mast cells.

KRN–glucose-6-phosphate isomerase arthritis

An intriguing, novel arthritis model emerged from experiments in transgenic mice overexpressing a self-reactive T-cell receptor (TCR). Arthritis developed in a cross of K/BxN mice.¹⁶ The beauty of the KRN model is elucidation of the driving antigen and identification that passive transfer with antibodies induces a protracted arthritis. The TCR recognized the ubiquitous self-antigen GPI and provoked, through B-cell differentiation and proliferation, high levels of anti-GPI antibodies. These antibodies are directly pathogenic on transfer and appear to recognize endogenous GPI, which seems to associate preferentially with the cartilage surface.³³ The latter may underlie the dominance of joint pathology in these mice, although GPI is also abundant in other sites in the body. IgG1 antibodies are the major subclass and cause a sustained, erosive arthritis after continued transfer, with high sensitivity in BALB/c mice. This pathology brings the model close to passive CIA or IC-induced arthritis with planted cartilage-associated antigen, all having IC formation at the cartilage surface. Differences relate to the IgG subclasses involved.

As an adaptation of this model, Kamradt and colleagues³⁴ immunized mice with GPI and showed the development of arthritis after a few weeks. This direct immunization model is a mix of GPI-specific T cells and anti-GPI antibodies; serum from these mice cannot transfer arthritis. The latter makes the direct immunization model different from classic KRN arthritis.

Strain and cytokine dependency of passive immune complex arthritis

The severity of arthritis is dependent on complement factors and Fcγ receptors. Activation of complement through the alternative pathway appears to be crucial in GPI arthritis, consistent with dominance of IgG1. The activity of complement and the level of expression of FcγR on phagocytes are different in various mouse strains, and this determines to a great extent the variable susceptibility. BALB/c mice are hyperreactive, whereas DBA/1 and C57Bl6 are less susceptible, and minor responsiveness is seen in 129/Sv mice, in strong contrast to the low sensitivity of BALB/c mice in other passive IC arthritis models. GPI antibodies are found in some RA patients but certainly not in all, and levels are moderate. Their role in RA remains to be identified.³⁵

IL-1 is obligatory, with no arthritis induced in IL-1–deficient mice. TNF is also essential, although less critically so than IL-1 because robust arthritis develops in a proportion of TNF-deficient mice. When compared with the passive arthritis induced with antibodies to the cationic antigen

PLL-lysozyme, higher TNF sensitivity is apparent, as well as a dependence on mast cells. These findings suggest a role of environmental initiating elements. It is likely that the onset of mild GPI arthritis is assisted by local TNF generation and mast cell-dependent release of histamine, whereas a model with a planted cationic antigen in the joint generates sufficient non-specific inflammation to initiate arthritis without the need for additional facilitating mediators such as TNF. Once affected, the role of TNF is limited, as in GPI arthritis. T cell-derived IL-17 can accelerate and enhance the expression of GPI arthritis,³⁶ thus making TNF redundant and illustrating the remarkable potency of the combination of IC and T-cell activation in the severity and chronicity of arthritis.

Citrulline-induced arthritis

ACPAs are a key feature of RA, and in recent years many researchers have attempted to prove the efficacy of such antibodies in RA patients to induce passive arthritis, thus far without much success. So the question remained whether the antibodies are pathogenic or just a marker of RA.³⁷ There is some suggestive evidence of a pathogenic role in the studies of Kuhn and colleagues,³⁸ which demonstrated that such antibodies are present in collagen-induced arthritis and that tolerization of mice to citrulline responses results in reduced arthritis. However, it cannot be excluded that the immunomodulation process caused innocent bystander effects, not necessarily solely reflecting suppressed anticitrulline responses.

Very recently, Holmdahl's group generated a range of monoclonal antibodies specific for citrullinated CII and demonstrated induction of arthritis on transfer of the antibodies. In addition, the antibodies could amplify smoldering arthritis.³⁹ This argues that defined anticitrulline antibodies can do the job, as was demonstrated earlier for anti-CII and anti-GPI antibodies. Whether similar antibodies occur in significant quantities in patients with RA remains to be proved.

Gene manipulation and transgenic models

Transgenic animals provide models that demonstrate the importance of certain principles in arthritis and are useful for distinct screening. They do not necessarily provide better translational models for drug targeting in RA.

In mice transgenic for the env-pX region of the human T-cell leukemia virus type 1 genome, a spontaneous chronic arthritis develops as a result of expression of the *tax* gene.²² Onset occurs at 2 to 3 months of age in female mice but is delayed several months in male animals. The ankle joints are most frequently affected, and pannus formation leading to severe erosion of cartilage and bone is observed in the transgenic mice after several months of disease. The mice produce autoantibodies, and collagen immunization can provoke the onset or exacerbation of arthritis. It is tempting to speculate that a retrovirus could be involved in the pathogenesis of RA, possibly by influencing T-cell responses to cartilage antigens.

Another example is the occurrence of chronic autoimmune arthritis in mice with a point mutation in the gene encoding ZAP-70, a key signal transduction molecule in T cells.²³ The aberrant TCR function leads to positive selection of otherwise negatively selected autoimmune T cells. It is of great interest that in these mice disease fails to develop under microbially clean conditions despite active production of arthritogenic autoimmune cells. A single injection of zymosan provokes arthritis in a Dectin-1-dependent but TLR-independent manner.

Mice with a homozygous mutation in the gp130 IL-6 receptor subunit show enhanced signal transduction and STAT3 activation, and a lymphocyte-mediated RA-like joint disease develops. The increased proliferation of CD4+ T cells is due to elevated production of T cell-activating IL-7 by nonhematopoietic cells.²⁴

Tumor necrosis factor transgenic arthritis

In an elegant series of experiments, Keffer and coworkers¹⁷ provided insight into the role of TNF in induction of arthritis. By the introduction into mice of a modified human TNF transgene lacking a TNF 3' untranslated region involved in translational repression of TNF, it was shown that pronounced TNF overexpression results in chronic polyarthritis with a 100% incidence. Hyperplasia of the synovium, inflammatory infiltrates in the joint space, pannus formation, and cartilage and bone destruction were observed. Intriguingly, a similar form of arthritis also developed in targeted mutant mice lacking the 3' AU-rich elements, thus confirming the role of these elements in maintenance of a physiologic TNF response in the joint.¹⁸ A proposed mechanism is the inability of natural antiinflammatory signals, such as IL-10, to suppress TNF production under these conditions. These exciting findings stimulated a major search for functional mutations in TNF production in RA patients. However, no clear indications have been found so far.

This model is of great interest in identifying pathways of TNF-induced arthritis and screening the efficacy of various TNF-directed therapies. It is not surprising that anti-TNF treatment blocks the pathology, but it is a remarkable observation that some of the pathology runs through IL-1. Crosses of TNF transgenic mice with IL-1-deficient mice identified that inflammation is mediated by TNF. Bone erosion is 50% dependent on IL-1, whereas cartilage erosion is a fully IL-1-dependent process.⁴⁰ The model does not need T or B cells because arthritis occurs in TNF transgenic mice backcrossed to RAG-/- mice, and the pathology can be transferred with selected TNF-producing fibroblasts. The p55 type 1 receptor mediates TNF pathology, whereas the p75 type 2 receptor mediates suppression. Selective blocking of TNFR1, with the antiinflammatory effects of TNFR2 left unaltered, markedly reduced bone erosion.⁴¹ These observations provide a rationale for future treatment of RA with selective anti-TNFR instead of anti-TNF antibodies.

Interleukin-1 transgenic mice and interleukin-1 receptor antagonist-deficient mice

Transgenic IL-1 α overexpression induces chronic, destructive arthritis.¹⁹ Transgenic mice expressing human IL-1 α had high serum levels of IL-1, and a severe polyarthritis developed by 4 weeks of age. Hyperplasia of the synovial lining, pannus formation, and ultimately, cartilage destruction were evident. T and B cells were scant, but active granulocytes were abundant.

The opposite approach, elimination of IL-1 control by gene targeting of the endogenous IL-1 receptor antagonist (IL-1ra), also yielded a model of arthritis. IL-1ra deficiency in a BALB/c background resulted in pronounced arthritis at the age of 8 weeks.²⁰ Marked synovial and periarticular inflammation with invasion of granulation tissue and articular erosion was noted. Moreover, elevated levels of antibodies against immunoglobulins, CII, and double-stranded DNA were found, suggestive of autoimmune responses. Overexpression of a range of cytokines, including IL-1 β , TNF and IL-6, was observed in the joints before the onset of arthritis. Interestingly, autoantibody levels did not correlate with disease severity, which may imply that it reflects a reaction to damaged joint tissue.

In sharp contrast to the TNF transgenic model, the arthritis in IL-1ra-/- mice is strongly dependent on T cells, in line with the remarkable genetic restriction. It is consistent with the view that IL-1 is a crucial regulator of T-cell function. Undisturbed IL-1 action, in the absence of IL-1ra, apparently permits activation of IL-17-producing T cells directed against exogenous triggers or endogenous autoantigens. The spontaneous arthritis in IL-1ra-/- mice does not develop in germfree conditions and is reduced in TLR4-deficient mice.⁴² Likewise, KRN arthritis is dependent on gut flora.⁴³ TLR4 blockers are effective in the IL-1ra model.⁴⁴ Both TNF and IL-17 deficiency prevent the onset of arthritis.²¹ Features are highlighted in Table 90.2.

CYTOKINES AS TARGETS IN SUSCEPTIBILITY AND DESTRUCTION

Findings on TNF, IL-1, and IL-17 involvement have been addressed partly under the headings of the various models and are further summarized in Table 90.3.

TNF is a major mediator in the early stages of joint inflammation in every model. Although IL-1 is not a dominant inflammatory cytokine in all models, it is certainly the pivotal cytokine in the inhibition of chondrocyte PG synthesis in all models studied thus far, and blocking of IL-1 has a great beneficial impact on net cartilage destruction.⁴⁵ In line with this, chronic destructive arthritis could not be induced in IL-1-deficient mice in any of the classic arthritis models. In contrast, TNF deficiency reduced the incidence of autoimmune arthritis, but once joints became afflicted, full progression to erosive arthritis did occur.⁴⁶ It is unclear why IL-1 is such a dominant target in IC- and T cell-driven models whereas a crucial role of IL-1 in autoimmune RA is evident only in joint erosion and a role in RA joint inflammation is unlikely.

The novel T-cell cytokine IL-17 provides an additional target apart from TNF and IL-1. Local overexpression showed that it can accelerate the inflammation and tissue destruction in CIA, independent of IL-1, and IL-17 blocking appeared to be superior in the T-cell flare of AIA.¹⁵ Studies of human RA synovium in mice with severe combined immunodeficiency suggest that anti-IL-17 therapy is probably effective only in subgroups of RA with a clear T-cell signature.⁴⁷

Cartilage and bone destruction

Animal models are excellent tools for characterizing the kinetics of destructive pathways. The cartilage damage observed in different models ranges from a selective loss of cartilage underneath pannus tissue to overall loss of

TABLE 90.2

Features of classic arthritis models

Features	AA	SCW-A	CIA	AIA	KRN	TNFtg	IL-1ra-/-
Impact of bacterial flora*	+	+	—	—	?	?	+
Stimulus	?	Persistent bacteria	CII	Planted Ag	GPI	TNF	Bacteria?
Self-limited arthritis	+	—	±	—	—	—	—
Flares	Refractory	Spontaneous	Inducible	Inducible	?	—	—
Chronic synovitis	±	++	+	++	+	++	++
Bone marrow inflammation†	++	+	±	±	?	+	+
Main site of expression	Ankle	Ankle	Peripheral	Chosen‡	Peripheral	Ankle	Ankle
Bone erosion	++	+	++	+	++	++	+
Cartilage erosion	±	±	++	++	++	±	+
Dominant feature	Periostitis	Fibrosis	Destructive	Local hyperreactivity	Destructive	IL-1	IL-17

*Impact on susceptibility of strains.

†As an early feature.

‡Chosen by intraarticular injection.

AA, adjuvant-induced arthritis; AIA, antigen-induced arthritis; CIA, collagen-induced arthritis; IL-1ra, interleukin-1 receptor antagonist; SCW-A, streptococcal cell wall-induced arthritis; TNFtg, tumor necrosis factor transgenic arthritis.

TABLE 90.3

Cartilage destruction and cytokine involvement in murine models

Model	Acute inflammation			Cartilage destruction					
	TNF	IL-1	IL-17	PG loss	Surface erosion	Chondrocyte death	TNF*	IL-1	IL-17
SCW	++	—	—	+	±	±	—	+	—
SCW flares	+	+	+	+	+	±	—	++	+
CIA	++	+++	+	++	++	++	+	++	+
AIA	±	±	—	++	±	±	—	++	—
AIA flare	+	+	++	++	++	++	—	++	+++
ICA‡	±	++	—	++	++	++	±	++	—
GPI-A‡	+	++	—	++	++	++	+	++	—
TNFtg	++	±	?	+	±	±	++	++	?
IL-1ra-/-	+	++	+	+	+	±	—	+++	++

*The role of TNF in destruction is mainly indirect by preventing onset of the arthritic process.

†ICA, passive immune complex-induced arthritis with poly-L-lysine lysozyme as antigen.

‡Passive arthritis induced with antibodies from K/BxN arthritic mice.

AIA, antigen-induced arthritis; CIA, collagen-induced arthritis; GPI, glucose-6-phosphate isomerase; IL-1ra, interleukin-1 receptor antagonist; PG, proteoglycan; SCW, streptococcal cell wall; TNFtg, tumor necrosis factor transgenic arthritis.

matrix, starting with release of PG and, later, collagen damage. Killing of chondrocytes and complete loss of the superficial and middle cartilage layers are noted in severe forms. This underlines the fact that arthritic processes can be more or less destructive, depending on the underlying process and cytokine mixture. Enhanced degradation of matrix and inhibited synthesis of PGs by chondrocytes are general findings in all models. Aggressive overall cartilage loss is predominantly noted in the presence of IC deposition, whereas milder, more gradual forms of damage are noted in models driven by macrophage, fibroblast, or T-cell activation. Large variations in progressive destruction are also found in populations of patients with RA, which may imply separate pathogenetic pathways.

Chronic, irreversible destruction can take place under conditions that will hardly be considered inflammatory, and the opposite occurs as well. Symptomatic relief with antiinflammatory therapy is promising, but the main challenge of interrupting joint destruction remains. As an example, local IL-4 gene transfer did not suppress local inflammation yet markedly reduced the cartilage and bone destruction in CIA.⁴⁸ Crucial enzymes involved in loss of PG in cartilage were identified. Studies in ADAMTS4 and ADAMTS5 knockout mice showed that ADAMTS5 is the crucial enzyme in the PG loss in AIA and that its absence prevents not only PG depletion but also collagen damage. Accordingly, it opens a novel, indirect way for targeted treatment of cartilage erosion.⁴⁹

RANKL is the crucial activating cytokine of the bone-resorbing osteoclasts. In the absence of RANKL, joint inflammation continues in the passive GPI IC model of arthritis, but bone erosion is prevented. Similarly, when

TNF transgenic mice were crossed with c-fos-deficient mice, joint inflammation continued yet bone erosion was fully absent. C-fos mice lack functional osteoclasts. TNF-driven bone erosion is dependent on osteoclasts, and absence of osteoclasts alters TNF-mediated arthritis from a destructive to a nondestructive phenotype. In line with this, treatment with OPG, which is the natural inhibitor of RANKL, does not reduce inflammation in AA and TNF transgenic mice, yet bone erosion is reduced.⁵⁰ Recently, a direct role of autoantibodies to citrullinated vimentin was identified in the activation of vimentin-expressing osteoclasts.⁵¹

Further improvement of therapy and even bone repair can be achieved by combined blocking of cytokines and RANKL, as well as by providing an additional anabolic stimulus such as parathyroid hormone.⁵² These studies indicate that repair of bone is achievable, in line with the bone recovery noted in well-treated RA patients. Repair of cartilage remains a major challenge that probably requires tissue-engineering approaches with stem cells, biodegradable matrices, and supplies of crucial growth factors. A final remark on bone erosion versus bone apposition is in order. Unlike the situation in patients with RA, many arthritis models exhibit not only bone erosion but also pronounced new bone formation. These phenomena occur at distinct sites of the joint. The latter process, bone apposition, is virtually absent in TNF transgenic mice, and a TNF-inducible regulator of bone apposition, DKK-1, was recently identified.⁵³ It might be argued that most murine arthritis models are relatively devoid of TNF when compared with TNF transgenic mice and human RA, herein providing a possible explanation for the excessive bone apposition. Further studies are warranted on

factors that regulate the impact of osteoclasts and osteoblasts on bone metabolism under inflammatory conditions and its dependence on the local cytokine milieu, including old and novel players such as DKKs, transforming growth factor- β , bone morphogenetic proteins, and members of the Wnt family. Proper identification of their involvement and targeting in models may provide new ways of treatment.

- Further insight on the relevance of findings on erosive processes in animal models to human RA are hampered by the paucity of information on progression of cartilage erosion in patients with RA. Radiographs are a proper tool to evaluate progression of bone erosion, but the joint space narrowing identified with this technique is a nonsensitive measure and overlooks focal erosions occurring in cartilage. It is recommended that upcoming clinical trials of RA pay attention to

advanced imaging technologies to monitor changes in cartilage damage, which have yet to be explored and validated in animal models of arthritis.

- Arthritis may be induced in animals by immunization with cartilage components, nonspecific immune stimuli, bacterial or viral components, or transgenic manipulation.
- Animal models are tools that mimic various aspects but never fully resemble human RA.
- Models have a defined onset and are useful for kinetic evaluation of arthritis, cell and mediator involvement, and detailed analysis of joint erosion.
- Animal models serve an important role in the evaluation of antirheumatic treatments and provide direction for novel approaches to treatments such as cytokine inhibition.

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91

Autoantibodies in rheumatoid arthritis

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- Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by the presence of autoantibodies in peripheral blood and synovial fluid. Most autoantibodies are not directed to joint-specific antigens.
- Autoantibodies are already present in the earliest stages of the disease and may precede onset of the disease by several years.
- Rheumatoid factors (RFs), or autoantibodies to the Fc portion of IgG, are the longest-known marker antibodies in RA. High-titer IgM-RF and also IgA-RF are of high diagnostic and prognostic value because they are associated with erosive and more severe disease.
- Anti-citrullinated protein/peptide antibodies (ACPAs) are directed to antigens containing the unusual amino acid citrulline. They are the most specific marker antibodies for RA and, like high-titer RF, are linked to erosive RA. Citrullinated antigens expressed in the inflamed joint include fibrinogen, vimentin, α -enolase, and collagen.
- Autoantibodies to carbamylated antigens containing the unusual amino acid homocitrulline may have similar specificity and prognostic value as ACPAs.
- Among other autoantigens, the heterogeneous nuclear ribonucleoprotein-A2 (RA33) may be of pathogenetic relevance because it is also a target of autoreactive T cells.
- Autoantibodies may contribute to the pathophysiology of RA by inducing, maintaining, or modulating the disease process. However, for none of the known autoantibodies has a direct pathogenic role been clearly verified, and the primary (disease-inducing) autoimmune targets remain to be identified.

INTRODUCTION

The presence of autoantibodies and autoreactive T cells in blood and joint fluid is a characteristic feature of rheumatoid arthritis (RA) that distinguishes this disease from other inflammatory or degenerative joint disorders such as psoriatic arthritis, reactive arthritis, or osteoarthritis. As in other systemic autoimmune diseases, most autoantibodies in patients with RA are directed to antigens that are widely expressed throughout the body, but joint-specific structures are not among the primary targets. The hallmark autoantibody of RA, rheumatoid factor (RF), is directed against immunoglobulin G (IgG), and the most specific autoantibodies—anti-citrullinated protein/peptide antibodies (ACPAs)—are directed to citrullinated epitopes contained in proteins such as fibrinogen, vimentin, or α -enolase. Other antigens described as targets of autoimmune responses in RA include carbamylated proteins containing the unusual amino acid homocitrulline, nuclear proteins, heat shock proteins, enzymes, or cartilage components such as collagen type II (CII) (Table 91.1). Although most antibodies appear to be of limited usefulness for diagnostic purposes, they may nevertheless contribute to the pathologic processes characteristic of RA, such as chronic synovitis and erosion of cartilage and bone, by immune complex formation with subsequent induction of proinflammatory immune responses. In the following sections the major antibody systems are described and their value as diagnostic tools, as well as their potential role in the pathogenesis of RA, is discussed.

RHEUMATOID FACTORS

RFs are a family of autoantibodies that recognize antigenic determinants on the Fc portion of IgG (Fig. 91.1). This part of the molecule is essential for

complement fixation and interaction with the Fc receptor and thus for the uptake of immune complexes. In contrast to most other autoantibodies, the major RF species is the IgM isotype, whereas IgG-RF and IgA-RF occur less frequently. RF can be measured by various methods, including agglutination techniques such as the classic Waaler-Rose test, turbidimetric techniques such as laser nephelometry, and enzyme-linked immunosorbent assay (ELISA), which allows determination of RF subtypes.

A transient increase in IgM-RF is part of the normal immune response that occurs during infections, and it is triggered by immune complexes containing microbial antigens. Low-titer IgM-RF can be found in 10% to 15% of healthy individuals, whereas chronic persistence of high-affinity IgM-RF at elevated titer, as well as the presence of IgG and IgA subtypes, is a characteristic feature of RA. Interestingly, genes encoding RF from patients with RA are often somatically mutated, whereas RF from healthy individuals is predominantly germline encoded and polyreactive. Somatic mutation of immunoglobulin genes and a class switch from IgM to other subtypes are indicators of a T cell-driven process that, however, is still not understood in full detail.^{1,2}

Role as diagnostic and prognostic markers

IgM-RF can be detected in 60% to 80% of RA patients with established disease, whereas its prevalence in patients with early RA ranges between 50% and 60%.^{3,4} RFs of all subtypes may already be present in the earliest stages of the disease and can precede the onset of RA by several years.^{5,6} IgM-RF is also present in high titer in the majority of patients with primary Sjögren syndrome or mixed cryoglobulinemia and can be found in lower titer in all other rheumatic autoimmune diseases. At the commonly used cutoff value of 15 or 20 IU/mL, IgM-RF shows only moderate specificity for RA, but specificity is considerably increased at higher titer, and RF above 40 or 50 IU/mL (high-titer RF) has been found to be quite specific for RA.⁷ However, high-titer RF is present in only 50% to 60% of RA patients with established disease and is even less frequent in patients with early RA. Importantly, high-titer IgM-RF, as well as IgA-RF, also has considerable prognostic value because it is associated with the severity of RA, such as erosiveness (Fig. 91.2), more rapid disease progression, worse outcome, and extraarticular manifestations.⁸⁻¹⁰ Therefore, IgM-RF is still the most widely used serologic marker of RA and part of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for the classification of RA.¹¹

Pathogenetic involvement

The physiologic role of RF during a normal immune response is to enhance the avidity and size of immune complexes, thereby improving clearance of the immune complexes. Immune complexes are also present in the joint, and complement fixation by IgG-containing immune complexes is enhanced by IgM-RF binding. This may be particularly important for immune complexes containing antibodies to cartilage antigens and other proteins expressed in the joint, including antigens that are not joint specific, such as stress proteins, citrullinated proteins, or nuclear antigens. Therefore, RFs may contribute to the activity and chronicity of the disease via complement-mediated pathways (Fig. 91.3). Furthermore, RF-bearing B cells may act as antigen-presenting cells and efficiently present (foreign or self) antigens to T cells via uptake of immune complexes. Because RF in serum and especially RF-producing B cells in the synovial tissue of patients with RA presumably exert such functions, they may thereby contribute to the pathophysiology of RA. Finally, the association of high-titer RF with more severe disease, particularly with bone erosion and extraarticular manifestations, may be considered additional, though indirect, evidence of a pathogenic role of RFs.⁷⁻¹⁰

TABLE 91.1

Targets of autoantibodies in rheumatoid arthritis

Antigen	Antibody	Specificity	T cells
Immunoglobulin G	Rheumatoid factors	Moderate to high*	Unknown
Citrullinated proteins	ACPA	High	Yes
Carbamylated proteins	Anti-carP	Unknown	Unknown
HnRNP-A2	Anti-RA33	Moderate	Yes
Collagen II	Anticollagen	Low	Yes
Stress proteins	Anti-BiP, anti-hsp90, anticalnexin, anti-Grp94	Low	Yes
Glucose-6-phosphate isomerase	Anti-GPI	Low	Unknown
High mobility group box 1 protein	Anti-HMGB1	Low	Unknown
Calpastatin	Anticalpastatin	Low to moderate	Unknown
Peptidyl arginine deiminase 4	Anti-PAD4	Moderate to high	Unknown

*Dependent on cutoff value.

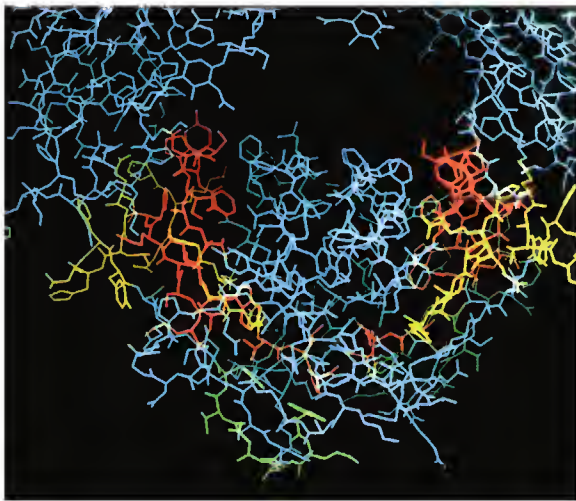


Fig. 91.1 Rheumatoid factor epitopes on IgG-Fc. A molecular model of the CH₂ and CH₃ domains of IgG show (in yellow) the antigenic sequence around His 435, which can be seen to protrude from the surface. Binding sites are scattered within the Cg2 and Cg3 regions of IgG-Fc. The presence of His 435 is an essential constituent of the Ga determinant and absent in IgG3. (With permission of Elsevier Science Ltd, reprinted from Peterson C, Malone CC, Williams RC Jr. Rheumatoid factor reactive sites on CH₃ established by overlapping 7-mer peptide epitope analysis. *Mol Immunol* 1995;35:57-75.)

ANTI-CITRULLINATED PROTEIN/PEPTIDE ANTIBODIES

The discovery in 1998 that citrulline is an essential constituent of epitopes recognized by autoantibodies in serum from patients with RA¹² has increased our understanding of the specific immune reactions that are thought to drive RA and has led to development of the most disease-specific diagnostic test for RA.¹³

Citrullination

Citrullination is the posttranslational conversion of peptidylarginine to peptidylcitrulline, a process catalyzed by a family of calcium-dependent peptidylarginine deiminases (PADs)¹⁴ (Fig. 91.4). This type of protein modification has been linked to apoptosis and terminal differentiation of cells, conditions that enables activation of PAD by increasing intracellular calcium levels. Thus, citrullination *per se* is not specific for RA. Increased citrullination has been associated with inflammation in various tissues, including the lungs, the central nervous system (CNS), and skeletal muscles. Citrullination of specific proteins with specific tissue distribution is also part of normal physiology, for example, citrullination of trichohyalin in the hair follicle, myelin basic protein in the CNS, histones in the nucleus, and keratin/filaggrin in the skin.¹⁵

BOX PLOTS SHOWING THE DIFFERENCE IN LARSEN SCORES IN RA PATIENTS WITH HIGH-TITER RF (>50 U/mL) VERSUS PATIENTS WITH LOW-TITER OR NEGATIVE RF

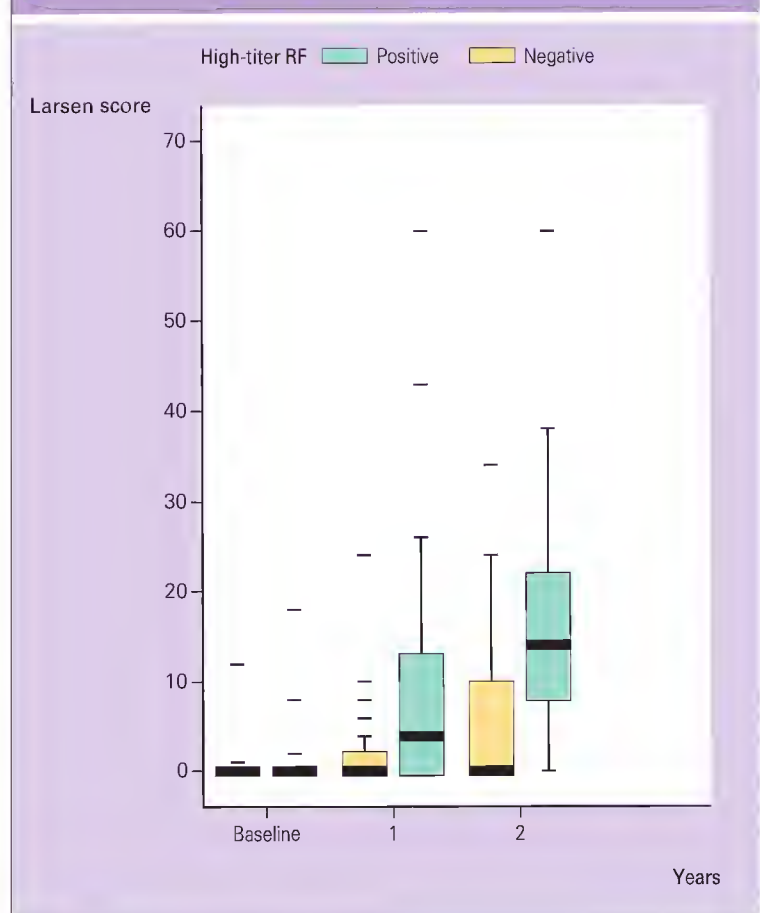


Fig. 91.2 The boxes show median values and 25th/75th percentiles. Baseline values were similar in both groups, but Larsen score progression was significantly higher in patients with high-titer rheumatoid factor (RF), both in the overall rheumatoid arthritis (RA) population ($P < .0001$) and in the subpopulation of anti-citrullinated peptide antibody-negative patients ($P = .0014$, not shown). (Adapted from Nell V, Machold KP, Stamm TA, et al. Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. *Ann Rheum Dis* 2005;64:1731-6.)

History of testing for anti-citrullinated peptide antibodies

The antiperinuclear factor described in 1964 and the antikeratin antibodies identified in RA sera a few years later were both found to target citrullinated filaggrin. Based on this finding, the first citrulline-containing peptide ELISA

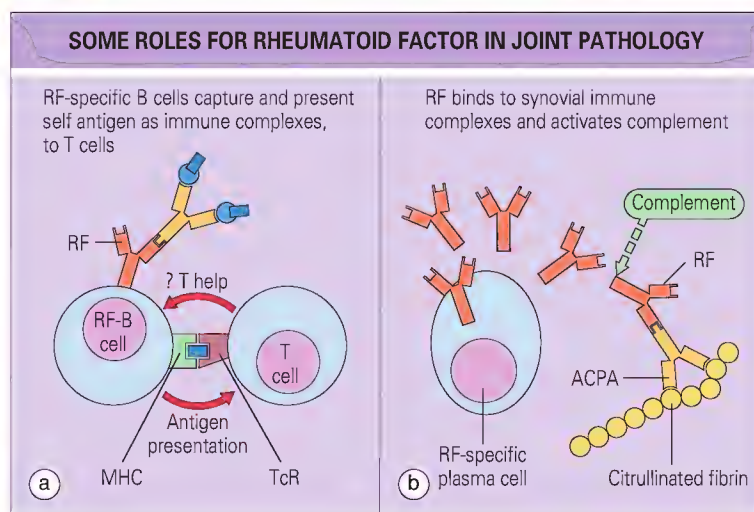


Fig. 91.3 (a) Rheumatoid factor (RF) may enhance autoimmune reactions by capturing immune complexes (composed of autoantibodies such as anti-citrullinated protein/peptide antibodies [ACPAs] and self antigens) and subsequently present peptides derived from the autoantigen to autoreactive T cells. (b) RF may bind autoantibodies directed to antigens expressed in the joint (e.g., ACPAs recognizing citrullinated antigens such as fibrinogen, vimentin, or α -enolase) and activate complement, further enhancing the inflammatory process. MHC, major histocompatibility complex; TcR, T-cell receptor.

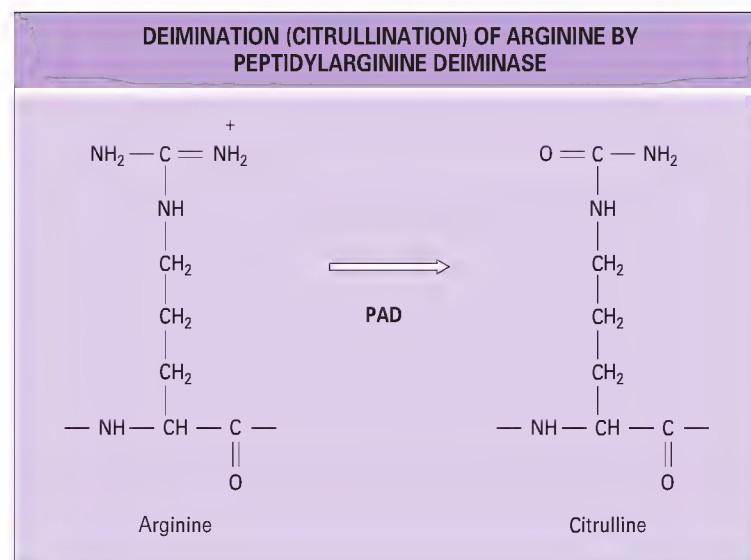


Fig. 91.4 Enzymatic conversion of arginyl to citrullyl is a posttranslational modification that changes the charge and biochemical properties of proteins. Citrullination is predominantly observed in proteins of the cytoskeleton such as cytokeratin, vimentin, or filaggrin and seems to represent a general regulatory mechanism that particularly occurs during apoptosis. PAD, peptidylarginine deiminase.

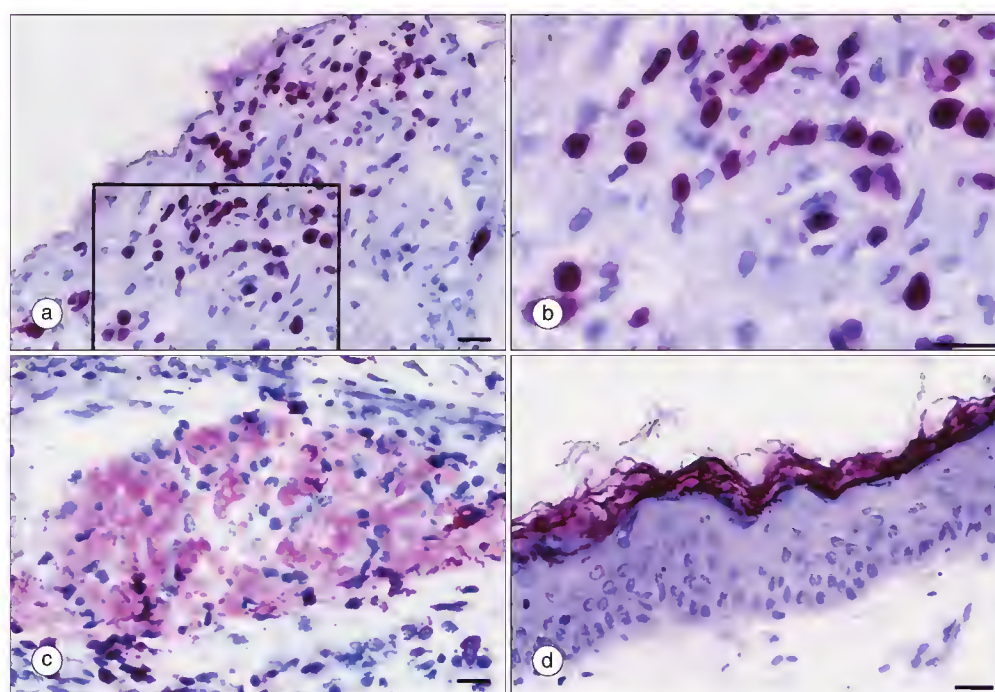


Fig. 91.5 Detection of deiminated (i.e., citrullinated) proteins in rheumatoid arthritis synovial tissue as demonstrated by immunoperoxidase staining with an antibody to modified citrulline. (a and b) In positive synovial membranes, the cytoplasm of numerous macrophage-like or fibroblast-like mononuclear cells, located in the lining or in the deep synovium, is intensely stained. (c) In addition, staining of interstitial amorphous deposits located in the vicinity or close periphery of labeled mononuclear cells is observed in the deep synovium. (d) For comparison, a section of human skin is shown in which the entire cornified layer of the epidermis (containing deiminated filaggrin) is stained. Scale bars, 50 μ m. (With permission of the American Association of Immunologists from Masson Bessiere C, Sebbag M, Durieux JJ, et al. In the rheumatoid pannus, anti-filaggrin autoantibodies are produced by local plasma cells and constitute a higher proportion of IgG than in synovial fluid and serum. *Clin Exp Immunol* 2000;119:544-52.)

was developed; it used linear citrullinated filaggrin peptides as antigen. By adopting a cyclic structure of the peptides, the sensitivity of the assay was increased, and the first-generation cyclic citrullinated peptide (CCP) ELISA was developed. The most frequently used ACPA test today is the second-generation CCP assay (CCP2), which is based on synthetic peptides that were identified after screening large peptide libraries.¹³

Citrullinated candidate autoantigens

With high sensitivity (approximately 60% to 70%) and high specificity (approximately 95%),^{3,4,13} the CCP2 assay is now considered a “gold standard” diagnostic test for RA. However, the artificial peptides in CCP2 do not correspond to any human protein sequence but rather mimic *in vivo*-generated citrullinated epitopes. Hence, research has been focused on the identification and characterization of physiologic ACPA targets, with citrullinated epitopes on fibrin(ogen),¹⁶ vimentin,¹⁷ CII,¹⁸ and α -enolase¹⁹ being the best described candidates today.

Extracellular fibrin deposits, including citrullinated forms of fibrin(ogen), are common features of rheumatic joints (Fig. 91.5), and immunodominant B-cell epitopes on the citrullinated α and β chains of fibrin(ogen) have been identified. Another citrullinated antigen of interest is the intermediate filament protein vimentin, first described as the Sa antigen. Vimentin, ubiquitously expressed as a cytoskeletal protein, exists in various citrullinated and mutated isoforms in inflamed joints.²⁰ Based on this observation, the anti-modified citrullinated vimentin (MCV) ELISA was developed. Several studies have now concluded that the MCV and CCP2 tests perform comparatively well in terms of sensitivity and specificity for RA.²¹ As the major component of articular cartilage and the most widely used antigen in experimental models of arthritis, CII represents another attractive candidate autoantigen in RA. Antibodies to the C1 epitope on citrullinated CII have been described in RA, and citrullinated CII peptides have been identified in synovial fluid from patients with RA. Citrullinated α -enolase, with its immunodominant B-cell epitope citrullinated α -enolase peptide-1 (CEP-1), is another well-characterized target of the ACPA response. As a glycolytic

enzyme and a plasminogen receptor on the cell surface, α -enolase is ubiquitously expressed and upregulated in response to proinflammatory stimuli.¹⁵

The frequency of ACPAs reactive with single peptides derived from citrullinated proteins is in most patient cohorts lower (typically around 40%) than the frequency of anti-CCP or anti-MCV antibodies (typically around 60% to 70%). However, the number of RA patients positive for any of these ACPA fine specificities is rather similar to the number of patients positive for CCP (or MCV).²²

Role as diagnostic and prognostic markers

ACPs are generally present early in the disease course and can even be detected years before joint symptoms develop.^{3,6} Although the prevalence of ACPAs in early RA is lower than in established disease, the significance of ACPAs in predicting progression from undifferentiated arthritis—or even arthralgia—to chronic RA has been demonstrated in several studies. These observations, together with high disease specificity (>95%), make ACPAs important serologic markers for early diagnosis and, accordingly, may identify a window of opportunity for early intervention.^{13,23} Even though ACPA-positive and ACPA-negative patients may have similar clinical symptoms at baseline, these two RA subsets demonstrate marked differences in disease course. Radiographic progression (Fig. 91.6), as well as extraarticular manifestations such as ischemic heart disease and lung pathology, is more common in ACPA-positive patients.²⁴ Importantly, the association of ACPA particularly with radiographic progression is not linked to the presence of RF, and therefore both antibodies are independent predictors of erosive disease (Fig. 91.7). The importance of ACPAs as diagnostic and prognostic markers has recently been acknowledged by the EULAR and ACR. In 2010, ACPAs (along with RF) were included in the new classification criteria for RA.¹¹

BOX PLOTS SHOWING THE DIFFERENCE IN LARSEN SCORES BETWEEN ACPA POSITIVE AND ACPA NEGATIVE RA PATIENTS (AS DETERMINED BY THE ANTI-CCP ELISA) WITH LOW-TITER (<50 U/mL) OR NEGATIVE RF

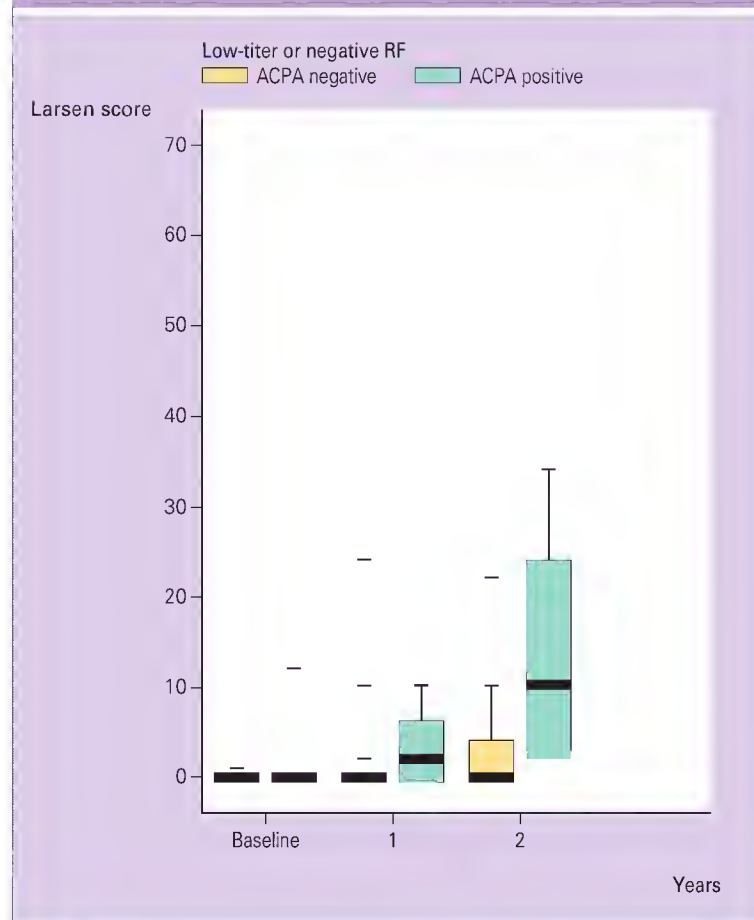


Fig. 91.6 The boxes show median values and 25th/75th percentiles. Baseline values were similar in both groups, but Larsen score progression was significantly higher in ACPA-positive patients ($p = .038$). ACPA, anti-citrullinated peptide antibody; CCP, cyclic citrullinated peptide; ELISA, enzyme-linked immunosorbent assay; RF, rheumatoid factor.

Role in disease etiology and pathogenesis

ACPs may antedate the symptoms and diagnosis of RA,^{5,6} with epitope spreading and increasing antibody titers as clinical onset approaches.²⁵ Hence, the development of ACPA-positive RA seems to progress through two phases: autoimmunity to citrullinated epitopes—in the absence of clinical symptoms—develops in the first phase, and autoimmune disease—characterized by clinical synovitis/arthritis—develops in the second phase (Fig. 91.8). The molecular pathways behind these events are not fully understood, but epidemiologic studies have identified genetic and environmental factors that may contribute.

HLA-DRB1 shared-epitope (SE) alleles constitute risk factors for the development of ACPAs rather than RA *per se*.^{26,27} and more recent data indicate that HLA-DRB1 SE alleles predispose to the development of certain ACPA fine specificities (i.e., anti-CEP-1 and anti-citrullinated vimentin antibodies), but not others (i.e., mainly anti-citrullinated fibrinogen antibodies), thus suggesting that the production of different ACPAs may be governed by partly different mechanisms.^{22,28,29} In view of the role of major histocompatibility complex (MHC) class II molecules in presenting antigens to T cells, it has been hypothesized that HLA-DRB1 SE preferentially presents citrullinated peptides to pathogenic T cells. Some evidence for this hypothesis comes from experimental studies. In DR4-IE transgenic mice, conversion of arginine to citrulline in a vimentin peptide was shown to increase MHC affinity and thereby enhance specific T-cell activation,³⁰ and T cells specific for a citrullinated vimentin peptide, but not the arginine-containing equivalent, were identified in human blood with the use of HLA-DR*0401 tetramers.³¹

Cigarette smoking has also been associated with ACPA-positive RA. The risk conferred by smoking is dependent on HLA-DRB1 SE alleles, and a gene-environment interaction has been demonstrated.²⁶ Increased expression of PAD enzymes and citrullination has been described in the lungs of smokers, thus suggesting exposure of autoantigens to the immune system in an inflammatory milieu, which may initiate loss of tolerance in genetically predisposed individuals (i.e., HLA-DRB1 SE positive) (Fig. 91.9). Increased immunogenicity by citrullination has been demonstrated in experimental animal models and may result from the formation of novel or altered self-epitopes.³²

The mechanisms responsible for the progression from autoimmunity to autoimmune disease are poorly understood, and whether ACPAs are involved is not known. However, circumstantial evidence points to a pathogenic role for ACPAs in RA, including the high predictive value and the association

THE PROBABILITY OF RADIOGRAPHIC PROGRESSION

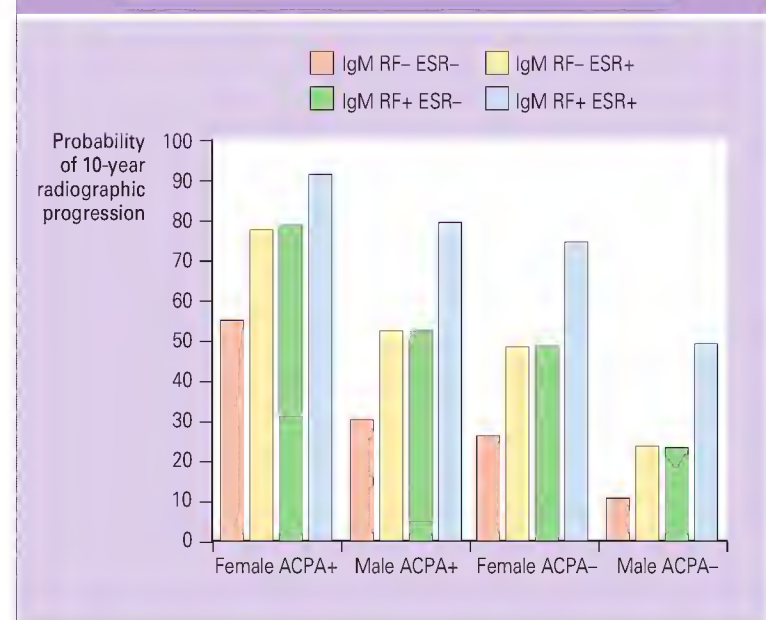


Fig. 91.7 Change in van der Heijde–modified Sharp score of the hands and feet greater than 10 U/10 yr according to different combinations of the independent predictors IgM–rheumatoid factor (IgM-RF), anti-citrullinated peptide antibody (ACPA), and erythrocyte sedimentation rate (ESR) from a logistic regression model. (From Syversen SW, Gaarder PI, Goll GL, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis* 2008;67:212-7.)

DEVELOPMENT OF AUTOIMMUNITY AND DISEASE IN RA PATIENTS

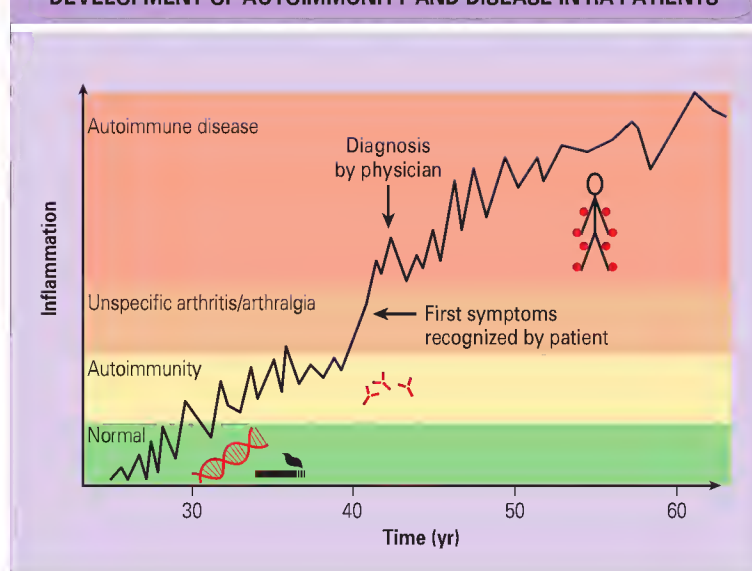


Fig. 91.8 Genetic and environmental risk factors, such as HLA-DRB1 shared epitope and smoking, drive the development of autoimmunity characterized by autoantibodies (anti-citrullinated peptide antibodies [ACPAs], rheumatoid factor [RF], etc.). Later, symptoms of arthritis develop, including arthralgia, and eventually rheumatoid arthritis (RA) is diagnosed. (Courtesy Rikard Holmdahl.)

ETIOLOGIC HYPOTHESIS FOR THE DEVELOPMENT OF ACPAs AND RA

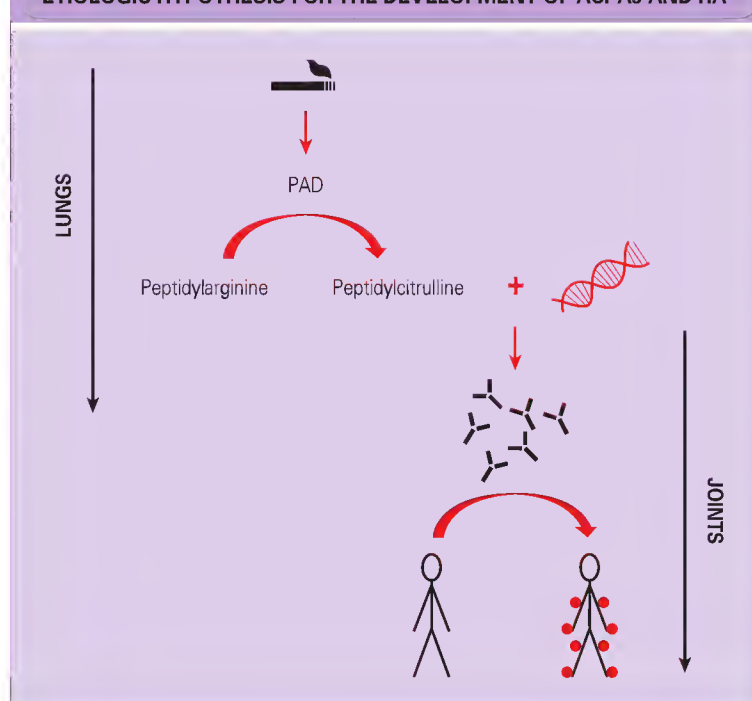


Fig. 91.9 Smoking induces inflammation in the lungs, with increased cell death and activation of peptidylarginine deiminase (PAD) enzymes subsequently leading to increased protein citrullination. In genetically predisposed individuals (i.e., HLA-DRB1 shared epitope positive), loss of tolerance to citrullinated antigens results in the production of anti-cyclic citrullinated protein/peptide antibodies (ACPAs), which later interact with citrullinated proteins present in the joint and thereby cause chronic joint inflammation. RA, rheumatoid arthritis.

with disease severity, as well as the enrichment of ACPAs in joints as compared with the circulation,³³ along with treatment data from studies using rituximab, which depletes CD20-positive B cells and reduces levels of ACPA in responders; conversely, relapse is associated with the return of ACPA-producing B cells.³⁴ Furthermore, in mouse models of arthritis, transfer of a monoclonal anti-citrullinated fibrinogen antibody could enhance disease development, whereas immunization with citrullinated CII increased the incidence and accelerated the onset of collagen-induced arthritis; both

POSTTRANSLATIONAL MODIFICATIONS OF ARGININE AND LYSINE

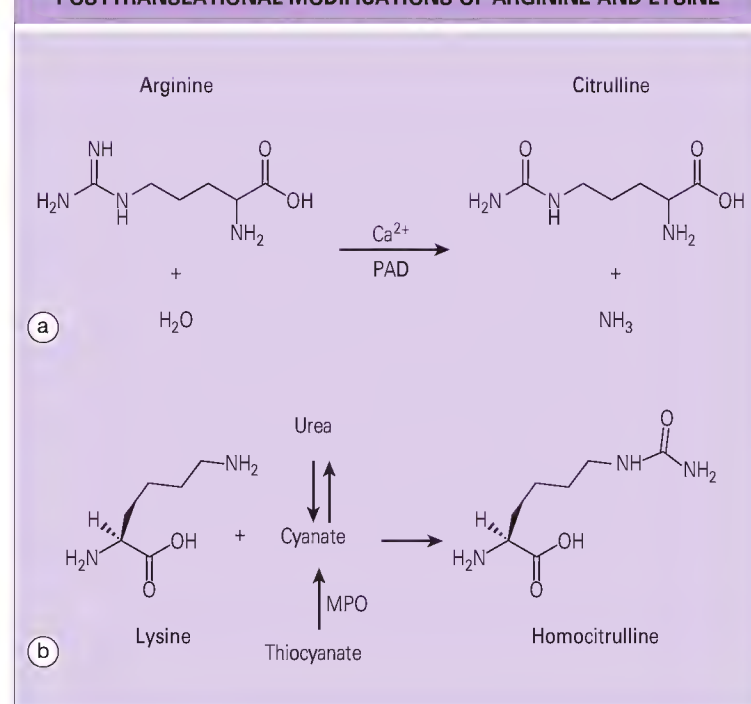


Fig. 91.10 (a) Citrullination (deimination) is an enzymatic reaction catalyzed by peptidylarginine deiminases in which the NH group of arginine is cleaved. (b) Homocitrullination (carbamylation) occurs via the nonenzymatic addition of a CONH₂ group to lysine. Carbamylation requires cyanate, which can be derived from urea or endogenously generated from thiocyanate via a myeloperoxidase (MPO)-catalyzed biochemical reaction.

citrullinated fibrinogen and α -enolase were shown to induce arthritis in DR4-IE transgenic mice, although it should be noted that this arthritis was mild and nonerosive.¹⁵

It has been hypothesized that ACPAs mediate pathology via the formation of immune complexes and engagement of Fc receptors, with the subsequent production of proinflammatory mediators. In support of this hypothesis, ACPA-mediated immune complexes were shown to induce the secretion of tumor necrosis factor (TNF) in human macrophages via the Fc γ IIa receptor (Fc γ RIIa) and Toll-like receptor 4, and activation of complement by ACPAs has been demonstrated.³⁵⁻³⁷

ANTIBODIES TO CARBAMYLATED (HOMOCITRULLINATED) ANTIGENS

A posttranslational modification very similar to citrullination is carbamylation, or the conversion of lysine to homocitrulline in a nonenzymatic reaction with cyanate, which is in equilibrium with urea in the body (Fig. 91.10). Under physiologic conditions the concentration of urea is too low for extensive carbamylation. Increased levels of cyanate occur with renal insufficiency or during inflammation when the enzyme myeloperoxidase, which catalyzes oxidation from thiocyanate to cyanate, is released from neutrophil granulocytes. Interestingly, plasma thiocyanate levels are also elevated in smokers.³⁸

Carbamylation changes the charge of proteins and, like citrullination, can impede biologic function. Carbamylation has also been shown to enhance the immunogenicity of proteins and increase reactivity to citrullinated peptides.³⁹ Because homocitrullinated proteins have been detected in the joints of patients with RA, carbamylation could have a role in the pathogenesis of RA.

IgG antibodies against carbamylated proteins (anti-CarP) are present in 45% of RA sera and IgA antibodies in 43%. Importantly, anti-carP antibodies do not cross-react with ACPA, and IgG anti-carP antibodies are present in 16% of ACPA-negative patients and, similar to ACPA, seem to be associated with a more destructive disease course.⁴⁰ Anti-carP autoantibodies are therefore an interesting new family of potential marker antibodies in RA, although their specificity for RA is not yet clear and it is presently not known which carbamylated proteins are recognized by anti-carP antibodies *in vivo*. Because the carbamylation reaction is almost irreversible, proteins tend to accumulate homocitrulline residues over time. Stable extracellular matrix proteins

in the joint, such as collagens or fibrinogen, are therefore attractive candidates for carbamylated autoantigens.

ANTIBODIES TO THE HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A2

The heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2) is a 36-kDa RNA- and DNA-binding protein that exerts multiple functions, including processing, transport, and translation of mRNA. Anti-hnRNP-A2 autoantibodies, which were initially termed anti-RA33, occur in 20% to 30% of RA patients and with comparable frequency also in patients with systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD).⁴¹ However, epitope recognition was found to differ in patients with RA, MCTD, and SLE. Because anti-RA33 antibodies are rare in other arthritides such as osteoarthritis, reactive arthritis, ankylosing spondylitis, or psoriatic arthritis, they can be helpful in the differential diagnosis, particularly in patients who are negative for RF or ACPA. Anti-RA33 antibodies have a specificity of approximately 90% for RA, which is lower than the specificity of ACPA or high-titer IgM-RF. Similar to RF and ACPA, anti-RA33 antibodies may already be present in the earliest stages of the disease.⁷ Importantly, they do not correlate with IgM-RF or ACPA and are not associated with radiographic progression but rather seem to predict a more favorable outcome.⁷ Autoimmunity to hnRNP-A2 may be involved in the pathogenesis of RA because pronounced T-cell reactivity has been observed in patients with RA⁴² and the antigen was found to be highly expressed in lymphatic organs and in inflamed synovial tissue. Synovial tissue overexpression and B- and T-cell reactivity to hnRNP-A2 can also be found in animal models of arthritis, namely, in TNF- α transgenic mice and in rats with pristane-induced arthritis.⁴³ In TNF- α transgenic mice, immunization with a peptide corresponding to a major B-cell epitope enhanced the arthritis significantly. Interestingly, in pristane-induced arthritis the autoantigenic (and potentially pathogenic) properties of hnRNP-A2 appear to be dependent on the nucleic acids associated with the protein.⁴⁴

ANTICOLLAGEN ANTIBODIES

Among the 14 different collagens, CII is the major collagen species in the joint and also the major collagen antigen. Anti-CII antibodies are found in many pathologic conditions and are therefore not specific for RA. Titers may be particularly high in early disease and decline as the disease progresses.⁴⁵ However, the prevalence of anti-CII antibodies is not higher in patients with early synovitis in whom RA develops than in those with other early synovitis.⁴⁶ Autoantibodies to collagen and other cartilage components may be contained within the cartilage and contribute to the local macrophage activation and inflammation in RA.

OTHER ANTIBODIES

Other antibodies reported to occur in patients with RA may be directed to quite diverse antigens, including nuclear proteins such as high mobility group box 1 protein (HMGB1), heat shock proteins, enzymes, and enzyme inhibitors (see Table 91.1). In general, these antibodies show low specificity for RA and are therefore of little if any usefulness for diagnostic purposes. An interesting exception is antibodies to PAD4, an enzyme involved in the citrullination of synovial proteins, and these antibodies appear to be rather specific for RA.⁴⁷ Because they are detected mainly in ACPA-positive patients, their diagnostic value is presumably limited. However, the antibodies might inhibit the enzymatic activity of PAD4.⁴⁸

THE IMPACT OF IMMUNOGLOBULIN G GLYCOSYLATION ON ARTHRITIS

IgG possesses a single N-linked glycan at the position asparagine 297 in the CH₂ domain of the two heavy chains (Fig. 91.11a). This glycan consists of a core polysaccharide of N-acetylglucosamine and mannose that can be further modified by the addition of terminal galactosidase or sialic acid (N-acetylneuraminic acid) or the addition of branching fucose (see Fig. 91.11b). More than 30 distinct forms of IgG glycosylation are currently known in humans.⁴⁹ Complete removal of the sugars by exchange of the asparagine through alanine or by treatment with peptide-N-glycosidase F has been shown to dramatically reduce the affinity to Fc γ Rs and the proinflammatory activity of IgG. In RA, three galactosylation subfamilies of IgG

have been classically distinguished: IgG-G0 completely lacks galactose, and IgG-G1 and IgG-G2 carry galactose on one or both arms of the biantennary glycan, respectively. Interestingly, agalactosylated IgGs (IgG-G0) are enriched in patients with RA and other autoimmune diseases.⁴⁹ Higher levels of IgG-G0 appear before onset of the disease and correlate with disease parameters in RA. Interestingly, agalactosylation occurs predominantly in females, and reduction of agalactosylated IgG correlates with remission during pregnancy in humans and mice.^{50,51} Importantly, reduced galactosylation appears to be more frequent in the ACPA fraction of total IgG.^{51,52} A skewed IgG glycosylation profile is also apparent in animal models of arthritis, and agalactosylated IgG can induce disease in an arthritis serum transfer model.⁵³

In contrast to the sugar moiety as a whole, the terminal sialic acid appears to confer antiinflammatory activity. In the healthy state most IgG is fully sialylated, but sialylation is reduced on antigen-specific IgG during the course of an immune response. Sialylated IgG has 5 to 10 times reduced binding affinity to Fc γ Rs. The pathogenicity of IgG-G0 residues is therefore thought to rather be caused by the lack of galactose-bound sialic acid than by galactose itself.⁵⁴ Terminal sialic acid is apparently recognized by the receptor DC-SIGN on macrophages or dendritic cells and induces secretion of the type 2 helper T-cell cytokines that increase expression of the inhibitory Fc γ RIIB.⁵⁵ Desialylation could therefore contribute to disease by enhancing proinflammatory activity.

Apart from galactose and sialic acid, fucose seems to influence IgG function. IgG without fucose has strongly increased affinity for activating Fc γ Rs and therefore higher proinflammatory activity.⁵⁶ Treatment of IgG with EndoS, an endoglycosylase purified from *Streptococcus pyogenes* that removes most of the aspartate 297-linked glycan on IgG but keeps one N-acetylglucosamine with its branching fucose residue intact (see Fig. 91.11b), has been shown to inhibit disease transfer in antibody-dependent mouse models of arthritis.^{57,58} Importantly, IgG2a, the IgG subclass mainly responsible for combating bacterial and viral infections, retains its affinity to Fc γ Rs after treatment with EndoS.⁵⁸ EndoS might therefore be considered an interesting therapeutic tool for the treatment of autoimmune diseases because the risk for opportunistic infections would be relatively low.

Glycosylation of IgG is particularly important for treatment with intravenous immune globulin (IVIG), which has been used as therapy for a growing number of autoimmune diseases in the last years and decades, RA among them as well. A potential mechanism of IVIG is reestablishment of sialin-rich IgG, which is reduced in patients with autoimmune diseases.^{54,57}

AUTOANTIBODIES AND DISEASE PATHOGENESIS

Although autoantibodies are commonly present in the sera and synovial fluid of most patients with RA, their pathogenic role has not been fully elucidated. Among the various autoantibodies described, only ACPAs (and possibly also anti-carP) appear to be truly specific for RA. It is currently unknown which citrullinated antigens initiate the ACPA response, but it is presumably not fibrin(ogen) because fibrin deposition and citrullination occur after the onset of joint inflammation and therefore are a consequence rather than the cause of arthritis. Thus, autoimmunity to citrullinated epitopes might be induced by ubiquitously expressed antigens such as vimentin or α -enolase. Once set in motion, this autoimmune response seems to inevitably lead to the development of RA because ACPAs are only rarely observed in healthy subjects or patients with other rheumatic diseases. The strong association of ACPA with certain HLA-DR alleles and with smoking provides a compelling link between genes, the environment, and disease. Remarkably, upregulation of PAD2 and the presence of citrullinated proteins have been demonstrated in the lungs of cigarette smokers and might represent the first event in the pathogenic chain of RA. Binding of ACPAs to their targets in synovial tissue probably has proinflammatory effects that lead to B- and T-cell stimulation and induce extravasation of fibrinogen, fibrin formation, and further deimination. This is most likely a self-maintaining process that is at least partly responsible for the chronicity of the disease (Fig. 91.12). The observation that citrullinated forms of collagen may be present in the synovial fluid of patients with RA suggests that collagen may become a target of ACPAs as well, which may take place later in the course of the disease. Immune complexes consisting of ACPAs and citrullinated antigens may represent the main target for RF, which would explain the close association of these two antibodies.

The lack of disease specificity of autoantibodies other than ACPAs does not necessarily exclude a pathogenic role for them, and also in other systemic autoimmune diseases only few antibodies are truly disease specific.

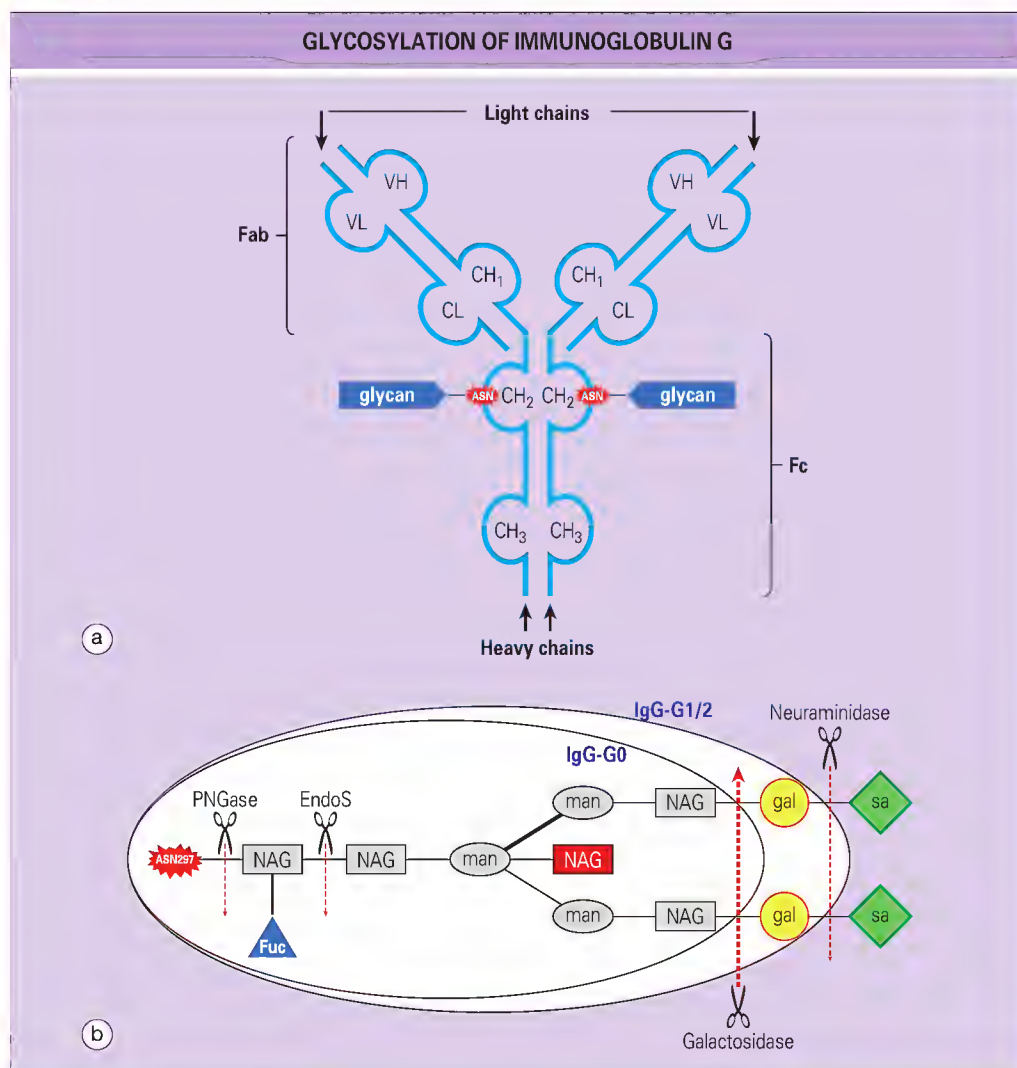


Fig. 91.11 (a) N-linked glycosylation occurs at asparagine 297 in both of the CH₂ domains of the heavy chains of the IgG molecule. (b) The sugar moiety of the IgG-Fc fragment. Shown are all sugar residues that might be present in the different IgG glycoforms found in serum. The core sugar contains four *N*-acetylglucosamine (NAG) and three mannose (man) residues. Terminal galactose (gal) and sialic acid (sa) or branching fucose (Fuc) or an additional NAG can be present. The cleavage sites of PNGase, EndoS, galactosidase, and neuraminidase are also indicated. Depending on the presence or absence of terminal gal and sa residues, IgG-G1/2 and IgG-G0 isoforms can be distinguished.

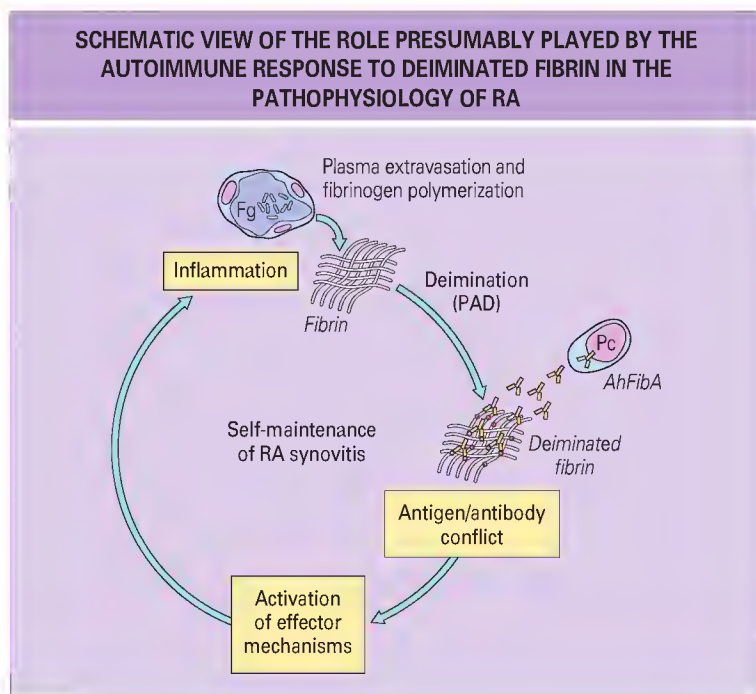


Fig. 91.12 In rheumatoid synovial tissue, fibrin is deiminated by the peptidylarginine deiminase (PAD) isoforms PAD2 and PAD4, which are abundantly expressed by synovial monocytes/macrophages and granulocytes, and it becomes the target of the disease-specific antibodies (AhFibA) locally produced by synovial plasma cells (Pc). This leads to antigen/antibody complexes, which via activation of effector mechanisms probably involving complement or Fc receptors (or both), have proinflammatory effects. In turn, these effects lead to plasma extravasation and fibrinogen polymerization and therefore provoke the formation of new fibrin deposits in the tissue, which become the substrate of one or several locally expressed PADs. This closes a vicious circle that could account for the self-maintenance of rheumatoid inflammation. In the synovial tissue of patients without rheumatoid arthritis (RA), even if deiminated fibrin is present, the absence of AhFibA prevents the establishment of this self-maintenance loop. Fg, fibrinogen.

For example, antiphospholipid antibodies are among the pathogenic key players of antiphospholipid syndrome but are also frequently found in patients with SLE. Therefore, antigens such as hnRNP-A2, collagen, or heat shock proteins may also contribute to the disease process by virtue of immune complex formation similar to ACPA.

Taking all these observations into consideration, a general model for the initiation of arthritogenic autoimmune responses is suggested in which an environmental trigger (e.g., a toxic substance or an infectious agent) induces

alterations in tissues (e.g., the lung or lymphoid organs) that lead to extensive modification (e.g., deimination, carbamylation, or phosphorylation) and degradation of proteins and inappropriate release of intracellular material because of apoptosis or necrosis. Uptake of apoptotic or necrotic material by dendritic cells will lead—in those with a susceptible genetic background—to activation of pathogenic T cells and autoantibody production, thereby setting in motion a chain of events that will eventually result in overt disease and irreversible joint damage.

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Cellular immunity in rheumatoid arthritis

■ J.S. HILL GASTON

- Susceptibility to autoantibody-positive arthritis correlates with particular major histocompatibility complex antigens that control T-cell recognition of antigens, including autoantigens.
- Cells of the immune system (B and T lymphocytes, dendritic cells, macrophages) are prominent in rheumatoid synovial membrane.
- Therapies directed against the cellular immune response system alleviate symptoms and prevent disease progression in animal models of arthritis and human rheumatoid arthritis.

INTRODUCTION

The immune functions critical to the pathogenesis of rheumatoid arthritis (RA) continue to be debated. What are the roles of innate versus acquired immune responses? Which is dominant? Does RA require an antigen-specific immune response? If so, what antigens are involved? Are they exogenous (e.g., from pathogens) or autoantigens? Alternatively, does RA result from activation of the immune system by stimuli unrelated to the joint and is inflammation maintained by nonspecific mechanisms that can produce proinflammatory cytokines, such as the antigen-independent interactions between activated T cells and synoviocytes? Given that immune responses to foreign antigens or autoantigens do not usually give rise to chronic unresolved inflammation, is the defect in RA a failure to regulate immune responses that would normally be manageable? Such failures could reflect imbalances in cytokines or lack of an adequate response by regulatory T or B cells.

These questions will be considered in this chapter. Animal models of RA will be used to illustrate the processes that can give rise to joint inflammation and destruction. Note, however, that “rodents don’t get RA”; that is, observations in animal models need validation in human disease.

POSSIBLE ANTIGENIC TARGETS OF THE IMMUNE RESPONSE IN RHEUMATOID ARTHRITIS

Much evidence suggests that a T cell–mediated immune response is critical to the pathogenesis of RA, but the antigen or antigens to which this response is generated remain unclear. Candidates include autoantigens, whether specific to the joint or more widely distributed, and foreign, pathogen-derived antigens (Box 92.1).

Autoantigens

RA has no “obvious” precipitant, such as a preceding specific infection. This, together with rheumatoid factors, the first autoantibody to be described, led to the assumption that the disease is autoimmune even though RA lacks tissue-specific autoimmune responses of the kind seen with diabetes and autoimmune thyroid disease. Rheumatoid factors, or antibodies to the Fc domains of IgG, cannot readily be linked to synovitis or cartilage destruction and commonly occur in chronic infections (e.g., endocarditis) without causing arthritis. Likewise, anti–citrullinated protein antibodies (ACPAs), which target posttranslationally modified (citrullinated) proteins, lack tissue specificity because such proteins are found at many sites outside joints. ACPAs are now generally measured with the use of artificial citrullinated cyclic peptides.

It is now very clear that “autoantibody-positive” RA is a different disease from “seronegative” RA. The latter lacks association with the HLA-DR shared epitope, nor is smoking implicated in the disease.¹ Therefore, when considering the pathogenesis of RA, careful distinction between findings in seropositive and seronegative disease should be made.

Joint components

Type II collagen

Arthritis is readily induced in rodents and primates by immunization with heterologous or homologous native type II collagen; such arthritis requires both collagen-specific B and T cells. Susceptibility depends on major histocompatibility complex (MHC) antigens, and the disease can be modulated by depleting specific T cells or inducing tolerance via the oral administration of type II collagen. Despite the attractiveness of the model, the importance of immune responses to type II collagen in RA remains unclear. Collagen-specific T and B cells can be isolated from some RA patients, especially if responses to glycosylated or other posttranslationally modified forms of type II collagen are examined.² Such cells may be more prevalent in synovial tissue but are not invariable, and attempts to induce oral tolerance to type II collagen did not produce consistent effects on RA activity. They might even arise secondary to joint destruction and exposure of otherwise cryptic epitopes in type II collagen to the immune system. Together, these findings do not strongly support type II collagen as the target autoantigen in RA. However, type II collagen can also be posttranslationally modified by citrullination; antibodies to citrullinated type II collagen are more frequent than those to unmodified collagen and highly correlated with ACPA titers,³ whereas citrullinated type II collagen induces more severe arthritis in rats than the native protein does. Thus, citrullinated type II collagen may be a true “target antigen” in RA.

Proteoglycans and chondrocyte proteins

Erosive arthritis, as well as spondylitis, develops in mice immunized with the human cartilage proteoglycan aggrecan, which suggests that this is a model of spondyloarthritis rather than RA. Other cartilage proteoglycan molecules, such as biglycan and decorin, could be targets in RA, and antibodies to a citrullinated biglycan peptide have been seen in patients in whom RA later developed. Human cartilage glycoprotein 39 (HCgp39) also induces arthritis in mice, and certain HCgp39-derived peptides bind strongly to the RA-associated HLA allele DRB1*0401. These peptides are recognized by T cells from some RA patients, but synovial HCgp39-specific T cells could not be identified in most DR4+ RA patients when using tetramers of HCgp39-derived peptide bound to DRB1*0401.⁴ Thus, the status of HCgp39 as a target antigen is unclear.

Proteins not restricted to the joint

If joint-specific constituents are not readily implicated as autoantigens in RA, more widely distributed antigens deserve consideration.

Glucose-6-phosphate isomerase

In the K/BxN mouse, arthritis occurs because of autoimmunity to a ubiquitous cellular antigen, glucose-6-phosphate isomerase (G6PI) (Box 92.2).⁵ This arthritis involves G6PI-specific T and B cells; even though disease can be transferred passively with antibody, it is transient when compared with what develops in the K/BxN mouse, which has autoreactive T cells. The pathogenic T cells are type 17 helper T (Th17) cells whose development requires certain gut bacteria.⁶ Even though G6PI is ubiquitous and not overexpressed in the joint, inflammation occurs mainly in the joint (and also the salivary glands). The autoreactive T cell drives the production of G6PI-specific autoantibodies, which can form immune complexes and activate synoviocytes and mast cells in a complement-dependent fashion.

BOX 92.1 CANDIDATE ANTIGENS THAT COULD DRIVE A PATHOGENIC IMMUNE RESPONSE IN RHEUMATOID ARTHRITIS**Autoantigens****Joint constituents**

Type II collagen
Proteoglycans
Human cartilage glycoprotein 39

Citrullinated proteins

Vimentin
Fibrinogen
 α -Enolase
Type II collagen

Ubiquitous proteins

Heat shock proteins
Glucose-6-phosphate isomerase

Foreign antigens

Bacteria
Viruses
Superantigens

BOX 92.2 SEQUENCE OF EVENTS IN THE DEVELOPMENT OF A MODEL OF EXPERIMENTAL ARTHRITIS CAUSED BY AUTOIMMUNE RECOGNITION OF A NORMAL CELLULAR ENZYME

1. A mouse T-cell receptor (termed KRN) was characterized that recognizes an experimental antigen (bovine ribonuclease) presented by the class II MHC antigen I-A^k.
2. I-A^k mice transgenic for the KRN T-cell receptor were produced (i.e., all their T cells express the same receptor); the mice were completely healthy.
3. In KRN T-cell receptor transgenic mice expressing a different class II MHC antigen (I-A^{B7}), an aggressive rheumatoid arthritis–like inflammatory arthritis developed (the “K/BxN” mouse).
4. Arthritis was produced because the KRN T-cell receptor can recognize a peptide from an autoantigen presented by I-A^{B7}—that is, “accidental” cross-reactivity of the T-cell receptor.
5. The autoantigen was identified as a ubiquitous cellular enzyme: G6PI.
6. Both antibody and T-cell responses to the autoantigen are required to produce arthritis (no disease occurs in B cell–deficient mice), and disease can be transferred with T cells or serum.
7. The arthritogenic T cells specific for G6PI make interleukin-17 and require gut flora to develop.

G6PI, glucose-6-phosphate isomerase; MHC, major histocompatibility complex.

Because the G6PI autoantibodies are clearly arthritogenic, the model suggests that RA need not require autoimmunity to a joint-specific antigen.

Citrullinated proteins

ACPAs are now recognized as a highly specific feature of RA. Citrullination is a posttranslational modification of a protein (deimination of arginine carried out by peptidylarginine deiminases [PADs]); such modifications are increasingly being recognized as targets of autoimmunity.⁷ Although most ACPA-positive patients are also rheumatoid factor positive, ACPAs have higher specificity for RA. Like rheumatoid factors, they can appear years before RA develops and are associated with erosive disease. ACPAs were first recognized as autoantibodies to keratin (which has many citrullines residues), but the relevant target of ACPAs in RA is still being debated. As noted earlier, immune responses to citrullinated type II collagen and biglycan are described, but responses to other citrullinated proteins unrelated to joints have also been examined, including vimentin, fibrinogen, aggrecan, heat shock proteins (hsps), and α -enolase.⁸ For α -enolase the immunodominant citrullinated peptide recognized is conserved in α -enolase from the bacterium *Porphyromonas gingivalis*, an etiologic agent of periodontitis, which is a condition common in patients with RA. Intriguingly, this bacterium uniquely possesses its own deiminase (i.e., a bacterial PAD). Enolases are common targets of the immune response to bacteria.

Because ACPAs are of high affinity and class switched, involvement of T cells in their generation can be assumed. T cells can recognize citrullinated peptides,⁹ although responses in RA patients were relatively weak and the particular antigen recognized varied from patient to patient. A shared epitope–containing HLA-DR allele was shown to bind a citrullinated peptide more strongly than the equivalent peptide containing arginine and to provoke an immune response (Fig. 92.1). If the unmodified peptide fails to bind strongly to the MHC in the thymus, T cells specific for that self-peptide will not be negatively selected and may later be available to recognize the citrullinated peptide that binds the MHC tightly—the citrulline residue confers binding to the MHC but does not need to contribute to what the

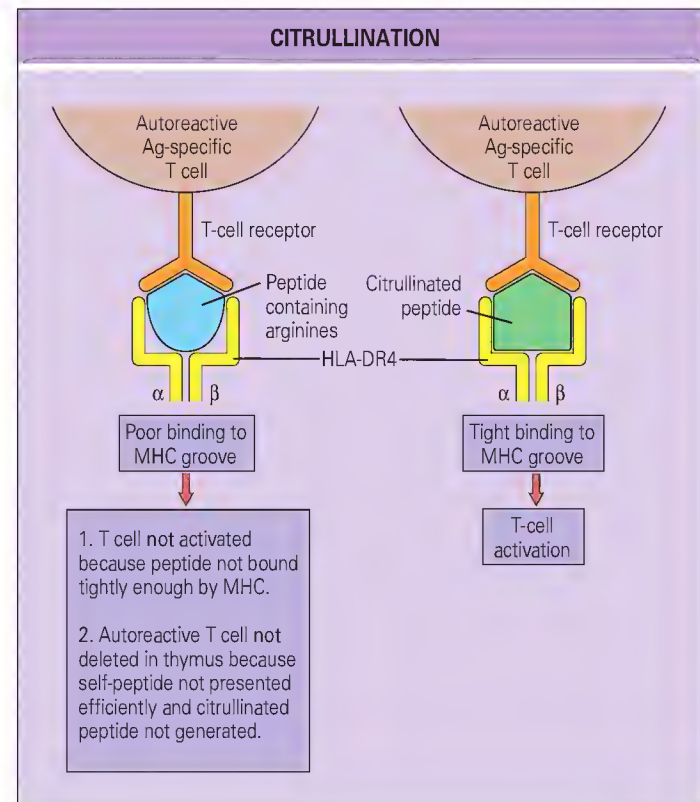


Fig. 92.1 A citrullinated self-peptide may bind tightly to class II major histocompatibility complex (MHC) alleles such as HLA-DR4 and can be presented to autoreactive T cells, whereas a weakly binding unmodified peptide would not occupy HLA-DR4 molecules long enough to stimulate autoreactive T cells. Likewise, the autoreactive T cells would not be not deleted centrally and would be released into the periphery if within the thymus only the weakly binding unmodified peptide were available for presentation and the citrullinated peptide were absent. Citrullination requires specific enzymes (peptidylarginine deaminases), which may not be available in the thymus. Ag, antigen.

T-cell receptor (TCR) “sees.” That tolerance can be broken in this way is illustrated by induction of arthritis in HLA-DR4 transgenic mice via citrullinated fibrinogen.¹⁰

Heat shock proteins

Hsps are ubiquitous cellular constituents; immune responses to an hsp (mycobacterial hsp60) were shown to cause adjuvant-induced arthritis in the rat. The amino acid sequences of hsps are highly conserved, so it was initially thought that bacterial hsp-specific T cells would cross-react with human hsp (see “Molecular Mimicry” later). However, more recent evidence suggests that self-hsp-specific T cells often *protect* against induction of arthritis.¹¹ Indeed, CD4+CD25+Foxp3+ regulatory cells may recognize self-hsp when being selected in the thymus.

Unidentified self-antigens

The SKG mouse, which has a mutation in the ZAP-70 signaling molecule downstream of the TCR, is unable to delete autoreactive T cells in the thymus, and therefore autoimmunity develops in this mouse, especially arthritis, with rheumatoid factors and antibodies to type II collagen.¹² The antigens recognized by T cells in this model are not known, but they make interleukin (IL)-17.¹³ Unlike the K/BxN mouse, disease is not transferable by serum; indeed, IL-6–deficient SKG mice have high titers of rheumatoid factor but no arthritis.

Summary

No autoantigen has been proved to be central to the pathogenesis of RA. Indeed, different joint antigens might be involved at various stages, perhaps through “epitope spreading,” in which autoimmune responses to one self-epitope are followed later by responses to separate epitopes in the same autoantigen or to other antigens in the same tissue. Some responses to autoantigens in RA may arise secondary to joint destruction and exposure of normally “hidden” antigens to the immune system (e.g., chondrocyte antigens).

Exogenous antigens

An infective etiology of RA has often been postulated, but no etiologic organism has been convincingly implicated.

Bacteria

Bacteria are attractive sources of putative RA-inducing antigens; mycobacterial and streptococcal antigens induce experimental inflammatory arthritis, as do organisms within the normal gut flora. Because RA does not exhibit the epidemiologic features of an infectious disease, a candidate etiologic agent should be ubiquitous and well tolerated by most of those infected. Disease would then occur only in those with susceptibility genes (e.g., *HLA-DR4*, *PTPN22*, *PADI4*) or additional environmental exposures (or both). Compare peptic ulcer disease and *Helicobacter* infection: even when many people carried *Helicobacter*, ulcer disease occurred mainly in smokers.

Reverse transcriptase polymerase chain reaction (RT-PCR), which amplifies conserved ribosomal RNA from all bacteria, has detected many bacterial rRNA sequences in RA synovium¹⁴ but no unique “RA-associated” organism. Instead, the presence of bacterial rRNA correlated with joint inflammation rather than a specific arthritis, whereas normal synovium was negative. This suggests that inflamed synovium receives bacteria (or bacterial nucleic acids), particularly from gut and skin commensals, that are probably brought to the joint within phagocytes because the inflamed synovium continuously recruits monocytes and dendritic cells. Although the organisms may be briefly viable (bacterial rRNA has a relatively short half-life), they do not replicate, and the joint remains sterile by conventional culture.

Such secondary “colonization” of inflamed synovium by bacteria could contribute to the pathogenesis of RA. Bacterial components are potent activators of the innate immune system and serve as adjuvants that allow adaptive T- and B-cell responses to be made. Such components include lipopolysaccharide, peptidoglycan, and bacterial DNA, all acting via Toll-like receptors (TLRs) to induce monokine secretion and upregulation of co-stimulatory molecules on antigen-presenting cells.¹⁵ Activation of antigen-presenting cells such as dendritic cells by bacterial DNA and other TLR ligands (i.e., an adjuvant function) might allow responses to self-antigens to be generated within the joint. Finally, given the findings regarding recognition of citrullinated α -enolase (see earlier), bacteria with α -enolases containing the same epitope as that found in *P. gingivalis* could contribute to joint inflammation on transport to the joint, particularly if tissue PAD enzymes could convert arginines in the bacterial α -enolase to citrullines.

Even though the possibility of bacteria as direct triggers of RA needs consideration, much attention is currently being paid to the critical role of commensal organisms, especially those of the gut, in shaping the immune system,¹⁶ particularly the generation of IL-17-producing cells.⁶ It remains possible that alterations in gut flora play a part in the pathogenesis of RA in this way, even if these organisms are not themselves recognized as antigens by the immune system.

Viruses

Several viruses cause joint inflammation (e.g., rubella, parvovirus B19, chikungunya); as with bacteria, PCR has been used to detect viruses in RA synovium with generally negative or inconsistent results. Herpesviruses such as Epstein-Barr virus (EBV) cause ubiquitous lifelong infection, thus making EBV an attractive candidate organism for RA. Abnormal immune responses to Epstein-Barr nuclear antigen-1 (EBNA-1) have been noted in RA. This antigen contains glycine-arginine repeats similar to those seen in several citrullinated autoantigens (e.g., keratin, fibrillarin). EBNA-1 can be citrullinated intracellularly and is then recognized by ACPAs from patients with RA.¹⁷ Expansions of EBV-specific T cells, particularly CD8+ T cells, have been identified in RA synovium, but this is not surprising because the joint is enriched with memory T cells, and those recognizing persistent viruses such as EBV and cytomegalovirus dominate the normal CD8+ T-cell repertoire. Thus, a role for EBV in the pathogenesis of RA remains unproven.

Molecular mimicry

Infectious agents have often been postulated to be involved in the pathogenesis of arthritis through “molecular mimicry” (i.e., foreign antigens “mimicking” joint autoantigens because of similarity in their amino acid sequences). In this way, immune responses correctly directed against components of a pathogen could cross-react with self-proteins and lead to autoimmunity. Molecular mimicry can be demonstrated by showing antibodies that bind to short linear peptides derived from a bacterial or viral protein and also to an autoantigen (Fig. 92.2a). Even though mimicry is also possible with regard to shared conformational epitopes (those not

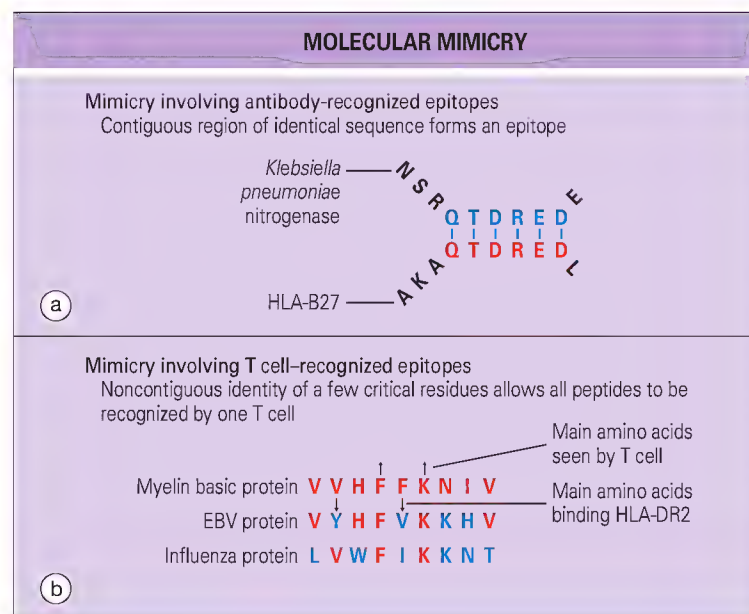


Fig. 92.2 Molecular mimicry of self-peptides by foreign peptides has different requirements for antibodies recognizing linear epitopes and for T-cell recognition. EBV, Epstein-Barr virus.

determined by simple similarity between linear peptides), this is not predictable from sequence data.

However, when molecular mimicry at a T-cell level is considered, the situation is more complex. T cells also recognize short linear peptides bound to the MHC, but only a small number of amino acids within a peptide are actually necessary for T-cell recognition: those that allow binding to the MHC and those that make contact with the TCR (see Fig. 92.2b). This means that two peptides with a very low level of overall sequence identity can both stimulate a given T cell provided that these critical residues are conserved; indeed, each TCR potentially recognizes many different peptides. For binding to the MHC there is a set of preferred amino acids, so the main determinants of specificity are the small number of amino acids that interact with the TCR, and these are not usually contiguous. Thus although searching protein databases for bacterial or viral peptides that share a high degree of sequence identity with a self-protein can reveal epitopes that are candidate mimics as far as antibody recognition of linear epitopes is concerned, for molecular mimicry at the T-cell level it is necessary to identify the critical MHC binding and TCR-interacting residues and then look for peptides that have these features, even if they have little overall sequence identity. In practice, almost all T cell-recognized epitopes in pathogens will have a potential “mimic” within some self-protein; that is, potential molecular mimicry is something with which the immune system deals routinely. In many cases the mimicking self-peptide is never presented to the immune system because antigen processing does not generate the cross-reactive self-peptide. If the self-peptide is generated by processing, both thymic and peripheral tolerance mechanisms will normally ensure that it is not recognized in either the self-protein or the mimicking pathogen. Thus, despite its obvious attraction as an explanation for autoimmunity, the idea of molecular mimicry lacks experimental support.¹⁸

Summary

Several potential mechanisms implicating infectious agents in the etiology of RA have been proposed, but none has been proved. The full implications of the traffic of phagocyte-associated bacteria or bacterial components to the inflamed synovium have yet to be explored, whereas the role of gut flora in shaping the immune system is an area in which knowledge is developing rapidly.

ANTIGEN-INDEPENDENT EFFECTS OF T CELLS IN RHEUMATOID ARTHRITIS

The most abundant cytokines in the joint that correlate with cartilage and joint destruction are the monokines tumor necrosis factor- α (TNF- α) and IL-1. Transgenic overexpression of TNF- α produces synovitis in mice, as does absence of the natural inhibitor of IL-1, IL-1 receptor antagonist. In RA, unlike these experimental transgenic systems, monokine production is

unlikely to be autonomous, at least in early synovitis, and is considered to be under T-cell control. However, T cells drive monokine production by antigen-presenting cells without necessarily recognizing specific antigens. Activated T cells (CD69+HLA-DR+) from synovium (see later) elicit monokine production from monocyte/macrophages and also interact with fibroblast-like synoviocytes to induce the production of metalloproteinases. The mechanisms underlying these effects remain unclear, but they require contact with T-cell membranes, either intact cells, membrane preparations, or microparticles shed by T cells.¹⁹ T cells may acquire this capacity as a result of the cytokine environment within the joint, because *in vitro* treatment with various “cocktails” of cytokines (e.g., IL-2, IL-6, and TNF- α) produces T cells capable of stimulating monokine production by monocytes or synoviocytes.²⁰ Many of these cytokines are present in the RA joint and might therefore contribute to antigen-independent activation of T cells. T cells eluted from RA synovial membrane have properties similar to those activated *in vitro* by cytokines in terms of their ability to induce TNF- α production by monocytes. Interestingly, the signaling pathways induced in monocytes by T cells activated via their TCR or via cytokines differ; nuclear factor κ B (NF- κ B) is critical to the latter, whereas phosphatidylinositol 3'-kinase (PI3-K) is required for the effects of TCR-stimulated T cells. The future introduction of PI3-K inhibitors to RA treatment might shed light on whether cytokine-activated or antigen-activated T cells are important in RA.

PROPERTIES OF SYNOVIAL T CELLS IN RHEUMATOID ARTHRITIS

Leaving to one side what activates T cells in RA (antigen vs. cytokines), clues to the pathogenesis of RA could come from examining different aspects of their phenotype in RA, especially at sites of disease. The features examined include TCR expression, activation and differentiation marker expression, and cytokine production.

T-cell receptor studies in rheumatoid arthritis

The use of TCR genes by peripheral blood or synovial T cells has been studied to determine whether patients with RA possess a disease-specific population of T cells that express identical or related receptors. The TCR is made up of two chains, α and β (or γ and δ), and rearrangement of the TCR genes (V, D, and/or J genes), plus nucleotide insertions or deletions in each case, produces unique α and β chains and hence a unique $\alpha\beta$ or $\gamma\delta$ TCR. Random recruitment of T cells to the joint would produce a population expressing many different TCRs, whereas recruitment of T cells all recognizing a small number of peptide epitopes would result in overrepresentation of identical or related TCRs (i.e., an oligoclonal rather than a polyclonal T-cell population). In experimental autoimmune diseases, autoantigen-specific T cells are often oligoclonal, but no oligoclonal expansions of T cells with the same or related CDR3 sequences has been reported in RA (discounting early studies, which probably detected expansions produced *in vitro*). However, the advent of next-generation sequencing allows a much more thorough examination of this question by sequencing many thousands of TCRs from synovium or blood, thereby producing greater power to detect small expansions of particular or related TCRs. A recent study showed expansions of several clones in synovium, especially in early disease; the same clones were seen in different joints of the same patient.²¹ This suggests that recognition of specific peptides is a feature of at least the early pathogenesis of RA.

Studies of the surface phenotype of lymphocytes in rheumatoid arthritis

The RA joint contains both natural killer (NK) cells and T cells. Synovial NK cells are CD56bright and CD16⁺,²² a subset that secretes cytokines, especially interferon- γ (IFN- γ), rather than mediating cytotoxicity. The role of NK cells in RA has not yet been clarified; effects on monocytes, fibroblasts, and osteoclasts could contribute to the inflammation and joint destruction, whereas IFN- γ production would decrease Th17 cell differentiation and could modulate IL-17-driven inflammation (see later).

Within the T-cell population, memory T cells predominate and are particularly highly differentiated; they have very low levels of expression of CD45RB, similar to those seen *in vitro* after T cells have undergone several rounds of division, and shorter telomeres, also reflecting increased numbers of divisions,²³ possibly exacerbated by a deficiency in telomerase (the enzyme that can maintain telomere length).²⁴ Such “end-stage” cells should undergo apoptosis, but synovial T cells are protected by factors within the synovial environment, including type I interferons and IL-15 produced by

synovial macrophages and fibroblasts.²⁵ CD4+ T cells that have lost expression of CD28 also resist apoptosis, and CD28⁻ cells are enriched in synovium and may be pathogenic because they are autoreactive, produce IFN- γ , and may be cytolytic.²⁶ Memory T cells are recruited to the synovium as a result of expression of adhesion molecules and are retained there through the actions of chemokines. Unusually, memory T cells in synovium continue to express CXCR4, which is normally lost during differentiation, and remain responsive to its ligand CXCL12 (SDF-1) produced by synovial fibroblasts.²⁷ This results in their retention within the tissue, where they may exert the antigen-independent effects noted earlier and induce synoviocytes to produce monokines and matrix metalloproteinases.

Cytokine production in rheumatoid arthritis

Initial studies of the cytokines produced by synovial T cells were surprising, particularly within the prevailing paradigm of the two major T-cell subsets: type 1 helper T (Th1) cells (proinflammatory and producing IFN- γ , lymphotoxin, and IL-2) and Th2 cells (allergy related and producing IL-4, IL-5, IL-10, and IL-13). RA was expected to be driven by Th1 cells, but IFN- γ concentrations in synovial fluid were very low in comparison to IL-1 and TNF- α , and IFN- γ +CD4+ T cells, detected by intracellular staining, were present only in small numbers. Interestingly, a similarly low proportion of IFN- γ -secreting T cells is seen in murine collagen-induced arthritis, a model that is completely T cell dependent. IL-4+ cells were also absent from the synovial T-cell population in established RA, although investigation of very early arthritis has shown that IL-4 and IL-13 (and IL-17) can be present and predict progression to established RA²⁸; these cytokines were not present at later time points. These puzzling observations have been clarified by the discovery of additional T-cell subsets, particularly Th17 cells. IL-17, unlike IFN- γ , is essential for collagen-induced arthritis²⁹; in fact, absence of IFN- γ exacerbates the disease. Th17 cells have also been clearly implicated in the K/BxN⁶ and SKG¹³ murine models of RA.

IL-17 is a particularly attractive candidate as a T cell–dependent arthritogenic cytokine. It shares some properties of IL-1 and TNF- α , including induction of cartilage degradation, and synergizes with these cytokines. It is also relevant to the erosive bone destruction of RA because it induces the expression of receptor activator of NF- κ B ligand (RANKL) by osteoblasts; RANKL is critical for the differentiation of osteoclasts.³⁰ IL-17 levels in joints and the proportion of Th17 cells in joints and peripheral blood are elevated in RA, and trials of IL-17–blocking antibodies have shown efficacy.³¹

If Th17 cells are indeed central to the pathogenesis of RA, factors that influence their generation become important. Initial studies involving mice implicated transforming growth factor- β (TGF- β) and IL-6 in their differentiation, with a role for IL-23 only in survival and expansion. More recent work, again murine, has shown that IL-23 + IL-6 + IL-1 not only allows differentiation of Th17 cells in the absence of TGF- β but also generates a different kind of Th17 cell with more proinflammatory properties than those generated with TGF- β .³² The pathogenicity of the subset has been linked to the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), although these observations were not made in an arthritis model. Nevertheless, the complete resistance to collagen-induced arthritis seen in mice unable to produce IL-23 suggests that the “more proinflammatory” Th17 subset is also needed for arthritis. IL-23 is made by dendritic cells and macrophages in response to TLR agonists, which also stimulate secretion of the Th1-driving (and Th17-inhibiting) cytokine IL-12. Thus, genetic and environmental influences on dendritic cells that alter the proportions of IL-12 and IL-23 produced may in turn affect the pathogenesis of RA.

Even though these lines of evidence emphasize the importance of IL-17–producing cells in arthritis, such cells are not present in large numbers in either blood or synovial fluid—usually a small percentage of the CD4+ T-cell population. This may relate to the relative plasticity of the Th17 subset, with loss of IL-17 production and substitution of secretion of GM-CSF or IFN- γ (or both), a process that may also require IL-23.³³ Such “ex-Th17” cells may contribute significantly to pathogenesis (Fig. 92.3).

REGULATORY T CELLS IN RHEUMATOID ARTHRITIS

Not all T cells within the joint are necessarily pathogenic; regulatory T-cell (Treg) subsets are known to protect against autoimmune disease, so some synovial CD4+ T cells could be beneficial, though obviously inadequate to stop arthritis. Tregs in peripheral blood³⁴ are CD4+CD25hi, express a transcription factor (Foxp3) that is critical to regulatory function, and suppress proliferation and cytokine production in a contact-dependent manner (Table 92.1). Two forms of Foxp3+ Tregs are recognized: those that develop

DIFFERENT EFFECTOR CELLS DIFFERENTIATE FROM NAIVE T CELLS

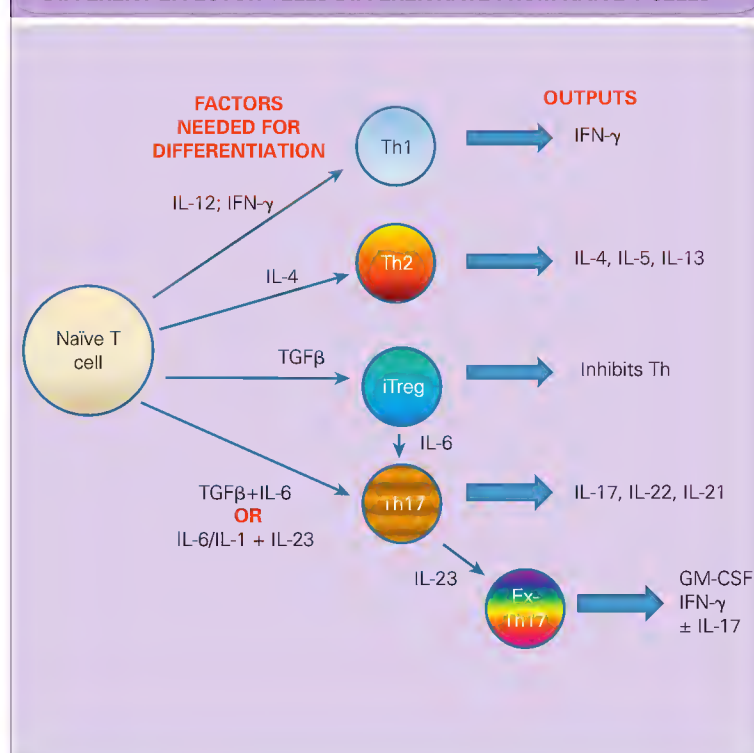


Fig. 92.3 Under the influence of cytokines, different effector cells differentiate from naive T cells and express transcription factors (not shown) that determine their function—cytokine secretion or inhibition of helper T-cell proliferation and cytokine production in the case of induced regulatory T cells (iTregs). Plasticity and interconversion of T-cell subsets are illustrated; for example, iTregs to Th17 and Th17 to “ex-Th17” with changes in effector function. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon- γ ; IL-2, interleukin-2; TGF- β , transforming growth factor- β ; Th1, type 1 helper T cell.

within the thymus (natural Tregs) and those generated in the periphery (induced Tregs), mainly through the actions of TGF- β . Mutations in the *FOXP3* gene cause severe spontaneous inflammatory and autoimmune disease in mice and humans. A relationship between Th17 and Tregs has been suggested because TGF- β can be involved in the generation of both subsets but IL-6 favors Th17 generation over Tregs.³⁵ Thus, an inflammatory environment containing IL-6 would enhance the generation of Th17 cells and increase inflammation while decreasing the generation of Tregs; these mechanisms might account for the efficacy of IL-6 blockade in RA.

Like synovial T cells, Tregs proliferate poorly *in vitro* and commonly produce IL-10, although this is not required for their regulatory function. Distinguishing Tregs in synovial fluid is difficult because activated human T cells (unlike their murine counterparts) express Foxp3. Increased numbers of CD4+CD25+ cells have been reported in synovial fluid, and they express other markers associated with Tregs (CTLA-4 and GITR), although again these markers appear on activated T cells.³⁶ They show regulatory function in *in vitro* assays, but it is unclear whether they are natural or induced Tregs. Other studies have suggested a functional defect in peripheral blood Treg

TABLE 92.1

Properties of human effector and regulatory CD4+ T cells

	Regulatory CD4+ T cells	Effector CD4+ T cells
CD25 expression	Constitutively high level	Only on activation
CTLA-4 expression	High, constitutive	Late, after activation
Responses to mitogens and anti-CD3	Poor	Vigorous
Foxp3 expression	Positive	Negative, except on activation
Typical cytokines	IL-10, TGF- β	IL-2, IFN- γ , IL-4, IL-17
Thymus dependent	Yes	Yes
Specificity	Self-peptides on class II MHC	Non-self-peptides on class II MHC
Affinity for self-antigens	Moderate	Low

IFN- γ , interferon- γ ; IL-10, interleukin-10; MHC, major histocompatibility complex; TGF- β , transforming growth factor- β .

function in RA, which was reversed by treatment with anti-TNF- α (specifically, infliximab). This was due to the appearance of induced Tregs mediating suppression through IL-10 and TGF- β production rather than by the contact-dependent mechanism used by natural Tregs.³⁷ Thus, within the joint, both pathogenic proinflammatory T cells and Treg populations (natural or induced) coexist. Their proportions may vary in different phases of disease and in response to different treatments and thereby influence activity and progression of disease. Measures to manipulate Treg function and hence ameliorate disease are under investigation but carry potential risks in view of the close relationship between Tregs and the Th17 subset. Tregs generated *in vitro* and transferred to decrease inflammation might differentiate into Th17 cells *in vivo* in a proinflammatory cytokine milieu³⁸ and instead exacerbate disease.

CONCLUSION

T cell-mediated immune responses are strongly implicated in the pathogenesis of RA both by the association of disease with HLA-DR and by the presence and properties of T cells in the synovium.

Whether the critical immune response in RA is directed against autoantigens or exogenous antigens is still unclear. Experimental models of arthritis show that immune responses to ubiquitous self-antigens and those expressed preferentially in the joint can both drive arthritis.

Synovial T cells are mainly highly differentiated memory cells and reflect recruitment to the joint and factors in the synovium that inhibit apoptosis. While activated, they make little IL-2 or IFN- γ ; instead, the proinflammatory cytokine IL-17 is produced, which synergizes with IL-1 or TNF- α to destroy cartilage and bone.

Cytokines produced by macrophage-like synoviocytes, especially TNF- α , IL-1, and IL-6, dominate the RA synovium. Their production could be stimulated either by antigen-specific T cells or by T cells activated in an antigen-independent fashion by cytokines through receptors other than the TCR.

The synovium also contains Tregs that turn off the proinflammatory T cell-mediated responses; persistence of RA may represent a failure of this mechanism.

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93

Angiogenesis and vasculogenesis in rheumatoid arthritis

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- Angiogenesis is the formation of new capillaries from preexisting vessels, whereas vasculogenesis is the generation of vessels from endothelial progenitor cells.
- The perpetuation of angiogenesis involving numerous soluble and cell surface-bound mediators has been associated with rheumatoid arthritis.
- Angiogenic mediators include growth factors, primarily vascular endothelial growth factor (VEGF), as well as proinflammatory cytokines, various chemokines, matrix components, cell adhesion molecules, proteases, and others.
- Among the several potential angiogenesis inhibitors, targeting of VEGF, hypoxia-inducible factor-1, angiogenic chemokines, tumor necrosis factor- α , and $\alpha_v\beta_3$ integrin may attenuate the action of angiogenic mediators and thus synovial angiogenesis.
- Vasculogenesis and the function of endothelial progenitor cells are impaired in rheumatoid arthritis but can be restored by the control of synovial inflammation.

INTRODUCTION

The formation of new capillaries from preexisting vessels, termed *angiogenesis*, is a key event underlying synovial inflammation, which perpetuates the recruitment of leukocytes into the synovium in rheumatoid arthritis (RA).¹⁻⁵ On the other hand, new vessel formation from endothelial progenitor cells (EPCs), termed *vasculogenesis*, is impaired in the inflammatory arthritides.⁶⁻⁸ This chapter reviews current issues regarding angiogenesis and vasculogenesis, the angiogenic process, its mediators and inhibitors, the most important regulatory networks, and finally the clinical relevance of angiogenesis and vasculogenesis in RA.

THE ANGIOGENIC PROCESS

Synovial angiogenesis consists of a cascade of multiple events. New capillaries develop from existing blood vessels. First, angiogenic mediators (described later) activate endothelial cells. This is associated with the production of proteases that degrade the basement membrane of the endothelium and the interstitium, thus enabling endothelial outgrowth. Migration of loose endothelial cells results in the formation of capillary sprouts. Endothelial cells in the midsection of the sprout undergo mitosis, whereas others at the tip of the sprout migrate only and do not proliferate. This step is followed by lumen formation within the sprout. Two sprouts then anastomose with each other to form capillary loops. New basement membrane is then synthesized. The continuous emigration of endothelial cells results in the development of second and further generations of new vessels. The outcome of angiogenesis is based on the imbalance between angiogenic mediators and angiostatic factors^{1,2,5,9,10} (Fig. 93.1 and Table 93.1).

Mediators of angiogenesis in rheumatoid arthritis

Several cytokines, growth factors, chemokines and their receptors, and certain cell adhesion molecules (CAMs), as well as other mediators, can modulate neovascularization in inflammation^{1-5,8} (see Table 93.1 and Fig. 93.1).

Among *growth factors*, vascular endothelial growth factor (VEGF) is of outstanding importance. VEGF directly induces angiogenesis and is also a

part of the hypoxia-hypoxia-inducible factor (HIF)-VEGF-angiopoietin (Ang) network discussed later in more detail. Among the isoforms VEGF-A to VEGF-E, VEGF-A may be the major regulator of angiogenesis. Other angiogenic mediators, such as interleukin-6 (IL-6), IL-17, IL-18, nitric oxide (NO), monocyte/macrophage migration inhibitory factor (MIF), endothelin 1 (ET-1), and others, may also act via VEGF-dependent or, in some, VEGF-independent mechanisms.^{2,11,12} Placenta growth factor (PlGF) is a member of the VEGF family, and this mediator also binds to the Flt-1/type 1 VEGF receptor (VEGFR1). PlGF is expressed abundantly in arthritic synovial tissue. Other growth factors, including fibroblast (FGF-1 and FGF-2), epidermal (EGF), hepatocyte (HGF), keratinocyte (KGF), insulin-like (IGF-1), connective tissue (CTGF), platelet-derived (PDGF), and transforming (TGF- β) growth factors, have been implicated in synovial angiogenesis. Many of these growth factors are bound to heparin and heparan sulfate proteoglycans in the synovial extracellular matrix (ECM), and they are mobilized by proteases during neovascularization.^{1-5,8}

Proinflammatory cytokines may exert direct angiogenic activity or may act indirectly via VEGF-dependent pathways. Among these mediators, tumor necrosis factor- α (TNF- α), IL-1, IL-6, IL-15, IL-17, IL-18, oncostatin M, MIF, and granulocyte (G-CSF) and granulocyte-macrophage (GM-CSF) colony-stimulating factors have been associated with synovial angiogenesis.^{2,5,13,14}

Numerous *chemokines* and *chemokine receptors* have been implicated in the angiogenesis underlying RA. The angiogenic nature of most CXC chemokines has been associated with the glutamyl-leucyl-arginyl (ELR) amino acid motif within their structure. The most relevant ELR-containing CXC chemokines that mediate angiogenesis include CXCL1 (GRO α), CXCL5 (ENA-78), CXCL7 (CTAP-III), and CXCL8 (IL-8).^{8,15-17} In contrast, ELR-lacking CXCL4 (PF4), CXCL9 (MIG), and CXCL10 (IP-10) inhibit angiogenesis. Some authors suggest that the effect of VEGF on endothelial cells may, in part, be mediated by CXCL10.¹⁸ CXCL12 (SDF-1) may play a significant role in RA-associated angiogenesis and synovial lymphoid neogenesis despite the fact that this chemokine lacks the ELR motif. Among CC chemokines, CCL2 (MCP-1) may induce endothelial cell chemotaxis *in vitro* and angiogenesis *in vivo*. CCL23 has been implicated in the migration of vascular endothelial cells and angiogenesis-associated matrix metalloproteinase (MMP) production. CX₃CL1 (fractalkine) is involved in both the angiogenesis and atherosclerosis underlying inflammatory rheumatic diseases. Among chemokine receptors, CXCR2 may be the most relevant one to ELR-containing angiogenic CXC chemokines, such as CXCL1, CXCL5, and CXCL8, on endothelial cells. CCR2-CCL2 and CCR7-CCL21 interactions are also involved in synovial neovascularization.^{18,19}

Several *ECM components*, *CAM*, and *proteases* have been implicated in the adhesive and angiogenic processes in RA. Type I collagen, fibronectin, laminin, vitronectin, tenascin, and proteoglycans mediate whereas thrombospondin-1 (TSP-1) inhibits endothelial cell adhesion and neovascularization. As described earlier, some growth factors bind to proteoglycans during angiogenesis. Among CAMs, most β_1 and β_3 integrins, E-selectin, the L-selectin ligand CD34, selectin-related glycoconjugates (including Lewis^x/H and MUC18), vascular cell adhesion molecule-1 (VCAM-1), platelet-endothelial cell adhesion molecule-1 (PECAM-1, CD31), endoglin, and junctional cell adhesion molecule A (JAM-A) and JAM-C are expressed on the endothelial surface and promote angiogenesis. $\alpha_v\beta_3$ Integrin seems to be of significant importance because this CAM is involved in osteoclast activation and subsequent development of erosions, as well as in synovial angiogenesis in RA. Focal adhesion kinases (FAKs) are involved in $\alpha_v\beta_3$ integrin signaling. FAKs have been detected in RA synovium, thus suggesting their role in synovial inflammation and angiogenesis. Other angiogenic factors, such as chemokines, may act via integrin-dependent pathways. MMPs, ADAM, and ADAMTS proteases digest the ECM, release growth

Fig. 93.1 Rheumatoid arthritis (RA) is associated with an abundance of angiogenic over angiostatic factors. Only the most important mediators and compounds are presented. DMARDs, disease-modifying antirheumatic drugs; ELR, glutamyl-leucyl-arginyl; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor.

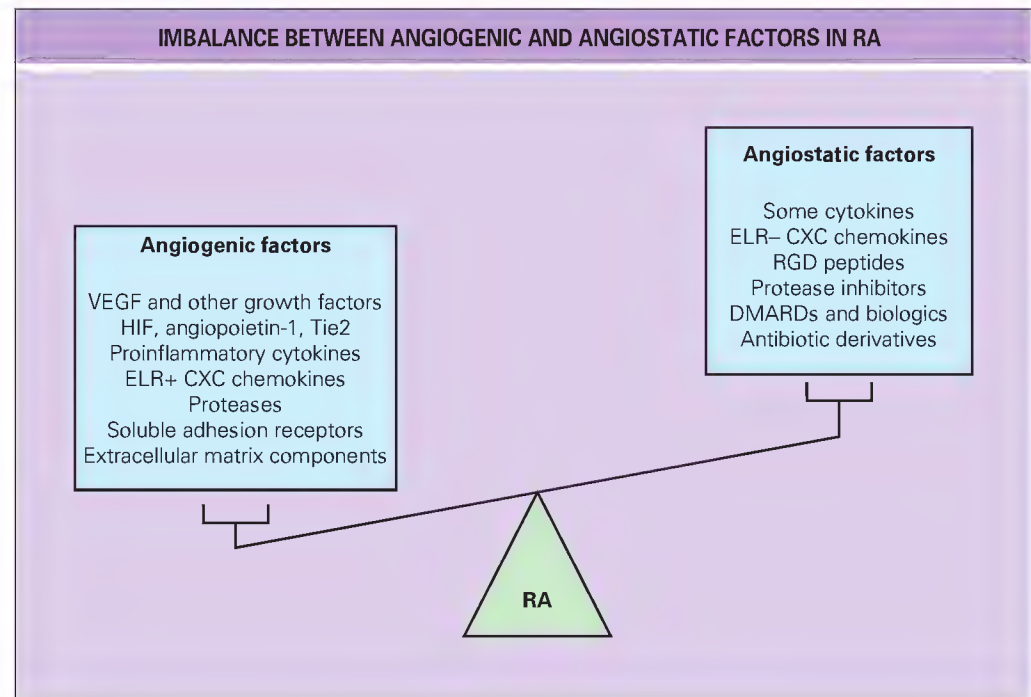


TABLE 93.1
Some angiogenic and angiostatic factors in rheumatoid arthritis*

	Mediators	Inhibitors
Chemokines	CXCL1, CXCL5, CXCL7, CXCL8, CXCL12, CCL2, CCL21, CCL23, CX3CL1	CXCL4, CXCL9, CXCL10, CCL21
Matrix molecules	Type I collagen, fibronectin, laminin, heparin, heparan sulfate	Thrombospondin, RGD sequence
Cell adhesion molecules	β_1 and β_3 integrins, E-selectin, P-selectin, CD34, VCAM-1, endoglin, PECAM-1, VE-cadherin, Le ^x /H, MUC18	RGD sequence (integrin ligand)
Growth factors	VEGF, bFGF, aFGF, PDGF, EGF, IGF-1, HIF-1, TGF- $\beta^{\dagger}$	TGF- $\beta^{\dagger}$
Cytokines	TNF- α , IL-6, [†] IL-15, IL-18	IL-4, IL-6, [†] IFN- α , IFN- γ
Proteases	MMPs, plasminogen activators	TIMPs, plasminogen activator inhibitors
Others	Angiogenin, substance P, prolactin	Disease-modifying antirheumatic drugs, infliximab, etanercept, angiostatin, endostatin

*See text for abbreviations.

[†]Mediators with both proinflammatory and antiangiogenic effects.

factors and other angiogenic mediators, and thus promote inflammatory neovascularization.^{2,9,10,20-23}

Additional *angiogenic factors* relevant to RA include, without mentioning further details, serum amyloid A (SAA), ET-1, members of the cyclooxygenase-2 (COX-2)–prostaglandin E₂ network, angiogenin, angiotropin, pleiotrophin, platelet-activating factor (PAF), substance P, erythropoietin, adenosine, histamine, prolactin, thrombin, sphingosine-1-phosphate (S1P), and possibly many others.^{1-4,8,12}

Vasculogenesis in arthritis

EPCs are hematopoietic stem cells that express, among other antigens, CD34, CD133, type 2 VEGF receptor (Flk-1/VEGFR2), and the CXCR4 chemokine receptor. During vasculogenesis, EPCs differentiate into mature endothelial cells. Defective vasculogenesis as a result of impaired EPC numbers and function has been described in RA. Effective control of inflammation with corticosteroids and anti-TNF agents may stimulate EPCs and thus restore vasculogenesis. In addition, induction of vasculogenesis may also suppress premature atherosclerosis in RA.⁶⁻⁸

Regulatory networks in synovial angiogenesis

The *hypoxia-HIF-VEGF-Ang/Tie* system seems to be of outstanding importance in RA-associated angiogenesis (Fig. 93.2). VEGF is induced by

hypoxia and HIFs (HIF-1 and HIF-2) in RA. Significant hypoxia is characteristic of RA joints, and a stimulatory effect of hypoxia on the angiogenic drive of RA synovial fibroblasts has been demonstrated. Low oxygen tension in the joint has been associated with disease activity and increased expression of angiogenic VEGF. Hypoxia enables the outgrowth of immature, unstable vessels. HIFs are master regulators of the adaptive responses to hypoxia. HIF is a heterodimeric transcription factor composed of HIF- α and HIF- β . Among the three known HIF- α subunits, HIF-1 α and HIF-2 α are able to dimerize with HIF-1 β and thus bind to hypoxia-response elements (HREs). VEGF is a target gene for HIFs, and its gene contains HREs. High oxygen tension leads to hydroxylation and thus degradation of HIF- α , whereas hypoxia inhibits HIF hydroxylation, thereby allowing stabilization of HIF-1 α , dimerization with HIF-1 β , and initiation of the transcription of genes containing HREs (see Fig. 93.2). Both HIF-1 α and HIF-2 α are strongly expressed in RA synovium. However, hypoxia may also act via HIF-independent regulatory pathways, including the peroxisome proliferator-activated receptors (PPARs). The Ang1/Tie2 complex interacts with VEGF during the stabilization of newly formed blood vessels. In contrast, Ang2, an antagonist of Ang1, inhibits vessel maturation. Both Ang1 and Tie2, as well as VEGF, have been detected in RA synovium even in very early phases of the disease. Toll-like receptors such as TLR2 may also induce VEGF-dependent angiogenesis, and this is mediated through Tie2 signaling in RA. Survivin, an inhibitor of apoptosis, is likewise involved in VEGF-dependent angiogenesis. Hypoxia also stimulates the production of

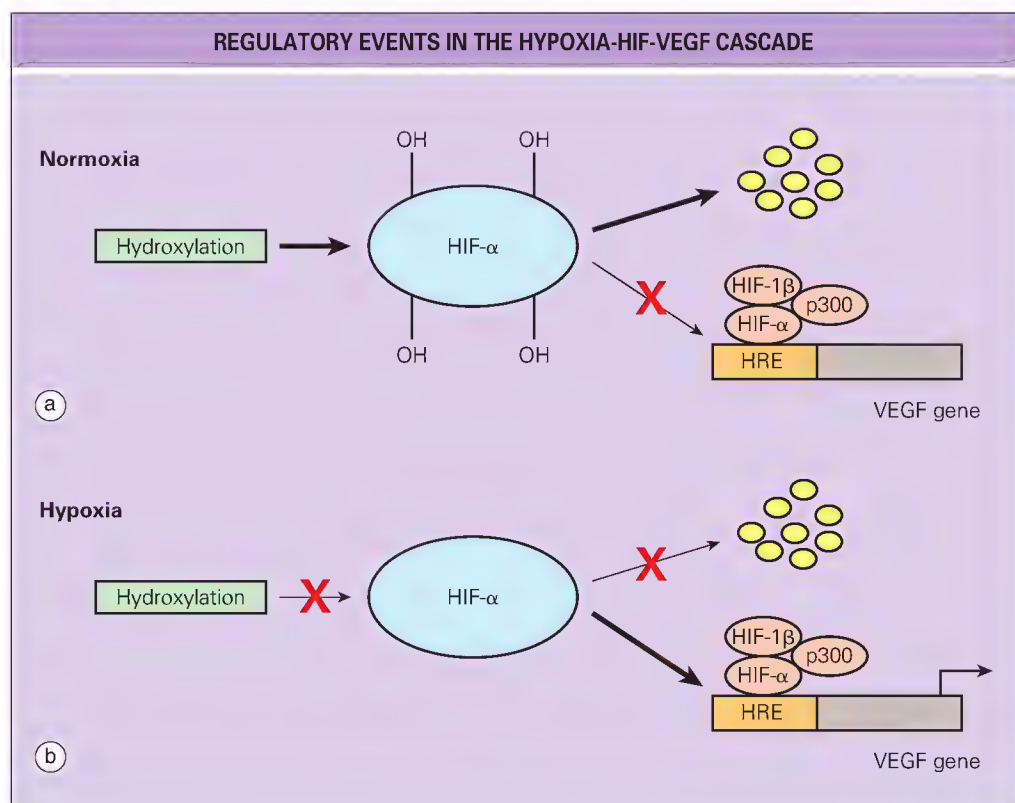


Fig. 93.2 In a normoxic state, hypoxia inducible factor- α (HIF- α) is heavily hydroxylated, which leads to destabilization and degradation of HIF. In cases of hypoxia, HIF- α is dehydroxylated, translocates to the nucleus, and binds to HIF-1 β and the coactivator p300. This will result in binding of the HIF complex to hypoxia responsive elements (HREs) found in the gene for vascular endothelial growth factor (VEGF) and other angiogenic mediators.

CXCL12, a major angiogenic chemokine described earlier, by RA synovial fibroblasts.^{2,11,12,19,24-26}

Perspectives of angiogenesis targeting and restoration of vasculogenesis in arthritis

Angiogenesis can be inhibited by either blocking the action of angiogenic mediators or by using angiostatic compounds^{2,11,12,27,28} (see Table 93.1 and Fig. 93.1). Currently used antirheumatic agents such as rofecoxib, dexamethasone, chloroquine, sulfasalazine, methotrexate, azathioprine, cyclophosphamide, leflunomide, thalidomide, tacrolimus, minocycline, and anti-TNF biologics, apart from other important antiinflammatory effects, nonspecifically suppress angiogenesis, including VEGF and Ang1/Tie2.^{2,27,28}

VEGF inhibitors have been tried in patients with arthritis, as well as in cancer studies. These inhibitors may include antibodies to VEGF or VEGFRs, soluble VEGFR constructs, small-molecule VEGF and VEGFR inhibitors, or inhibitors of VEGF and VEGFR signaling. The VEGF tyrosine kinase inhibitor vatalanib (PTK787) and an anti-VEGFR1 antibody exerted significant angiostatic and antiarthritic effects in animal models of arthritis. A soluble VEGFR1 chimeric protein inhibited synovial endothelial proliferation. Soluble Fas ligand (sFasL, CD178) is a functional inhibitor of the 165-amino acid form of VEGF (VEGF165), and it inhibited angiogenesis in arthritis.^{2,4,11,12,27,28}

The involvement of PPARs in hypoxia-induced VEGF production was discussed earlier. The PPAR- γ ligands rosiglitazone and pioglitazone inhibited VEGF-induced angiogenesis.² HIFs may also be targeted in arthritis. For example, YC-1, a superoxide-sensitive stimulator of soluble guanylyl cyclase and an HIF-1 inhibitor, may potentially be used to suppress inflammatory angiogenesis.^{25,27} The benzophenone analogue BP-1, an HIF-1 α inhibitor, ameliorated adjuvant-induced arthritis (AIA) in rats. HIF-1 signaling has also been targeted in inflammatory bowel disease.^{2,25,27} As far as the Ang1/Tie2 system is concerned, a soluble Tie2 receptor transcript delivered via an adenoviral vector to mice attenuated the incidence and severity of collagen-induced arthritis (CIA).^{2,27} Very recently, an Ang2-targeting peptide was genetically fused to the anti-TNF antibody adalimumab. This novel bispecific antibody enhanced the efficacy of anti-TNF.²⁹

Regarding the targeting of other growth factors, imatinib mesylate, an inhibitor of PDGF receptor activation, inhibited synovial pannus formation in murine CIA. An anti-Flt-1/VEGFR1 hexapeptide, GNQWFI abrogated PlGF-induced angiogenesis, cytokine production, and the development of CIA in mice.^{2,27}

The anticytokine therapy currently used to treat arthritides may also influence angiogenesis. For example, TNF- α blockade by infliximab reduced

VEGF expression and vascularity in RA synovium. Infliximab also reduced synovial Ang1 and Tie2 expression. The anti-IL-6 receptor antibody tocilizumab also decreased serum levels of VEGF in RA.^{2,12,13}

The role of proteases in angiogenesis was described earlier. Numerous protease inhibitors, including tissue inhibitors of metalloproteinases (TIMPs) and plasminogen activator inhibitors (PAIs), which antagonize the effects of proteases, have been tried in angiogenesis models.^{2,27,30}

Antibiotic derivatives, including minocycline, fumagillin analogues, deoxyspergualin, roxithromycin, and clarithromycin, also inhibit the release of VEGF and other angiogenic mediators and thus neovascularization. The synthetic fumagillin derivatives TNP-470 and PPI-2458 inhibited VEGF and VEGF-dependent angiogenesis. Human RA trials have been conducted in which minocycline, roxithromycin, and clarithromycin were found to exert moderate, but significant clinical effects.^{1,2,27,28}

Among other inhibitors of angiogenic mediators, the ET-1 antagonists currently used for the treatment of pulmonary hypertension may also exert antiangiogenic effects.³¹ The microtubule destabilizer paclitaxel (Taxol), used in cancer therapy, also acts via HIF-1 α blockade. SIP is also angiogenic, and SIP inhibitors, such as fingolimod (FTY720), are in clinical trials for various autoimmune diseases. FTY720 also acts as an inhibitor of the FAKs described earlier. Chemical lead 2 (CL2, Edg-1) is a non-SIP analogue. CL2 inhibited tube formation in endothelial cultures, suppressed VEGF-induced angiogenesis, and attenuated arthritis in the CIA model.^{2,23,27,28} Very recently, peptides have been isolated from libraries of phages preferentially homing to the inflamed joints of AIA rats. Some of these peptides that bound to synovial endothelial cells were able to inhibit arthritis, as well as VEGF signaling and angiogenesis.²⁹

Recently, an emerging number of compounds in traditional Chinese and Korean medicine have been implicated in angiogenesis. Among these compounds, scopolin (a coumarin derivative found in *Erycibe obtusifolia* Benth), celastrol (an active ingredient of *Tripterygium wilfordii*, also known as the "Thunder God vine"), or fisetin (the active ingredient of *Rhus verniciflua* Stokes) may also have angiostatic effects in arthritis.²

Apart from inhibition of angiogenesis, endogenously produced angiostatic compounds, such as VEGF, HIFs, or $\alpha_v\beta_3$ integrin, also block the action of angiogenic mediators and thus indirectly suppress neovascularization. Some of these compounds have already been used in an attempt to target tumor- or inflammation-associated neovascularization. Angiostatic cytokines include interferon- α (IFN- α), IFN- γ , IL-4, IL-12, and leukemia inhibitory factor (LIF). These cytokines inhibit the release of VEGF and other angiogenic mediators. IL-4 and IL-13 gene transfer inhibited synovial angiogenesis in rats. Angiostatic CXC chemokines that lack the ELR motif include CXCL4 (PF4), CXCL9 (MIG), and CXCL10 (IP-10),¹⁸ CCL21 (SLC) is an

angiostatic CC chemokine that inhibits tumor progression. *Angiostatin* (a fragment of plasminogen), *endostatin* (a fragment of type XIII collagen), and their derivatives block $\alpha_v\beta_3$ integrin-dependent angiogenesis. *Type IV collagen derivatives*, including arrestin, canstatin, and tumstatin, also inhibit neovascularization. *2-Methoxyestradiol (2-ME)*, a natural metabolite of estrogen, inhibits angiogenesis by disrupting microtubules and by suppressing HIF-1 α activity.^{13,14,18,19,27,28}

As discussed earlier, corticosteroids and anti-TNF agents may stimulate EPCs and thus *restore vasculogenesis* in RA. The CXCL12 (SDF-1) inhibitor bicyclam (AMD3100) mobilized EPCs in mice. Because the number of EPCs correlates with improvement in the 28-joint disease activity score (DAS28) in RA, suppression of systemic inflammation and disease activity by any means would improve vasculogenesis.^{7,8}

SUMMARY

This chapter discussed the pathogenic role of angiogenesis and vasculogenesis in RA. A number of soluble and cell-bound factors may stimulate or inhibit angiogenesis. The outcome of such “angiogenic diseases” depends highly on the imbalance between angiogenic and angiostatic mediators. Impaired EPC function and vasculogenesis have been associated with RA. Several attempts have been made to therapeutically interfere with the cellular and molecular mechanisms described in this chapter. Specific targeting of abundant synovial angiogenesis, as well as restoration of defective vasculogenesis, may be useful for the future management of RA.

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94

The rheumatoid joint: synovitis and tissue destruction

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- Synovial tissue in joints with rheumatoid arthritis (RA) is markedly expanded by the recruitment and retention of inflammatory cells along with the formation of villous projections and the generation of pannus tissue that invades and destroys cartilage and bone.
- The pathogenic events in RA probably occur in stages, and mechanisms leading to initiation of the disease appear to be distinct from those involved in the perpetuation of inflammation and eventual destruction of joint tissue.
- Chronic synovitis is maintained by the interactions of cell types native to the joint and inflammatory cells recruited to the joint, with the subsequent establishment of cytokine "networks."
- Cartilage destruction results from the production of enzymes that destroy components of the cartilage extracellular matrix by cells within synovial tissue and by chondrocytes; osteoclasts contribute to the destruction of articular bone.

INTRODUCTION

Inflammation of joints lined by synovium (synovitis) is the hallmark of rheumatoid arthritis (RA). Associated with synovitis is a propensity to destroy articular cartilage and bone, the structural components of the joint. Consequently, joint tissue from patients with RA has been the subject of extensive research, which has led to tremendous advances in our understanding of the pathogenesis of synovitis and the subsequent rational development of effective new therapies. This chapter reviews the pathologic changes seen in RA synovium, followed by a detailed summary of the phenotypic and functional changes that occur in synovitis in RA, including the cell types and inflammatory mediators responsible for establishing and maintaining chronic inflammation. Mechanisms of joint destruction are reviewed. Finally, this information is synthesized into a proposed model of pathogenesis that integrates knowledge gained from the study of synovial tissue, animal models of arthritis, and insight from clinical trials.

NORMAL SYNOVIUM

In a normal joint the synovium is a thin membrane derived from cells of the embryonic mesenchyme that lines the fibrous joint capsule (Fig. 94.1). The synovium and joint capsule attach to skeletal tissue at the interface of cartilage and bone, and normal synovial tissue does not encroach on articular cartilage. The structural features of normal synovium are covered in detail in Chapter 4, and thus only a brief summary is included here.

The most superficial layer of the synovium, lying adjacent to the joint cavity, is known as the synovial intima or synovial lining cell layer. Electron microscopic (EM) images have demonstrated that the cells within this layer are loosely adherent to the synovial subintimal or sublining tissues and that these cells form a discontinuous layer lacking a true basement membrane.¹ Cells within the synovial lining layer are 6 to 12 μ m in diameter, excluding the numerous finger-like projections extending from the cell surface. Two distinct populations of cells have been identified on EM images: type A or macrophage-like synoviocytes and type B or fibroblast-like synoviocytes (FLSs). Type A synoviocytes contain filopodia, a prominent Golgi apparatus, lysosomes, and vacuoles.¹ These cells have a sparse endoplasmic reticulum because they are primarily phagocytic cells that are presumably present in the joint to clear particulate matter from the joint cavity. In addition, they

express receptors for the Fc domains of IgG. In contrast, type B synoviocytes are fibroblast-like cells that contain abundant machinery for protein synthesis and fewer filopodia and vacuoles and lack Fc receptors (Fig. 94.2).¹ These cells can be distinguished by surface marker expression using immunohistochemical techniques (Fig. 94.3).

SYNOVIUM IN RHEUMATOID ARTHRITIS

In RA, chronic, clinically significant synovial inflammation develops and eventually leads to destruction of cartilage and bone. At the gross level, the inflamed synovial tissue in RA demonstrates marked expansion, with the synovial surface thrown into innumerable hyperemic and edematous villous projections that extend into the joint cavity. The microscopic changes seen in the synovium of patients with RA are not unique to this disease and can occur in other inflammatory arthritides. However, certain characteristic histologic findings can support the clinical diagnosis, including hyperplasia of the synovial lining layer, a mixed inflammatory cell infiltrate in the subsynovium with follicle and germinal center formation in some cases, neovascularization, and in clinically active disease, deposition of fibrin (Fig. 94.4).

In RA the synovial lining layer may be up to 12 cells in thickness, and individual cells may appear hypertrophic. Much of this increase is due to recruitment of cells of the monocyte-macrophage lineage from bone marrow. Evidence for recruitment of these cells into normal synovial tissue comes from studies of radiation chimeras of normal and beige mice. In beige mice, giant secondary lysosomes are present in cells of the monocyte-macrophage lineage. After bone marrow cells from beige mice were engrafted into normal irradiated histocompatible recipient mice, giant granules were identified in up to 7% of type A synovial lining cells.² Because macrophages are present in the sublining as tissue macrophages, as well as in the lining as type A synoviocytes, it is not entirely clear whether the greatly increased number seen in rheumatoid synovial tissue arises from division of local precursors or differentiation from newly recruited blood monocytes, but the latter mechanism is presumed to be the major source. The degree to which *in situ* division of resident cells in synovial tissue occurs and contributes to hyperplasia of the lining layer is still a matter of debate, but markers of cell proliferation, including proliferating cell nuclear antigen, have been identified in type B synoviocytes in the lining layer, thus demonstrating that some cell division does occur.³ The increase in the number of synovial lining cells in RA is significant because these cells are a source of a panoply of cytokines and other inflammatory mediators that contribute to chronic inflammation, as well as a source of matrix-degrading enzymes.

The inflammatory infiltrate within synovium in patients with established RA is heterogeneous and composed of T and B cells, plasma cells, and macrophages, as well as a lesser number of dendritic cells (DCs), mast cells, natural killer (NK) cells, and occasionally, neutrophils. Neutrophils are more commonly seen in synovial fluid but can be present in significant number in synovial tissue during an acute flare of disease. Most studies demonstrate a predominance of CD4+ over CD8+ T cells, with CD4+ cells being present diffusely, in aggregates, and in perivascular areas. B cells are also present diffusely and in aggregates, and immunoglobulin-producing plasma cells, some of which synthesize rheumatoid factor (RF), are the predominant infiltrating cells in some cases. Macrophages are usually present in significant number between and sometimes within lymphoid aggregates. Although macrophages may act as antigen-presenting cells to resident T cells, DCs, which are more potent antigen-presenting cells, have also been shown to interdigitate among T-cell aggregates. In addition, resident B cells may also serve as antigen-presenting cells, particularly for antigens internalized via their surface immunoglobulin receptors.

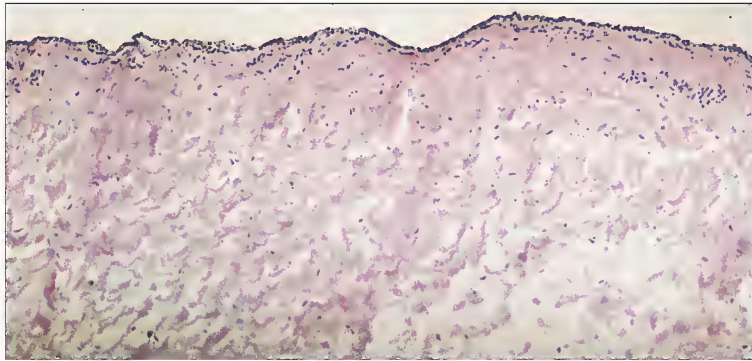


Fig. 94.1 Low-power view of normal synovial tissue. The intimal lining shown at the top of this section is only one or two cell layers deep, and sublining blood vessels and mononuclear cells are sparse.

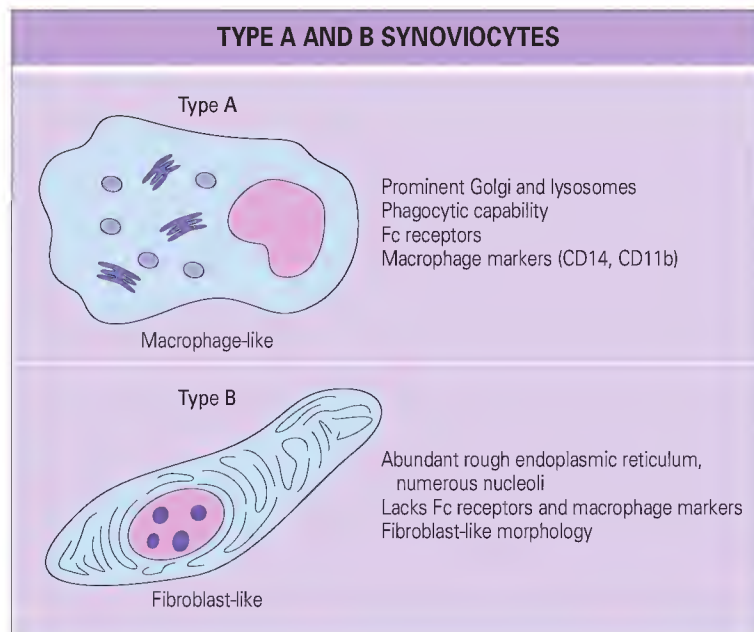


Fig. 94.2 Features of type A (macrophage-like) and type B (fibroblast-like) synoviocytes are shown.

A definite heterogeneity of histologic findings is seen in patients with RA. However, distinct patterns of cellular infiltration take place and have only recently been categorized. Although cells within the synovium can move through tissue in a dynamic fashion, synovial tissue from patients with RA typically has one of three histologic patterns of inflammatory cell infiltration, and these patterns appear to be preserved over time. Furthermore, these patterns of inflammation have been associated with typical and distinct cytokine profiles and may therefore have clinical relevance.⁴

The most common histologic pattern is a diffuse inflammatory infiltrate in which infiltrating immune cells, predominantly lymphocytes and macrophages, are interspersed in a haphazard manner among resident synovial fibroblasts and blood vessels. This form of synovitis is associated with low levels of messenger RNA (mRNA) for interferon- γ (IFN- γ) and interleukin-4 (IL-4), as well as low levels of tumor necrosis factor (TNF) and IL-1 β mRNA. In addition, patients with this form of synovitis tend to have clinically milder disease. A second pattern is follicle formation in which infiltrating T and B cells are arranged in distinct follicles or aggregates. In some cases these follicles become highly organized into true, functionally competent germinal centers similar to those present in lymph nodes.⁵ Finally, in the rarest form of synovitis, which occurs in only a small percentage of cases, a granulomatous inflammatory infiltrate is seen in which granulomas resembling rheumatoid nodules are present within synovial tissue. Both IFN- γ and IL-4 mRNA is characteristically produced in this form of synovitis, as are high levels of TNF and IL-1 β , thus suggesting that these tissues are associated with significant T-cell and macrophage stimulation. Patients with granulomas in synovial tissue also typically have rheumatoid nodules in their skin.⁴

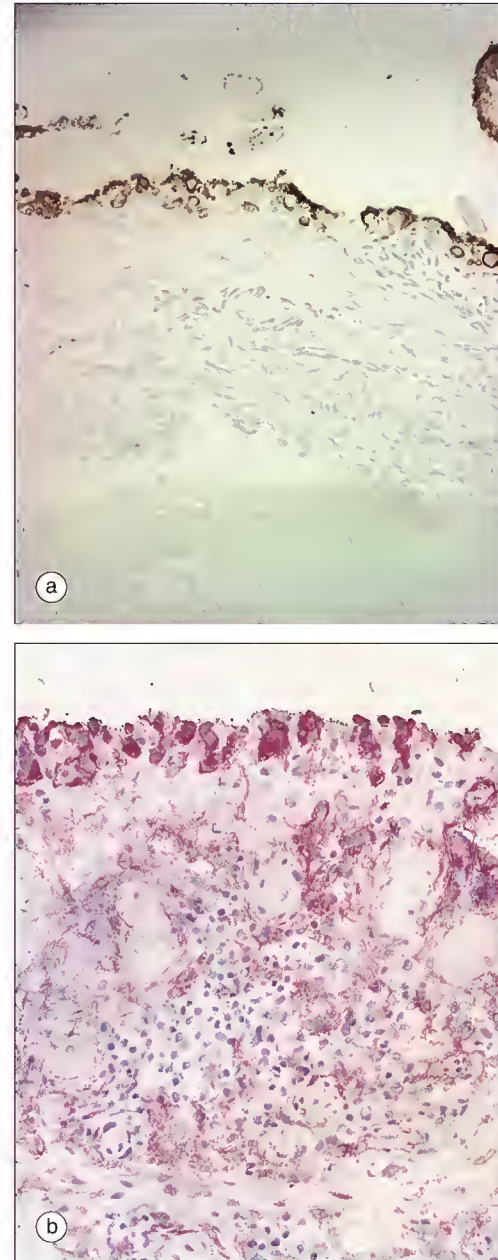


Fig. 94.3 Immunohistochemical staining of rheumatoid synovium. (a) Staining (brown) for CD55 demonstrates type B (fibroblast-like) synoviocytes in the lining layer. (b) Staining (red) for CD14 demonstrates type A (macrophage-like) synoviocytes in the lining layer, as well as macrophages in the sublining tissue.

MECHANISMS OF CHRONIC SYNOVITIS IN RHEUMATOID ARTHRITIS

Mechanisms for the recruitment and retention of inflammatory cells in chronic inflammatory diseases, including RA, have been the subject of intense investigation in recent years. The influx of inflammatory cells into synovial tissue occurs primarily through tethering of cells via selectins; upregulation of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), ICAM-2, and others on postcapillary venules; and chemokine-chemokine receptor interactions, which act as cellular “homing signals.” The proinflammatory cytokines produced within RA synovial tissue, including TNF and others, can induce the expression of several adhesion molecules on vascular endothelium.

Once inflammatory cells have served their purpose at a site of injury, these cells are normally cleared via apoptosis or emigration from the site. In RA, however, chronic inflammation persists because of an imbalance between cell recruitment, proliferation, and retention on the one hand and cell death and emigration from the tissue on the other hand. In the case of RA, interactions between T cells and stromal cells in synovial tissue favor

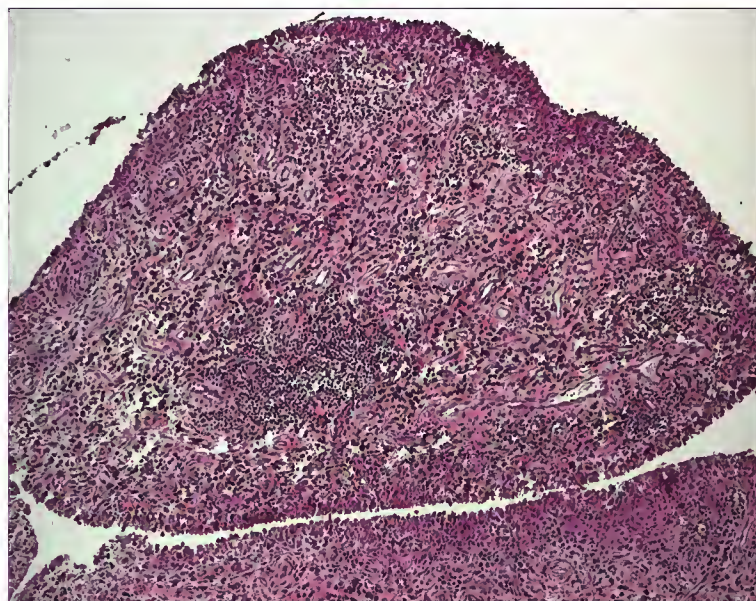


Fig. 94.4 Histologic evaluation of the synovium in chronic rheumatoid arthritis demonstrates hyperplasia of the synovial lining layer, infiltration of a heterogeneous admixture of mononuclear cells, including lymphocytes and plasma cells in the sublining tissue, and numerous blood vessels.

inhibition of T-cell apoptosis⁶ via the expression of IFN- β by resident synovial macrophages and fibroblasts. T-cell retention is also probably favored through upregulation of the chemokine receptor CXCR4 on T cells, which is induced by locally expressed transforming growth factor- β (TGF- β). The ligand for CXCR4, stromal cell-derived factor-1 (SDF-1 or CXCL12), is expressed on synovial cells and upregulated on RA as compared with osteoarthritis (OA) synovial fibroblasts. Blockade of the interaction between these factors has been demonstrated to decrease the clinical severity of arthritis in an experimental model.⁷

Pannus

A characteristic histologic feature seen in patients with RA is the presence of a distinctive tissue located at the interface between synovium and cartilage/bone at sites of joint destruction. This tissue is known as *pannus*, which is Latin for “cloth” or “covering.” Pannus tissue, not seen in this exact form in other inflammatory or noninflammatory arthritides, was so named because of its location—draped over cartilaginous surfaces and adherent to these surfaces. It is derived from the synovial membrane and is thought to mediate the process of tissue destruction. EM studies of the cellular composition of pannus have demonstrated that fibroblast-like cells predominate in this tissue, especially on the surface, but that in deeper layers and admixed with fibroblasts are cells with the EM appearance of macrophages.⁸ Pannus tissue has fewer lymphocytes and other inflammatory cells than synovial tissue remote from bone does, although such cells are often present (Fig. 94.5).

COMPONENTS OF RHEUMATOID SYNOVIUM

Cells of rheumatoid synovium

Macrophages

Macrophages are abundant in rheumatoid synovium and are readily identified in tissue sections or after dispersion of tissue into cell suspensions by their morphology and by surface markers such as CD14 and CD68. The number of macrophages noted in biopsy specimens correlates with risk for radiographic joint destruction.⁹ Although heterogeneity is undoubtedly present, cells of this lineage in rheumatoid synovium and synovial fluid show evidence of activation, such as surface markers characteristic of mature phagocytic cells and high levels of major histocompatibility complex (MHC) class II molecules important for the presentation of peptide antigens to CD4+ T cells.

Macrophages within the lining layer appear to differ from those in the sublining in their expression of adhesion molecules and secreted mediators.⁹ By analysis of tissue sections or freshly dispersed synovium, macrophages,

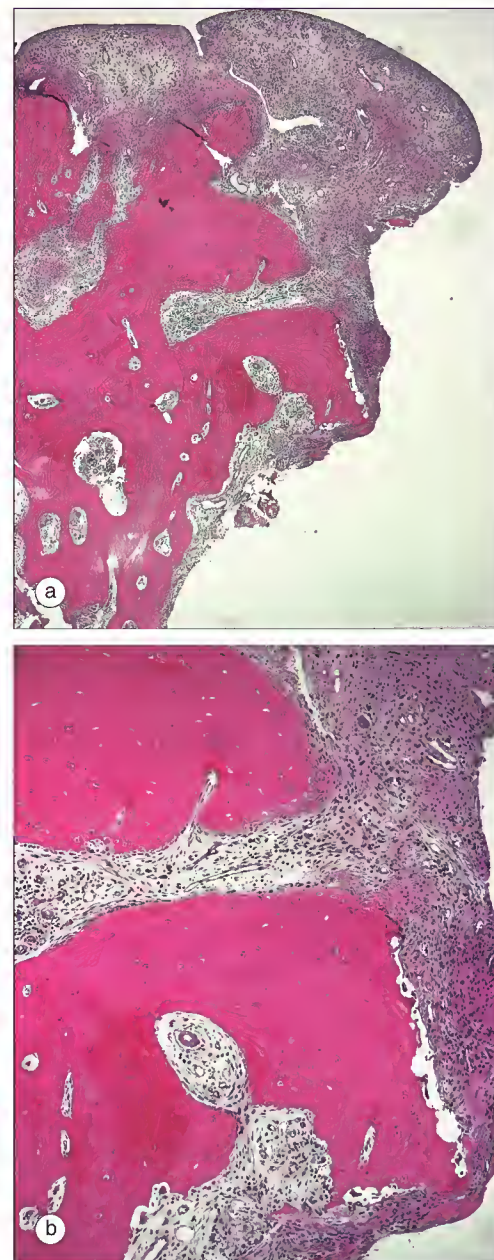


Fig. 94.5 Histology of the pannus-bone interface. (a) Low-power view demonstrating invasion of pannus tissue into cartilage and bone. (b) High-power detail demonstrating multinucleated osteoclast-like cells at the interface of pannus and bone.

especially those in the lining layer, appear to be a major source of numerous cytokines, including two known to be critically involved in the pathophysiology of RA, TNF and IL-1,¹⁰⁻¹³ as well as other cytokines that have well-described effects on immune and inflammatory responses, either stimulatory (IL-6, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor [GM-CSF]) or inhibitory (IL-1 receptor antagonist [IL-1Ra], TGF- β).^{10,11,14,15} Many cell-surface receptors influence the activity of macrophages. Notable examples expressed on synovial macrophages *in vivo* include the p55 and p75 TNF receptors, the low-affinity IgG receptors Fc γ RII and Fc γ RIII, and the adhesion molecules CD31 and CD44. Investigation is ongoing into the expression by synovial macrophages of more recently described inflammatory mediators and receptors, such as the ligand-receptor pair of high mobility group box 1 (HMGB1) chromosomal protein and the receptor for advanced glycation end products, Toll-like receptors (TLRs) for microbial products, novel interleukins, and novel members of the TNF superfamily, including B-lymphocyte stimulator (BLyS).

Although macrophages have the machinery to participate importantly in the synthesis of lipid mediators of inflammation, destruction of cartilage and bone, and antigen presentation to T cells, it is unclear how their contribution to these activities compares with that of FLSs (for the former two functions) or that of DCs and B cells (for the latter). Macrophage cell lines

derived from synovial tissue have been relatively difficult to obtain. Instead, macrophages derived from synovial fluid or from peripheral blood monocytes have been studied *in vitro* to determine the effects of various mediators on macrophage expression of cell-surface molecules, proinflammatory cytokines, and effector functions.¹⁶ At a level of great simplification, cytokines that stimulate macrophages include TNF, IL-1, IL-15, IL-17, and IL-18, and suppressive cytokines include IL-1Ra, IL-4, IL-10, IL-11, and IL-13.^{16,17} Macrophages are also stimulated by cell-surface molecules on activated T cells, even if those T cells have been killed.¹⁸

Fibroblast-like synoviocytes

Like type A synoviocytes, type B synoviocytes, or FLSs, are greatly expanded in number in rheumatoid synovium, although type A cells remain more abundant. FLSs in normal synovial lining differ from fibroblasts in the sub-lining and other tissues, most notably by the expression of VCAM-1, cadherin-11, and the intracellular enzyme uridine diphosphate glucose 6-dehydrogenase (UDPGD).^{19,20} Rheumatoid FLSs are notable for their ability to produce enzymes with the capacity to degrade cartilage (see later in the section "Joint Destruction"). Other pathologic functions that have been ascribed to FLSs include differentiation into follicular DCs, which organize germinal centers for B-cell maturation,²¹ and an ability to present superantigens (bacterial proteins that bind MHC and the T-cell receptor [TCR] outside the usual interface), but not necessarily conventional peptide antigens, to T cells.²²

FLSs are strikingly active within the innate immune system based on responsiveness to and secretion of various cytokines and other mediators. IL-1 and TNF appear to be the major stimulators of FLSs and have been used in many *in vitro* studies; receptors for these cytokines are also detectable on FLSs in tissue sections.^{13,23} Bacterial products such as lipopolysaccharide (LPS) and peptidoglycan are also stimulatory, presumably through specific receptors such as TLR4 and TLR2, respectively. Under such stimulation, FLSs secrete IL-6, the related cytokine IL-11, and numerous chemotactic cytokines (chemokines) capable of acting on a variety of hematopoietic cell types.^{24,25} Some of these products are also produced at detectable levels without exogenous stimulation. Some evidence indicated that FLSs are the predominant source of other mediators such as IL-16 and nitric oxide.

The concept of rheumatoid pannus as a benign tumor has been discussed for many years, with a focus on the FLS as a "partially transformed" cell. Rheumatoid FLSs indeed share many features of transformed cells, such as anchorage-independent growth *in vitro* and expression of proto-oncogenes and telomerase. Genetic analysis of individual cells suggests division of FLSs or precursor clones in erosive pannus.²⁶ However, these features are characteristic of not only premalignant cells but also otherwise normal cells that have the potential to divide and are not terminally differentiated. Despite evidence of genetic instability in FLSs based on the loss or duplication of chromosomal markers, this is equally true of FLSs derived from patients with OA or RA.²⁷ Thus, although FLSs in RA do have durable phenotypic changes based on their growth properties *in vitro*, as well as on their ability to degrade cartilage *in vivo* when cotransplanted with normal cartilage into mice with severe combined immunodeficiency (SCID),²⁸ use of the terms *benign tumor* and *partially transformed* suggests a potential that remains unsubstantiated.

B cells

The prevalence and distribution of B cells are two of the most variable features of rheumatoid synovium. Circulating autoantibodies are characteristic of RA but are of uncertain pathologic significance. Studies of B cells in rheumatoid synovium have therefore focused heavily on local production of autoantibodies and evidence for local maturation of antibody-producing cells. B cells have other functions, including presentation of antigens to CD4+ T cells and secretion of cytokines, but the importance of such functions in RA is unclear.

Sequencing of the immunoglobulin genes expressed in RA synovium has suggested that local clonal expansion of B cells takes place, but recent studies have questioned whether the lymphoid follicles and germinal centers seen in some rheumatoid synovium promote the maturation and expansion of antigen-specific B cells as they do in lymphoid organs.²⁹ Determination of which antigens might be recognized by synovial B cells has been approached in four ways. First, levels of specific autoantibodies in synovial tissue and fluid have been compared with those in blood from the same patients. Levels of RF and anti-citrullinated peptide antibodies (ACPAs) are locally enriched according to these studies,^{30,31} which are quantitative but do not distinguish between local synthesis and local deposition. Second, synthesis of antibodies has been measured in tissue explants with use of biosynthetic labeling or inhibition of protein synthesis to differentiate between local synthesis and deposition. Rheumatoid synovium synthesizes

a large amount of IgG, IgM, and IgA, comparable to that produced by explanted lymphoid organs. Synovial B cells produce RF of all three of these isotypes and in higher relative concentrations than do peripheral blood B cells from RA patients.³²

Third, the ability of individual synovial B cells to produce antibodies of particular specificity has been assessed by plaque-forming cell and enzyme-linked immunosorbent spot (ELISpot) assays. Large numbers of B cells secreting antibodies to type II collagen and C1q have been detected in the majority of synovial tissue from both RF-seropositive and RF-seronegative patients.³³ Notably, none of these patients had detectable circulating antibodies to these autoantigens. Fourth and finally, hybridomas have been made from synovial B cells, and the monoclonal antibodies produced by these cells have been evaluated for binding to antigens. Cells making antibodies to cartilage oligomeric matrix protein, the bacterial heat shock protein hsp60, and several other proteins have thus been identified.³⁴ This apparent diversity of local autoantibodies makes it clear that evaluation of serum may greatly underestimate synovial levels of potentially pathogenic antibodies.

T cells

T cells are the dominant lymphocytes infiltrating rheumatoid joints, and CD4+ cells predominate over CD8+ cells in most RA patients, as is true in lymph nodes and blood. A key role of CD4+ T cells in the pathogenesis of RA is suggested by the strong genetic linkage of disease susceptibility to HLA-DR alleles. However, various findings regarding synovial T cells have led to disagreement about their role in chronic disease, as discussed later in this chapter.

Many synovial T cells express surface markers suggesting prior activation, such as particular CD45 isoforms, CD44, and MHC class II molecules.³⁵ No clear evidence has demonstrated that activation occurs locally despite the various potential antigen-presenting cells in inflamed synovium. Previously activated T cells home nonspecifically to inflamed sites by virtue of their expression of particular adhesion molecules. Therefore, previously activated T cells are likely to be recruited into the synovium from peripheral blood independent of their antigen specificity.

Despite expression of activation markers, T cells from RA patients are paradoxically hyporesponsive to further stimulation through the TCR *in vitro*. First described in circulating cells, this observation has been extended to cells from synovial fluid and tissue.³⁶ Synovial T cells have decreased levels of the ζ chain of the TCR, a key element in antigen-driven signaling³⁷; this abnormality has also been found in systemic lupus erythematosus and other chronic inflammatory states, as well as in an animal model of chronic infection, thus suggesting that it is a generic response to chronic immune stimulation. Other defects in intracellular signaling and cell-surface phenotype characterize synovial T cells, but whether these changes are all part of a single differentiation program is unknown. Strikingly, at least some of these defects can be produced by chronic stimulation of normal T cells *in vitro* with TNF.³⁷

Once immunologic studies had defined subsets of CD4+ T cells that secrete distinct panels of cytokines, often falling into the patterns of type 1 helper T (Th1) cells (expressing IL-2, IFN- γ , lymphotoxin- α [LT- α]) and Th2 cells (expressing IL-4, IL-5, IL-10, and IL-13), it became important to determine the expression of specific cytokines by T cells in rheumatoid synovium because these cytokine panels have very different influences on immune responses. The salient finding in these studies is the dearth of T cell-derived cytokines (Table 94.1), whether measured by *in situ* hybridization or immunostaining of tissue sections^{38,39} or by Northern blot or polymerase chain reaction of either whole synovium¹⁴ or T cells isolated from synovium.⁴⁰ Low numbers of cells staining for IFN- γ are found in both early (<1 year) and late (>5 years) RA.³⁸ Nevertheless, cytokine-producing T cells are present in synovial tissue and were originally reported to demonstrate a Th1 pattern of cytokine expression, but with some deviation from that paradigm. Thus, IFN- γ and LT- α are expressed and IL-4 is not^{39,40}; however, IL-2, a product of Th1 cells, is not found, whereas IL-10, a product of Th2 cells, is expressed.⁴⁰ Expression of the chemokine receptors CCR5 and CXCR3, which are associated with the Th1 phenotype, by the majority of synovial T cells also suggested Th1 dominance,⁴¹ and discordant results were obtained regarding production of IL-6 by synovial T cells.

The paradigm of predominance of Th1 over Th2 cells in rheumatoid synovium has been challenged by the more recent discovery of a new CD4+ effector helper T-cell subset, the Th17 cell.⁴² Th17 cells express IL-17A and IL-17F, along with IL-6, TNF, GM-CSF, and other cytokines. Much of the work in defining the Th17 cell has been performed in mice, in which this subset is most clearly distinguished from Th1 and Th2 cells. Th17 cells have also been identified in humans, although the cytokine expression pattern of human Th17 cells is somewhat less distinct than that of other helper T-cell

TABLE 94.1

Cytokines that have been intensively studied in rheumatoid arthritis*

	Proinflammatory/ antiinflammatory [†]	Increased in RA? [‡]	Clinical trial support [§]	Cytokine cellular sources	Salient effects, stimulatory [¶]	Salient effects, inhibitory [¶]
TNF	Pro	+	+	Mφ , many others	COX, IL-1, TNF, IL-6, chemo, MMP	
IL-1	Pro	+	+	Mφ , many others	COX, TNF, IL-6, chemo, MMP, endo	Proteoglycans
IL-2	Pro	—		Th1	T-cell proliferation, NK	
IL-4	Anti	—		Th2	Abs	IL-1, TNF
IL-6	Pro/anti	+	+	Mφ , FLS, chond	Abs, acute phase, FLS proliferation	IL-1, TNF, chemo
IL-10	Anti	+	—	Mφ , Th2, B	Abs	IL-1, TNF, chemo, COX, MMPs
IL-11	Anti	±		FLS	Acute phase	IL-1, TNF
IL-13	Anti	±		Th2		IL-1, TNF, COX
IL-15	Pro	+		Mφ , FLS, endo	T-cell proliferation, TNF, chemo	
IL-17	Pro	+		Th17	COX, chemo, osteoclasts	
IL-18	Pro	+		Mφ, FLS, chond	TNF, Th1	
IFN-α/β	Pro/anti	NR		DC		
IFN-γ	Pro/anti	±	±	Th1, NK	TNF	IL-1, COX, MMPs
GM-CSF	Pro	+		Mφ, many others	Nφ/Mφ differentiation/activation	
M-CSF		±		FLS, chond	Osteoclast precursors	
TGF-β	Anti	+		Mφ, many others	FLS proliferation, ECM	IL-1, TNF, T cells
Chemokines	Pro	+		Mφ, FLS , endo, others	Leukocyte chemotaxis	
RANKL		+		T, FLS, osteoblasts	Osteoclasts	

*Antagonists such as interleukin-1 receptor antagonist and soluble (decoy) receptors are not shown.

[†]Predominant effect of the cytokine.[‡]Increased (+) or not (—) versus osteoarthritis or normal synovium. ±, small differences or conflicting results; NR, not reported.[§]Importance established (+ or —) by clinical trials involving the cytokine itself (e.g., IL-10, IFN-α/β) or an agent that blocks its activity (e.g., TNF, IL-1, IL-6, IFN-γ). ±, uncertain result.^{||}Major sources of factors clearly upregulated in RA synovium are indicated in **bold**. B, B lymphocyte; chond, chondrocyte; DC, dendritic cell; endo, vascular endothelial cell; FLS, fibroblast-like synovial cell; Mφ, macrophage; NK, natural killer cell; Th1, Th2, subsets of CD4+ helper T cells.[¶]Stimulatory or inhibitory for production of the factors or activity of the cells listed. Abs, antibodies; chemo, chemokines; COX, cyclooxygenase-2 enzyme; Nφ, neutrophils.

ECM, extracellular matrix; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL-1, interleukin; M-CSF, macrophage colony-stimulating factor; MMPs, matrix metalloproteinases; RANKL, receptor activator of nuclear factor κB ligand.

subsets. Differentiation factors for Th17 cells in mice (predominantly TGF-β and IL-6) also differ from those in humans (IL-1β and IL-23).⁴³

Regulatory T cells (Tregs) are a recently defined subset of T cells that are important for prevention of autoimmune disease and control of inflammation via secretion of IL-10 and TGF-β and also by mechanisms dependent on cell-cell contact.⁴⁴ The transcription factor Foxp3 is the most specific marker for Tregs, but they also express high levels of CD25, which has been used more frequently because of greater ease of detection. Data obtained by quantifying or manipulating cells using CD25 carry the caveat that this marker is also expressed on activated T cells at a somewhat lower level. Reports differ regarding whether Tregs circulate at higher levels in patients with RA than in healthy controls, but higher numbers have consistently been found in synovial fluid than in blood.⁴⁵ However, the *in vitro* suppressive function of circulating Tregs from RA patients is reduced by a mechanism dependent on TNF because suppressive function is restored by anti-TNF therapy⁴⁶ and addition of TNF to Tregs from healthy donors reduces suppressive activity.⁴⁷

The interaction of human T cells with other cell types infiltrating inflamed tissues, most notably monocytes/macrophages, has been studied *in vitro*. Work on co-cultures of normal human T cells and monocytes has shown that previously activated T cells induce the production of monocyte mediators such as IL-1, TNF, IL-10, and matrix metalloproteinases (MMPs) and that such induction involves both contact-dependent and contact-independent signals.⁴⁸ Effects on monocytes differ depending on whether the T cells are activated by stimulation through the TCR or by incubation with cytokines. Cytokine-activated T cells stimulate the release, from monocytes/macrophages, of TNF but not IL-10, whereas TCR-activated T cells stimulate the production of both cytokines.⁴⁸ Most interestingly, T cells freshly isolated from rheumatoid synovium behave like cytokine-stimulated and unlike TCR-stimulated T cells in this assay,⁴⁹ which has helped bolster the provocative hypothesis that antigen-specific T-cell activation is of little relevance in established RA.

Indeed, evidence for local expansion of antigen-specific T cells within the synovium has been difficult to obtain. Synovial T cells have been

described that react to peptides derived from the bacterial heat shock protein dnaJ⁵⁰ and to peptides from the matrix protein gp39,⁵¹ but in general, the search for autoreactive T cells has not been as fruitful as that for autoantibodies. Indirect evidence of skewed recruitment or local expansion of T cells has been sought by comparing TCR variable-region gene use in synovial and peripheral blood T cells in RA patients and controls, with the results summarized in a thorough review as being “notable for their contradictory and confusing nature.”³⁵

Despite these results, it is important to note that even in known antigen-driven responses, the percentage of antigen-specific T cells within an inflammatory lesion is quite low because of the nonspecific homing of previously activated cells to inflammatory sites, and the techniques used thus far may simply not be sensitive enough to detect an adaptive immune response, even one that is functionally important. Because previously activated T cells home nonspecifically to inflamed sites, the discovery of reactivity to common pathogens within inflamed tissue such as RA synovium must also be interpreted cautiously.

Neutrophils

Neutrophils are the predominant cell type in rheumatoid synovial fluid but are present only sparsely in inflamed synovium and pannus, although they have been located by EM studies at the cartilage-pannus junction.⁵² Neutrophils can, however, predominate in synovial tissue early in an acute flare of RA, and the histopathologic characteristics of a synovial biopsy specimen taken at this time may resemble those of a septic joint. Many synovial fluid neutrophils express surface markers indicative of activation by cytokines, such as the high-affinity IgG receptor FcγRI, the complement receptor CR3, and lactoferrin. In addition, synovial fluid contains antimicrobial peptides thought to be derived specifically from neutrophil granules.⁵³ There is little reason to propose that activation of neutrophils in rheumatoid joints differs from that in other inflamed but uninfected sites. Likewise, interaction of circulating neutrophils with endothelial cells in the joint is thought to use the same set of adhesion molecules as in other sites. Initial tethering and rolling are mediated by selectins (L-selectin on neutrophils, E-selectin on

endothelial cells) interacting with receptors containing sialyl-Lewis^x carbohydrate moieties. Tight adhesion is mediated by interaction of the β_2 integrins on neutrophils (LFA-1/CD11aCD18 and Mac-1/CD11bCD18) with ICAM-1 and ICAM-2 on endothelium.⁵⁴ Neutrophils do not express the integrin VLA-4, which may explain why they do not remain in synovial tissue, where expression of its counterreceptor VCAM-1 appears to be important in the retention of other kinds of leukocytes.

Details about the chemotaxis and activation of neutrophils have been gleaned from analysis of normal peripheral blood neutrophils cultured *in vitro*. IL-8/CXCL8, other ligands for the chemokine receptors CXCR1 and CXCR2, and TGF- β have been identified as important chemotactic factors for neutrophils.⁵⁴ Normal neutrophils can be induced to express many cytokines and chemokines *in vitro*, including IL-1 β and IL-8. In turn, IL-1 and IL-8 induce neutrophil effector functions such as degranulation, phagocytosis, and the respiratory burst.⁵⁴ In the case of IL-8, these effects are likely to be direct, but the priming of neutrophil functions by IL-1, more prominently seen *in vivo* than *in vitro*, is probably secondary to upregulation of the adhesion molecules E-selectin and ICAM-1 on endothelium⁵⁴ rather than a direct effect of IL-1 on neutrophils.

Dendritic cells

DCs, the cells most potent at presenting peptide antigens to T cells, are derived from precursors that migrate into joints and other tissues from peripheral blood. DCs make up 1% to 5% of the cells in rheumatoid synovial fluid⁵⁵ and can be isolated from synovial tissue as well. DCs can be distinguished from monocyte-derived cells by differences in surface markers, such as lower levels of CD14,⁵⁶ and the absence of phagocytic capacity. Synovial DCs express the co-stimulatory molecule CD40 and high levels of MHC class I and II molecules,⁵⁶ although divergent results have been obtained for expression of the co-stimulatory molecule CD80/B7-1.^{56,57} Thus, like other leukocytes in inflamed synovium, DCs appear to be activated. Considering the two predominant DC subtypes, the ratio of myeloid to plasmacytoid DCs is higher in RA than in non-RA synovium.⁵⁸ The role of DCs in initiating and perpetuating RA through the presentation of antigen to synovial T cells is a point of ongoing investigation and debate.

Mast cells

Mast cells are found in small numbers in rheumatoid synovium but perhaps at an increased density in comparison to normal tissue.⁵⁹ Interest in a potential role for mast cells in RA has been aroused by their importance in a mouse model of IgG-mediated inflammatory arthritis⁶⁰ and by their ability to secrete tryptases and other proteases, preformed cytokines, and vasoactive and chemotactic factors. It is possible that mast cell phenotypes are more diverse and tissue specific than the classic delineation of connective tissue and mucosal subtypes. For example, mast cells in RA synovium differ from those in normal or OA synovium in their expression of surface markers, such as corticotropin-releasing hormone receptor 1 and the chemokine receptor CXCR3.

Chondrocytes and endothelial cells

In addition to their complex structural role in cartilage, chondrocytes, the cellular elements of articular cartilage, have been found to be surprisingly interactive with inflammatory mediators. Most studies supporting this conclusion have been performed *in vitro* on cells cultured from OA or normal cartilage or on immortalized chondrocyte cell lines, but studies involving intact OA cartilage have also demonstrated the production of cytokines by chondrocytes, including IL-1, TNF, and IL-6. It is therefore likely that the chondrocytes in a rheumatoid joint are immunologically active and participate in cytokine networks (see later). Vascular endothelial cells proliferate in rheumatoid synovium and are important contributors to inflammation, as reviewed in Chapter 93.

SOLUBLE FACTORS IN RHEUMATOID SYNOVIUM

Interactions between the various cell types just described are critical for the development and maintenance of synovitis. Cellular communication is mediated by a large number of membrane-bound and secreted factors; the secreted factors have been easier to identify and manipulate and are therefore better understood. Protein mediators secreted by inflammatory cells are categorized as cytokines, chemokines, or growth factors based on the activity that they most prominently display: modulation of immunologic activity, chemotaxis, or cell growth and division, respectively. However, this classification is artificial, and many factors have characteristics of two or all three categories. Detailed knowledge of the function of individual cytokines and other factors in RA has generally come from the study of genetically

manipulated animal models or from studies manipulating the activity of only one or two mediators in explanted synovial tissue or dispersed synovial cells, an environment that may or may not resemble that of unmanipulated tissue.

In this section, rheumatoid synovitis is approached from the viewpoint of the role of soluble mediators in pathogenesis, with particular attention on those that have been investigated both *ex vivo* (in synovial extracts or sections) and *in vitro* (using explants and cell lines) and that have also been assessed in animal models of inflammatory arthritis. The key roles predicted for a few mediators have been convincingly confirmed by using specific inhibitors in patients with RA, thus demonstrating the value of basic scientific investigation in the development of therapies. Table 94.1 provides a summary of cytokines that are relevant to the pathogenesis of RA, their cellular sources, and salient effects.

Tumor necrosis factor

TNF is the prototype of a large family of cytokines. The simplified name TNF is now preferred over the former designation TNF- α because the corresponding term TNF- β , an alternative name for LT, is now obsolete. TNF and other family members are active as trimers, some being secreted and some membrane bound. TNF itself is synthesized first as a membrane-bound protein that is subsequently cleaved to a soluble form, primarily by an enzyme known as TNF- α -converting enzyme (TACE). Both forms of TNF are biologically active. TNF has two cell-surface receptors: TNFR1 (p55) and TNFR2 (p75). Both receptors are ubiquitously expressed,²³ either constitutively (TNFR1) or inducibly (TNFR2). Both receptors can be cleaved from the cell surface to produce soluble proteins that can neutralize TNF and thus play a regulatory role. Soluble p55 and p75 TNFRs are found in both the blood and synovial fluid of RA patients, with concentrations being greater in synovial fluid. TNF production is regulated to a remarkable degree at the posttranscriptional level by a network of positive and negative regulators that act on the 3' end of its mRNA.

TNF is synthesized by a wide variety of cell types, but most prominently by cells of the monocyte-macrophage lineage. These cells appear to be the major producers of TNF in the rheumatoid joint,¹² where this cytokine is readily detected by various methods.^{12,14} TNF production by macrophages *in vitro* is induced by various pathogens and cytokines, including but not limited to IL-1, IFN- γ , and TNF itself. In turn, TNF has a wide range of effects on various cell types and induces the production of numerous cytokines by immune cells, with a net proinflammatory effect. In cultured rheumatoid synovial explants, addition of TNF induces the expression of IL-6, IL-8, and IL-10, and blockade of TNF greatly reduces the production of IL-1 and GM-CSF.⁶¹ Salient effects of TNF on cultured FLSs include induction of prostaglandin E₂, MMPs, and chemokines, including IL-8/CXCL8; TNF and IL-1 often act synergistically in these processes.⁶²

TNF is a critical player in all animal models of inflammatory arthritis in which it has been evaluated, generally by using neutralizing antibodies or soluble receptors or by using mice deficient in TNF.⁶³ The most dramatic demonstration of the ability of TNF to cause arthritis has come from a transgenic mouse aberrantly expressing human TNF as a result of deletion of the aforementioned negative regulatory sequences in its mRNA. This mouse expresses TNF at high levels in synovium, and destructive inflammatory arthritis develops even in the absence of lymphocytes.⁶⁴ IL-1, however, is still essential in this model.

Blockade of TNF with either monoclonal antibodies (infliximab, adalimumab) or a soluble p75 TNFR (etanercept) has proved to be highly effective in treating patients with RA and several other inflammatory diseases. Several features of anti-TNF therapy will be notable as the pathogenesis of RA is considered later in this chapter: prompt improvement in symptoms in the majority of patients, marked improvement in synovial pathology with a significant decrease in the number of activated macrophages, and usually prompt return of disease when anti-TNF therapy is discontinued.

Among the many other members of the TNF superfamily, those that have been implicated in mouse models of RA include LIGHT (TNFSF14) and BlyS/BAFF, and LT is likely to be important in the generation of ectopic germinal centers.

Interleukin-1

Like TNF, IL-1 is the prototype of a phylogenetically ancient family of cytokines that includes IL-1 α , IL-1 β , IL-1Ra, IL-18, and at least six others of little-known function.⁶² IL-1 α is primarily a cytosolic protein and is thought to act in an autocrine manner. It is released from cells only during cell death and therefore circulates in tiny amounts. IL-1 β is also initially cytosolic but is then secreted by a novel and undefined mechanism after cleavage by a

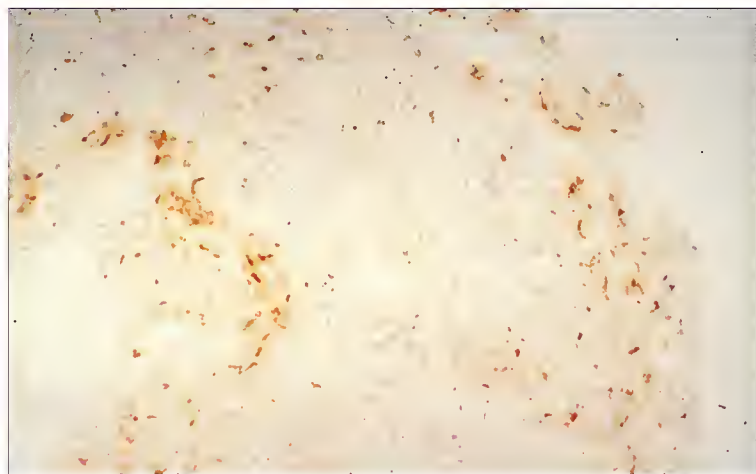


Fig. 94.6 Distribution of interleukin-1 protein in rheumatoid arthritis synovial tissue using an immunoperoxidase technique on a section lacking counterstain. Prominent staining (brown) is seen in the perivascular regions, with less staining in the intimal lining. (Courtesy Dr. M. Field.)

specific protease, the IL-1-converting enzyme (ICE, caspase-1). In addition to this posttranslational regulation, IL-1 production is also regulated transcriptionally and posttranscriptionally.

IL-1 is produced by many cell types relevant in rheumatoid synovitis, including FLSs, endothelial cells, lymphocytes, and neutrophils, but monocytes and macrophages appear to be the major source. IL-1 is readily detected in rheumatoid joints (Fig. 94.6), both in synovial fluid (IL-1 β) and within cells (IL-1 α > IL-1 β).⁶⁵ Synthesis of IL-1 by monocytes *in vitro* is induced by activated T cells and by a variety of cytokines, including TNF and IL-1 itself. Numerous cell types express IL-1RI, and the effects of IL-1 are similar to those of TNF, that is, broadly proinflammatory. Of relevance in the rheumatoid joint, IL-1 stimulates the release of prostaglandin, MMP, and chemokine (IL-8/CXCL8 and others) from FLSs; nitric oxide and prostaglandin production and adhesion molecule expression by endothelial cells; secretion of TNF (and further IL-1) by macrophages; and production of IL-6 and IL-8 but reduced synthesis of proteoglycans by chondrocytes.⁶⁵ In addition, IL-1 and TNF are synergistic in the induction of proteinases, prostaglandins, and cytokines by FLSs. Although IL-1 and TNF upregulate their own and each other's expression, it has been argued that IL-1 is functionally downstream of TNF in the cytokine network of the rheumatoid synovium because blockade of IL-1 does not reduce the synthesis of either TNF or IL-1 in synovial explants,⁶⁶ whereas blockade of TNF markedly reduces the production of IL-1.⁶¹ Blockade of IL-1 in this system does reduce the synthesis of other factors, including IL-6 and IL-8.⁶⁷

The activity of circulating IL-1 (primarily IL-1 β) is regulated by a remarkable array of naturally occurring inhibitors. IL-1Ra, a member of the IL-1 family, is secreted by the conventional endoplasmic reticulum-to-Golgi route; it binds to IL-1RI but does not activate signaling. A second cell-surface receptor for IL-1, IL-1RII, appears to be devoid of signaling potential and thus is viewed as a decoy receptor for excess IL-1. Both IL-1RI and especially IL-1RII also circulate in soluble forms and are thought to perform a similar decoy function.⁶⁵ Finally, antibodies that neutralize IL-1 are induced during immune responses at sufficient levels to have dampening effects.⁶⁷ The overall balance of IL-1 agonists and inhibitors is thought to be the critical factor in whether IL-1 contributes to an inflammatory state. Indeed, although IL-1Ra is detectable in the rheumatoid joint, the ratio of IL-1 to IL-1Ra favors IL-1 and inflammation.¹⁰

Animal models have indicated a central role for IL-1 in inflammatory arthritis. Expression of human IL-1 β in rabbit knee joints causes synovial inflammation,⁶⁸ and local or systemic administration of IL-1 exacerbates arthritis in several mouse models. In mice deficient in IL-1Ra, inflammatory diseases develop that differ depending on genetic background and possibly also environment; inflammatory polyarthritis develops in the BALB/c strain.⁶⁹ Mice deficient in IL-1 or IL-1RI or treated with IL-1Ra or IL-1–blocking antibodies are highly resistant to induction of experimental arthritis in a wide range of models.⁶³ Data from these studies suggest that in mice, IL-1 and TNF both play important roles in inflammation but that IL-1 is more important in joint destruction.

IL-1Ra (anakinra) has been shown to be modestly effective in patients with RA and interferes with both inflammation and joint destruction. Based on studies in animal models, it might have been predicted that IL-1 blockade

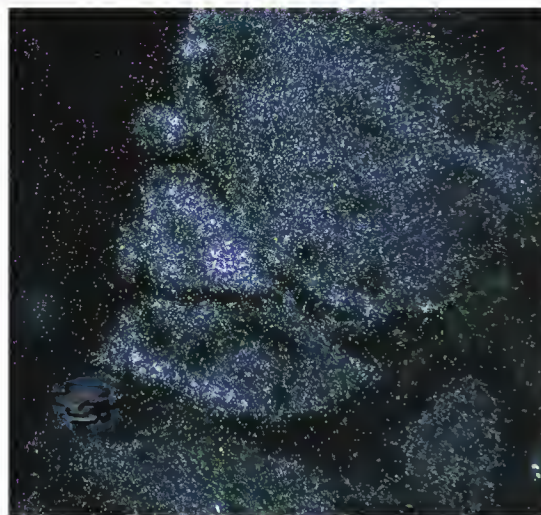


Fig. 94.7 Dark-field view of *in situ* hybridization identifying interleukin-6 messenger RNA expression in rheumatoid arthritis synovium.

would be as effective as TNF blockade in controlling inflammation, which has not been borne out in humans. This discrepancy may reflect either the unfavorable pharmacokinetics and pharmacodynamics of current methods of IL-1 blockade or fundamental differences in pathogenic mechanisms between animal models and human RA.

T cell–derived cytokines: IL-2, IL-4, IL-5, IL-13, and IFN- γ

Space constraints do not permit full discussion of the cytokines primarily produced by T cells, but one of the most striking findings in the study of mechanisms of chronic synovitis is the lack of evidence of the importance of these cytokines to the pathogenesis of RA.

Interleukin-6

IL-6 is the prototype of a family of cytokines that share a common signal transduction pathway. Its receptor consists of two chains: a ligand-specific IL-6R that is found on most hematopoietic and some nonhematopoietic cells and a signal-transducing chain, gp130, that is found on most cell types and is used by all the IL-6 superfamily members. A soluble form of IL-6R (sIL-6R) exists and serves to promote signaling when bound by IL-6 rather than functioning as a blocking or decoy receptor as do the soluble receptors for TNF and IL-1. IL-6 has many effects on hematopoietic and nonhematopoietic cells, both proinflammatory and antiinflammatory. It is perhaps best known for stimulating B cells to increase IgG production and differentiate into plasma cells. IL-6 is an endogenous pyrogen and a potent inducer of the acute-phase response in the liver.

In RA, IL-6 is produced by FLSs²⁴ and by chondrocytes,¹¹ but the major local source is probably macrophages (Fig. 94.7).^{11,70} Production is induced synergistically by TNF and IL-1. In turn, however, IL-6 decreases expression of TNF and IL-1, as well as the neutrophil-attracting chemokines CXCL8/IL-8 and CXCL1/MIP-2.⁷¹ Levels of IL-6 are elevated in the synovial fluid and serum of patients with RA, and serum levels correlate with levels of acute-phase reactants.⁷²

Blockade of IL-6 activity reduces or prevents arthritis in several mouse models, but only in those that include a phase of induction of autoimmunity after immunization. IL-6 has not been found to have a role in the effector phase of experimental arthritis after the production of autoantibodies.⁶³ A blocking antibody against human IL-6R (tocilizumab) has been shown to be effective in improving both symptoms and inflammatory markers (especially C-reactive protein) in RA in several controlled clinical trials.⁷³

Other cytokines of the IL-6 family that are being studied for potential roles in RA include oncostatin M (OSM), IL-11, and leukemia inhibitory factor (LIF).

Interleukin-10

More clearly than the IL-4 family members, IL-10 is a predominantly anti-inflammatory cytokine. Though initially described as a characteristic product of the Th2 subtype of CD4+ T cells, IL-10 is made in larger amounts

by macrophages and is also produced by Tregs and other cell types. Non-T cells, presumably macrophages, appear to be the major producers of IL-10 in rheumatoid synovium.⁷⁴ IL-10 levels are higher in RA than in OA synovial fluid,⁷⁴ and increased IL-10 levels are inversely correlated with joint destruction.⁷⁵ In cultures of synovial fluid mononuclear cells, blockade of IL-10 increases and the addition of IL-10 decreases the production of IL-1, TNF, and other inflammatory mediators.⁷⁶ The actions of IL-10 are not universally immunosuppressive, however, because this cytokine can stimulate B cells to proliferate and differentiate into plasma cells *in vitro*.

IL-10 has been studied extensively in animal models. An inflammatory bowel disease that is dependent on TNF and IL-1 develops spontaneously in IL-10-deficient mice. Collagen-induced arthritis is more severe in IL-10-deficient mice, but the arthritis induced by anticollagen antibodies is, surprisingly, less severe.⁷⁷ Addition of IL-10 by gene transfer in the active immunization model of collagen-induced arthritis decreases inflammation, but only if therapy is begun before clinical evidence of disease.⁷⁸ IL-10 gene therapy also decreases invasion of pannus into cartilage in a model in which human cartilage and synovium are cotransplanted into SCID mice.⁷⁹ Efforts to use recombinant IL-10 to treat established human RA have been disappointing.

IL-19, IL-20, and IL-22 are homologues of IL-10 but have proinflammatory activity. All these cytokines are expressed in RA synovium, but their roles in RA or in animal models are not yet known.

Interleukin-12 and interleukin-23

IL-12 is primarily of macrophage origin and is a major driver of Th1 differentiation and secretion of IFN- γ by both T cells and NK cells. IL-12 is a heterodimer composed of two subunits, p40 and p35. The p40 subunit is also used by IL-23, and indeed, mice lacking p40 or treated with antibodies that block p40 are deficient in IL-23, as well as in IL-12. IL-23 is a major driver of Th17 differentiation.

IL-12 and IL-23 are expressed in rheumatoid synovium, but whether at levels greater than those found in OA is unclear.⁸⁰ Divergent results have been reported with manipulation of IL-12 in the mouse model of collagen-induced arthritis, but before the distinction between IL-12 and IL-23 was recognized. A recent study comparing mice lacking either IL-12 or IL-23, but not both, has helped clarify this issue. IL-23-deficient mice were completely resistant to collagen-induced arthritis, whereas more severe disease developed in IL-12-deficient mice,⁸¹ thus suggesting that IL-23 is an essential mediator of arthritis whereas IL-12 protects against it.

Interleukin-15

IL-15 invites comparison with IL-2 by virtue of their shared signaling apparatus, but IL-15 and its receptor are much more widely expressed.⁸² Based on the phenotype of IL-15-deficient mice, the salient function of IL-15 is as a survival factor for naive T cells, particularly CD8+ cells, but this cytokine has other, generally proinflammatory effects as well.

In rheumatoid synovium, IL-15 is prominently expressed by lining macrophages but is also found in FLSs and endothelial cells,¹⁵ and it is secreted in sufficient amount to be detectable in synovial fluid in RA but not OA. Studies of patients with RA have demonstrated a significant relationship between levels of IL-15 and TNF in synovial fluid (Fig. 94.8). *In vitro*, IL-15 is important in the contact-dependent stimulation by T cells of TNF production from macrophages⁸³ and in the stimulation of T cells by FLSs. In mice, recombinant IL-15 can replace adjuvant in the induction of collagen-induced arthritis, thereby obviating the need for the immunostimulatory mycobacterial products present in complete Freund adjuvant. Conversely, blockade of IL-15 or IL-15R decreases the severity of collagen-induced arthritis.⁸⁴

Interleukin-17

IL-17 has proinflammatory effects on a variety of cell types, which leads to the induction of prostaglandins, nitric oxide, cytokines, and chemokines. Six IL-17 family members have been identified (IL-17A to IL-17F), and IL-17A is a proinflammatory cytokine whose importance in the pathogenesis of RA has already been highlighted. IL-17A and IL-17F are produced by Th17 cells. IL-17 induces IL-1 and TNF production in synovial macrophages and fibroblasts^{85,86} and can be synergistic with IL-1 in the upregulation of certain inflammatory mediators produced by FLSs. Some unusual activities ascribed to IL-17 include induction of osteoclastogenesis through upregulation of RANKL (receptor activator of nuclear factor κ B [NF- κ B] ligand) on osteoblasts and synovial fibroblasts⁸⁷ and stimulation of the synthesis of complement components by fibroblasts.

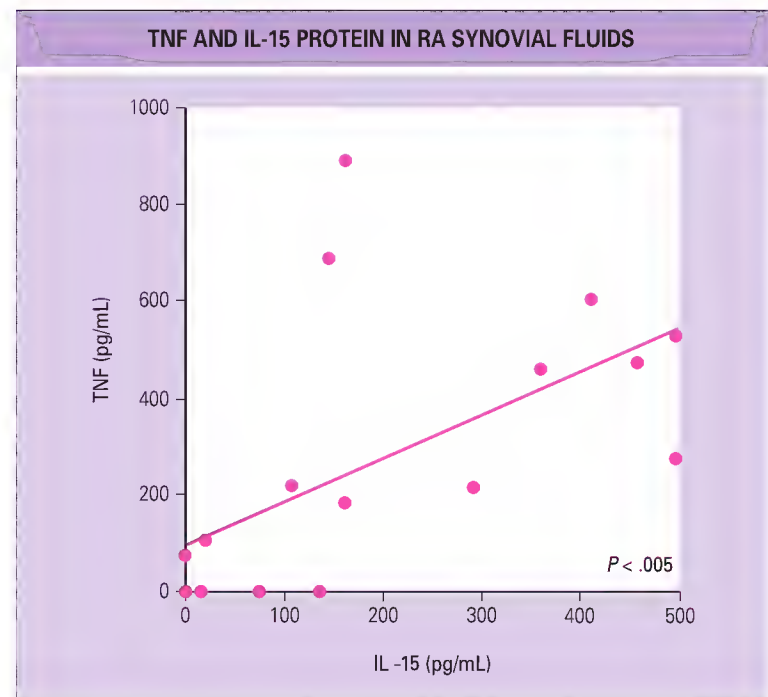


Fig. 94.8 Enzyme-linked immunosorbent assay demonstrating the simultaneous detection of interleukin-15 (IL-15) and tumor necrosis factor (TNF) in rheumatoid arthritis synovial fluid. (Courtesy Drs. B.P. Leung and I.B. McInnes.)

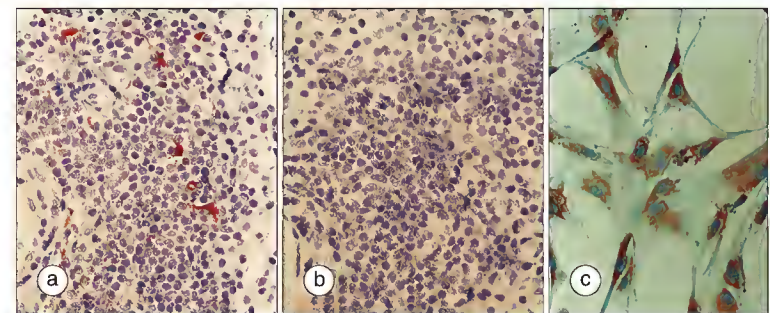


Fig. 94.9 Immunohistochemistry demonstrating interleukin-18 (IL-18) staining in rheumatoid arthritis synovium. (a) IL-18-expressing cells (brown) in lymphoid aggregate. (b) Neutralization of staining with recombinant IL-18. (c) IL-18 expression in cultured synovial fibroblasts. (Courtesy Drs. J.A. Gracie and I.B. McInnes.)

Synovial explants from the great majority of RA patients, but from few OA and nonarthritic patients, secrete IL-17.⁸⁸ Expression is high in T cell-rich areas, as expected.⁸⁸ In these explants, production of IL-17 is inhibited by the addition of two of the cytokine products of Th2 cells, IL-4 or IL-13, and IL-17 appears to be important for the local production of IL-6.⁸⁸ IL-17R uniquely binds IL-17 and is expressed on various synovial cell types in different arthritides, most notably endothelial cells and chondrocytes.

Blockade of IL-17 reduces inflammation, joint damage, and systemic levels of IL-6 in the mouse model of collagen-induced arthritis. This therapeutic effect occurs even if treatment is started after the onset of clinical disease, thus indicating that the proinflammatory rather than solely the immunomodulatory effects of IL-17 are important in this model.⁸⁹

Interleukin-18

IL-18 is related in structure to IL-1 and also has broadly proinflammatory actions. In rheumatoid joints, macrophages,⁹⁰ FLSs,⁹¹ and chondrocytes can all produce IL-18, although there is some disagreement regarding whether macrophages are the predominant cell type producing this cytokine (Fig. 94.9).^{90,91}

IL-18R is a heterodimer of α and β chains, and its intracellular signaling is similar or identical to that of IL-1R. Soluble splice variants of the IL-18R

α chain are secreted, can block the activity of the cytokine, and thus may play a role in regulation.⁹¹ IL-18R is expressed on many cell types potentially relevant to synovitis, including naive T cells, NK cells, macrophages, neutrophils, and chondrocytes. Notably, however, the β chain is not expressed on rheumatoid FLSS.⁹² Based on experiments in mice and *in vitro*, IL-18 promotes Th1 responses and IFN- γ secretion (particularly in combination with IL-12), RANKL expression, and osteoclastogenesis through actions on T cells and macrophage production of TNF and the innate immune receptors TLR2 and TLR4.

IL-18 mRNA and protein are found at higher levels in RA than in OA synovium,¹⁷ and IL-18 levels correlate with other markers of disease activity.⁹³ In synovial explants, addition of TNF and IL-1 induces the production of IL-18, and addition of IL-18 induces TNF, IFN- γ , GM-CSF, and nitric oxide.¹⁷ Thus, IL-18, like IL-1, probably plays an important role in the cytokine network in rheumatoid synovitis. In mice, IL-18 can promote collagen-induced arthritis by substituting for adjuvant.¹⁷ IL-18-deficient mice have a decreased incidence of collagen-induced arthritis, with defects in both the priming and effector phases of disease,⁹⁴ and anti-IL-18 antibodies inhibit the arthritis induced by injection of streptococcal cell wall material.⁹⁵ In addition, IL-18 is a chemoattractant for T cells, derived from RA synovium, that express IL-18R.

Transforming growth factor- β

TGF- β is the prototype of a large family of mediators that includes the bone morphogenic proteins (BMPs). It is broadly immunosuppressive and anti-inflammatory, but as an example of its complex actions, it can both stimulate and inhibit angiogenesis under different conditions. TGF- β increases the production and decreases the breakdown of extracellular matrix (ECM) and is thought to be a major factor in both physiologic wound healing and pathologic fibrosis.

TGF- β activity is readily detectable in rheumatoid synovial fluid,⁹⁶ and by immunohistochemistry TGF- β_1 is present at increased levels in RA versus OA synovial tissue,⁹⁷ apparently produced by macrophages, FLSS, endothelial cells,⁹⁷ chondrocytes,¹¹ and DCs⁹⁸; TGF- β_2 and TGF- β_3 appear to be synthesized at lower levels.⁹⁸ TGF- β has many effects when added to FLSS *in vitro*, including an increase in the synthesis of fibronectin-rich matrix, a decrease in the secretion of hyaluronic acid, and inhibition of induced apoptotic cell death.

The suppressive effects of TGF- β on experimental arthritis have been shown by using purified cytokine or blocking antibodies. Mice engineered so that TGF- β signaling is defective only in T cells are more susceptible to collagen-induced arthritis.⁹⁹ Conversely, local injection of TGF- β into affected knee joints in murine arthritis induced by zymosan (a direct activator of complement) does not decrease inflammation but does restore the proteoglycan content of cartilage.¹⁰⁰ In addition, some investigators have found a genetic association between a polymorphism in the TGF- β_1 gene and the incidence or severity of human RA.

Other cytokines and growth factors

Space limitations prevent discussion of these mediators in detail, but it is worth noting that the distinction between cytokines and growth factors is somewhat arbitrary. Just as cytokines influence the growth and function of nonimmune cells in the RA joint, so do these growth factors also influence immune cells and the network of inflammatory mediators. Macrophage migration inhibitory factor (MIF), OSM, and three hematopoietic colony-stimulating factors (GM-CSF, G-CSF, and M-CSF) have all been implicated in promoting inflammatory arthritis in mouse models.

Chemokines

Chemokines, the name being an abbreviation of the term *chemotactic cytokines*, are protein mediators that cause the migration of various cell types, usually toward the source or highest concentration of the stimulus. Forty-eight human chemokines and 19 chemokine receptors have been described, with multiple ligands binding to a given receptor and, for additional complexity, multiple receptors often binding a given ligand. Both are grouped into four families—CC, CXC, C, and CX₃C—based on the positions of conserved cysteine residues.

The biology of chemokines is so complex that it makes detailed discussion here impractical. The potential roles for specific chemokines in RA have been reviewed in detail.¹⁰¹ Although chemokines as a group are clearly critical for the production of inflammation, the prospect of treating RA by blocking one or two chemokines is made challenging by the striking redundancy of the system.

Arachidonic acid metabolites

Prostaglandins and leukotrienes are lipid mediators that are generally pro-inflammatory. The cyclooxygenase enzymes (COX-1 and COX-2) and the leukotriene-producing enzymes are expressed by multiple cell types in rheumatoid synovium, and prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄) are important in multiple animal models. However, it is notable that although nonsteroidal antiinflammatory drugs have a long track record in treating the symptoms of RA, they do not appear to be disease modifying, and reports of the use of leukotriene inhibitors and antagonists for RA have been few and preliminary. Probable roles for more recently described anti-inflammatory lipids such as lipoxins are also being investigated.

Ligands for Toll-like receptors

TLRs are a family of membrane-associated receptors that are activated by a variety of unique microbial products and play an important role in “innate” immunity, that is, antimicrobial defense that does not require the development of antigen-specific T- or B-cell responses. Activation of TLRs stimulates proinflammatory pathways in leukocytes, endothelial cells, and parenchymal cells and also promotes antigen-specific immune responses both directly in B cells and indirectly via antigen presentation to and co-stimulation of T cells.¹⁰² In addition to microbial products, endogenous molecules (e.g., hyaluronic acid, HMGB1, heat shock proteins, chromatin, and fibrinogen) have also been shown to interact with and activate TLRs *in vitro*. Because these endogenous molecules are released in association with cell death and tissue damage, settings in which host defense needs to be activated, their binding to TLRs is probably relevant *in vivo* as well and particularly in chronic inflammatory diseases.¹⁰²

All these putative endogenous TLR ligands are abundant in joints with established RA. In addition, bacterial products have been detected in a majority of joints inflamed as a result of different causes.¹⁰³ TLRs are expressed on multiple cell types in RA synovium. For example, TLR1 through TLR6 but not TLR7 to TLR10 are expressed by FLSS,¹⁰⁴ and expression of TLR2, TLR3, and TLR4 is higher in RA than in control fibroblasts.^{104,105} Stimulation of TLR2 induces the secretion of several chemokines, VEGF, MMPs, and IL-15 by FLSS.¹⁰⁶⁻¹⁰⁹ Expression of TLR2 and TLR4 is also elevated on macrophages in inflamed synovium,^{110,111} and ligation of these receptors leads to the production of TNF and IL-8.¹¹¹

TLRs play complex roles in mouse models of RA as well. Certain TLR ligands can produce inflammatory arthritis after intraarticular injection: hypomethylated CpG-containing DNA via TLR9¹¹² and streptococcal cell walls via TLR2.¹¹³ Stimulation of TLR4 by bacterial LPS facilitates the induction of arthritis by antibodies to type II collagen or glucose-6-phosphate isomerase (GPI),^{38,114} and blockade or absence of TLR4 reduces the severity of collagen-induced arthritis, chronic streptococcal cell wall-induced arthritis, and spontaneous arthritis arising in mice genetically lacking IL-1Ra.¹¹⁵⁻¹¹⁷ On the other hand, stimulation of TLR9 or TLR3 ameliorates different autoantibody-mediated arthritides via induction of type I interferons,^{38,118} and absence of TLR2 is associated with more severe arthritis in mice lacking IL-1Ra.¹¹⁷ Interference with signaling via the endosomally localized TLR3, TLR7, and TLR9 has been proposed as an important mechanism of action of antimalarial agents in treating autoimmune inflammatory diseases.¹¹⁹

Complement and immune complexes

Circulating complement is depleted in RA only in the setting of rheumatoid vasculitis. However, RA is apparently unique among the arthritides in the depletion of complement in synovial fluid in comparison to blood.¹²⁰ In addition, complement degradation products are found in rheumatoid synovial fluid. Deposits containing both immunoglobulin and C3 are readily detected in the articular cartilage of patients with RA (Fig. 94.10). Similar deposits are found in articular cartilage in various mouse models; in the K/BxN mouse model, for example, these deposits also contain the specific target antigen GPI.¹²¹ Arthritis in several mouse models is dependent on the complement cascade and particularly on C5. Together, these findings suggest that immune complexes form or are deposited in RA joints and locally activate complement, with the probable consequence of chemotaxis and activation of leukocytes by the cleavage products C3a and C5a. Which autoantibodies participate in the formation of these immune complexes is unknown; antibodies of several specificities, including RF, ACPA, and anti-type II collagen, are found at higher concentration in synovial tissue than in the circulation, but whether this finding indicates local deposition in addition to local synthesis is unclear.

Arthritis in several mouse models is also dependent on the low-affinity stimulatory receptor for IgG, Fc γ RIII. The low-affinity inhibitory FcR,

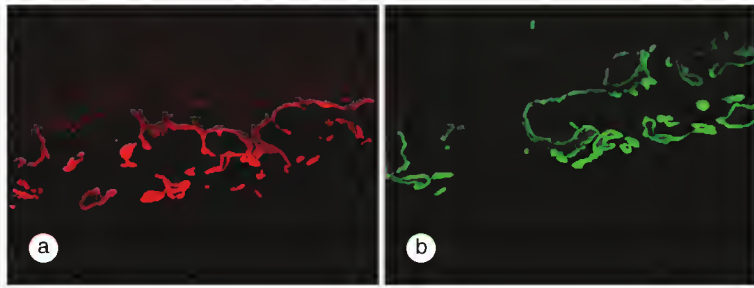


Fig. 94.10 Deposition of IgG (a, red) and C3 (b, green) on the cartilage surface of the knee, as shown by immunofluorescence staining. The patient was an 82-year-old woman with a 10-year history of rheumatoid factor–positive rheumatoid arthritis.

FcγRII, plays a protective role against arthritis in these models. Because low-affinity FcRs bind to aggregated but not monomeric IgG, their importance provides evidence for a key role in the handling of either immune complexes or surface-bound IgG in these models. Although roles for the FcRs have not been directly investigated in RA, polymorphisms in the genes for FcγRIIIA and FcγRIIA (both stimulatory, low-affinity FcRs) have been linked to susceptibility to or severity of RA by several groups.

JOINT DESTRUCTION

Enzymatic destruction of components of the ECM is the major mechanism proposed for the cartilage, ligament, and tendon destruction in RA. In particular, cartilage destruction has been attributed to the combined actions of several distinct families of proteinases, each of which has defined substrate specificity. Proteinases are produced by cells within the invasive pannus tissue, by cells in the synovium remote from bone, and by chondrocytes themselves under certain conditions of activation. These enzymes represent a potential therapeutic target for protection from joint destruction in RA.

Matrix metalloproteinases

Perhaps the best studied family of enzymes implicated in the joint destruction in RA is the MMP family, whose member interstitial collagenase (MMP-1) was the first to be identified in media from cultured RA synovial tissue.¹²² Subsequently, studies using *in situ* hybridization of whole synovial tissue identified synoviocytes within the synovial lining layer as the exclusive source of mRNA for MMP-1 and another MMP family member, stromelysin-1 (MMP-3), in RA synovium (Fig. 94.11).¹²³ In addition, MMP-1 and MMP-3 proteins have been demonstrated in synovium remote from bone, as well as at sites of cartilage erosion.¹²⁴ Several additional MMP family members have now been identified as being expressed in RA synovial tissue or in synovially derived pannus tissue invading into cartilage. MMPs can act at neutral pH and have the ability, in aggregate, to degrade the components of the ECM of cartilage.

The MMP family comprises 25 members. Classification of an enzyme as a member of this family depends on the presence of conserved “pro” and “catalytic” domains. These enzymes are named “metallo” because of the presence of a zinc ion in the active site of the catalytic domain. Within the prodomain is a conserved cysteine residue that interacts with Zn²⁺ in the catalytic domain. When this interaction is disrupted by removal of the propeptide via proteolytic cleavage, the enzyme’s active site becomes available and the enzyme is thus activated. Expression of MMP enzymes is regulated at several steps, including at the levels of gene transcription, activation of the proenzyme to the active enzyme, focality of expression within tissues, and finally, enzyme inactivation.¹²⁵

Collagenases

Collagenases were the first of the MMP enzymes to be implicated in the process of cartilage destruction in RA. This group of enzymes cleaves the collagen triple helix at a defined site near its N-terminus. Accordingly, the major substrates of the collagenases are native interstitial collagens types I and II, the latter being the predominant collagen component of cartilage.¹²⁵ Members of this group include fibroblast or interstitial collagenase (collagenase-1, MMP-1), neutrophil collagenase (collagenase-2, MMP-8), and collagenase-3 (MMP-13).

Neutrophil collagenase (MMP-8) and collagenase-3 (MMP-13) have also been implicated in the joint destruction in RA. In particular, MMP-13 is

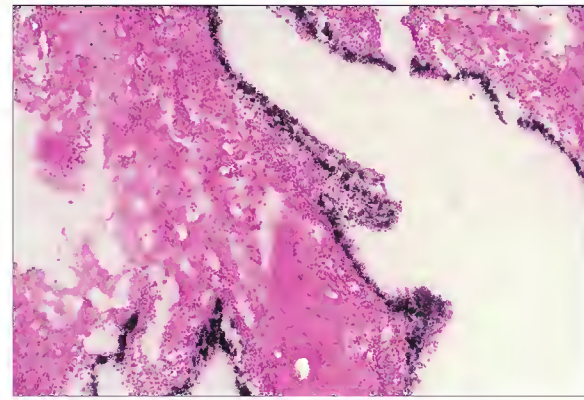


Fig. 94.11 Bright-field image of *in situ* hybridization in rheumatoid arthritis synovial tissue. A low-power view demonstrates abundant expression of mRNA (black dots) for matrix metalloproteinase-3 (stromelysin-1). (From Gravalles EM, Darling JM, Ladd AL, et al. *In situ* hybridization studies of stromelysin and collagenase messenger RNA expression in rheumatoid synovium. *Arthritis Rheum* 1991;34:1076-84. Reprinted with permission of Wiley-Liss, Inc., Wiley Publishing, Inc., a subsidiary of John Wiley & Sons, Inc.)

expressed by cells within the RA synovium, as well as by chondrocytes in areas of cartilage damage. Because MMP-13 is efficient in cleaving native collagens, as well as aggrecan, and because gene expression of MMP-13 is also upregulated by TNF and IL-1, this enzyme has been implicated as a uniquely important therapeutic target for protection against cartilage destruction in RA.

Stromelysins

The stromelysin group of MMPs has broad substrate specificity for components of the ECM. This group of enzymes degrades noncollagen connective tissue components, including proteoglycans, fibronectin, and laminin, as well as some of the minor collagens. In addition, MMP-3 has the ability to cleave and activate procollagenase, thereby providing additional matrix-degrading capability. The first observation of the potential importance of MMP-3 in inflammatory arthritis was the demonstration, in Lewis rats with streptococcal cell wall–induced arthritis, of transin (MMP-3 rat homologue) protein in the synovial lining layer and in the underlying stroma.¹²⁶ However, when collagen-induced arthritis was generated in MMP-3–deficient mice, severe inflammation and cartilage and bone destruction resulted, thus demonstrating that MMP-3 is not unique in its matrix-degrading capability.¹²⁷

Of the three members of the stromelysin group (stromelysin-1 [MMP-3], stromelysin-2 [MMP-10], and stromelysin-3 [MMP-11]), MMP-3 is by far the most abundantly expressed in RA. *In situ* hybridization studies demonstrate that like MMP-1, gene expression of MMP-3 is greater in RA than in OA synovium.¹²³ Although very low levels of MMP-3 are expressed by unstimulated synoviocytes, TNF and IL-1 are potent stimulators of MMP-3 gene expression, as are fibronectin fragments through engagement and cross-linking of fibronectin receptors on synoviocytes.

Other matrix metalloproteinases and related enzymes

Other MMP family members have been implicated in the process of cartilage destruction in RA, including the gelatinases: gelatinase A (72-kDa gelatinase, MMP-2) and gelatinase B (92-kDa gelatinase, MMP-9). These enzymes are expressed in RA synovium and can degrade partially cleaved collagens (gelatins). Aggrecan is a major proteoglycan component of articular cartilage. Cleavage of the aggrecan core protein in cartilage leads to destabilization of the protein with subsequent loss of cartilage compressibility. Although several MMPs can cleave aggrecan, it has long been clear that another enzyme or enzymes must also be responsible for cleavage because products were found in which cleavage took place between Glu373 and Ala374, a site that none of the known MMPs is able to cleave. A related but distinct family of enzymes was thus identified that may also play a role in the cartilage destruction in RA—the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family of proteinases. Two members of this family implicated in cartilage destruction are aggrecanase-1 and aggrecanase-2, both of which are expressed in synoviocytes and synovial tissue in RA and OA.

Role of matrix metalloproteinases in inflammation

Although MMPs have long been considered to be enzymes whose purpose is to remodel and degrade the components of the ECM, data have

demonstrated that these enzymes also play an important role in regulating the process of inflammation. It has become clear that many MMPs can also act on nonmatrix proteins, including cytokines, chemokines, and their receptors, and play a role in the innate immune system and in tissue repair.¹²⁵ The role of MMPs in the inflammatory process is evident from the results of experiments in which mice deficient in certain MMPs were challenged with inducers of arthritis. Surprisingly, a more severe immune-mediated arthritis developed in MMP-2-deficient and MMP-3-deficient mice than in their control littermates,^{127,128} thus suggesting that these enzymes may actually provide protection from inflammation, whereas less severe arthritis developed in MMP-9-deficient mice.¹²⁸

Protease inhibitors

In addition to the regulatory mechanisms described earlier, the activity of MMP enzymes is also regulated by naturally occurring inhibitors, including the tissue inhibitors of metalloproteinases (TIMPs), of which four family members are recognized (TIMP-1 to TIMP-4). Specific TIMPs have affinity for specific MMP family members and act by binding with high affinity to the catalytic domain of the enzyme in a 1:1 stoichiometry to render it inactive. Two other known inhibitors of MMP activity are α_2 -macroglobulin, which binds active MMP enzyme in the circulation, and RECK (reversion including cysteine-rich protein with kazal motifs), which inhibits the function of MMP-2, MMP-9, and MMP-14. The α_2 -macroglobulin molecule forms a covalent link with the protease to render it inactive and is the main inhibitor of collagenase activity in serum. Neutrophil-derived elastases and serine proteinases can in turn inactivate α_2 -macroglobulin.

Cysteine and serine proteases

Since discovery of the MMP family of enzymes in RA synovium and pannus, several other classes of enzymes have also been reported to be expressed by cells within RA synovial tissue or pannus tissue (or both) and have been implicated in causing cartilage destruction in arthritis. Included among these are the cysteine protease family of enzymes, especially cathepsins B, L, and K. As a class, the cathepsins have a wide range of substrate specificity, including native collagens, proteoglycans, fibronectin, fibrinogen, elastin, and laminin. Cathepsin K is another family member implicated in joint destruction. This enzyme is secreted in high amount by osteoclasts and is largely responsible for the degradation of type I collagen in bone by these cells. Cathepsin K is also expressed by synovial fibroblasts in RA. The serine proteinases, including granzymes, neutrophil elastase, and mast cell chymases, have also been implicated in the joint destruction in RA. In addition, several of these enzymes have the ability to activate pro-MMPs. Serine proteinase inhibitors (SERPINs) are present in plasma and synovial fluid and serve to block ECM degradation by this class of enzymes.

Bone destruction

Although the action of proteinases in degrading the various components of the ECM probably plays a major role in the destruction of cartilage, tendon, and ligament in RA, destruction of bone requires removal of the mineralized bone matrix. In physiologic bone remodeling associated, for example, with microfracture or altered mechanical loading, removal of bone is accomplished by osteoclasts. Osteoclasts are specialized cells, differentiated from cells of the monocyte-macrophage lineage, that have the capacity to bind to the surface of bone and create a tight "attachment zone" via interactions between integrins, including $\alpha_v\beta_3$, on the osteoclast membrane and matrix components in bone, including bone sialoprotein and osteopontin. Creation of this tight seal with bone allows the osteoclast to generate an acidic environment through the action of carbonic anhydrase II and a proton pump, thereby leading to removal of mineral from bone. Osteoclasts also release lysosomal proteinases into this acidic environment, perhaps the most important of which is cathepsin K, as well as enzymes of the MMP group, including MMP-9, which leads to degradation of the organic component of the bone matrix.

A role of osteoclasts in the focal bone erosion in RA was suspected initially on the basis of indirect evidence, including identification of multinucleated cells at sites of erosion in subchondral bone and at the pannus-bone interface in tissue samples from patients with RA (Fig. 94.12).¹²⁹ Studies using immunohistochemistry and *in situ* hybridization have demonstrated that these multinucleated cells express characteristic markers of osteoclasts, including a marker unique to osteoclasts.¹³⁰ Similarly, osteoclasts have been identified at erosive surfaces in arthritic joints in numerous animal models of RA.

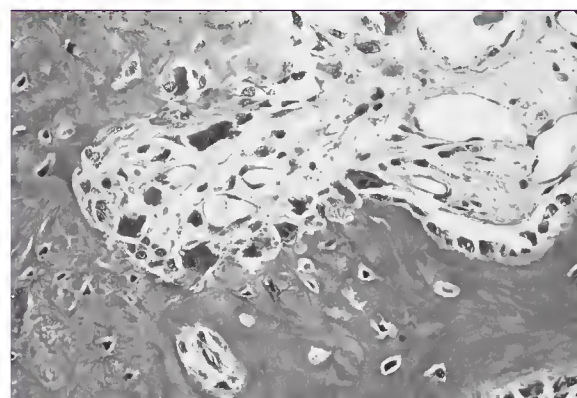


Fig. 94.12 Focal subchondral bone erosion in rheumatoid arthritis. Note that osteoclasts are present at a site of resorption. (From Gravalles EM, Goldring SR. Cellular mechanisms and the role of cytokines in bone erosion in rheumatoid arthritis. *Arthritis Rheum* 2000;43:2143-51. Reprinted with permission of Wiley-Liss, Inc., Wiley Publishing Inc., a subsidiary of John Wiley & Sons Inc.)

Our understanding of the pathogenesis of bone erosion and the role of osteoclasts in RA was greatly augmented by the discovery of a cytokine system now known to be the key regulatory system of osteoclast differentiation and activation. RANKL, also known as osteoprotegerin ligand (OPGL), osteoclast differentiation factor (ODF), and TNF-related activation-induced cytokine (TRANCE), is a cytokine initially identified as being important in the regulation of interactions between DCs and T lymphocytes, as well as in regulating lymph node organogenesis and lymphocyte development.^{131,132} It was also recognized that RANKL is essential for osteoclast differentiation and activation, thereby providing a link between the immune system and bone. RANKL binds to its receptor RANK, present on osteoclast precursor cells, to effect its biologic functions. OPG, a decoy receptor for RANKL, is the third member of this cytokine system. OPG can bind to RANKL with high affinity, thus preventing binding of RANKL to RANK and blocking the biologic activity of RANKL (Fig. 94.13). The expression of RANKL protein relative to OPG protein at a given site is the critical determinant of the degree to which osteoclast-mediated bone resorption occurs at that site.

RANKL is expressed predominantly by two cell types within rheumatoid synovial tissue: FLSs and T cells.¹³³ Cells isolated from cultured RA synovium also generate multinucleated cells that can resorb bone,¹³⁴ a definitive demonstration that these multinucleated cells are osteoclasts. RANKL is expressed at sites of bone resorption in tissue from patients with RA (Fig. 94.14). The first definitive demonstration of the critical role of RANKL and osteoclasts in the bone erosion in arthritis was reported in studies using the rat adjuvant-induced arthritis model, a model in which activated T cells have been shown to express RANKL protein. Treatment of arthritic rats with OPG was initiated at disease onset, and it was demonstrated that although levels of inflammation were similar in treated and untreated rats, arthritic rats treated with OPG exhibited complete protection from bone erosion.¹³⁵ Furthermore, studies in mice deficient in osteoclasts (as a result of deficiencies in different factors critical to osteoclastogenesis), including RANKL-deficient mice¹³⁶ and c-fos-deficient mice,¹³⁷ have demonstrated dramatic protection from bone erosion in models of experimental arthritis driven by autoantibodies or by overexpression of TNF, respectively.

In addition to the RANKL/RANK/OPG system, other cytokines and growth factors produced by synovial tissue or pannus tissue in RA can influence the differentiation and activation of osteoclasts. Factors that can play a direct role in osteoclast differentiation include TNF, which is a potent differentiation factor for osteoclast precursor cells in synergy with RANKL; M-CSF, which expands the pool of osteoclast precursor cells; and IL-1, which prevents apoptosis of osteoclasts and augments their bone-resorbing potential.^{138,139} Therapeutic blockade of IL-1 or TNF in patients with RA can modulate both inflammation and bone erosion.^{140,141} In addition, factors produced by RA synovial tissue, including IL-1, TNF, and parathyroid hormone-related protein, may act indirectly on osteoclast genesis and activity by increasing the RANKL/OPG expression ratio in the local bone micro-environment. T cells within the rheumatoid lesion may also contribute to osteoclast-mediated bone resorption, not only via expression of RANKL by activated T cells but also via production by a subset of T cells of IL-17, which is a potent stimulator of osteoclastogenesis by indirect mechanisms. The rheumatoid synovium is also a source of factors that can inhibit osteoclastogenesis, including IL-4, IL-10, IFN- β , and IFN- γ .

Fig. 94.13 Osteoclasts are derived from cells of the monocyte-macrophage lineage. Macrophage colony-stimulating factor (M-CSF) derived from bone-lining (stromal) cells induces expansion of the osteoclast precursor pool and expression of receptor activator of nuclear factor κ B (RANK). Binding of the RANK ligand (RANKL) to RANK leads to osteoclast differentiation, fusion, and activation. Tumor necrosis factor (TNF) can synergize with RANKL to induce osteoclast differentiation. Possible sources of RANKL in rheumatoid arthritis (RA) include bone-lining cells, fibroblast-like synoviocytes (FLSs), and activated T cells. Bone stromal cells and FLSs are also sources of the RANKL decoy receptor osteoprotegerin (OPG). Cells from RA synovium produce factors that could influence osteoclast differentiation, fusion, and activation at a number of steps. In addition, activated macrophages from synovial tissue can act as osteoclast precursor cells. IL-17, interleukin-17.

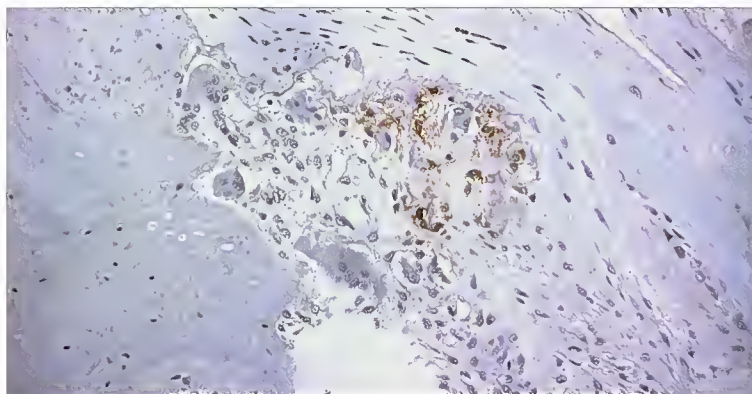
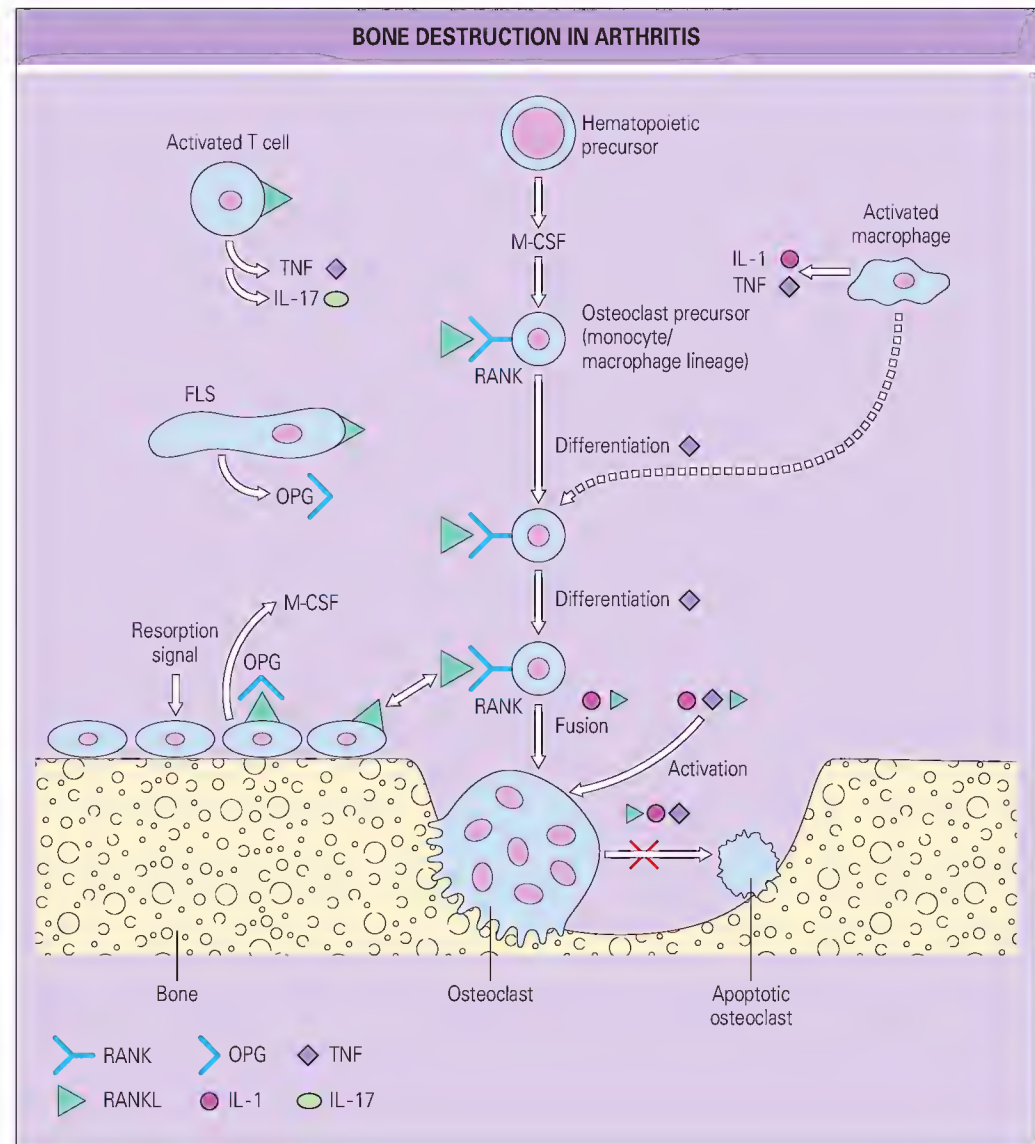


Fig. 94.14 Immunohistochemistry of the pannus-bone interface in rheumatoid arthritis demonstrating cells expressing receptor activator of nuclear factor κ B ligand (brown) in areas of osteoclast-mediated bone resorption.

PATHOGENESIS

Any theory of the pathogenesis of RA must extend beyond observations of synovial pathology and consider the epidemiology and clinical features of the disease as well. Although patients with RA often have extraarticular features, the dominant and defining clinical manifestation of this disease is chronic inflammation of joints lined by synovium. This fact undoubtedly provides a significant clue to the pathogenic mechanisms underlying RA. One can propose a host of factors that could contribute to the joint-specific

nature of RA, including unique structural features of the joint and the proximity of synovium to cartilage and bone, unique cell populations within the joint and the organization of these cell types, tropism of pathogens to the joint, and joint-specific antigens (Box 94.1). Contributions from these factors are not mutually exclusive, and it is likely that some—or many—may play a role in the initiation or chronicity of this disease, or in both.

Genetics and autoimmunity

Twin studies have indicated both that genetic and nongenetic (environmental or “chance”) factors are involved in RA. A major breakthrough in our understanding of the pathogenesis of RA came from studies demonstrating a genetic link to HLA-DR genes containing a common five-amino acid motif known as the “shared epitope”¹⁴²; subsequent genome-wide association studies have identified polymorphisms in multiple additional genes plausibly related to lymphocyte activation or inflammation (see Chapter 89). Because HLA-DR proteins present peptide antigens to CD4+ T cells, the existence of a shared epitope strongly suggests a role for T cells in the pathogenesis of RA and implies that one or a few antigenic peptides initiate or “drive” disease in patients expressing the shared epitope. Citrullinated peptides from fibrinogen bind to a shared-epitope HLA molecule,¹⁴³ and shared-epitope HLA genes are associated with ACPA-positive but not ACPA-negative RA. Nevertheless, it is premature to conclude that presentation of citrullinated peptides to T cells by shared-epitope HLA molecules is “the cause” of RA. It is sobering to note that no single peptide antigen has been identified to underlie the much stronger association of HLA-B27 with ankylosing spondylitis.

One additional clinical feature of RA that must be taken into account in any discussion of the pathogenic mechanisms of disease is the presence of circulating autoantibodies, not only ACPA but also RF and others that are not in clinical use. Strikingly, detectable serum RF and ACPA usually

BOX 94.1 FACTORS THAT COULD CONTRIBUTE TO THE JOINT-SPECIFIC NATURE OF RHEUMATOID ARTHRITIS**Structural features of the joint**

Synovial fluid = unique plasma ultrafiltrate

Unique vasculature

Trapping of immune complexes

Response to immune complexes

(Response to vasoactive mediators)

Proximity of tissue-specific cell types

Chondrocytes

Osteoclasts

Osteoblasts

Cartilage = acellular surface

Trapping of positively charged molecules

(Dysregulated complement activation)

Chronic trauma

(Proinflammatory byproducts)

Low oxygen tension

Unique cell populations/organization in synovium

Type A synoviocytes (and sublining macrophages)

Type B synoviocytes

Propensity to form ectopic germinal centers

(Tropism of lymphocyte subsets)

(Peripheral nervous system interactions)

Interaction with pathogensTropism of chronic pathogens, e.g., *Borrelia*

Trapping of bacterial products

Joint-specific antigens to which tolerance could be lost

Native antigens: e.g., type II collagen, gp39

Neoantigens: e.g., citrullinated proteins

Factors that are plausible but have little or no experimental support are in parentheses.

precede the clinical onset of RA, often by many years.¹⁴⁴ The best interpretation of these data is that humoral autoimmunity, following a breakdown in T-cell tolerance, precedes chronic inflammation in RA, thus suggesting that autoantibodies and possibly immune complexes play a role in disease pathogenesis. To gain further insight into the pathogenic mechanisms involved in RA, investigators have turned to animal models in an attempt to define both the events that may initiate the disease and those that can produce a state of chronic synovitis that eventually leads to the destruction of joint structures.

Lessons from animal models

All animal models of RA differ in important ways from the human disease, most notably in their rapidity of onset and progression, the details of the autoimmunity, and the requirement for either immunization or an overt genetic defect or manipulation (see Chapter 90). Starting from the perspective that models help define what could cause a human disease rather than what does or does not, the first important lesson from study of the large and growing number of animal models of RA is that there are many ways to cause a pathologic process that resembles the human disease. Second, these studies clearly demonstrate that TNF and IL-1 are critical players in all the models in which they have been evaluated⁶³ and that dysregulated overexpression of these cytokines in the joint is sufficient to cause chronic arthritis.^{64,68}

Thus, any mechanism leading to excess TNF and IL-1 in the joint would probably produce RA-like disease. This can readily be achieved by adaptive immunity to autoantigens or foreign antigens, beginning with the activation of T cells and leading in many models to the production of pathogenic autoantibodies. Activation of innate immune cells, including macrophages, mast cells, and neutrophils, may prime the joint for subsequent inflammation. Moreover, it is essential that cells of the innate immune system, to different degrees in different models, be recruited to the joint to mediate the proinflammatory effects of immune complexes or T cells (or both). However, the adaptive immune response is critical for the production of TNF and IL-1 and the subsequent development of arthritis in most models.⁶³ How, then, is the chronic production of TNF and IL-1 achieved in human RA and what are the roles of T cells, B cells, autoantibodies, and immune complexes in the pathogenesis of this disease?

In what way is the pathogenesis of rheumatoid arthritis dependent on T cells?

The strong association of ACPA-positive but not ACPA-negative RA with HLA alleles containing the shared epitope strongly implicates CD4+ T cells reacting to citrullinated antigens in pathogenesis. However, it may be that the role of antigen-specific T cells is primarily or entirely to provide help for B cells in producing ACPA. Most T cell-derived cytokines are not prominent in synovium, and T cells isolated from synovium behave more like T cells stimulated by cytokines than like T cells stimulated by antigen. Further evidence against a prominent role of CD4+ T cells in established RA might seem to be obtained from disappointing clinical trials of anti-CD4 antibodies, but follow-up studies have indicated that this agent did not cause depletion within the synovium as expected. The clinical effectiveness of abatacept (CTLA4-Ig) in human RA argues that co-stimulation of T cells remains important throughout the natural history of RA, but it is difficult to rule out effects of this drug on the antigen-presenting cells (including macrophages, B cells, and DCs) to which it binds. Discovery of the Th17 subset and demonstration that IL-17 levels are elevated in RA synovial fluid and that IL-17 plays an important role in mouse models have rekindled interest in T-cell involvement in the chronic phase of RA. Trials of anti-IL-17 antibodies in human RA are under way and will be of great interest.

Cell-cell and cytokine interactions in the perpetuation of inflammation in rheumatoid arthritis

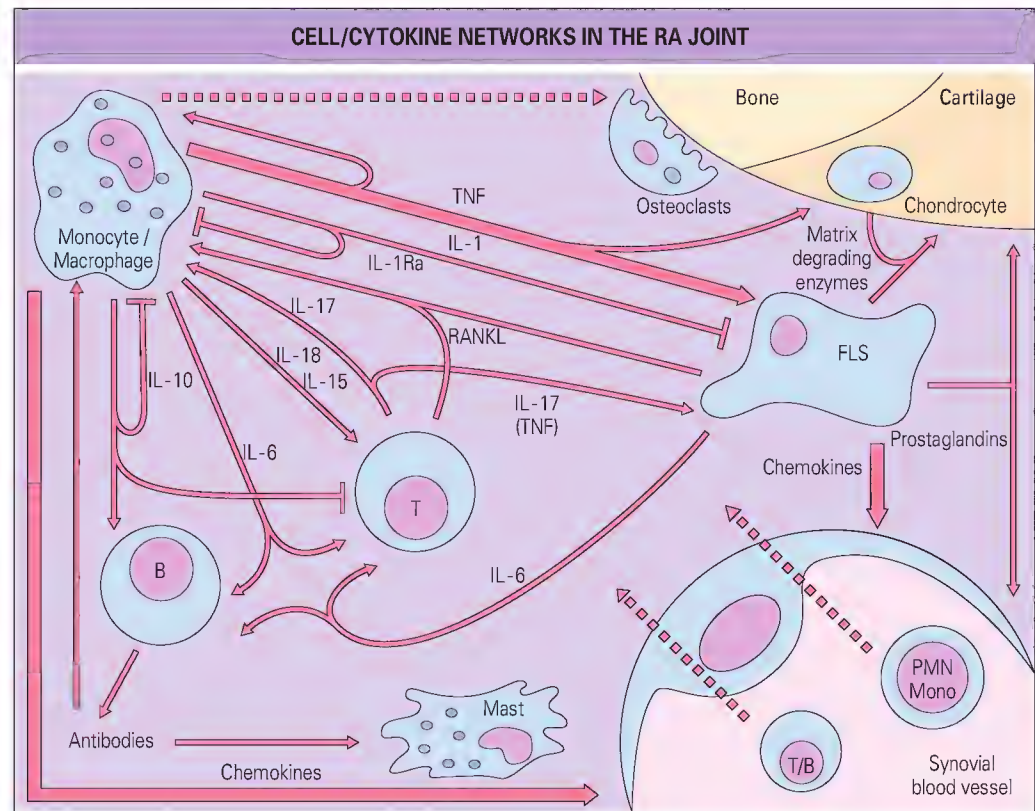
Based on studies involving animal models of RA, both the initiation and perpetuation of TNF and IL-1 production within inflamed synovial tissue, as well as maintenance of an activated phenotype of synovial lining cells and sublining fibroblasts and macrophages for the continued production of these and other critical proinflammatory cytokines, are essential in the pathogenesis of RA. It has been hypothesized that the chronic inflammatory state in RA is maintained by complex interactions and positive feedback loops between cell types resident within and recruited to the synovium. In addition to myeloid and nonhematopoietic cells, T and B cells may play roles in these complex interactions. Interactions between T cells and synovial macrophages and fibroblasts are mediated through CD69, LFA-1/ICAM-1 (CD54), and other ligand-receptor interactions. Previously activated T cells may contribute to the maintenance of chronic inflammation in RA through antigen-independent mechanisms by direct cell-cell interaction with macrophages or fibroblasts (or both) and thereby lead to the augmented production of effector molecules, including TNF and joint-damaging enzymes. For example, membranes from synovially derived T-cell clones have been shown to stimulate the production of MMP-1 and PGE₂, but not the inhibitor TIMP-1, in long-term culture.¹⁴⁵

Many of the mediators previously described in this chapter, most notably TNF, IL-1, IL-6, IL-17, prostaglandins, and chemokines, contribute to these feedback loops. For example, IL-18 induces the production of TNF as well as GM-CSF and IFN- γ , by RA synovial macrophages, an effect that is enhanced by IL-15 or IL-12. IL-18 directly activates both synovial macrophages and T cells and has a potent enhancing effect on the production of TNF induced by T cell-monocyte interactions. Figure 94.15 demonstrates interactions between resident FLSs and monocytes/macrophages that produce cytokines, chemokines, and other factors that activate cells in the local environment and maintain the chronic inflammatory state. Adhesion molecules on endothelial cells are upregulated by these products, which leads to further recruitment to the synovium of inflammatory cells expressing the proper chemokine receptors. These interactions could also augment T-cell activation and stimulate B cells to produce antibodies.

Autoantibodies and immune complexes

Since the discovery of RF by Rose and Waaler and the subsequent identification of RF as an autoantibody directed against the Fc portion of IgG, autoantibodies have been thought to play a role in the pathogenesis of RA. Early theories suggested that RF might initiate disease in RA via deposition of immune complexes in the joint, with the subsequent fixation of complement components, the generation of chemotactic factors including C5a, and the influx of inflammatory cells to the joint. In support of this theory, intracellular and extracellular deposits containing both immunoglobulin and C3 have been identified in synovium and on the cartilage surface in patients with RA, and there is evidence of local complement activation in RA synovial fluid. Such deposits could facilitate the recruitment of inflammatory cells and activation of phagocytes. This paradigm had largely been abandoned because RF is not specific for RA. RF is present in some healthy

Fig. 94.15 Schematic showing some of the key cytokines and other soluble factors and the local cellular interactions that mediate rheumatoid synovitis and joint destruction. Cells are recruited into the synovium from the vasculature. Chronic inflammation in rheumatoid arthritis synovium leads to the activation of macrophages and fibroblast-like synoviocytes (FLS), thereby resulting in joint destruction. Dashed lines depict either movement of cells (i.e., transmigration across the vascular endothelium) or differentiation of cells (i.e., differentiation of monocytes into osteoclasts). IL-1, interleukin-1; IL-1Ra, IL-1 receptor antagonist; mast, mast cell; mono, monocyte; PMN, polymorphonuclear leukocyte (neutrophil); RANKL, receptor activator of nuclear factor κ B; TNF, tumor necrosis factor.



individuals and in patients with other chronic inflammatory diseases that are not associated with synovitis, and it is absent in about 20% of patients with RA.

However, the notion that autoantibodies and immune complexes play an important role in disease pathogenesis has been reinvigorated by the discovery of ACPA, the demonstration that the B cell-depleting antibody rituximab is an effective treatment of RA, and the finding that immune complexes or antibodies binding to endogenous components of cartilage initiate disease in rodents that is similar in many respects to human RA.^{121,146}

Lessons from treatment of human rheumatoid arthritis

Treatments that are effective in reducing synovial inflammation in RA can provide essential confirmation that particular cells or mediators remain important in chronic RA. Although detailed mechanisms can only be proposed from mouse models or *in vitro* studies, any theory of the pathobiology of RA must incorporate the following:

- **TNF.** Relevant ancillary findings include the demonstration that synovitis often improves and that clinical relapse occurs in most patients in whom treatment is stopped. Thus, TNF is a particularly important component of synovitis, but the driving force behind TNF production remains intact.
- **IL-1.** IL-1Ra may not be as effective as TNF blockade, but the significant improvement found in controlled trials demonstrates that IL-1 is important in human RA, though perhaps not as critical as it is in mouse models.
- **IL-6.** The rapid time course of improvement with therapies directed against IL-6 suggests that it acts in the synovium rather than through inhibition of antibody production by B cells. Although blockade of IL-6 reduces the production of C-reactive protein and other acute-phase reactants in the liver, these mediators are thought to be markers of inflammation, not causal in tissues.
- **B cells.** The effectiveness of rituximab (anti-CD20 antibody) shows that B cells play a role in established RA, but it does not prove that they do so through the production of ACPA or other antibodies. Correlation of clinical improvement and relapse with titers of RF or ACPA varies among patients.
- **CD80/86 (B7-1/B7-2).** These co-stimulatory markers expressed on the surface of macrophages, DCs, and B cells are important for the activation of T cells that are concurrently being stimulated through their antigen receptors. The clinical effectiveness of abatacept argues that

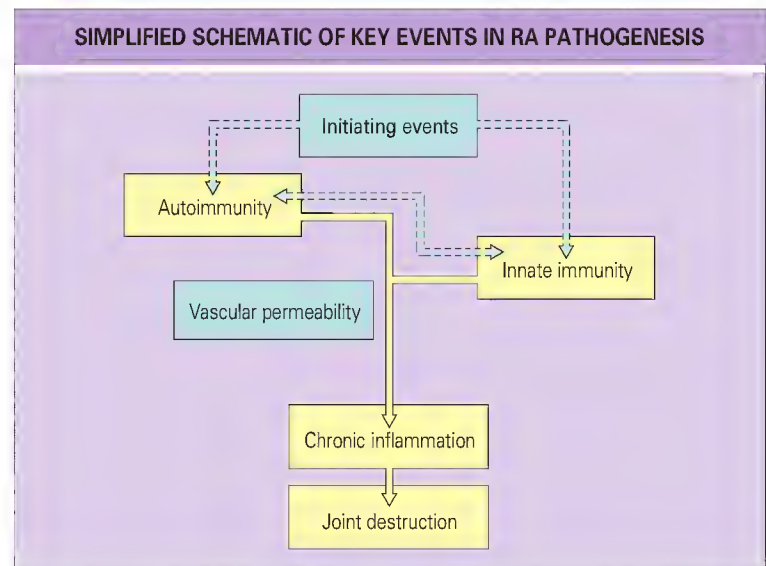


Fig. 94.16 Dotted arrows reflect pathways that are plausible but for which no detailed information is available, such as the origins of autoimmunity, the source of initial activation of innate immune cells in the synovium, and the possible contribution of activation of innate immune cells to the initiation or amplification of autoimmune responses. RA, rheumatoid arthritis.

co-stimulation of T cells remains important in established RA, but an alternative explanation is that this soluble receptor has direct effects on cells bearing CD80/B7.

Unifying hypothesis

A unifying hypothesis for the pathogenesis of RA must attempt to incorporate information obtained from both human RA and animal models of disease. What seems clear is that RA can best be conceptualized in stages that include disease initiation, establishment and maintenance of chronic inflammation, and destruction of joint tissue (Fig. 94.16), the latter two of which certainly coexist temporally. The event or events that initiate RA are likely to be distinct from those responsible for the establishment and perpetuation of chronic inflammation in the synovium, and destruction of joint

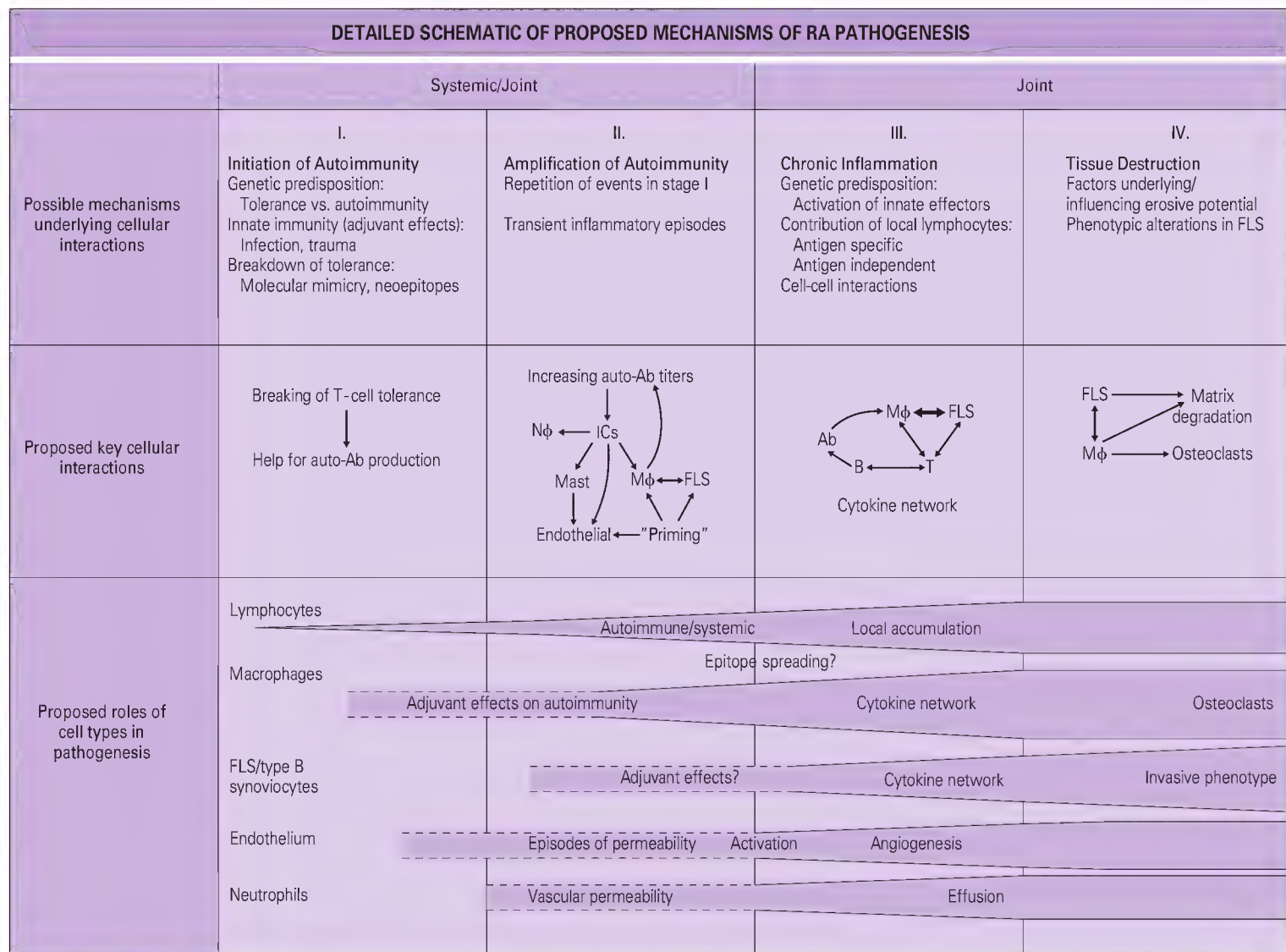


Fig. 94.17 The early phases of the pathogenesis of rheumatoid arthritis (RA) are speculative but probably involve initiation of autoimmunity and activation of the innate immune system (stage I) and amplification of autoimmunity (stage II). These events take place both systemically and within the joint. The pathogenic events in the joint-based chronic inflammatory phase (stage III) are better established. The contributions of immune complexes, antigen-reactive T cells, and antigen-independent T cells probably vary among patients. Tissue destruction (stage IV) coexists temporally with chronic inflammation (stage III). Changes in the number and activity of various cell types over time in the pathogenesis of RA are depicted in the bottom panel, with events depicted in stages I and II being speculative. Ab, antibody; FLS, fibroblast-like synoviocytes; ICs, immune complexes; Mφ, macrophages; Nφ, neutrophils.

structures proceeds by distinct mechanisms that are driven by chronic synovial inflammation. Several possible contributors to RA at these different stages are shown in Figure 94.17.

CONCLUSION

Tremendous progress has been made in understanding the pathogenic mechanisms involved in RA, particularly with regard to those involved in

the chronic phase of this disease. Out of this work have come new and effective targeted therapeutic interventions that have benefited patients with RA, as well as new concepts for future therapies. However, many questions are still unanswered, especially with regard to the initiating events in RA and the exact pathway involved in the establishment of chronic disease. The inroads that have now been made in both the clinical and basic science arenas has certainly set the stage for further investigation and a clearer understanding of these mechanisms in the future.

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Evaluation and management of early inflammatory polyarthritis

■ KLAUS P. MACHOLD

- Early institution of disease-modifying antirheumatic drug (DMARD) therapy for persistent or destructive arthritis such as rheumatoid arthritis can prevent joint damage and long-term disability.
- Early recognition of an unfavorable prognosis is a prerequisite for mitigating the consequences of persistent or destructive arthritis with the early institution of DMARD therapy.
- Differential diagnostic support comes from the number of involved joints, duration of symptoms, and the presence of serologic markers such as acute-phase reactants and autoantibodies.
- The American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for rheumatoid arthritis support early diagnosis.
- Early referral of patients with synovitis to the rheumatologist is a prerequisite for early diagnosis and therapy.

THE CONCEPT OF EARLY POLYARTHRITIS

Many inflammatory rheumatic diseases have a chronic course, sometimes spanning decades. From this perspective, the “early” period of arthritis was assumed to last up to several years.¹⁻³ Research involving early arthritis patient cohorts, however, has demonstrated a remarkably short period during which arthritis, in particular, rheumatoid arthritis (RA), may be regarded as “early.”^{2,4,5} It has been implied that interventions such as DMARD treatment would have a much greater effect than would therapy initiated at a later time during the “disease career.” This period has also been named the “window of opportunity” (Fig. 95.1).

Among the (chronic) inflammatory arthritides, RA is considered the most problematic because of its characteristics of joint destruction, functional impairment, disability, and premature mortality.⁶ In addition, other destructive arthritides, most notably psoriatic arthritis, may have similar outcomes.⁷ Retardation of progression or prevention of destruction is possible in both early and later stages of disease^{8,9} by using glucocorticoids, “conventional” DMARDs, biologic agents, or combinations thereof.

Studies on synovial cytokine patterns in patients with early arthritis¹⁰ support the hypothesis that the early months of (rheumatoid) arthritis are characterized by a pathophysiology different from that in later stages. This suggests that the pathogenetic events may change in the course of the disease. These observations are corroborated by clinical studies in which remission was more frequent in RA patients with a disease duration of 4 months or less than in those with a longer duration.¹¹ Likewise, delayed radiologic progression was demonstrated if DMARD treatment was instituted early after symptom onset as opposed to delayed therapy (see meta-analysis¹²). In contrast to these observations, other studies comparing early (symptom duration <1 year) and established RA did not demonstrate any differences between early and long-standing disease, both in the composition of cellular infiltrates and in cytokine expression in the synovium.^{13,14}

Because damage accumulates in the chronic destructive arthritides, it is also possible to define a disease stage as “early,” in which this damage has not yet occurred. Thus the criterion is not a time threshold, which has to be somewhat arbitrary, but the opportunity to preserve joint integrity by timely intervention. In clinical practice, most rheumatologists now define “early RA” as disease with a duration of less than 3 months.¹⁵ It has been hypothesized, however, that the threshold for an optimal treatment response

may be even shorter, about 8 weeks.¹⁶ In any case, if destruction has occurred, immediate institution of effective treatment is mandatory to delay the pace of further damage.

This pace of damage varies substantially. In the majority of RA patients in whom erosive disease developed, it did so within the first year after the onset of symptoms, and approximately 75% of the patients had erosions at 2 years.^{17,18} These findings underscore the necessity to consider effective treatment well before the first year of symptoms has elapsed. On the other hand, a sizable minority of patients with overt synovitis had relatively benign arthritis with self-limited disease or little, if any damage.^{18,19} Likewise, progression patterns in patients in whom destruction or erosions develop are quite variable.²⁰ Sharp and colleagues²¹ suggested that the pace of damage slows down after a longer duration. However, this slowing was only modest and did not appear before the third decade after onset of the disease. At this time a substantial proportion (≈20%) of the joints of these patients already showed “maximum erosion scores.” This observation further supports the requirement for DMARD treatment as early as possible to prevent this catastrophic outcome.

CRITERIA FOR EARLY ARTHRITIS

Patients with arthritis have substantial variability in clinical as well as laboratory or imaging abnormalities.^{20,22} Well-validated criteria to differentiate groups of patients with arthritis at this stage currently do not exist. Classification criteria for “established” RA²³ (as well as for psoriatic arthritis, osteoarthritis, seronegative spondyloarthritis, and other such conditions) were developed for clinical research and are not intended primarily for diagnosis. Rather, they should be used to identify groups of patients with a given disease as clearly as possible and to standardize the characteristics of these patients for clinical studies. Evaluation of an individual patient early in the course of disease must capture many more features of the clinical picture. These features are mandatory for further diagnostic and therapeutic decisions. In addition, given the inherent variability of most arthritides that may have similar clinical manifestations at the onset, prognostication is important for both the physician and patient to select the appropriate therapy. With this knowledge in mind, recent efforts have been directed primarily at identifying risk factors to help define “early RA” or, as has been done in developing the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA criteria,²⁴ patients who would need to be treated with DMARDs (e.g., methotrexate). These criteria for RA are intended to identify the necessity for DMARD treatment rather than “diagnosis” and encompass the pattern of joint involvement (large vs. small, as well as the number of joints), serology (rheumatoid factor [RF] and anti-citrullinated peptide antibody [ACPA]), duration of synovitis, and acute-phase reactants (APRs). Validation of these criteria over the past years has indeed demonstrated superior sensitivity over the 1987 ACR RA criteria, in particular, in early disease. On the other hand, the 2010 RA criteria appear to be less specific. This relatively low specificity points to the importance of a thorough workup of early arthritis to avoid overtreatment or misdiagnosis.

Taking a slightly different approach, the Leiden group has developed a scoring system to predict RA in a cohort with undifferentiated arthritis (i.e., not classifiable according to the 1987 ACR criteria) lasting less than 1 year. The score includes easily determinable clinical and laboratory characteristics (age, gender, distribution and symmetry of arthritis, morning stiffness, tender and swollen joint counts, C-reactive protein [CRP], RF, and ACPA) and yielded positive and negative predictive values in the vicinity of 90%.²⁵ Like the 2010 ACR/EULAR criteria, this score may guide treatment decisions and thus fulfil the requirement of both avoiding overtreatment and

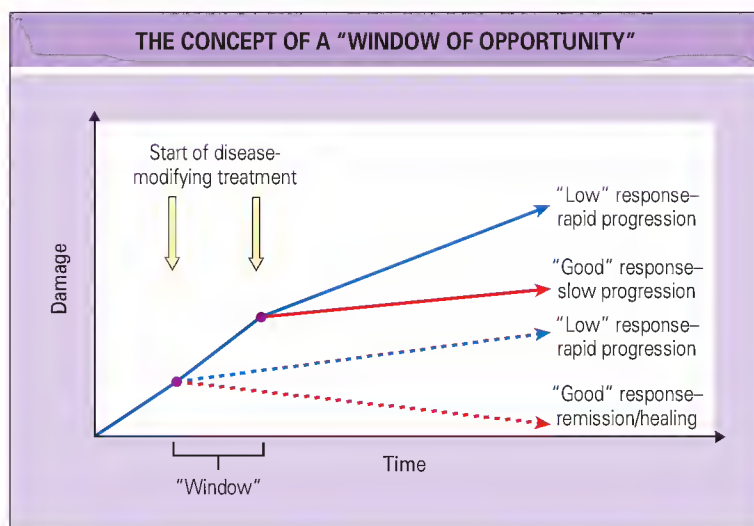


Fig. 95.1 Initiation of disease-modifying treatment leads to retardation of the disease process, although the effects may vary from patient to patient (“low” or “good” response). In a patient showing a “good” response, early treatment may be able to reverse the disease process. This effect may be lost if the same treatment is started later.

initiating (even very aggressive) treatment in patients in whom RA is highly likely to develop.

CLINICAL DETECTION OF SYNOVITIS

Arthritis is usually painful; conversely, joint pain does not always correspond to synovial inflammation. Swelling—the hallmark of synovitis—may be subtle or hidden beneath muscle or bone (hip, shoulder) or subcutaneous fat (obesity). This causes considerable uncertainty in the clinical assessment of synovitis, with high interobserver variability. Higher sensitivity for synovitis may be achieved by ultrasonography.^{26,27} However, this technique is still not universally available and is time-consuming and costly. Therefore one still needs to rely on clinical examination. At least for the purpose of evaluating joints longitudinally, this should be done in a “standardized” way. The EULAR has issued an illustrated guidebook that offers instructions on joint examination.²⁸ Because pain may be present even if joint swelling is subtle, a positive metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joint compression test (Gaenslen test) offers additional evidence for MCP and MTP arthritis. A positive compression test provides a major contribution to diagnostic algorithms in early arthritis and is present in more than 60% of the patients in whom RA will be diagnosed. Stiffness after rest (frequently referred to as “morning stiffness”) of long duration (more than several minutes) is another typical symptom of joint inflammation. The 1987 RA classification criteria require a duration of at least 1 hour. The stiffness associated with osteoarthritis is typically much shorter. Therefore morning stiffness lasting longer than 30 to 45 minutes may be seen as characteristic of an inflammatory joint disease.²⁵

Many patients whose arthritis will subsequently be diagnosed as RA have low numbers of swollen or tender joints at onset of the disease or at initial physician consultation. In one study involving a very early arthritis cohort, more than 25% of the individuals in whom erosion developed within 1 year had 5 or fewer swollen joints on a 28-joint count at initial evaluation.¹⁸ In another study, patients with early arthritis in whom RA developed had a median of 4 swollen joints and more than 25% had fewer than 4 tender joints on a 44-joint count. In recognition of the implications of these observations, a EULAR task force recommended consideration of early RA even with only one persistently swollen joint.²⁹ Nevertheless, the proposed algorithms for early detection of RA,^{25,30} as well as the ACR/EULAR criteria for RA, weigh polyarthritis more than monoarthritis or oligoarthritis.

EVALUATION AND DIFFERENTIAL DIAGNOSIS OF EARLY ARTHRITIS

Arthritis occurs in many diseases, such as metabolic, degenerative, infectious, and neoplastic disorders. In evaluating arthritis patients, special attention should be directed to the history, to extraarticular signs of disease and the pattern of joint involvement, and to serologic and imaging studies.

In light of the lack of validated recommendations regarding which studies should (or need not) be performed in early arthritis, clinicians may adhere to either of two sets of recommendations. One of these³¹ suggests rapid referral to a rheumatologist in the event of clinical suspicion of RA. According to this guideline, such suspicion should be supported by three characteristics: three or more swollen joints, positive MCP or MTP compression test, and morning stiffness lasting longer than 30 minutes. The other expert panel recommended referral of patients with one or more swollen joint within 6 weeks of the onset of symptoms to a rheumatologist. Careful history taking and clinical and laboratory examinations to exclude other diseases were also suggested. It was emphasized that the probability of persistence increases with the number of swollen and tender joints, with the presence of APRs, and with autoantibody (RF, ACPA) levels; radiographs should be taken to reveal erosive disease.^{24,29}

History and extraarticular clinical signs

Transient arthritis (frequently caused by viral infections) is usually self-limited and thus easily differentiated from RA. Therefore in patients whose arthritis has been present for only several days (up to a few weeks), it may be sufficient, in addition to clinical joint examination, to take a thorough history with special attention directed to exposure to infectious agents (such as contact with people suffering from a rash or fever); preceding infection, rash, or fever in the patients themselves; weight loss; or previous arthritis episodes (such as may occur with crystal-induced arthritis).

Once the duration of arthritis exceeds a few weeks (the threshold most likely lying between 6 and 12 weeks), the differential diagnosis becomes much broader. The differential diagnoses encompass forms of seronegative spondyloarthritis such as reactive arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, and psoriatic arthritis. In addition, sarcoidosis with arthritis (Löfgren syndrome), connective tissue diseases, rheumatic fever, gout and pseudogout, and osteoarthritis with inflammatory activation are part of the differential diagnostic list. Thus the examination and history should focus on signs of psoriasis (or patients may have a relative with psoriasis), urogenital or gastrointestinal infection, and “inflammatory” back pain. Extraarticular involvement (eyes, mucous membranes, skin) may be subtle and needs to be sought and inquired about. Erythema nodosum may be a sign of sarcoidosis or inflammatory bowel disease, and the arthritis frequently involves the ankle joints symmetrically. In sarcoidosis, typical changes may be present on the chest radiograph; inflammatory bowel disease may be revealed by upper or lower gastrointestinal endoscopy. The rare connective tissue diseases generally show additional clinical manifestations such as myalgias, skin changes (e.g., an ultraviolet light–induced rash, alopecia, sclerosis, telangiectases, Raynaud phenomenon, and others), lymphadenopathy, and manifestations of internal organ involvement. A history of an untreated upper respiratory tract infection (e.g., tonsillitis) may be suggestive of rheumatic fever (or reactive arthritis if the time between the infection and the arthritis is less than 1 or 2 weeks). The characteristic history of crystal arthropathies (including an acute onset of gout after heavy meals or alcohol intake, immobilization, chemotherapy, and preceding episodes of a similar arthritis) is usually diagnostic.

Patterns of joint involvement

Chronic arthritis may show a number of more or less distinct “joint patterns” (Fig. 95.2). This has also been recognized in development of the aforementioned algorithms for risk stratification. Monoarthritis or oligoarthritis (i.e., involvement of two to four joints), though regarded to be a sign of less aggressive disease, may nevertheless represent the initial manifestation of a chronic destructive arthritis. Hand involvement, in particular, is considered to confer a high probability of destructive arthritis. Arthritis mostly in large joints, asymmetric patterns, and early spinal symptoms may be indicative of seronegative spondyloarthritis. In addition, inflammatory/active osteoarthritis of the hands may be manifested as oligoarthritis or polyarticular arthritis, albeit usually with clinically detectable preexisting bony proliferation (Bouchard or Heberden nodes). Although these patterns are sometimes quite characteristic and may be diagnostic (e.g., psoriatic skin or nail lesions), exceptions and “overlap” manifestations (e.g., development of classic seropositive RA in an individual with preexisting Bouchard nodes) occur frequently.

Laboratory and imaging studies

In a patient with early polyarthritis, careful history taking and clinical examination with special attention paid to synovitic swelling and its distribution may allow a preliminary classification and thus an appropriate

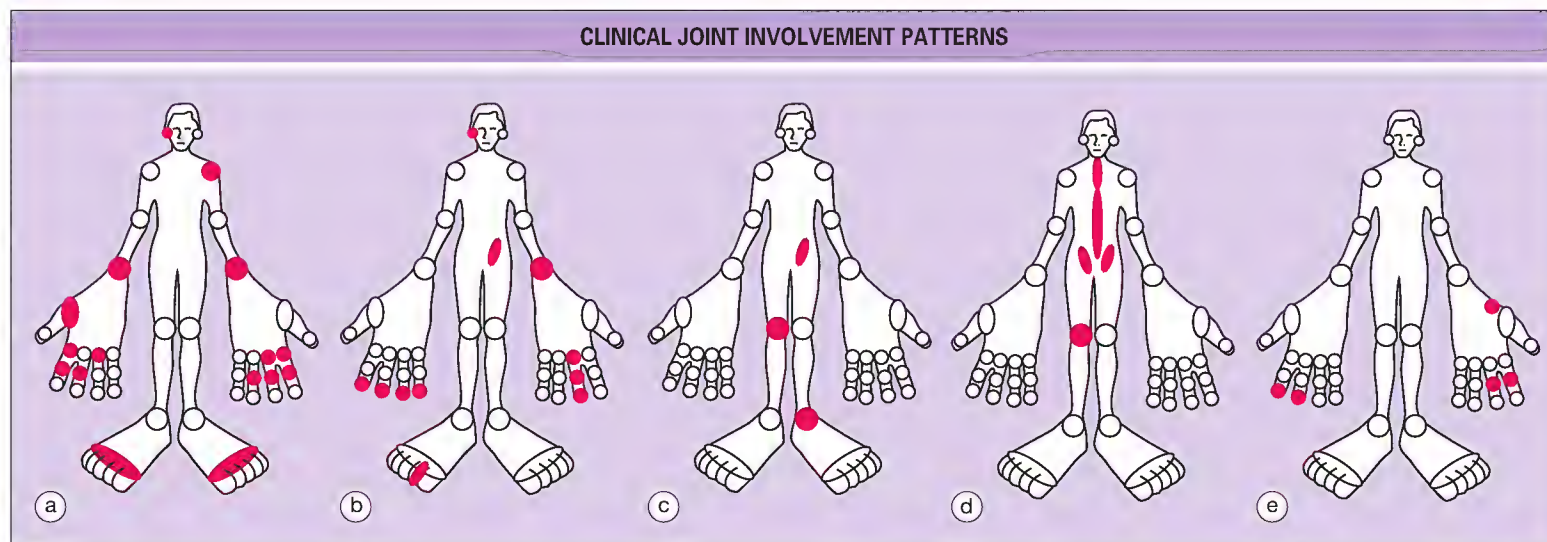


Fig. 95.2 (a) "RA pattern." In rheumatoid arthritis (RA), symmetric involvement of small joints (in particular, the hand and feet joints) is considered characteristic. Involvement of larger joints and the temporomandibular joints, however, may also occur. "Symmetry" is not always absolute; in particular, involvement of "joint regions" such as the "metacarpophalangeal joints" or "proximal interphalangeal (PIP) joints" rather than individual joints is observed. The distal interphalangeal (DIP) joints are usually spared. (b) "PsA pattern." Psoriatic arthritis (PsA) typically affects joints in a "longitudinal" ("ray," left side) or "transverse" (right side) pattern. DIP involvement is found, in contrast to RA. In addition, involvement of the axial joints (e.g., sacroiliac joints, frequently asymmetric) is common. Inflammation of periarticular soft tissues and enthesitis (inflammation of insertions of tendons or ligaments) together with skin changes and arthritis may lead to dactylitis, the so-called sausage digits (as on the right second toe in the panel). (c) "ReA pattern." Reactive arthritis (ReA) is typically a monoarthritis or oligoarthritis with predominance of large joints (mostly of the lower extremities) or sacroiliitis. (d) "AS pattern." Inflammation of the joints of the axial skeleton and, in particular, symmetric sacroiliitis, is the hallmark of ankylosing spondylitis (AS). In addition, enthesitis such as in PsA and large-joint involvement may occur. (e) Osteoarthritis of the hands is characterized by bony enlargement (osteophytes) of affected joints, which are frequently the second and third DIP or PIP joints, as well as the first carpometacarpal joint. In affected joints, inflammatory activation with bony destruction may occur and thus make differentiation from RA or PsA difficult.

estimate of the risk for chronic or destructive/disabling disease. Laboratory and imaging studies, however, not only provide additional information related to this risk but may occasionally also show unexpected results, such as evidence of crystal deposits on radiographs or ultrasound or high-titer antinuclear antibodies in a patient with symmetric polyarthritis of the hands. Therefore all classification, stratification, and diagnostic criteria also include recommendations to perform a minimum set of laboratory investigations, as well as imaging studies. In addition, if the clinical "index of suspicion" is high enough, extended laboratory investigations (e.g., screen for antinuclear antibodies, infections, metabolic disease, and genotyping, such as for HLA-B27 and other genetic traits) may be justified. Most criteria recommend performing tests for APRs and for RF and ACPA.

RF, an antibody specific for IgG, is known to be one of the characteristics of RA and is part of almost all RA classification criteria. Between 46% and 75% of patients with early RA test positive for RF.^{18,32} However, RF is not pathognomonic for RA and frequently occurs in those with connective tissue diseases, hematologic and solid neoplasms, and chronic infections, as well as in healthy individuals, mostly in low titer.³³ High-titer RF (>50 IU/mL), in contrast, has been shown to be highly discriminative between RA and non-RA in patients with early arthritis.³⁴ More recently, ACPAs have been reported to occur relatively specifically in RA³⁵; ACPAs are found in the sera of approximately 50% of patients with early arthritis that is subsequently diagnosed as RA and may be present even before the onset of symptoms. Even more importantly, RF or ACPA (or both) can give prognostic information: they are highly predictive of erosive disease and associated with more rapid progression of joint destruction.^{18,35} Moreover, RF is associated with persistence of arthritis.

In addition to these autoantibodies, elevated APRs are another, albeit nonspecific hallmark of early inflammatory arthritis. Patients with early arthritis destined to suffer from RA usually have higher APRs, such as CRP or the erythrocyte sedimentation rate, than do those in whom RA does not develop.²⁵ Characteristically, in the seronegative spondyloarthritides, APRs are less elevated. However, considerable variability between patients and broad overlap make such distinction difficult for individual patients. Moreover, initially normal or negative tests for APRs do not rule out later evolution of erosive disease. On the other hand, joint damage in early RA increases with increasing APRs.¹⁸

Because the genetic background of RA, as well as reactive arthritis, ankylosing spondylitis, systemic lupus erythematosus, and other rheumatic diseases, is quite characteristic, at least in white populations, it is tempting to

use genetic tests for the differential diagnosis. However, the cost of accurate analyses, as well as the complexities of the genetic influences on a given individual's arthritis, currently precludes the use of these tests for routine diagnosis or prognostication.

At present, the only standard technique for visualizing the changes associated with destructive arthritides is conventional radiography (projection radiography). Unfortunately, this technique is notoriously insensitive to small and early changes.²⁶ Magnetic resonance imaging (MRI) and ultrasonography may allow earlier detection of erosions.³⁶ In addition, if the symptoms raise suspicion for shoulder, hip, or spine involvement (e.g., sacroiliitis in psoriatic arthritis or ankylosing spondylitis), MRI is currently probably the most accurate imaging method.

It is also important to recognize that the experience of the reader determines the accuracy of the radiographic diagnosis. Thus only a specialist (radiologist, rheumatologist) experienced in assessing RA radiographs should perform the reading. The presence of erosions, which occur in a majority of RA patients, is very characteristic, albeit not to be expected in the very early stages of the disease. Occurrence of radiographic erosions early after the onset of symptoms is indicative of RA³⁰; however, at a mean of 8 weeks after the onset of arthritis, these changes are found in less than 10% of patients.¹⁸ Therefore this is not a characteristic of early RA. More importantly, the very aim of early diagnosis and treatment is prevention of (possibly irreversible) joint destruction. Thus the diagnosis needs to be made before the appearance of joint destruction.

PROGNOSTICATION IN EARLY ARTHRITIS

The major purpose of diagnosing a disease in a patient is to guide treatment decisions on the basis of prognosis. This prognosis, in turn, determines the timing and intensity of treatment. These treatment decisions determine the frequency of reassessment and follow-up. From the patients' view, the prognosis will also determine the risk involved in taking potentially toxic drugs or undergoing unpleasant or time-consuming treatments such as wearing splints, exercising, or physical therapy. Early prognostication should identify patients who may benefit most from therapeutic intervention and separate them from individuals in whom possibly toxic treatment might cause more harm than benefit. The improved sensitivity of the 2010 ACR/EULAR criteria may help guide these decisions, particularly when differential diagnoses are carefully considered.

TREATMENT OF EARLY ARTHRITIS

Nonsteroidal antiinflammatory drugs and nonmedicinal therapies

Up to 60% of all patients with early arthritis may have a self-limited or benign course.^{19,30} For these patients, only temporary symptomatic relief through the use of nonsteroidal antiinflammatory drugs (NSAIDs), which may also shorten the duration of arthritis, is necessary. NSAIDs do not alter the course or outcome of the arthritis, and long-term use of them may be associated with considerable side effects.

In all forms of arthritis, physical measures such as the application of cold packs or using splints to prevent mechanical irritation have been advocated as temporary or long-term measures. Evidence of effectiveness of these measures, however, is still insufficient or even negative.^{37,38} Given the lack of side effects and possible individual benefits, however, most authors recommend the use of these treatments as palliative or adjunctive measures combined with exercises.

Glucocorticoids

Before the threshold of several weeks or a few months for “persistence” is reached, DMARDs may not be appropriate because they are prescribed for longer periods and their toxicities outweigh the risk associated with a self-limited condition. In clinical practice, glucocorticoids are often used, either by intraarticular or intramuscular injection. Alternatively, short courses of oral glucocorticoids may be prescribed in these patients with very early arthritis. In one of the few studies explicitly addressing the issue of treatment of very early (*not* rheumatoid) arthritis, Green and colleagues³ administered a single dose of 120 mg of methylprednisolone intraarticularly or intramuscularly. The results of this open study suggested that this approach is safe and leads to a significant number of disease remissions. More recently, two additional studies explored the value of glucocorticoids for the management of such patients with very early arthritis^{16,39}: the STIVEA (Steroids in Very Early Arthritis) study found a small, though significant benefit of three weekly injections of depot glucocorticoids in a population with early (<12 weeks' duration) undifferentiated arthritis; however, the SAVE (Stop Arthritis Very Early) study, which used only a single injection in a very similar patient population, could not confirm these findings.

Unlike maintenance therapy with oral glucocorticoids, short-term intermittent use of them is considered safe despite limited scientific evidence to underscore this.⁴⁰

Disease-modifying antirheumatic drugs

In persistent early arthritis (i.e., after 6 to 12 weeks), DMARDs, either singly or combined with glucocorticoids, are appropriate and necessary. Glucocorticoids are regarded as both safe and efficacious singly or combined with DMARDs.^{41,42} In this setting, superiority of early initiation of DMARDs over delayed treatment or treatment with NSAIDs alone has been demonstrated conclusively.⁴³ Because the characteristic bone or cartilage destruction of erosive arthritis rarely, if ever, heals^{44,45} and thus damage accumulates over time, these agents will have better effects on outcome the earlier they are started.

As in established RA, methotrexate is regarded as the drug of first choice in view of its favorable risk-benefit ratio. Other DMARDs such as leflunomide, (hydroxy-)chloroquine, or sulfasalazine may be considered in “mild” cases or in patients with contraindications, such as the desire to become pregnant or significant comorbid conditions such as liver or kidney disease. Likewise, at least in patients who at these stages were classified as having RA, a combination of glucocorticoids and DMARDs offered additional benefits in terms of clinical response, as well as radiologic outcomes,^{41,46} although these findings have not been universally reproducible.⁴⁷

More recently, “aggressive” treatment strategies have been proposed that use combinations of DMARDs or the addition of tumor necrosis factor (TNF) antagonists to “conventional” DMARDs for early “criteria-positive”

RA.^{2,32,48,49} In these randomized trials, combination therapies or the addition of “biologic” drugs resulted in outcomes superior to those with less aggressive “conventional” approaches. It is important to mention that some, but not all combinations of (conventional) DMARDs may be superior to using the same DMARDs singly.⁵⁰ Furthermore, an important limitation in interpreting the results of these trials is that all of them included only patients who fulfilled the 1987 ACR RA criteria at the time of inclusion. Thus it remains unclear whether the possibly higher risk associated with more aggressive strategies is warranted, at least in the subset of patients with less destructive disease.

Biologic agents

Biologic drugs are currently licensed only for established RA and after the failure of at least one DMARD. The BeSt (Behandel-Strategieën [Treatment Strategies]) trial revealed that TNF blockade in patients with early RA yields good clinical results, although combination therapy with DMARDs and intermediate-dose glucocorticoids had similar clinical, functional, and radiographic outcomes.⁴⁹ Currently, several trials are testing TNF antagonists for early undifferentiated arthritis with substantial potential for destruction or persistence (such as RF or ACPA positivity or inflammatory arthritis for a minimum duration). These studies are attempting to clarify whether such extremely early intense intervention might substantially and possibly permanently influence long-term outcomes or even prevent the development of “full-blown” RA (etanercept: the EMPIRE [Etanercept and Methotrexate in Patients to Induce Remission in Early Arthritis] and RIVERA [Remission Induction in Very Early Rheumatoid Arthritis] trials, controlled-trials.com-number, International Standard Randomised Controlled Trial Number [ISRCTN] 55428162 and ISRCTN 49682259; infliximab: DINORA [Definitive Intervention in New-Onset Rheumatoid Arthritis] trial, ISRCTN 21272423).

A recent analysis has revealed that the fate of any DMARD therapy, methotrexate or biologic, can be predicted within 3 to 6 months after commencement. Thus starting patients with early RA on a more traditional therapeutic approach and then switching rapidly to another compound may be the most practical strategy.

CONCLUSION

Early inflammatory arthritis represents a challenge in everyday practice. Differentiation should be made as quickly as possible (within several weeks) between relatively benign disease and conditions needing urgent, highly active treatment. In addition, the treatment intensity selected should avoid the excessive risk associated with at least some of the therapies. Because earlier intervention may be more effective before the underlying pathogenic processes are “fully established” and have reached the “autonomous” stage thought to prevail in the later phases of RA, it seems advisable to treat as early as possible, ideally before damage (the visualized destruction of cartilage, bone, or both) has occurred. The only, albeit still unresolved obstacle to early therapy remains early diagnosis or prognostication (or both). In recent years, however, knowledge of risk factors has advanced and criteria for therapeutic decisions have been refined. In particular, certain disease features appear to indicate an unfavorable prognosis: a higher number of swollen joints, a positive Gaenslen test, RF levels of 50 IU/mL or higher or a positive ACPA test, and elevated CRP appear to confer a very high risk for persistent (and erosive) disease. In addition, the presence of erosions on radiographs confirms the destructive nature of the arthritis. Persistence of arthritis for more than 6 weeks and (initial) oligoarthritis accompanied by serologic evidence of inflammation (RF ≥50 IU/mL or ACPAs) are likewise regarded as indicators of a high risk for the development of chronic and destructive joint disease. In all instances, other diseases associated with arthritis should have been excluded. In a patient fulfilling these criteria, prompt DMARD therapy is advisable to prevent further persistence, joint damage, and disability. In addition, expert consensus calls for rapid referral to a rheumatologist in the event of clinical suspicion of persistent arthritis or RA.

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96

Evaluation and outcomes of patients with rheumatoid arthritis

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- Assessment of patients with rheumatoid arthritis is aimed at evaluating or prognosticating the disease process or disease outcome.
- The 2010 classification criteria for rheumatoid arthritis were developed jointly by the American College of Rheumatology and the European League Against Rheumatism to allow assessment and timely institution of treatment in patients with very early and established disease.
- Core sets of individual measures of the disease process have been defined and include joint swelling and tenderness, the acute-phase response, pain, patient global assessment, and evaluator global assessment.
- These individual measures can be effectively integrated into composite indices that allow determination of actual disease activity, as well as disease activity states.
- In clinical practice, disease activity (the disease process) is the immediate target of therapeutic interventions, whereas the ultimate goal of treatment is improvement of disease outcomes and health-related quality of life.
- In clinical trials, disease activity states and responses, as well as their time of onset and sustainment, should be reported.
- The typical proxy for disease outcome is radiographic damage, which is a surrogate for the accrued joint destruction and can be assessed by a variety of quantitative scores.
- Impairment of physical function (disability) is another important outcome and can be assessed with questionnaires, typically the Health Assessment Questionnaire, or direct functional performance tests, such as grip strength.
- Physical function is influenced by both disease activity and joint damage; functional disability related to joint damage is currently considered to be irreversible.

INTRODUCTION

Over the past 2 to 3 decades the approach to treating patients with rheumatoid arthritis (RA) has undergone a spectacular evolution that still continues to advance and has led to unprecedented outcomes. It is a consequence of better insight into the natural history of the disease, better understanding of pathogenic pathways, a burst of novel therapies, innovative clinical trial design, recognition of the importance of treatment strategies over and above the mere application of drugs, and the development of tools to assess RA and its progression reliably.¹ It is particularly the latter that has allowed one to comprehend many aspects of the natural and therapeutically modified course of RA, to design elegant clinical trials, and to develop and modify strategic targets in RA therapy. Many of the instruments developed can be applied in clinical practice quite easily, thus signifying the translation of clinical trial results into the reality of daily patient care. In this chapter the various ways of assessing patients with RA are discussed. However, before assessment of RA can be discussed, adequate diagnosis or classification is needed. In this regard, the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA have been published.²⁻⁴ In the first section of this chapter a brief overview of these new criteria is presented.

2010 AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

Until 2010, the classification criteria used for RA were those promulgated by the American Rheumatism Association in 1987. These criteria have increasingly been debated in the recent past because of their lack of sensitivity for early disease, given that they had been derived mostly from patients with long-standing, established RA. The joint working group of the ACR and the EULAR therefore aimed to develop new classification criteria for RA that would replace the 1987 criteria. From July 2007 to June 2010 the working group engaged in a three-step procedure that included a data analysis phase involving cohorts with early arthritis, a consensus science phase, and a refinement phase that led to three publications detailing the process and the final criteria.²⁻⁵

As shown in [Table 96.1](#), the 2010 criteria comprise four domains: (1) a joint domain, including the number and type of affected joints; (2) an autoantibody domain encompassing rheumatoid factor (RF) and anti-citrullinated peptide/protein antibodies (ACPAs); (3) a domain of surrogates of the inflammatory response, namely, acute-phase reactants (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]); and (4) a domain related to the duration of symptoms. For evaluation of a patient, the highest category within each domain is used and the four respective numbers are added. The maximum possible score is 10, with any score of 6 or higher indicating the presence of definitely classifiable RA. Another way to classify RA based on the same rules is with the use of a tree algorithm, which leads to the same classification results as the numerical approach. Radiographic evidence of erosions may be considered *prima-facie* evidence of RA, and patients can be directly classified as such. A respective algorithm has been put forward,⁶ and the term “erosiveness” has been clarified in this context as at least three joints with a minimum of one erosion each.⁷

The 2010 criteria should be applied to any patient with at least one clinically swollen joint for which another disease is not the most likely cause. A large number of studies have in the meantime been published that investigated the performance and substantiated the validity of the new criteria in different settings. These studies have very recently been summarized in a systematic review of the literature.⁵

These classification criteria, though especially useful for groups of patients entering clinical trials, can help support a clinical diagnosis of RA but cannot replace it. Establishment of a clinical diagnosis by a physician is the most important step before appropriate therapy can be instituted. Thereafter, it is of utmost importance to monitor patients regularly with respect to their disease activity and outcome. These aspects are discussed in the next sections of this chapter.

CONCEPTS

From pathogenesis to measurement

It is currently not possible to capture the cellular and molecular events leading to RA at the site of involvement, such as the joint or lymphatic organs. Even if we could routinely obtain snapshots of the expectedly manifold and heterogeneous interactions of pathogenic cells and molecules, their hierarchy or relative dominance would not yet be evident to us. As a consequence, measurements have to rely on phenomena that are further downstream from these pathogenetic events.

TABLE 96.1
ACR/EULAR classification criteria for rheumatoid arthritis*

	Score
Joint involvement (0-5)^a	
1 medium to large joint ^b	0
2-10 medium to large joints	1
1-3 small joints (with or without involvement of large joints) ^c	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least one small joint) ^d	5
Serology^e (0-3)^f	
Negative RF and negative ACPAs	0
Low-positive RF or low-positive ACPAs	2
High-positive RF or high-positive ACPAs	3
Acute-phase reactants^f (0-1)^g	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms^g (0-1)	
<6 wk	0
≥6 wk	1

*Score-based algorithm for classification of an eligible patient (cut point for rheumatoid arthritis: ≥6/10).

^aIndividuals should be scored with these criteria only if at least one serologic test and at least one acute-phase reactant test result is available. When a value for a serologic test or acute-phase reactant is not available, that test should be considered "negative/normal."

^bJoint involvement refers to any swollen or tender joint on examination or evidence of synovitis on magnetic resonance imaging or ultrasonography. The distal interphalangeal joints (DIPs), first carpometacarpal (CMC) joint, and first metatarsophalangeal (MTP) joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of the involved joints, with placement into the highest category possible based on the pattern of joint involvement.

^cMedium to large joints refer to the shoulders, elbows, hips, knees, and ankles.

^dSmall joints refer to the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, metatarsophalangeal (MTP) joints 2 to 5, thumb interphalangeal (IP) joints, and wrists.

^eIn this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular).

^fNegative refers to international unit (IU) values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are greater than the ULN but less than or equal to three times the ULN for the laboratory and assay; high-positive refers to IU values that are more than three times the ULN for the laboratory and assay. When RF is available only as positive or negative, a positive result should be scored as "low-positive."

^gNormal/abnormal is determined by local laboratory standards.

^hDuration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) in joints that are clinically involved at the time of assessment.

ACPs, anti-citrullinated protein/peptide antibodies; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; RF, rheumatoid factor.

From Aletaha D, Neogi T, Silman AJ, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1580-8.

For example, the acute-phase reactant CRP is known to be induced by interleukin-6, which in turn can be activated by tumor necrosis factor, interleukin-1, and other pathways. Thus, CRP and other acute-phase reactants, which can easily be measured in peripheral blood, constitute downstream manifestations of cytokine activation. Likewise, joint swelling is the downstream ("clinical") expression of synovial inflammation and, consequently, the totality of the underlying inflammatory events, not just for a particular segment such as cytokine activation. Another example is joint destruction, which is elicited by osteoclasts on the one hand (bony damage) and chondrocytes and metalloproteinases on the other hand (cartilage damage), both of which are induced during the active disease process. Currently, we are likewise unable to directly visualize this process as it occurs, but radiographic scores constitute the cumulative downstream markers of these events. Novel imaging techniques, such as methods of molecular and cellular imaging, may shift this paradigm upstream in the future and allow earlier detection and measurements.

The previous list could be expanded broadly but was just meant to exemplify the difficulty in depicting the basic pathogenetic pathways and the need to use their downstream expressions, ideally in some kind of combination, to best summarize the basic events, which are currently still enigmatic, at least from the perspective of accurate measurement.

INTERRELATIONSHIP OF DISEASE PROCESS AND OUTCOMES, AND THE ROLE OF THERAPY

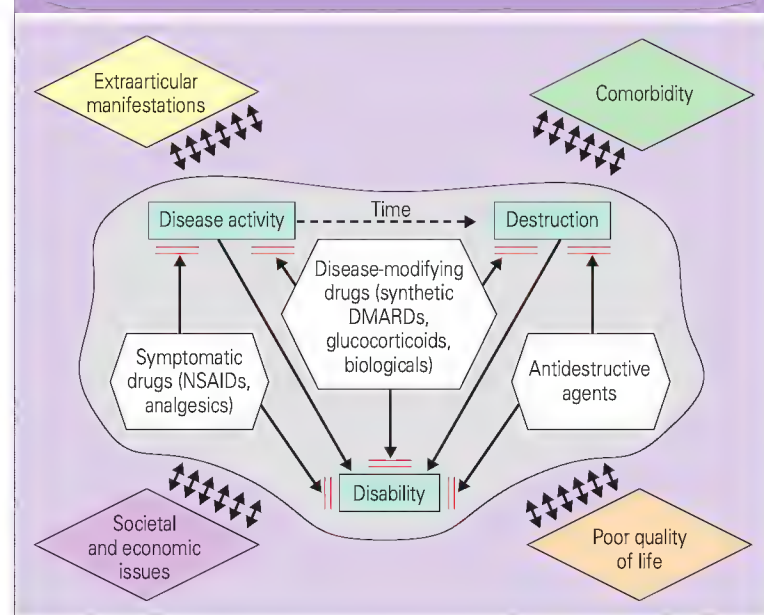


Fig. 96.1 Interaction of disease activity, structural damage, and impaired physical function in rheumatoid arthritis. The effects of different classes of therapeutics are indicated in the hexagons. At any point in time for a patient with rheumatoid arthritis, there is also an interaction with the environment. DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal antiinflammatory drug.

Validity of assessments

Assessment is all about measurement and its use to characterize attributes of a disease, including its outcome and prognosis. Any measurement used to evaluate aspects of a disease, be it laboratory tests or clinical measurement tools, must comply with a variety of requirements. It should reflect an important aspect of the disease (as judged by investigators, patients, or both), be reliable, be sensitive to change and thus fulfill the fundamental validity criteria, and be practical and easy to use (feasibility).

Disease process ("disease activity") and consequence ("disease outcome")

In the context of the assessment of patients with RA it is essential to bear in mind that RA, like many other disorders, has several facets that need to be captured. The cardinal elements are disease activity and joint damage, which are both reflections of the underlying pathobiology. At the same time they are intimately associated with other important attributes, such as impairment of physical function, reduction in quality of life, extraarticular manifestations, systemic effects on patient well-being, comorbidity, societal and economic aspects, and mortality (Fig. 96.1). It is legitimate to focus on some of these facets more than on others because, first, there is a hierarchy within this diversity; second, they are all intertwined; and third, some are relatively specific for RA, whereas others are common to many disorders. However, all these components must be taken into account when evaluating RA, and each has its inherent complexity.

Process variables reflect the actual pathophysiologic events and thus constitute mostly instant measures of disease activity, such as swollen joint counts or acute-phase reactant levels. Outcome variables measure the long-term consequences (or sum) of the disease process and include joint damage and physical disability.^{8,9} However, many variables constitute mixtures of both, thereby adding another layer of complexity (see Fig. 96.1). Thus, several process variables, when integrated over time, reflect outcome and several outcome measures reflect actual disease activity, at least in part. Impaired physical function or quality of life, for example, will not only be a long-term product of the process but will also result from actual manifestations, such as pain, joint swelling, and stiffness.

Measures of disease activity may therefore be better defined as variables reflecting the underlying events, which can fluctuate rapidly, spontaneously, or with treatment and have the principal potential to normalize. In contrast, measures of disease outcome, even if they may additionally mirror the actual disease process at an individual point in time, reflect an abnormality that may become fixed in the course of the disease and then no longer bears the

potential to improve, let alone normalize. In other words, *outcome* relates to (a varying degree of) irreversibility (with the ultimate worst outcome being death), and *disease activity* relates to reversibility, amenability to interventions, and possible prevention of bad outcomes. The disease process (“disease activity”) and disease outcome are linked by a temporal relationship (see Fig. 96.1). The strength of this link might be predetermined in individual patients, and prognostic markers may help define subgroups of patients (Fig. 96.2).

Effective treatment includes a reversal of the symptoms caused by disease activity and prevention of the natural course of RA, which results in a bad outcome, that is, structural, functional, and all other consequences of the disease. Sometimes, disease activity markers are used as surrogate markers of disease outcome because their presence reflects the future presence of a bad outcome. Here, the concept of prognostication mixes into the mere evaluation process.

Evaluation versus prognostication

An important concept that needs to be derived from the link mentioned between process and outcome is the distinction between evaluation and prognostication. Although evaluation of disease activity at a given time is aimed at improving outcome, that is, changing the prognosis, in practice it is different from the concept of prognostication by measurement of specific markers: a prognostic marker is generally thought to be relatively constant (“fixed”) and therefore relatively consistent if evaluated repeatedly or at different times, whereas an evaluative marker is supposed to vary, especially in the course of treatment, although again some markers may be valuable for both evaluation and prognostication. Evaluative markers are the main content of this chapter. Typical examples of “fixed” prognostic markers are genetic markers, but autoantibodies can sometimes also be regarded as such, given the information provided by their presence or absence at baseline or at the time of diagnosis, although they might still change over the course of the disease. For completeness, the aims and types of prognostic markers are discussed in the following section.

Two questions have historically always been important in this regard: “Will early undifferentiated arthritis evolve into persistent erosive disease?” and “Will severe disease develop in patients with established RA?”

A number of prognostic factors for disease severity have been found, including the presence and titer of autoantibodies such as RF or ACPAs, (early) joint damage, and the HLA-DRB1 shared epitope alleles. The prognostic value of genetic markers for severe, destructive RA probably reflects an indirect relationship that is due to their association with autoantibody production rather than a stand-alone genetic risk factor. However, even the prognostically relevant autoantibodies have the potential—at least in some patients—to improve in levels or turn negative with effective treatment.¹⁰ Similarly, sociodemographic characteristics and behavioral markers can be mentioned here.

Predicting the course of disease in an individual patient is essential for the interaction between rheumatologist and patient and in the context of therapeutic decision-making. Prognostic indicators can be weighted and combined, and algorithms allowing one to recognize patients in whom persistent destructive arthritis will develop among those with early undifferentiated arthritis have been published but need further validation. However, many of the evaluative markers of the disease process, such as joint counts, acute-phase reactants, and others, collected in untreated patients at baseline also have prognostic value.¹¹

Individual measures versus composite indices

Each individual measure of disease activity may relate only to a portion of disease expression. Also, individual patients differ with regard to the features and course of their disease, and even within an individual patient, disease expression may vary during its course. Moreover, each of the surrogates casts particular emphasis on one aspect of the disease, and evaluation of any one of these aspects over time will not allow reliable identification of a patient’s disease activity and response to therapy. In clinical trials, independent evaluation of each variable is afflicted with methodologic difficulties.¹² Composite indices of disease activity overcome these problems^{13,14} by allowing more consistent follow-up of patients in clinical practice, which will improve outcomes of the disease (Fig. 96.3). In addition, patients’ compliance will be improved by enhanced understanding of the treatment targets, which can be expressed by a single number. In clinical trials, sample size requirements will be reduced by having more power provided by a pooled index.

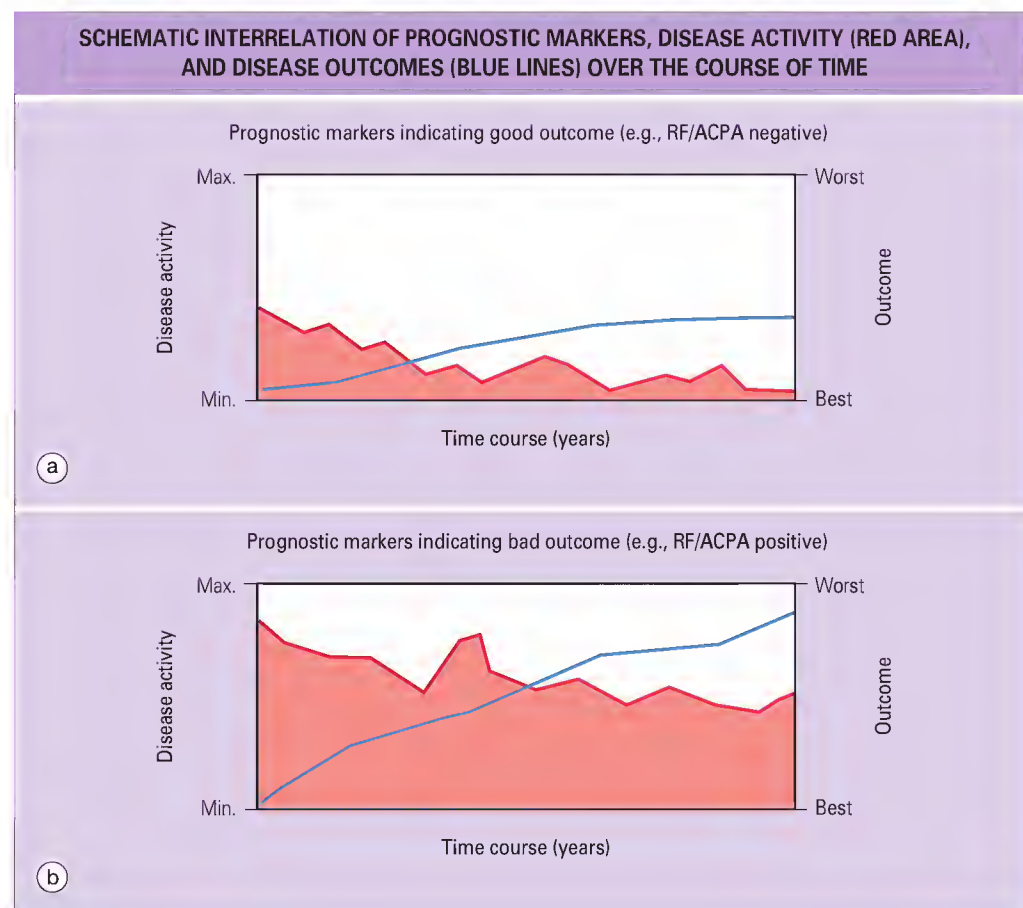


Fig. 96.2 (a) Example of a patient with good markers. (b) Example of a patient with bad markers. ACPA, anti-citrullinated peptide antibody; RF, rheumatoid factor.

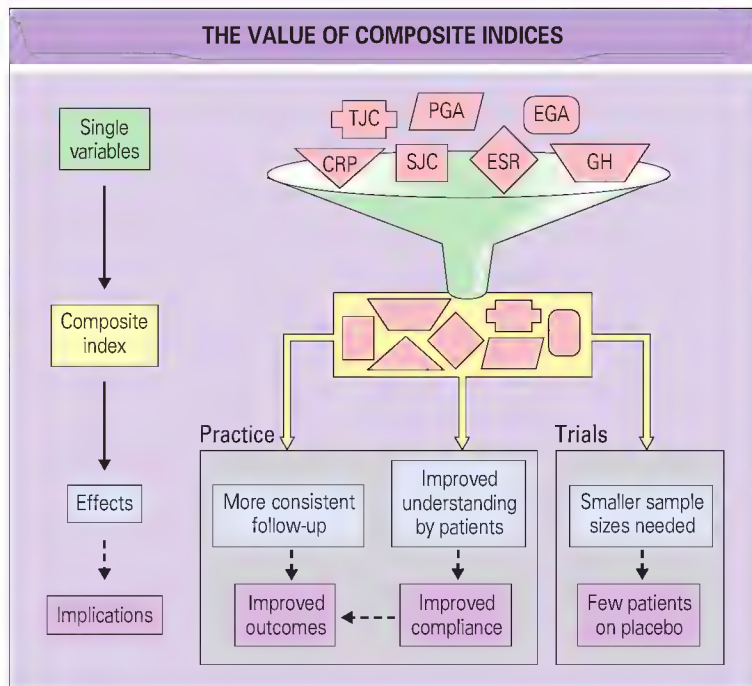


Fig. 96.3 Integration of individual variables into composite indices has beneficial effects in clinical practice and clinical trials. CRP, C-reactive protein; EGA, evaluator's assessment of global disease activity; ESR, erythrocyte sedimentation rate; GH, global health; PGA, patient's assessment of global disease activity; SJC, swollen joint count; TJC, tender joint count.

Definition and evaluation of treatment targets in clinical practice

It is of paramount importance that effective treatment be started in the very early stages of the disease.^{15,16} Once therapy is instituted, a clear therapeutic target needs to be defined. It has become evident that adapting therapy to a predefined target value of a disease activity index (e.g., low disease activity) is by far superior to an unstructured change in treatment.^{17,18} Likewise, the lower the disease activity state and the earlier it is achieved, the less destructive the joint damage will be.¹⁹ Thus, the use of dynamic treatment strategies aimed at a predefined goal is one of the most recent innovative steps.

Importantly, the goal should be to reach a certain level or state of disease activity rather than achieve a particular change ("response") from baseline. Respective evidence comes from secondary analysis of clinical trial data in which patients with ACR 50% or 70% response rates (see later) had worse radiographic outcomes if they achieved only a moderate- rather than a low-disease activity state or remission²⁰; additional evidence comes from patient-reported outcomes in observational studies in which patients judge their disease to have undergone major improvement only if a low- to moderate-disease activity state had been attained, irrespective of baseline disease activity.²¹

Given that the long-term response to therapy can already be predicted 3 to 6 months after initiation,²² therapy should be switched or adapted if no improvement is seen within 3 months or if the predefined goal is not achieved within 6 months. Consequently, especially after the start of treatment or with active disease, follow-up examinations using the appropriate instruments for assessment of disease activity need to be performed at least every 3 months to decide on continuation or adaptation of treatment. Outcome measures such as joint radiographs are needed less frequently, although functional evaluation may complement the insight gained from assessment of disease activity.

Assessment strategies in clinical trials

Although in clinical practice the ultimate goal is to measure each individual patient's disease activity most accurately, this focus shifts a little bit when it comes to measuring disease activity in clinical trials. The purpose of clinical trials is to show that interventions work on the *group* level when compared with another group treated differently. For clinical trial reporting, core set variables have been defined internationally,²³⁻²⁵ and criteria for improvement have been established.^{26,27} More recently, the ACR and EULAR have developed a minimal standard of core information to be provided when reporting

BOX 96.1 EULAR/ACR RECOMMENDATIONS FOR REPORTING CLINICAL TRIAL RESULTS IN RHEUMATOID ARTHRITIS*

Preamble

Several domains are important in reporting clinical trials: disease activity, function, and damage. For each of these domains, response and state should be assessed and reported in clinical trials when appropriate.

However, the following recommendations deal specifically with *disease activity*.

- Each trial should report both the disease activity response and disease activity states.
 - Response*: ACR and EULAR response criteria.
 - States*: Continuous composite indices of disease activity with cut points to define various disease activity states; they include DAS/DAS28, CDAI, and SDAI. Appropriate descriptive statistics of the baseline, the endpoint, and change in composite indices should be reported.
- Each trial should report the appropriate descriptive statistics of the baseline, the endpoint, and change in the single variables included in the core set.
- Each trial should report the baseline disease activity levels, which could have relevance when interpreting the results.
- Each trial should report the percentage of patients achieving a low-disease activity state and remission.
 - Definitions that should be used for low disease activity include cut points for low disease activity for DAS/DAS28, CDAI, and SDAI and MDA.
 - Definitions that could be used for *remission* include preliminary ARA remission criteria and respective cut points for DAS/DAS28, CDAI, and SDAI.
- Each trial should report the time to onset of the primary outcome (a particular response or a certain disease activity state).
- Each trial should consider and report the sustainability of the primary outcome (as opposed to evaluating it at a single predefined point during the trial).
- Each trial should report on fatigue.

*For the definition of the various instruments, please see the respective sections in the chapter.

ACR, American College of Rheumatism; ARA, American Rheumatism Association; CDAI, Clinical Disease Activity Index; DAS28, 28-Joint Disease Activity Score; EULAR, European League Against Rheumatism; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index. Adapted from Aletaha D, Landewe R, Karonitsch T, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Arthritis Rheum* 2008;59:1371-7; and Aletaha D, Landewe R, Karonitsch T, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Ann Rheum Dis* 2008;67:1360-4.

on clinical trials; such information includes baseline *and* endpoint data for the core set variables and composite scores, *as well as* response *and* state data, including proportions of patients with low disease activity and in remission (Box 96.1).²⁸ Inherent in these recommendations is the goal of achieving trial reporting in RA that is consistent across clinical trials rather than varying depending on selected endpoints and that is also meaningful from the clinical rheumatologist's perspective rather than being meaningful merely because of the statistical properties of a specific measure.

INSTRUMENTS FOR ASSESSING DISEASE ACTIVITY

Joint swelling and tenderness, pain, as well as the global impression of disease activity by the patient and the person evaluating the patient, and laboratory measures of the acute-phase response are regarded as the major (core) variables for assessment of disease activity. These measures have been defined in respective core sets of the various organizations (see later). In addition, a variety of other variables exist, such as morning stiffness, squeeze pain, and fatigue, and deserve being addressed in this context.

Core sets of disease activity variables

In the early 1990s, efforts to select a minimum set of measures to be included for assessment of disease activity in RA clinical trials arrived at similar results across various international organizations. The core sets comprise tender and swollen joint counts (TJCs, SJC), patient assessment of pain and global disease activity (PGA), evaluator assessment of global disease activity (EGA), acute-phase reactants (CRP, ESR), physical function, and radiographic assessment of joint damage. Derivation of these measures was driven by data, was supported by consensus, and showed validity in all respects (see Box 96.1). The ACR and World Health Organization/

International League Against Rheumatism core sets were identical and originally called for examination of 66 joints to determine the SJC, examination of 68 joints to determine the TJC, and evaluation of physical function as assessment of disease activity, whereas radiographic changes were the sole outcome measurement. The EULAR core set did not include EGA and used 28 joints for the SJCs and TJCs. Subsequently, the ACR also approved the application of reduced joint counts. Moreover, the EULAR regarded functional assessment as an outcome measure, in addition to joint damage, rather than a measurement of activity. In the context of this chapter, activity measures, damage, and physical function are discussed separately because we believe in the conceptually distinct, though intertwined nature of activity (process), damage (structural changes), and function, with the latter constituting a hybrid measure comprising the two former and more (see Fig. 96.1).

Swollen and tender joint counts

Joint involvement is the fundamental hallmark of RA. Joints are the “organ involved” for the patient and the “organ of interest” for the rheumatologist. It is therefore virtually obligatory to assess the organ joint at every patient visit. Inflammation of the joint leads to soft tissue swelling (synovitis, effusion), tenderness, pain on motion, reduced range of motion, and in the longer term, damage and deformity. Several joint counts and indices have been developed over the decades that differ in the number of joints assessed or in the way that joints are aggregated into joint regions.

The 66/68-joint count assesses, among many other joints, the distal interphalangeal joints of the hands, which are not usually involved in RA

but frequently affected in osteoarthritis and psoriatic arthritis. The 28-joint count excludes these joints, as well as the joints of the ankles and feet, which are often painful and tender for reasons other than RA; also, these regions are often swollen because of comorbid conditions, thus entailing the possibility of misjudgment. Moreover, the 28-joint count frequently captures involved joints and reflects the complete joint count very well. Importantly, however, use of the 28-joint count for assessment of disease activity does not negate the importance of other joints, particularly those of the feet, which clearly need to be evaluated in the course of thorough follow-up. A variety of other joint counts have been published in the literature, some of which are presented in Table 96.2, which has been adapted from a recent review.²⁹ However, the 28-joint count seems to be the most established reduced joint count at present. Indeed, the 28-joint count is simple and fast to assess and has all the validity attributes.

Joint counts differ not only in the number of joints assessed but also by the fact that some (older) scales weight joints by surface area (usually referred to as “weighted” joint counts) whereas other indices weight joints by severity of swelling and tenderness (usually referred to as “graded” joint counts) (see Table 96.2). Some historic joint indices are discussed in the supplement. Importantly, neither do expanded joint counts convey more information than reduced ones nor does weighting or grading provide added value. Instead, interobserver error increases with the use of more complex means of evaluating joint involvement, which is indeed one of the major problems with joint counts. However, within a single observer, joint counts are reliable. This is also the case with self-assessed joint counts, but the differences from assessor-derived joint counts are tremendous; therefore,

TABLE 96.2
Various joint counts in rheumatoid arthritis

	Ritchie	Lansbury	ACR joint count	CSSRD	44-joint count	Reduced joint survey	32-joint count	28-joint count	18-joint count	16-joint count
Characteristics of the joint score										
Year of publication	1968	1956	1965	1983	1992	1985	NN	1989	2001	2001
Swollen (S)/tender (T)	T	S/T	S/T	S/T	S	S/T	S/T	S/T	S/T	S/T
Number of assessed joints	78	86	68/66	60	46/44	36	32	28	18	16
Joints effectively evaluated			68/66	60	54/52	36	40	28	42	40
Graded	0-3*	0-4	†	0-3						
Weighted		X						‡		
Joint regions included (number of counts on both sides)										
DIP (4 joints)		8	8							
PIP/IP1 (hands) (5 joints)	2	10	10	10	10	10	10	10	2	2
MCP (5 joints)	2	10	10	10	10	10	10	10	2	2
Carpometacarpal (5 joints)		2								
Carpus		2								
Wrist	2	2	2	2	2	2	2	2	2	2
Elbow	2	2	2	2	2	2	2	2	2	2
Shoulder	2	2	2	2	2		2	2	2	2
DIP (feet) (5 joints)		8								
PIP/IP1 (feet) (5 joints)		10	10	10	2 (IP1)					
MTP (5 joints)	2	10	10	10	2	10	2		2	
Tarsometatarsal (5 joints)	2	2								
Tarsus	2	6	2	2	4					
Ankle	2	2	2	2	2		2		2	2
Knee	2	2	2	2	2	2	2	2	2	2
Hip	2	2	2	2					2	2
Acromioclavicular	1	2	2	2	2					
Sternoclavicular	1	2	2	2	2					
Temporomandibular	1	2	2	2	2					
Cervical spine	1									

*Modified by Hart and colleagues to exclude grading of severity.

†The 66/68-joint counts were initially graded for the degree of tenderness and swelling.

‡A weighting of the 28-joint count has been proposed but has never been established in practice.

CSSRD, Cooperative Systematic Study of Rheumatic Diseases; DIP, distal interphalangeal; IP1, first interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal. Adapted from Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9-44.

patient assessment of joint counts is not recommended³⁰ except in those with no or only a few affected joints (i.e., near remission), in which case self-assessment of recurrent joint activity might be a reliable option.

TJCs and SJCes may run common as well as disparate courses. Although TJCs and SJCes correlate with each other, TJCs correlate with pain and are more sensitive to change. TJCs also correlate with disability. In contrast, SJCes correlate much better than TJCs with progression of joint damage, thus suggesting that they reflect the pathogenetic events typical of RA more accurately. Likewise, SJCes correlate well with acute-phase reactants, but when it comes to states near remission, residual joint swelling appears to be structurally more relevant than residual elevations in acute-phase reactants.³¹

Pain

Pain is a prominent symptom in RA. It is assessed mostly on a 100-mm horizontal visual analog scale (VAS) and typically evaluates the period of the last week. Numerical or verbal rating scales are also used, frequently as 5-, 11-, or 21-point scales (the latter in steps of 0.5). Horizontal and vertical VAS scales are well correlated, but vertical scales tend to produce systematically higher values, although patients' ability to complete a VAS is considerably heterogeneous. In this respect, 11-point numerical rating scales of pain seem to be similarly reliable and responsive but are easier for patients to use. The ACR recommends the use of a 10-cm horizontal VAS with "no pain" at one end and "worst possible pain" at the other, without intermediate categories, or the Likert scale (1 = asymptomatic, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) to assess current pain in clinical trials.

Patient and evaluator assessment of global disease activity

Global disease activity rated by the patient or the physician (or practically any other third person evaluating the patient, i.e., the "evaluator") is also typically assessed on a 10-cm VAS. In addition to the PGA, sometimes the global health scale is evaluated, which essentially also includes all possible domains of health outcomes that are not directly related to "disease activity." The subjective PGA and the integrative and more objective EGA are usually assessed in combination. Patients tend to rate their disease activity higher than their evaluators do, a systematic difference, which is a good argument for evaluating both in common ("averaging" effect). One reason for this difference might be that patients relate their disease state to their experience with the disease whereas evaluators relate an individual patient's disease status to their experience with all their patients; more likely, however, it is related to the fact that patients inevitably include their pain levels into assessment of their disease activity.³² If the pain levels are related to chronic problems (i.e., not related to disease activity), a discordance with the evaluator global score may be obvious. The responsiveness of measures of global disease activity is good, and such measures discriminate well between different levels of response and treatment groups.

Acute-phase reactants

The most frequently used and most reliable biomarkers for RA are the acute-phase reactants CRP and ESR. Although many other biomarkers, especially proinflammatory cytokines, also reflect the events ongoing in active RA and may even more directly mirror the disease process and response to treatment, they have not been shown to provide information superior to that afforded by acute-phase reactants. Indeed, biomarkers reflecting joint damage or synovial inflammation have not been shown to provide information superior to that conveyed by CRP. The acute-phase reactants, however, correlate well with SJCes, and time-integrated acute-phase reactants also correlate well with radiographic progression. However, in composite indices, acute-phase reactants, especially CRP, add only little information (unless they are heavily weighted such as in the DAS28 [see later]), although they increase the content validity of a score by encompassing an "objective" laboratory measure. Moreover, acute-phase reactant levels are also prone to elevations because of other reasons, such as infection, whereas they are normal in many patients with RA at initial evaluation. When it comes to radiographic progression, normalization of the acute-phase response is not as important as achieving absence of any joint swelling.³¹

Composite indices of core set measures

Composite measures of disease activity are able to capture the spectrum of the disease despite its variations. This is relevant because RA has very heterogeneous manifestations across individuals and even within individuals when assessed longitudinally. Many features of disease activity provide overlapping information, but they are still complementary in some respects. Thus, evaluation of any single measure does not allow sufficiently accurate

determination of the present level of a patient's disease activity or response to therapy. In addition, it is difficult to decide which single measure should be used as a disease activity marker in clinical trials, and moreover, independent evaluation of all variables is associated with methodologic problems.¹² Composite indices are a solution to this problem because they provide a single result but are based on a combination of several measures. The indices differ in terms of what they measure (i.e., current disease activity or change) and their scales (e.g., continuous or ordinal). Continuous measures usually allow one to determine an "absolute" value of disease activity at any point in time or—by virtue of established cut points—the current disease activity state, such as remission. Historic composite scores are discussed in the supplement.

The composition of various composite scores is shown in Table 96.3. The *Disease Activity Score* (DAS) was derived statistically and based on physicians' decision to start or stop treatment with disease-modifying antirheumatic drugs (DMARDs). This was related to states of high and low disease activity, respectively.³³ The DAS therefore uses a complex formula that involves transformations and weighting of variables (see Table 96.3). The original DAS used the graded Ritchie Articular Index to evaluate joint tenderness and a 44-joint SJC (see Table 96.2), whereas its modification, the DAS28, uses condensed 28-joint counts.³⁴ The DAS and DAS28 have also been modified to include CRP instead of ESR (DAS-CRP and DAS28-CRP) or to exclude assessment of global health (DAS-3 and DAS28-3), and cut points for disease activity states have been derived (Table 96.4). For the DAS28, cut points between high disease activity, moderate disease activity, low disease activity, and remission are 5.1, 3.2, and 2.6, respectively. Although with high ranges of composite indices the probability is high that all or most components contribute fairly equally to the result, the situation is different in the lower ranges of the DAS/DAS28. In this case a single component, such as an acute-phase reactant or a patient's assessment of disease activity, may dominate the score and be misleading of overall disease activity. In fact, many patients in DAS28 remission may have significant residual disease activity, especially a high number of swollen joints, because of the low weight of swollen joints in the formula.³⁵ Moreover, because the ESR is strongly weighted, small changes in the ESR, even within the normal range, may lead to categorization of patients as being in remission even though they have many swollen joints. Therefore, in states of low disease activity, a separate look at the contributing components may be worthwhile before drawing therapeutic conclusions. Given the complex formulas of the DAS and DAS28 and the computational complexity in calculating them, simpler indices were sought and developed.

The variables of the *Simplified Disease Activity Index* (SDAI)³⁶ (see Table 96.4) were selected from the core set of the ACR and the EULAR.^{23,24} It was the first index for RA to use a linear sum of variables that were untransformed and unweighted, a concept based on previous studies on reactive arthritis. The SDAI has been widely validated, and definitions of states of remission and of low, moderate, and high disease activity have been elaborated.³⁷ The SDAI, DAS, and DAS28 require the availability of an acute-phase reactant (CRP or ESR), which frequently precludes immediate assessment because of the unavailability of laboratory results. However, even in the absence of CRP values, the resulting score comprising the residual SDAI components was shown to have correlational and construct validity, as well as sensitivity to change.³⁶ The statistical rationale and validity of such a clinical index, then named the *Clinical Disease Activity Index* (CDAI), were subsequently shown (see Table 96.4).³⁸ The value of the CDAI lies particularly in allowing the treating physician to make prompt treatment decisions based on actual levels of disease activity. Similar to the DAS28, cut points between the states of high disease activity, moderate disease activity, low disease activity, and remission have been defined as 26, 11, and 3.3, respectively, for the SDAI and as 22, 10, and 2.8, respectively, for the CDAI (see Table 96.4). The SDAI and CDAI both have stringent measures of remission that allow only a maximum sum of two swollen or tender joints (2 + 0, 1 + 1, or 0 + 2, respectively).

A variety of patient-reported questionnaires for evaluation of disease activity in RA have been published. The *Rapid Assessment of Disease Activity in Rheumatology* (RADAR)³⁹ is a brief, two-page, patient self-assessed questionnaire that includes six items (see Table 96.3). RADAR requires expert interpretation of its individual items—or the use of other studies as references—but does not provide a single "total" result. Another instrument developed for clinical practice is the *Rheumatoid Arthritis Disease Activity Index* (RADAI),⁴⁰ a five-item questionnaire (see Table 96.3). The RADAI requires the use of a calculator, and its agreement with scores encompassing physician assessment is low. Both the RADAR and RADAI are rarely used in clinical practice and clinical trials; rather, patient self-assessment of physical function is frequently used. Another series of summary measures based primarily on patient report, called the *Routine Assessment of Patient Index*

TABLE 96.3

Indices for evaluation of rheumatoid arthritis activity

	Steinbrocker therapeutic scorecard	Lansbury systemic manifestations	Mallya-Mace*	Paulus criteria	DAS/DAS28 (4 items)	RADAR	ACR response criteria	RADAI	SDAI	CDAI
Year published	1966	1956	1981	1990	1990-1995	1992	1995	1995	2003	2003-2005
Number of swollen joints	X			X	X	X [†]	X	X [†]	X	X
Number of tender joints	X	X		X	X	X ^{†‡}	X	X ^{†‡}	X	X
Joint motion/pain on motion	X	X								
Morning stiffness		X	X	X				X		
ESR/CRP	ESR	ESR	ESR	ESR	ESR/CRP [§]		Either		CRP	
Hemoglobin (Hb)/anemia (An)	Hb	An	Hb							
Weight	X									
Fever		X								
Pain	X	X	X			X	X	X		
Global health	X				X					
Patient assessment of global disease activity				X		X	X	X	X	X
Evaluator assessment of global disease activity				X			X		X	X
Function	X					X	X			
Grip strength			X							
Muscle weakness		X								
Fatigue		X								

*The index was later modified by van Riel and colleagues to include only the number of tender joints, morning stiffness, Hb, and ESR.

[†]Overall swelling and tenderness in joints are graded by the patient.

[‡]List of joint regions, graded for tenderness from 0 to 3.

[§]The DAS/DAS28 was originally calculated by using the ESR and subsequently modified to also allow the use of CRP instead of ESR.

^{||}Global health excluded in the three-variable DAS/DAS28.

^{||}Global disease activity over the past 6 months.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Scale; ESR, erythrocyte sedimentation rate; RADAI, Rheumatoid Arthritis Disease Activity Index; RADAR, Rapid Assessment of Disease Activity in Rheumatology; SDAI, Simplified Disease Activity Index.

Adapted from Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9-44.

TABLE 96.4

Calculation, cut points, and ranges of composite indices

DAS*	4	ESR [†]	$= 0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.33 \times \log_{\text{nat}}(\text{ESR}) + 0.0072 \times \text{GH}$	REM < 1.6	0.23-9.87
	4	CRP [†]	$= 0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.17 \times \log_{\text{nat}}(\text{CRP} + 1) + 0.0072 \times \text{GH} + 0.45$	LDA < 2.4	0.57-9.58
	3	ESR	$= 0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.33 \times \log_{\text{nat}}(\text{ESR}) + 0.22$	MDA < 3.7	0.45-9.37
	3	CRP	$= 0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.17 \times \log_{\text{nat}}(\text{CRP} + 1) + 0.65$	HDA ≥ 3.7	0.77-9.06
DAS28*	4	ESR	$= 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \log_{\text{nat}}(\text{ESR}) + 0.014 \times \text{GH}$	REM < .6	0.49-9.07
	4	CRP	$= 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.36 \times \log_{\text{nat}}(\text{CRP} + 1) + 0.014 \times \text{GH} + 0.96$	LDA < 3.2	1.21-8.47
	3	ESR	$= 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \log_{\text{nat}}(\text{ESR}) \times 1.08 + 0.16$	MDA < 5.1	0.68-8.44
	3	CRP	$= 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.36 \times \log_{\text{nat}}(\text{CRP} + 1) \times 1.10 + 1.15$	HDA ≥ 5.1	1.42-7.87
SDAI	5	CRP	SJC28 + TJC28 + PGA + EGA + CRP	REM ≤ 3.3 LDA ≤ 11 MDA ≤ 26 HDA > 26	0-100
CDAI	4	—	SJC28 + TJC28 + PGA + EGA	REM ≤ 2.8 LDA ≤ 10 MDA ≤ 22 HDA > 22	0-76

*Formulas for the DAS and the DAS28 variations were obtained from the website www.das-score.nl/www.das-score.nl/index.html. Accessed November 2012.

[†]Range of ESR assumed to be 2 to 100 mm/hr and range of CRP assumed to be 0 to 24 mg/dL.

CRP, C-reactive protein; DAS, Disease Activity Score; DAS28, DAS joint count based on 28 joints; EGA, PGA, patient and evaluator assessment of global disease activity; ESR, erythrocyte sedimentation rate; GH, global health; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; REM, remission; SJC, swollen joint count; TJC, tender joint count.

Adapted from Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9-44.

Data (RAPID) scores, have been published recently and include three to five of such measures.⁴¹ RAPID-3 includes three patient-reported measures: physical function, pain, and global estimate; RAPID-4 adds a self-reported joint count from the RADAI (see earlier); and RAPID-5 adds a physician estimate of global status. Thus, RAPID does not include a formal evaluator-assessed joint count and includes physical function, which may be partially irreversibly impaired and therefore limited in its sensitivity to change (see later).

Improvement criteria

Assessing improvement with treatment is important in clinical trials, as well as in clinical practice. The term *improvement* incorporates a time component

and implies that disease activity is assessed and compared with baseline activity. In clinical trials the baseline is usually the trial baseline, whereas in clinical practice it is often less clearly defined. Frequently, it will be the start of a therapeutic segment, which can be a visit of a patient to a specific clinic or (more often) the start of DMARD treatment.

Improvement can be assessed by looking at absolute or relative changes from baseline. However, improvement can also be evaluated by looking at whether a patient has achieved a good clinical state. In principle this evaluation does not depend on comparison to baseline and therefore is more feasible in clinical practice. Finally, there is also the option to assess improvement by combining a change with achievement of a particular disease activity state.

An important step in distinguishing between active medication and placebo was the *Paulus* criteria (see supplement). The ACR improvement criteria²⁶ are a modification of the Paulus criteria and have been used widely in clinical trials in the past decade. They require 20% improvement (“ACR20”) in SJCs and TJCs and in three of the five remaining core set variables (patient and evaluator global assessments, pain assessment, physical function, and acute-phase reactant level). These criteria were developed to best discriminate the effects of active drug from placebo in clinical trials. The minimal improvement is a 20% response (ACR20), but the criteria have also been applied to study more profound responses, such as ACR50 and ACR70, although the latter do not discriminate better between placebo and active medication and may even have less statistical power. Similar to the Paulus criteria, the ACR criteria do not consider the starting level of a patient’s disease activity and provide only a dichotomous “yes/no” result. The numerical ACR response, the ACR-N, has been developed to create a continuous scale ranging from 0% to 100%, and it uses the original structure of the ACR response criteria. The readout is the smallest relative improvement in three measures: SJC, TJC, and the median of the five remaining core set variables.⁴² One point of criticism regarding the ACR type of response criteria is the issue of neglecting deterioration (0% is the minimum). In addition, the ACR-N response cannot be assessed over time (area under the curve) since the results may be inflated because of calculation of response in comparison to baseline at every time point. It should be emphasized that an area under the curve analysis of continuous composite indices (cumulative disease activity over time) can be useful for determining differences between treatment groups when rapidity of response is an issue.

A few years ago the ACR response criteria were modified, and the ACR adopted the so-called Hybrid-ACR criteria as its new official response measure.⁴³ The *Hybrid-ACR* is a pseudo-continuous index that is based on the traditional ACR response assessment. To obtain the Hybrid-ACR, first the average percent improvement in the core set measure needs to be determined, but in the case of worsening, the percentage is censored by 100%, even if the respective measure deteriorated by much more. Thereafter, two outcomes are determined: first, the average of the percent changes across all core set measures and, second, the level of traditional ACR response (i.e., ACR nonresponse or ACR20, ACR50, or ACR70 response). The Hybrid-ACR, then, is the first of these two (mean percent change across the core set variables), except if it does not fall within the respective range of the traditional ACR response. In such cases the response is categorized to values of 19.99, 49.99, and 69.99 if the mean core sets are lying above the traditional ACR categories achieved, or they are set to 20, 50, or 70 if the mean core sets are lying below the respective ACR categories. The Hybrid-ACR is therefore a rather complex index with an unusual distribution that has natural peaks at the values mentioned. Its statistical properties have not yet been determined clearly. Although it has been adopted because it discriminates active drug from comparator at the highest level of statistical significance, it has not been a primary outcome measures in major clinical trials to date.

The EULAR response criteria require not only a certain degree of improvement but also attainment of a good (or moderate) disease activity state (Fig. 96.4).²⁷ The EULAR criteria are based on DAS or DAS28 measurements. They classify improvement into no, moderate, or good response. In clinical trials, good plus moderate responses tend to be somewhat higher than the ACR20 response, and a good EULAR response is usually more frequent than an ACR50 response.

Finally, response criteria have recently been introduced for the SDAI and CDAI.⁴⁴ Their development process was based on using the ACR 20/50/70 response criteria as the comparator, and complex statistical methods to derive a comparable SDAI (or CDAI) 50%, 70%, and 85% response were included. Calculation of the SDAI and CDAI response level is a simple relative change from a given baseline, which typically would be the start of a clinical trial or initiation of a new DMARD in clinical practice. For each level it produces a yes/no response similar to the ACR criteria and allows quantification of patients who have reached the respective mark.

Remission criteria

Today’s ultimate treatment goal for RA is remission. At no point during the history of RA have so many patients been able to achieve remission. Remission is regarded as no or only minimal residual disease activity. Remission criteria have historically been complex and required a time frame of presence; however, remission is currently considered a state that can occur at any point in time, whereas remission over a certain period would be regarded as sustained remission.⁴⁵ Likewise, remission on or off therapy is another quality of remission that cannot influence the definition of the remission state.

RESPONSE CRITERIA FOR RHEUMATOID ARTHRITIS BY THE EUROPEAN LEAGUE AGAINST RHEUMATISM (EULAR) BASED ON IMPROVEMENT AND STATE OF THE 28-JOINT DISEASE ACTIVITY SCORE (DAS28)

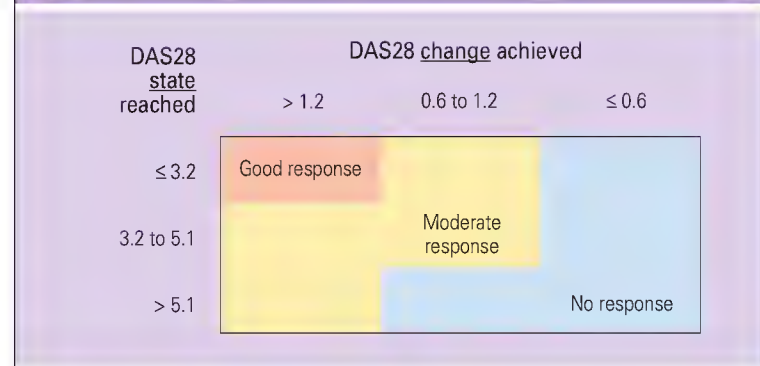


Fig. 96.4 Response criteria for rheumatoid arthritis by the European League Against Rheumatism (EULAR) based on improvement and state of the 28-joint Disease Activity Score (DAS28).

TABLE 96.5

ACR-EULAR provisional definition of remission

Remission definition for clinical trials		Remission definition for clinical practice (no CRP)	
Index-based	SDAI ≤3.3	Index-based	CDAI ≤2.8
Boolean (all at the same time)	SJC ≤1 TJC ≤1 PtGA ≤1 cm CRP ≤1 mg/dL	Boolean (all at the same time)	SJC ≤1 TJC ≤1 PtGA ≤1 cm

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; PtGA, patient global assessment; SDAI, Simplified Disease Activity Index; SJC, swollen joint count (28 or expanded); TJC, tender joint count (28 or expanded).

Subsequently, remission was defined in terms of the DAS and DAS28 (DAS <1.6, DAS28 <2.6); however, because of the preponderant weight of tender joints and acute-phase reactant levels,³⁵ DAS and DAS28 remission can be accompanied by significant residual disease activity. Recently, the ACR and EULAR addressed this issue in an extensive analysis and provided provisional remission definitions (Table 96.5) that are stringent and do not allow residual disease activity beyond a minimal extent of residual joint swelling or tenderness.⁴⁵

INSTRUMENTS FOR ASSESSING PHYSICAL FUNCTION

Physical function is a central aspect of life for patients with RA and thus a major focus of patient care. Physical function can be regarded as one domain within the wider concept of health status and a key driver of a patient’s quality of life. Improving functional outcomes is therefore a central goal of RA therapy. Physical function can most directly be assessed by subjecting individuals to performance tests. Such tests are often too complex to implement in a broader group of patients or to assess function of only specific body parts, such as hand function. Some of these tests are detailed in the online supplement. In clinical practice, function is most commonly evaluated with questionnaires, which are described in the following text.

A large number of questionnaires can be used to assess physical disability or quality of life in patients with RA. For a comprehensive examination of these questionnaires the reader is referred to relevant review articles.⁴⁶ The most frequently used ones will be discussed briefly. The Medical Outcomes Study Short Form-36 (SF-36)⁴⁷ is the most commonly used generic (i.e., non-disease specific) measure, and it includes physical function as one of its eight scales (domains). From its 36 items, eight subscales, including physical functioning, physical role, pain, and general health, as well as vitality, emotional role, social functioning, and mental health, can be calculated from 2 to 10 items of the questionnaire. Two summary measures, the physical component score (PCS) and the mental component score (MCS), can be

calculated for the first and the latter four, respectively, whereas one item on reported health transition stands alone. Each scale is expressed with values from 0 to 100, and a lower score indicates poorer health. The PCS and MCS are expressed by using norm-transformed domain scores that yield normative values of 50 with a standard deviation of 10 to allow comparison across populations, although such normalization may reduce the degree of potential change. The minimal clinically important difference (MCID) for the PCS is 5 to 10 points in individual domains and 2.5 to 5 points for the MCS domains. As a generic tool, the SF-36 is useful because it allows comparison of patients with different diseases and with the normal population. It is a valid and reliable tool with good psychometric properties.

The Health Assessment Questionnaire (HAQ)⁸ is a more disease-specific functional instrument. The “full” HAQ includes assessment of discomfort, drug side effects, cost, mortality, and the Disability Index (HAQ-DI). Only the latter is in widespread use. The HAQ-DI evaluates the ability to perform activities of daily living. It comprises 20 questions on activities involving the upper or lower extremity (or both), which are organized into eight categories (dressing, rising, eating, walking, hygiene, reach, grip, and usual activities). For each question there is a four-level difficulty scale ranging from 0 to 3 that represent no difficulty (“0”), some difficulty (“1”), much difficulty (“2”), and inability to do (“3”). The final HAQ score is the mean of the highest scores across the eight categories and ranges from 0 to 3, with higher levels indicating more disability. Since its introduction, many modifications of the original HAQ have been published; Pincus and colleagues developed the modified HAQ (MHAQ) to simplify scoring for daily clinical care, although the original HAQ remains the most widely used instrument. In the MHAQ, questions from the original HAQ were reduced to one or two per category, and its total score is also derived by taking the average of the eight categories. In 1999, Pincus and associates introduced the multidimensional HAQ (MDHAQ), which amended the 8-item MHAQ to 14 items.⁴⁸ These additional items improved the floor effect that had been noticed with use of the MHAQ. Because the intervals between scores at different points of the HAQ scale did not translate into similar changes in functional impairment, Wolfe and colleagues recently developed the HAQ-II, in which this psychometric problem has been addressed.

The MCID of the HAQ has been suggested to be 0.22. However, recent studies have shown that the potential for change in HAQ scores may differ depending on the average duration of RA. The amount of underlying damage may reduce the reversibility of HAQ scores in individual patients. Likewise, in highly active RA, HAQ scores vary little with respect to differences in underlying damage because of the great impact of activity on the HAQ, with an average HAQ score of about 1.3 (and up to a mean of 1.9 in trials), whereas in remission, HAQ scores differ considerably but were mostly less than 0.6. Thus, it is important to bear in mind that the HAQ as a measure of functional limitation is determined by both activity (reversible component) and accrued damage (irreversible component). In early stages of RA the HAQ score is usually fully reversible, although this may not at all be the case in very late stages. It has been well established that the HAQ-DI increases with increasing duration of RA because of the accumulated joint damage and even more directly by the fact that over the longer term the correlation between HAQ-DI and radiographic damage increases. It has been observed that over a range of about 20 to 100 points of the radiographic Sharp score or its van der Heijde modification (see later), each point corresponds to a 0.01 irreversible HAQ score.⁴⁹

The Arthritis Impact Measurement Scale (AIMS)⁵⁰ includes nine domains, each of which consists of 4 to 7 questions for a total of 49 questions. Different versions of the original AIMS have been published, including the longer AIMS2 (12 domains and 78 questions) and the shorter AIMS2-short form (5 domains and 26 questions). In one study the AIMS2-SF was shown to reduce completion time while maintaining the properties of the longer AIMS2. Wolfe and colleagues developed the clinical HAQ (CLINHAQ), which in addition to the eight categories of the original HAQ, borrowed the depression and anxiety scales from the AIMS and included five additional VASs and a pain diagram. The Euro-QoL 5-D (EQ-5D) is a simple standardized self-reported questionnaire for use as a measure of health outcome (“health states”).⁵¹

INSTRUMENTS FOR ASSESSING STRUCTURAL PROGRESSION

Scoring of radiographs

Radiographic damage is the hallmark of RA, and it usually progresses over time. Most radiographic scoring methods are based on assessment of the hands and feet, joint areas that are thought to be representative of overall

radiographic damage. Because measurement error is an issue in radiographic scoring, it is recommended that readers be trained and the mean of two independent readers be calculated. If the purpose is assessing structural damage, annual radiographs of the hands and feet are generally satisfactory, but for particular research questions or in early RA, smaller intervals or the inclusion of more joints (or both) might be appropriate. It is still a matter of debate whether radiographs should be read in random or chronologic order because reading radiographs in random order reduces expectation bias (improving the signal-to-noise ratio) but the ability to determine small changes is decreased. A large number of instruments are in use for radiographic scoring and can be categorized into three groups (Table 96.6): (1) instruments assigning a single radiographic grade to a patient (no longer in use; see supplement), (2) those that provide an overall score for a given joint and sum the scores of multiple joints, and (3) those that score two or more features of each joint separately and then sum multiple joints into the radiographic score (by feature or as a total sum of scores on different features).

The most prominent scoring method that combines all features of a particular joint globally is the Larsen method (soft tissue swelling or osteoporosis = 1; erosions of increasing extent = 2 to 5). Standard atlas radiographs are provided for all joints as a comparative means. The method was later modified by Larsen to remove soft tissue swelling and osteoporosis.⁵² In the new method, a score of 1 already required erosions or joint space narrowing to be present. Since its development, the Larsen score has been modified manifold times (see Table 96.6).

The Sharp score⁵³ was the first instrument to include separate scoring for erosions and joint space narrowing (see Table 96.6) as a reflection of bone and cartilage damage, respectively, which may provide independent information. It initially evaluated joints of only the hands and wrists but was further modified by Sharp to enable evaluation of the feet as well (see Table 96.6). A modification of the Sharp score by van der Heijde⁵⁴ also introduced the 10 metatarsophalangeal joints and the interproximal joints of the big toes, whereas some areas of the wrist were excluded because of difficulty assessing them. The Sharp–van der Heijde (SvdH) score is widely used now (Fig. 96.5). In this score, erosions of the feet are scored 0 to 10 (see Table 96.6). Another score that has been used in recent clinical trials is the Genant-modified Sharp score, which assesses fewer joint regions than the Sharp and SvdH scores do, uses a scale of 0 to 3.5 for erosions and 0 to 4 for joint space narrowing, and ranges from 0 to 150 rather than beyond 400 (see Table 96.6). A Simple Erosion and Narrowing Score (SENS) counts the number of eroded joints and the number of joints exhibiting narrowing and sums them. Several other modifications use different joint regions or other features, such as malalignment, in addition to erosion and joint space narrowing (see Table 96.6). In general, the Sharp and the Larsen methods provide similar estimates of radiographic severity, but the Sharp score and its modifications are more sensitive to change.

A single radiograph in conjunction with knowledge of a patient's duration of RA allows estimation of the annual progression rate. This rate integrates an individual patient's history (RA severity and treatment) as a

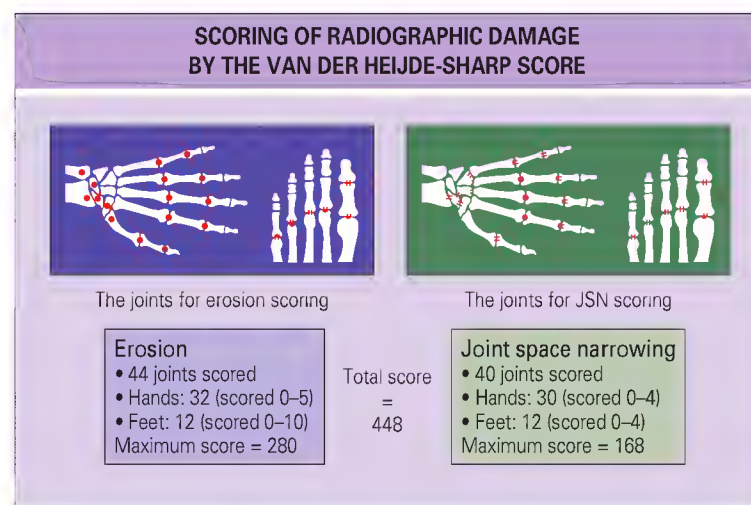


Fig. 96.5 Separate evaluation of erosions (0 to 5) and joint space narrowing (JSN) (0 to 4) in the joints of the hands and the feet. (Adapted from van der Heijde DM, Van't Hof MA, van Riel PL, et al. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. *Ann Rheum Dis* 1992;51:177-81.)

TABLE 96.6

Radiographic scoring methods for rheumatoid arthritis

	Level of assessment	Scale/joint	Joints/regions assessed	Total score	Hands	Feet	Year
Steinbrocker	Patient			0-4	X		1969
Kellgren	Patient			0-5	X		1963
Sievers	Patient			0-8	X		1965
Berens	Patient			0-5	X		1969
Scores based on the method developed by Sharp							
Sharp	Features	0-5 ERO, 0-4 JSN	54 ERO, 54 JSN	0-486	X		1971
Sharp (modified Sharp)	Features	0-5 ERO, 0-4 JSN	46 ERO, 48 JSN (42 JSN)	0-422 (-398)	X	X	2000
Genant (modified Sharp)	Features	0-3.5 (steps of 0.5) ERO, 0-4 JSN	28 ERO, 13 JSN	0-150	X	X	1983
Bluhm (modified Sharp)	Features	0-5 ERO; 0-4 JSN	34 ERO, 36 JSN	0-314	X		1983
Nance/Kaye (modified Sharp)	Features	0,2-4 ERO, 0,2-5 JSN, 0,2-4 MLG	22 ERO, 28 JSN, 30 MLG	0-348	X		1986
van der Heijde (modified Sharp)	Features	0-5 (10)* ERO, 0-4 JSN	32 ERO, 30 JSN	0-448	X	X	1989
Simple Erosion Narrowing Score (SENS)	Features	0-1 ERO, 0-1 JSN	22 ERO, 21 JSN	0-86		X	1999
Scores based on the method developed by Larsen							
Larsen	Joint	0-5	22 (-28) 0-110 (-140)		X	X	1974
Gofton (modified Larsen)	Joint	0-4 ERO	48 ERO	0-192	X		1982
Scott (modified Larsen)	Joint	0-5	22 (-28)	0-110 (-140)	X	X	1995
Rau (modified Larsen)	Features	0-5 ERO	38 ERO	0-190	X		1995
Kaarela/Kautiainen (modified Larsen)	Joint	0-5	20	0-100	X	X	1997

*Erosions of the feet are scored on the proximal and distal aspect of the joint, which results in a possible score per joint of 10.

ERO, erosions; JSN, joint space narrowing.

Adapted from Aletaha D, Smalen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9-44.

benchmark to assess structural effects induced by subsequent therapeutic regimens.

Other imaging modalities

Radiographic scoring appears to be a crude way to determine joint damage, and more sophisticated modalities are therefore of significant interest. Magnetic resonance imaging (MRI) and ultrasonography are two of these. By using contrast media (MRI) and power Doppler imaging, the vascularity of a lesion, such as in a synovial membrane, can easily be determined. Ultrasonography also allows one to assess cartilage thickness and to depict some erosions. MRI enables detection of erosions relatively early. Means of assessing cartilage damage by MRI are currently in development and primarily comprise measurement of joint space narrowing⁵⁵ because the currently routinely used MRI (1.5 and even 3 T) cannot easily depict cartilage anatomically. However, neither of these methods has been sufficiently validated as being meaningful to outcome. In addition, both have a number of limitations. Although ultrasonography is cost-effective, it is very time-consuming if one wants to depict all joints that are evaluated by hand and foot radiographs. Also, handling of the transducer is dependent on the investigator, and the angle may differ even within an individual patient with different states of joint swelling or stiffness. Moreover, some areas may escape visibility by ultrasonography. With MRI, on the other hand, aside from its cost, it is still difficult to depict changes in cartilage. Furthermore, the currently used MRI scoring system, the RA-MRI score (RAMRIS) and its modification,⁵⁶ looks at the wrist and metacarpophalangeal joints and thus does not account for the proximal interphalangeal joints, which are frequently involved in RA and included in the radiographic scores. Interestingly, in a recent trial, radiographic scores were found to be as sensitive to change as the RAMRIS.⁵⁷ Additionally, on a group level, radiographic changes can be depicted within 3 months of the start of treatment,⁵⁸ thus suggesting that radiographic assessment in RA is currently not inferior to other imaging modalities in its sensitivity to change or time until detectability of change, whereas other modalities are still more expensive, more time-consuming, or both. Most importantly, although radiographic changes have been associated with time-integrated disease activity on the one hand and disability on the other hand, these data still need to be provided and validated for ultrasonography and MRI.

For further reading on imaging, see Chapter 88.

OTHER INSTRUMENTS: FATIGUE, WORK PRODUCTIVITY, AND COMORBIDITY

It has already been mentioned that one of the many features of RA is fatigue. Although the mechanisms underlying fatigue are not clear but might involve direct or indirect consequences of the release of cytokines on the central nervous system or may be related to pain, depression, anemia, or other aspects of the disease, it is a fact that clinical improvement generally leads to improvement in fatigue. Various scales have been used, among them simple VAS or the more complex Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale,⁵⁹ which ranges from 0 to 52, with higher scores meaning less fatigue and an MCID of 4.

Another important outcome relates to work productivity. A variety of instruments have been developed and validated and are increasingly being used in clinical trials to address the impact of the disease and consequences of therapeutic interventions on ability to work. The data provide one of the bases for health economic analyses. Providing information on these instruments would go beyond the scope of this chapter, and the reader is referred to recent review articles.⁶⁰

Likewise, comorbid conditions not only influence disease outcome but also frequently limit the applicability of certain therapies. Several instruments are available.⁶¹ Although their value in RA has not yet been sufficiently validated, assessment of comorbidity may provide additional important insight in our understanding of RA, response to therapy, and the extent of loss of physical function and productivity with this disease. Finally, a very important aspect of caring for patients with chronic disease is prevention of drug toxicity. Clinical trials usually report on the more frequent adverse events within the short-term horizon of the respective studies, but observational studies and registries have been set up to identify rarer events and the long-term consequences of therapy. No uniform method of assessing toxicity is currently available, especially when feasibility is an issue, such as in clinical practice.

CONCLUSION

RA is a complex systemic disease. Outcomes assessment in RA is therefore also more complex than for other chronic diseases. The three main areas of

outcomes are disease activity, joint damage, and functional impairment. Each of these areas is represented by various domains, each of which again can be assessed with various instruments. This makes the field not easily transparent at first sight. Consistently, though, in the past until now, disease activity has been found to be reflected best by using a core set of measures that include joint counts, global scales, pain scores, and acute-phase response. Ideally, however, in clinical trials and clinical practice, these measures need to be combined into single summary measures (scores, indices)

so that clear targets for treatment can be defined. The benefit of treatment strategies targeted at specific outcomes has been elucidated only in the past few years and cannot be overemphasized. At the same time, the level of functional capacity and radiographic damage needs to be considered when outcomes are assessed or treatment decisions are made. All three areas—activity, function, and damage—are linked, with one influencing the other, and all three are determinants of the most important outcome, which is a patient's quality of life.

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Management of rheumatoid arthritis: synovitis

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- Complete remission of rheumatoid arthritis (RA) disease activity should be the ultimate goal of treatment for all RA patients.
- Early, aggressive treatment of synovitis is desirable to have the greatest impact in preventing damage and disability.
- Patients with risk factors for poor prognosis warrant the most aggressive suppression of synovitis.
- Step-up combination approaches, beginning with rapidly titrated methotrexate, are the best studied and most commonly used strategies in clinical practice.
- First-line combinations of biologic and nonbiologic disease-modifying antirheumatic drugs may be warranted in patients with the poorest prognosis.
- Emerging targeted therapies hold great therapeutic promise and may alter current treatment paradigms in the future.
- The use of bridging and/or low-dose corticosteroids, nonsteroidal antiinflammatory drugs, and simple analgesics is often required for maximal management of symptoms.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic disease with both articular and extraarticular features and a primary pathologic process characterized by inflammation and hypertrophy of the synovial lining of diarthrodial joints, a process referred to as *synovitis* (see Chapter 20). If left untreated or inadequately suppressed, chronic synovitis will result in joint destruction and dysfunction. In general, only treatment strategies that successfully suppress synovitis are associated with improvements in articular pain, stiffness, and physical functioning as well as reduction of joint deformity, disability, and, possibly, mortality.

The currently available therapeutic agents used for the treatment of RA have been discussed in detail in previous chapters (Chapters 46 to 70). Drawing on the American College of Rheumatology (ACR) 2012 RA treatment guidelines and U.S. Food and Drug Administration (FDA) indications, this chapter outlines management strategies for RA taking into account individual characteristics of the patient, the disease, and the therapies that will influence outcomes and response to treatment. The important roles of physical and occupational therapy (Chapter 47), pain control (Chapter 50), joint surgery (Chapter 69), patient education (Chapter 46), complementary therapies (Chapter 48A), and a multidisciplinary approach to RA (Chapter 98) are reviewed in detail in other sections of this book.

HISTORICAL BACKGROUND

Finding safe and effective strategies to suppress synovitis in order to reduce or prevent disability and pain has always been the primary aim of the pharmacologic management of RA. However, only in the past several decades, with the evolution of molecular biology and a concomitant explosion in large-scale randomized clinical trials, have therapies with favorable benefit-risk profiles have been identified or confirmed.

The use of high doses of salicylates and glucocorticoids in the first half of the 20th century, although revolutionary, was accompanied by unacceptable degrees of toxicity. From the mid-20th century until the mid-1980s, a

slow, cautious approach to the treatment of RA, known as the *pyramid approach*, was most widely practiced. This consisted of a prolonged period of treatment with nonsteroidal antiinflammatory drugs (NSAIDs), with or without glucocorticoids, before adding a disease-modifying antirheumatic drug (DMARD). The prescription of one of a limited array of DMARDs available at the time (e.g., gold salts, penicillamine) was often delayed because of their limited efficacy, risk of major toxicities, and potential to lose their effectiveness over time. If the DMARD of choice was ineffective in controlling synovitis, it was discontinued in favor of an alternative DMARD. Not surprisingly, the pyramid approach inevitably resulted in some degree of joint destruction and disability in nearly all RA patients.

By the 1980s, the introduction and gradual acceptance of low-dose weekly methotrexate as a highly effective treatment for RA with relatively low toxicity prompted the abandonment of the pyramid approach in favor of much earlier DMARD use in RA patients. The use of nonbiologic DMARDs in combination and the recent introduction of biologic DMARDs have moved the notion of early, aggressive treatment of RA forward, so that complete remission of RA disease activity should be the ultimate goal of treatment for all RA patients.

WHAT IS AGGRESSIVE THERAPY?

More than half of RA patients develop erosions visible on plain radiographs within just 2 years of disease onset, and some data suggest that the rate of radiographic damage may be higher in the first years of disease.¹ Thus early and aggressive treatment is desirable to achieve the greatest impact in preventing damage and disability,² yet treatment initiated or ramped up at any phase of the disease will still be capable of decreasing inflammation and preventing additional damage.

The importance of “aggressive” management of RA is now generally accepted. A reasonable definition of aggressive management is a treatment strategy that is rapidly and maximally escalated to a level that suppresses synovitis without inducing an unacceptable burden of adverse effects. The ACR 2012 recommendations for the use of nonbiologic and biologic DMARDs in RA present evidence-based treatment algorithms for initiating or changing agents based on the duration of disease, level of disease activity, and features indicating poor prognosis (described later).³ Under these guidelines, in patients with early RA who have no risk factors for poor prognosis, early initiation and rapid dose escalation of nonbiologic DMARD monotherapy may be sufficient to control disease activity effectively. In contrast, in those with early RA who have moderate or high disease activity and poor prognostic features, the use of nonbiologic DMARD combination therapy or a tumor necrosis factor (TNF) inhibitor biologic with or without methotrexate is recommended. Thus the notion of aggressive management is somewhat fluid with regard to the choice of agent(s), the number of agents, and the rapidity of dose escalation of each of the agents, because these are dictated by the profile of the patient being treated. For each individual, the choice of treatment depends on an analysis of the benefit the patient is expected to gain from that treatment versus the potential risks associated with the treatment or combination of treatments. The ability early in disease to differentiate patients with a poor prognosis from those with a good prognosis allows therapeutic regimens to be individually tailored to produce the highest benefit-risk ratio for each patient.

PREDICTORS OF POOR OUTCOME

There is no single clinical, laboratory, or imaging parameter that is sufficiently sensitive to clearly identify patients who are at the highest risk of a

poor outcome (e.g., disability). However, prediction models based on combinations of factors have been developed⁴ in which radiographic progression of erosive disease serves as the surrogate for poor outcome because periarticular erosions can be assessed inexpensively over time, accumulate in proportion to burden of disease, and predict long-term disability.⁵

Several patient characteristics assessed early in disease have been associated consistently with the likelihood of developing erosive damage. The factors with the strongest predictive value include presence and titer of autoantibodies (e.g., rheumatoid factor [RF] and anti-cyclic citrullinated peptide [anti-CCP] antibodies); genetic factors (the presence of HLA-DRB1 “shared epitope” alleles, especially HLA-DRB1*0401 and HLA-DRB1*0404); radiographic factors (the presence of erosive disease on plain radiographs at presentation); inflammatory markers (e.g., elevated C-reactive protein [CRP] level and erythrocyte sedimentation rate [ESR]); and degree of functional disability (measured using the Health Assessment Questionnaire).^{6,7} All of these variables are easily and inexpensively assessed in the routine clinical setting. However, because the shared epitope status correlates closely with other clinical risk factors (e.g., anti-CCP antibodies) and thus adds minimal additional predictive value, it is not routinely assessed in clinical practice.⁴ The ACR 2012 treatment recommendations specifically define poor prognostic features as the presence of one or more of the following: functional limitations (measured by the Health Assessment Questionnaire or similar validated tools), extraarticular disease (e.g., rheumatoid nodules, RA vasculitis, Felty syndrome), the presence of RF or anti-CCP antibodies, and bony erosions by radiograph. It is important to keep in mind that, although the presence of these factors increases the risk of erosive disease, their absence does not guarantee a benign course.

Currently international efforts are underway to systematically evaluate imaging modalities with greater sensitivity for detecting erosions, such as ultrasonography and magnetic resonance imaging, for their potential role in enhancing detection, monitoring disease progression, and predicting future joint damage in patients with RA (see Chapters 41 and 42).

TREATMENT STRATEGIES

Rationale

No single clinical, laboratory, or radiographic parameter has been identified to date that can reliably predict a favorable response to a particular therapy. Furthermore, the paucity of head-to-head comparisons of different DMARDs does not allow, as yet, the rank ordering of individual DMARDs, or combinations of nonbiologic and/or biologic DMARDs, with regard to safety and efficacy. Nonetheless, a number of highly effective treatment strategies have been identified through clinical trials in RA that allow the clinician to organize the selection, order of use, and dosing of DMARDs for an individual patient. There are three general strategies for DMARD treatment of RA: sequential monotherapy, step-up combination therapy, and initial combination (induction) therapy.

Sequential monotherapy, a strategy in which an ineffective DMARD is replaced by an alternate DMARD, has largely been abandoned in favor of step-up and initial combination approaches. The last two approaches use combinations of nonbiologic DMARDs or a combination of a nonbiologic and a biologic DMARD. These approaches can be applied early or in established disease, although most commonly these strategies are discussed in reference to patients with early (DMARD-naïve) disease.

Criteria for assessing response to therapy have been developed for use in clinical trials and are discussed in detail in Chapter 96. Among these, the Disease Activity Score (DAS) and the modified DAS based on evaluation of 28 joints (DAS28), have been the most commonly used in clinical trials. However, because use of the DAS system requires complex calculations that limits their use in clinical practice, simpler scores have been developed and validated, including the Composite Disease Activity Index and the Simplified Disease Activity Index.³ Changes in disease activity scores with treatment are used to define outcomes as well as states of low disease activity and remission.

The step-up approach is currently the most widely practiced strategy in clinical practice for the management of RA⁸ and is the strategy used in the majority of clinical trials in RA to date. In this approach, a second agent (e.g., another nonbiologic DMARD or a TNF inhibitor) is added to the first DMARD (e.g., methotrexate) if a response to the first DMARD is inadequate. In most published step-up combination approaches, methotrexate serves as the “anchor” DMARD. The advantage of the step-up strategy is that it permits graded escalation of therapy up to the desired level of control of synovitis without exposing the patient to more DMARDs than are necessary. The disadvantage is that a lag time, which varies depending on how many

steps are required, must elapse before disease control is attained. During this time, irreversible articular damage may occur. For this reason, the model step-up strategy outlined in the 2012 ACR guidelines for the management of RA³ advocates frequent evaluation and rapid escalation of therapy in the face of incomplete response.

In contrast, in induction therapy (modeled after cancer chemotherapy strategies) the patient is immediately given a combination of DMARDs. Once maximal or acceptable control of synovitis is achieved, the combination may be continued indefinitely or stepped down to a single DMARD for maintenance. The theoretical advantage of induction therapy is more rapid control of synovitis and thus less accumulation of joint damage compared with the sequential monotherapy and step-up approaches. The disadvantages of the induction approach are potential overtreatment and exposure to unnecessary toxicities in patients in whom disease may have been adequately controlled by a single DMARD; in addition, there can be difficulty in attributing an adverse event to a specific drug.

A landmark study of induction with step-down was the Dutch Combinatietherapie Bij Rheumatoïde Artritis (COBRA) trial⁹ in which patients with early RA were randomly assigned to initial treatment with sulfasalazine alone or sulfasalazine plus methotrexate plus high-dose prednisolone, with taper from high-dose to low-dose prednisolone by week 6 and taper to sulfasalazine monotherapy by 6 months. Radiographic outcomes in the induction/step-down group were superior to the those in the monotherapy group at the end of 6 months, a difference that persisted through 5 years of follow-up even though the randomized treatment phase had long since ended. Similar clinical and radiologic results were reported in the Finnish Rheumatoid Arthritis Combination Therapy Study (FIN-RACo)¹⁰ in which treatment with combination DMARDs with step-down was compared with DMARD monotherapy over 5 years of follow-up.

The results from these studies and others² have led to the speculation that a window of opportunity exists early in the disease during which aggressive treatment may serve to permanently slow, or even halt, disease activity.¹¹

A head-to-head comparison of induction versus step-up versus sequential monotherapy strategies was performed in the Behandel-Strategieën in Reumatoïde Artritis (Treatment Strategies in Rheumatoid Arthritis, or BeSt) trial.¹² Data from this study indicate that two different induction regimens—(1) the COBRA induction/step-down regimen of nonbiologic DMARDs, and (2) a combination of infliximab plus methotrexate—were superior to sequential monotherapy and step-up combinations in slowing radiographic progression over 12 months, but all four regimens attained comparable clinical improvements by month 12. More recently the Treatment of Early Aggressive RA (TEAR) trial¹³ assessed the DAS28-ESR values from week 48 to week 102 in patients with early RA immediately treated with a combination of methotrexate plus etanercept or a combination of methotrexate plus sulfasalazine plus hydroxychloroquine, compared with step-up from methotrexate monotherapy at week 24 to one of the two induction regimens if the DAS28-ESR was 3.2 or higher. Immediate induction regimens were superior to methotrexate monotherapy at week 102, but there was no difference in the mean DAS28-ESR during weeks 48 to 102 for the methotrexate plus etanercept and triple-therapy groups regardless of whether they had received immediate induction or step-up from methotrexate monotherapy. However, radiographic progression was modestly lower in the methotrexate plus etanercept group than in the triple-therapy group.¹³ Moreover, data from the Swefot trial¹⁴ demonstrated that in patients with early RA refractory to methotrexate monotherapy after 3 to 4 months of treatment, those given methotrexate plus infliximab showed better clinical response than patients given methotrexate plus sulfasalazine plus hydroxychloroquine at 12 months but not at 24 months, although better radiographic outcome at 24 months was seen in the methotrexate plus infliximab arm.

Finally, “individualized targeted tight control” is a variant on each of these approaches in which the rapid attainment of low disease activity or remission is set as the goal of therapy. The prototype of this approach was the regimen used in the Tight Control for Rheumatoid Arthritis (TICORA) trial¹⁵ in which treatment in an “aggressively managed” group was escalated at each study visit if the DAS score was higher than 2.4. In contrast, in the “routine care” group, the DAS score was not a part of the clinical decision-making, and these patients received therapy at the discretion of the treating rheumatologist. At the end of 18 months of treatment, patients treated intensively showed superior clinical responses and fewer radiographic erosions than those in the routine care group.

In summary, the evidence to date suggests that aggressive treatment to rapidly achieve a low level of disease activity, which often necessitates use of a combination of agents, is more effective than conservative approaches that involve sequential low-dose monotherapy. Given the expense of combination therapy, especially treatment with the biologic agents, and the

TABLE 97.1

Disease-modifying antirheumatic drugs (DMARDs) and biologic agents

DMARDs	Mechanism of action	Biologics	Mechanism of action
Methotrexate	Inhibition of purine biosynthesis and cytokine expression; induction of monocyte apoptosis	Etanercept	Soluble 75-kDa TNF receptor; inhibits TNF- α .
Sulfasalazine	Inhibition of cytokine expression and neutrophil migration	Infliximab	Chimeric anti-TNF- α antibody; inhibits TNF- α .
Leflunomide	Inhibition of pyrimidine biosynthesis, cytokine expression, and neutrophil migration	Adalimumab	Human anti-TNF- α antibody; inhibits TNF- α .
Hydroxychloroquine	Unknown	Golimumab	
Minocycline	Inhibition of metalloproteinases—exact mechanism unknown	Certolizumab	Pegylated human anti-TNF- α antibody; inhibits TNF- α .
		Abatacept (CTLA-4-immunoglobulin)	Inhibits T-cell costimulation.
		Rituximab	Anti-CD20 monoclonal antibody; depletes B cells.
		Tocilizumab	Humanized anti-IL-6 receptor antibody; inhibits IL-6.
		Anakinra	Recombinant IL-1 receptor antagonist; inhibits IL-1.

IL, interleukin; TNF, tumor necrosis factor.

current environment of cost containment, the step-up approach rather than the induction (combination) approach remains the most common in clinical practice.⁸ However, the ACR 2012 treatment guidelines³ do sanction the use of initial combination regimens of DMARDs with or without a TNF inhibitor for patients with high disease activity and features indicating poor prognosis.

The remainder of this chapter focuses on specific nonbiologic and biologic DMARDs (Table 97.1), as well as DMARD combinations, with the step-up approach in mind.

CHOICE OF INITIAL THERAPY

In most cases, except when there are specific contraindications or high disease activity with poor prognostic features, a nonbiologic DMARD is recommended as the initial therapy in a DMARD-naïve patient with early disease.³ Although biologic agents are also effective in early disease, their significantly higher cost generally limits their use as first-line agents.

In DMARD-naïve patients with early RA (disease duration of less than 6 months), the ACR 2012 panel recommends starting DMARD monotherapy for disease of all degrees of severity in the absence of poor prognostic factors. In the presence of poor prognostic features and moderate or high disease activity, double- or triple-DMARD combination therapy or an anti-TNF agent (with or without methotrexate) is recommended.

In DMARD-naïve patients with longer disease duration (6 months or more), low disease activity, and no features of poor prognosis, DMARD monotherapy is recommended.³ For those with poor prognostic factors and/or moderate to high disease activity, methotrexate monotherapy or DMARD double or triple therapy is recommended as initial treatment.

Methotrexate monotherapy as the standard first-line DMARD

Methotrexate is generally accepted as the first-line DMARD of choice due to its marked efficacy, safety, tolerability, and sustainable effect (see Chapter 56). Consequently, most clinical trials have tested the safety and efficacy of new drugs in combination with methotrexate.

Aggressive dose escalation of methotrexate has gained relatively widespread acceptance in recent years on the basis of its favorable safety profile. A paradigm for rapid escalation was provided by the Early RA (ERA) study¹⁶ in which methotrexate treatment was initiated at a dosage of 10 mg/wk and escalated by 5 mg every 4 weeks until a weekly dose of 20 to 25 mg was achieved, provided that adverse effects did not necessitate stopping at a lower dosage. In practice, many patients tolerate an initial dose of 15 mg/wk. In this study and others in patients with either early¹⁶⁻¹⁸ or advanced¹⁹ RA, aggressively titrated methotrexate monotherapy was comparable to TNF inhibitor monotherapy in reducing clinical signs and symptoms of RA, although cumulative radiographic joint damage over several years was slightly higher in the methotrexate group at 1 to 2 years of follow-up.

Because of the slow onset of action of methotrexate, an interval of 4 to 6 weeks is generally required to determine whether a patient has responded to a dose increase. Thus when the dosing strategy described earlier is used,

an interval of 3 months is recommended to evaluate the initial response to methotrexate monotherapy. For patients who have had an inadequate response to 20 to 25 mg/wk of oral methotrexate, substitution of an equivalent dose of subcutaneous or intramuscular methotrexate may enhance efficacy. However, given the availability of an array of other DMARDs on the market, the addition of a second DMARD is the preferred next step in most patients showing no response to, or intolerant of, oral methotrexate.

Although the majority of patients tolerate rapid escalation of methotrexate, dose-limiting adverse effects related to drug-induced folate deficiency, such as hepatic transaminitis, stomatitis, nausea, cytopenias, and hair loss (see Chapter 56), may present barriers to continuing or escalating the drug. Methotrexate-induced folate deficiency has also been implicated as a contributor to the enhanced risk of cardiovascular disease in RA patients. Consequently, supplementation with folate (in the form of folic or folinic acid) is recommended for all methotrexate-treated patients because this appears to reduce adverse effects with minimal compromise of overall efficacy.²⁰ Although methotrexate is generally appropriate for most patients, absolute contraindications to it include active liver disease (including chronic hepatitis B and C), alcohol abuse, pregnancy, and breastfeeding. Alternative DMARD choices for these patients are discussed next.

First-line monotherapy with other nonbiologic DMARDs

Given the limited evidence for the use of nonbiologic DMARDs other than methotrexate in early RA, these agents are generally reserved for patients who have a contraindication to methotrexate use. Of this group of DMARDs, sulfasalazine, leflunomide, and hydroxychloroquine are the most commonly used. The first two of these drugs were shown in placebo-controlled randomized clinical trials^{21,22} to be relatively comparable in their abilities to reduce articular signs and symptoms of RA, improve physical function, and retard radiographic progression (Chapters 55 to 57).

Leflunomide, a pyrimidine synthesis inhibitor (see Chapter 57), has been shown in head-to-head trials in established RA to have efficacy equivalent to that of methotrexate or sulfasalazine in suppressing synovitis and inhibiting radiographic progression,^{21,22} although it could be argued that both methotrexate and sulfasalazine were underdosed in these trials. The usual dosage of leflunomide is 20 mg/day, but it can be reduced to 10 mg/day in cases of toxicity. Its contraindications for use (alcoholism, pregnancy, active liver disease, and renal impairment) and adverse effect profile (requiring routine monitoring of transaminase levels) are similar to those of methotrexate.

The efficacy of sulfasalazine (see Chapter 55) in the treatment of RA was first recognized in the 1940s, although its mechanism of action in RA has never been clearly elucidated. Head-to-head studies have shown it to be generally equivalent in efficacy to methotrexate and leflunomide,^{23,24} although methotrexate was underdosed in these studies relative to current clinical practice. The usual dosage of sulfasalazine for the treatment of RA is 1 to 3 g/day in divided doses. Sulfasalazine is contraindicated in patients with sulfa allergy or glucose-6-phosphate dehydrogenase deficiency. Potential advantages of sulfasalazine over methotrexate include its reduced cost, relative safety during pregnancy, and low incidence of hepatotoxicity and

bone marrow toxicity. Sulfasalazine is an important option for RA patients with chronic hepatitis C or other liver conditions. Comparative disadvantages include a higher rate of early discontinuation due to intolerance (usually gastrointestinal adverse effects) and the potential for lower patient compliance because of the need for twice-daily dosing.

Neither leflunomide nor sulfasalazine has been studied in combination with other nonbiologic and biologic DMARDs as rigorously as has methotrexate. For these and the other reasons cited earlier, methotrexate remains the most commonly used first-line DMARD for RA, although both leflunomide and sulfasalazine are reasonable alternatives.

Hydroxychloroquine (see Chapter 55) has a long track record of use in the treatment of RA. Its low toxicity, ease of administration (orally once or twice daily), low cost (comparable with that of methotrexate and sulfasalazine), and apparent safety in pregnancy make it an attractive agent for use in RA. However, head-to-head studies comparing it with the other conventional DMARDs² confirm that hydroxychloroquine is a comparatively less potent DMARD. Furthermore, limited data on its ability to slow radiographic progression largely relegate this agent to treatment of very mild disease without poor prognostic factors or use in combination with other DMARDs. The usual dosage is 200 to 400 mg/day with monitoring for retinal toxicity advised at baseline and annually after 5 years.

Other agents once used to treat RA, including oral and injectable gold, D-penicillamine, minocycline, cyclosporine, tacrolimus, cyclophosphamide, and azathioprine (see Chapters 55 and 58), are now rarely used due to a poor evidence base for efficacy in RA and/or high toxicity relative to currently available agents.

First-line monotherapy with biologic DMARDs

Five TNF inhibitors (etanercept, infliximab, adalimumab, certolizumab, and golimumab) are U.S. FDA approved for the treatment of RA (see Chapter 63). Each has been demonstrated to be efficacious as monotherapy for the treatment of RA, although infliximab is recommended only in conjunction with methotrexate (to suppress antichimeric antibodies). Compared with aggressively dosed methotrexate, monotherapy with etanercept, adalimumab, or golimumab failed to show superiority in reducing clinical signs and symptoms of disease, although each did exhibit modest superiority in reducing radiographic progression.^{16,18,19,25,26} Nonetheless, this modest advantage is arguably offset by the high costs of these agents, so that methotrexate remains the preferred first-line DMARD. There are patients, however, in whom first-line monotherapy with TNF inhibitors other than infliximab is preferred, such as those with contraindications to nonbiologic DMARDs. Evolving clinical experience suggests that TNF inhibitors may be relatively safe during conception and possibly even during pregnancy,²⁷ although more study is required. Insofar as the most common use of TNF inhibitors is in combination with methotrexate, these drugs are addressed in greater detail in the discussion of step-up therapy.

Step-up therapy

Approximately 50% of patients have an inadequate response to monotherapy with an aggressively dosed DMARD.^{16,17,21,22,24} If after 3 months of monotherapy with a nonbiologic DMARD a patient's condition deteriorates from low to moderate or high disease activity, then the addition of a second nonbiologic DMARD is recommended at this point. As always, the addition of any new DMARD poses additional risks that must be weighed against the potential benefit of additional treatment. If the disease activity remains moderate or high after 3 months of methotrexate monotherapy or methotrexate in combination with another nonbiologic DMARD, it is recommended to add or switch to another nonmethotrexate DMARD, or to add or switch to one of the following biologics: a TNF inhibitor, abatacept, or rituximab.

If moderate to high disease activity still persists after 3 months of intensified DMARD combination therapy or after either switching to a second DMARD or adding one, then either adding or switching to an alternate TNF inhibitor or non-TNF-inhibitor biologic is recommended. If a TNF inhibitor is discontinued due to a serious adverse event and the patient has persistent high disease activity, switching to a non-TNF-inhibitor biologic agent is recommended. If the TNF inhibitor is discontinued due to a nonserious adverse event and the patient has persistent moderate to high disease activity, then switching to another TNF inhibitor is appropriate.³

Nonbiologic DMARD combinations

As noted previously, combinations of nonbiologic DMARDs administered using the induction approach have shown substantial superiority to

monotherapy for the treatment of RA. This is also demonstrated in clinical trials using the step-up approach. For example, the combination of sulfasalazine plus hydroxychloroquine plus methotrexate was superior to methotrexate alone, to sulfasalazine alone, and to the dual combinations²⁸ for reducing signs and symptoms of disease, although radiographic assessments were not performed in these studies. This strategy, termed *triple therapy*, is generally well tolerated and is relatively low in cost. Disadvantages include a dosing scheme that may present barriers to adherence in some patients and the potential for a negative effect of sulfasalazine plus methotrexate due to sulfasalazine's inhibition of cellular uptake of methotrexate by the reduced folate carrier.

The addition of leflunomide to methotrexate in patients showing an inadequate response to methotrexate was also associated with enhanced clinical improvement compared with methotrexate alone, but no radiographic endpoints were assessed. Drug-related toxicities associated with the combination are relatively low; however, careful monitoring of hepatic function is advised in patients receiving this combination. Suggested ways to minimize toxicity are the initiation of leflunomide at the lower (10 mg/day) dosage and reduction of the dosage of methotrexate. Head-to-head comparisons pitting methotrexate plus leflunomide against regimens containing a TNF inhibitor have not been performed. For these reasons, nonbiologic DMARD combinations are often selected in patients with contraindications to TNF inhibitors (e.g., patients with recurrent serious infections) or those with an aversion to self-injection or infusion.

Biologic agents

Tumor necrosis factor inhibitors

The combination of a TNF inhibitor plus methotrexate has been demonstrated to be superior to monotherapy with methotrexate in reducing signs, symptoms, and radiographic progression of disease in patients with early or advanced RA; this superiority was shown for etanercept in the TEMPO trial,¹⁹ for infliximab in the ASPIRE and ATTRACT trials,^{29,30} for adalimumab in the PREMIER and ARMADA trials,^{18,31} for certolizumab in the RAPID 1 and 2 trials,^{32,33} and for golimumab in the GO-FORWARD, GO-FORTH, and GO-FURTHER trials.^{26,34,35} The ability of TNF inhibitors to produce robust, rapid, and sustainable clinical responses in many patients has overshadowed, but not eclipsed, concerns about short- and long-term toxicities. These toxicities include enhanced risk of serious and opportunistic infections, induction of autoantibodies, and risk of inducing or exacerbating symptoms of congestive heart failure and of demyelinating diseases (see Chapter 63). Fortunately, the incidence of these potential adverse effects is low. The increasing prescription of TNF inhibitors over the years since FDA approval has demonstrated that self-injection and intravenous infusion are acceptable routes of administration for the treatment of patients with RA. In patients at high risk of joint damage, the high cost of TNF inhibitors is expected to be balanced or offset in the long term by a reduction in joint surgeries, disability, and unemployment. Thus their use as add-on therapy on a background of methotrexate in patients with moderate to high disease activity is now relatively commonplace.

No evidence suggests that one TNF inhibitor is superior to another. Furthermore, potential adverse effects are generally comparable among the five, although infliximab treatment has been associated with a higher incidence of opportunistic infection.³⁶ Therefore the selection of a TNF inhibitor is often based on patient preference. Etanercept, adalimumab, certolizumab, and golimumab are self-administered via subcutaneous injection (50 mg weekly or 25 mg twice per week for etanercept; 40 mg every 1 to 2 weeks for adalimumab; 400 mg at 0, 2 and 4 weeks then 200 mg every 2 weeks or 400 mg every 4 weeks for certolizumab; and 50 mg every 4 weeks for golimumab). Infliximab is administered as an intravenous infusion every 8 weeks (after an initial loading regimen). The standard dose of infliximab, 3 mg/kg, can be titrated up to 10 mg/kg if needed and/or the dosing interval can be decreased (to every 6 or 4 weeks). It is recommended that infliximab be administered concurrently with methotrexate (at least 7.5 mg/wk) to prevent the development of neutralizing antibodies. Data suggest that the combination of a TNF inhibitor with DMARDs other than methotrexate (e.g., leflunomide and/or sulfasalazine) is safe and perhaps efficacious as well.³⁷⁻³⁹ Formal drug interaction studies, however, have not been done with these drugs and the anti-TNF therapies. Combining TNF inhibitors or combinations of TNF inhibitors with other biologic agents is not recommended³ because of the risk of enhanced infection and other toxicities.⁴⁰

In general, the onset of action of TNF inhibitors is more rapid than that of nonbiologic DMARDs, and many patients show a clinical response after only 8 to 12 weeks of therapy. However, some patients may be slower to respond, and, as with methotrexate, approximately 50% of patients fail to

show a robust response to anti-TNF therapy at all.^{16,17,30,31} The factors responsible for this variability are not known.

T-cell costimulatory modulators

The T-cell costimulatory modulator abatacept (soluble CTLA-4-immunoglobulin) (see Chapter 59), is FDA approved as monotherapy or in combination with nonbiologic DMARDs for moderate to severe RA given its efficacy in reducing clinical signs and symptoms as well as radiographic progression in methotrexate-naïve patients⁴¹ and those showing inadequate response to nonbiologic DMARDs and/or TNF inhibitors.⁴²⁻⁴³ In a randomized trial performing a head-to-head comparison of the efficacy of abatacept and a TNF inhibitor (infliximab) in patients who had active RA despite treatment with methotrexate, clinical response outcomes were similar over 1 year,⁴⁶ although infliximab was initiated at the minimum (3 mg/kg) dose with no provision for escalation.

Overall, the safety profile of abatacept based on clinical trial data is modestly superior to that of TNF inhibitors. Infusion reactions were lower in abatacept-treated patients than in infliximab-treated patients,⁴⁶ and no cases of tuberculosis or other opportunistic infections were associated with abatacept use in the 5-year safety data from the ATTAIN trial.⁴⁷ In particular, potential signals of lung cancer and exacerbations of chronic obstructive pulmonary disease noted in a large safety trial (ASSURE)⁴⁴ have not been replicated in subsequent studies, but further monitoring is warranted.

Abatacept is the only biologic agent available in both subcutaneous and intravenous formulations. It is administered according to weight and a loading regimen is recommended. Thereafter, infusions every 4 weeks or subcutaneous injections every week are administered. Because the onset of clinical effect can be delayed, a recent consensus statement recommends continuing abatacept for at least 16 weeks before evaluating efficacy.

Abatacept should not be combined with TNF inhibitors because the combination has been associated with higher infection rates in the absence of improved efficacy.

B-cell depleter

Rituximab is a chimeric monoclonal antibody directed against CD20 (see Chapter 60). It has been approved by the FDA for use in combination with methotrexate for the treatment of moderate to severe RA in adults who have shown an inadequate response to one or more TNF inhibitors because of its efficacy in reducing synovitis and in slowing radiographic progression in this population.⁴⁸⁻⁵⁰ Rituximab has also been tested in combination with TNF inhibitors plus methotrexate but did not offer any further advantage in efficacy compared with combined TNF inhibitor/methotrexate therapy and increased the number of severe adverse events.⁴⁰ Evidence suggests enhanced efficacy in RA populations who are seropositive for RF; however, rituximab has been used with success in seronegative patients as well.⁴⁸ These and other studies showing lack of correlation between peripheral depletion of B cells, or change in titers of RF and/or anti-CCP titers, with clinical response call into question the exact mechanism of action of rituximab in RA.

The safety profile for the first treatment course of rituximab is generally favorable, with few serious infections and no opportunistic infections noted in clinical trials. Infusion reactions are more frequent with rituximab than with the other infused biologic agents, which led to the recommendation for pretreatment with corticosteroids. Infusion reactions tend to diminish with repeated infusions. Reductions in immunoglobulin levels have been noted over repeated courses of treatment. These decreases have not been associated with an increased risk of infection to date, although in the 1% of patients with sustained decreases in immunoglobulin G, a non-statistically significant trend toward an increased risk of infection was noted. Furthermore, low pretreatment levels of immunoglobulin G have been identified as a risk factor for severe infections.⁵¹ Sporadic cases of progressive multifocal leukoencephalopathy have been reported in patients receiving rituximab for non-Hodgkin lymphoma, systemic lupus erythematosus, and RA,⁵² although most of these patients were also receiving immunosuppressive agents.

Rituximab is administered as two doses of 1000 mg separated by 2 weeks (hereafter referred to as a *treatment course*), although one study showed nearly equivalent efficacy with two 500-mg infusions. The duration of effect is variable but is typically longer than 6 months.⁵³ Durable responses of 18 months and longer have been reported after one course of treatment.⁵⁴ In some cases, subsequent treatment courses resulted in longer duration of response. Although levels of peripheral B cells are rapidly diminished after treatment in most cases, reemergence of B cells does not predict loss of response and continued depletion does not guarantee maintenance of response. In the SUNRISE⁵⁵ trial, those who were treated with a second rituximab course at 6 months had improved and sustained efficacy at 1 year compared with those treated with only one course, and the safety profiles

for the two treatment conditions were similar. Although initially it was thought to be futile to administer a second course of treatment to patients unresponsive to the first course, a more recent study showed that administration of a second treatment course was associated with a significant improvement in the DAS28 score in 72% of patients.⁵⁶

Some concern has been raised about the safety of initiating another biologic therapy in patients who have shown an inadequate clinical response to rituximab but still have peripheral B cell depletion. However, preliminary evidence suggests that starting a TNF inhibitor in this setting may be safe.⁵⁷

Interleukin-6 inhibitor

Tocilizumab is a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody (see Chapter 62) approved for treatment of systemic juvenile idiopathic arthritis and adult RA in patients in whom treatment with at least one TNF inhibitor has failed. Several randomized controlled trials⁵⁸ and additional open-label phase 3b/4 trials have shown its short- and long-term efficacy in improving RA signs and symptoms and slowing radiographic progression in treatment-naïve patients and in patients showing inadequate response to nonbiologic and biologic (TNF inhibitor) DMARDs, both as monotherapy and in combination with methotrexate. Clinical response and decrease in C-reactive protein levels have been noted as early as 4 and 2 weeks, respectively, and improvement in hemoglobin levels is seen in the majority of those who meet response criteria.

The recommended starting dose is 4 mg/kg intravenously every 4 weeks with the option to increase to 8 mg/kg if needed for clinical response.

Overall, the safety profile of tocilizumab based on clinical trials is similar to that of the TNF inhibitors. Increased risk of infection (including tuberculosis and other opportunistic infections), rash, and abnormalities in laboratory values (e.g., neutropenia, elevations in liver enzyme and lipid levels) have been noted. Perforations of the gastrointestinal tract were also seen in a small number of patients treated with tocilizumab, especially those with a history of diverticular disease.

Although no head-to-head trials have been performed comparing tocilizumab with other DMARDs, tocilizumab appears to have efficacy comparable to that seen with TNF inhibitors in both clinical and radiographic outcomes. It is currently unknown which subset of patients would benefit most from this biologic agent, and at this time tocilizumab is usually administered as third-line therapy in patients in whom methotrexate and TNF inhibitor treatment has failed.

Interleukin-1 inhibitor

Anakinra (recombinant soluble IL-1 receptor antagonist), the only FDA-approved IL-1 inhibitor for the treatment of RA (see Chapter 61), is administered as a once-daily subcutaneous injection. It has been shown, both as monotherapy and in combination with methotrexate, to be superior to placebo in reducing signs, symptoms, and radiographic progression in patients with advanced RA. Although it has not been compared head to head with any of the TNF inhibitors, its efficacy in clinical trials is substantially lower than that of the TNF inhibitors. This, coupled with the inconvenient dosing schedule, has resulted in its diminished use in clinical practice and its exclusion from the ACR 2012 treatment recommendations.³

Glucocorticoids

Glucocorticoids (see Chapter 54) are potent antiinflammatory drugs that constitute important adjunctive therapy for RA but should never suffice as monotherapy for any prolonged period of time due to their substantial adverse event profile. In general, glucocorticoids should be prescribed at as low a dosage and for as short a time as possible. They can be administered orally or by intraarticular injection, intravenous infusion, or intramuscular injection. Glucocorticoids are particularly useful at the onset of disease because they produce a rapid and substantial reduction in pain and synovitis,⁹ and thus decrease patient discomfort while the slower-acting DMARD(s) takes effect. This bridging strategy, in which glucocorticoids are tapered and discontinued as the DMARD takes full effect, can also be applied during disease flares. In view of the adverse effects associated with long-term glucocorticoid administration (see Chapter 54), the associated benefit must always be weighed against the risk of toxicity.

Nonsteroidal antiinflammatory drugs

Concomitant prescription of an NSAID along with DMARDs intermittently or continuously throughout the course of RA is not uncommon. Many NSAIDs are available commercially and are discussed in detail in Chapter 53. Along with well-recognized gastrointestinal adverse effects, concerns of an increased risk of cardiovascular events have drawn into question the use

of this class of drugs for long-term treatment of RA and other inflammatory conditions.

MAINTENANCE OF THE TREATMENT RESPONSE

RA is a chronic disease that rarely remits spontaneously. Consequently, DMARD treatment must be continued indefinitely because its discontinuation generally leads to reemergence of signs and symptoms of disease within weeks to months. Patients who have been treated according to an induction regimen may tolerate a simplification of their treatment regimen to a single DMARD. Many patients experience a flare in disease activity over the course of their illness that necessitates an adjustment in treatment, usually in the form of increased dose or number of DMARDs.

FUTURE

A subset of RA patients do not respond adequately to aggressive therapy, and to date, no cure for RA is available. Fortunately, a number of new drugs with novel mechanisms of action and/or more convenient routes of administration (see Chapters 63 to 66) may provide alternatives for these patients. The most promising of these appear to be the small-molecule inhibitors of tyrosine kinases (i.e., syk and jak). In phase 2 studies, the syk inhibitor fostamatinib was shown to be efficacious in patients who showed inadequate response to methotrexate but not in those who showed inadequate response to biologic agents. In contrast, in two phase 3 randomized controlled trials the JAK-3/2 inhibitor tofacitinib showed clinical efficacy in patients with inadequate response to nonbiologic DMARDs, both as monotherapy and in combination with methotrexate, at 3 and 6 months, respectively.^{59,60} The dosages studied were 5 mg or 10 mg taken orally twice a day. Throughout the studies, the most frequent adverse events were infections, elevation in lipid levels, and cytopenias (mainly neutropenia and anemia). No data are available yet on the ability of either fostamatinib or tofacitinib to slow radiographic progression of disease.

In the coming years, additional research will establish where these agents fit in the evolving treatment algorithms for RA.

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OTHER CONSIDERATIONS

Screening for latent tuberculosis is recommended for all RA patients being considered for therapy with biologic DMARDs. For patients with latent tuberculosis, antitubercular treatment should be initiated before biologic DMARD therapy is begun. Patients with risk factors for tuberculosis should continue to undergo annual screening while receiving biologic therapy. Regarding vaccinations, administration of killed vaccines (pneumococcus, influenza, hepatitis B), recombinant vaccines (human papillomavirus), and live attenuated vaccines (herpes zoster) is recommended before nonbiologic or biologic DMARDs are started. For nonvaccinated patients who are already receiving nonbiologic DMARDs, administration of all the aforementioned vaccines still is recommended. For nonvaccinated patients who are already receiving a biologic DMARD, live vaccines (e.g., herpes zoster) should be avoided, whereas the killed and recombinant vaccines may be administered.

BARRIERS TO AGGRESSIVE MANAGEMENT

The ability to escalate therapy to the desired level in an individual RA patient may be limited by the presence of one or more comorbid illnesses and/or patient behaviors. Comorbidities such as recurrent or chronic infections, chronic liver disease, malignancy, and moderate to severe congestive heart failure are relative contraindications to the use of some biologics or DMARDs as discussed earlier and in other chapters.

CONCLUSION

The treatment of RA has changed dramatically in the past decades. The initiation of treatment very early in disease, the use of combinations of DMARDs, and the emergence of the biologic agents have made it possible to achieve control of synovitis and improvement in quality of life in the majority of RA patients. Complete remission or low disease activity should be the goal of treatment in all RA patients. Indeed, emerging clinical and epidemiologic data suggest that excellent long-term control of synovitis will result in significant reductions in rates of unemployment, joint surgeries, disability, and mortality in RA patients.

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98

Multidisciplinary approach to rheumatoid arthritis

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- Patient education may improve pain, functional ability, depression, coping, and self-efficacy and should be a cornerstone in the multidisciplinary care of persons with rheumatoid arthritis (RA).
- Cognitive-behavioral therapy and mindfulness-based group intervention programs may improve fatigue and psychological distress.
- Nursing care provides continuity and the opportunity for shared decision making and focuses on the patient's coping strategies.
- Persons with RA have increased risk of cardiovascular diseases and osteoporosis. Health professionals should therefore promote physical activity and guide patients in achieving and maintaining a healthy lifestyle.
- Dynamic exercises are safe and beneficial for patients with RA, but patients with extensive joint damage or joint prostheses should be careful with high-intensity weight-bearing exercises.
- Physical modalities are a possible adjunctive method with uncertain benefits but no harmful effects.
- Orthopedic shoes, insoles, wrist orthoses, and splints correcting for foot or hand deformities, as well as assistive devices, may decrease pain and improve function.
- Persons with RA should follow a healthy diet, avoid certain foods if they have allergies or intolerance, and consult a nutritionist if they want to try any special diet.
- Persons at risk of being work disabled should have rapid access to vocational rehabilitation because prevention of work disability is probably more effective than correction of work disability after work loss.
- Team care such as comprehensive inpatient and day patient programs is more effective than regular outpatient care to control disease activity and improve functional ability.
- Transdisciplinary models, in which clinicians take on extended roles, may in many cases be at least as effective as and more cost effective than extensive team care.

INTRODUCTION

Over the past decades, new medical and surgical treatments have improved prognosis and quality of life for people with RA. Still, most patients experience periods with pain, fatigue, and loss of function and benefit from therapeutic interventions implemented by a variety of health professionals. The expectations for level of functioning and participation in society have also been raised along with these new opportunities for improvement.

A consumer-centered approach is now widely applied in disease management. Individual goals and treatment plans are jointly set by the patient and the rest of the team. The roles and areas of expertise of the potential team members¹ are described in Table 98.1. Even if each profession has different areas of expertise, a common goal is always to reduce and control disease activity, to maintain or improve function and work ability, and to enhance coping strategies and the quality of life of the patient and his or her family. How a team of health professionals work together depends, to a large degree, on the problems of the patient, the treatment setting, and the treatment goals. Traditionally, two models of care have been distinguished: a multidisciplinary approach, in which different team members cooperate on a regular basis while staying within their professional boundaries, and an

interdisciplinary team model, in which the members analyze, synthesize, and harmonize links between disciplines to establish a shared basis of knowledge and common goals in the treatment or rehabilitation of the patient.² Although patients with an aggressive disease, multiple problems, and/or a complex life situation may profit from application of the latter model, the multidisciplinary team model may be appropriate for patients with a stable disease and life situation. Also, some patients may prefer to interact with one or a few health professionals rather than an extensive team, and the involvement of fewer persons is likely to assist communication and partnership with the patient.¹

Lately, a third, so-called *transdisciplinary model* has emerged. In this approach, members transcend their traditional boundaries and take on extended roles to be able to meet a patient's need for more rapid access to care, to provide more time and continuity in care, or to provide a more optimal treatment when funding or human resources are limited. Examples of such models are care by clinical nurse specialists who conduct examinations and treatment monitoring usually performed by a rheumatologist and the primary therapist model, in which specially trained physical or occupational therapists function as multiskilled health professionals working in consultation with or with referral to peers or other services when necessary.²

Published recommendations for disease management often divide the recommendations into pharmacologic and nonpharmacologic interventions.³ Health professionals primarily work with nonpharmacologic interventions. This chapter reports the evidence for such interventions and discusses different care models.

NONPHARMACOLOGIC INTERVENTIONS

Successful multidisciplinary care depends on the availability of skilled health professionals as well as timely and coordinated delivery of the relevant interventions.

Patient education

The primary target of patient education is the disease consequences: symptoms and disability. Promoting independence, feelings of being in control, and confidence are also major aims. The implication is that cognitive-behavioral skills must be addressed in addition to disability and symptoms.

Patients want and are entitled to get the information they need, in both written and oral form. However, self-management and shared decision-making are important means to cope with the disease consequences. Interactive computerized patient education may be a valuable supplement today, also to improve cognitive-behavioral outcomes. Lorig developed and implemented patient education programs in arthritis on the basis of the concept of self-efficacy. Lorig's arthritis self-management programs (ASMPs) have been disseminated internationally, and evidence supports that increased self-efficacy mediates improvement in perception of control, health behaviors, and health status (grade A).^{4†}

A systematic review has shown that patient education has a greater beneficial effect on symptoms and health status than on disease activity and

[†]Evidence rated as "grade A*" represents data from systematic reviews and meta-analyses of randomized trials. If there is no systematic review and/or meta-analysis addressing the given issue, then the authors cite data from individual randomized controlled trials (grade A) to support the recommendations. Recommendations based on results from observational studies (grade B) and/or case series (grade C) is used only when data from randomized controlled trials are not available.

TABLE 98.1

Roles and areas of expertise of the potential members of a multidisciplinary team

Profession	Roles and areas of expertise
Clinical pharmacist	The clinical pharmacist identifies, solves, and prevents drug-related problems such as unnecessary drug use, nonoptimal drug or dosage, need for additional drug, interaction between drugs, adverse drug reactions, and need for more information or therapy discussion.
Nurse	The nurse assists the patient in the performance of health-promoting activities to meet needs when altered ways of self-care are required due to disease or treatment. Nurses focus on activities that the patient would perform unaided given the skill, will, or knowledge, and thus the mobilization, strengthening, or compensation of these resources. Optimal levels of physical, mental, and social coping and symptom relief are important targets.
Nutritionist/dietician	The nutritionist/dietician assesses, diagnoses, and treats nutrition-related problems and gives practical guidance regarding diets to individuals and to the public. He or she is qualified to treat a range of medical conditions with dietary therapy on the basis of current literature, scientific evidence, best practices, and the individual needs of the person.
Occupational therapist	The occupational therapist evaluates the impact of rheumatic diseases on function and performance of daily tasks and valued life roles, using interviews, observation, and standardized assessments. Personal goals, interests, and resources are screened to develop an individualized program aimed at assisting adjustment to new or modified life roles, and the home/school/work environment is assessed to determine if adjustments are necessary to enhance the person's abilities. The most important interventions in occupational therapy are patient education concerning ergonomic principles and energy conservation, therapeutic exercise and activity programs, provision of orthoses and assistive technology, and environmental and task modifications.
Orthopedic surgeon	An orthopedic surgeon trained in the treatment of people with rheumatoid arthritis is responsible for performing surgical procedures and, together with the patient, rheumatologist, and relevant team members, establishing a plan for surgical procedures that should be coordinated with the timing of other interventions.
Podiatrist/orthopedic shoemaker/orthotist	The orthopedic shoemaker evaluates the foot and ankle to define deformities, instabilities, and painful areas. Custom-made insoles, prefabricated orthopedic shoes, and custom-made shoes are common interventions in pain relief and stabilization of an unstable and/or painful rheumatoid foot and ankle. The orthotist can supply prefabricated or custom-made orthoses for all body parts to prevent or correct deformities, reduce pain, or increase function. Lightweight and soft materials with an easy closure system are preferred. Because rheumatoid arthritis usually affects multiple joints, it is important to have an overall and integrated view when planning the orthotic treatment.
Psychologist	The role of the clinical psychologist is to assist the patient and family in managing emotional and psychological stress and to assist in living and coping with a chronic disease. On the basis of an evaluation, the psychologist tailors a treatment plan to meet the needs of the patient. The clinical psychologist provides a wide range of interventions designed to enhance coping, including cognitive therapy; pain, sleep, and stress management; sexual and relationship counseling; and psychotherapy. The psychologist may also have a consultation role in the interdisciplinary team.
Physical therapist	The physical therapist assists patients in achieving optimal function, pain relief, and physical recovery. On the basis of an evaluation of physical and functional status, the physical therapist uses therapeutic exercises and manual techniques to improve patients' muscle strength, joint mobility, and cardiovascular function. Physical modalities such as heat, cold, electrical therapy, and hydrotherapy may also be used to achieve temporary pain relief and reduce muscle spasm, so that the patient is prepared for exercise and activity.
Rheumatologist	The rheumatologist is primarily responsible for diagnosis and the total management. His or her main responsibility is usually pharmacologic interventions and disease monitoring. The rheumatologist works with the patient and members of the multidisciplinary team to identify needs for nonpharmacologic interventions.
Social worker	The social worker plays a role in preventing and solving personal problems and problems regarding networks of interpersonal relations within and outside the family. He or she also addresses economic problems and limitations regarding education, work, and/or a professional career.

anxiety, and that the efficacy mostly is seen only at the first follow-up visit (grade A*) (Table 98.2).⁵ Another systematic review highlighted that educational programs improved knowledge and compliance without improving in health status, whereas psychoeducational programs improved coping behavior. Further, short-term effects in program targets were generally observed, whereas long-term changes in health status were not convincingly demonstrated (grade A*).⁶

Hewlett and colleagues have recently shown that a group cognitive-behavioral therapy program could improve fatigue impact and coping (grade A).⁷ Another recent randomized controlled trial was able to demonstrate that a mindfulness-based group intervention reduced psychological distress and fatigue in patients with inflammatory rheumatic joint diseases (grade A).⁸

Almost all persons with RA use medications, and in a Norwegian study, up to 60% of patients with RA or polyarthritis reported using five or more drugs when admitted to a hospital.⁹ Not surprisingly, issues concerning medication and adverse effects are frequently raised in studies exploring unmet health care needs in this patient population. Clinical pharmacists are educated to identify and prevent drug-related problems.⁹ Counseling with pharmacists should thus be available on an individual basis as well as in group-based patient education programs.

Joint protection is a self-management program that aims to maintain functional ability by teaching participants to use altered movement patterns, alternative working methods, assistive devices, and activity pacing.¹⁰ Studies of such programs using standard methods of information communication

and training have shown little or no effect. However, better results on several outcomes were observed in individuals with early RA who were exposed to a joint protection program based on educational-behavioral teaching methods compared with those who underwent a program based on traditional practice (grade A).¹⁰ This suggests that joint protection programs can help slow the progression of the effects of RA over and above the benefits of drug therapy alone.

In conclusion, patient education should be an integrated part of the total management of RA. Elements that focus on aspects like self-efficacy and coping behavior seem to increase the likelihood of an effect on symptoms and health status.

Nursing care

Nursing care for patients with RA includes providing emotional support for adaptation to the new diagnosis; knowledge about the disease, consequences, and treatment; and discussions on self-management in general and on symptoms. This type of care was previously performed only in the setting of hospitalization, but the principles are increasingly transferred into day care or outpatient clinics. It is not known whether nurse-led clinics can prevent or reduce the impact of the disease, but significant increases in patient satisfaction have been recorded (grade A).¹¹

Assessments in nursing care should address needs on the basis of what is most important to the patients. Pain, physical functioning, and fatigue

TABLE 98.2
Effect of patient education interventions on various outcomes at first and last follow-up visits

Outcome measure	First follow-up		Last follow-up	
	Exp/control (no.)	SMD (95% CI)	Exp/control (no.)	SMD (95% CI)
Pain	1119/1000	−0.08 (−0.16-0.00)	530/543	−0.07 (−0.019-0.05)
Functional disability	1153/1122	−0.17 (−0.25-0.09)	651/657	−0.09 (−0.20-0.02)
Joint count	585/573	−0.13 (−0.24-0.01)	484/490	−0.08 (−0.22-0.07)
Patient global assessment	181/177	−0.28 (−0.49-0.07)	302/316	−0.06 (−0.22-0.10)
Psychological status	561/577	−0.16 (−0.28-0.04)	392/402	−0.04 (−0.10-0.19)
Anxiety	671/657	−0.04 (−0.15-0.07)	481/509	−0.01 (−0.12-0.13)
Depression	899/871	−0.14 (−0.23-0.05)	564/579	−0.09 (−0.21-0.02)
Disease activity	326/321	−0.03 (−0.19-0.12)	359/359	−0.05 (−0.20-0.10)

Negative results favor patient education.

CI, confidence interval; Exp, experimental; no., numbers for experimental versus control intervention; SMD, standardized mean difference.

Modified from Riemsma RP, Taal E, Kirwan JR, Rasker JJ. Systematic review of rheumatoid arthritis patient education. *Arthritis Rheum* 2004;51:1045-59.

are the most frequently reported prioritized symptoms and areas of disease impact, and the recently developed Rheumatoid Arthritis Impact of Disease score may be helpful in identifying areas of particular importance to patients.¹²

The assessment of patients' own resources is central in nursing care. Nursing care aims to mobilize, strengthen, or compensate for deficiencies in dimensions of self-care. Importantly, the European League Against Rheumatism (EULAR) has recently published recommendations on the role of the nurse in the management of chronic inflammatory arthritis (grade A*).¹³

Physiotherapy

Physiotherapy, including exercise, hands-on techniques, and different physical modalities, is an important component of the nonpharmacologic care of people with RA.

Exercise

Patients with RA have been shown to have reduced muscle strength, endurance, and aerobic capacity compared with age-matched controls (grade B).^{14,15} Due to fear of aggravation of disease activity and symptoms, people with RA were earlier advised to limit the amount of physical activity and protect their joints when exercising physically. However, deconditioning and low muscle strength predict earlier mortality in both diseased and normal populations at levels of significance similar to or greater than biomedical predictors (grade B).^{14,15} In general, physical activity is associated with better physical and mental health, prevention of disease, and reduced risk of all-cause mortality, and based on consistent findings in the literature, aerobic and strengthening exercise are safe and beneficial for people with RA (grade A*).¹⁶⁻¹⁸ A systematic review of 14 randomized controlled trials encompassing 1040 RA patients found that cardiorespiratory aerobic exercise improved physical function (Health Assessment Questionnaire score), pain, and quality of life, and the authors concluded that cardiorespiratory exercise appeared safe for people with RA (grade A*).¹⁷ Further, a meta-analysis of 10 randomized controlled trials encompassing a total of 547 patients evaluated the efficacy of resistance exercises in RA patients and found that such training is safe and beneficial. Several measures of muscle strength and function improved, and subgroup analyses revealed a trend toward higher efficacy for high-intensity programs (grade A*).¹⁸

The effectiveness and safety of a high-intensity program was confirmed in a multicenter study in the Netherlands that included 300 RA patients (grade A).¹⁹ Compared with usual care, the high-intensity program was more effective in improving the functional ability of RA patients, and the progression of radiographic damage of the small joints of the hands and feet was not increased by the long-term, high-intensity, weight-bearing exercises (grade A).¹⁹

The beneficial effects and safety of exercise was also supported in a review of 15 clinical trials evaluating aerobic and strengthening exercises, which concluded that aerobic capacity and strength improved without negative effects on pain and disease activity (grade A*).¹⁶ Based on the results of this review, the authors provided the following recommendations for aerobic exercises: the intensity level should be moderate to hard (i.e., 60% to 85% of maximum heart rate), and exercises should be performed three

times weekly for a duration of 30 to 60 minutes. The recommendations are similar to those for the general population, except that the following special considerations may be necessary for people with RA:

- Careful progression of intensity and individual adjustments of the program may be necessary due to disease fluctuations and/or disease activity.
- Caution should be used because of increased risk of fractures due to osteoporosis or treatment with glucocorticoids.
- Patients with joint replacements should be careful with heavy loads.
- During periods of high disease activity, flexibility and range-of-motion exercises together with strength training of large muscles are preferred.

Most of the studies on the effects of exercise interventions involved patients with established, stable RA, but a randomized controlled study conducted in Finland included patients with early RA (grade A).²⁰ A strength training program was compared with a program of range-of-motion exercises, and during the 2-year training period, a statistically greater improvement in muscle strength and functional capacity occurred in the strength training group. The results of this study indicate that, in patients with early RA as well, dynamic strength training should be recommended. However, to maintain adequate joint flexibility, range-of-motion exercises should also be part of exercise programs for patients with RA, even if high-quality studies evaluating the effect of such exercises are lacking.

The increased risk of cardiovascular disease represents an excess burden of morbidity and mortality in RA patients (grade A*).²¹ A review of studies investigating exercise interventions in relation to cardiovascular disease in RA patients provided strong evidence that exercise of various modes from low to high intensity is effective in improving disease-related characteristics and functional ability in RA patients (grade A*),²² but future studies are required to investigate the effects of exercise in improving the cardiovascular status of this patient population.

In summary, dynamic exercises are safe and beneficial for patients with both early and established RA. For most patients, no harmful effects in terms of radiologic damage of the joints are reported, but patients with extensive joint damage should be careful with high-intensity weight-bearing exercises. The mode of exercising should be based on the individual patient's preferences, because there is lack of evidence on the optimal mode of exercise delivery (land or water based, group or individual) (grade A*).²³ Due to the increased risk of comorbidities such as cardiovascular disease, it is important that health professionals promote physical activity and guide patients in achieving and maintaining a healthy lifestyle.

Hands-on techniques and physical modalities

Several passive physiotherapy modalities are also frequently used in the management of RA, including joint mobilization or manipulative techniques, electrotherapy, thermal agents, and balneotherapy. Many RA patients prefer these treatment alternatives for pain control and increased joint mobility.

Patients with limited range of motion of peripheral joints may benefit from passive mobilization, but in general, the evidence for hands-on

techniques is scarce (grade A*).²³ Some physical modalities, like transcutaneous electrical nerve stimulation (TENS), therapeutic ultrasound, low-level laser therapy, and thermotherapy, have been recommended for the management of rheumatoid arthritis (grade A)²⁴ (see Chapter 47). TENS is used for pain control or muscle stimulation, and there are conflicting results on the effect of TENS on pain outcomes in patients with RA (grade A*).²⁵ More well-designed studies with a standardized protocol are needed to provide further evidence of the efficacy in RA (grade A*)²⁵ (see Chapter 47). Ultrasound in combination with some other treatment modalities (exercises, faradic current, and wax baths) was not found to be effective in a Cochrane review. However, some studies, mostly of poor quality, indicated that ultrasound alone applied to the hand may have a beneficial effect on grip strength, wrist motion, morning stiffness, and joint counts. No harmful effects have been reported (grade A*).²⁶ An updated review of the use of low-level laser therapy in people with RA concluded that this modality could be considered for short-term treatment for relief of pain and morning stiffness, particularly because it has few adverse effects (grade A*).²⁷

Superficial moist heat and cryotherapy can be used as palliative therapy. Paraffin wax baths combined with exercises can be recommended for beneficial short-term effects on arthritic hands, but the conclusions are limited by the poor quality of the trials (grade A*).²⁸ Similarly, there is insufficient evidence to support the use of balneotherapy. Although many studies report positive findings, the studies suffer from poor methodology and the results must be considered with caution (grade A*).²⁹

Hand exercises and orthoses

Many of the activity limitations seen in persons with RA are explained by impaired hand function, with grip force as the most important determinant.³⁰ Hand exercises are therefore a recommended strategy to improve hand function. In 2004 a systematic review concluded that there is some, but limited, evidence that long-term hand exercise may increase grip strength in patients with RA (grade A*).³¹ More recent studies have confirmed that intensive hand exercise programs are well tolerated and effective in improving hand function in terms of decreased pain and increased strength (grade B).³² However, more research is necessary to determine the optimal combinations of different kinds of exercises, variations in resistance, number of repetitions, and daily or weekly frequency for patients with early or established RA.

The wrists and finger joints are the most frequently involved joints in persons with RA. Thus hand splints or orthoses are often prescribed to reduce pain and/or swelling, prevent contractures and deformities, and increase joint stability. Working wrist orthoses, resting splints for the wrist and hand, and splints to correct specific deformities are three commonly used hand orthoses in RA (Fig. 98.1). A systematic review of the use of splints and orthoses for treatment of RA concluded that working wrist splints have no positive short- or long-term effect on pain, grip strength, or range of motion (grade A*).³³ Still, the authors recommended that patients try inexpensive, ready-made wrist orthoses because studies indicate that they may provide pain relief for some patients in some activities.

The authors of the systematic review of orthoses also concluded that current evidence does not allow recommendations to be made regarding the use of resting hand splints to reduce pain and swelling, even though patients in one of the two studies preferred wearing the splints to not wearing them (grade A*).³³

Small custom-made splints have been shown to correct deformities and improve pain³⁴ (grade A), whereas specially designed silver ring splints may improve dexterity in patients with swan neck or boutonnière deformity^{35,36} (grade B).

Foot orthoses, insoles, and orthopedic shoes

More than 85% of people with established RA have involvement of the joints in the foot, which can lead to pain, joint instability and deformities, walking difficulties, and limitations in performance of daily activities.³⁷ In addition, joint abnormalities in the foot may alter walking patterns and thereby the biomechanics of the entire lower extremity. Persons with RA are therefore advised to use appropriate footwear, such as light-weight running shoes or rocker shoes, and many also use foot orthoses, insoles, or orthopedic shoes to relieve foot pain and normalize gait. A variety of prefabricated and custom-made orthoses and shoes are available. Soft insoles made of viscoelastic materials may attenuate shock during walking; semirigid orthoses are made to promote a more uniform pressure distribution in the foot; and rigid foot orthoses are designed to reduce unwanted motion and maintain desired structural alignment. Orthopedic shoes are made with extra depth in the shoe box, greater foot stability, and/or padded heel collars for improved



Fig. 98.1 Hand orthoses may decrease pain and correct deformities. From top to bottom: a resting splint that restricts motion and maintains a functional position, a functional wrist splint that supports the wrist during hand activities, and a silver ring splint that corrects and/or prevents deformities.

fit. Often, a combination of orthopedic shoes, orthoses, and soles is used to achieve an optimal effect.

In general, current research supports the use of these interventions. The results of a systematic review of interventions for foot disease in RA indicates that shoes with extra depth have beneficial effects on pain and function and that the benefit is greater if the shoes are combined with orthoses (grade A*).³⁷ In a recent review, some evidence was found that custom foot orthoses may reduce pain and forefoot plantar pressures, and inconclusive evidence was noted for an effect of orthoses on foot function, walking speed, gait parameters, and the rate of progression of hallux valgus deformities (grade A*).³⁸ However, studies have not clearly shown which type of shoes or foot orthoses is most effective.

Assistive technology

Assistive technology is prescribed and used as a means to reduce pain and compensate for impairment and environmental demands, and it is one of the most frequently used self-help strategies reported by persons with RA.³⁹ It includes a wide range of products, from low-tech devices to technologically complex equipment; some of these are designed for the general population, whereas others have been developed to meet the needs of people with functional limitations or disabilities (Fig. 98.2). Studies indicate that two thirds of all persons with arthritis use assistive devices on a daily basis and that use of such technology is associated with more severe disease, longer disease duration, and loss of grip strength and functional ability. However, even if provision of assistive devices is a widely used multidisciplinary intervention, there is a general lack of studies evaluating the benefit of such devices. Only one small study assessing the effect of an eye drop delivery device met the inclusion criteria for a review of assistive technology use in RA (grade A*).³⁹ One reason for the small number of studies and low level of formal evidence may be that the effect of some assistive devices seems rather obvious, such as the benefit of using raised seats, grab bars, or canes or crutches to ease safe transfer or increase mobility.

Psychological interventions

Living with a persistent and chronic disease like RA may lead to psychological distress and reduced quality of life. Psychological interventions are



Fig. 98.2 Use of assistive devices is one of the most frequent self-help strategies reported by persons with rheumatoid arthritis. From left to right: an enlarged grip for opening bottles, a self-opening scissor tong, and a bread knife with an ergonomic handle.

therefore often used to improve pain, anxiety, and/or depression. These interventions may consist of one or a combination of modalities such as relaxation strategies (e.g., progressive muscle relaxation), biofeedback therapy for reduction of muscle tension, cognitive-behavioral strategies (e.g., cognitive reconstruction, pain coping), and patient education. Research indicates that these approaches may be effective adjuncts to conventional medical management. In a review based on data from 25 randomized controlled studies, statistically significant improvement was noted in pain, functional ability, depression, coping, and self-efficacy immediately following psychological treatment, but the effect sizes were small (grade A*),⁴⁰ and the effects were not maintained to the follow-up examinations performed at an average of 8.5 months. Subgroup analyses revealed that psychological interventions may be more effective in patients with shorter disease duration. These results were confirmed to a large degree in a more recent review in which psychological interventions also were found to have a significant positive impact on physical activity levels (grade A*).⁴¹

Nutrition

People with RA may try to replace their traditional food with special diets.⁴² The most common diets are vegetarian (usually eliminating meat and fish), vegan (eliminating meat, fish, eggs, and milk), Mediterranean (including small amounts of meat and more fish, fruits, vegetables, and olive oil), and elemental or elimination diets. Elemental diets are usually liquid diets containing nutrients that are broken down to make digestion easier, whereas elimination diets are used to exclude foods that might worsen the disease. A systematic review of dietary interventions in RA concluded that the effects of diet on pain, stiffness, and physical function were uncertain (grade A*).⁴² However, the results of one single trial indicated that both fasting followed by a vegetarian diet and a Cretan Mediterranean diet may improve pain compared with an ordinary diet, whereas the effects of vegan and elimination diets are uncertain (grade A*).⁴² Higher dropout rates and weight loss in the intervention groups also indicate that dietary manipulations have potential adverse effects.

Many dietary interventions are in line with what may be considered a healthy diet, with a focus on fiber, fruits, vegetables, antioxidants, fish, moderate amounts of lean meat, and reduction of saturated fat and sugar. In general, persons with RA should therefore be given the same advice as the general population, which is to follow a healthy diet, avoid certain foods that may cause allergies or intolerance, and consult a nutritionist if they want to try any special diet.

Vocational rehabilitation

Functional limitations may cause productivity loss in terms of work disability, work loss (synonymous with absenteeism or short-term sick leave), or work limitation (reduction in productivity while still present at work). A systematic review examining productivity loss due to RA showed that RA-related work disability rates were similar in the United States and European countries and that a median of 66% of employed RA patients had experienced work loss due to RA for a median duration of 39 days in the previous year (grade A*).⁴³ However, the time between diagnosis of RA and a 50% probability of being work disabled varied from 4.5 to 22 years. The results also showed that the prevalence of RA-related work disability has

decreased over time, which may be due to advances in drug treatment of RA, a general decrease in the proportion of people engaged in manual or physically demanding work, or changes in social policies, level of education, age, and disease duration (grade A*).⁴³

To enable persons with RA to maintain or return to work, multidisciplinary vocational rehabilitation programs have been developed (see Chapter 47). In the aforementioned systematic review, it was concluded that even though some positive effect of such programs on vocational status was demonstrated in five of the six studies included, the proof of the effect was limited because all included studies were uncontrolled trials and five had a retrospective design. Since then, a randomized controlled trial has demonstrated that targeted, comprehensive occupational therapy significantly improves functional and work-related out-comes in employed RA patients at risk of work disability (grade A).⁴⁴

Prevention of work disability is probably more effective than correction of work disability after work loss. One program included self-management group sessions combined with individual professional assessments and interventions, with a follow-up by telephone 1 month after patient completion of the program. As a consequence of the program, participants were more able to adapt their work to their arthritis, and improvements in fatigue, self-efficacy, and at-work productivity over 12 months were shown (grade B).⁴⁵ Another randomized controlled study examined job loss in individuals with early RA who were randomly assigned to receive adalimumab combined with methotrexate or methotrexate alone. The proportion experiencing job loss after 56 weeks was significantly lower in the group receiving combination therapy (grade A).⁴⁶ This current evidence indicates that more attention should be directed to rapid identification and treatment of persons at risk of being work disabled.

Team care involving multiple disciplines

In many countries access to a multidisciplinary team is considered a part of the standard care for patients with RA. However, access to services from health professionals differs and may be influenced not only by socioeconomic factors but also by factors such as awareness of doctors about treatment opportunities, availability of health professionals, existence of waiting lists, residence in rural areas, and insufficient funding for effective services.

A review of the effects of comprehensive rehabilitation concluded that inpatient and day patient programs were equally effective with regard to disease activity and functional ability (grade A*).⁴⁷ In many countries, a clinical nurse practitioner care model exists. Nurse practitioners have extended their roles to incorporate some of the services that usually have been offered by the rheumatologist or other health professionals, and the aim of nurse-led clinics is to assist in access to services and clinical communication for patients with rheumatic diseases. The number of studies evaluating clinical nurse practitioner models are few, but the clinical effectiveness of three different care models (care delivered by a clinical nurse specialist, inpatient team care, and day patient team care) were compared in one randomized controlled trial (grade A).⁴⁸ Care provided in nurse-led clinics produced similar clinical outcomes in terms of disease activity, functional ability, and quality of life compared with inpatient and day patient team care, but at a significantly lower cost. All patients reported high satisfaction with multidisciplinary care, although patients who attended a nurse-led clinic were slightly less satisfied than those who received inpatient or

day patient team care. Thus nurse-led clinics appear to be an effective innovation in the care of patients with RA, and the role of nurses is further emphasized in the recent EULAR recommendations (grade A*).¹³

The primary therapist model (PTM) is another transdisciplinary model in which specially trained health professionals assume the roles of case managers and health care providers rather than general therapists.⁴⁹ If it is considered safe, they will consult with their colleagues, rather than transfer a patient to the provider in the other discipline, for completion of a rehabilitation regimen. In this way, they transcend their professional boundaries and take on extended roles and responsibilities. The model has been tested in a randomized controlled study with 111 participants. Patients received 6 weeks of rehabilitation treatment consisting of either services from a primary therapist (PTM) or traditional care from physical therapists and/or occupational therapy (grade A).⁴⁹ After 6 months, a significantly greater proportion of patients in the PTM group showed a clinical response; the PTM group also showed a greater improvement in quality-adjusted

life-years, but the costs were higher. The authors concluded that the PTM has the potential to be an alternative to traditional physical and occupational therapy, and further research should focus on strategies to reduce the costs of the model and assess the long-term economic consequences in managing RA (grade A*).⁴⁹

In summary, team care, defined as care provided by a group of health professionals with different professional backgrounds, seems to be beneficial for patients with RA. Further, it appears that similar effects, but at lower costs, may be achieved by transdisciplinary models in which clinicians take on extended roles coordinating multidisciplinary care in an outpatient setting. Flexible models of care should be provided for patients with RA that meet the varying needs and preferences of people of different ages, genders, and life and disease stages. Future research should address the effect of the content and composition of the team care on relevant outcomes and identify patients and contextual factors that enhance or limit the efficacy of team care interventions.

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PEDIATRIC RHEUMATOLOGY

99A

Evaluation of musculoskeletal complaints in children: clinical evaluation

■ NORA G. SINGER ■ ANGELO RAVELLI

- A systematic approach should be used to assess symptoms of musculoskeletal and rheumatic diseases in children.
- The physical examination is used to distinguish between inflammatory rheumatic and mechanical musculoskeletal diseases of children.
- Specific clinical maneuvers can be employed to identify the range of musculoskeletal disorders in children.

HISTORY TAKING FOR THE MUSCULOSKELETAL SYSTEM IN CHILDREN**General approach**

Children of all ages should be spoken to directly, honestly, and at an age-appropriate level. In this manner, verbal and nonverbal reassurance can be given, and at the same time the physician can explain what the visit will entail. For very young children, talking first to their parents while they are held in a parent's lap may reduce their fear. Major sources of anxiety for children and their parents include fear both of the unknown and of pain (such as might occur during physical examination or collection of specimens for laboratory testing). Telling a child what is required of him or her establishes trust in the long term even though it may be stressful at the initial encounter. How much of the history is reported by the parents and how much by the children themselves depends on the age of the child; adolescents should be engaged to provide their own history and require the opportunity at some point to be alone in the examination room without the parents. For younger children the sense of time and pain localization may be difficult to elicit directly from the patients themselves. Disparity in the historical narratives provided by the patient and the parent should be noted and may provide clues to the underlying problems. Discrepancies may be due to genuine mistakes, inaccurate recall, or errors of interpretation, or may be manifestations of a serious underlying issue, such as abuse. Child abuse at any level (physical, psychological, or sexual) may present as rheumatic complaints, particularly musculoskeletal pain.

Constitutional features

Most chronic inflammatory diseases are accompanied by a constellation of relatively nonspecific but potentially important constitutional features, such as lethargy and/or fatigue, mood change, irritability, reduced appetite, and weakness. Fever is a prominent indication of inflammation and may be typical, as in the evening fevers of systemic arthritis, or episodic, as in periodic fever syndromes such as familial Mediterranean fever or tumor

necrosis factor receptor-associated periodic syndrome. More chaotic or less localizing fever may be seen in disorders such as systemic lupus erythematosus. Complaints of muscle weakness are common in inflammatory myopathy, whereas complaints of muscle pain may be more profound in infectious and postinfectious inflammatory myopathy (e.g., pyomyositis, influenza associated myopathy) and may be seen in juvenile dermatomyositis. Absence of weakness may point toward complex regional or generalized pain disorders, whereas proximal muscle weakness typifies myopathy in chronic inflammatory disorders.

Joint pain

Joint pain is a key clinical feature of the history, and its description should include whether it interferes with function (e.g., walking, running, or writing), aggravating and relieving factors, diurnal variation, and progression. Pain reporting can be improved through use of an age-appropriate visual analogue scale such as one with happy and sad faces and may also be deduced by observing a child's pain avoidance behavior, for example, limping in the absence of pain complaints. Enlisting the parent's assessment of pain complaints is important, as is exercising caution in interpreting dramatic complaints of musculoskeletal pain by either the parent or the patient because pain also has an affective (psychological) component. The pain associated with inflammation tends to be mild to moderate in intensity (Table 99A.1), whereas the pain of infection is, in general, severe.

Joint swelling and stiffness

Any reported history of joint swelling should be assessed and confirmed during the physical examination (see later). Joint stiffness, the reporting of reduced, uncomfortable range of joint movement, seems to be at its worst on awakening in the mornings ("early morning stiffness") and improves throughout the day in inflammatory arthritis. "Gelling" may occur after prolonged inactivity, such as sitting in a car or at a desk.

EXAMINATION OF THE MUSCULOSKELETAL SYSTEM**General examination**

The child's general condition and appearance, including recorded growth and percentiles, skin color and condition, overall nutritional status, muscle bulk, vital signs (temperature, blood pressure), and joint movement when playing, can help in forming an overall assessment of whether the child is well or sick (Table 99A.2). Careful assessment of the eyes and peripheral pulses should also be included as part of the routine physical examination of these children.

TABLE 99A.1

Relative contribution of musculoskeletal clinical features in differential diagnosis in children

	Inflammatory disease	Mechanical disorder	Amplified pain disorders
Pain*	+/-	+	+++
Joint stiffness	++	+/-	+
Joint swelling	+++	+/-	+/-
Joint instability	+/-	++	+/-
Sleep disturbance	+/-	-	++
Physical signs†	++	+	+/-

*May depend on both the age of the child and the age appropriateness of the tool used to measure pain.

†Changes in temperature may be found in inflammatory disease and in amplified pain disorders but are more frequently accompanied by complaints of dysesthesia in the latter. From Southwood TR. Evaluating musculoskeletal and rheumatic disorders in children. In: Hochberg M, Silman AJ, Smolen JS, et al, editors. Rheumatology. Philadelphia: Mosby; 2007, p. 961-73.

TABLE 99A.2

Functional musculoskeletal examination

Position	Musculoskeletal features examined
Sitting cross-legged	Hip abduction, external rotation and flexion, knee flexion
Rising to stand straight	Leg extension, back extension, lower limb muscle power
Bending forward	Anterior spinal curvature, scoliosis
Removing shoes and socks	Hip and knee flexion, hand and wrist function
Removing top	Shoulder and elbow range of movement
Walking normally	Gait phases: stance, toe off, swing, heel strike
Tiptoe walking	Toe extension, ankle plantar flexion, muscle power
Heel walking	Ankle dorsiflexion, knee extension, pain at entheses
Hands pronated, arms extended	Elbow extension, shoulder power
Making a fist	Finger flexion
"Hands praying" position	Wrist extension, elbow flexion, finger extension
Arms above the head, reaching	Shoulder flexion
Looking over each shoulder	Cervical spine rotation

From Southwood TR. Evaluating musculoskeletal and rheumatic disorders in children. In: Hochberg M, Silman AJ, Smolen JS, et al, editors. Rheumatology. Philadelphia: Mosby; 2007, p. 961-73.

Joint assessment

Conducting a standardized joint examination minimizes the risk of omission (a side-to-side comparison should always be made). Head-to-toe joint examination commonly is performed so that one will remember to examine all joints; starting by examining the extremities may be less threatening to the young child.

Suggested steps in the joint examination include the following:

1. **Look:** Inspect the position of the joint at rest, its surface anatomy, contours, color, scar, size and muscle bulk, and limb length.
2. **Feel:** Palpate for skin warmth, joint swelling, and tenderness. Swelling includes any increase in joint size that alters the normal surface markings of the joint. The key sites for observing swelling depend on the particular joint and the nature of the swelling itself. Swelling may be due to intraarticular effusion, periarticular fluid, soft tissue changes (edema; joint capsule thickening; inflammation of muscle, ligament, and/or subcutaneous or cutaneous tissues), or bony hypertrophy. Joint margin tenderness and/or tenderness and inflammation at the site of tendon insertion into bone or ligament, fascia, or joint capsule may indicate the presence of enthesitis.



Fig. 99A.1 Relaxed passive extension of the knees. The right knee has subtle loss of relaxed passive extension indicating loss of joint range secondary to juvenile idiopathic arthritis. (From Southwood TR. Evaluating musculoskeletal and rheumatic disorders in children. In: Hochberg M, Silman AJ, Smolen JS, et al, editors. Rheumatology. Philadelphia: Mosby; 2007, p. 961-73.)

3. **Move:** Include motion by the examiner (passive range of motion) and by the patient (active range of motion), noting any pain or irritability on motion, especially at the end range of joint motion.
4. **Test:** Assess joint stability, particularly for the stability ligaments of the knee (cruciate and collateral ligaments), and assess for pain referable to other joint structures such as the menisci and associated structures such as the iliotibial bands and bursa.

In young children, beginning the examination with the toes and feet is the least upsetting. Examining the most painful areas at the end of the examination often facilitates performing a complete examination.

Feet and ankles

With the child supine, observe the leg lengths carefully for any discrepancy. Asking the patient to curl his or her toes allows observation of flexion and extension metatarsal and interphalangeal joint movement. Carefully squeeze the metatarsophalangeal joints in such a manner as not to cause alarm, and if tenderness is noted, assess each metatarsophalangeal joint for synovitis by gently palpating the joint margins while moving the joint through its range of motion. Examine the midtarsal joints by stabilizing the calcaneus while inverting and evertting the forefoot. Assess the subtalar joints by inverting and evertting the calcaneus (hindfoot) and the ankle (tibiotalar) joints by dorsiflexion and plantar flexion at the ankle to detect synovitis. Synovitis is sometimes appreciated only when observed posteriorly; observation from the posterior view also allows detection of Achilles tendon thickening. To detect enthesitis palpate for tenderness at the insertion of the plantar fascia to the metatarsal heads, fifth metatarsal base, calcaneus, and Achilles tendon insertion into the posterior aspect of the calcaneus.

Knees

Loss of vastus medialis muscle bulk and/or bulk in the gastrocnemius may result from muscle atrophy due to reduced use and/or guarding of a painful joint. Subtle loss of knee extension may be seen using relaxed passive extension of both knees by lifting the patient's feet gently up off the table (Fig. 99A.1). Mild swelling obscuring the medial and lateral contours of the patella can be confirmed by palpating and inspecting for a synovial fluid wave or bulge sign (medial compression followed by lateral "reexpression" of the swelling) and by balloting the patella. Joint margin tenderness is often maximal just medial to the lower patellar border. Key points for palpation of entheses are at the tibial tuberosity and the 2, 6, and 10 o'clock positions around the patella. Knee locking or giving way may indicate a mechanical disorder and requires assessment of knee stability. The most useful examination techniques for medial and lateral collateral ligament integrity are the application of gentle valgus and varus pressure, respectively, on the knee (while the knee is held in 5 degrees of flexion), which may result in abnormal abduction or adduction (Fig. 99A.2). The anterior cruciate ligament is also vulnerable to sports injuries in children and young people; that, and the posterior cruciate, can be assessed using anterior and posterior drawer tests. These and other tests to elicit derangement or tightness of structures in and around the knee are listed in Table 99A.3.

Fig. 99A.2 Valgus stressing (a) and varus stressing (b) performed to detect any abnormalities in the medial and lateral collateral ligaments of the knee.



TABLE 99A.3

Maneuvers that may be used to diagnose mechanical disorders of the knee

Maneuver name	Structure(s) tested	Description
Patellar apprehension	Patella (laxity)	Knee is placed in relaxed flexion (30 degrees) and the patella is subluxed laterally using gentle pressure (not so much pressure that it could displace the patella).
Lachman	Anterior cruciate ligament (ACL) (integrity)	Knee is flexed to 20 degrees; the examiner holds the distal thigh above the knee, pressing down with that hand while simultaneously grasping the tibia with the other hand and pulling it forward. Excess motion or no sharp stop compared with the other side indicates possible injury to the ACL.
Anterior drawer	ACL	Knee is flexed to 90 degrees with foot stabilizing the knee. The proximal tibia is held with both hands, thumbs in front reaching circumferentially; the tibia is displaced anteriorly. Excess laxity compared with the other side is considered a positive finding, although asymmetric pain and any abnormal movement should be noted.
McMurray	Menisci	With a thumb and fingers placed over the medial and lateral joint line, the knee is moved through range of motion by holding the foot with the other hand and applying medial or lateral rotational pressure. The knee is extended passively and the procedure repeated to detect pain at the joint line. Pain, sometimes accompanied by a “thunk,” suggests the presence of meniscal abnormality.
Valgus stress	Medial collateral ligament (MCL)	With the knee extended, the upper hand is placed above the knee laterally and the lower hand over the gastrocnemius on the medial aspect. Pressure is applied outward on the calf, and laxity and pain are noted if the MCL is not functioning normally.
Varus stress	Lateral collateral ligament (LCL)	With the knee extended, the upper hand is placed above the knee medially and the lower hand over the gastrocnemius laterally. Pressure is applied inward on the calf, and laxity and pain are noted if the LCL is not functioning normally.
Posterior drawer	Posterior collateral ligament	Performed in the same manner as the anterior drawer test except that the tibia is forced posteriorly.
Ober test	Iliotibial bands	Patient is placed on the nonpainful side. The affected hip is placed in a slightly extended position with the hip flexed and pain or limitation is observed when the affected leg is no longer held in the air by the examiner but instead returns to the surface.
Thomas test	Quadriceps (flexibility)	A hand is placed under the lumbar lordosis and the patient is asked to flex one knee to the chest; if the other hip flexes, tightness of the quadriceps is suggested.

Hips

Detection of intraarticular effusion requires ultrasonography or magnetic resonance imaging. Screening for hip disease on examination is accomplished by passive internal and external rotation with the hip and knee flexed at 90 degrees; at least 45 degrees of internal rotation can usually be elicited in a normal child's hip. Extension range, which is normally 30 degrees beyond neutral when the patient is lying prone, tends to be lost early in hip arthritis, whereas loss of flexion in the hip generally indicates more advanced disease. Enthesitic points to be examined include the greater trochanter and anterior superior iliac spines.

Hands and wrists

Hand and wrist examination begins with a child sitting up with hands held out in front of the body. Begin by inspecting the dorsal aspect of the hands and fingers and eliciting active finger flexion by asking the child to “make fists” and “bury the fingernails” (Fig. 99A.3) (nail pitting may predate or accompany psoriasis). Joint swelling can be palpated with the hands in a prone position, and joint margin tenderness and passive range of joint movement also noted. Rotation of the wrists at the distal radioulnar joint allows inspection of the palmar surfaces of the hands and fingers. Active finger flexion at the interphalangeal joints should normally result in the fingertips making contact with the palms overlying the metacarpal joints. By using



Fig. 99A.3 “Burying the fingers.” Being able to perform the maneuver suggests the presence of normal flexion at the second through fifth metacarpophalangeal (MCP) joints, proximal interphalangeal joints, and distal interphalangeal joints. Some examiners have children make a full fist and also assess the first MCP and interphalangeal joint at the same time.

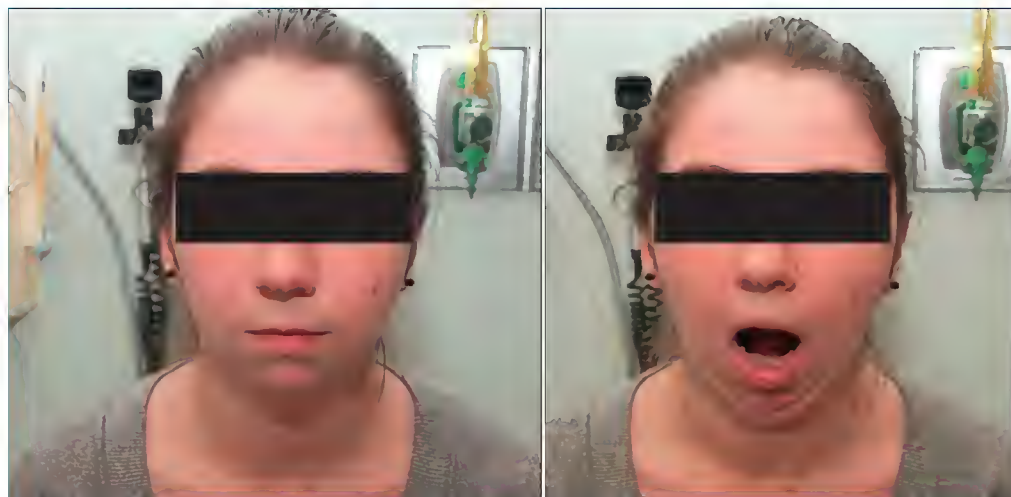


Fig. 99A.4 Asymmetric mouth opening and an abnormally small oral aperture due to mandibular hypoplasia and temporomandibular joint arthritis in a young adult who has had juvenile idiopathic arthritis since the age of 1 year.

the “prayer” position with palms placed together, finger flexion or wrist extension deformities can be detected, which has the advantage of highlighting asymmetry at the wrists and small joints of the hand.

Elbows and shoulders

The elbows are extended fully with hands reaching toward the ceiling (sometimes called *reaching for the sky*, which also demonstrates shoulder flexion) and then are lowered in an extended position to allow palpation of the olecranon bursa itself (which rarely swells in children except in injury or infection) and either side of the olecranon process. Functional elbow flexion can be demonstrated by placing the hands to the mouth. Pronation and supination of hands with the elbows at 90 degrees of flexion may reveal disruption of the proximal radioulnar joint. Assessment of the glenohumeral joint itself may proceed by palpating the joint margin with the humerus abducted to 90 degrees and rotated internally and externally (using the forearm as a lever down and up, respectively). The sternoclavicular joints should be palpated for tenderness and/or swelling.

Cervical spine and temporomandibular joints

Detection of limitation or loss of motion in the cervical spine and temporomandibular joints may raise the possibility of systemic arthritis, even if the child does not have complaints specifically referable to these joints (e.g., a teenager with ankylosing spondylitis as a cause of hip joint space narrowing may complain of hip pain but also have restricted neck motion). Lateral rotation and extension are most likely to be lost early if the cervical spine is affected by arthritis. Rotation can be evaluated by asking the patient to place the chin on each shoulder. The normal extension range on tipping the head back is greater than 20 degrees. Having the child place the ear on the shoulder allows assessment of lateral flexion. The face should be inspected for asymmetry or mandibular hypoplasia (Fig. 99A.4). The temporomandibular joints can be palpated just anterior to the tragus of the ear, where tenderness may be demonstrated and asymmetric movement detected, particularly on asking the patient to open the mouth widely (see Fig. 99A.4). An oral aperture below 40 mm is considered to be abnormal.

Spine and gait

The spine is best examined with the patient standing on bare feet and viewed from behind. Observe the position of the feet for loss of medial longitudinal arch contour (pes planus) and the hindfoot for overpronation, which suggests hypermobility (Fig. 99A.5). Check that the pelvis is horizontal; leg-length discrepancy is best detected clinically when the patient is standing. Assess for scoliosis by noting the symmetry of the spine in standing and gentle forward flexion (Fig. 99A.6). Palpation over the sacroiliac joints may reveal tenderness, although this maneuver may be insensitive for detection of inflammation. Checking particularly for abnormal flattening of the lumbar spine, which might suggest spondylitis, is important. Pain on hyperextension of the spine, which puts the only synovial joints (the apophyseal joints) in the spine on the stretch, can be seen in sacroiliac joint disease or spondylolysis. Gait should be assessed when the patient is wearing shorts and walking with bare feet. Note is made of each of the gait phases (heel-strike, stance, toe-off, and swing phases), with observation for antalgia, Trendelenburg abnormality (a waddling gait caused by weakness of hip stability muscles), and any other asymmetry.



Fig. 99A.5 Overpronation of both ankles associated with hypermobility. (From Southwood TR. *Evaluating musculoskeletal and rheumatic disorders in children*. In: Hochberg M, Silman AJ, Smolen JS, et al, editors. *Rheumatology*. Philadelphia: Mosby; 2007, p. 961-73.)

DIFFERENTIAL DIAGNOSIS

When a diagnosis of musculoskeletal or rheumatic disease is considered in a child, the history is of principal importance in distinguishing whether the complaints or physical findings are more likely related to congenital or acquired abnormalities of the developing musculoskeletal system or due to autoinflammatory or autoimmune disorders with tissue-specific manifestations. In children, overdiagnosis of mechanical musculoskeletal “disorders,” such as the variations in normal alignment in the growing skeleton, can be avoided through recognition of normal findings during an examination. Prompt recognition of abnormalities is key, because delay in diagnosis of either inflammatory disease or mechanical disorders may also delay appropriate and timely therapy.

Transient musculoskeletal complaints are common in children and adolescents and are often associated with sports-related conditions or non-rheumatologic disease. When present, systemic symptoms such as fever, rash, headache, listlessness or lethargy, limping, weakness, anorexia, or pain, which may be transient or chronic, should lead the examiner away from primary mechanical and noninflammatory disorders as the cause of the complaints. Knowledge of features that may distinguish inflammatory from noninflammatory conditions (see Table 99A.1) and a fundamental understanding of the spectrum of pediatric diseases that primarily involve other body systems but are known to have musculoskeletal manifestations (Table 99A.4) also help to focus the diagnostic strategy. Astute clinicians incorporate symptom combinations into their clinical reasoning rather than depending on isolated symptoms or laboratory examinations to arrive at a correct diagnosis. Disease features such as peripheral joint swelling increase the likelihood of a rheumatic diagnosis, whereas demonstration of joint instability, pain with maneuvers to isolate specific structures, and the absence of



Fig. 99A.6 Gentle forward flexion of the spine in a preadolescent boy who had normal examination findings.

TABLE 99A.4

Some major pediatric diseases that may have musculoskeletal manifestations

Disease	Musculoskeletal manifestation
Cystic fibrosis	Large and small joint arthropathy
Down syndrome	Carpal osteolysis
Diabetes	Cheiroarthropathy
Hypothyroidism/hyperthyroidism	Musculoskeletal pain
Hemophilia	Intraarticular and muscle hemorrhage
Hemoglobinopathies	Avascular necrosis, septic arthritis
Pancreatitis	Osteolytic lesions
Inflammatory bowel disease	Erythema nodosum, large-joint arthritis, spondyloarthritis
Cyanotic congenital heart disease	Hypertrophic osteoarthropathy
Malignancies	Metastases, hypertrophic osteoarthropathy

From Southwood TR. Evaluating musculoskeletal and rheumatic disorders in children. In: Hochberg M, Silman AJ, Smolen JS, et al, editors. Rheumatology. Philadelphia: Mosby; 2007, 961-73.

local inflammation and/or systemic symptoms are more suggestive of non-inflammatory rheumatic disease (see Table 99A.3).

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REFERENCES

See references at the end of Chapter 99B.

99B

Evaluation of musculoskeletal complaints in children: nonautoimmune musculoskeletal disorders

■ NORA G. SINGER

- Regional syndromes affecting the lower limb joints, particularly the hip and knee, are the most important nonautoimmune musculoskeletal disorders in children.
- Legg-Calvé-Perthes disease and slipped capital femoral epiphysis are important causes of hip pain in children.

INTRODUCTION

Understanding the spectrum of musculoskeletal disorders that occur in different age groups is helpful in focusing the clinician on a working diagnosis because childhood musculoskeletal diseases may be identified in part by the age at which symptoms appear. The acronym **ARTHRITIS**, proposed by Taunton Southwood, is a helpful mnemonic ([Box 99B.1](#)). The most important noninflammatory disorders and the typical age at which they occur are described in this chapter and are listed in [Table 99B.1](#), along with the symptoms with which they may present and important clinical features that help to distinguish them.

ARTHRITIC DISORDERS

In addition to juvenile idiopathic arthritis, there are other, typically acute forms of arthritis that are important in childhood.

Septic arthritis

Septic or infectious arthritis is a serious infection that should be recognized promptly because it can rapidly lead to joint destruction, sometimes within 24 hours of onset. Monarticular disease is much more common than polyarticular disease in infections with most organisms; the exception is *Neisseria* infection, especially gonococcal arthritis in teenagers. The hip joint is the most commonly septic joint in young children, and septic arthritis more frequently affects boys than girls. *Staphylococcus aureus* is now the most common bacterium causing septic arthritis; routine use of *Haemophilus influenzae* vaccine has drastically reduced the incidence of *H. influenzae*-related invasive disease. In the setting of congenital or acquired immunodeficiency (including sickle cell disease), suspicion of septic arthritis is increased. Children with infected joints generally look unwell and sometimes have a “toxic” appearance, with high fever and severe pain limiting the ability to bend the affected joint. Septic arthritis usually results from hematogenous spread but may also occur after a puncture wound or infected skin lesions (e.g., chickenpox). In young children, it may result from spread from adjacent osteomyelitis into joints where the capsule inserts below the epiphyseal growth plate; coexistent osteomyelitis occurs in up to 15% of affected children. Aspiration of the affected joint space for fluid analysis (the definitive test) and drawing of blood for cultures is best performed before intravenous antibiotics are started unless doing so would delay therapy unacceptably.

Reactive or postinfectious arthritis

Reactive arthritis is the most common form of arthritis in childhood and is defined as time-limited joint swelling (usually lasting less than 6 weeks) following (or rarely accompanying) evidence of extraarticular infection. The enteric bacteria (*Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia*) are implicated in most pediatric cases of reactive arthritis. Arthritis following infection with parvovirus B19, influenza viruses, coxsackieviruses, *Mycoplasma*, or *Borrelia* or after infection with or vaccination against rubella virus or herpesviruses is also seen. Whether persistence of infection or immune response to prior infection drives ongoing symptoms in chronic Lyme arthritis and some postviral arthritides is still controversial. Acute rheumatic fever and poststreptococcal reactive arthritis may be classified within the broader category of reactive arthritis. If *Streptococcus*-associated joint symptoms occur when the original streptococcal infection was not recognized or treated, then antibiotic therapy is used to eradicate the organism and is indicated along with symptomatic treatment with nonsteroidal antiinflammatory drugs (NSAIDs) or, less commonly, salicylates.

MUSCULOSKELETAL SYNDROMES

Musculoskeletal syndromes may be general, affecting a number of joint areas, or specific to particular joint sites. Hypermobility syndrome is one of the most common noninflammatory diagnoses in children and is discussed in Chapter 210.

Benign limb pains

Benign limb pains, also known as *growing pains*, occur in 10% of children between the ages of 4 and 14 years. The relationship with growth is uncertain because this period is not the time when maximum linear growth occurs. Children typically awaken at night with deep thigh or calf pain that responds to analgesics, massage, and heat, and there may be a family history of similar problems in one of the parents. Normal findings on physical examination along with a history of normal activity once the episode resolves are helpful in distinguishing benign limb pain from a more serious cause of night pain (e.g., osteoid osteoma or malignancy-associated limb pain). No further workup is needed if there is a typical history and absence of any physical abnormalities. Atypical presentations may require further workup to exclude more serious problems. Growing pains frequently remit, although intermittent night pain may continue for many years.¹

REGIONAL SYNDROMES: HIP

Developmental dysplasia of the hip

Developmental dysplasia of the hip (DDH) is a spectrum of disorders with a number of predisposing factors: family history of DDH, female gender, first-born birth order, breech presentation, and oligohydramnios. Early detection, institution of corrective treatment, and prevention of long-term disability are the aims of routine screening programs at birth and the routine

6-week postnatal checkup; however, the evidence level to justify screening and intervention is fair to poor, and the issue is confounded by the knowledge that, in a substantial proportion of hips initially labeled as having DDH, the abnormality will resolve spontaneously without intervention.² The techniques of examination vary but usually involve examining one hip at a time while steadying the contralateral pelvis with the other hand. The upper portion of the femur is carefully rocked back and forth to check whether the hip can be dislocated posteriorly out of the acetabulum (Barlow maneuver) or relocated back into the acetabulum on abduction (Ortolani maneuver). It is important not to exert excessive force during these maneuvers. Asymmetry of skinfolds around the hip may be observed later in childhood. Limited abduction of the hip, shortening of the affected leg, or a limp or abnormal gait may also be seen with congenital hip disorders. A radiograph

supporting the diagnosis of DHH is seen in Fig. 99B.1. Ultrasonographic screening of all neonates is highly specific for detecting the condition but is expensive and has a high rate of false-positive findings. Orthopedic consultation is indicated if DHH is suspected. The affected infant may be placed in a positioning device to put the hips in abduction for several months. Progress is then monitored by ultrasonography or radiography. If the hip has not stabilized or the condition is diagnosed late, hip abduction using traction and a further period of splinting (in a plaster hip spica) may be

BOX 99B.1 AN APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF RHEUMATIC CLINICAL FEATURES IN CHILDREN AND YOUNG PEOPLE

Avascular necrosis, orthopedic diseases (e.g., slipped upper femoral epiphysis, osteochondritis)

Reactive arthritis

Trauma associated, including nonaccidental injury and hypermobility

Hematologic: bleeding diatheses, hemoglobinopathies

Rickets and other metabolic and endocrine diseases: diabetes and thyroid diseases

Infection of bone or joint

Tumor, leukemia, neuroblastoma

Idiopathic/psychosomatic disorders, including musculoskeletal pain amplification syndromes

Systemic connective tissue diseases: multisystem inflammation of muscle, skin, blood vessels



Fig. 99B.1 Developmental dysplasia of the left hip with failure of acetabular formation and “telescoping” of the left femur.

TABLE 99B.1

Noninflammatory musculoskeletal disorders: symptom combinations and pivotal clinical features

“Typical” symptom combinations	Pivotal clinical features	Possible diagnoses
“Clunk” on hip movement screening, limping in an older infant	Asymmetric upper leg skinfolds, limited hip abduction	Developmental dysplasia of hip
Nocturnal awakening with leg pain in a young child	Normal child	“Growing pains” Osteoid osteoma
Sudden limping in an otherwise well young child	Unilateral restricted hip movement	Toxic synovitis
Joint effusion with or without pain	Effusion with hemorrhagic fluid on aspiration	Hemarthrosis after trauma or if recurrent Pigmented villonodular synovitis
Hip pain in a preadolescent (boys more than girls)	Loss of joint range, pain on motion, may be bilateral	Legg-Calvé-Perthes disease
Hip pain in an obese preadolescent boy	Unilateral hip restriction	Slipped upper femoral epiphysis
Hip pain and limp in adolescent girl	Unilateral pain and stiffness	Idiopathic chondrolysis
“Snapping” hip	Sensation of internal or external hip	Internal movement of the iliopsoas muscle over iliopectineal eminence, lesser trochanter, or anterior superior iliac spine; external movement of the iliotibial band over the greater trochanter hip
Localized pain	Point tenderness with or without localized swelling	Stress fracture
Anterior knee pain	Pain with use of stairs (ascending or descending), stiffness Tenderness over the tibial tuberosity Tenderness over inferior pole patella	Patellofemoral syndromes Osgood-Schlatter disease (apophysitis of the tibial tuberosity) Sinding-Larsen-Johansson syndrome Apophysitis of the inferior pole of the patella
Lateral knee pain	Pain over patellar tendon or quadriceps tendon Pain where iliotibial band courses over lateral femoral epicondyle; also may radiate proximally into iliotibial band Pain over lateral joint line, possible positive finding on McMurray test	Extensor tendinitis Iliotibial band syndrome Lateral meniscal injury
Medial knee pain	Intermittent pain and effusion with or without locking, usually increased with activity Popping or snapping medially when extending from flexion Pain inferior to medial joint line/tibia	Osteochondritis dissecans Medial plica syndrome Pes anserine bursitis

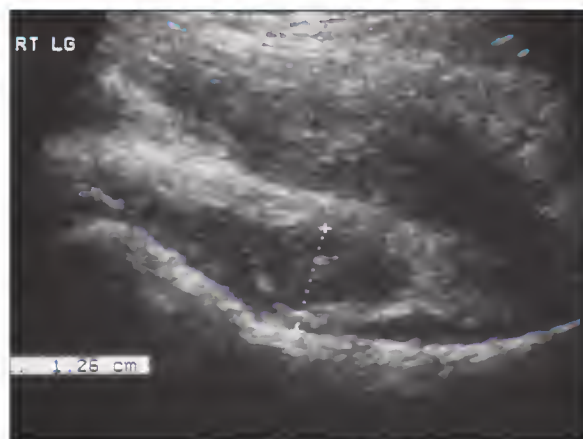


Fig. 99B.2 Ultrasound image in a patient with irritable hip (transient synovitis of the hip) demonstrating effusion.

tried. Weight bearing on a dislocated hip is avoided because of concern that it may further damage the femoral head and acetabulum. Open reduction and derotation femoral osteotomy are required if conservative measures fail. A risk of aseptic necrosis of the femoral head has been reported with both closed and surgical procedures, although it is a rare complication.

Transient (toxic) synovitis (irritable hip)

Toxic synovitis is the most common cause of acute hip pain in children. It occurs in children aged 2 to 12 years and often follows or occurs at the time of a viral infection. The syndrome most commonly presents with the sudden onset of pain in the hip and a reluctance to weight bear in the young child or a limp in the older one. There may not be pain at rest, but there typically is decreased range of motion; the hip is held in external rotation, which is the position of greatest comfort, and the pain may be referred to the knee. Fever may be present but is typically mild, and the affected child does not appear overly ill. The neutrophil count and levels of acute-phase reactants may be normal or slightly elevated and radiographic findings are normal, but a small joint effusion is frequently apparent on ultrasound evaluation (Fig. 99B.2). The most important differential diagnosis is septic arthritis, but this is usually distinguished from the more benign transient synovitis by the presence of high fever, severe illness, pain at rest, minimal or no movement of the hip, marked elevation of the neutrophil count and acute-phase reactant levels, and frequent association with positive blood culture results. Aspiration of the hip joint allows infection to be excluded and may temporarily relieve most or all of the symptoms. Management of transient synovitis is with NSAIDs; there is no definitive evidence indicating whether rest or activity as tolerated influences its course because it usually improves within a few days. Occasionally transient synovitis is assumed to underlie the presentation of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis.

Legg-Calvé-Perthes disease

Legg-Calvé-Perthes disease (LCP) was described independently by Legg, Calvé, Perthes, and Waldenström.³ It is an idiopathic hip disorder hypothesized to be caused by reduced vascular flow to the affected area. It is more common in boys than in girls with a peak incidence between 4 and 10 years of age; onset is insidious with the disorder manifesting as a limp or persistent hip or knee pain. Up to 13% of children have bilateral involvement, and often the second hip is asymptomatic.³ When bilateral, the hips are usually in different stages of disease. Ischemia is thought to occur within the femoral epiphysis, but damage may be cumulative with more than one episode of ischemia leading to the observed avascular necrosis. Revascularization and reossification follow over 18 to 36 months, and the goal of treatment is to have the femoral head remodel in a spherical fashion within the acetabulum. Mutation in the *COL2A1* gene (which encodes a precursor of the type II collagen $\alpha 1$ chain) has been associated with LCP.^{4,5} The severity of hip involvement and long-term risk is similar in boys and girls; fever and elevated inflammatory parameters are typically absent.

Imaging

Initial radiographic findings may be normal, but radiographs eventually show increased density in the femoral head, which subsequently becomes



Fig. 99B.3 Avascular necrosis of the right hip.

fragmented (Fig. 99B.3) during revascularization and irregular, which results in superior and lateral subluxation. By 3 to 6 months after symptom onset, the proximal femoral epiphysis is smaller and denser than normal and the joint space wider than in the normal hip. On radiographs four stages of the pathologic process can be identified: initial, fragmentation, healing, and reossification. Healing is manifested by new bone formation and reossification, with or without residual deformity. Changes in the acetabulum are important in the long term, and the radius of the acetabulum may be the most sensitive measurement to detect the pathologic changes.^{6,7} At least two radiographic classification systems for LCP exist and are based either on the extent of involvement of the femoral head (Stulberg classification)⁸ or on the height of the lateral epiphysis on anteroposterior radiographs (lateral pillar classification system); the latter system appears to be more reproducible.⁹

In LCP, the amount of femoral head involvement and the degree of lateral subluxation are such important prognostic factors that assessment often requires magnetic resonance imaging (MRI), which is superior to conventional radiography and bone scanning in determining the extent and location of involvement in the femoral head and the degree of lateral subluxation.¹⁰⁻¹³

Before the advent of MRI, technetium-based bone scanning was the gold standard for evaluation of this disease; reduced uptake occurs initially followed by foci of increased accumulation in the femoral head as revascularization occurs; bone scanning may still be useful in situations in which MRI scans cannot be obtained (Fig. 99B.4b).

MRI adds additional anatomic visualization in LCP. Early on there is low signal intensity in T1-weighted images and an area with a secondary double line of low and high signal intensity on T2-weighted images. Widening of the medial joint space may be due to more than one mechanism. The presence of a subchondral fracture line on MRI predicts eventual necrosis better than it does the extent of necrosis.¹⁰ Gadolinium-enhanced subtraction MRI can improve sensitivity in early diagnosis of LCP and may be used to monitor subluxation.¹³ Synovitis was observed by MRI in 72 LCP patients, with a correlation between the severity of the synovitis and the severity of the necrosis.¹³⁻¹⁵ Cartilaginous physeal and metaphyseal abnormalities are common and frequently are associated with growth arrest.

Pathophysiology

Ischemic necrosis precedes collapse of the head and subsequent repair of the femoral capital epiphysis. The initial event is silent clinically, and with collapse and repair of the bone, pain and limitation of motion, particularly abduction and internal rotation, develop to varying degrees.^{7,11} The extent of subsequent growth disturbance of the proximal femur where the epiphyseal and physeal cartilage are located depends on the extent of the avascular event. The pathogenesis involves a disruption or interruption of the blood supply to the femoral head (Fig. 99B.5). Thrombophilia (enhanced ability to form clots), hypofibrinolysis (decreased clot breakdown), or both may contribute to the pathogenesis of LCP; LCP with thrombophilia secondary to protein C and S deficiency as well as Leiden V mutation has been reported.¹⁶⁻¹⁸

Treatment

Children with mild LCP often do not require intervention but instead can be observed and managed symptomatically with activity restriction and

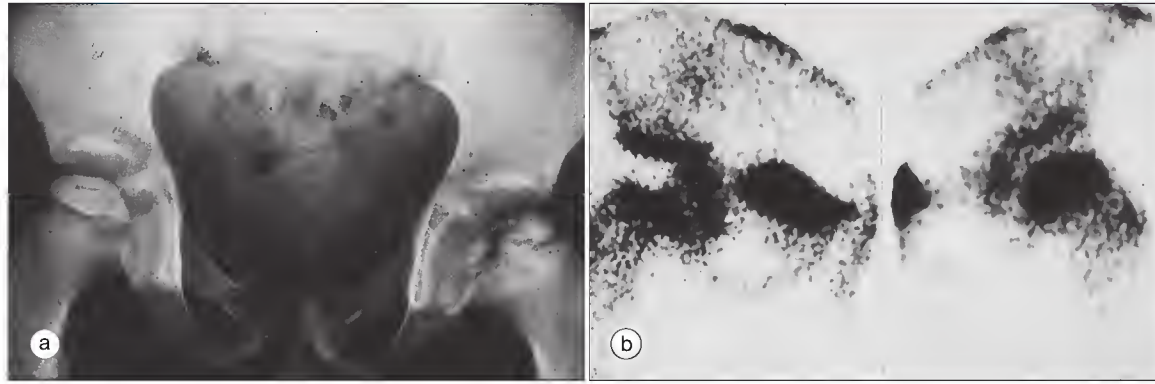
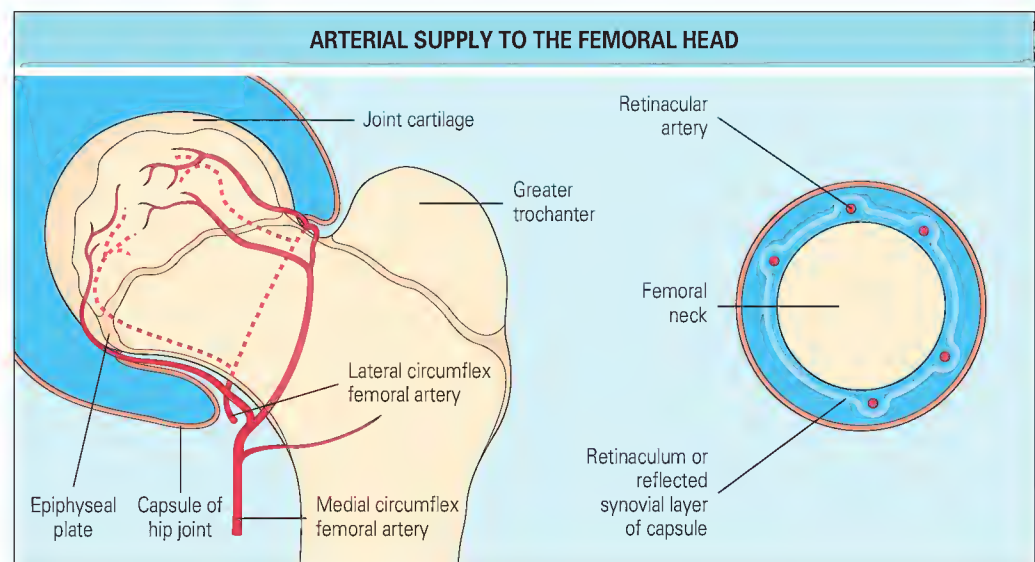


Fig. 99B.4 Pelvic radiograph and technetium bone scintiscan for an 8-year-old with Legg-Calvé-Perthes disease. (a) The child has early involvement of the right hip, with relatively subtle changes apparent on the radiograph. (b) The bone scintiscan, however, shows complete blood loss in the right femoral head, consistent with osteonecrosis. The left hip shows classic, more advanced stages of Legg-Calvé-Perthes disease (in the revascularization phase), with return of normal blood flow visible on the scintiscan.

Fig. 99B.5 Normal blood supply to the femoral head in a 4-year-old child. A blockage of this blood supply, which is yet not fully understood, leads to Legg-Calvé-Perthes disease.



physical therapy. This low-risk group includes children who maintain good hip motion (at least 30 degrees of abduction) or who are younger than 6 years of age. However, about 60% require mechanical treatment, which is based on the principle of containment of the femoral head within the acetabulum so that, during healing, the head is molded by the acetabulum. Containment is accomplished by bracing or by surgical intervention using an innominate (Salter) osteotomy, femoral osteotomy, or combination of the two. The role of bisphosphonate therapy in limiting damage by reducing osteoclast and remodeling is still under investigation.¹⁹⁻²¹

Prognosis

Overall prognosis is good, particularly in those younger than 6 years of age with less than half of the epiphysis involved. When more than 50% of the epiphysis is affected and the child is older than 6 years, deformity of the femoral head and metaphyseal damage are more likely, resulting in secondary osteoarthritis in adult life. In more severe disease, the femoral head needs to be covered by the acetabulum to act as a mold for the reossifying of the epiphysis. Age determinations show chronologic age to exceed pelvis bone age and hand-wrist bone age in individuals of both sexes with LCP.²²

Long-term follow-up

A review of 20- to 40-year follow-up studies found that 70% to 90% of patients are active and pain free, regardless of treatment.²³ Growth studies in children followed longitudinally show that affected children are slightly shorter at birth and that they remain shorter over the entire growth period. The femoral head and neck deformity can lead to a “functional retroversion,” causing an externally rotated gait.²⁴

Slipped capital femoral epiphyses

Slipped capital femoral epiphyses (SCFE) is most likely to occur in preteen and early teenaged boys; its overall incidence in the general population is 0.7 to 3.4 per 100,000.^{25,26} Boys are affected at least two to five times more frequently than girls. Peak age at onset is 11.5 years in girls and 13 years in boys.²⁷ Acute SCFE occurs up to 10% to 15% of the time.²⁸ In SCFE, the term *acute* refers to the interval between the onset of pain and presentation to the practitioner (less than 3 weeks), whereas the term *unstable*, as it applies to SCFE, refers to lack of ability of the child to bear weight even with the use of assistive devices such as crutches. Prognosis appears more closely related to whether SCFE is stable or unstable than whether it acute or chronic. In SCFE the slip occurs at the weakest part of the physal plate and results in displacement of the head from the metaphysis. Risk factors for SCFE include obesity, hypothyroidism, and hypoparathyroidism, and perhaps treatment with growth hormone.

Clinical findings

Patients may have no pain at presentation; patients with pain may have had subclinical symptoms such as mild pain or limp for 1 to 3 months. The slip itself usually occurs during the preadolescent growth spurt and is more common in obese children. Up to 25% to 40% of children have bilateral slips, and up to half of children with bilateral slips are asymptomatic for the slip on the side without pain. SCFE should be in the differential diagnosis for hip, thigh, or knee pain in children aged 10 to 15. In unstable SCFE the child most often has severe pain of acute onset comparable to that of a displaced femoral neck fracture.²⁸ A history of mild trauma is frequently present.²⁸ The prognosis is guarded in cases of an unstable slip because a

proportion of children with unstable SCFE go on to develop avascular necrosis of the femoral head.

Imaging

In acute SCFE an anteroposterior radiograph of the pelvis confirms the finding of an abrupt displacement of the epiphysis on the metaphysis. If the acute slip occurs in the setting of a chronic clinically unnoticed slip, then metaphyseal remodeling will be seen along the superior and anterior femoral neck.²⁸ A cross-table lateral view of the hip but not a lateral view in frog-legged position (which could exacerbate the slip) may help assess the presence of anterior physeal separation, a risk factor for avascular necrosis; a cross-table frog-legged view of the contralateral hip should also be obtained.²⁸

Treatment

There is controversy regarding operative treatment of acute SCFE with regard to timing of surgery, method (internal fixation with one or two screws), bone graft epiphysiodesis, reduction of the hip, decompression of the hip joint, and the role of femoral osteotomy; however, a recent meta-analysis concluded that, for stable SCFE, fixation with a single screw without surgical dislocation is superior.²⁹ In contrast, unstable SCFE requires reduction, decompression, and internal fixation. Controversy also exists about whether there is a role for prophylactic pinning of the contralateral hip. Zoledronic acid increases bone density and reduces bone turnover markers in LCP and SCFE but has not yet become standard of care in treating these disorders; adverse effects of zoledronic acid therapy were similar to those reported in adults.^{20,30} Currently there is no effective treatment for traumatic femoral head necrosis in adolescents, although some have suggested that vascularized fibular grafting could be helpful.

Idiopathic chondrolysis

Idiopathic chondrolysis is an uncommon disease in which there is progressive necrosis of hyaline cartilage of both the femoral head and the acetabulum.³¹ Occurring predominantly in teenaged girls, idiopathic chondrolysis is associated with severe pain, stiffness, and an abnormal gait and leads to premature osteoarthritis of the hip. Bilateral disease has been reported.³² Chondrolysis can also occur in association with other conditions, including SCFE, pin perforation during treatment for SCFE, immobilization, hip tumors, traumatic subluxation, intraarticular leak of bone cement, Stickler syndrome, psoriatic arthritis, and septic arthritis.

Imaging

Radiographically, concentric narrowing of the articular space to less than 3 mm (normal range, 3.5 to 7.0 mm) is considered to be diagnostic, and the physeal injury can be associated with decreased width of the femoral neck and head and shortening of the femur. Maximal narrowing appears to develop during the first year, followed by an increase in joint space and motion over the first few years, but then progression occurs with osteoporosis, osteophyte formation, and sometimes protrusio acetabuli. Technetium bone scans show marked periarticular uptake and premature fusion of the epiphysis of the greater trochanter, findings that may precede the abnormalities seen on MRI scans and plain radiographs.

Treatment and prognosis

The prognosis is generally poor, and many patients eventually require hip replacement.

REGIONAL SYNDROMES: KNEE

Patellofemoral dysfunction

Patellofemoral dysfunction, also known as *patellofemoral pain syndrome*, is a common cause of pain in adolescents and in some children; it is described in detail in Chapter 77.

Chondromalacia patellae

Chondromalacia patellae results from softening of the articular cartilage of the patella. The disorder most commonly affects adolescent females, and pain can be reproduced when the patella is tightly apposed to the femoral

condyles, as in standing up from sitting or walking up stairs. Treatment is conservative with rest and physical therapy for quadriceps muscle strengthening.

Bone lesions that mimic mechanical knee disease

Malignant tumors fortunately are rare; osteogenic sarcoma and Ewing tumor may present with pain and/or swelling and may be accompanied by pathologic fracture. Osteoid osteoma is a benign tumor that may affect adolescents (boys more than girls) and usually involves the femur or tibia. Typically pain is most severe at night; the symptoms are thought to be due to local release of prostaglandins and often improve with NSAID therapy. Radiographs are usually diagnostic and show a sharply demarcated radiolucent focus of osteoid tissue surrounded by sclerotic bone. Computed tomography or MRI is sometimes required to detect smaller lesions. Treatment is by surgical removal or curettage. Tumors of bone are described in more detail in Chapter 212.

Osgood-Schlatter disease

Osgood-Schlatter disease is a traction apophysitis seen primarily in boys between the ages of 11 and 17. Physical examination frequently shows tenderness and/or protuberance of the tibial tuberosity. The bone at the age span indicated is thought to be more susceptible to repetitive injury than the patellar tendon, which results in fragmentation of the bone. Disease may be unilateral or bilateral. Treatment consists of icing after activity. NSAIDs can be given to control pain but not at doses that would ease the way for further overuse. Physical therapy to increase flexibility of the thigh muscles accompanied by core strengthening is helpful. Rarely, casting or surgical excision of ossicles is required.

Other knee disorders

Knee extensor tendinitis (jumper's knee) may be seen in young athletes. This disorder, pes anserine bursitis, and iliotibial band syndrome are described in Chapter 77. Performing the Ober test can be quite helpful in diagnosing iliotibial band syndrome. Finally, osteochondritis dissecans is another common cause of knee pain in children and adolescents that typically presents as intermittent knee pain and effusion. The subchondral bone is involved. Treatment is frequently surgical and depends on the size of the lesion. Osteochondritis desiccans, a defect in cartilage, has been treated with débridement, autologous chondrocyte transplantation, and osteochondral allografts; there have been no head-to-head or comparative efficacy studies to support one method over another.

REGIONAL SYNDROMES: FOOT

Talipes equinovarus (*clubfoot*) refers to a condition in which the foot is inverted and supinated and the forefoot is adducted. The affected foot is shorter with less calf muscle bulk than normal, and the condition is frequently bilateral. During plantar flexion the heel rotates inward. *Talipes equinovarus* occurs approximately twice as frequently in male as in female infants, and the overall incidence approaches 1 in 1000 live births. Oligohydramnios, spina bifida, and other congenital disorders may precede this condition. Physical therapy, positional splinting, and surgical correction may be required. *Talipes equinovarus* should be differentiated from *talipes calcaneovalgus*, in which the foot is dorsiflexed and everted. The latter usually self-corrects, but passive foot exercises are sometimes advised. Positional *talipes* from intrauterine compression is common, and if the deformity is mild and foot size is normal, it can be corrected to the neutral position with passive manipulation and exercises.

Skeletal dysplasias and heritable disorders of connective tissue are covered in Section 17.

Acknowledgments

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100

Classification and epidemiology of juvenile idiopathic arthritis

■ KIRSTEN MINDEN

- Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease in the pediatric age period.
- JIA has an annual incidence of approximately 10 per 100,000 children and a prevalence of about 100 per 100,000 in North American and European white populations. For other populations, estimates on occurrence of JIA are almost impossible because of lack of data.
- JIA is a heterogeneous condition and currently classified into seven different categories based on clinical and laboratory features.
- Risk for JIA is attributed to a complex combination of environmental and genetic factors, with a heritable risk of 30%.

CLASSIFICATION OF CHILDHOOD ARTHRITIS

History of childhood arthritis classification

Since the description of the first case series at the end of the 19th century, there have been many names for and attempts at classifying the clinically heterogeneous group of chronic arthritides in children. In the 1970s two classification systems became accepted: in North America, the classification of *juvenile rheumatoid arthritis* (JRA) proposed by the American College of Rheumatology (ACR),¹ and in Europe, the classification of *juvenile chronic arthritis* (JCA) of the European League Against Rheumatism (EULAR).² Both were based on the concept of classification by mode of onset of arthritis and distinguished the same subsets: systemic arthritis, oligoarthritis, and polyarthritis. However, the two classifications did not include identical spectra of disease (Table 100.1), thus impeding comparison of epidemiologic, clinical, serologic, and genetic data.

In an effort to overcome the limitations of the preexisting, somewhat discordant classification systems and to replace them with one unified, internationally accepted classification, in 1993 the International League of Associations for Rheumatology (ILAR) Task Force on the Classification of Childhood Arthritis proposed a new classification using the term *juvenile idiopathic arthritis* (JIA) for all chronic childhood arthritides of unknown cause.^{3,4} According to the ILAR classification, JIA is defined as definite arthritis for a minimum of 6 weeks in a child younger than 16 years. There is no biologic relevance to this age criterion. The term “idiopathic” emphasizes that the cause of the arthritis is unknown. A diagnosis of JIA requires that other known conditions be excluded. This applies, for example, to infection-related arthritides (e.g., Lyme disease). Similarly, arthritis accompanying connective tissue, metabolic, and other genetic disorders is not regarded as JIA.

Role of the International League of Associations for Rheumatology classification

JIA can be diagnosed as early as 6 weeks after the onset of symptoms, whereas allocation to a specific JIA category requires the duration of the disease to be up to 6 months. The ILAR criteria were not developed for clinical decision-making, and therefore their use for clinical diagnosis is inappropriate. The ILAR criteria are based on inclusion and exclusion criteria and seek to define groups of patients with a high degree of internal homogeneity without overlap among the six specific categories. The JIA categories (Table 100.2) are distinguished on the basis of clinical features over the first 6 months of disease, especially the number of affected joints, but also the presence of extraarticular manifestations and rheumatoid factor

(RF). The number “4” as the criterion for assignment to oligoarthritis or polyarthritis is an arbitrary value; however, in an evaluation study of the ACR criteria, Cassidy and colleagues⁵ showed by cluster analysis that involvement of more than four joints is the most important variable associated with outcome in polyarthritis.

A number of “descriptors” have been proposed to gather further information about the pattern of these diseases (e.g., age at onset, antinuclear antibody [ANA] positivity, chronic or acute uveitis), but they are not part of the JIA classification.

Many papers have acknowledged that the ILAR classification distinguishes immunogenetically distinct groups of patients, with variations in regard to the underlying pathogenesis, clinical phenotypes, treatment responses, and disease outcomes.^{6,7} For example, systemic-onset JIA (soJIA) and enthesitis-related arthritis (ERA) are acquired autoinflammatory diseases, whereas other JIA categories are a consequence of a disturbed balance between proinflammatory effector cells and antiinflammatory regulatory cells.^{8,9}

Even though the ILAR classification yields greater clarity and homogeneity than previous classifications do, overlap between and heterogeneity within categories of JIA remain. Overlap exists, among others, between the categories of RF-negative polyarthritis and oligoarthritis; patients with early-onset polyarthritis and oligoarthritis share common clinical and genetic features.¹⁰ This is supported in a study by Ravelli and colleagues¹¹ in which it was demonstrated that ANA-positive patients have similar characteristics but are classified into different JIA categories. On the other hand, heterogeneity within one category has been shown in soJIA,¹² RF-negative polyarthritis,¹⁰ and psoriatic arthritis.¹³ For example, two subtypes of psoriatic arthritis have been recognized. One is similar to early-onset oligoarticular and polyarticular JIA; the other shares features of ERA.

Classification of juvenile-onset spondyloarthritis

The family of juvenile-onset spondyloarthritis (SpAs), which includes juvenile ankylosing spondylitis, reactive arthritis, subsets of psoriatic arthritis, enteropathic arthritis, and undifferentiated juvenile SpA, is not completely encompassed under the term JIA. Diseases included in the juvenile SpA group exhibit overlapping clinical features, such as asymmetric involvement of large joints in the lower extremities, enthesopathy, HLA-B27 positivity, and a family history of this group of diseases. Most children with such features, especially those with isolated forms of arthritis, the seronegative enthesopathy and arthropathy syndrome, and juvenile ankylosing spondylitis, are classified as having ERA in the ILAR approach to classification. Patients with juvenile psoriatic arthritis are considered to have a distinct entity. This is in contrast to the traditional concept of SpA behind the European Spondylarthropathy Study Group (ESSG) classification and the Assessment of SpondyloArthritis international Society (ASAS) axial and peripheral SpA criteria.^{14,15} Both the ERA (ILAR) and the ESSG criteria may properly classify children with SpA. The ERA criteria, however, correspond better to the clinical picture of juvenile-onset SpA because the relevance of enthesopathy in the whole group is much greater than that of inflammatory back pain. The latter is the major diagnostic criterion, besides synovitis, according to the ESSG but is an infrequent event in children with recent-onset disease. Whether the ASAS criteria for axial and peripheral SpA have any role in the classification of children with SpA remains to be determined.¹⁶

Validity of the International League of Associations for Rheumatology criteria

The proposed ILAR classification has been evaluated in more than 15 studies, the majority of which compared the Durban criteria³ with other published classification sets. In these studies, which included almost 3500

TABLE 100.1

Classifications of childhood arthritis

Classification according to	ACR	EULAR	ILAR
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile chronic arthritis (JCA)	Juvenile idiopathic arthritis (JIA)
Age at onset of arthritis	<16 yr	<16 yr	<16 yr
Duration of arthritis	≥6 wk	≥3 mo	≥6 wk
Types of onset	3	3	6 (2 oligoarthritis course subtypes)
Exclusion	Juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter syndrome	Rheumatoid factor–positive polyarthritis	Reactive arthritis

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ILAR, International League of Associations for Rheumatology.

children, performance of the ILAR classification has not been analyzed adequately, however. The reliability and precision of the criteria have not been tested, and their feasibility has been rated as relatively low. Berntson and colleagues¹⁷ reported on the difficulties of fulfilling the specified exclusion criteria in clinical work. Face validity of the ILAR classification was, however, affirmed. The ILAR classification is, like its predecessors, based on published literature and expert opinions. The criteria have not been tested against non–rheumatic disease control groups or other rheumatic disease control groups; thus its sensitivity and specificity are unknown.

Nevertheless, the ILAR classification constitutes the currently agreed-on international system of definitions for chronic childhood arthritides of unknown etiology. The proposed classification has restrictions intrinsic to any classification founded on clinical criteria, but it will probably be modified as progress is made in understanding the pathophysiology and phenotypic expression of JIA. Genome-wide technologies for measurement of both DNA and RNA, the increasing availability of validated disease-specific biomarkers, and the development of novel analytic strategies hold promise for providing a biologic basis for classification and a new clinical-immunopathologic classification of childhood arthritis.

DESCRIPTIVE EPIDEMIOLOGY

Published data on occurrence, clinical phenotypes, risk factors, and the natural course of chronic childhood arthritis vary and are difficult to compare and interpret because of the heterogeneity of the disease, differences in the classification criteria used for definition and inclusion, and differences in source populations and case ascertainment.

Incidence and prevalence

JIA is the most common chronic inflammatory rheumatic disease experienced in childhood. Calculation of the incidence and prevalence of JIA incurs three methodologic problems:

1. JIA is a diagnosis of exclusion that is identified clinically without specific diagnostic tests.
2. Because of its low incidence, large sample sizes are needed to provide statistically precise estimates.
3. Non–community-based studies are likely to underestimate the true incidence and prevalence of JIA because of underdiagnosis.

JIA occurs worldwide, but the occurrence of JIA has hitherto been estimated only in European populations (Table 100.3).¹⁸⁻⁴⁹ The incidence is reported to be 3 to 23 per 100,000 children younger than 16 years, and the prevalence is reported to be 16 to 140 per 100,000. These rates were obtained from practitioner-based studies. Oen and Chang⁵⁰ demonstrated that in contrast to the approach of case ascertainment, the kind of classification criteria applied has only relatively little influence on the estimated frequency of childhood-onset arthritis. Therefore, studies on the incidence and prevalence of JRA or JCA according to the ACR or EULAR criteria, respectively, can provide a useful overview of the relative frequency of childhood arthritis in different populations. Restricting consideration to studies published since

TABLE 100.2

Current International League of Associations for Rheumatology classification of juvenile idiopathic arthritis

Category	Definition	Exclusions
Systemic arthritis	Arthritis with or preceded by daily fever of at least a 2-wk duration that is documented to be quotidian for at least 3 days and accompanied by one or more of the following: Evanescent, nonfixed erythematous rash Generalized lymph node enlargement Hepatomegaly and/or splenomegaly Serositis	a, b, c, d
Oligoarthritis	Arthritis affecting 1-4 joints during the first 6 mo of disease	a, b, c, d, e
Persistent	Arthritis affecting no more than 4 joints throughout the course of disease	
Extended	Arthritis affecting a total of more than 4 joints after the first 6 mo of disease	
Polyarthritis (RF negative)	Arthritis affecting more than 4 joints during the first 6 mo of disease; tests for RF are negative	a, b, c, d, e
Polyarthritis (RF positive)	Arthritis affecting more than 4 joints during the first 6 mo of disease; tests for RF are positive (on at least 2 occasions more than 3 mo apart)	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of the following: Dactylitis Nail abnormalities (pitting or onycholysis) Psoriasis in a first-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with at least two of the following: Presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain Presence of HLA-B27 Onset of arthritis in a male older than 6 yr Acute (symptomatic) anterior uveitis History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a first-degree relative	a, d, e
Other arthritis	Arthritis that fulfills the criteria in no category or in two or more of the above categories	

a, Psoriasis or a history of psoriasis in the patient or a first-degree relative.

b, Arthritis in an HLA-B27–positive male beginning after the sixth birthday.

c, Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis or a history of one of these disorders in a first-degree relative.

d, Presence of IgM RF on at least two occasions at least 3 months apart.

e, Presence of systemic juvenile idiopathic arthritis.

Data from Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001.

J Rheumatol 2004;31:390-2.

1990, including contemporary studies of JIA frequency, annual incidence rates of chronic childhood arthritis vary from 0.8 to 23 per 100,000, and prevalence rates range from 15 to 400 per 100,000 worldwide (see Table 100.3). Population surveys (with case verification by specialists) yielded the highest prevalence values, between 200 to 400 cases per 100,000, thus pointing to a significant number of children with undiagnosed JIA in a community.

Geographic and ethnic variation

Most studies on JIA frequency are from North America and Europe (see Table 100.3). In the most heavily populated areas of the world, epidemiologic data on JIA are scarce. The studies available from different geographic regions are difficult to compare, but it seems that in North America and Europe, the overall prevalence of JIA is higher than in Asia. The prevalence rate of 0.83 per 100,000 children in Japan is among the lowest documented.⁴⁵

TABLE 100.3

Incidence and/or prevalence estimates of childhood chronic arthritis worldwide, from studies published since 1990

Population/country	Years	Case ascertainment	Classification system	Incidence (per 100,000 at risk and year)	Prevalence (per 100,000 at risk)
Europe					
Iceland ¹⁸	1997-1998	Practitioner based	ILAR	7	—
Norway ¹⁹	2004-2005	Practitioner based	ILAR	14	—
Norway ¹⁸	1997-1998	Practitioner based	ILAR	19-23	—
Norway ²⁰	1985-1994	Clinic based	EULAR	23	148
Finland ¹⁸	1997-1998	Practitioner based	ILAR	21	—
Finland ²¹	2000	Practitioner based	ILAR	23	—
Finland ²²	1980-1995	Register based	ACR	20	—
Sweden ¹⁸	1997-1998	Practitioner based	ILAR	15	—
Sweden ²³	1984-1988	Practitioner based	EULAR	11	86/64*
Denmark ¹⁸	1997-1998	Practitioner based	ILAR	9-16	—
Denmark ²⁴	1988-1991	Register based	EULAR	6	—
Estonia ^{25,26}	1998-2000	Practitioner based	ILAR	22	84
U.K. ²⁷	1990-1995	Clinic based	EULAR	10	—
Belgium ²⁸	—	Community based	EULAR	—	167/100*
Germany ²⁹	1995	Practitioner based	EULAR	7	15
Germany ³⁰	1980-1989	Clinic based	EULAR	4	20
Austria ³¹	1997-1998	Clinic based	ACR	4	—
Czech Republic ³²	2002-2003	Practitioner based	ILAR	13	140
France ³³	2001	Practitioner based	ILAR	3	20
France ³⁴	2006	Practitioner based	ILAR	—	16
Spain ³⁵	1989-2005	Practitioner based	ILAR	4	51
Spain ³⁶	2004-2006	Practitioner based	ILAR	7	40
North America and Hawaii					
Canada ³⁷	2000	Register based	ACR	18	—
Canada ³⁸	1991-1993	Clinic based	ACR	3	—
Canada ³⁹	1975-1992	Clinic based	ACR	5	97
American Indians, USA ⁴⁰	1998-2000	Register based	ACR	—	53
USA ⁴¹	1960-1993	Register based	ACR	12	86-94
Costa Rica ⁴²	1993-1995	Practitioner based	EULAR	7	35/31*
Hawaii ⁴³	1993-2002	Clinic based	ACR	—	38-70
Australia					
Australia ⁴⁴	—	Community based	EULAR	—	400
Asia					
Japan ⁴⁵	1994	Clinic based	ACR	0.8	—
Middle East					
Turkey ⁴⁶	—	Community based	ACR	—	32
Turkey ⁴⁷	1996	Community based	EULAR	—	64
Egypt ⁴⁸	—	Community based	EULAR	—	330
Kuwait ⁴⁹	1981-1988	Clinic based	EULAR	3	19

*Active cases.

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ILAR, International League of Associations for Rheumatology.

Variation in occurrence of JIA has also been observed in populations of different ethnic origin from the same region. In a multiethnic cohort from Toronto, Canada, consisting of more than 800 children and adolescents, European descent was significantly associated with an increased risk for the development of JIA.⁵¹ In contrast, children with Afro-Caribbean, Asian, or Indian ethnic background were less commonly affected by JIA. Lower frequencies of childhood arthritis have also been reported in children of Japanese, Filipino, or Samoan origin than in white children living in Hawaii.⁵²

In Europe, there is a tendency toward a falling north-to-south gradient in the incidence of JIA, with the highest incidence rate registered in northern

Norway (23 per 100,000) and the lowest rate in France (3 per 100,000). There is evidence of a relationship between the latitudinal gradient and occurrence of other autoimmune diseases (e.g., pediatric Crohn disease, multiple sclerosis). The role of latitude (or vitamin D status) with regard to the occurrence of JIA has not been studied adequately.⁵³

Time trends

It is uncertain whether the occurrence of JIA is increasing. Some studies investigating trends recorded a doubling or tripling of the incidence of JIA in observation periods ranging from 3 to 17 years.^{22,25,35}

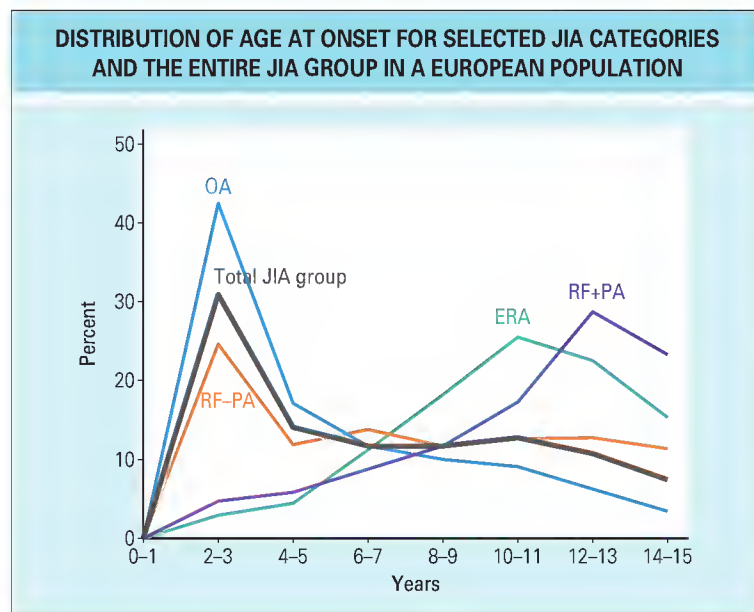


Fig. 100.1 Age at onset of selected categories of juvenile idiopathic arthritis (JIA) and the entire JIA group in a European population. Data were derived from 5994 patients with JIA recorded in the German pediatric rheumatologic database in 2011. ERA, enthesitis-related arthritis; OA, oligoarthritis; RF- PA, rheumatoid factor-negative polyarthritis; RF+ PA, rheumatoid factor-positive polyarthritis.

In addition, temporal variability in the incidence of JIA has been observed in several studies, thus supporting a possible environmental etiopathogenesis of the disease.⁵⁴

Descriptive epidemiology of the different disease categories

The picture of JIA differs around the world, which suggests true differences in disease manifestations because of immunogenetic or environmental factors or a combination of both.

In white populations from North America and Europe, oligoarthritis constitutes at least half of all incident JIA cases⁵⁵⁻⁵⁷; progression to a polyarticular disease course, labeled as extended oligoarthritis, has been described in a third of cases with oligoarthritis.⁵⁵ Approximately 20% of children with newly diagnosed JIA have polyarticular disease, 10% have ERA, and less than 10% have psoriatic arthritis and soJIA. RF-positive polyarthritis is the rarest JIA category and accounts for less than 5% of cases.⁵⁵⁻⁵⁷

Overall, more girls than boys are affected by JIA, but the sex distribution varies with the JIA category, with a striking female preponderance in oligoarticular and polyarticular onset (girl-to-boy ratio of approximately 3:1), an even distribution of sexes with soJIA, and a male preponderance (male-to-female ratio of 2:1 to 3:1) in ERA.

The different JIA categories have characteristic distributions of age at onset. Oligoarthritis is typically a disease of young children, although onset before 6 months of age is highly unusual. The peak age at onset of oligoarthritis and RF-negative polyarthritis is 2 to 3 years, whereas ERA and RF-positive polyarthritis occur predominantly in children older than 8 years (Fig. 100.1). In general, two major peaks in JIA onset have been observed: at 2 to 3 years and between the ages of 11 and 12 years.

ANAs (for the most part of unknown specificity) are the most frequently detected autoantibodies in JIA (in 40% to 50% of cases).^{51,55,57} They are most commonly seen in patients with oligoarthritis.^{51,55} IgM RFs are rarely found in JIA (<5%) and, by definition, are found only in those with RF-positive polyarthritis or other arthritis.

Extraarticular features differ among the various JIA categories. Systemic manifestations such as fever characterize soJIA, whereas enthesitis is a distinguishing feature of enthesitis-related arthritis. Dactylitis is most commonly seen with juvenile psoriatic arthritis. Uveitis can be observed most frequently in patients with oligoarthritis of the extended course type (cumulative incidence of 25% to 30%), followed by persistent oligoarthritis (16% to 18%) and RF-negative polyarthritis (4% to 14%) or psoriatic arthritis (10% to 12%).^{58,59} Several studies have shown that ANA positivity, age younger than 6 years at onset of JIA, and subtype of JIA are independent

risk factors for uveitis. Uveitis develops in about 90% of cases within the first 4 years of JIA. It is manifested mainly as anterior uveitis but is usually asymptomatic in the most affected JIA subgroups.

In non-European populations, the picture of JIA is different. Oligoarthritis is reported to be relatively uncommon. Its relative rarity has been documented in reports from the Indian subcontinent⁶⁰; Japan, Taiwan, and Thailand⁶¹; and South Africa.⁶² In contrast, polyarticular JIA, ERA, or both have been demonstrated to be more common in Asia, Africa, and Canadian aboriginal groups.⁶² In addition, several studies found a lower frequency of ANA (in particular in oligoarthritis), a lower frequency of uveitis, older age at onset, and no female preponderance in JIA patients from these populations in comparison to European populations.^{60,61} A significant difference in the distribution of JIA subtypes and JIA features among different ethnic groups was confirmed by Saurenmann and colleagues⁵¹ in their cohort study. They demonstrated an underrepresentation of oligoarticular JIA in patients of Asian, Afro-Caribbean, and North American origin. On the other hand, overrepresentation of polyarticular JIA was observed in children of Afro-Caribbean and native North American origin. In particular, the prevalence of RF-positive polyarthritis (16% and 20%, respectively) was higher than in children of European descent (2%).

Risk factors

Evidence suggests that JIA develops as an untoward consequence of interactions between genetic susceptibility and environmental risk factors in a manner that is incompletely understood.

Genetic factors

Familial risk

Compelling evidence for a genetic component in childhood arthropathies has been derived from twin, family, and association studies. Twin studies have shown a concordance rate of 25% to 40% in monozygotic twins for a disease with a population prevalence of 0.1%, thus implying a relative risk of 250 to 400 for a monozygotic twin of a JIA proband. The sibling recurrence risk (λ_s) was estimated to be 12 to 30, and the relative risk for JIA in first cousins of probands with JIA was calculated to be 6.⁶³ Affected sibling pairs are concordant for clinical phenotype, age at onset, and human leukocyte antigen (HLA) haplotypes, which strengthens the evidence that genetic factors play an important role not only in determining susceptibility to JIA but also in the expression of JIA.⁶⁴

Role of HLA

All JIA subsets are complex genetic traits because they lack single-gene, mendelian patterns of inheritance. Genetic variation within the HLA region defines the strongest known genetic risk factor for JIA. Both HLA class I and class II haplotypes, which are associated with JIA, are largely distinct from those in adults with rheumatoid arthritis (RA) and differ among JIA categories. The shared epitope (consisting of selected HLA-DRB1*01/*04 alleles) is associated only with RF-positive polyarticular JIA,⁶⁵ a finding supporting the fact that this JIA subtype is the juvenile equivalent of adult RA. In contrast, HLA-DRB1*04 and HLA-DRB1*07 are protective of the most common JIA subtypes.¹⁰ Interestingly, there is an apparent lack of association between soJIA and HLA.

The most consistent HLA associations have been found for oligoarthritis and include at least three interacting major histocompatibility complex (MHC) components: one class I HLA, a second from DR/DQ, and a third from DP. There are three oligoarthritis-predisposing haplotypes from the DR/DQ loci: DRB1*0801;DQA1*0400;DQB1*0402, DRB1*1103/04;DQA1*0500;DQB1*0301, and DRB1*1301;DQA1*0103;DQB1*0603; all show very strong effects (odds ratios [ORs] of 7.7, 4.8, and 2.3, respectively). Hollenbach and colleagues¹⁰ found that the effects are attributable to DRB1, with no evidence of a role for DQA1 or DQB1. The presence of two predisposing DRB1 alleles significantly increases risk for disease, with ORs ranging from 13 to 23 relative to only a single predisposing DRB1 allele. The DRB1*0801 haplotype is associated with disease regardless of age at onset, whereas the remaining predisposing DRB1 alleles show significant associations only with early-onset disease. Therefore, the very strong effect by two copies of predisposing DRB1 alleles may be related to an age-at-onset effect of the non-DRB1*0801 allele.

HLA variants, however, explain just part of the genetic burden of JIA. It has been estimated that the HLA-DR region accounts for only about 17% of the genetic risk for JIA, which suggests that other variants within and outside the MHC play a role in susceptibility. A recent genome-wide association study estimated that 30% of JIA risk is attributed to common genetic variation and that the extended MHC region accounts for approximately a fourth of the heritable risk.⁶⁶

Role of non-HLA genes

The non-HLA genetic component of JIA appears to be mediated by multiple low-risk polymorphisms. In the past few years, researchers have identified numerous non-HLA risk alleles for JIA through association using both genome-wide and candidate gene approaches. For example, variants at the PTPN22, STAT4, TNF- α , TNFAIP3, MIF, WISP3, SLC11A1 (formerly NRAMP1), and IL-2Ra loci have been shown to be associated with JIA by several groups. Most of these genes/loci confer only modest ORs of about 1.5 and are not unique to JIA but have also been associated with various other autoimmune disorders. It is therefore not surprising that autoimmune diseases cluster in JIA patients, as well as in families. An increased prevalence of other autoimmune disorders, such as autoimmune thyroid disease, diabetes mellitus, or celiac disease, has been found in patients with JIA, with a history of autoimmunity having been demonstrated in 12.6% of first- and second-degree relatives of JIA patients as opposed to 4% of the control population.⁶⁷ A higher prevalence of autoimmunity in maternal versus paternal relatives of children with JIA has been found. Moreover, a significantly higher prevalence of autoimmune diseases has been demonstrated in maternal relatives of JIA cases than in relatives of controls, which suggests a maternal parent-of-origin effect in JIA.

Environmental factors

When compared with identification of genetic risk factors for JIA, research to identify environmental factors has received less attention.

Infectious agents

Seasonal variation in the incidence of JIA (in particular, soJIA) and changes in the incidence of JIA in general over time have been observed. This led to the hypothesis that seasonal differences might reflect differences in the risk for exposure to infectious agents.^{53,54} Oen and coworkers³⁹ correlated yearly incidence trends in Manitoba, Canada, with the occurrence of *Mycoplasma pneumoniae* infection. Other support for the role of infectious agents includes an increase in the incidence of soJIA correlated with enteroviral infections.

A possible link between rubella virus, Epstein-Barr virus (EBV), and parvovirus B19 infection and JIA has been assessed by comparing seropositivity for antiviral antibodies and the presence of viral DNA in patients with JIA and controls, but the studies provided contradictory results.⁵⁵ The study by Massa and colleagues,⁶⁸ however, indicated a possible interaction between genes and infectious agents in determining disease risk. The authors identified sequence homologies between EBV proteins and HLA alleles associated with oligoarticular JIA. They observed a different response of cytotoxic T-cell lines from patients and controls to class II self-HLA-derived peptides homologous to EBV-derived peptides.

In addition, a few studies have pointed to a link between exposure to infections in early life and later disease risk. Pritchard and colleagues⁶⁹ noted an association between intrauterine or neonatal exposure to influenza A and the much later development of polyarticular JCA. A Swedish nationwide register-based case-control study demonstrated an increased risk for later-onset JIA in children hospitalized for any infection during the first year of life (OR, 1.9).⁷⁰

Proxy measures of early-life microbial exposure, such as exposure to pets or animals during the first year of life, living in a rural area or on a farm, birth order, and sibship size, were also used to examine the role of early-life infections or hygiene with regard to risk for the development of JIA. A national Danish cohort study of incident JCA cases found an eight times higher risk for arthritis in an only child living in an apartment with high-income parents than in a child with siblings living on a farm with low-income parents.⁷¹ Other studies could not confirm these findings.⁷²

Stress and psychological factors

Major life events and chronic minor stress have been shown to be risk factors in the pathogenesis of JIA in some studies. Stressful life events were reported in up to a third of JIA patients within a year before disease onset and more often in JIA patients than in controls. In the study by Henoch and associates,⁷³ for example, children whose parents were unmarried as a result of divorce, separation, or death accounted for 28.4% of the JIA population as opposed to 10.6% of the controls. The rate of adoption was more than three times higher in patients than in controls.

Air pollution

Several studies have found that inhalation of airborne substances (e.g., cigarette smoke, particulate matter) can increase the risk for autoimmune diseases.⁷⁴ A Finnish birth cohort study demonstrated an association between fetal exposure to tobacco smoke products and risk for development of

chronic inflammatory polyarthropathies, especially JRA, in the first 7 years of life. Risk for JRA was threefold higher in girls whose mothers had smoked more than 10 cigarettes per day in pregnancy than in girls of nonsmoking mothers.⁷⁵ Another study, however, could not confirm an association between maternal smoking and risk for JIA.⁷⁰

Nutrition

The role of breastfeeding in risk for JIA was assessed in a few studies. Their results, though generally inconsistent, suggest a relationship between breastfeeding and disease risk. One study of infant feeding patterns concluded that children who were breastfed had a lower incidence of JRA (OR, 0.31) than did those who were fed cow's milk. Two other studies could not confirm this but found a difference in the duration of breastfeeding between JRA subtypes.

Summary

Altogether, conflicting data exist regarding each environmental factor that has been investigated, and no final conclusions on environmental risk factors for JIA can be drawn thus far. The scarce data available support the hypothesis that environmental exposures early in life, which might induce changes in functional development, are important in the etiology of JIA.

Course and prognosis

Mortality

The prognosis of patients with JIA has improved considerably in recent decades. Mortality rates in children with chronic arthritis were 4% to 7% in the 1970s, which represented a 10-fold increase over the general population. Survival has improved such that in 2010, Hashkes⁷⁶ reported a mortality rate in children with JIA not significantly different from that in the general population (standardized mortality ratio of 0.57). However, JIA patients are at increased risk for mortality in their adult years. Two population-based studies demonstrated that young adults with childhood-onset arthritis have a roughly fourfold higher overall mortality than the general population does.⁷⁷ Knowledge about specific causes of death in patients with JIA is very limited. In the 1970s the major causes of death were renal failure (in half the cases secondary to amyloidosis) and infections. Currently, macrophage activation syndrome is the leading cause of JIA-related mortality in childhood. It occurs mainly in soJIA, which still accounts for two thirds of the mortality seen in those with JIA. To what extent cardiovascular diseases, infections, or even hematopoietic malignancies contribute to the increase in mortality, especially later in life, has been unidentified. Preliminary data point to an increased rate (threefold higher) of incident malignancy (particularly of the lymphoproliferative type) in patients with JIA that cannot be explained by the introduction of biologic therapies.⁷⁸

Outcome

Outcome studies published since 2000 show that JIA frequently continues into adulthood. Most remissions occur in the first 5 years after disease onset. After more than 10 years of disease duration, 40% to 60% of the patients still have active arthritis. The probability of remission varies significantly with the type of disease onset, being best for oligoarticular JIA, at approximately 50%, and worst for polyarticular JIA, in which it approaches 15%. After a duration of disease of 15 years, more than a third of young people with JIA have experienced significant articular or extraarticular damage (or both), such as radiographic joint changes, growth disturbances, osteopenia, osteoporosis, and visual loss.⁷⁷

Despite the long-term persistence of disease activity or the need for drug treatment in most patients, a pronounced improvement in functional outcome has been documented. In the 1970s, the percentage of patients with serious functional disability (American Rheumatism Association functional classes III and IV) ranged from 17% to 22%, whereas a lower percentage of patients with serious functional disability ranging from 2% to 10% has been observed since the 1990s. According to the results from a more sensitive measure of function, the Health Assessment Questionnaire (HAQ), approximately 40% of young adults with JIA are somewhat limited in their functional capacity (HAQ > 0) and 10% are in need of assistance or aids to manage their daily routines.⁷⁷ There is also a negative effect of JIA on general health status and quality of life, and despite better than average educational achievements, patients with JIA have lower employment rates.

Several indicators of a poor JIA outcome have been identified, including greater severity or extension of arthritis at onset, symmetric disease, early wrist or hip involvement, the presence of RF, and persistent active disease. Most interesting so far has been prediction of prognosis based on early treatment response, with outcomes at 3 to 12 months predicting response at later points in time.

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Clinical features of juvenile idiopathic arthritis

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- Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks, provided other known conditions are excluded.
- JIA is the most commonly diagnosed rheumatic disease in children and an important cause of disability and acquired blindness.
- The clinical features of JIA are heterogeneous. When the International League of Associations for Rheumatology criteria are used for classification, eight clinical categories can be identified. Different clinical pictures at onset and during the course of the disease can provide guidance for treatment and prediction of outcome.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most commonly diagnosed rheumatic disease in children and can be an important cause of disability. The disorder is nearly as common as diabetes in children and four times more common than childhood leukemia.^{1,2} The classification of juvenile arthritis has been a challenge because of the heterogeneity of the disease. The International League of Associations for Rheumatology (ILAR) classification³ aims at defining biologically more homogeneous groups than the formerly used classification systems to enhance scientific and clinical communication globally. However, the ILAR criteria represent a change not only in terminology but also in definition of the categories. Because many studies have used the American College of Rheumatology or European League Against Rheumatism criteria, it is still important to be aware of these differences in definitions.^{4,5} The classification and descriptive epidemiology of JIA are reviewed in Chapter 100.

There is no single diagnostic test available for JIA. The diagnosis is based on a combination of findings from a careful history taking, a thorough physical examination, and unspecific laboratory tests. Many disorders can cause arthralgia and a limp (Tables 101.1 and 101.2). The rest of this chapter describes symptoms and signs that can aid in reaching a correct diagnosis and categorization and allow evidence-based predictions on the course and outcome of JIA.

GENERAL CLINICAL FEATURES

Arthritis is the main clinical feature in JIA and is defined as swelling within a joint or limitation in range of joint movement with joint pain or tenderness that persists for at least 6 weeks, is observed by a physician, and is not due to primary mechanical disorders or other identifiable causes (Table 101.3).³

Children with chronic arthritis most commonly have joint swelling and gait disturbance. Joint swelling in children is not always easy to notice, complaints are diffuse, and more than one joint may be involved. A thorough evaluation of all joints is therefore warranted. Morning stiffness is often intense, and nonspecific symptoms such as tiredness, mood changes, loss of appetite, and low-grade fever may be seen. Although musculoskeletal pain is the most common reason for referral to pediatric rheumatology clinics, isolated musculoskeletal pain is rarely a presenting complaint in children with chronic arthritis.⁶ Pain is, on the other hand, an important component in the management of JIA (see later).

LABORATORY INVESTIGATIONS

There is no single laboratory test that differentiates JIA from other diseases. The main role of laboratory investigations is to exclude other diseases such as leukemia or infectious arthritis. Antinuclear antibodies (ANAs), rheumatoid factor (RF), and HLA-B27 all lack any discriminatory ability to identify children with JIA. They are mainly useful in further categorization and the prediction of outcome.

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and thrombocyte count are useful tests to differentiate children with JIA from children with noninflammatory disorders. However, a normal ESR and/or CRP level cannot be used to rule out JIA when convincing clinical signs are present, because almost half of children with JIA have normal values at the onset of the disease in a population-based setting.⁷ The ESR and CRP level can be very high in the systemic and polyarticular categories of JIA, and thrombocytosis may be present.

Anemia can occur in all forms of JIA but is more pronounced in the systemic and polyarticular groups. Usually the anemia is secondary to chronic inflammation, as reflected by low serum iron level, low iron-binding capacity, and normal hemosiderin stores. Serum ferritin level may be elevated because it is an acute-phase protein mirroring inflammatory activity and not iron stores. In systemic JIA very high ferritin levels can be found and are a signal of complication with macrophage activation syndrome.⁸ Treatment with corticosteroids and nonsteroidal antiinflammatory drugs may cause intestinal blood loss and secondary iron deficiency, which usually responds to iron supplementation.

Leukocytosis with a neutrophil predominance is seen in children with systemic JIA and is also common in those with polyarticular JIA. Although mild to moderate thrombocytosis is common, thrombocytopenia is not part of JIA and should prompt a workup for systemic lupus erythematosus (SLE) or malignancy, especially leukemia. Serum immunoglobulin levels can be elevated, as can the antistreptococcal titers, even in the absence of a recent streptococcal infection.

ANAs are found in 40% to 85% of cases of early-onset oligoarticular JIA and are associated with chronic uveitis. The specific antinuclear antigen(s) responsible for the ANA positivity in JIA have not been identified. However, there are some indications that antihistones may be associated with JIA and serve as predictors of uveitis.⁹ The disease-specific ANAs that are detected by most enzyme-linked immunosorbent assay-based ANA tests are not associated with JIA or uveitis, and if they are found a workup for juvenile SLE is warranted, especially in teenagers with arthritis.

Immunoglobulin M (IgM) RF and anti-citrullinated protein antibodies (ACPAs) are almost exclusively present in teenagers with polyarticular JIA.¹⁰ Both ANA immunofluorescence and RF IgM may be transiently and non-specifically present in any inflammatory reaction. Two positive test results at least 3 months apart are needed for these markers to be recognized as disease descriptors in JIA.³

HLA-B27 is found in 14% to 42% of JIA patients in different populations.^{11,12} The exact role of HLA-B27 in JIA is not fully understood. It can be found in all JIA categories but is most common in enthesitis-associated arthritis. It is associated with clinical manifestations of enthesitis and sacroiliitis as well as more severe outcome.¹³

At present, research into new biomarkers of disease activity, such as cytokines and MRP8/14, in addition to immunogenetic markers is ongoing, but no test has yet been established as a routine clinical tool to help in diagnosis, categorization, or outcome prediction in JIA.¹⁴⁻¹⁶ Synovial fluid shows white blood cell counts ranging from 600 to 100,000 cells/mm³ (0.6 to 100 × 10⁹/L).

TABLE 101.1
Conditions with arthralgia/arthritis that might be confused with juvenile idiopathic arthritis

Type of condition	Examples
Infections	Bacterial arthritis and osteomyelitis Borreliosis (Lyme disease) Viral and mycoplasmal arthritis Tuberculosis
Postinfectious conditions	Rheumatic fever Poststreptococcal arthritis Postenteritis and other reactive arthritis (<i>Salmonella</i> , <i>Campylobacter</i> , <i>Chlamydia</i>)
Noninflammatory conditions	Hypermobility and Ehlers-Danlos syndrome Growing pains, trauma, patellofemoral and other overuse syndromes Osgood-Schlatter disease and other juvenile osteochondroses Legg-Calvé-Perthes disease Slipped capital femoral epiphysis Foreign body synovitis Other congenital and genetic disorders of supportive tissue
Hematologic disorders	Sickle cell anemia Hemophilia Von Willebrand disease
Systemic inflammatory disorders	Juvenile systemic lupus erythematosus Juvenile dermatomyositis Mixed connective tissue disease Scleroderma Vasculitis (e.g., Henoch-Schönlein purpura, Kawasaki disease, Behçet disease)
Autoinflammatory disorders	Cryopyrin-associated periodic syndrome Familial Mediterranean fever Other monogenic diseases (e.g., mevalonate kinase deficiency [hyperimmunoglobulinemia D], Blau syndrome, tumor necrosis factor receptor–associated periodic syndrome) Chronic recurrent multifocal osteomyelitis Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA syndrome)
Malignancies	Leukemia Neuroblastoma Localized bone tumors
Pain	Complex regional pain syndrome Pain amplification syndromes and fibromyalgia Nonspecific musculoskeletal pain
Miscellaneous conditions	Primary immunodeficiencies Sarcoidosis

Imaging

Traditionally, radiography was the imaging modality of choice in JIA but could only indirectly describe synovial and soft tissue inflammation. Radiography is not able to detect the presence and degree of inflammation or the precursors of bony destruction for prediction of permanent damage. Newer modalities like ultrasonography and magnetic resonance imaging (MRI) have therefore assumed increasing importance in the diagnostic workup as well as in assessment of inflammatory activity and response to medical treatment. Whether these newer modalities will also prove superior to radiography in assessing damage and predicting outcome remains to be seen. Ossification of cartilage increases with age in children.¹⁷ A major challenge in pediatric rheumatologic imaging is differentiating early signs of permanent bone and cartilage destruction from normal alterations in bone marrow composition, skeletal growth, and maturation.

Early radiographic changes in JIA include soft tissue swelling around affected joints and juxtaarticular osteopenia and periosteal new bone formation (Fig. 101.1), resulting in a widened midportion of the phalanges. In contrast with adult RA, erosions are a late finding because much of the cartilage in growing joints is not calcified, and visualization of erosions is possible only after the cartilage has calcified. Joint space narrowing is an early, but indirect, sign of cartilage destruction. Erosions or joint space narrowing can be found as early as a couple of years from the onset of active arthritis in a child with systemic or polyarticular JIA. Even in severe JIA destroyed cartilage can be replaced with fibrocartilage if the disease becomes quiescent (Fig. 101.2). Growth-arrest lines may result from temporary loss of growth velocity and may be seen around the knee. The sacroiliac joints in young patients are difficult to interpret because of the open epiphysis at the sacroiliac joints in growing children. Radiographic scoring systems specific for JIA have been suggested.^{18,19}

MRI can be an excellent modality for demonstrating the articular cartilage, fluid, and soft tissue structures in the joint. Contrast-enhanced sequences are valuable because they can demonstrate synovitis (Fig. 101.3).²⁰ Dynamic MRI can be used to demonstrate sacroiliitis in children with clinical characteristics consistent with spondyloarthritis.²⁰ An increasing range of MRI techniques with different pulse sequences are presently used to improve the visualization of relevant tissue, but challenges remains in defining and standardizing normal developmental changes in children.¹⁷ No reliable MRI-based scoring system for synovitis in JIA is yet available because the systems published so far have shown high interobserver variability.²¹ MRI is also expensive and time consuming, and general anesthesia is often necessary in young children.

Ultrasonography, which can be done at the bedside, is helpful in visualizing joint effusions, synovitis, and other soft tissue inflammations, including enthesitis, and has the advantage of being easier to perform with no need for general anesthesia.²⁰ It can be used to guide the needle for intraarticular injections, and with power Doppler function it is possible to follow synovial inflammation during the disease course and interventions (Fig. 101.4).²² To assess inflammation and erosion in the developing and maturing skeleton and soft tissue remains a particular challenge in children, and

TABLE 101.2
Common musculoskeletal causes of limp in children other than juvenile idiopathic arthritis

Cause	Age		
	1-4 yr	5-10 yr	11-15 yr
Vascular disorder		Legg-Calvé-Perthes disease, Köhler disease, and similar diseases	Freiberg disease Osteochondritis dissecans
Infection/inflammatory disorder	Septic arthritis Osteomyelitis Diskitis Postinfectious arthritis	<i>Borrelia</i> arthritis	<i>Borrelia</i> arthritis Septic arthritis (tuberculosis, gonococcal infection)
Trauma	Fracture Child abuse		Osgood-Schlatter disease
Malignancy	Leukemia		Osteosarcoma Osteoid osteoma
Anomaly	Hip dysplasia	Diskoid meniscus	Tarsal coalition
Metabolic disorder	Rickets Renal disease		Osteoporosis
Neuromuscular disorder	Cerebral palsy Muscular dystrophy		

TABLE 101.3
Characteristics of the various categories of juvenile idiopathic arthritis

Category	Age at onset	Affected joints	Systemic features	Major complications
Oligoarticular persistent	Early childhood	Large joints, asymmetric (knee, ankle, wrist, elbow, temporomandibular, cervical spine)	No	Chronic uveitis Local growth disturbances
Oligoarticular extended	Early childhood	Same as above, but >4 joints involved after the first 6 months of disease	No	Chronic uveitis Local growth disturbances
Polyarticular RF negative	Throughout childhood	Any, often symmetric, often small joints	Malaise (subfebrile)	Chronic uveitis Local growth disturbances
Polyarticular RF positive	Teenage years	Any, usually symmetric and involving small joints	Malaise (subfebrile)	Local growth disturbances and articular damage
Systemic	Throughout childhood	Any (not necessarily at disease onset)	High fever, rash, polyserositis, marked acute-phase response	Acute: macrophage activation syndrome Chronic: general growth disturbance, amyloidosis
Psoriatic	Late childhood	Spine, lower extremities, distal interphalangeal joints, dactylitis		Psoriasis Local growth disturbances
Enthesitis-related	Late childhood	Spine, sacroiliac, lower extremities, thoracic cage joints	Inflammatory bowel disease	Acute symptomatic uveitis

RF, rheumatoid factor.



Fig. 101.1 Extended oligoarticular juvenile idiopathic arthritis in an 8-year-old. Epiphyseal destruction and undergrowth of the third metacarpophalangeal joint of the left hand are seen, as well as overgrowth of the carpal bones of the right wrist compared with the left wrist. Also note the widened appearance of the third phalanges caused by periosteal new bone formation.

standardizations and definitions used in adult rheumatology are not always suitable.²³

CLINICAL FEATURES OF DIFFERENT CATEGORIES OF JUVENILE IDIOPATHIC ARTHRITIS

Systemic arthritis

Systemic arthritis is the category most often associated with severe short- and long-term morbidity as well as increased mortality. Today it is viewed as a different entity than the other categories of JIA and is considered to belong to the autoinflammatory disorders.⁸ It typically comprises 5% of the total unselected JIA population and is defined by its extraarticular features of fever and rash. Girls and boys are affected equally, and onset can occur throughout childhood. The extraarticular manifestations may precede the articular signs by weeks, months, or even years. The fevers typically rise to more than 39° C daily and return to less than 37° C between fever peaks for at least 2 weeks before this diagnosis can be confirmed. Fever usually occurs daily or twice daily and often appears late in the afternoon or



Fig. 101.2 Hip arthritis in systemic juvenile idiopathic arthritis. (a) Hip joint space narrowing bilaterally. (b) There was recovery of joint space 2 years later (standing view).

evening, returning to normal or below normal in the morning (Fig. 101.5). Classically, the child appears toxic with the fever and can have accompanying shaking chills, but not rigor.

In 90% of cases a characteristic evanescent salmon-colored macular or maculopapular rash (Fig. 101.6) occurs on the trunk and thighs, most commonly when the fever is present. The rash can be brought out by scratching

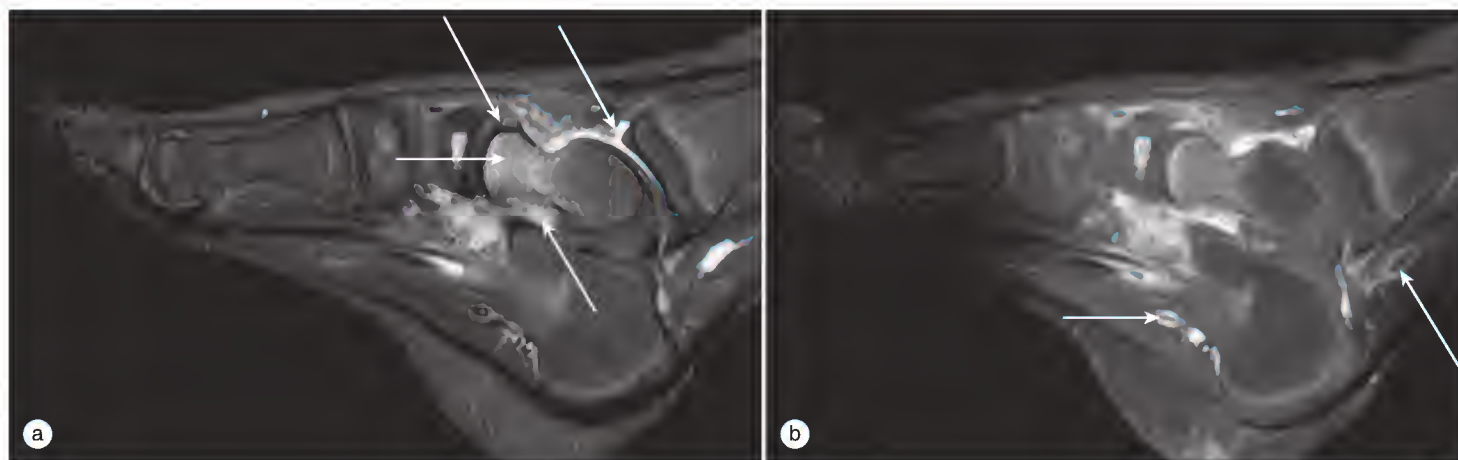


Fig. 101.3 Magnetic resonance images of a swollen ankle in a 5-year-old boy. In addition to talocrural arthritis, joint fluid and synovitis are also present in the subtalar and the talonavicular joint (arrows). There is bone marrow edema of the talus on the short tau inversion recovery image (a). Fat-suppressed T1 image after administration of intravenous contrast (b) shows tenosynovitis (arrows).

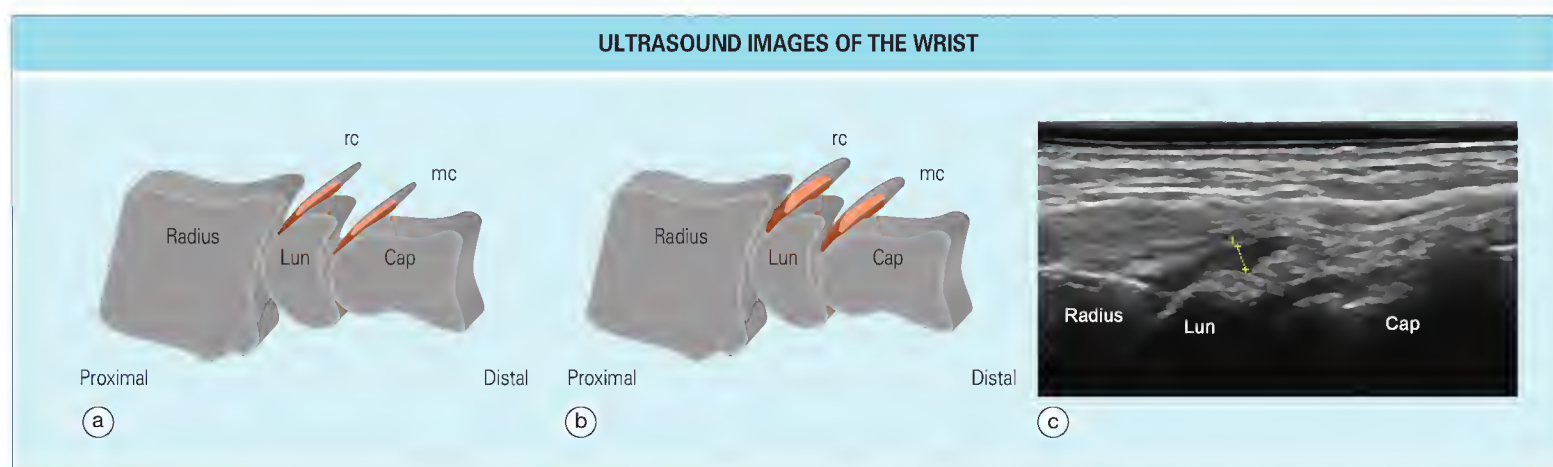


Fig. 101.4 (a) Drawing of the normal thin dorsal recesses of the radiocarpal (rc) and midcarpal (mc) joints, pointing distally. (b) Drawing of hypertrophic thickened synovial recesses of the radiocarpal and midcarpal joints. (c) Dorsal sagittal ultrasonographic scan of a hypoechoic thickened radiocarpal recess, Lun, lunate bone; Cap, capitate bone. (From Laurell L, Court-Payen M, Nielsen S, Zak M, Fasth A. *Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the wrist region. A descriptive interventional study. Pediatr Rheumatol* 2012;10:11. Available at www.ped-rheum.com/content/10/1/11. Accessed April 21, 2012.)

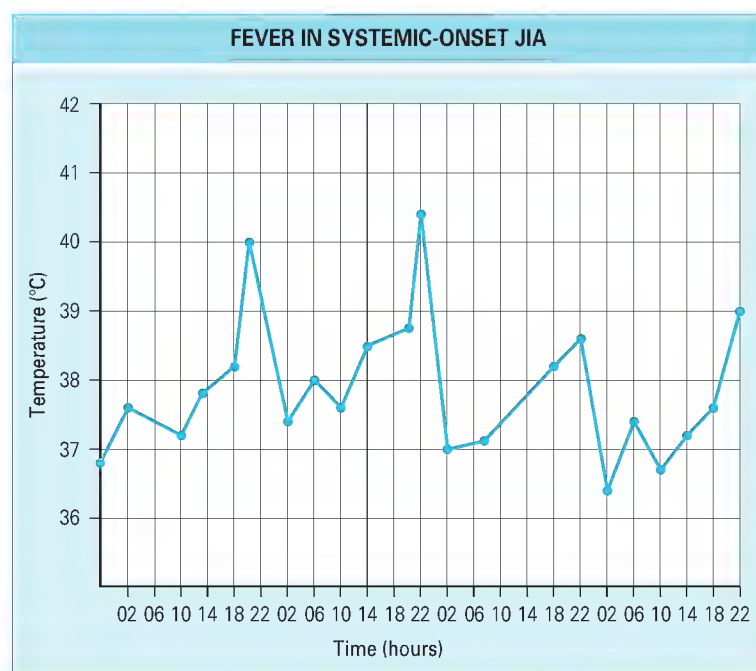


Fig. 101.5 An example of the typical fever curve seen in systemic juvenile idiopathic arthritis (JIA).



Fig. 101.6 The rash of systemic juvenile idiopathic arthritis. Larger lesions are becoming confluent (a). This must be differentiated from erythema marginatum (b), characteristic of the rash seen in rheumatic fever.

of the skin (Köbner phenomenon) or a hot bath and is occasionally pruritic. Generalized lymphadenopathy and hepatosplenomegaly occur in 50% to 75% of patients. The child may complain of abdominal pain secondary to hepatomegaly. Liver enzyme levels may be slightly elevated, although fulminant hepatic failure is rare. Polyserositis is common, with about one third of patients having documented pericarditis (Fig. 101.7). Most pericardial involvement is subclinical. Tamponade and myocarditis rarely occur. Pulmonary disease is equally unusual and manifests as pneumonitis, pleural effusion, or pulmonary fibrosis. Central nervous system involvement with coma and meningitis is very unusual.²⁴

Approximately half of the children with systemic JIA develop polyarthritis within 3 to 12 months of the onset of the fever. The wrists, knees, and ankles are most commonly involved, with the cervical spine, hips, temporomandibular joints, and hands also being affected. Cricoarytenoid arthritis resulting in hoarseness, permanent voice changes, and laryngeal stricture has been reported.²⁵

Macrophage activation syndrome or secondary hemophagocytic lymphohistiocytosis is a serious complication that occurs in about 5% of children with systemic JIA. Macrophage activation syndrome is characterized by the rapid development of fever, rash, and encephalopathy; rapid rise of liver transaminase levels; disseminated intravascular coagulopathy; neutropenia; thrombocytopenia; increased triglyceride levels; low albumin level; and a low ESR associated with hypofibrinogenemia. A coagulopathy is present with an increase in fibrin degradation products and prolonged prothrombin time and partial thromboplastin time. The diagnosis is made clinically and is supported by very high ferritin levels (often more than 10,000 mg/L), soluble transferrin receptor (sCD25), and demonstration of hemophagocytosis in the bone marrow, liver, and/or spleen. Because the mortality has been as high as 50% in some series, prompt treatment with corticosteroids and cyclosporine is necessary and, if there is a poor response, also etoposide or antithymocyte globulin.^{26,27}

Oligoarthritis: persistent and extended

Cases in which fewer than five joints show active disease during the first 6 months of the disease course may be classified into many of the JIA categories depending on additional features. Psoriasis, enthesitis or sacroiliitis, and genetic traits for psoriasis or ankylosing spondylitis are exclusion criteria for oligoarthritis. The disease may instead be categorized as psoriatic arthritis, enthesitis-related arthritis, or undifferentiated arthritis (see later).^{3,28} Most often, however, arthritis in a child with fewer than five actively affected joints fits into the most common category of oligoarticular JIA, which may be further divided into persistent or extended oligoarthritis, according to the number of joints involved after the first 6 months. At least one third of children develop extended oligoarticular disease with five or more joints involved during the disease course.²⁹

The majority of children with oligoarticular JIA are younger than 5 years of age at presentation, with a peak onset between 1 and 3 years of age. Oligoarticular JIA occurs more frequently in girls, with a female-male ratio of 2:1 for the persistent category and 5:1 for the extended category. Commonly, such children are brought to the physician because of a limp⁷;

complaints of pain are infrequent. Typically there are no constitutional signs or symptoms. In the majority of cases laboratory findings are close to normal, with little or no increase in CRP level and ESR and no leukocytosis. If only one joint is involved and the joint is painful and red, a more likely diagnosis is septic arthritis, especially if the child has a fever or there is a marked inflammatory response. The knee is the most commonly affected joint (47%) (Fig. 101.8), followed by the ankle and then either the small joints of the hand or the elbow. Involvement of the temporomandibular joint and cervical spine is also common, whereas involvement of other joints occurs less frequently. Arthritis limited to the hip is extremely rare in this category, and if it is present the diagnosis should be questioned.

The immunofluorescence ANA test yields positive results in 40% to 85% of children with oligoarticular JIA, both persistent and extended, and a positive ANA finding is associated with chronic asymptomatic anterior uveitis. The association with uveitis is particularly strong for girls (younger than 5 years) with ANA-positive arthritis, regardless of number of active joints.⁹

Polyarthritis

Approximately 25% of children with JIA have polyarticular onset with five or more joints involved in the first 6 months of disease. Two categories of polyarthritis are defined depending on the existence of persistent serum IgM RF.

Rheumatoid factor–negative polyarticular juvenile idiopathic arthritis

In RF-negative polyarticular JIA the joints tend to be symmetrically involved, with the knees, wrists, and ankles being most commonly affected. In the hands the metacarpophalangeal and proximal interphalangeal joints are involved, and flexor tenosynovitis is common (Fig. 101.9). The cervical spine is often affected, and occasionally patients have torticollis. Hip and shoulder involvement may occur, but rarely at onset. Systemic features such as fatigue, low-grade fevers, mild hepatosplenomegaly, and anemia may occur.

Rheumatoid factor–positive polyarticular juvenile idiopathic arthritis

Teenagers with early involvement of the small joints, unremitting inflammatory activity, nodules similar to those seen in adult rheumatoid arthritis (RA), and early development of erosions on radiographs are more likely to have IgM RF and ACPAs,¹⁰ disease persistence, and poor outcome. Systemic features are rare, except for fatigue and anemia. The presentation of this category of JIA is very similar to that of seropositive adult RA. Most patients are female and older than age 12 at presentation. Symmetric involvement of the small joints is most typical, including the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints as well as sometimes the distal interphalangeal joints. Large joints tend to be involved only in association with small-joint involvement. Flexor tenosynovitis is common and often results in trigger fingers.



Fig. 101.7 Radiograph of a 3-year-old with systemic juvenile idiopathic arthritis who had pericardial effusion at presentation.

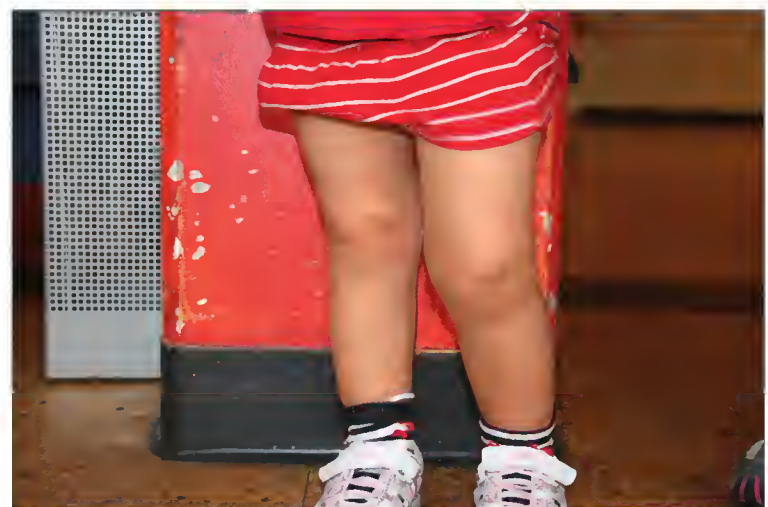


Fig. 101.8 Oligoarticular juvenile idiopathic arthritis in a 2-year-old girl with arthritis in her left knee.



Fig. 101.9 Finger joint involvement. (a) Symmetric involvement of metacarpophalangeal and proximal interphalangeal (PIP) joints typical of polyarticular juvenile idiopathic arthritis (JIA) in a 9-year-old girl. (b) More advanced changes can evolve over time with joint deviations, as in this teenage boy. (c) Asymmetric arthritis with swelling and extension deficit in the fourth PIP joint in a young girl with oligoarticular JIA. (Courtesy Ellen Nordal.)

Psoriatic arthritis

Dactylitis, nail pitting, distal interphalangeal arthritis, and asymmetric RF-negative peripheral arthritis are typical findings in juvenile as well as adult psoriatic arthritis. A significant proportion of children may develop inflammatory back disease, including spondyloarthritis and sacroiliitis. Results of an ANA immunofluorescence test were positive in one third of children fulfilling the ILAR criteria for psoriatic arthritis in one epidemiologic study in Scandinavia.²⁸ Because juvenile psoriatic arthritis is such a heterogeneous category, some have recently also questioned whether psoriasis should define a distinct disease category in JIA.³⁰

Enthesitis-related arthritis

Enthesitis-related arthritis affects boys more than girls and presents most commonly after the age of 9 years.²⁸ Arthritis typically involve the lower extremities, most commonly the knees and ankles, but the hip can also be affected.³¹ Enthesitis, defined by ILAR as “tenderness at the insertion of the tendon, ligament, joint capsule or fascia to bone,”³³ occurs frequently and is commonly seen as plantar fasciitis, Achilles tendinitis, and patellar tendon enthesitis. Enthesitis can be difficult to differentiate from arthritis, especially in a child with back pain. Inflammatory back pain is often seen, defined as “lumbosacral spinal pain at rest with morning stiffness that improves on movement.”³³ Many of these children later develop sacroiliitis and spondyloarthritis (Fig. 101.10).

The enthesitis-related arthritis category in JIA incorporates those conditions traditionally viewed as spondyloarthritis in adults, including juvenile ankylosing spondylitis, the syndrome of seronegative enthesopathy and arthropathy (SEA syndrome), but also arthritis associated with inflammatory bowel disease.³¹

Enthesitis-related arthritis is difficult to diagnose correctly during childhood because some of the features defining the category typically develop over many years of disease, which causes much frustration for the family and physician. The full picture might not be seen until adulthood. Also, this is a category in which pain, especially diffuse back pain, might be the initial symptom bringing the teenager to seek medical advice. The association with HLA-B27 is strong, and those with HLA-B27, a family history of spondyloarthritis, and definite arthritis are more likely to develop a definite spondyloarthritis at follow-up. Iritis, usually acute and symptomatic, occurs in 15% to 25% of children in this group. Another major complication can be severe hip disease, requiring early total hip replacement. In this category, inflammatory bowel disease must be considered if there is a persistent fever associated with the arthritis.

Undifferentiated arthritis

Undifferentiated arthritis is a rather unsatisfactory defined category that results from the goal of the present ILAR classification to form homogeneous categories. Cases are excluded from the other categories either because they fulfill criteria for two or more categories or because an exclusion criterion did not allow them to be put into any of the other categories. In a Scandinavian epidemiologic study using the present ILAR criteria, about 15% of JIA cases could not be classified into any of the other categories.²⁹ Almost

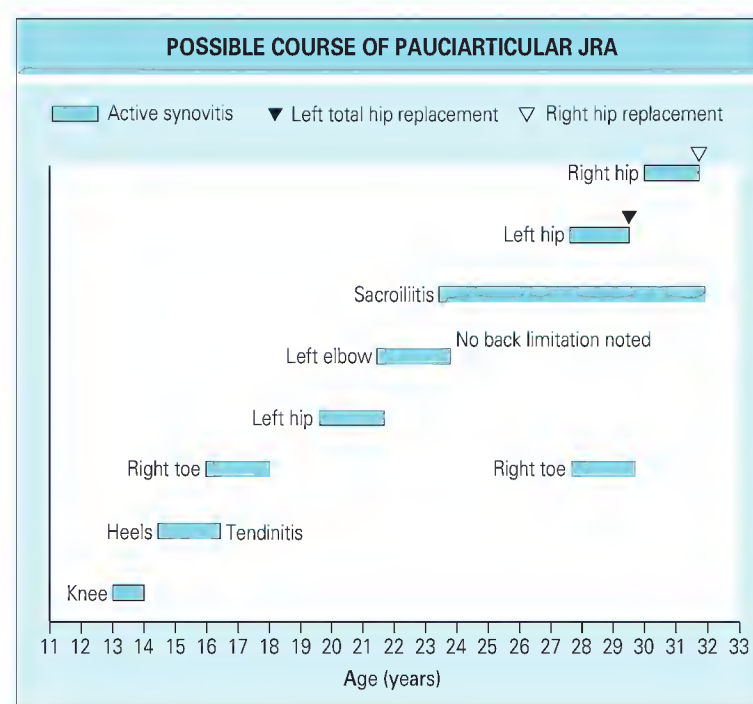


Fig. 101.10 Disease course and joint involvement in enthesitis-related arthritis in a HLA-B27 positive boy.

all of these children had oligoarthritis, extended or persistent, or enthesitis-related arthritis, and the main reason for exclusion was a family history of psoriasis or fulfillment of the criteria for more than one category.

SPECIAL PROBLEMS OF ARTHRITIS IN THE CHILD

Children and adolescents with rheumatic diseases have specific problems that do not pertain to adults. For example, delayed physical development as shown by growth and puberty may occur in all childhood rheumatic diseases and must be carefully monitored. Growth disturbances can be local or general. Osteopenia in the growing child can result in later osteoporosis. The chronic, asymptomatic uveitis that may occur in childhood arthritis is specific to children. Pain and fatigue have different manifestations in children and may severely affect daily life.

Local growth disturbances

Local factors that influence bone growth include cytokines produced as a result of the joint inflammation. The cytokines stimulate osteoblasts to increased epiphyseal growth but also stimulate maturation and closure of

the epiphysis if the condition is very long-standing. Also, muscle spasm, capsular and ligamentous contracture or rupture, destructive synovitis, erosion of articular surfaces, and subluxation of articular surfaces can influence local growth.

Knee

The most frequent site of overgrowth is the inflamed knee. The result is leg-length inequality, with the longer leg on the side of the involved knee, particularly if the disease begins before the age of 3 years (see Fig. 101.8).³² To prevent functional scoliosis shoe lifts can be used to equalize the difference in leg length. Valgus deformity and atrophy of the muscles in the affected thigh might be seen as a complication of long-standing knee arthritis, especially in the youngest children. Occasionally, the local growth disturbance results in early epiphyseal closure, causing a permanently shorter leg on the side of the involved knee (Fig. 101.11).

Ankle

Valgus deformity in the ankle is a common sequela of arthritis in the talocrural, subtalar, or tarsal joints (Fig. 101.12). These changes may be reversible in a growing child if the arthritis responds to treatment. Pain at walking may otherwise limit physical function, although correction of the deformity by orthopedic soles is usually helpful.

Wrist and hand

Another common joint to experience growth abnormalities is the wrist. In contrast to the knee, many growth defects seen radiographically in the wrist

are not observed clinically. The wrist can show increased bone age (see Fig. 101.1) and carpal bone fusion with long-standing involvement. Growth defects are also seen in the ulna, the carpal length, and the fourth and fifth metacarpal bones. Because of epiphyseal undergrowth, the ulna can become shorter than the radius, which results in ulnar migration of the carpal bones, subluxation, and severe deformity. Brachydactyly can occur in the fingers or toes as a result of early epiphyseal closure (see Fig. 101.1). In polyarticular disease, especially if RF positive, radiologic abnormalities of the wrist and hand can already be seen at the time of diagnosis.³³

Hip

Growth abnormalities in the hip include lack of growth of the iliac bone and a coxa valga deformity with widening of the femoral neck and/or premature fusion leading to stunting of the femoral neck.

Cervical spine

The cervical spine can develop growth abnormalities that result in apophyseal joint space narrowing and bony ankylosis (especially C2-C3) (Fig. 101.13). Similar findings are not seen in the lumbar spine, but compression fractures of the thoracic spine occur, particularly in children taking corticosteroids.

Temporomandibular joint

Temporomandibular joint involvement is very common and is often overlooked because young children have difficulties describing symptoms in the area. Thus clinical signs of mandibular dysfunction such as reduced opening of the mouth, TMJ crepitations, and restricted horizontal movements are important to look for. Even a thorough evaluation still might not reveal the early signs of condylar lesions, which can present early, can progress insidiously, and might lead to malocclusion and severely alter the craniofacial profile. Unilateral TMJ disease can result in deviation to the affected side of the jaw on opening the mouth resulting in facial asymmetry due to mandibular hypoplasia (Figs. 101.14 and 101.15). TMJ involvement occurs in all categories of JIA. Regular evaluation of all children with JIA by a pediatric dentist or orthodontist is therefore recommended to enable early detection and intervention.³⁴

General growth disturbance

Generalized growth disturbance has been observed and is related to active disease intensity and duration. During quiescent periods of the disease, height can return to normal in 2 or 3 years if premature closure of the epiphysis has not occurred.



Fig. 101.11 Oligoarticular juvenile idiopathic arthritis with arthritis in the right ankle. (a) A shorter leg length from the knee to the ankle is seen. (b) The right foot is smaller, with underdevelopment of the right forefoot due to disuse.



Fig. 101.12 Valgus deformity in the left ankle due to longstanding arthritis in a 5-year-old girl with juvenile idiopathic arthritis since age 21 months. (Courtesy Marite Rygg.)



Fig. 101.13 Systemic juvenile idiopathic arthritis in a child who had a polyarticular course. Her neck shows apophyseal fusion of C2 to C4 and undergrowth of adjacent vertebrae.



Fig. 101.14 Temporomandibular joint involvement. Note growth failure of lower jaw (a) and malocclusion on the radiograph (b).

The cause of delayed growth is unclear, but it is tightly linked to the level of general inflammation. Studies suggest that severe weight loss or lack of weight gain may also contribute to the lack of growth. Nutritional studies have suggested that decreased caloric intake, increased metabolic needs beyond recommended daily requirements, or lack of essential vitamins can result in decreased weight and growth velocity. Even today with better control of the disease, 5% to 10% of children with JIA are estimated to be growth restricted,^{35,37} mainly patients with unremitting systemic, polyarticular, or extended oligoarticular disease. Corticosteroid therapy also inhibits growth, but usually not skeletal maturation (Fig. 101.16). Growth retardation is likely to occur with corticosteroid dosages higher than 5 mg/m²/day (corresponding to about 0.125 mg/kg/day) for 6 months or longer, but individual tolerance may vary.³⁸

Levels of growth hormone (GH) and insulin-like growth factors 1 and 2 (IGF-1, IGF-2) are usually normal but occasionally reduced. Levels of IGF-1 have been found to be inversely correlated with interleukin-6 levels in systemic disease.³⁹ GH has been given to children with JIA with normal GH levels and has resulted in increased mean height velocity. Response to GH is best when the disease is inactive and no or very low doses of corticosteroids are used.⁴⁰ Careful monitoring of the growth of the child with JIA



Fig. 101.15 Failure of development of the lower jaw 5 years after onset of systemic juvenile idiopathic arthritis. The neck is short and slightly flexed.

is mandatory in the follow-up, and when reduced growth is assessed, it is also important to evaluate the nutritional status of the child.

Osteopenia

Osteopenia, or low bone mass for age, is a well-known complication of JIA. An important determinant of future fracture risk is the attainment of a high peak bone mass, which is completed during adolescence. Peak bone mass is determined by genetic as well as environmental factors, such as nutrition, exercise, and levels of hormones, especially estrogen. In children with JIA, active disease, poor nutrition such as low calcium and vitamin D intake, use of drugs such as corticosteroids, lack of exercise, and delayed menarche all can affect the peak bone mass.⁴¹

Uveitis

According to data from population-based JIA series, uveitis occurs in 3% to 21% of patients.^{29,42,43} In the majority of cases the uveitis is “silent” and asymptomatic. Uveitis occurs more commonly in children with early-onset arthritis, and 50% to 80% test positive for ANAs by immunofluorescence. Interestingly, some geographic areas (e.g., Costa Rica, India, and South Africa) report very few or no patients with ANA-positive oligoarthritis associated with uveitis,⁴⁴ which suggests true differences in disease manifestations pertaining to immunogenetics or environmental factors, or a combination of both. Uveitis is rare among children with systemic and polyarticular RF-positive arthritis. Symptomatic uveitis occurs more often in boys and is associated with HLA-B27 and enthesitis-related arthritis.⁴³ Most cases of symptomatic uveitis are acute and episodic, but the uveitis may take a chronic course.

According to population-based data, the median age at onset of JIA associated with uveitis is 5 years (range, 1 to 16 years), that is, lower than the age at onset in the total cohort of JIA. In about 80% of patients uveitis appears within the first 4 years after arthritis onset, but late cases may occur.^{9,43,45} The uveitis is bilateral in about half of the cases.

Because the uveitis is mostly asymptomatic, a slit-lamp examination is necessary in all children with JIA for early detection of eye involvement. A cloudy light path looking like a light shaft in a smoky room is seen when the anterior chamber contains inflammatory cells and fibrin debris. The iris may demonstrate irregularities due to posterior synechiae when a bright light shines into the pupil (Fig. 101.17). The outcome is worse when uveitis occurs before or at the onset of JIA and when the uveitis is severe at onset and continually active.⁴⁶ Complications associated with ongoing active inflammation and prolonged local corticosteroid treatment are synechiae, band keratopathy, cataracts, glaucoma, and finally macular edema, phthisis, and loss of vision.⁴⁶ To avoid sight-threatening complications, the American Academy of Pediatrics Sections on Rheumatology and Ophthalmology have produced recommendations for regular eye examinations (Table 101.4) in children with JIA.⁴⁷

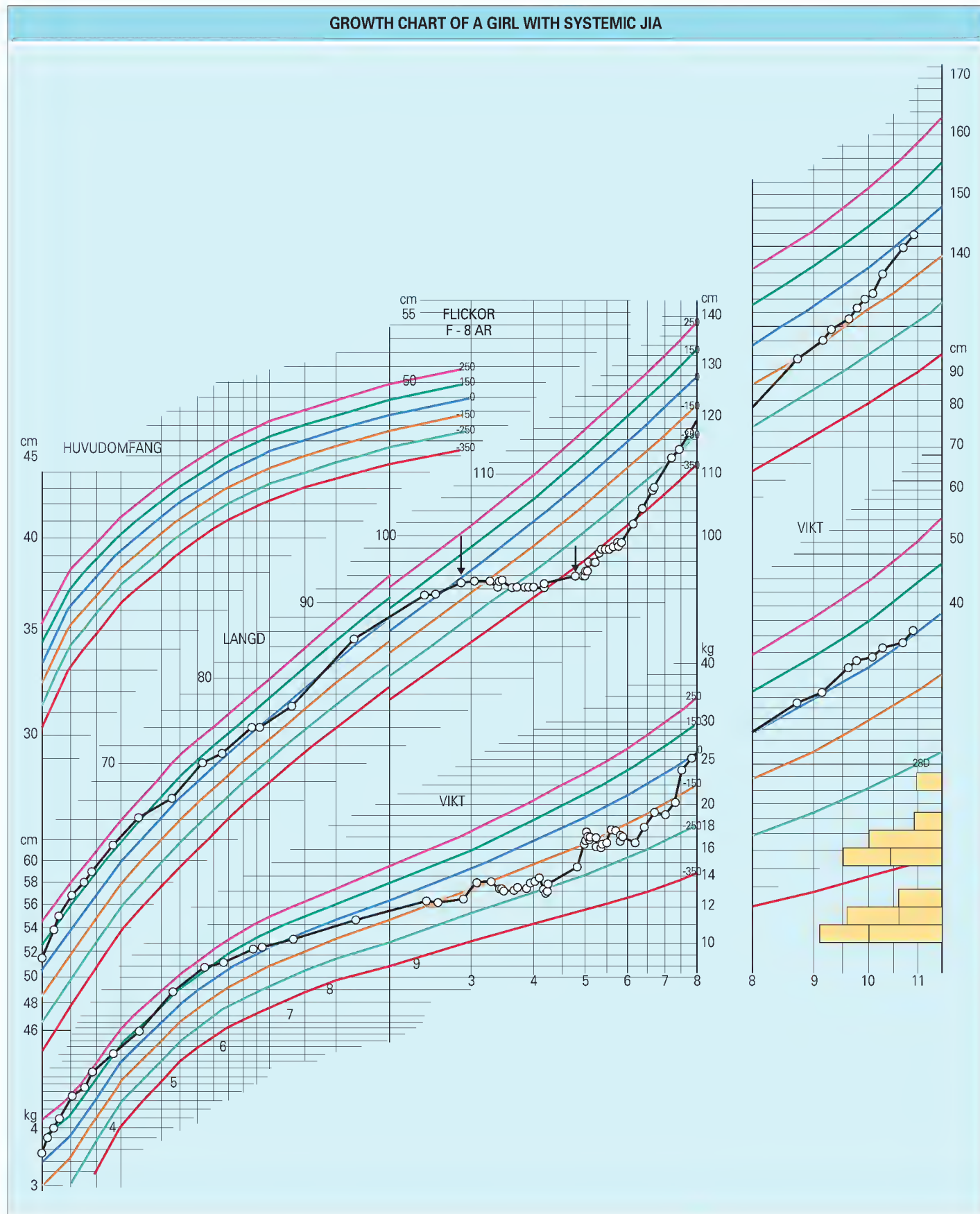


Fig. 101.16 Inhibition of growth by corticosteroid therapy in a girl with systemic juvenile idiopathic arthritis (JIA). First arrow indicates start of corticosteroid treatment. Second arrow indicates time of autologous stem cell transplantation.

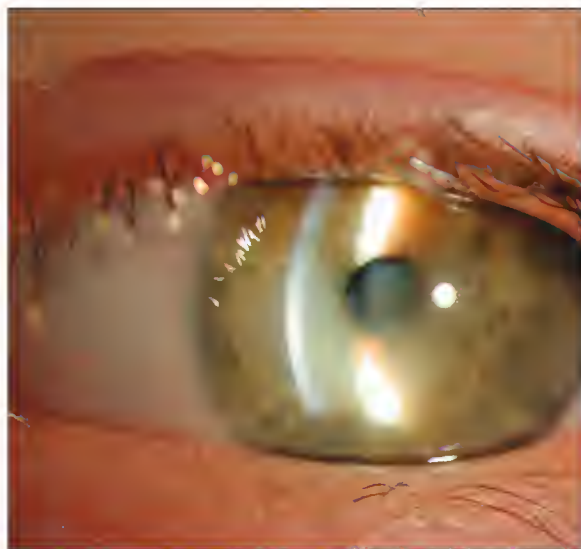


Fig. 101.17 Chronic anterior uveitis with band keratopathy and keratic precipitates, flair in the anterior chamber, cataract, and irregular pupil due to synechiae. Note that the eye of this 5-year-old boy is not red. (Courtesy Terje Christoffersen.)

TABLE 101.4
American Academy of Pediatrics guidelines for screening eye examinations in juvenile rheumatoid arthritis

Type	ANA	Age at onset (years)	Disease duration (years)	Risk category	Examination frequency (months)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4 ≤ 7	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
Systemic disease	–	≤6	NA	Low	12
	NA	NA	NA	Low	12

Recommendations for follow-up continue through childhood and adolescence in the 2006 guidelines.⁴⁷

ANA, antinuclear antibodies; NA, not applicable.

Pain

Pain is a frequent complaint in all children, and musculoskeletal pain, headache, and abdominal pain are the most frequent types.⁴⁸ Girls and older children experience pain more often than boys and younger children, and the majority of adolescents with chronic pain report some subjective disability. Self-reported pain is influenced by previous experience, development, and beliefs as well as life-style factors, anxiety and depression, and family function.^{49,50}

Sällfors and coworkers⁵¹ found a strong influence of experienced pain in the daily life of children with juvenile arthritis. Pain created uncertainty, especially in older children, because they could never predict if it would be a “good” day with little pain or a “terrible” day with severe pain. The uncertainty came from the many social consequences, such as not being able to predict whether he or she would be able to go to school that day, whether it would be possible to take part in physical education, as well as from the increased dependence on parents at an age when increasing independence is the norm. Also, the fact that pain cannot be seen made obtaining understanding from peers difficult.

Sleep disturbance and fatigue

Sleep is of primary importance for physical and intellectual growth, and sleep disturbances that begin in childhood may persist into adulthood. Studies show that sleep disturbances are common in children with JIA and that sleep patterns in these children are different in multiple sleep domains

compared with patterns in children without disease.^{52,53} The cause is multifactorial but leads to a common endpoint of sleep fragmentation and/or deprivation. Factors that may contribute include anxiety, pain, and in rare cases breathing problems caused by micrognathia and cervical spine compromise, and autonomic nervous system imbalance. Children's self-reports reveal that sleep disturbance correlates well with pain, whereas parents' reports do not show such a correlation. This emphasizes both the importance of listening to the child's own experience and the need for good pain management programs. Sleep disturbance may lead to daytime fatigue and irritability, which in turn have effects on social life and school performance. It may also interfere with GH secretion and thus affect growth.⁵⁴

Fatigue is acknowledged as an important manifestation of rheumatic disease in adults and has also received increasing attention in children. Varni and associates⁵⁵ studied the use of the PedsQL Multidimensional Fatigue Scale in pediatric patients with rheumatic diseases and confirmed that the instrument has good validity and reliability. Clinical follow-up studies using this instrument show that fatigue is prevalent among children with JIA.⁵³ However, the findings of the instrument should be interpreted with care if the child reports pain because this may act as an important confounder and pain is shown to interfere significantly with the perception of fatigue.⁵⁶

OUTCOME

JIA may have considerable impact on physical function and psychosocial well-being throughout childhood and into adult life. To what degree the early, more aggressive, and tailored treatment of today improves outcome for the child with JIA compared with that noted in previous reports remains to be seen. Outcome is a complex phenomenon that needs to be viewed from many perspectives. Most studies have focused on traditional disease-centered outcomes, including clinical remission, physical disability, and structural damage. To get a true picture of the impact of JIA, a broader perspective that includes psychosocial well-being and quality of life as well as socioeconomic attainments must be adopted.⁵⁷ To better categorize outcome, the pediatric medical community has developed standardized outcome measures to objectively define and monitor disease activity, disease improvement, flare, and damage.⁵⁸ The Juvenile Arthritis Disease Activity Score (JADAS) is a validated measure of disease activity.⁵⁹⁻⁶¹ It is a simple composite score consisting of the patient/parent and physician global assessment, the number of active joints, and the ESR or CRP level. These same variables, together with results on the Child Health Assessment Questionnaire (CHAQ),⁶² make up the core set of outcome variables.⁵⁸ The Juvenile Arthritis Damage Index (JADI) is another validated tool aiming to score all forms of long-term articular and extraarticular morbidity in patients with JIA.^{63,64} New tools to monitor disease activity and improvement are likely to allow individually tailored early treatment with drugs demonstrated to decrease joint destruction and thereby improve the long-term outcome of JIA.

Remission

A common misconception has been that most childhood arthritis disappears in adulthood. However, ongoing or intermittent disease activity into adulthood has been found in more than half of the children in several long-term follow-up studies.^{29,37,65} The outcome of JIA is variable depending on the category and course of disease. The remission rate is highest in persistent oligoarticular arthritis (50% to 80%), whereas it is lower in extended oligoarticular arthritis and polyarticular disease (20% to 30%) and is especially low among RF-positive patients.^{7,29,35,37,66} Remission rates in studies of systemic disease are more variable (0% to 80%), probably owing to the heterogeneity of this category.^{29,35,37} The long-term remission rates in enthesitis-related arthritis as well as in juvenile psoriatic arthritis seem to be low (0% to 30% and 30% to 40%, respectively).^{7,35,37,66-68}

Continuous activity and damage

The most consistent risk factors for continued disease activity in JIA are polyarticular and extended oligoarticular disease, especially in females; elevated inflammatory markers at onset; and RF positivity. Predictors for disability and joint damage are mostly the same factors (i.e., continuous disease activity, polyarticular course, female sex, and RF positivity).⁶⁸⁻⁷⁰ Attainment of disease inactivity at least once in the first 5 years is found to be associated with less long-term joint damage and a trend toward less functional impairment.⁶⁹ In systemic JIA, children with disease onset before age 5 years, accelerated radiologic changes, pericarditis, and thrombocytosis are at higher risk for having a poor functional outcome.⁷¹

Vision

A major cause of morbidity in JIA is uveitis. Early detection and intensive treatment seem to have improved the prognosis for vision considerably. In population-based studies in Finland and the United States (Minnesota), the prognosis regarding blindness and severe vision loss is good. In the Finnish study, at a median follow-up of 7 years, one third of patients still had active uveitis, but only 3% had severe visual loss. In the study in Olmsted County, Minnesota, only 3% developed uveitis, and none had visual impairment after 8 to 24 years.^{42,72} The course of uveitis is unrelated to the course of the arthritis and may persist after arthritis has remitted. The importance of screening for uveitis (see Table 101.4) and early and intensive treatment of inflammation and its complications must be stressed. However, a few patients who do not respond even to the most intensive treatments available today still develop severely impaired vision.

Mortality

The most recent studies show no increased mortality rate in JIA, whereas in early reports mortality ranged from 2% to 7%.^{7,73,74} A small but significant increased risk of cancer is found in large epidemiologic studies of JIA. The increased risk of cardiovascular disease seen in adult rheumatic arthritis has so far not been verified in children, but there are indications of blood vessel endothelial dysfunction that may be attributed to inflammation or medications.⁷⁵ Today amyloidosis is a very rare complication of JIA in the systemic category, probably owing to the more aggressive antiinflammatory therapy given. Amyloidosis should be suspected in patients with persistent disease activity who develop proteinuria and a rising ESR with falling hemoglobin and serum albumin levels.

Functional outcome and disability

The functional outcome of JIA seems to have improved considerably over the past decades. The proportion of patients classified in Steinbrocker class III or IV in studies published after 1990 is 3% to 15%.⁷⁶ The decline in the number of patients with severe functional disability is likely due to early and more active treatment with disease-modifying antirheumatic drugs such

as methotrexate and biologic agents, treatment with intraarticular corticosteroids, and implementation of team-based comprehensive care. However, changes in the natural history of the disease and better general health status in children are possible contributing factors.⁶⁵

Functional outcomes in individual disease categories are fairly distinct when evaluated by the CHAQ.⁵⁸ Overall, 80% of patients with persistent oligoarticular JIA report no difficulties at 15-year follow-up.³⁷ However, of those with an oligoarticular extended or polyarticular arthritis, more than half develop some functional disability, and it is mainly in these categories that those with the most severe functional limitations are found, with highest rates among RF-positive patients.⁶⁶ Poor functional outcome can also be seen in patients with systemic JIA who develop polyarticular disease.

Even with aggressive treatment, a small proportion of children with JIA continue to experience poor health and psychosocial and educational limitations. A 25-year population-based follow-up study comparing juvenile rheumatoid arthritis patients with sex- and age-matched peers with no history of the disease showed that those with juvenile rheumatoid arthritis had greater disability, more pain, increased fatigue, poorer health perception, decreased physical functioning, and less involvement in exercise.⁷⁷ School attendance and participation in social activities are often influenced by the disease, but the majority of long-term follow-up studies show that educational levels and spousal relationships are similar to those of healthy control subjects.^{35,78-80} Some studies have found a lower employment rate among adults with juvenile-onset arthritis than in the background population.^{80,81}

Transition of care

Many young people have continued active disease into adulthood, and this group needs continuity of care in the transition from child-centered to adult-oriented systems. Young people should be given the chance to express their views and should be seen without their parents at visits.⁸² Continuity in health personnel, individualized timing of information provision and transition, and increasing self-advocacy over several years are important elements of a successful transition process, and this process needs time.^{83,84} Implementation of a structured and evidence-based transitional care program is recommended because it has been shown to increase health-related quality of life in adolescents moving from pediatric to adult care.⁸⁵

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Etiology and pathogenesis of juvenile idiopathic arthritis

■ RACHELLE DONN

- Juvenile idiopathic arthritis (JIA) encompasses several subgroups that have distinct clinical, immunologic, and genetic differences.
- JIA subgroups are each complex traits with contributions from both genetic and environmental parameters.
- Synovium and cartilage are both affected. Triggers for initiation and progression of the pathology that is manifested as JIA have not been identified.
- Association and linkage to HLA loci have been confirmed for certain JIA subgroups.
- A limited number of non-HLA loci have been shown to be significant in conferring susceptibility to JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA)* is the most common rheumatic disease of childhood. It encompasses a heterogeneous group of chronic arthropathies, all of which share persistent idiopathic inflammation of one or more synovial joints. The subtypes of JIA differ in their clinical manifestations, prognosis, and specific autoimmune characteristics.

Classification of chronic arthritis of childhood onset remains problematic. Different classifications exist in the literature, be it International League of Associations for Rheumatology (JIA), European Leagues Against Rheumatism (juvenile chronic arthritis [JCA]), or American College of Rheumatology (juvenile rheumatoid arthritis [JRA]) naming conventions (see Chapter 100). This makes comparisons of the research literature difficult.

PATHOLOGY

JIA is an inflammatory disorder that primarily affects synovial joints.

The clinical characteristics of joint involvement vary across the different JIA subgroups but are generally manifested as swelling, stiffness, pain, or loss of function of the affected joint (or any combination). The disease process of JIA includes synovial hyperplasia causing soft tissue swelling, joint effusion, and cartilage destruction, which result in bone erosions. Lymphocytes, plasma cells, macrophages, and dendritic cells are all present in increased number within the inflamed JIA joint.² The typical manifestation of oligoarthritis is shown in Figure 102.1, together with a schematic representation of the pathology within the JIA-affected joint.

The immunopathogenic mechanisms underlying JIA have been the subject of intensive study but have not yet been elucidated. The detection of T cells and chronic synovial inflammation has indicated cellular mediation, whereas the finding of immune complexes and complement has suggested a possible B-cell-mediated response.

Synovial fluid

The volume of synovial fluid in affected joints is increased in JIA, with viscosity being decreased mainly because of reduced concentrations of hyaluronic acid. Synovial fluid contains various inflammatory cells, including

neutrophils, plasma cells, dendritic cells, and a high proportion of T cells expressing markers of activation.³ These cells are most likely to extravasate from the inflamed synovial lining. Mediators of inflammation such as cytokines and cleavage products of the complement system are also abundant.

Synovial tissue

One of the hallmarks of the pathology of JIA and, in particular, rheumatoid factor–positive (RF+) polyarticular JIA is the tumor-like expansion of inflamed synovial tissue, or pannus, which causes much of the joint damage in this disease.⁴ With progression of the disease, the pannus spreads over the synovial space and adheres to intraarticular cartilage. It is in the areas of pannus-cartilage junctions that the cartilage eventually degrades (Fig. 102.2). Such expansion results from invasion of the synovial tissue by inflammatory cells recruited from the peripheral circulation and the proliferation of synoviocytes.

Cartilage

Cartilage is a primary target organ that is affected as part of the pathogenic process of JIA.^{5–7} Superficial cartilage thinning is a feature of early and untreated JIA. Complete cartilage destruction and cartilage erosions leading to bone erosions can occur with long-standing disease.^{8,9} Magnetic resonance imaging enhanced with gadolinium tetraazacyclododecane tetraacetic acid increases sensitivity for detection of the inflammatory changes in JIA¹⁰ (Fig. 102.3).

T cells and juvenile idiopathic arthritis

CD4+ T lymphocytes are the predominant cell population in JRA synovium and exhibit the phenotypic and functional characteristic of cells that have previously undergone activation *in vivo*.⁴ These characteristics include expression of interleukin-2 (IL-2) receptors (CD25), early activation antigen CD69, CD45RO (memory phenotype), very late activation antigen type 1 (VLA-1), and HLA class II antigens.³ It has been suggested that such activation might be induced by an autoantigen located in the inflamed joints.

Analysis of several experimental antigen-driven models has shown that antigen-specific T cells often make up only a very small proportion of all T cells present at the site of the immune response, thus suggesting that most of the other cells are recruited in a nonspecific manner. Extrapolation of these data to the pathogenesis of JRA suggests that the numbers of T cells critical for an autoimmune response in inflamed joints may be very small.

Regulatory T cells, type 17 helper T cells, and juvenile idiopathic arthritis

CD4+ helper T (Th) cells help regulate the immune response. Characterization of effector Th cell subsets by their differential cytokine production has resulted in the Th1-Th2 paradigm. Th1 cells produce interferon- γ and regulate antigen presentation and immunity against intracellular pathogens. Th2 cells produce IL-4, IL-5, and IL-13 and mediate some humoral responses and immunity against parasites. However, observations by several different groups have described the proinflammatory cytokines IL-17 and IL-17F to be expressed by distinct Th cells that did not express either interferon- γ or IL-4. This has resulted in the discovery of Th17 cells as a Th lineage independent of Th1 or Th2 cells.

Regulatory T (Treg) cells have the phenotype CD4+CD25+. These spontaneously occurring T cells can actively and dominantly prevent the activation and effector function of autoreactive T cells that escape other mechanisms of tolerance. A role for CD4+CD25+ Treg cells in the

*This chapter essentially focuses on JIA (as defined by the International League of Associations for Rheumatology¹) but refers to the terms cited in the original papers throughout.

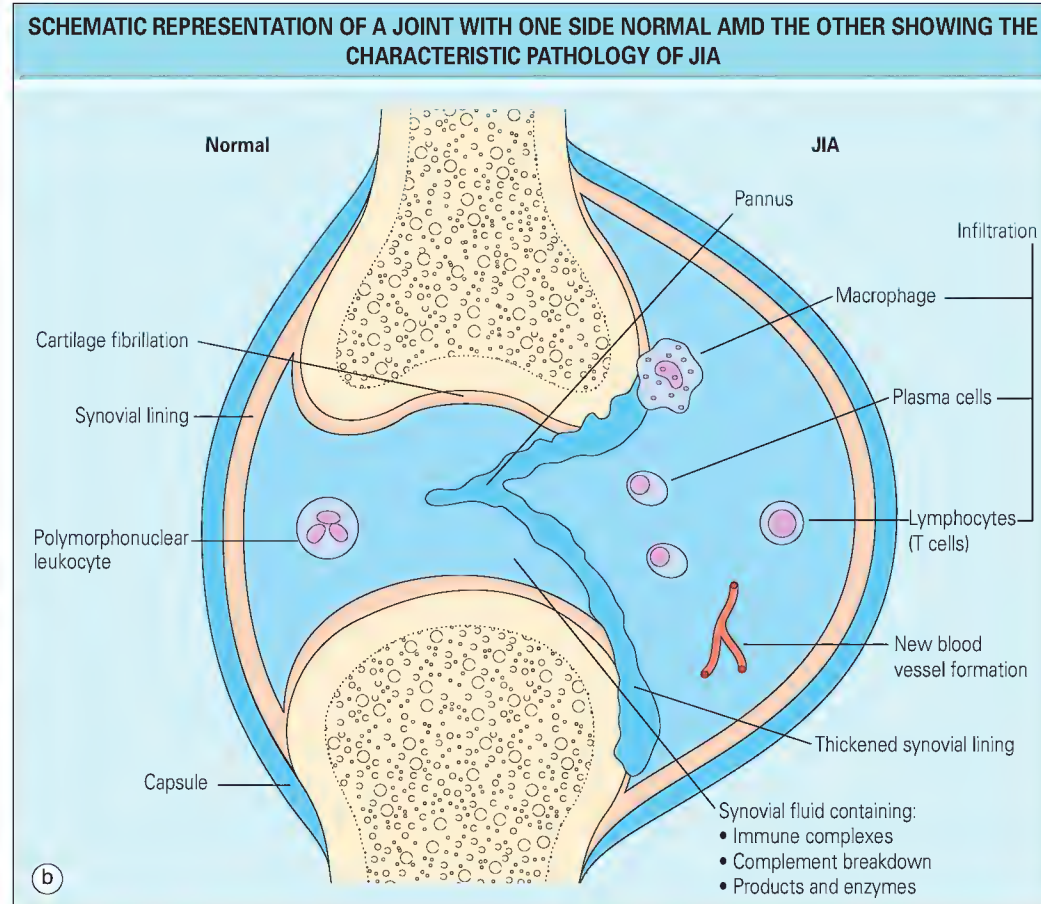


Fig. 102.1 (a) Typical manifestation of oligoarthritis. (b) Joint in which one side is normal and the other shows the characteristic pathology of juvenile idiopathic arthritis (JIA). (a, Original from <http://pediatric-orthopedics.org/from-toddler-to-adolescence/41-juvenile-rheumatoid-arthritis.html>; b, modified from Chapel H, Haeney M, Misbah S, et al. *Essentials of clinical immunology*. Oxford: Blackwell Science; 1999.)

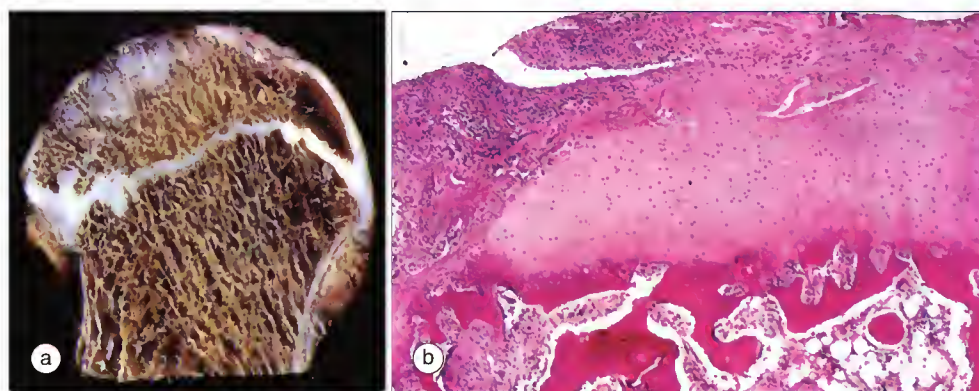


Fig. 102.2 Destructive inflammatory pannus in juvenile rheumatoid arthritis (JRA). (a) Photograph of a frontal section taken through the femoral head of a child with JRA. Extensive destruction of articular cartilage has occurred, with associated erosion of subchondral bone. (b) Photomicrograph of a section taken at the articular margin of the specimen demonstrated in (a) showing a destructive inflammatory pannus extending onto the articular surface. (With permission from Bullough PG. *Orthopaedic pathology*. 3rd ed. London: Mosby-Wolfe; 1997.)

pathogenesis of JIA has been considered by a number of groups.¹¹⁻¹⁴ More recently, a role of IL-17-producing T cells has been shown. IL-17+ T cells are enriched within the joints of children with JIA, and the number of such cells was found to be higher in patients with extended oligoarthritis than in those with the milder persistent oligoarthritis. An inverse relationship between IL-17+ T cells and Fox3P+ Treg cells was found.¹⁵ This suggests that Th17 cells are contributing to the joint pathology of JIA and that the balance between IL-17+ T cells and Treg cells may influence disease outcome.

Macrophage and fibroblast contribution to the pathogenesis of juvenile idiopathic arthritis

Increased numbers of macrophages and dendritic cells and proliferation of fibroblast-like and macrophage-like synoviocytes are typical features of JRA

synovium.⁴ The abundance of cytokines secreted by these cells provides further evidence for a major role of these cells in perpetuation of the synovial inflammation. Martini and colleagues¹⁶ in 1986 noted high spontaneous production of IL-1 by mononuclear cells derived from the peripheral blood of patients with juvenile arthritis. More recently, an abundance of IL-1-producing macrophages has also been demonstrated in inflamed JRA synovial tissue.¹⁷

Analysis of tumor necrosis factor (TNF) expression and the distribution of TNF receptors in JRA synovial tissues provided strong evidence for the role of both TNF- α and TNF- β in amplification of the synovial inflammation in JRA.¹⁸ Numerous cells staining for TNF- α were found in the majority of synovial tissue samples, and the pattern of distribution of TNF- α cells was similar to the distribution of macrophages. The level of expression of TNF- α correlated closely with the degree of inflammatory infiltration of the synovial membrane.



Fig. 102.3 A T2-weighted fat-suppressed image in a 10-year-old child shows high signal from both the synovium and synovial fluid, which are difficult to distinguish. Numerous erosions, cartilage loss, and fat pad irregularity are seen on this image. (Image reproduced, with permission, from Gardner-Medwin J, Southwood T. *Current developments in juvenile arthritis. Topical Reviews No. 5, Reports on Rheumatic Diseases, Series 4, 2001. Published by the Arthritis Research Campaign. Available at www.arc.org.uk*.)

IL-6, another macrophage-derived product, has been consistently found in the synovial fluid of patients with JIA. More importantly, in systemic-onset JIA, IL-6 concentrations are increased not only in the synovial compartment but also in serum, and serum concentrations of IL-6 protein correlate with the extent of joint involvement and peripheral thrombocytosis. High levels of expression of IL-6 in synovial tissue samples have been shown to distinguish patients with systemic JRA, even at later stages of the disease.^{19,20}

B-cell contribution to the pathogenesis of juvenile idiopathic arthritis

B-cell activity

Although macrophages and T cells are usually more numerous in inflamed synovial tissue, B-cell activity also appears to be enhanced in both peripheral blood and the synovial compartment. Lindblad and associates²¹ described synovial tissue specimens from patients with juvenile arthritis that contained significantly increased numbers of focally aggregated immunoglobulin-synthesizing cells. As a consequence of increased B-cell activity, hyperglobulinemia and circulating immune complexes, antinuclear antibodies (ANAs), and RFs are common findings in many patients with JIA.

Rheumatoid factor (RF)

RFs, or autoantibodies directed against the Fc region of human IgG, are found in the serum and synovial fluid of the majority of patients with rheumatoid arthritis (RA). RF can be detected only rarely in patients with JIA by the classic Rose-Waaler reaction or latex fixation method, although the probability of finding RF increases with the age and duration of the disease. Allen and Kunkel²² demonstrated a so-called hidden RF defined as IgM 19S antiglobulin. This antiglobulin is “hidden” because of its occupied binding sites. Gel filtration at acid pH dissociates IgM from IgG and allows IgM RF to fix complement in hemolytic assays. This technique makes it possible to detect the presence of RF in a much larger proportion of patients with JIA, specifically the polyarticular subgroup.

Anti-cyclic citrullinated peptide antibodies

Citrulline is a translational modification of the amino acid arginine by peptidyl arginine deiminase (PAD). Citrulline becomes part of a protein following posttranslational modification by PAD enzymes. Antibodies to citrullinated proteins have been shown to aid in the determination of disease prognosis in adult patients with RA. The autoantibody system

involved includes antiperinuclear factor, antikeratin antibodies, antifilaggrin antibodies, anti-citrullinated fibrin antibodies, and anti-Sa (citrullinated vimentin) antibodies. A number of studies have now evaluated anti-cyclic citrullinated peptide (anti-CCP) antibody levels in patients with JIA. These studies show that anti-CCP positivity is significantly raised only in children with RF+ polyarticular JIA. Specifically, Ferucci and colleagues²³ found anti-CCP antibody formation in HLA-DR4+ cases, and the anti-CCP antibodies were associated with polyarticular onset and erosive disease.

Antinuclear antibodies (ANAs)

The reported incidence of ANAs in patients with juvenile arthritis varies from 4% to 88%, depending on the clinical subtype and the laboratory technique used.²⁴ ANAs are uncommon with systemic-onset disease, whereas more than 50% of children with oligoarticular JCA have ANAs in their serum. Children who are ANA+ carry an especially high risk for the development of chronic anterior uveitis.

The full specificity of these antibodies remains to be determined. Some studies have indicated that ANAs in most patients are directed to a ribonucleoprotein that requires both RNA and protein components for antigenic integrity. Szer and coworkers²⁵ concluded that ANA specificity profiles were highly individual and did not appear to correlate with disease subtype or activity. Several studies have revealed that antibodies to many antigens typical of other rheumatic diseases—for example, extractable nuclear protein, centromere proteins, scleroderma Scl-70, Ro, La, and double-stranded DNA—are generally absent in JIA. More recently, antibodies to the 45-kDa DEK nuclear antigen, a putative oncoprotein, have been associated with the oligoarticular type of JCA, particularly in patients with a history of iridocyclitis. However, the presence of these antibodies does not appear to be limited to or specific for JIA.

GENETIC FACTORS

Genetic epidemiology

Evidence for a genetic component of a disease can come from a variety of sources, such as twin, family, or case-control association studies. The degree of disease concordance in monozygotic (MZ) twins gives an indication of the level of involvement of genetic factors within a given disease. An alternative estimate of the genetic component of a disease can be obtained from family studies by using the sibling recurrence risk, or lambda *s* (λ_s), calculated as the prevalence of the disease in siblings of affected individuals divided by the prevalence of the disease in the general population.

The largest study of both affected sibling pairs (ASPs) and twins with JRA comes from the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS)-sponsored Research Registry for JRA. Of 118 ASPs on the register in 2000, there were 14 pairs of twins in which both twins had arthritis.²⁶ One pair consisted of a girl with polyarticular JRA and a boy with pauciarticular JRA. The other 13 pairs (11 MZ and 2 of unknown zygosity) were concordant for gender (9 female, 4 male), disease onset (10 pauciarticular, 3 polyarticular), and disease course (8 pauciarticular, 5 polyarticular).

In a Finnish study of JIA multicase families, eight sets of twins were identified, two of which were concordant for arthritis. A concordance rate of 25% for a disease with a population prevalence of 1 per 1000 implies a staggering relative risk of 250 for JIA in an MZ twin.²⁷ By comparison, for adult RA the risk to an MZ twin has been reported to be 12 to 62 (reviewed in reference 28).

As noted, the largest series of ASPs has been collected as part of NIAMS' JRA registry. In 1997 the registry contained a series of 71 ASPs; 63% were concordant for gender and 76% for onset type, higher than expected based on comparisons with non-ASP populations. This study gave an estimate of the λ_s for JRA of approximately 15, a value similar to that seen with insulin-dependent diabetes mellitus and multiple sclerosis. It also provided evidence that this value is likely to differ between subtypes, with the strongest genetic component being attributable to the pauciarticular JRA subtype.^{29,30} The most recent report from the registry includes 183 ASPs from 164 families, 19 of which are twin pairs.³¹ The degree of disease-onset-type concordance between the ASPs is relatively high, 53% concordant for pauciarticular onset and 19% for polyarticular onset. The concordance is, however, markedly less for systemic-onset disease. The clinical manifestations seen in the ASPs are very similar to those of a comparative simplex JRA study population, with the exception of the number of affected joints at the onset of JRA in the polyarticular-onset disease group.³¹ Among the ASPs, age at the onset of JRA (sibling 1 versus sibling 2) was not significantly different. However, the disease does not develop in ASPs at the same point in real time (mean

real-time difference of 5.1 years). Familial aggregation was marked for tenosynovitis (λ s of 29.5), leukocytosis (λ s of 25), and RF (λ s of 11). Such familial aggregation of clinical features in ASPs adds strongly to the evidence of a genetic background for the disease.

Similarly, from Finland, 49 ASPs from 37 families were identified in a population of approximately 2000 with JIA. Within the ASPs, little difference was found in either onset type (57% concordance in ASPs) or disease course (61% concordance in ASPs) when compared with a population-based JIA series. Given a population prevalence of JIA in Finland of approximately 1 per 1000, this study suggests that the λ s for JIA is around 25, again supporting the idea of a substantial genetic component in the etiology of JIA.³²

HLA associations

Much of the genetic work in the past 3 decades has centered around HLA genes. A complete description of the HLA system can be found in Chapter 11. The fact that HLA molecules play a central role in the immune system has led to HLA genes being considered as candidates in association studies in many diseases, particularly those thought to have an immune basis such as JIA. A summary of HLA class I and class II associations with different subgroups of juvenile arthritis is presented in Table 102.1.

HLA linkage and juvenile idiopathic arthritis

A number of studies have confirmed the HLA associations by establishing linkage. Moroldo and colleagues³³ showed linkage to both HLA class I and class II with the transmission disequilibrium test (TDT) in patients with pauciarticular-onset JRA. HLA-A2, HLA-B27, HLA-B35, HLA-DR5, and HLA-DR8 all showed excess transmission, whereas HLA-DR4 was under-transmitted. A second study using the TDT in a U.K. cohort of patients with oligoarticular JIA confirmed the linkage.³⁴ Here, HLA-A2, HLA-DRB1*08, and HLA-DRB1*11 were overtransmitted and HLA-A3, HLA-DRB1*04, and HLA-DRB1*07 under transmitted. This study demonstrated that the effects at these two loci were independent. Finally, linkage analysis using the ASPs within the NIAMS-sponsored registry for JRA has confirmed linkage of pauciarticular JRA and HLA-DR and also established linkage for polyarticular JRA and HLA-DR.³⁵ Prahalad and associates³⁵ estimated that the proportion of the sibling recurrence risk attributable to HLA (λ_{HLA}) is 2.5, thus indicating that HLA accounts for 17% of the total genetic component of pauciarticular JIA. Hence, other non-HLA genes must play a role in susceptibility.

TABLE 102.1
HLA class I and class II associations and juvenile arthritis

HLA association	Patient subgroup
Class I	
HLA B27	Male late-onset pauciarticular Enthesitis-related arthritis
A2	Pauciarticular and young age at disease onset
Class II	
HLA-DRB1*11 (a subtype of HLA-DR5) and HLA-DRB1*08	Early-onset pauciarticular/oligoarthritis
HLA-DRB1*04 and HLA-DRB1*07 [†]	Early-onset pauciarticular/oligoarthritis
HLA-DPB1*0201	Early-onset pauciarticular Persistent and extended oligoarthritis
HLA-DR8/HLA-DRB1*08	RF-negative polyarthritis
HLA-DQ4 (DQA1*0401/DQB1*0402)	RF-negative polyarthritis
HLA-DP3/DPB1*0301	RF-negative polyarthritis
HLA-DR4	RF-positive polyarthritis
HLA-DR5 and HLA-DR8	Systemic onset
HLA-DRB1*11	Systemic onset
HLA-DR4	Systemic onset

[†]Decreased risk for susceptibility. All the other HLA associations listed in the table confer an increased risk for susceptibility.

Non-HLA candidate genes and juvenile idiopathic arthritis

Multiple different non-HLA genetic loci have been investigated in children with arthritis (reviewed in reference 36). Arguably, any association reported is only of value in helping decipher the etiopathogenesis of JIA if the genetic findings are replicated and provide robust evidence of a true effect. To date, for only a handful of these candidate genes has replication been achieved (Table 102.2).³⁷⁻⁴³

Genome-wide association studies and juvenile idiopathic arthritis

Genome-wide association studies (GWASs) examine, in an unbiased analysis, hundreds of thousands of single nucleotide polymorphism (SNP) variants in a large number of unrelated cases and controls. In 2007 the U.K. Wellcome Trust Case Control Consortium published its seminal manuscript detailing a GWAS of 14,000 cases of seven common diseases and 3000 shared controls.⁴⁴ This represented a turning point in the approach to studying complex genetic diseases.

A rich seam of positive associations for JIA has been garnered by studying GWAS loci associated with other clinical conditions that may have some degree of disease overlap with JIA. In particular, multiple SNP associations found to be positive from RA GWASs are also positive for JIA⁴⁵⁻⁴⁷ (Table 102.3). The overlap extends, however, to other autoimmune and inflammatory diseases, as summarized in Table 102.3.

To date, only two JIA GWASs have been performed. The first, by Hinks and coworkers,⁴⁸ was of modest size and used the Affymetrix GeneChip 100K arrays in only 279 cases and 184 controls. This identified a replicated association with SNPs in the *VTCN1* gene.

More recently, Thompson and colleagues⁴⁹ used the high-density Affymetrix Genome-Wide SNP 6.0 Array (Million SNP array) in a well-powered study and found replicated evidence of association for SNPs at 3q13, within *C3orf1* and near *CD80*, and at 10q21, near *JMJD1C* with JIA. These findings were supported by gene expression analysis.

TABLE 102.2
Non-HLA genetic loci associated with juvenile idiopathic arthritis that have been independently confirmed

Gene	References
<i>PTPN22</i>	Hinks, ³⁷ Viken ³⁸
<i>MIF</i>	Donn ^{39,40}
<i>WSP3</i>	Lamb ⁴¹
<i>SLC11A1</i> (NRAMP)	Smerdel, ⁴² Sanjeevi ⁴³

TABLE 102.3
GWAS-identified loci associated with juvenile idiopathic arthritis and multiple other autoimmune diseases

Gene	Autoimmune diseases
<i>PTPN22</i>	RA, SLE, AITD, T1DM, MS, celiac disease, autoimmune hepatitis
<i>PTPN2</i>	
<i>CCR5</i>	RA, MS, T1DM
<i>COG6</i>	RA, T1DM, psoriasis
<i>ANGPT1</i>	RA
<i>IL2RA</i>	RA, T1DM
<i>STAT4</i>	RA, SLE
<i>TNFAIP3</i>	RA, SLE, celiac disease
<i>C12orf30</i>	T1DM
<i>TRAF1/C5</i>	RA, SLE
<i>PRKCQ</i>	RA, celiac disease

AITD, autoimmune thyroid disease; GWAS, genome-wide association study; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus.

ENVIRONMENTAL FACTORS

In an attempt to identify the causative agent or agents implicated in the etiopathogenesis of juvenile arthritis, associations with a number of potential viral and bacterial pathogens have been sought. A self-limited polyarthritis can follow a wide variety of viral infections, including Coxsackie B virus, Epstein-Barr virus, parvovirus, and rubella.^{50,51} Studies reporting positive findings of viral antigens in JCA patients, however, are limited. Rubella virus has been implicated for some time,⁵² and an arthritis very similar to pauciarticular JCA develops in a small proportion of individuals who received rubella immunizations.⁵³

Pritchard and coworkers⁵⁴ noted birth date clustering among polyarticular JCA patients in whom progressive disease developed after the appearance of influenza A H₃N₂ in 1977. These patients had all been born in 1963, a year in which an epidemic of influenza A H₂N₂ had occurred. Raised levels of antibody to H₂N₂, the strain of influenza A prevalent at the time at which they were born, was recorded in this cohort. This led to the suggestion that arthritis developed in these individuals in 1977 because they had been pre-sensitized to influenza A by contact with the earlier strain when *in utero*. In a follow-up study on a similar cohort, influenza-specific cytotoxic T-cell clones were identified in blood and synovial fluid, but no evidence of sequestration to the joints of such clones was found.⁵⁵

The clinical features of systemic-onset JIA are particularly suggestive of a viral origin, and rising antibody titers to Coxsackie B4 were found during the acute stages in such patients.⁵⁶ Feldman and coauthors addressed seasonal differences in the onset of systemic-onset JRA by examining data collected from all patients with systemic-onset disease from 1980 to 1992 seen at pediatric rheumatology clinics across Canada. The onset pattern of systemic-onset JRA was then compared with the incidence data on viral infection.⁵⁷ Across Canada the onset of systemic-onset JRA was found to be constant across the seasons. However, in the prairie region a significant

seasonal pattern was detected, with peaks occurring in the autumn and early spring, but there was no evidence that viral infection correlated with disease incidence. Furthermore, a large multicenter European study failed to show a seasonal pattern in the onset of systemic or any other form of JCA.⁵⁸

HLA-B27-associated forms of JCA may be triggered by bacterial infections. A bacterium-specific synovial cellular immune response was found in spondyloarthritis patients to *Chlamydia trachomatis* and *Yersinia enterocolitica*, organisms known to be important in reactive arthritis.⁵⁹ In addition, an immunodominant epitope, Gro EL of *Escherichia coli* heat shock proteins, is one target of immune responsiveness in HLA-B27+ JCA.⁶⁰

Cellular immune responses to dnaJ, an *E. coli* heat shock protein, were found to be related to disease activity in a study of 25 JRA patients.⁶¹ No immunologically cross-reactive human homologue to this bacterial dnaJ has yet been identified.

Specific humoral reactivity against two proteins from Epstein-Barr virus, Bolf1 and Balf2, has been described in oligoarticular JIA cases. These viral proteins share sequence homologies with HLA antigens known to be associated with this patient subgroup.⁶²

CONCLUSION

JIA is an intriguing collection of phenotypes. Many diverse features occur and a limited number of unifying ones (onset before 16 years of age, chronic synovitis of joints). Much research still needs to be done to elucidate the etiopathogenesis of JIA. Despite some advances in SNP association studies, multiple other facets need to be considered to understand a complex genetic condition such as JIA. Analysis of gene-gene as well as potential gene-environment interactions needs to be done, but the numbers involved to make such studies feasible is large and will be achieved only via international consortia.

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Management of juvenile idiopathic arthritis

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MEDICAL MANAGEMENT

- Early “aggressive” therapy has resulted in improved outcomes for patients with juvenile idiopathic arthritis (JIA).
- Treatment is individualized according to the clinical manifestations of JIA and the presence of uveitis.
- Many new medications with effects on various immunologic pathways, especially biologic modifiers, are available for children.
- The American College of Rheumatology has developed recommendations for the treatment of JIA based on various clinical findings, prognostic signs, and clinical severity.

SURGICAL MANAGEMENT

- The need for surgical therapy may be decreasing as a result of improved medical management.
- Children have several specific issues with regard to arthroplasty.

OTHER ISSUES OF MANAGEMENT

- Greater attention needs to be directed to the treatment of pain.
- Issues of growth need to be addressed.
- Physical and occupational therapy, as well as assistive devices, splints, and orthotics, is an important part of therapy (addressed in detail in Chapter 106).

INTRODUCTION

Treatment of juvenile idiopathic arthritis (JIA) has changed dramatically in the past 25 years. The first change occurred in the late 1980s with the increasing use of intraarticular corticosteroid injections in children with oligoarthritis and the use of methotrexate (MTX) in those with polyarthritis. The second major change occurred in the late 1990s with the development of biologic modifiers, first anti-tumor necrosis factor (TNF) medications and later biologic modifiers targeting other cytokines involved in the inflammatory process or lymphocyte receptors.

The discovery of new effective medications was facilitated by the development of research networks. The Pediatric Rheumatology Collaborative Study Group in North America and the Pediatric Rheumatology International Trials Organization in Europe and elsewhere have conducted high-quality, multicenter, multinational controlled trials. Another important development was the validation of efficacy outcome measures (Table 103.1). The American College of Rheumatology (ACR) Pediatric 30 (Pediatric ACR30) defines patients as responders or nonresponders (Box 103.1).¹ This outcome measure has been modified for systemic arthritis studies (includes the absence of fever and characteristic rash) and to define a flare outcome in drug withdrawal studies, used mainly for studies of rapidly acting biologic modifiers. However, patients and physicians expect to achieve much better than a Pediatric ACR30 response. Thus, most new studies also report the Pediatric ACR50/70/90 and even ACR100 response criteria. Preliminary definitions of three levels of remission have been reported: inactive disease, clinical remission on medication, and clinical remission off medication (Box 103.2).² Several functional tools and quality-of-life tools have been validated and adapted for JIA. Other composite/multidimensional and long-term outcome tools are being developed or are in the process of validation (see Table 103.1).

The treatment philosophy for JIA has also undergone transformation. In the past, treatment was based on the “pyramid” approach, which initially used various types of nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids and gradually advanced to other medications. Studies in the late 1980s indicated that earlier assumptions on the course and outcome of JIA were incorrect. Radiologic joint damage, previously thought to take place late in the course of the disease, occurs in most patients with systemic arthritis and polyarthritis within 2 years and in those with oligoarthritis within 5 years of disease onset and perhaps earlier as shown by magnetic resonance imaging (MRI).

The assumption that JIA will usually resolve by adulthood is also incorrect. Studies in the “pre-MTX era” have shown that between 50% and 70% of patients with polyarthritis or systemic arthritis and 40% to 50% of those with oligoarthritis continue to have active disease in adulthood.³ Only a minority of patients attained clinical remission off medications for at least 2 years, and only 4% attained a remission for at least 5 years.⁴ Between 30% and 40% of patients had significant long-term disabilities, including unemployment, and between 25% and 50% required major surgery, including joint replacement.³ Leg-length inequality and muscle atrophy near affected joints developed frequently in patients with oligoarthritis. Patients with systemic arthritis have an increased mortality rate. Thus, the burden of disease on the patient, family, and ultimately society is large, and it is crucial that the disease be recognized and treated early and aggressively before the soft tissue deformities and joint damage become irreversible.

Several predictors of a poor outcome can help determine which patients require early aggressive therapy. Patients with polyarthritis (especially when involving the hip and cervical spine) and positive rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPAs), the presence of HLA-DR4, nodules, early-onset symmetric small-joint involvement, and existing radiologic damage have a worse prognosis.³ Patients with systemic arthritis who are dependent on corticosteroids for control of systemic symptoms and have a platelet count greater than 600,000/mm³ after 6 months of disease have a worse outcome.³

Treatment of JIA depends to a large extent on the disease subtype (Table 103.2) and clinical findings and combines antiinflammatory and immunomodulatory medications with physical and occupational therapy, an occasional need for surgery, nutritional support, and psychosocial and educational partnership with patients and parents. The treatment plan should be as simple as possible based on studies showing relatively low adherence to recommendations, both to medications and, to a larger extent, to physical therapy and exercise. Fortunately, many of the current JIA medications are given once weekly or less often (many by injection or infusion), which makes it easier to adhere to the treatment plan.⁵ The increased efficacy has decreased the rate of many complications and deformities, thus somewhat diminishing the roles of rehabilitation therapy and surgery as compared with the past. This chapter presents the new ACR recommendations for medical treatment of the arthritis of JIA⁶ based on the subtypes of JIA (including uveitis) and offers a rational approach to treatment of the various clinical manifestations of the disease. This is followed by a detailed discussion of the individual medications (including new biologic-modifying drugs) used to treat JIA and other components of treating JIA, such as managing pain and surgical interventions.

TREATMENT RECOMMENDATIONS FOR THE SUBTYPES OF JUVENILE IDIOPATHIC ARTHRITIS (Table 103.3)

The current aim of treatment is to achieve a state of disease inactivity. Treatment recommendations published by the ACR in 2011 used the best avail-



TABLE 103.1
Assessment and outcome measure tools for juvenile idiopathic arthritis

Domain	Assessment tools
Disease activity	Active joint count, acute-phase reactants, Juvenile Arthritis Disease Activity Score (JADAS)
Global assessment	Physician, patient visual analog scale
Multidimensional assessment	Juvenile Arthritis Multidimensional Assessment Report (JAMAR)
Functional assessment	Childhood Health Assessment Questionnaire (CHAQ), Juvenile Arthritis Functional Assessment Report (JAFAR), Juvenile Arthritis Functional Status Index (JASI)
Quality-of-life assessment	Childhood Health Questionnaire (CHQ), Peds-Quality of Life (QOL)—Rheumatology subset, pain visual analog scale
Radiologic damage	Poznanski, Dijkstra scores
Disease-related irreversible damage	Juvenile Arthritis Damage Index (JADI)
Clinical trial outcome measures	American College of Rheumatology Pediatric 30 (Pediatric ACR30) (modified for systemic arthritis and flare) criteria for inactive disease or clinical remission

TABLE 103.2
Subtypes of juvenile idiopathic arthritis

Subtype	Proportion of patients (%)
Systemic arthritis (starts with a spiking fever, rash)	5-10
Oligoarthritis (≤ 4 joints in the first 6 mo)	40-50
Persistent oligoarthritis course	25-35
Extended polyarticular course	15-20
Polyarthritis rheumatoid factor negative (≥ 4 joints in the first 6 mo)	25-30
Polyarthritis rheumatoid factor positive	5-10
Enthesitis-related arthritis (formerly called spondyloarthritis)	Undetermined
Psoriatic arthritis	5
Other (fits none or >1 category)	Undetermined

Adapted from Petty RE, Cassidy JT. Chronic arthritis in childhood. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. *Textbook of pediatric rheumatology*. 6th ed. Philadelphia: Saunders; 2011, p. 212.

TABLE 103.3
Major medications and indications for treatment of juvenile idiopathic arthritis

Medication	Arthritis subtype	Indication
NSAIDs	All types	Symptomatic: pain, stiffness, fever, antiinflammatory in mild cases
Intraarticular corticosteroids	All types, mainly oligoarthritis	Injection of few active joints
Systemic corticosteroids	Systemic, polyarthritis	Fever, serositis, bridging medication, macrophage activation syndrome
Methotrexate	All types, less effective for systemic and enthesitis-related axial disease	Disease modifying
Leflunomide	Polyarthritis	Disease modifying
Sulfasalazine	Oligoarthritis, polyarthritis, enthesitis-related peripheral disease	Disease modifying
Cyclosporine	Systemic	Macrophage activation syndrome
Thalidomide	Systemic	Biologic modifier
Anti-TNF (etanercept, infliximab, adalimumab)	Polyarthritis, enthesitis-related, uveitis (infliximab, adalimumab), less effective for systemic disease	Biologic modifier
Abatacept	Polyarthritis, including anti-TNF failure, uveitis	Biologic modifier
Anti-IL-1 (anakinra, rilonacept, canakinumab)	Systemic	Biologic modifier
Anti-IL-6 (tocilizumab)	Systemic, polyarthritis	Biologic modifier
IVIg	Systemic	Steroid sparing

IL-1, interleukin-1; IVIg, intravenous immune globulin; NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor.

BOX 103.1 PEDIATRIC ACR30 FOR JUVENILE IDIOPATHIC ARTHRITIS TRIALS

1. Active joint count (joints with swelling or tenderness/pain on motion with limitation of motion)
2. Joints with limited range of motion
3. Parent/patient global assessment (measured on a 0 to 10 visual analog scale)
4. Physician global assessment (measured on a 0 to 10 visual analog scale)
5. Laboratory measure of inflammation (erythrocyte sedimentation rate, C-reactive protein)
6. Functional assessment (Childhood Health Assessment Questionnaire)

Note: A patient's disease is considered to have responded if at least three variables have improved by at least 30% and not more than one variable has worsened by more than 30%. From Giannini EH, Ruperto N, Ravelli A, et al. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202-9.

BOX 103.2 CRITERIA AND TYPES OF REMISSION* IN JUVENILE IDIOPATHIC ARTHRITIS

1. No active arthritis
2. No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to juvenile idiopathic arthritis
3. No active uveitis
4. Normal erythrocyte sedimentation rate or C-reactive protein
5. Physician's global assessment of disease activity at the best score possible for the instrument used

*Clinical remission on medication: 6 continuous months of inactive disease during medication; clinical remission off medication: 12 months of inactive disease without any antiarthritis (and antiuveitis) medication.

From Wallace CA, Ruperto N, Giannini E, et al. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290-4.



able evidence to propose treatment based on the disease course of the individual patient (see Table e103.1).⁶ Clinical scenarios that included features of a poor prognosis and disease activity levels (low, moderate, and high) were developed for each JIA subtype, and treatment recommendations were developed accordingly.⁶ A summary of these recommendations follows.

Oligoarthritis

Patients with low disease activity (based on the number of active joints, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], physician and patient or parent global assessments) and no features of a poor prognosis (arthritis of the hip, cervical spine, wrist, or ankle with prolonged marked elevation of ESR/CRP or radiographic damage) may respond to NSAIDs. In patients not responsive to NSAIDs after 2 months or in patients with local complications, including flexion contractures and leg-length discrepancies, intraarticular corticosteroid injections with triamcinolone hexacetonide are effective in many patients (Fig. 103.1). If the response lasts less than 4 months or extended oligoarthritis develops, treatment should proceed as for patients with polyarthritis. For patients with high disease activity and features of a poor prognosis, MTX should be initiated (or leflunomide if MTX is not tolerated). Patients who fail to respond to MTX should start an anti-TNF medication. Sulfasalazine should be initiated in patients with enthesitis-related arthritis who have peripheral oligoarthritis with at least moderate disease activity.

Polyarthritis course (regardless of onset)

NSAID monotherapy for longer than 2 months is inadequate to treat polyarthritis, even in patients with low disease activity (same parameters as for oligoarthritis) and no poor prognostic features (arthritis of the hip or cervical spine, positive RF or APCAs, or radiographic damage) (Fig. 103.2). MTX with adjunctive NSAIDs or intraarticular corticosteroid injections should be prescribed for NSAID failure or patients with high disease activity or moderate disease activity and poor prognostic features. Leflunomide may be considered as well (mainly in patients intolerant of MTX). Failure to respond to 3 to 6 months of MTX or leflunomide treatment (with moderate to high disease activity or with low disease activity, respectively) is an indication for initiation of an anti-TNF medication, again with adjunctive NSAIDs or intraarticular corticosteroid injections. Patients who fail 4 months of this treatment with at least moderate disease activity should be switched to a second anti-TNF medication, abatacept or tocilizumab. Occasionally,

systemic corticosteroids may be necessary as a bridging medication or during flares, but there is no evidence that systemic corticosteroids are disease modifying. Though not yet studied in controlled studies involving children, other medications (e.g., rituximab) and combination therapy effective for rheumatoid arthritis may be beneficial, especially in patients with positive RF or APCAs.

Systemic arthritis

Many advances in the treatment of systemic arthritis have recently been made (Fig. 103.3). For patients with active systemic features (with or without arthritis), a short course of NSAID monotherapy may be indicated in the initial workup of these patients but is not considered appropriate in those with high fever and a physician global assessment score of greater than 7 of 10. For such patients, systemic corticosteroids are often needed for symptomatic relief. No evidence has shown a preferred method of corticosteroid administration, although one controlled study found that patients administered intravenous methylprednisolone early needed fewer total systemic corticosteroids than did patients starting corticosteroids orally. Initiation of anakinra was recommended for all patients with active fever and features of a poor prognosis, as well as for patients who sustain or develop fever while taking corticosteroids. Canakinumab, approved in 2013 by the FDA for systemic JIA, can also be used. The role of rilonacept is currently under review. Anti-IL-1 treatment may be used to avoid administering corticosteroids or as steroid-sparing agents. Similarly, anti-IL-6 therapy has been shown to be beneficial in controlling systemic symptoms and could be considered in these situations.

For patients with active arthritis (with or without systemic features), a maximum of 1 month of NSAID treatment (with intraarticular corticosteroid injections as needed) was recommended, followed by MTX with adjunctive NSAIDs or intraarticular corticosteroid injections as needed. Recommendations for the treatment of patients with moderate disease activity irrespective of prognostic features after 3 months included either anti-TNF or anti-IL1 medications, with adjunctive NSAIDs or intraarticular corticosteroid injections prescribed as needed. If anti-TNF medications are chosen, patients should be switched to abatacept or anti IL-1 medications

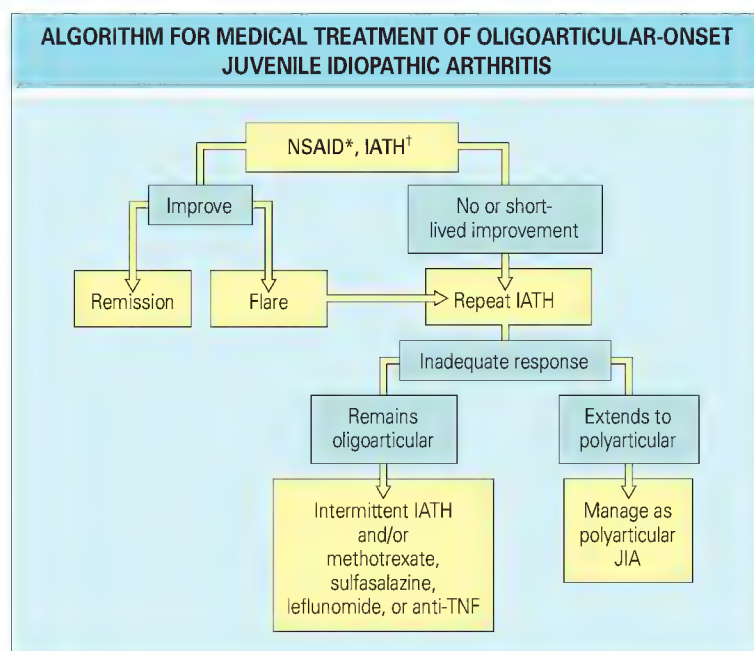


Fig. 103.1 Medical treatment of the oligoarticular subtype of juvenile idiopathic arthritis (JIA). *NSAID trial for 4 to 6 weeks. †Prefer early IATH if knee monoarthritis is present and/or the patient has local complications: contractures, leg-length discrepancy, significant muscle atrophy. IATH, intraarticular triamcinolone hexacetonide; NSAID, nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

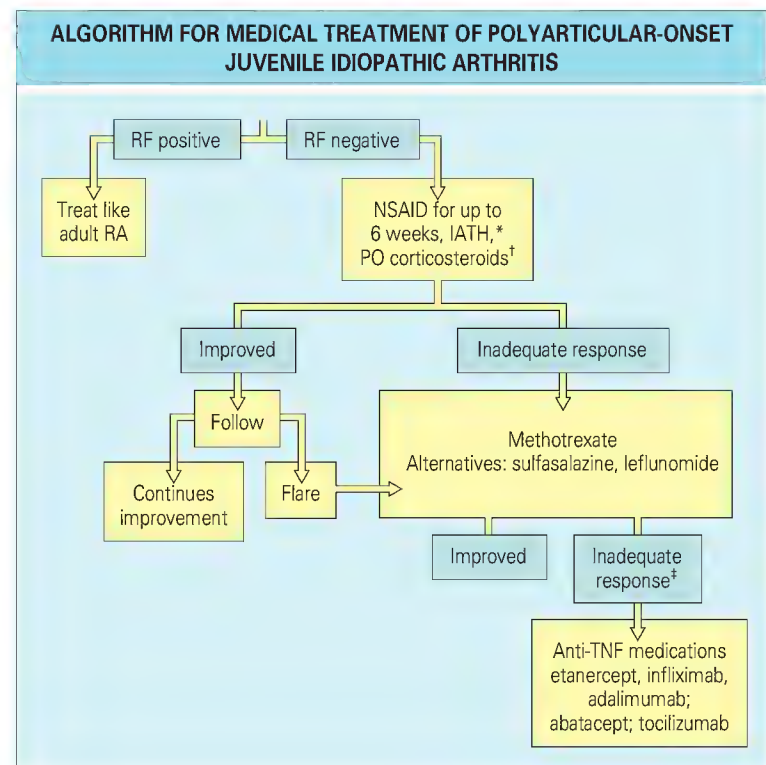


Fig. 103.2 Medical treatment of polyarticular course of juvenile idiopathic arthritis. *IATH for selected joints. †PO steroids can be considered as bridging medicine or during significant flares. ‡If fails to respond to one anti-TNF agent, consider changing to another, to abatacept, or to tocilizumab. IATH, intraarticular triamcinolone hexacetonide; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; PO, oral; SC, subcutaneous; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumor necrosis factor.

TABLE e103.1
Features of a poor prognosis and levels of disease activity

Type of juvenile idiopathic arthritis	Features of a poor prognosis	Disease activity levels		
		Low disease activity (must satisfy all)	Moderate disease activity (does not satisfy criteria for low or high activity)	High disease activity (must satisfy at least 3)
History of arthritis in 4 or fewer joints	Arthritis of the hip or cervical spine Arthritis of the ankle or wrist AND marked or prolonged elevation of inflammatory markers Radiographic damage (erosions or joint space narrowing on radiography)	One or fewer active joints Normal ESR or CRP Physician global assessment of overall disease activity <3 of 10 Patient/parent global assessment of overall well-being <2 of 10	One or more features greater than low-disease activity level AND fewer than 3 features of high disease activity	Two or more active joints ESR or CRP greater than twice the upper limit of normal Physician global assessment of overall disease activity ≥7 of 10 Patient/parent global assessment of overall well-being ≥4 of 10
History of arthritis in 5 or more joints	Arthritis of the hip or cervical spine Positive rheumatoid factor OR anti-cyclic citrullinated peptide antibodies Radiographic damage (erosions or joint space narrowing on radiography)	Four or fewer active joints Normal ESR or CRP Physician global assessment of overall disease activity <4 of 10 Patient/parent global assessment of overall well-being <2 of 10	One or more features greater than low-disease activity level AND fewer than 3 features of high disease activity	Eight or more active joints ESR or CRP greater than twice the upper limit of normal Physician global assessment of overall disease activity ≥7 of 10 Patient/parent global assessment of overall well-being ≥5 of 10
Sacroiliac arthritis	Radiographic damage in any joint (erosions or joint space narrowing on radiography)	Normal back flexion Normal ESR or CRP Physician global assessment of overall disease activity <4 of 10 Patient/parent global assessment of overall well-being <2 of 10	One or more features greater than low-disease activity level AND fewer than 2 features of high disease activity	ESR or CRP greater than twice the upper limit of normal Physician global assessment of overall disease activity ≥7 of 10 Patient/parent global assessment of overall well-being ≥4 of 10
Systemic arthritis with active systemic features	6-mo duration of significant active systemic disease, as defined by fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids	Disease activity levels (2 levels) Active fever AND physician global assessment of overall disease activity <7 of 10 Active fever AND systemic features of high disease activity (e.g., significant serositis) that result in physician global assessment of overall disease activity ≥7 of 10		
Systemic arthritis with active arthritis	Arthritis of the hip Radiographic damage (erosions or joint space narrowing on radiography)	Four or fewer active joints Normal ESR or CRP Physician global assessment of overall disease activity <4 of 10 Patient/parent global assessment of overall well-being <2 of 10	One or more features greater than low-disease activity level AND fewer than 3 features of high disease activity	Eight or more active joints ESR or CRP greater than twice the upper limit of normal Physician global assessment of overall disease activity ≥7 of 10 Patient/parent global assessment of overall well-being ≥5 of 10

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

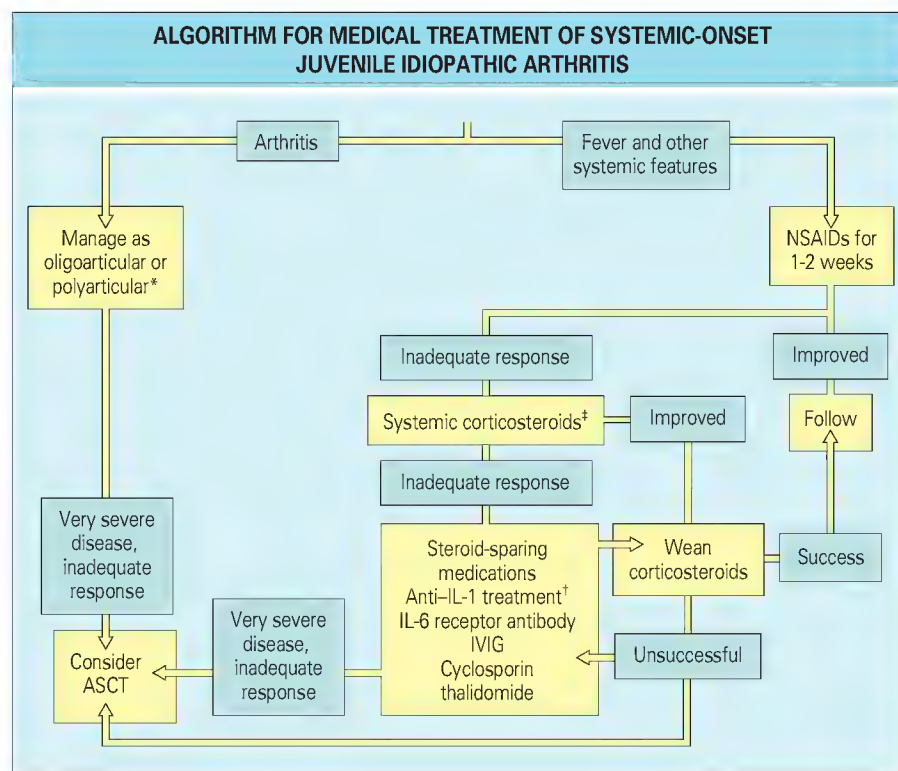


Fig. 103.3 Medical treatment of systemic juvenile idiopathic arthritis. *Methotrexate, intraarticular corticosteroids and, anti-tumor necrosis factor drugs are less effective for systemic-onset JIA; anti-IL-1 and IL-6 receptor antibody may be more effective. †See text for additional details. ‡May consider intravenous in first week or intermittent intravenous corticosteroid pulses. ASCT, autologous stem cell transplantation; IL, interleukin; IVIG, intravenous immune globulin; NSAID, nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

if moderate disease activity persists after 4 months. Similarly, anti-IL-6 therapy has been shown to be beneficial in controlling arthritis and could be considered in these situations.

Intraarticular corticosteroid injections, MTX, and anti-TNF medications appear to be less beneficial than in other subtypes of JIA for both the systemic and arthritis components of the disease. Although intravenous immune globulin (IVIG) is not effective in treating the arthritis component, there may be some benefit, including a corticosteroid-sparing effect, on the systemic component and on macrophage activation syndrome complicating systemic arthritis.

Thalidomide or early treatment with a combination of cyclophosphamide, MTX, and intravenous pulse corticosteroids may be an alternative in unresponsive patients; however, with increased and early use of anti-IL-1 and anti-IL-6 therapy, these medications should not generally be needed. For patients with severe unresponsive systemic and polyarticular JIA, autologous stem cell transplantation (ASCT) may be used as a last resort, although substantial morbidity and mortality are associated with this therapy.

Macrophage activation syndrome

Treatment of JIA-related macrophage activation syndrome includes high-dose intravenous corticosteroid pulses; if this therapy is not rapidly effective, dexamethasone should replace methylprednisolone and cyclosporine should be added. The role of IVIG is unclear, although it is often used. Strong consideration should be given to therapy with etoposide in patients whose disease is progressing rapidly. Recently, anti-IL-1 and perhaps anti-IL-6 therapy have been found to be effective in some patients. Failure of these therapies may require even more aggressive treatment such as antithymocyte globulin or alemtuzumab (Campath).

Enthesitis-related arthritis

Strong evidence is lacking for treating this form of JIA. Open series have indicated that sulfasalazine may be beneficial in these patients, particularly older boys with peripheral oligoarthritis, although in the one small controlled study of patients with this type of arthritis, no significant benefit of sulfasalazine was found. No studies of MTX for this subtype of JIA have been performed. Open series have found anti-TNF therapy to be highly effective.

Active sacroiliac arthritis

The recommendations addressed only anti-TNF medications, and initiation of these medications was recommended in patients with high disease activity

(based on back flexion, ESR/CRP, and physician and patient or parent global assessments) and features of a poor prognosis (radiographic damage in any joint) who failed NSAID treatment, as well as for patients who failed 3 months of MTX or sulfasalazine therapy. Failure of 6 months of MTX or sulfasalazine treatment in patients with moderate disease activity should lead to initiation of a TNF inhibitor.

Psoriatic arthritis

One small series has shown anti-TNF medications to be efficacious for the arthritis of psoriasis but with much less or even a paradoxical effect on the skin disease.⁷ The signs and symptoms of psoriatic arthritis can be the same as those for oligoarticular-onset, polyarticular-onset, and enthesitis-related arthritis, and until other evidence is reported, this disease should be treated like the parallel JIA subset.

Uveitis

Topical therapy for uveitis consisting of corticosteroid drops and mydriatics to prevent posterior synechiae is the treatment of choice. Other local therapies include sub-Tenon corticosteroid injections or long-acting corticosteroid implants. However, it is often hard to wean patients with JIA-related uveitis from topical therapy, and the treatment-related complications of cataract and glaucoma develop in many patients. In such patients, early use of corticosteroid-sparing, disease-modifying therapy, especially MTX, is warranted.⁸ Most patients respond to therapy, and more than 50% attain remission while taking MTX. However, not all patients respond to MTX, and uveitis develops in some even during MTX therapy. To prevent an uveitis flare it is necessary to continue MTX for longer periods (perhaps as long as 2 years) in patients who attained a status of inactive uveitis than in patients who have only arthritis (see later).⁸

Etanercept does not appear to be effective in the treatment of JIA-related uveitis. A small, controlled, double-blind study of 12 patients, as well as uncontrolled studies, did not find etanercept to be effective, and new cases of uveitis or uveitis flares have been reported during etanercept therapy.⁹ For patients nonresponsive to MTX or other immunosuppressive medications, several series have found infliximab and adalimumab to be effective in inducing remission, including discontinuation of topical corticosteroids by most patients.⁸ However, in many patients the effect of infliximab and adalimumab wears off with time. In some patients it is necessary to increase the dose and frequency of infliximab to 20 mg/kg or greater every 4 weeks or to prescribe weekly adalimumab. Some series have indicated that abatacept may be effective for uveitis, including anti-TNF failures.¹⁰ A recent series showed that azathioprine may be effective in the majority of patients

with JIA-related uveitis.¹¹ A small series reported that mycophenolate mofetil was not as effective for JIA-associated uveitis as for other types of uveitis. A preliminary study of high-dose daclizumab, an IL-2 receptor antibody, showed improvement in the majority of patients, but there were substantial safety concerns.¹² For very severe cases, chlorambucil has been used. Cyclosporine does not appear to be very effective for JIA uveitis.

In summary, in patients not responsive to MTX or azathioprine, infliximab and adalimumab appear to be effective, but not etanercept. Abatacept may be used for patients in whom anti-TNF therapy has failed. Cyclosporine does not appear to be very effective. Mycophenolate mofetil has not been adequately studied for JIA-related uveitis. There is still a lack of controlled studies for the treatment of uveitis, but preliminary, still unvalidated consensus outcome measures for these trials have recently been defined.¹³

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

The actual efficacy of NSAIDs (Table 103.4) is unknown because none of the studies (even in the 1970s) were placebo-controlled. In a summary of studies, only 25% to 33% of patients, mainly those with oligoarthritis, showed a significant response to NSAIDs.⁵ A minimum of a 4-week trial of an individual NSAID is necessary to assess its efficacy. Because NSAIDs were not shown to alter the disease course or prevent joint damage, they are used more to treat pain, stiffness, and the fever associated with systemic arthritis. No individual NSAID has been demonstrated to have a clear advantage over others in treating arthritis. It is important to consider the dosing schedule and form of NSAID administration, with a preference for once- or twice-daily dosing to improve adherence to the treatment plan. Suspension preparations are available for naproxen, ibuprofen, meloxicam, and indomethacin, and celecoxib is available as sprinkle capsules. NSAIDs approved by the U.S. Food and Drug Administration (FDA) for use in patients with JIA include tolmetin, naproxen, ibuprofen, meloxicam, and celecoxib (see Table 103.4).

Serious gastrointestinal adverse effects of NSAIDs are rare, although gastrointestinal symptoms do develop in many children. Adverse effects can often be prevented by taking NSAIDs with food, but if not, switching to another NSAID, including cyclooxygenase-2–selective NSAIDs (celecoxib) or using H₂ blockers or proton pump inhibitors, may improve the symptoms. Another important adverse effect is the development of pseudoporphyria, which is most often associated with the use of naproxen in fair-haired, white patients and usually occurs within 2 years of use.⁵ The superficial skin scarring resulting from pseudoporphyria may not resolve for years. Central nervous system adverse effects may occur, including headaches and disorientation, especially with indomethacin. Renal adverse effects, particularly papillary necrosis or tubular function abnormalities, are uncommon in

children but are more frequent during the concurrent use of more than one NSAID. The issue of cardiovascular adverse effects has not been addressed in children.

CORTICOSTEROIDS

Because of many deleterious effects, especially the effect on bone and growth and, in a recent study, a threefold increase in the risk for infection,¹⁴ the use of systemic corticosteroids for JIA should be minimized. No evidence has established that systemic corticosteroids are disease modifying. The main indications for the use of systemic corticosteroids are severe fever, serositis, and macrophage activation syndrome in patients with systemic arthritis. They are also frequently used as a bridging medication until other disease-modifying medications take effect. In some patients, periodic intravenous pulses of corticosteroids (30 mg/kg per dose, maximum of 1 g, usually given for 1 to 3 consecutive days) are used instead of high-dose daily oral corticosteroids, although no controlled studies have shown fewer adverse effects with this modality in children and the effect is short-lived. Calcium and vitamin D supplementation should be used in children receiving systemic corticosteroids.

Evidence of the efficacy of intraarticular injections of corticosteroids is strong, mainly in patients with oligoarthritis. As many as 70% of patients with oligoarthritis do not have reactivation of disease in the injected joint for at least 1 year, and in 40% to 60% of patients this period may be longer than 2 years.⁵ Radiographic and MRI studies have shown a marked decrease in synovial volume after injection without deleterious effects on cartilage. Significantly fewer patients have leg-length discrepancies and joint contractures. Its efficacy is reduced in patients with systemic arthritis. The long-acting agent triamcinolone hexacetonide is more effective and has a longer effect than other forms of injectable corticosteroids, and thus its use is considered standard of care.⁶ Intraarticular corticosteroid injections are also useful for the treatment of temporomandibular joint (TMJ) arthritis. Dexamethasone iontophoresis has been proposed as an alternative to TMJ injection.¹⁵ It may be preferable to use radiologic guidance for joints difficult to access, such as the hip, subtalar, or temporomandibular joints or complex multiple joints such as the wrist.

Few adverse effects are associated with these injections, most often the development of periarticular subcutaneous atrophy or asymptomatic intraarticular calcifications (Fig. 103.4). In some joints, especially the subtalar joint, these effects may occur in as many as half of injections. They may be prevented by injecting small amounts of saline into the joint after the injection and by applying pressure to the injection site. Repeated injections in an individual joint should not be done at less than 3-month intervals; this approach has not resulted in joint or cartilage damage. Patients must be

■ TABLE 103.4 Dosage and special characteristics of nonsteroidal antiinflammatory drugs commonly used to treat juvenile idiopathic arthritis

NSAID	Dose			How supplied	Special characteristics
	mg/kg/d	Maximum, mg	Times per day		
Acetylsalicylic acid	80-100	4000	3-4	Tablet	Need to measure levels, liver enzyme abnormalities, risk for Reye syndrome
Naproxen*	15-20	1000	2	Tablet, suspension	Pseudoporphyria
Ibuprofen*	30-50	2400	3-4	Tablet, suspension	
Indomethacin	1.5-3.0	200	1-2	Capsule, suspension	More gastrointestinal and neurologic adverse events, perhaps more beneficial for fever, pericarditis with systemic arthritis and enthesitis-related arthritis
Tolmetin*	20-30	1800	3	Tablet	
Sulindac	4-6	400	2	Tablet	Fewer renal adverse events
Diclofenac	2-3	200	2	Tablet	
Piroxicam	0.2-0.3	20	1	Tablet	More gastrointestinal adverse effects
Etodolac	10-20	1000	2	Tablet, capsule	
Meloxicam*	0.25-0.375	15	1	Tablet, suspension	
Nabumetone	30	2000	1	Tablet	
Celecoxib*	3-6	200	2	Capsule (can open and use sprinkles)	Use for bleeding disorders, cross-reacts with sulfa allergies

*Approved by the U.S. Food and Drug Administration for the treatment of juvenile idiopathic arthritis.

warned about the risk for infection, although infection is extremely rare when done in aseptic conditions. Occasional cases of aseptic necrosis more likely result from severe underlying disease than from the joint injection itself.

Younger children or children needing multiple joint injections usually require sedation during the procedure. Various types of sedation have been used, including nitrous oxide, various methods of conscious sedation, and general anesthesia.



Fig. 103.4 Radiograph of an ankle joint demonstrating calcifications secondary to corticosteroid injection.

METHOTREXATE

Use of MTX is the cornerstone in the treatment plan for patients with a polyarticular course of JIA (Table 103.5).^{5,6,16} The ACR recommends administering MTX by subcutaneous injection at a dose of 15 mg/m²/wk (maximum of 30 mg).⁶ A large, open, randomized study showed no additional advantage in giving higher doses up to 30 mg/m²/wk.¹⁷

The efficacy of MTX differs by the subtype of JIA, with the greatest efficacy seen in patients with extended oligoarthritis and much lower effects in patients with systemic arthritis.^{5,6} The presence of the 1298C allele in the methylenetetrahydrofolate reductase (*MTHFR*) gene was associated with higher efficacy than was the presence of the A allele,¹⁸ whereas single nucleotide polymorphisms in the 5-aminoimidazole-4-carboxamide ribonucleotide transformylase gene were associated with a lack of response.¹⁹ The radiologic damage progression rate was decreased in two small uncontrolled series, thus suggesting that MTX may exhibit a disease-modifying effect. MTX treatment was also found to improve growth parameters at 1 and 3 years, both for height and for weight, in prepubertal children who responded to MTX.²⁰ Early response to MTX may be predictive of the long-term outcome. Patients with a Pediatric ACR70 response to MTX by 6 months had significantly fewer active joints than did patients with a lesser or no response years later. MTX also improves health-related quality of life.

A recent study showed that about 50% of patients will have flares within 2 years regardless of whether MTX was discontinued 6 or 12 months after attaining a status of inactive disease.²¹ Thus, MTX can be discontinued 6 months after attaining this status. The level of myeloid basic protein 14 was a good measure to predict which patients would experience a flare when MTX was discontinued, thus suggesting that some patients continue to have active disease that is difficult to detect clinically.²¹ Nearly 90% of patients will respond when MTX is restarted. There is no reliable evidence about the preferred method of tapering MTX before discontinuation.

Because food decreases the bioavailability of MTX, it is advised that MTX be taken on an empty stomach. At doses of 10 mg/m²/wk there is no difference in the efficacy of MTX whether administered orally or parenterally.²² MTX at

TABLE 103.5
Dosages and major adverse reactions of other major medications used to treat juvenile idiopathic arthritis

Medication	Dose	Main adverse reactions
Methotrexate	10-15 mg/m ² /wk (parenteral if >12.5 mg/m ²), maximum of 30 mg	Gastrointestinal symptoms, mouth sores, liver enzymes, cytopenia
Sulfasalazine	30-50 mg/kg/day, maximum of 2000 mg, divided into 2 doses	Gastrointestinal symptoms, rash (Stevens-Johnson syndrome), cytopenia
Leflunomide	<20 kg: 10 mg every other day 20-40 kg: 10 mg/day >40 kg: 20 mg/day	Gastrointestinal symptoms, increased liver enzymes
Etanercept	0.8 mg/kg, maximum of 50 mg, SC injection once weekly or 0.4 mg/kg twice weekly	Injection site reaction, upper respiratory symptoms, infections
Adalimumab	<30 kg: 20 mg SC injection every other week ≥30 kg: 40 mg SC injection every other week	Injection site reaction, upper respiratory symptoms, infections
Infliximab	6 mg/kg intravenously at wk 0, 2, and 6 and then every 6-8 weeks (may need to administer every 4 wk as much as 20 mg/kg)	Infusion reactions (allergic), infections
Anakinra	2 mg/kg/day SC injection, maximum of 100 mg	Injection site reaction, upper respiratory symptoms, infections
Rilonacept	Loading dose of 2.2 mg/kg (maximum, 160 mg), then 2.2 mg/kg/week SC injection, maximum of 160 mg	Injection site reaction, upper respiratory symptoms, infections
Canakinumab	4 mg/kg every 4 weeks, SC injection, maximum of 300 mg	Upper respiratory symptoms, infections (particularly pneumococcal), vertigo
Abatacept	10 mg/kg intravenously at wk 0, 2, and 4 and then every 4 wk; maximum of 1000 mg	Infections
Tocilizumab	<30 kg: 12 mg/kg intravenously every 2 wk for systemic arthritis, every 4 wk for polyarthritis ≥30 kg: 8 mg/kg intravenously every 2 wk for systemic arthritis, every 4 wk for polyarthritis	Infections, liver enzymes, hypercholesterolemia
Triamcinolone hexacetonide	For large joints: 1 mg/kg intraarticularly, maximum of 40 mg	Potential for infection, subcutaneous atrophy, intraarticular calcifications

SC, subcutaneous.

greater doses is usually given by subcutaneous or intramuscular injection because oral MTX is not as well absorbed at doses of 12 mg/m² or higher.⁵

MTX should be administered with folic acid, 1 mg/day, or folinic acid, 25% to 50% of the MTX dose, given once weekly the day after MTX. A controlled study of folic acid and a retrospective study of folinic acid found a decreased in the adverse effects of nausea, oral ulcerations, and perhaps liver enzyme abnormalities without decreasing the efficacy of MTX.³

Nausea and other gastrointestinal symptoms are frequent. Strategies to decrease the severity of these events include taking MTX before bed, switching the mode of administration (oral to parenteral), giving MTX in two divided doses (on the same day), and using antiemetics. Many children, especially adolescents, develop a psychological aversion to MTX, which may include anticipatory nausea or behavioral distress before the administration of MTX. This adverse effect may be alleviated by behavioral therapy, including teaching relaxation or self-hypnosis techniques. Although mild elevations in liver enzymes occur frequently throughout the course of treatment, no cases of severe, irreversible liver fibrosis have been reported in patients with JIA.⁵ Routine liver biopsy is not recommended.

Recommendations to monitor for MTX toxicity include complete blood cell counts, liver enzymes, and renal function, although the optimal frequency of testing is unclear.^{5,6} One study reported that tests at 3-month intervals with doses of up to 15 mg/m²/wk detected significant hematologic and liver enzyme abnormalities as often as testing at monthly intervals did. Pulmonary toxicity is very rare in children. Nodulosis has been reported rarely. Very few severe infections have been reported in children. Studies showing the efficacy of mumps, measles, and rubella and varicella vaccines without causing disease flares have resulted in many pediatric rheumatologists modifying previous recommendations that children avoid live vaccinations while taking MTX.²³ Nonlive vaccinations are safe to give, and seasonal influenza vaccine is recommended. Current data do not suggest that the rate of malignancies is greater than in children with JIA not treated with MTX.²⁴ There does not seem to be any long-term impact on fertility.

OTHER DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND IMMUNOSUPPRESSIVE MEDICATIONS

(Table 103.6, and see Table 103.5)

Most controlled studies in children did not find hydroxychloroquine, oral gold, azathioprine, or D-penicillamine to be significantly effective in the treatment of JIA.⁵ A controlled study showed that sulfasalazine is effective in treating oligoarthritis and polyarthritis,⁵ and earlier introduction of treatment may result in better long-term outcomes. Sulfasalazine may also have disease-modifying effects on radiologic progression.

In a small placebo-controlled study of juvenile spondyloarthritis and in a study in which sulfasalazine was compared with chloroquine for oligoarthritis and polyarthritis, no significant differences were found.⁵ In many open studies, sulfasalazine was most effective in older males with oligoarthritis, which perhaps represents children with enthesitis-related arthritis. Adverse reactions are reported frequently, especially rashes, gastrointestinal symptoms, and leukopenia, and use of sulfasalazine is discontinued in nearly one third of patients. The dose of sulfasalazine is usually increased gradually to 50 mg/kg/day (maximum of 1 g twice daily) to prevent some of these adverse events. Adverse effects may be especially severe in patients with systemic arthritis, with potential for the development of macrophage activation syndrome. Sulfasalazine is contraindicated in patients with porphyria and glucose-6-phosphate dehydrogenase deficiency.

In a controlled study comparing leflunomide with MTX in patients with polyarthritis, significantly more responders were found in the MTX group, although high response rates were also achieved with leflunomide.⁵ Most of the patients responsive to leflunomide maintained their response in a 2-year open-label extension study. No significant differences in adverse effects were found. Leflunomide is used most often in patients who cannot tolerate MTX. Cyclosporine may be more beneficial for controlling fever and reducing corticosteroid doses than for treating arthritis in patients with systemic arthritis and may be especially effective in patients with macrophage activation syndrome. Many adverse effects, especially renal, are associated with cyclosporine.

Two multicenter series found that thalidomide was effective in the majority of patients with refractory systemic arthritis, both for systemic features and for arthritis, with most patients able to significantly reduce their corticosteroid use and obtaining at least a Pediatric ACR30 response.⁵ However, in addition to concern for teratogenicity with thalidomide, careful observation for the development of peripheral neuropathy is necessary. Drowsiness may be significant and require dose reduction or discontinuation.

TABLE 103.6

Efficacy of common medications used to treat juvenile idiopathic arthritis

Medication	Efficacy		
	Persistent oligoarthritis	Polyarticular-course JIA	Systemic-onset arthritis
NSAID	Mild to moderate	Mild	Mild
Intraarticular corticosteroids	Significant	Moderate	Mild to moderate
Methotrexate	Significant	Significant	Mild
Leflunomide	Unknown	Significant	Unknown
Sulfasalazine	Unclear	Moderate	Contraindicated*
Etanercept	Significant	Significant	Moderate
Infliximab	Unknown	Significant†	Moderate
Adalimumab	Unknown	Significant	Unknown
Abatacept	Unknown	Significant	Unknown
Anakinra	Unknown	Mild‡	Moderate to significant
Rilonacept	Unknown	Unknown	Moderate to significant
Canakinumab	Unknown	Unknown	Significant
Tocilizumab	Unknown	Significant	Significant

Mild: effective in up to 25% of patients; moderate: effective in 25% to 50% of patients; significant: effective in more than 50% of patients. For intraarticular corticosteroids, efficacy was measured as benefit for more than 6 months.
Note: Noneffective medications (i.e., hydroxychloroquine, penicillamine, oral gold, azathioprine) or medications not commonly used (cyclophosphamide, intravenous immune globulin, thalidomide, collagen) or not studied in controlled studies in children (rituximab, minocycline) were not included in this table. Evidence is lacking on the utility of medications for the other types of JIA.
*Sulfasalazine is associated with the development of macrophage activation syndrome in patients with systemic disease.
†Was not significantly more effective than placebo in a controlled study.
‡More effective in patients with a systemic-onset arthritis course.
JIA, juvenile idiopathic arthritis; NSAID, nonsteroidal antiinflammatory drug.

BIOLOGIC-MODIFYING MEDICATIONS

Anti-tumor necrosis factor medications

Three anti-TNF medications are currently used for JIA: (1) etanercept, a genetically engineered p75-soluble TNF receptor fused to the Fc domain fragment of human IgG1; (2) adalimumab, a humanized TNF antibody; and (3) infliximab, a murine-based TNF antibody. Newer anti-TNF agents, including golimumab and certolizumab, are currently undergoing trials for polyarthritis.

Etanercept and adalimumab have both been approved by the FDA and European Medicines Agency (EMA) for use in patients with polyarticular-onset JIA after they were found to be effective in two-phase withdrawal studies.^{25,26} Several uncontrolled studies and surveys have suggested that etanercept and infliximab are less effective in patients with systemic arthritis and that the initial response is often not sustained in these patients.⁵ Excellent responses to anti-TNF medications have been reported in uncontrolled studies of patients with juvenile spondyloarthritis.²⁷ These agents usually have a rapid onset of action, but the maximal effect may take several months to achieve.

The dose of etanercept is either 0.4 mg/kg (maximum of 25 mg) given subcutaneously twice weekly or 0.8 mg/kg (maximum of 50 mg) once weekly and is approved from the age of 2 years. Adalimumab is given subcutaneously at a dose of 20 mg every other week in children weighing less than 30 kg and at a dose of 40 mg every other week in children larger than 30 kg and is approved from the age of 4 years. In a controlled study, infliximab did not attain statistical significance in comparison to placebo for the primary outcome, probably because of study design and conduct issues, but it was still effective in the majority of patients.²⁸ Infliximab is given intravenously, initially at a dose of 6 mg/kg at weeks 0, 2, and 6 and then every 8 weeks together with MTX. This dose is associated with fewer adverse effects than 3 mg/kg is, especially infusion reactions and the development of human antichimeric antibodies to infliximab.²⁸

Open-label extension studies of the original pivotal study etanercept cohort for up to 8 years, as well as other registries, have shown continued efficacy in the majority of patients with a polyarticular course, although

MTX was added to the treatment of many of the patients and prednisone to some. More than 65% of patients taking anti-TNF medications have a response greater than the Pediatric ACR50 level. These and other studies have shown a drug survival rate with the first anti-TNF medications of 50% to 60% after 4 years, with the major cause of discontinuation being lack of efficacy and to a lesser degree adverse events, especially with infliximab. Switching to another anti-TNF medication is often effective and safe. However, if the reason for switching is lack of efficacy, the subsequent anti-TNF medications is usually less effective and continued for a shorter period than the first.²⁹ In systemic JIA, switching to (or starting with) anti-IL-1 treatment may be more effective.⁶ Factors associated with an excellent or good response to etanercept are administration at a young age and lower functional disability at the start of treatment. Factors associated with a poor response include systemic JIA and female gender.³⁰ Few data are available on when and how to successfully discontinue anti-TNF therapy, but it appears that approximately 33% of those who discontinue anti-TNF medication after attaining inactive disease status remain disease free for at least 1 year after discontinuation.³¹

Though not specifically studied in the major studies and registries, data suggest that the combination of anti-TNF medications and MTX may be more efficacious than MTX or anti-TNF medications alone, with no significant safety differences, perhaps due to prevention of antibodies formation to the anti-TNF medications.^{5,26}

Initial signs of a disease-modifying effect of anti-TNF medications have been found in uncontrolled studies, including slower radiologic progression, increase in bone strength measured by ultrasound, improved growth velocity independent of the corticosteroid dose and pubertal stage,³² and improved functional status and quality of life.

Adverse effects of anti-TNF medications, though potentially severe, are generally mild and consist of mainly infusion and injection site reactions, upper respiratory infections, and headaches.³³ Overall, the rate of serious adverse effects from anti-TNF medications is estimated to be 0.03 to 0.12 event per patient-year of treatment.³³ Adverse events with infliximab, especially infusion reactions, may lead to discontinuation of the medication more often than with etanercept. Administering infliximab at a dose of 6 mg/kg, as well as premedication with acetaminophen, diphenhydramine, and occasionally hydrocortisone, may prevent or minimize severe infusion reactions. Severe bacterial and varicella infections with complications have been reported, but in general children respond well to standard antibacterial treatment. Autoimmune phenomena have been reported in several children or young adults with JIA, including the development of diabetes mellitus, drug-induced lupus, cutaneous vasculitis, psoriasis, and central nervous system demyelination. Uveitis flare or the new development of uveitis, as well as inflammatory bowel disease, was reported during the use of etanercept, although the causative association has not been proved. Other important adverse events include neurologic symptoms, psychiatric problems, and pancytopenia. Attention should be paid to any family history of demyelinating disease, including consideration of performing screening MRI, and consultation with a neurologist should be obtained if symptoms and signs consistent with demyelination develop.

Rare cases of tuberculosis and histoplasmosis have been reported with the use of anti-TNF medications for JIA. Purified protein derivative skin testing before (and annually during therapy in high-risk patients) anti-TNF therapy is advised in the ACR recommendations for JIA.⁶

At least 48 cases of malignancy, mainly lymphoma, have been reported in children and young adults treated with anti-TNF for JIA and Crohn disease,^{33,34} but in recent studies this rate does not appear to be greater than that children with JIA not treated with anti-TNF medications.^{24,35} Despite these data, the FDA has issued an updated boxed warning highlighting an increased risk for cancer, including lymphoma, leukemia, and melanoma, in children and adolescents who receive anti-TNF agents. Although several small studies suggest that live vaccines may be safe to administer in patients receiving anti-TNF therapy, current recommendations are to avoid them.²³

Abatacept

Abatacept, a selective T-cell costimulator inhibitor (CTLA-4Ig), was found to be effective for JIA with a polyarthritis course in a controlled two-phase withdrawal study involving 190 patients treated with 10 mg/kg (maximum of 1000 mg) intravenously at weeks 0, 2, and 4 and then every 4 weeks.³⁶ Although abatacept was effective in 76% of anti-TNF-naïve patients, nearly 40% of patients who were anti-TNF failures were also considered Pediatric ACR30 responders. Extension studies have shown that abatacept remains effective and improves health-related quality of life for up to 2 years of treatment. In a decision analysis model, abatacept was the most cost-effective biologic agent in achieving a single-patient Pediatric ACR 30 response.³⁷

Adverse effects were generally mild, with rare serious adverse infectious events being reported. Abatacept has been approved by the FDA for use in JIA with a polyarticular course from the age of 6 years. The EMEA, however, approved abatacept only after anti-TNF failure and in combination with MTX.

Anti-interleukin-1 medications

IL-1 has an important role in the pathogenesis of systemic JIA, particularly in early disease. Thus, anti-IL-1 therapy has an increasingly important role in the treatment of systemic JIA. Three anti-IL-1 medications are currently available: anakinra, an IL-1 receptor antagonist; rilonacept, an IL-1 trap (soluble receptor); and canakinumab, a selective IL-1 β antibody.

Several studies, including one controlled study, demonstrated the efficacy of anakinra in patients with systemic JIA, especially for the systemic features of the disease.³⁸ Some studies have suggested that there are two subsets of patients in regard to response to anakinra, with about 50% exhibiting a dramatic response and others having a minimal response.³⁹ It appears that patients with a higher number of active joints respond less well to anakinra, particularly when administered later in the disease process.³⁹ Furthermore, the effect of anakinra appears to dissipate in many patients, and the dose of anakinra often needs to be increased to even higher than 5 mg/kg/day.³⁸ Recent studies have suggested that anakinra may be used as a first-line medication for systemic JIA in patients requiring more than NSAIDs, especially in those with highly active disease and poor prognostic factors as outlined in the ACR JIA treatment recommendations.^{6,40} Anakinra may be effective as part of the treatment of macrophage activation syndrome, but in other patients this syndrome may develop during or after the start of anakinra therapy.⁴⁰ Anakinra has not shown clinically significant effectiveness for polyarthritis JIA.

A small pilot phase 1 study of rilonacept for systemic arthritis showed that it was safe at a dose of 2.2 mg/kg/day administered subcutaneously (maximum of 160 mg), but only about 50% of the patients were responders. In the controlled phase of this trial (not designed primarily for efficacy), no significant differences versus the placebo group were detected.⁴¹ An additional increase in the dose to 4.4 mg/kg/day did not result in improved efficacy. A further large study of rilonacept is nearing completion.

In a phase 2 study, the optimal dose of canakinumab to be further studied was determined to be 4 mg/kg (maximum of 300 mg) given by subcutaneous injection every 4 weeks.⁴² Two controlled phase III studies (a traditional placebo-controlled study and a withdrawal study among responders) showed remarkable efficacy of canakinumab, particularly in patients with fever and rather early disease. The response was seen as early as 15 days following the first injection.⁴³ As a result in 2013 the FDA approved canakinumab for treating systemic arthritis.⁴³

The major adverse effects of anti-IL-1 therapy include injection site reaction (anakinra > rilonacept > canakinumab) and infections, particularly gram-positive (especially pneumococcal) infections.³³ Up-to-date vaccinations, including pneumococcal vaccination, should be ensured in children receiving anti-IL-1 therapy.

Anti-interleukin-6

IL-6 is an important cytokine in the pathogenesis of systemic arthritis, especially for systemic symptoms, thrombocytosis, osteoporosis, and growth retardation. A controlled two-phase withdrawal study of tocilizumab, an antibody to the IL-6 receptor, for systemic arthritis given intravenously at a dose of 8 mg/kg every 2 weeks, with a 48-week open extension, showed a Pediatric ACR30 response rate of 91% and a Pediatric ACR70 rate of 68%.⁴⁴ Flares were significantly increased in the placebo withdrawal group. Another placebo-controlled study in patients with severe and prolonged disease showed similar highly significant improvements, including an open extension for up to 2 years with the ability to significantly reduce corticosteroid use.⁴⁵ A controlled study showed that tocilizumab is also very effective for polyarthritis.⁴⁶ Tocilizumab was approved in 2011 for use in patients from 2 years of age with systemic arthritis by the FDA and EMEA and by the FDA in 2013 for patients with polyarthritis. Serious adverse events have included anaphylaxis, gastrointestinal perforation, and nonopportunistic infections.³³ Hyperlipidemia may also occur. Several deaths took place in the second controlled systemic JIA study, so careful postmarketing safety surveillance is necessary.

Intravenous immune globulin

Two controlled studies did not find IVIG to be effective in treating the arthritis component of systemic and polyarticular JIA.⁵ However, both

studies were small and had insufficient power to detect significant differences. There may be more benefit with IVIG in the first year of the disease and for treatment of the systemic features of systemic-onset arthritis, but this has not been examined in a controlled study. IVIG is often used for the treatment of macrophage activation syndrome at a dose of 2 g/kg, although the evidence to support its use is minimal.

Rituximab

No controlled studies of the use of rituximab (anti-CD20 mature B-cell antibodies) for JIA have been reported. A recent large series (N = 55) showed substantial efficacy for both polyarthritis and systemic JIA refractory to therapy, including infliximab, when rituximab courses were repeated every 24 weeks for up to 96 weeks.⁴⁷

Autologous stem cell transplantation

Evidence that abnormal autoreactive T-cell clones have an important role in the pathogenesis of JIA is substantial. The largest series of patients undergoing ASCT has been reported from the Netherlands, predominately patients with systemic JIA.⁴⁸ Complete drug-free remission was reported in approximately 50% of patients, partial response according to the Pediatric ACR criteria in around 20%, and no improvement in about 20%. The mortality rate was around 10% to 15%, mainly from early post-ASCT infection-associated macrophage activation syndrome (triggered by Epstein-Barr virus, cytomegalovirus, and *Toxoplasma*) and in nonresponsive patients. However, because in longer follow-up many patients experience a relapse of their disease, the long-term effect of ASCT is still not clear.

Many issues regarding patient selection, conditioning protocol, graft preparation, and posttransplant care are still unknown. Improvements in patient selection and pretransplant protocol have resulted in decreased mortality. However, anti-IL-1 and anti-IL-6 medications have decreased the need for ASCT. ASCT must still be regarded as an experimental procedure for selected patients with severe and unremitting disease despite all modern therapies.

STUDIES OF DISEASE-MODIFYING ANTIRHEUMATIC DRUG VERSUS BIOLOGIC COMBINATION THERAPY FOR JUVENILE IDIOPATHIC ARTHRITIS

In the only controlled (open-label) study that included a nonbiologic arm of combination disease-modifying antirheumatic drug (DMARD) therapy it was shown that treatment of patients with early polyarthritis (less than 6 months) with MTX, hydroxychloroquine, and sulfasalazine was superior to MTX monotherapy in attaining a Pediatric ACR75 and inactive disease response, although the combination of infliximab and MTX was superior to both DMARD-only arms.⁴⁹

A controlled, blinded trial of early aggressive therapy (TREAT) for early polyarthritis (less than 1 year) compared treatment with subcutaneous MTX alone (15 mg/m²/wk, maximum of 40 mg) and treatment with a combination of prednisone (weaning over a 4-month period), MTX, and etanercept. Although the study did not attain the primary outcome of a significant difference in the rate of inactive disease at 6 months, there were significant differences in the rate of attaining a Pediatric ACR70 response at 4 months and a status of remission on medication at 1 year. Furthermore, it was shown that the main factor in attaining inactive disease status (for either treatment arm) was initiation of treatment early in the disease course.⁵⁰

MANAGEMENT OF PAIN

Pain, the most common symptom in children with JIA, is an important determinant of physical function and quality of life. Higher pain predicts higher functional disability,⁵¹ and even a modest reduction in pain can result in an improvement in the quality of life of children with JIA.

Control of inflammation is critical to the management of pain. Because multiple factors can lead to pain, specific treatment above and beyond antiinflammatory treatment, including pharmacologic and psychosocial approaches, should be pursued.⁵² Cognitive-behavioral therapy approaches may assist with strategies for coping with pain. Improved fitness may reduce disease activity and pain. Because poor sleep may be a contributing factor to pain, sleep hygiene should be monitored.

Pharmacologic approaches to pain control have traditionally used a “step-up” approach, beginning with acetaminophen and progressing to NSAIDs and opioids. Most pediatric rheumatologists are reluctant to prescribe opioids for fear of their side effects and potential for addiction despite evidence that addiction is not a problem when these medications are used appropriately and prescribed by experienced practitioners in a well-controlled and monitored environment.⁵² The development of localized and diffuse pain syndromes such as fibromyalgia in patients with JIA must also be addressed and treated.

REHABILITATION

The principles of rehabilitation in children with JIA are discussed in detail in Chapter 106. Physical and occupational therapists are integral members of the team and play critical roles in working with the child and family to preserve and improve range of motion and muscle strength. Because of the chronicity of the disease, slow improvements, and pain induced by exercise, adherence with an exercise regimen is often a challenge, and techniques to improve adherence must therefore be used. It was recently shown that this can be done through implementation of an Internet-based program.⁵³ An experienced occupational therapist can be of great benefit in working with the child to find ways to improve function and provide assistive devices, such as ring splints for inflamed fingers and orthotics for inflamed and deformed feet, and to enhance activities of daily living. Customized semi-rigid foot orthotics were found to be superior to both prefabricated “off-the-shelf” shoe inserts and supportive athletic shoes in pain reduction, speed of ambulation, and level of disability in patients with JIA and foot pain.⁵⁴

Children and adolescents with JIA are not as fit as their peer groups and are not as active physically. Multiple reports have demonstrated the safety of increased exercise intensity in most children with JIA, with improved range of motion, increased muscle strength, and some improvements in achieving aerobic fitness. However, high-intensity exercise does not seem to confer added benefits in function or fitness relative to less strenuous exercise.⁵⁵ Hydrotherapy may not offer sufficient benefit to support its routine use.

Approaches to physical activity and participation in sports by children with JIA have recently been published.^{55,56}

MANAGEMENT OF GROWTH RETARDATION

Several factors, most prominently persistent inflammation and the need for corticosteroid treatment, plus early onset of disease, are associated with growth delay. With new treatments resulting in a reduced need for corticosteroids to control symptoms (especially systemic JIA), growth retardation should be less of a problem, although long-term studies are still lacking. Treatment with anti-TNF agents has resulted in improved growth in patients with polyarticular JIA.³² Nevertheless, some patients may still fail to grow adequately; in fact, even patients with oligoarticular JIA treated with just intraarticular corticosteroids may be at risk for growth retardation.⁵⁷ Nutrition assessment and support are necessary to increase caloric intake in patients who fail to gain weight. Some patients may benefit from nighttime tube feeding. Nutrition consultation is also needed for corticosteroid-treated patients on issues such as calorie restriction, adequate calcium and vitamin D, and low sodium intake.

Several studies have shown growth hormone to be of benefit in increasing height growth velocity, even in patients treated with corticosteroids.⁵⁸ Earlier institution of treatment will probably lead to better results. In most studies no significant disease flares were found,⁵⁹ although the authors and others have noticed flares in some patients with disease that is not completely controlled. There are also metabolic concerns, particularly involving lipids, of growth hormone use in patients treated with corticosteroids.

SURGICAL INTERVENTIONS

With improved medical management, the indications for surgical intervention in patient with JIA are fewer; nevertheless, appropriately timed surgery may offer important benefits and improved outcomes in individual patients.

Synovectomy

Removal of inflamed synovial tissue might theoretically be beneficial in children with only one or a few persistently active joints despite appropriate therapy. In general, however, the effect of synovectomy is transient, and thus it should be reserved for specific painful inflamed joints interfering with

function following failure of the medical treatment outlined in the ACR recommendations.⁶ Factors predicting a more sustained response in one study included isolated monoarticular disease, shorter disease duration, and normal acute-phase reactant levels.⁶⁰ A high recurrence rate is seen after synovectomy. Despite excellent or good subjective outcomes, there is frequently no significant improvement in functional ability or range of motion, and complete pain relief is achieved in less than half of the patients. Although there may not be any long-term efficacy, the benefit of arthroscopic synovectomy may be to temporize while systemic medications such as MTX or biologic agents are taking effect.

Epiphysiodesis

With the early institution of more “aggressive” medical management, including intraarticular corticosteroids, the development of leg-length discrepancy and progressive valgus deformity of the knee is less common than in the past. Appropriately timed epiphysiodesis (fusion of the epiphyseal growth plate) plus temporary stapling of the femoral epiphyses, with or without the tibial epiphyses, has resulted in excellent short- and long-term outcomes in correcting leg-length discrepancy with few complications (such as growth plate damage and deep infection).⁶¹ Patients must be monitored closely to avoid overcorrection. This procedure is preferable to surgical epiphysiodesis, which is not reversible. Epiphysiodesis with stapling may also be considered in patients with valgus deformity of the knee, a common knee deformity with JIA. Although the possible benefit in postponing the need for total knee arthroplasty appears to be limited, it may ultimately make the procedure easier by reducing the soft tissue and bony imbalance.

Arthroplasty

Even though current approaches to treatment have led to marked improvements in outcomes, significant joint damage, debilitating pain, and loss of function still develop in a small number of children. It is for these indications that joint replacement surgery may be contemplated. When this is considered, a number of specific issues relevant to pediatric patients must be taken into account. Because of the extensive rehabilitation required and the necessity of adhering to a rehabilitation regimen, the emotional and psychosocial state of the child and family must be assessed to ensure that compliance with the program will be maintained. Special attention must be paid at the time of surgery to joint contractures and soft tissue management, which require release of soft tissues and correction of bony changes. The effect of the disease on growth may result in small bones and difficulty using a standard prosthesis, and therefore custom-made prostheses are often required. Finally, bone quality is often poor because of the underlying disease activity, poor nutrition, immobility, and sometimes corticosteroid therapy. This may result in difficulty using the usually preferred uncemented prosthesis. In general, attempts should be made to delay surgery until the child has stopped growing. However, this must be balanced with the degree of disability and pain. It is important to keep all these principles in mind when considering total joint replacement in patients with JIA.

Total hip and knee arthroplasty results in better improvement in pain than in function.^{62,63} Revisions may be necessary because of aseptic loosening with functional impairment. Prolonged corticosteroid use has a negative

impact on implant survival.⁶² Even in experienced hands, revision surgery is difficult.

Even though outcomes with total knee arthroplasty, as measured by standard assessments, are not as positive as in patients with osteoarthritis, patients report an overall improvement in quality of life and satisfaction with the procedure. A decrease in pain is observed, although improvement in range of motion is not as significant.⁶³ A number of postoperative complications related to poor range of motion of the knee and continuing anterior knee pain may be seen.

When the disease is bilateral, simultaneous procedures should be done if possible. Hip replacement should precede knee replacement to improve the chance of successful rehabilitation. Bilateral combined hip and knee arthroplasty in young patients with JIA has been reported with good success. Reports on shoulder arthroplasty are limited. Pain relief is the major goal of shoulder arthroplasty and can be achieved. A small improvement in range of motion may have a significant impact on function. The results of total elbow arthroplasty are not as satisfactory as with other joints, and it is associated with significant early and late complications.

Surgical treatment of temporomandibular joint deformities

Surgical treatment of TMJ deformities involves a team consisting of a dentist, orthodontist, and craniofacial surgeon, in addition to the rheumatologist. Most case series have reported both improved occlusion and better facial aesthetics postoperatively. Some patients may still be left with TMJ pain, and numbness of the lip, chin, teeth, and gums may develop. A number of different procedures have all been reported to have good outcomes. However, a systematic review was unable to conclude that these procedures were beneficial.⁶⁴

CONCLUSION

The development of new therapies has already markedly increased our ability to effectively treat children with JIA, and the future appears promising, especially for difficult patients with systemic-onset and polyarticular arthritis. However, there is still a lack of evidence-based medicine in the treatment of JIA, especially for enthesitis-related and psoriatic arthritis. Recent sobering studies have shown our inability to induce long-term medication-free remission in most patients, even with modern therapy. Study of the effect of early aggressive therapy on the course of the disease, including the potential use of combination “induction” therapy, has just begun. The long-term disease-modifying effects of MTX and the new “biologic” medications on remission rates, radiologic changes, bone strength, growth, functional capabilities, quality of life, and prevention of surgery are still mostly unknown despite encouraging initial signals of benefit in many of these outcomes. It is necessary to study the long-term adverse effects of these medications, especially if used as combination therapy. Future multicenter controlled studies and postmarketing surveillance with large registries are necessary to address these issues.

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Juvenile-onset spondyloarthritis

■ RUBÉN BURGOS-VARGAS

- Juvenile-onset spondyloarthritis is characterized by its association with HLA-B27 as well as by synovitis and enthesitis of peripheral sites in the initial years of disease and, in some patients, the sacroiliac and spinal joints some years later.
- Enthesitis-related arthritis (ERA) and psoriatic arthritis are subgroups of juvenile idiopathic arthritis that are strongly related to juvenile-onset spondyloarthritis (joSpA).
- HLA-B27 and other alleles confer susceptibility to the disease; in some cases, bacterial infections may play a role in the pathogenesis of joSpA and ERA.
- Tumor necrosis factor- α (TNF- α) is prominently expressed in the synovial membrane.
- Patients with joSpA/ERA may have severe short- and long-term functional impairment and persistent disease activity
- TNF- α blockers are likely to be the best treatment of joSpA/ERA.

INTRODUCTION

Juvenile-onset spondyloarthritis represents a group of HLA-B27–associated pediatric rheumatic diseases characterized by the involvement of the synovium and entheses of the peripheral joints in the initial years of disease and, in some patients, the sacroiliac and spinal joints some years later.¹

NOMENCLATURE AND CLASSIFICATION

Juvenile-onset spondyloarthritis (joSpA) and *enthesitis-related arthritis* (ERA) are currently the terms used to describe this group of disorders. The former corresponds to adult-onset terminology and classification, whereas the latter corresponds to one of the seven categories of juvenile idiopathic arthritis (JIA) described by the International League of Associations for Rheumatology (ILAR).² joSpA and ERA differ in that ERA excludes psoriatic arthritis (PsA), reactive arthritis (ReA), and inflammatory bowel disease (IBD) from its boundaries. Thus, the joSpA and ERA concepts are not exactly the same, and not all patients classified as having spondyloarthritis (SpA) or PsA according to several criteria fulfill the ILAR criteria for ERA or PsA.³ Nonetheless, the acronym joSpA/ERA will be used to facilitate comprehension in this chapter despite the fact that some articles refer to SpA and others to ERA.

EPIDEMIOLOGIC ASPECTS

The incidence of joSpA/ERA in American and Canadian children varies from 2.1 per 100,000⁴ to 24.0 per 100,000 children in western Canadian Indians.⁵ The relative proportion of joSpA/ERA in children with all forms of JIA varies from greater than 10% to 36% in different populations.^{6,7} An alternative approach in considering the epidemiology is to examine the proportion that arise in childhood across all ages. When compared with the United States, which has only a very small proportion, around one third of Mexicans, Indians, North Africans, and some Asian groups have an onset before the age of 16 years.⁸

PATHOGENESIS

The etiology of SpA, including joSpA/ERA and adult-onset disease, is still unknown. As suggested in adult SpA, genetic susceptibility and perhaps bacterial infections could be implicated in the pathogenesis of the disease, but the role of mechanical, growth, and developmental factors needs to be investigated.

Genetic factors

joSpA is strongly linked to HLA-B27 across all populations. Chronic SpA develops in 85% of HLA-B27+ children with JIA.⁹ HLA-B27 is linked with specific B27 subtypes in some populations, such as B*2705 in Mexicans¹⁰ and B*2704 in Han Chinese.¹¹ HLA-B27 determines the prevalence of SpA in the general population and in families. Explanations of how HLA-B27 contributes to susceptibility to ankylosing spondylitis (AS) include the arthritogenic peptide hypothesis, the HLA-B27 misfolding and unfolded protein response hypothesis, and the HLA-B27 free heavy-chain and surface homodimer hypothesis.¹² Genome-wide screens in adults have implicated a number of other genetic candidates that may also be relevant to childhood disease. Thus, strong associations have emerged between the genes *RUNX3*, *TNFR1/LTBR*, *IL-12B*, *PTGER4*, *TBKBP1*, *ANTXR2*, *CARD9*, *IL-1R*, *TRADD*, *STAT3*, and *KIF21B*. Of these, *ERAP1* and *IL-23R* have been implicated in pathways such as antigen presentation to interleukin-23 receptor (IL-23R)/type 17 helper T cell (Th17) and tumor necrosis factor (TNF)/Th1 signaling/development.^{12,13} Studies in children have been much less frequent, but interestingly, some of the same candidates, specifically *ERAP1* and *IL-23R*, have been linked to joSpA/ERA and juvenile PsA.¹⁴

Infection

As with their adult forms, both juvenile-onset ReA and other SpAs are linked to bacterial infections. Evidence for joSpA/ERA includes humoral and cellular responses to bacterial constituents such as peptidoglycan¹⁵ and the outer membrane protein of *Salmonella typhimurium*.¹⁶ Likewise, a number of bacteria may trigger disease in patients with ReA and AS, and a variety of bacterial DNA have been found in the synovial fluid cells of patients with joSpA/ERA.¹⁷ Finally, expression of Toll-like receptors 2 and 4 in peripheral blood and synovial fluid cells, which may recognize microbial ligands, is increased in those with joSpA/ERA.¹⁸

HISTOPATHOLOGY

The peripheral joint synovial membrane of patients with joSpA/ERA shows hyperplasia of the lining cells with some CD68 expression and CD163+ macrophages in the sublining layer. There is marked neovascularity with increased numbers of CD146+ endothelial cells,¹⁹ high levels of CD8-activated cells, TNF- β , interferon- γ , IL-2, IL-4, and IL-6.²⁰ Of note, TNF- α is prominently expressed, and most cells express the TNF receptors p55 and p75.²⁰ The metatarsal entheses show scarce inflammatory infiltrates, as well as marked bone proliferation and mucopolysaccharide deposits in soft tissues. The entheses of patients with adult-onset SpA have inflammatory infiltrates in the bone marrow; in fibrocartilage, which also shows increased vascularity and macrophage infiltration; and in the interface between the zones of calcified fibrocartilage and subchondral bone. Studies in animal models have now provided new insight into the pathogenesis of enthesopathy, including the role of bone morphogenetic protein signaling²¹ and the role IL-23 on enthesal resident T-cell receptors.²²

CLINICAL MANIFESTATIONS

The clinical manifestations of joSpA/ERA differ from those of adult-onset SpA in some aspects, particularly AS. Children and adolescents with AS typically have peripheral arthritis and enthesitis in the initial years, with axial symptoms not emerging for 5 to 10 years later, whereas most adults with AS have inflammatory back pain (IBP). Early limb involvement may lead to a greater need for hip replacement than in those with AS commencing in adulthood. This may be a manifestation of more serious peripheral involvement or its longer duration. In general, more childhood-onset cases end in functional classes III and IV, and their mean Bath functional index score is higher.

General aspects

Lower limb peripheral arthritis or enthesitis (or both) occurs in nearly all patients, and their patterns differ very little among specific diagnostic entities (Fig. 104.1). Arthritis and enthesitis may not parallel each other, however, in their severity, duration, and consequences. The distinction between arthritis and enthesitis may be also difficult to determine clinically at some sites, for example, the sacroiliac joints and the feet. Imaging is of major benefit here. Magnetic resonance imaging (MRI) of the spine, sacroiliac joints, and feet (Fig. 104.2) shows hyperintense signals (edema) in the bone, bursa, synovial sheaths, and synovium, consistent with inflammation in short tau inversion recovery (STIR) sequences; structural changes, specifically erosions, bone destruction, enthesophytosis, and ankylosis, may be seen in T1 sequences. Ultrasonography of joints and entheses may provide useful information in patients with active disease, and computed tomography may show structural changes. Radionuclide imaging lacks specificity and does not discriminate inflammation from growing plates.

Peripheral arthritis

Peripheral arthritis is the most frequent sign of joSpA/ERA. At the onset, most patients have unilateral or asymmetric monoarthritis or oligoarthritis involving the knee, midtarsus, and ankle. Less commonly affected are



Fig. 104.1 Involvement of the feet in patients with spondyloarthritis (SpA). (a) Dactylitis of the third digit in a 12-year-old boy with undifferentiated SpA. (b) Diffuse swelling of the tarsal region of an 11-year-old boy with juvenile-onset ankylosing spondylitis. (c) Tarsal swelling, hyperextension of the digits, and keratoderma blennorrhagica in a 16-year-old boy with chronic reactive arthritis. (d) Diffuse swelling of the posterior aspect of the feet, including the ankles and the Achilles, peroneal, and tibial posterior tendons, in a 12-year-old boy with undifferentiated SpA. (Modified from Burgos-Vargas R, Vázquez-Mellado J. *Reactive arthritides*. In: Cassidy JT, Petty RE, editors. *Textbook of pediatric rheumatology*. 5th ed. Philadelphia: Saunders; 2005. p. 604-12; and Burgos-Vargas R. *The juvenile-onset spondyloarthritides*. In: Weisman MH, van der Heijde D, Reveille JD, editors. *Ankylosing spondylitis and the spondyloarthropathies*. St. Louis: Mosby; 2006. p. 94-106.)

the hips, upper extremity joints (shoulders, elbows, and joints of the hands from the wrist to the distal interphalangeal joints), and rarely, the metatarsophalangeal (MTP) and interphalangeal (IP) joints. The course of arthritis typically consists of recurring episodes of monoarthritis or oligoarthritis for 3 to 6 months. In some cases these recurrent episodes of inflammation are followed by some remission, but in others they may lead to severe and persistent polyarthritis. Involvement of the hips and MTP and foot IP joints, as well as some joints of the upper extremities, increases during the course of the disease. Radiographic findings include osteopenia, joint space narrowing, and in some cases, ankylosis. Except for the small joints of the feet and hands in some patients, erosive and destructive changes are rare.

Peripheral enthesitis

Enthesitis and its consequences—osteocartilaginous proliferation and enthesophytosis—are the most specific feature of SpA in children and adults. Enthesitis may occur within the joints (i.e., the sacroiliac joints) and in extraarticular sites (i.e., Achilles tendon and plantar fascia attachments to the calcaneus), and the most frequently involved joints in children are those of the feet (plantar fascia and Achilles tendon attachments to the calcaneus, the fifth metatarsal/cuneal joint, and the functional entheses over the tarsal bones) and then those of the knees (tibial anterior tuberosity and patella), hips (greater trochanter), and pelvis (iliac crest and tuberosity of the ischium); involvement of the upper limb entheses is rare. Enthesitis is associated with pain and sometimes swelling (mainly of the bursae and synovial sheaths) and some reduced mobility. Although some patients have single or very few short episodes of inflammation, others have long episodes of enthesitis. Radiographic changes range from bone overgrowth and enthesophytosis to bone bridging and ankylosis; on the other hand, subcortical bone cysts and erosions may sometimes occur at tendon attachments in peripheral sites, particularly the feet.

Spinal and sacroiliac arthritis

Axial symptoms may accompany disease activity at peripheral sites, particularly severe polyarthritis and enthesitis. The entire spine may be involved, but the thoracolumbar junction and the cervical spine seem to be the most frequently affected. Although children and adolescents with SpA may have back pain, stiffness, and reduced mobility, they usually lack some of the most important characteristics of IBP, specifically, insidious onset, improvement with exercise but not with rest, and pain at night; costosternal and alternating gluteal pain are also rare. In most cases the relevance of axial symptoms increases during the course of the disease, and in most patients AS is diagnosed 5 to 10 years after the onset of peripheral symptoms. Few children and adolescents with prominent axial symptoms and radiographic sacroiliitis fulfill the criteria for AS within 3 years of disease onset. Even though demonstration of sacroiliitis by MRI favors the recognition of adults with preradiographic AS and the early use of TNF blockers, MRI of the sacroiliac joints or the spine has no clear rationale for the same purpose in children and adolescents without axial symptoms. Peripheral symptoms may be so persistent and severe that they should be treated with TNF blockers regardless of axial disease.

Health-related quality of life and functioning

In the absence of successful disease-modifying therapy, only 17% of patients with joSpA/ERA are in remission 5 years after onset²³ and less than 50% by 10 years.²⁴ More than 50% of patients still have active disease 17 years after onset,²⁵ and 60% have functional limitations after 10 years, particularly if they had disease activity for more than 5 years.²⁴ When compared with other JIA subgroups, patients with joSpA/ERA have more pain, as well as higher Childhood Health Assessment Questionnaire scores, poorer physical health, lower physical functioning, and lower health-related quality-of-life scores.²⁶ Patients with juvenile-onset PsA have poorer health than the healthy population and lower 36-item Short-Form Health Survey (SF-36) scores than other JIA subgroups do.²⁷ There are no long-term data on the use of TNF blockers in these patients yet, but it is expected that their prognosis will be substantially improved.

CLINICAL TYPES

Before the 1980s most clinical descriptions referred to juvenile-onset AS and Reiter syndrome; undifferentiated forms became clearly recognized in the early 1980s.^{28,29} Currently, recognition of undifferentiated SpA or joSpA/ERA

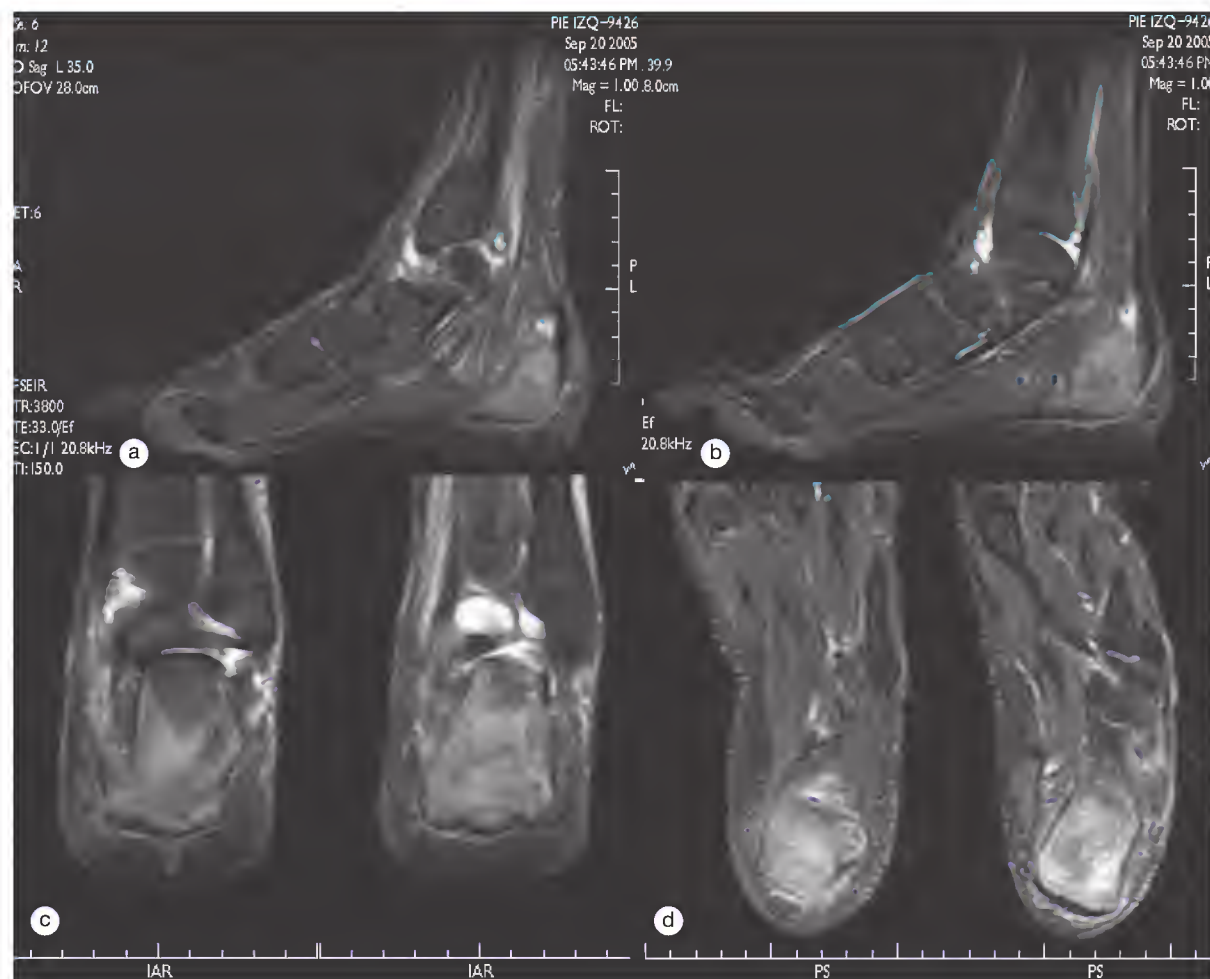


Fig. 104.2 T2-weighted fat-suppressed magnetic resonance images of the foot of a 15-year-old boy with ankle swelling and a painful heel (Achilles tendon and plantar fascia) for approximately 6 months. (a and b) Sagittal-lateral views showing synovial fluid effusion in the posterior and anterior ankle joints, the retrocalcaneal bursae, and possibly the fat as well as bone edema of the calcaneus, including the attachments of the Achilles tendon and its continuation to the plantar fascia. (c) Synovial fluid effusion of the ankle joint, edema around the posterior peroneal tendon and extensive edema of the calcaneus on sagittal-posterior views. (d) Coronal views showing extension of the edema to the calcaneus.

is of major importance because of its potential to evolve to more severe forms. Despite the fact that the ILAR JIA classification does not recognize the various types of SpA and that PsA is considered a separate entity, SpA current concepts include all the clinical forms detailed in the following sections.

Undifferentiated spondyloarthritis

Undifferentiated SpA is the most common type of SpA in children and, in a variable proportion of cases, is the earliest form of AS. In the past they were referred as seronegative enthesopathy and arthropathy syndrome²⁰ and as HLA-B27-associated SpA and enthesopathy in childhood,²⁸ among other terms. Today, most patients correspond to the ERA subgroup of JIA. This subgroup may consist of slight or mild conditions entering into full remission or the earliest manifestation of AS and PsA. Approximately 70% to 90% of Canadian and Mexican patients fulfill the criteria for AS approximately 10 years after onset.^{30,31,32} The frequency of polyarthritis, enthesopathy, and IBP is increased in HLA-B27+ children. MRI may reveal subclinical sacroiliitis in a few cases,^{33,34} but there is no clear evidence that MRI-detected sacroiliitis might predict AS. Besides clinical features, HLA-B27 might help in differentiating joSpA/ERA from other JIA subgroups.

Juvenile-onset ankylosing spondylitis

This term refers to AS starting before the age of 16 years. The diagnosis is usually made 5 to 10 years after onset.^{32,35} This situation makes the diagnosis of AS rare before the age of 16. Back complaints in children and adolescents with AS can rarely refer to symptoms of IBP. Radiographic sacroiliitis (Fig. 104.3) is usually found in symptomatic patients. MRI may show acute sacroiliitis. Early-stage AS corresponds to “undifferentiated” SpA. During episodes of disease activity, 5% to 10% of patients have high-grade fever, weight

loss, muscle weakness, fatigue, lymph node enlargement, leukocytosis, or anemia.^{1,32,35} Up to 27% have acute uveitis, and around 80% have nonspecific gastrointestinal manifestations. Cardiovascular manifestations are rare in children,³⁶ and amyloidosis seldom occurs.

Reactive arthritis

In general, this term is restricted to HLA-B27-associated arthritis triggered by *Salmonella*, *Yersinia*, *Campylobacter*, *Shigella*, or *Chlamydia*. Reiter syndrome (an eponym of historical interest) refers to ReA with associated conjunctivitis and urethritis or cervicitis. ReA has occurred in up to 10% of children with yersiniosis,³⁷ 8% with salmonellosis,³⁸ and 12% with *Salmonella typhimurium* phage type 135a infection.³⁹ ReA predominates in the lower extremities,^{40,41} but some patients with *Salmonella* and *Yersinia* ReA have involvement of the hand joints.^{42,43} ReA is usually mild in HLA-B27-children or those with *Yersinia* or *Campylobacter* infection. In contrast, ReA in HLA-B27+ children may evolve into AS. Infection occurs 2 to 4 weeks before the onset of arthritis, but many patients might not report any symptom of infection. Definitive diagnosis requires identification of a triggering infection. Extraarticular manifestations include aphthous stomatitis, conjunctivitis, erythema nodosum, circinate balanitis, keratoderma blennorrhagica, uveitis, urethritis and cervicitis, aortic insufficiency, myocarditis, and pericarditis.⁴⁰⁻⁴³

Juvenile-onset psoriatic arthritis

Juvenile-onset PsA is defined as concomitant occurrence of arthritis and psoriasis in individuals younger than 16 years. According to the ILAR criteria,² the definition may also include patients with either arthritis or psoriasis and dactylitis, nail pitting, or a family history of psoriasis. Diagnostic exclusions include HLA-B27+ boys older than 6 years and the presence of

AS, ERA, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis in the patient or a first-degree relative. In contrast to the ILAR classification,² the clinical picture of such a group of patients^{3,44,45} is akin to the SpA concept and PsA classification. Moreover, around 25% of patients with juvenile-onset PsA according to the Vancouver criteria⁴⁶ may not fulfill the ILAR criteria.⁴⁷

The age at onset is usually between 7 and 13 years. Predictors of PsA in children with JIA in the initial 6 months are psoriasis in a first-degree relative, age at onset older than 6 years, and HLA-DRB1*11/12, as well as dactylitis and ankle or toe arthritis.²⁷ Some PsA features are associated with HLA-B27,^{27,46-48} but other HLA alleles are only weakly associated.

Juvenile-onset PsA includes two subpopulations⁴⁶⁻⁴⁸: the younger group is composed mainly of girls with polyarthritis involving the hands, dactylitis, and antinuclear antibodies; the older group includes boys with persistent oligoarthritis, enthesitis, and axial symptoms.⁴⁸ Overall, arthritis is the initial manifestation in 50% of cases, psoriasis in 40%, and their combination in 10%. At onset, 70% of children have oligoarthritis^{27,44}; in a short time, polyarthritis develops in most patients. Small-joint and wrist arthritis differentiates oligo-PsA from oligo-JIA.⁴⁹ Radiographic changes include osteopenia and joint space narrowing, periostitis, erosions, destructive changes, or ankylosis of the hand, cervical spine, and hip joints. MRI might show inflammatory changes in the sacroiliac and spinal joints, as well as in peripheral sites.⁴⁵

Most children have slight or mild skin and nail lesions; 80% have psoriasis vulgaris.^{43,46} Systemic manifestations include chronic iridocyclitis in 15% of patients and fever, pericarditis, IBD, or amyloidosis in a very few cases.^{45,46}

The arthropathy of inflammatory bowel disease: Crohn disease, ulcerative colitis, and indeterminate colitis

In 18% to 30% of patients with Crohn disease and 15% of those with ulcerative colitis the disease starts before the age of 20.⁵⁰ Nine percent of those with Crohn disease and 10% to 20% of those with ulcerative colitis have peripheral arthritis: 1.7% 1 year after the onset of IBD and 4.2% by 10 years.⁵¹ Most patients have peripheral arthritis with or without axial symptoms. Around 50% of children with arthritis associated with IBD have single or recurrent attacks of lower limb monoarthritis or oligoarthritis for less than 4 weeks⁵²; half of such children have simultaneous episodes of

arthritis and gut exacerbations.^{51,52} This type of arthritis does not resemble that of joSpA/ERA, and permanent functional limitations or joint damage do not develop in most patients. In contrast, spondylitis and radiographic sacroiliitis are associated with HLA-B27 in older boys, but this type of arthritis is rare.

Ankylosing tarsitis

This term refers to a set of clinical and radiographic findings, including inflammatory (joint synovitis, enthesitis, tenosynovitis, and bursitis) and proliferative (periostitis, enthesophytosis, and bony ankylosis) changes originally described in HLA-B27-associated joSpA/ERA (Fig. 104.4).⁵³ Some



Fig. 104.3 Grade 3 bilateral sacroiliitis of 6 years' duration in a 14-year-old boy. There is subchondral sclerosis of the iliac bone, joint surface irregularities, which include some erosions on both sides, and joint space narrowing of the hips. (From Burgos-Vargas R. *The juvenile-onset spondyloarthritides*. In: Weisman MH, van der Heijde D, Reveille JD, editors. *Ankylosing spondylitis and the spondyloarthropathies*. St. Louis: Mosby; 2006. p. 94-106.)

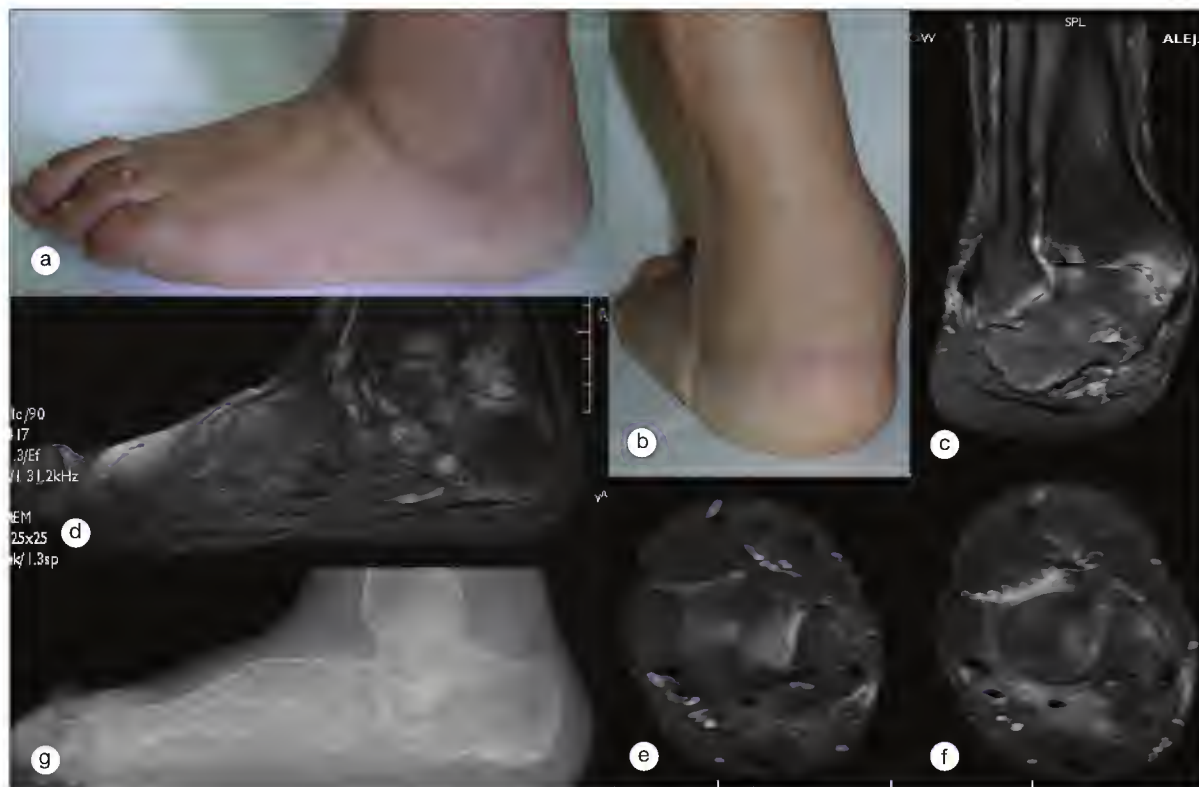


Fig. 104.4 Composite images of ankylosing tarsitis in a 16-year-old boy with ankylosing spondylitis of 9 years' duration, complete ankylosis of the tarsal bones, and grade 2 bilateral sacroiliitis. (a and b) Flatfoot and swelling around the ankle. (c to f) T2-weighted fat-suppressed magnetic resonance images showing edema in various tarsal bones, joint spaces (c and d), and soft tissues (e and f) surrounding the tendons of the posterior aspect of the foot on the coronal view (g). Complete ankylosis of the tarsal bones and an enthesophyte at the plantar fascia attachment are seen. (Modified from Burgos-Vargas R. *A case of childhood-onset ankylosing spondylitis: diagnosis and treatment*. *Nat Clin Pract Rheumatol* 2009;5:52-7.)

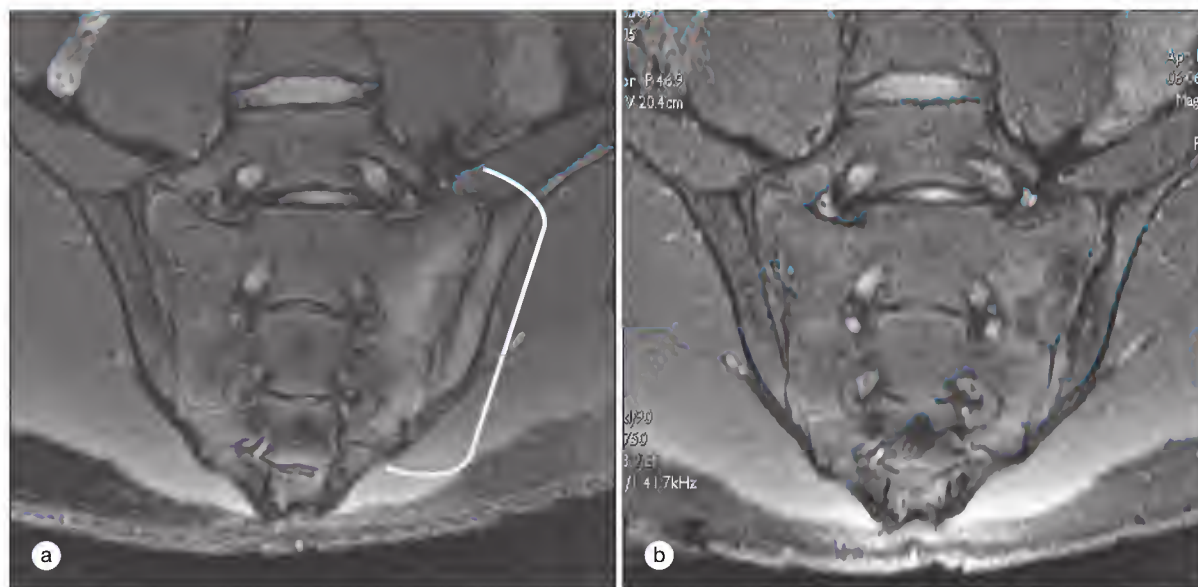


Fig. 104.5 Short tau inversion recovery (STIR) magnetic resonance image of the sacroiliac joints of a 16-year-old boy with a 3-month history of gluteal pain and a 3-year history of peripheral arthritis and enthesitis before (a) and 14 weeks after (b) treatment with infliximab, 5 mg/kg, at baseline and at weeks 2 and 6. Note edema of the iliac bone and sacrum (line) and part of the inferior quadrant of the sacrum on the opposite side, which cleared after treatment.

of these findings resemble those of the spine and sacroiliac joints in AS. Patients with ankylosing tarsitis have midfoot swelling associated with perimalleolar and Achilles tendon swelling; decreased mobility of the tarsal, ankle, and MTP joints; pes planus; and hyperextension of the MTP joints. Radiographic features include diffuse osteopenia, joint space narrowing, and ankylosis of most tarsal joints, as well as bone cysts, erosions, and osseous proliferation at the enthesis. MRI shows hyperintense signals in bones, synovial sheaths, bursae, and rarely, the joint space. Histopathologic findings include slight inflammatory changes but striking osteocartilaginous proliferation. Ankylosing tarsitis may occur in patients with undifferentiated juvenile-onset SpA and with AS before radiographic sacroiliitis.

THERAPEUTIC APPROACH

Treatment is directed at reducing the intensity and duration of the signs and symptoms of disease and consequently improving health-related quality of life.⁵⁴ There is still no evidence that any treatment might halt disease progression.

NSAIDs provide symptomatic relief for most patients with mild symptoms. Oral and intraarticular glucocorticoids may be beneficial in patients with moderate or severe disease activity who do not respond to NSAIDs. Most patients receive sulfasalazine, which has shown some efficacy,⁵⁵ or MTX without any clear evidence of efficacy in patients with joSpA/ERA arthropathy or enthesopathy. It seems that these drugs may improve psoriasis, anterior uveitis, and keratoderma blennorrhagica in some patients.

The use of TNF- α blockers represents the most significant advance in therapy for joSpA/ERA, including AS and PsA.⁵⁶⁻⁶⁰ The antiinflammatory effect of etanercept, infliximab, and adalimumab is clearly noticed within the first few weeks of treatment, and long-term administration of these drugs provides sustained relief. However, retrospective studies of joSpA/ERA suggest that fewer patients evolve to inactive disease and, moreover,

discontinuation of TNF blockers seems to be less successful than in other JIA subgroups.⁶⁰⁻⁶³ MRI of peripheral and sacroiliac joints may also show significant improvement of inflammation with TNF- α blockers (Fig. 104.5). TNF- α blockers have been considered safe and well tolerated. The U.S. Food and Drug Administration (FDA) issued a boxed warning* highlighting the increased risk for cancer, including lymphoma, leukemia, and melanoma, in children and adolescents who receive anti-TNF agents. However, because of the relatively rare occurrence of these cancers, the limited number of pediatric patients treated with TNF blockers, and the possible role of other immunosuppressive therapies used concomitantly with TNF blockers, the strength of the association between TNF blockers and development of a malignancy cannot be fully characterized.⁶⁴

Lower limb involvement may affect walking, climbing stairs, and the standing position. Those with axial involvement may have an important reduction in spinal mobility and chest expansion. Therefore, patients should be enrolled in physical and occupational therapy programs in which rest, dynamic splints, and exercises for muscle strength and stretching are implemented on an individual basis. Surgical modalities such as soft tissue release, synovectomy, tendon repair, arthroplasty, and joint replacement may be indicated for some forms of hip, knee, and MTP disease.

joSpA may profoundly harm the quality of life of children and adolescents and therefore their transition to adulthood. Thus, it is important to consider the psychological, educational, and socioeconomic aspects of the patient's life. Disease activity and, later, disease damage may affect these individuals' social life, including personal and family activities, education, and jobs.

*Cancer warnings required for TNF blockers. Available at <http://www.fda.gov/>. Accessed August 5, 2009.

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Connective tissue diseases in children

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- Connective tissue diseases of children differ from their adult counterparts in important characteristics, including presentation, course, subtypes, responses to therapy, and morbidities.
- Juvenile-onset systemic lupus erythematosus is a severe, relapsing, chronic multisystem disease, characterized by widespread inflammation and damage to any organ. There is a marked difference in the pattern of organ involvement compared with adult-onset disease, with more severe disease in childhood.
- Juvenile dermatomyositis is a complex multifactorial disease whose management requires participation of a wide range of specialists over many years; better recognition to aid rapid diagnosis and international collaborative efforts will ultimately lead to more individualized treatment choices and improved outcomes.
- Localized linear scleroderma is the most common form of childhood scleroderma and can show good response to corticosteroid and immunosuppressant therapy.
- Management of these disorders has been hampered by severe lack of an evidence base; significant progress is now being made in determining the specific characteristics of these pediatric diseases, including describing etiopathogenesis, developing disease activity measures and outcome scores, and establishing the best treatment modalities.
- Caring for children and young people with these complex diseases requires an age-appropriate and multidisciplinary approach to encompass developmental, growth, and family needs of the patient.

INTRODUCTION

Connective tissue diseases of children include a wide range of multisystem disorders, most of which may present with multiple and varying symptoms. The pediatric connective tissue diseases include juvenile dermatomyositis, juvenile systemic lupus erythematosus, childhood scleroderma, and a range of overlap disorders and less clearly differentiated conditions. Although these diseases have parallel conditions in adults (e.g., systemic lupus erythematosus and dermatomyositis), they also differ from their adult counterparts in presentation, course, subtypes, responses to therapy, and morbidities. The treatment of children and young people with complex disease requires an age-appropriate and multidisciplinary approach to encompass developmental, growth, and family needs of the patient. Chronic disease in young people affects the child's whole physical and emotional development; thus time devoted to discussing all aspects with children, young people, and their families is essential. In addition, it is increasingly recognized that pediatric connective tissue disorders may be active well into adult years or may produce lifelong sequelae, such as increased risk of cardiovascular disease.

This chapter focuses on childhood lupus, dermatomyositis, and scleroderma. As well as these delineated conditions, children with connective tissue diseases frequently have features of more than one connective tissue disorder, so that their disease is said to "overlap." An example is a child with juvenile dermatomyositis with features of scleroderma, such as Raynaud phenomenon. Additionally, it is well recognized that these conditions may evolve, with new features appearing over time that may be more typical of a different disease. For example, children with arthritis may develop lupus-like features. Such overlap between connective tissue disorders means that children need to be carefully assessed and reexamined on a regular basis.

JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

Juvenile-onset systemic lupus erythematosus (JSLE) is a severe, relapsing, chronic multisystem disease, characterized by widespread inflammation and damage to any organ. It is lifelong and potentially life threatening, and at present there is no cure.

Epidemiology

Robust epidemiologic data in childhood are lacking. Overall, 15% to 20% of patients with lupus develop the disease in childhood, but its true annual incidence is unknown. Prevalence rates vary widely between 4 and 250 per 100,000, with greater prevalence in Afro-Caribbean, Asian, Latino, and Native American children. The female-to-male ratio (approximately 5:1) is lower in the pediatric population than in adult-onset disease, especially in prepubertal children. Male gender, early onset of disease, and nonwhite ethnicity are all associated with worse outcome.

Etiopathogenesis

JSLE is the archetypal pediatric systemic autoimmune disease. Its cause remains unknown. Hormonal and environmental factors act on genetically prone individuals over time, which results in the development of autoimmunity and disease progression.¹ Hormonal influences are less likely to play a significant role in children who develop lupus before puberty. JSLE is more common in children with genetic defects of the immune system, including complement deficiencies and selective immunoglobulin A deficiency. Rare genetic disorders associated with pediatric lupuslike syndromes offer important insight into immune dysregulation resulting in lupus development.

Few studies have investigated the specific immunopathologic characteristics of JSLE; increased apoptosis and defective clearance of apoptotic material probably contribute to the pathogenesis. Neutrophil apoptosis is significantly increased and dysregulated in JSLE patients compared with control subjects.² Increased Toll-like receptor expression triggered by auto-antigen binding induces an interferon- α response.³ JSLE patients demonstrate a strong type I interferon signature.⁴

Clinical presentation

Lupus is a complex illness at any age. Diagnosis can be particularly challenging during childhood and adolescence. Extremely variable in its clinical manifestations, it ranges from a relatively mild to a severe life-threatening illness.⁵ Its nonspecific features, including fever, fatigue, weight loss, mouth ulcers, arthralgia, and headaches, often occur in children for other reasons. Revisions to the American College of Rheumatology (ACR) classification criteria for lupus⁶ need to be formally assessed in the pediatric age group. Failure to meet ACR criteria at time of presentation does not exclude lupus; individuals with two or three features may develop others later. A marked difference is noted in the pattern of organ involvement and severity in JSLE compared with adult-onset disease (Table 105.1).^{7,8} The butterfly rash may be subtle or absent in children (Fig. 105.1), but many exhibit marked photosensitivity. Cardiopulmonary manifestations in JSLE are increasingly recognized. Significantly more major organ disease occurs in childhood, especially at diagnosis, including hematologic, renal, and neurologic involvement.⁸ Hematologic involvement is frequent. Neuropsychiatric manifestations are common and need careful evaluation. They cause significant long-term morbidity, manifesting as headaches, mood disturbance, confusion, seizure activity, psychosis, and aseptic meningitis. Renal involvement

TABLE 105.1

Difference in pattern of presentation, disease severity, and damage between childhood- and adult-onset systemic lupus erythematosus

	Childhood onset (n = 67)	Adult onset (n = 131)	P value
Duration of follow-up (in years, mean ± SD)	3.2 ± 2.0	3.5 ± 2.6	
Patients with any renal involvement	52 (78%)	68 (52%)	.0005
Oral prednisolone	65 (97%)	92 (70%)	<.0001
Pulse methylprednisolone	20 (30%)	15 (11%)	.001
Immunosuppressive medications	44 (66%)	48 (37%)	.0001
SLEDAI score at diagnosis (mean ± SD)	16.8 ± 10.1	9.3 ± 7.6	<.0001
Adjusted mean SLEDAI score (mean ± SD)	5.70 ± 2.68	4.59 ± 3.05	.012
Adjusted mean renal SLEDAI score (mean ± SD)	2.37 ± 2.38	0.82 ± 1.59	<.0001
Mean SDI score at end of follow-up (mean ± SD)	1.70 ± 2.67	0.76 ± 1.16	.008

SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. Adapted from Brunner HJ, Gladman DD, Ibanez D, et al. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2008;58:556-62.



Fig. 105.1 Cutaneous manifestations of juvenile-onset systemic lupus erythematosus. (a) Severe confluent, photosensitive, erythematous malar or “butterfly” rash in a 7-year-old boy with grade IV lupus nephritis and C1q deficiency. (b) Symmetrically distributed, maculopapular, erythematous to violaceous, pruritic rash in the same child, also on the trunk, with accentuation in ultraviolet light—exposed areas and typical sparing of the knuckles. (c) Widespread symmetric facial erythema, edema, and malar rash with typical nasolabial sparing in a teenage girl with severe cutaneous, pulmonary, and hematologic involvement. (d) A wide range of other skin manifestations may be noted, including nail-fold capillary changes, vasculitis, and chilblainlike lesions, nodules, and erythematous plaques.

occurs very frequently in JSLE.⁹ Children with lupus are at particular risk of infection, which is associated with a worse prognosis, from the disease process itself and use of immunosuppressants. Pneumococcal sepsis is a particular risk, and vaccination is recommended.

Assessment of disease severity and monitoring of outcome

Optimizing disease control depends on assessing disease activity, but the complexity and variability of pediatric lupus make this difficult.⁵ Numerous composite scores have been developed for adult SLE to standardize assessment of disease activity, and many are being used in JSLE. The Systemic Lupus Erythematosus Disease Activity Index, Systemic Lupus Activity Measure, and British Isles Lupus Assessment Group score are all highly sensitive to clinical change in children. A disease activity score is a component of the validated Pediatric Rheumatology International Trials Organization pediatric lupus disease activity core set and is included in a proposed definition of response to therapy.¹⁰ Preliminary criteria have been developed for global disease flare in JSLE.¹¹

It is important to assess patients carefully for complications associated with JSLE and adverse effects arising from their therapy. Building on the adult-based Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), a preliminary core set of JSLE measures of damage highlights important differences in pediatrics.¹⁰

SDI modifications for JSLE include growth and development assessments, and need prospective validation.¹² These modifications, and the potential for repair in children, challenge the concept of permanency of damage in JSLE. Adding pediatric-specific domains and revising existing SDI domains to reflect the specific characteristics of JSLE will promote accurate follow-up of patients through to adulthood. Careful clinical assessment, knowledge of normal variation with age, and ability to communicate well with young patients is vital.

Management

The challenges of pediatric practice are especially important in treating lupus patients. The holistic approach to managing JSLE patients increasingly recognizes the specific obligations to provide an expert, multidisciplinary team of specialized health care workers looking after young people and their families. Close collaboration with other specialists is important. The key goals of managing patients with JSLE are to control or abolish inflammatory disease activity, to maintain function and quality of life as they grow and develop, to minimize risk of permanent organ damage (resulting from the disease, its treatment, or complications), to minimize other treatment-related adverse events, and to prevent premature death.

A major difference from adult practice in managing patients with JSLE is lack of a robust evidence base with no controlled clinical trials of any drugs commonly used. Intensive drug regimens are frequently instigated

based on adult data, clinician's experience, retrospective case series, and best-practice guidelines. Adverse effects of these drugs, together with the disease, contribute to associated morbidity, including organ dysfunction, premature ovarian failure and infertility, malignancy, osteoporosis, accelerated cardiovascular disease, and severe and/or recurrent infections. Poor adherence to the treatment regimen is often a major problem. Drug formulation and dosing schedule are also crucial to consider. Less toxic regimens of new drugs and/or combinations of existing drugs that allow reduced dosage are needed. Despite the lack of clinical trials, hydroxychloroquine is widely used in JSLE in view of beneficial outcomes shown in adult studies.¹³ Of particular relevance to long-term care of JSLE patients, hydroxychloroquine has been demonstrated to reduce flare rate and damage accrual; to prevent or alleviate cutaneous and articular manifestations; to have steroid-sparing, cholesterol-lowering, and antiatherogenic effects; and to maintain lupus nephritis remission.

Glucocorticoids remain the mainstay of initial JSLE treatment when there is significant organ involvement. The safest dose, route, frequency, and weaning regimen of steroids remain unknown in JSLE.¹³ However, pulse methylprednisolone (30 mg/kg/day up to a maximum of 1 g for 3 days), repeated after a week and then weekly for up to 6 weeks is a standard induction regimen widely used, along with a weaning dose of oral prednisolone, starting at between 1 and 2 mg/kg/day. In moderate to severe disease, immunosuppressive agents are needed. Methotrexate is steroid sparing and improves mucocutaneous and articular disease in adults; its effect in JSLE is mixed. Azathioprine is widely used in JSLE as a corticosteroid-sparing agent; in cutaneous, hematologic, or renal disease; or after standard cyclophosphamide therapy in lupus nephritis.

The gold standard until recently for treating major organ involvement has been monthly intravenous pulse cyclophosphamide for 6 months, followed by quarterly infusions for up to 2 years.¹³ Small, nonrandomized studies have demonstrated improved renal parameters in lupus nephritis treated with cyclophosphamide.¹⁴ Although cyclophosphamide is better tolerated in younger people, nausea, hair thinning, and infection can be troublesome. Premature gonadal failure is a serious potential complication, although risks are lower among younger women and prepubertal girls with current treatment regimens. Fertility issues are more significant for adolescent males, in whom there is some evidence of reduced fertility even without cyclophosphamide. Risks and benefits, and potential sperm banking before treatment of older teenagers, needs careful discussion.

Mycophenolate mofetil is a widely used alternative for moderate to severe renal and nonrenal disease. It is generally well tolerated with a better safety profile and shows beneficial effects especially in renal disease. To date, experience with mycophenolate mofetil in JSLE is limited, although it offers a significant therapeutic opportunity by being corticosteroid sparing, improving renal function, and reducing disease activity.¹⁵ Recently developed consensus treatment plans for lupus nephritis aim to improve outcome and support conduct of comparative effectiveness studies aimed at optimizing therapeutic strategies.¹⁶

Biologic therapies offer great therapeutic potential in JSLE, although randomized controlled trials of their safety and efficacy are warranted. A number of these are now under way, including a phase 2 trial of belimumab, a human monoclonal anti-BLyS antibody (<http://clinicaltrials.gov/ct2/show/NCT01649765>). Rituximab, a chimeric mouse-human monoclonal antibody resulting in B-cell depletion, has been used in a number of open-label studies for treatment of JSLE¹⁷; results indicate that it can be effective in combination with standard immunosuppressive agents, although safety issues and reemergence of underlying disease may occur.

Clinical severity and outcome

Comparisons with SLE in adult cohorts demonstrate that JSLE is more severe, with greater disease activity, higher cumulative SDI scores, and greater renal damage accrual.^{7,8} Greater use of corticosteroids and immunosuppressant drugs in JSLE and their associated adverse effects emphasize the importance of developing more effective treatments for JSLE. Ten-year survival, which has markedly improved over recent decades, is now approaching 90%. Despite this, mortality in JSLE is higher than in adult SLE, and JSLE remains a devastating disease.

Neonatal lupus syndrome

Neonatal lupus syndrome is caused by transplacental passage of maternal autoantibodies to SSA/Ro and SSB/La to the fetus.¹⁸ Regular fetal monitoring from 16 weeks' gestation is mandatory in all affected mothers to detect evidence of cardiac conduction defects, and careful postnatal monitoring is essential. Skin, hepatic, and hematologic manifestations are self-limiting and

resolve. Cardiac disease can be fatal. Heart block is typically permanent, often requiring cardiac pacing. Affected infants are at an increased risk of subsequent autoimmune disease.

THE PEDIATRIC INFLAMMATORY MYOPATHIES: JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is the most common of the pediatric idiopathic inflammatory myopathies; it typically presents with proximal muscle weakness and rash but frequently affects other organs. Because JDM is a complex multisystem disease, management requires a multidisciplinary team of experts and is aimed at early recognition and aggressive treatment to prevent complications. Proximal weakness in a child needs to be distinguished from an acute infectious process, a neuromuscular disease such as a dystrophy, or myositis that is part of another connective tissue disorder. Other idiopathic inflammatory myopathies, including juvenile polymyositis, in which there is no rash, inclusion body myositis, and eosinophilic myositis, are rare in children.

Epidemiology

The annual incidence of JDM is 2 to 3.5 per million per year with some differences between ethnic groups.^{19,20} Mean age at onset is around 7 years of age,²¹ although JDM may begin at a very young age. JDM is more common in girls (approximate female-to-male ratio of 2.3:1), but there is a lower ratio in children with disease onset at younger than 5 years.^{20,22}

Etiopathogenesis

The pathogenesis of JDM is unknown. A working hypothesis is that environmental triggers affect the immune system of genetically susceptible individuals, leading to damage of capillaries and small vessels of skin, muscle, and other organs.²³ Typical pathologic features in affected muscle are endothelial and small-vessel abnormalities, including capillary dropout, inflammatory changes, muscle fiber major histocompatibility complex (MHC) class I protein overexpression, muscle fiber regeneration or necrosis, and fiber atrophy (Fig. 105.2). An international consensus group has proposed a system to score severity of JDM in biopsy specimens in four domains: vascular/endothelial changes; inflammatory signs; muscle fiber abnormalities, including MHC class I overexpression; and connective tissue changes.²⁴

Like other idiopathic inflammatory myopathies, JDM is a complex disease with polygenic effects, and so large cohorts are required for genetic study; this has been facilitated by large collaborative cohort studies in recent years.^{25,26} The genetic region with the strongest associations for JDM is the human leukocyte antigen (HLA) region: thus HLA-B*08, DRB1*0301, and DQA1*0501 (the extended ancestral haplotype) confer risk of adult and pediatric myositis, and HLA-DPB1*0101 confers independent risk of myositis in particular serologic subgroups. Several HLA alleles, including DQA1*0201, DQA1*0101, and DQA1*0102, are protective in JDM.²⁷ Other loci that may confer risk include the cytokine genes for tumor necrosis factor- α (TNF- α), interleukin-1 α , and interleukin-1 β . Evidence suggests that genes that confer risk for many autoimmune conditions, such as *PTPN22*, are also associated with JDM.²⁸ A recent genomewide association study of both adult and childhood dermatomyositis confirms that many genes known to confer risk of other autoimmune diseases such as diabetes are also associated with myositis.

Autoantibodies are common in JDM; up to 70% of cases are antinuclear antibody positive. The autoantibody profile of both myositis-specific and myositis-associated antibodies in adult and childhood idiopathic inflammatory myopathies is tightly linked with HLA haplotypes and specific autoantibodies associate with particular clinical phenotypes.²⁹ Thus antisynthetase antibodies associate with joint involvement; anti-PM-Scl, with scleroderma-like features; anti-Jo-1, with lung disease; and anti-Mi-2, with classic rashes and milder disease. Recently identified autoantibodies in JDM include anti-p155/140 antibody, present in 23% to 29% of cases and associated with more severe skin involvement and lipodystrophy, which in adults is associated with risk of cancer. Another recently discovered antibody, anti-p140, confers risk of calcinosis in JDM.²⁹ It is not clear whether these antibodies are themselves pathogenic, although immunoglobulin G and complement deposition on small vessels has long been recognized in JDM. However, even in the absence of a direct pathologic role, autoantibodies may provide valuable diagnostic and prognostic tools in the future.

Although triggers of JDM remain unknown, several studies have suggested that infections are common before onset. Evidence from gene expression profiling in muscle tissue suggests a strong type I interferon signature

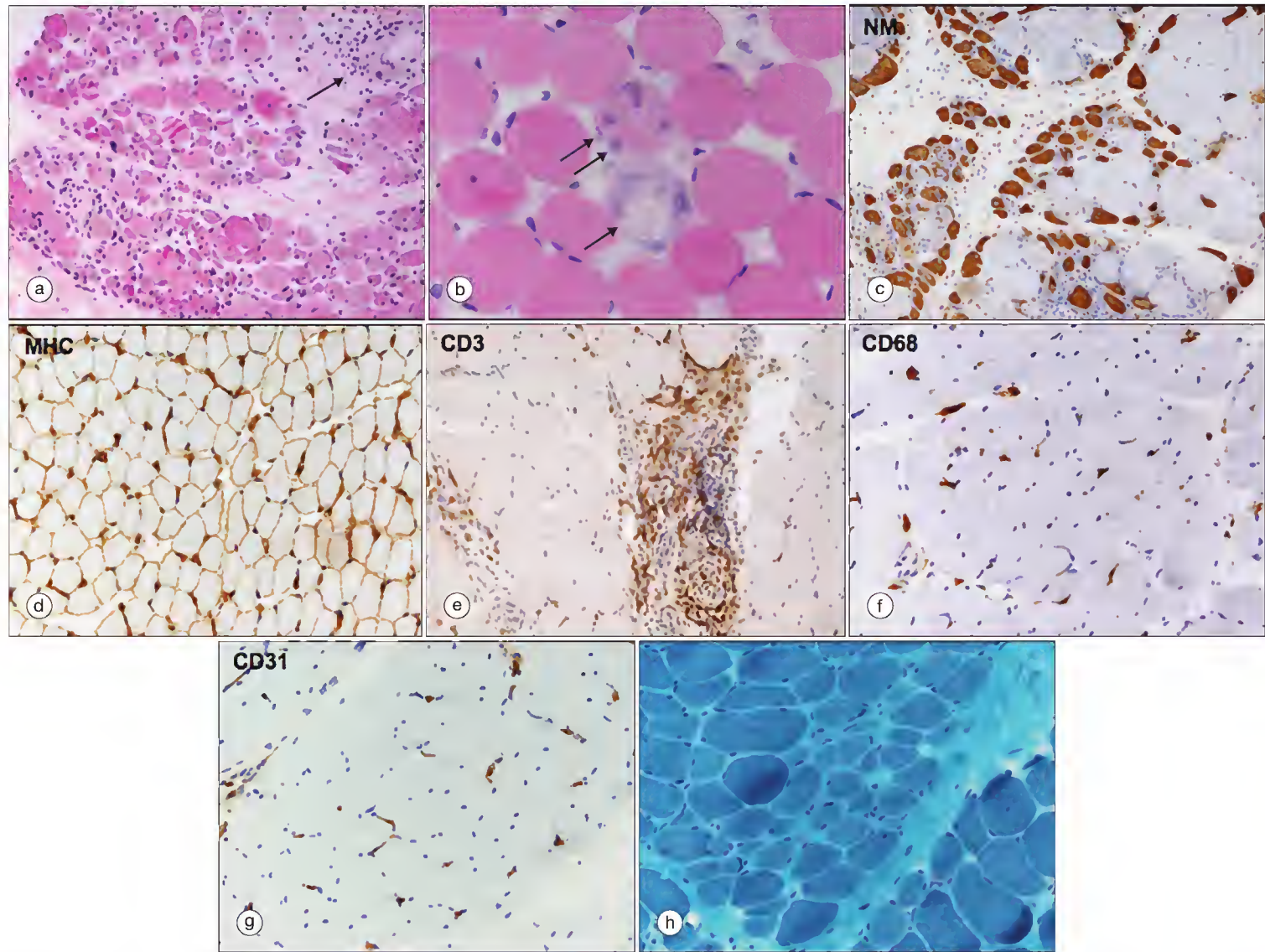


Fig. 105.2 Histologic features seen on muscle biopsy tissue from patients with juvenile dermatomyositis. (a) Variation in fiber size, fiber necrosis, perifascicular atrophy, inflammatory infiltrate (arrow), and increased numbers of internal myonuclei. (b) A necrotic fiber (single arrow) and a fiber with features of regeneration (double arrows) in a high-power photomicrograph. (c) Expression of neonatal myosin, predominantly in a perifascicular pattern. (d) Increased sarcolemmal expression of major histocompatibility class I protein on muscle fibers. (e) Infiltrating T lymphocytes (CD3+) in a perivascular pattern. (f) Infiltrating myeloid cells (CD68+), both perivascular and diffusely infiltrating. (g) Capillary density depletion, as indicated by CD31-stained capillary endothelium. (h) Increased endomysial and perimysial connective tissue deposition. (a and b, hematoxylin-eosin; c to g, immunohistochemical staining for markers as shown; h, Gomori trichrome stain.)

that would support a viral trigger.³⁰ Interferons, likely produced within the muscle by infiltrating dendritic cells,³¹ are powerful mediators of MHC protein upregulation, a characteristic feature of JDM muscle.³² MHC protein overload may contribute to endoplasmic reticulum stress, which is highly damaging to muscle tissue.

Clinical presentation and features

Classic cases of JDM present as proximal muscle weakness and rash, most typically a rash over the knuckles (Gottron papules) and/or a heliotrope rash around the eyes (Fig. 105.3). Onset may be rapid, or slow and insidious, the latter making diagnosis difficult. JDM may present with less typical rashes on the face, extensor surfaces, or axillae. Early ulceration and calcinosis are poor prognostic signs.³³ Nail-fold capillary changes and periungual erythema are common and suggest ongoing active disease. Nail-fold capillaroscopy is a sensitive, easy-to-use bedside investigation that may show typical dilated capillary loops and capillary dropout (see Fig. 105.3).

Diagnostic criteria for JDM, still those of Bohan and Peter,³⁴ require rash with symmetric proximal muscle weakness, raised serum muscle enzyme levels, and abnormal findings on muscle biopsy and electromyography. However, because magnetic resonance imaging (MRI) is increasingly the investigation of choice and electromyography is now rarely performed in children, these criteria are no longer representative of current practice. International efforts to generate more appropriate modern criteria are under

way. A protean range of other clinical features may occur in JDM at presentation or during disease. These include arthritis (approximately 60% of cases), Raynaud phenomenon (which in affected children shows overlap with scleroderma), dysphagia, dysphonia, fevers, mood changes, irritability, anorexia, and abdominal symptoms (Table 105.2).

Assessment and monitoring

History taking, examination, investigation, and ongoing assessment of children with JDM are ideally performed in specialist centers. Muscle strength should be assessed using a validated method such as the Childhood Myositis Assessment Scale (CMAS) or manual muscle testing of a standardized set of muscles (MMT8). Skin involvement should be carefully sought and documented—not only the typical rash but also edema, ulceration, nail changes, and calcinosis. Several tools for skin assessment in JDM have been proposed, including the Cutaneous Assessment Tool (CAT)³⁵ and the skin domains of the Disease Activity Score (DAS).³⁶ Work by the Pediatric Rheumatology International Trials Organization and the International Myositis Assessment and Clinical Studies Group led to proposed core sets of measures of disease activity and damage in JDM^{10,37} that are being validated³⁸; both include parent/patient assessment, physician's overall assessment, muscle strength measurement, functional assessment, and assessment of extramuscular disease.²⁷ Recently criteria for remission have been proposed.³⁹ At presentation, laboratory measurement of blood cell count,

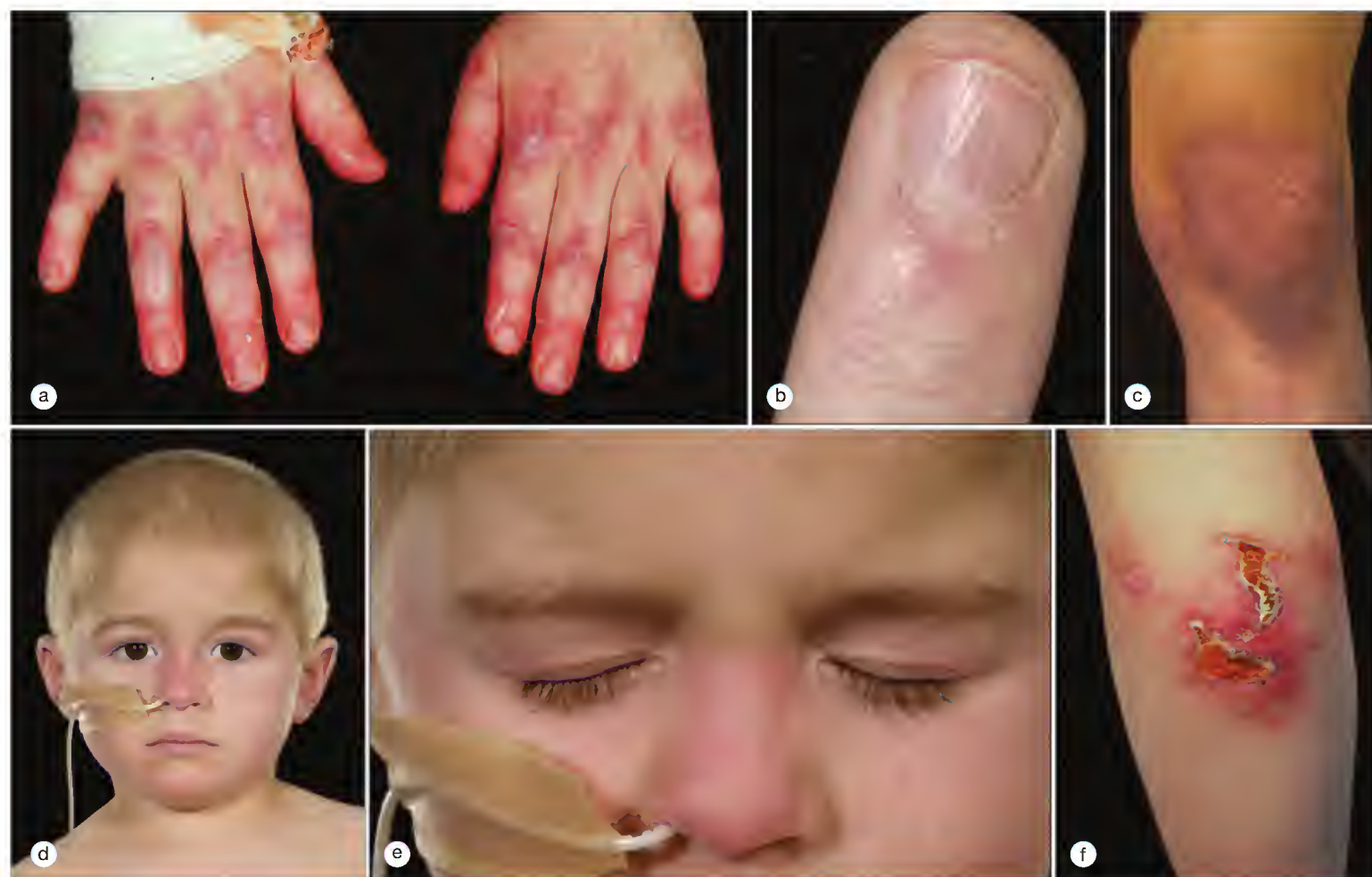


Fig. 105.3 Skin and nail involvement in juvenile dermatomyositis (JDM). (a) Classic Gottron papules over metacarpophalangeal and distal and proximal interphalangeal joints. (b) Periungual erythema and nail-fold capillary loops. (c) Scaly erythematous rash over knees that may be mistaken for other conditions, such as psoriasis. (d) Facial rash in a periocular and nasal distribution, including across the bridge of the nose in a child requiring nasogastric feeding due to dysphagia and risk of aspiration. (e) Close-up of facial rash in same child as in (d). (f) Scarring lesions in a child with JDM with ulcerative skin disease.

erythrocyte sedimentation rate, levels of serum muscle enzymes (creatinine kinase, alanine transaminase, and aldolase if available), autoantibodies, immunoglobulins, and renal and hepatic function should be performed; the latter are also important for drug monitoring. Assessment of autoantibodies may help to delineate overlap disease, such as JDM-scleroderma or JSLE. In the future, autoantibodies may prove useful as prognostic biomarkers in JDM. The use of markers of endothelial activation to measure JDM disease activity is a novel area to date.²⁷ Muscle biopsy can provide useful diagnostic information and helps exclude differential diagnoses such as the dystrophies but is not used in all centers. Quantitative MRI findings can correlate with clinical disease activity,⁴⁰ but protocols are not yet standardized. Specific investigation of complications, such as videofluoroscopy in cases of suspected pharyngeal involvement or high-resolution computed tomography with respiratory involvement, should be considered. Regular monitoring of disease activity over time by measurement of muscle strength, examination of skin and nail folds, and quantification of functional status is vital. Serial MRI assessments may prove sensitive to detect flare of disease, whereas determination of serum enzyme levels is less useful once treatment has been initiated.

Management and outcome

The management of JDM is hampered by a scant evidence base; there are no published randomized controlled trials in JDM, although some are under way. Data from a randomized trial to study the addition of methotrexate or cyclosporine to prednisolone compared with prednisolone alone, given at diagnosis, are currently being analyzed (www.printo.it). The mainstay of treatment remains corticosteroids, usually combined with a disease-modifying antirheumatic drug (DMARD), most commonly methotrexate at a dose of 15 mg/m² per week, preferably given subcutaneously. Because evidence suggests that gastrointestinal involvement leading to poor oral absorption is common, corticosteroids are ideally initially given

intravenously. Pulse methylprednisolone (30 mg/kg/day up to a maximum of 1 g, for 3 days, repeated after a week) is given along with weaning doses of oral prednisolone, starting at 1 to 2 mg/kg/day. Evidence suggests that early use of methotrexate with corticosteroid reduces overall corticosteroid dose and long-term adverse effects such as osteoporosis and growth retardation, while providing disease control as good as that with a corticosteroid alone.⁴¹ Other DMARDs used in some centers include azathioprine (3 to 5 mg/kg/day); hydroxychloroquine (3 to 6 mg/kg/day), especially for rash; cyclosporine (total of 4 to 10 mg/kg/day in two divided doses, with the goal of a trough level of 75 to 100 ng/mL), and mycophenolate mofetil (starting at 150 mg/m² bid, and gradually increasing to a maximum oral dose of 600 mg/m² bid).⁴² Intravenous immune globulin has been shown to provide clinical benefit in a controlled trial in adults and in a number of series in JDM. Recently consensus-based protocols for treatment of JDM have been developed⁴³; with standardized treatment and data collection, it may be possible to assess such treatment protocols outside of conventional randomized controlled trials.

As well as medication, intensive physiotherapy assists in maintaining and restoring muscle strength, and there is evidence that this is safe in JDM.⁴⁴ Use of photoprotection for skin must be emphasized. Other interventions, such as nasogastric tube feeding in cases of dysphagia, speech and language therapy in cases of dysphonia, and specialist skin care, may be needed.

For severe or refractory cases various therapeutic options exist, with the choice being led largely by local experience. Cyclophosphamide, given intravenously monthly at 0.5 to 1 g/m², was shown to be beneficial in a series of refractory cases of JDM with severe features, including severe weakness, dysphagia, skin or gastrointestinal ulcerations, or central nervous system disease.⁴⁵ More recently, severe cases have been treated with biologic agents, including TNF blockers (etanercept and infliximab) and the B-cell-depleting monoclonal antibody rituximab.⁴⁶ The first international randomized controlled trial of rituximab in myositis included adults and children but failed to reach its primary endpoint; however, the data

TABLE 105.2
Clinical features of juvenile dermatomyositis

Feature	Approximate frequency (%)
Musculoskeletal	
Weakness	85-100
Myalgia	62-73
Arthritis/arthralgia	6-66
Raynaud phenomenon	14-25
Mucocutaneous	
Gotttron papules	57-100
Heliotope rash	66-99
Malar or facial rash	42-73
Other rash	
Skin ulceration	23
Calcinosis	6-30
Nail-fold changes	50-91
Mouth ulcers	25-35
Lipoatrophy	10-21
Edema	11-36
"V" sign	2
Gastrointestinal	
Dysphagia	18-44
Dysphonia	17-43
Abdominal pain/discomfort	21-37
Respiratory	
Dyspnea	18-47
Constitutional	
Fevers	16-65
Mood change, irritability	11-45
Fatigue, lethargy	10-85

Figures with wide ranges reflect values from various reports, which may be due to differences in ascertainment or criteria for inclusion in cohorts, time to referral and diagnosis, data at presentation or during disease, or examination protocols.
*Data summarized from McCann LJ, Juggins AD, Maillard SM, et al. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)—clinical characteristics of children recruited within the first 5 yr. *Rheumatology* 2006;45:1255-60; Pachman LM, Hayford JR, Chung A, et al. Juvenile dermatomyositis at diagnosis: clinical characteristics of 79 children. *J Rheumatol* 1998;25:1198-204; Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. *Rheum Dis Clin North Am* 2002;28:833-57; and from unpublished findings.*

suggested that rituximab provided a valuable steroid-sparing effect.⁴⁷ A few very severe cases have been successfully treated by autologous stem cell transplantation.⁴⁸

Long-term outcome of JDM in the modern era is unknown. The high mortality rate experienced before the use of DMARDs has improved, with current mortality estimated at 1% to 2% of cases. However, over time, new features of JDM can develop if disease is not fully controlled and cause serious morbidity and disability, including ulcerations, calcinosis, and contractures. When widespread, the severe "exoskeleton" form of calcinosis in JDM is highly disabling (Fig. 105.4). In a long-term study of 65 patients, 35% were still receiving medication and 40% still had rash at a median follow-up of 7 years; despite this, educational and vocational achievements were high.⁴⁹ Little is known about long-term cardiovascular risk in JDM; as with JSLE there is concern that this will prove to be a serious risk in patients with long-term inflammatory activity. In addition to disease burden, treatment of JDM generates morbidity through adverse effects, in particular from corticosteroids, including osteoporosis, weight gain, and growth retardation; these need to be set against growth inhibition and osteoporosis caused by active inflammatory disease itself. Long-term immune effects of biologic agents such as TNF blockade are not yet known, but careful screening for malignancy is mandatory.



Fig. 105.4 Calcification in juvenile dermatomyositis. (a) Calcinotic lesions on the forearm. (b) Extensive calcification in subcutaneous tissues of the legs seen on a plain radiograph.

JDM is a complex multifactorial disease whose management requires participation of a wide range of specialists over many years. Improved recognition to aid rapid diagnosis, as well as collaborative international sharing of data and a protocol-driven approach to treatment, should ultimately lead to more individualized treatment choices and improved outcomes.

SCLERODERMA

Scleroderma is a rare disorder in which the skin becomes thickened and hard. Scleroderma is divided into two forms: localized scleroderma and systemic sclerosis (SSc). Unlike in adults, localized scleroderma is the most common form in children. Recognition is often late. Scleroderma affects skin, subcutaneous tissues, and underlying muscle or bone. In SSc, the disease involves internal organs and is often preceded by Raynaud phenomenon.

Epidemiology

A British Paediatric Surveillance Unit survey was undertaken to establish the incidence of newly diagnosed childhood scleroderma in the United Kingdom.⁵⁰ Pediatricians and dermatologists reported 94 confirmed cases over 2 years—87 cases of localized scleroderma and 7 of SSc—which gives an estimated annual incidence of 3.4 per million for localized scleroderma (of which 2.5 per million were linear disease) and 0.27 per million for SSc. The localized cases occurred mostly in Europeans (87%), most were linear (68%), and a third of patients had lesions affecting the face and head.

Etiopathogenesis

The cause of scleroderma is unknown. Initiating factors are thought to be multifactorial: environmental triggers acting on a genetically susceptible individual. The hallmark of the disease is increased fibrosis, leading to thickened, hardened skin. There is increased deposition of collagen type I and II, which are synthesized by skin fibroblasts. This may be preceded by endothelial cell injury causing activation of perivascular fibroblasts, which leads to inflammation and tissue edema. Early lesions of the skin can look swollen and red, with a "woody" feel to the subcutaneous tissues. Later on, the fibrotic skin becomes relatively avascular and tight. In SSc, the inflammation and progressive fibrosis are most obvious in the skin but can also affect the

gastrointestinal, respiratory, renal, cardiovascular, and genitourinary systems. Vascular alterations show a predilection for the small arteries and arterioles, with vascular dysfunction as one of the earliest symptoms seen; Raynaud phenomenon occurs in 95% of adults and 75% of children.⁵¹

Clinical presentation

Localized scleroderma

Raynaud phenomenon is uncommon in localized scleroderma (12 of 750 patients in one study).⁵² Localized scleroderma is subdivided into morphea and linear scleroderma. In morphea, oval patches of thickened skin are seen (which can be pigmented), usually on the trunk (rarely on the digits). Linear scleroderma is the most common form seen in children. Thickened bands of skin can follow a dermatomal pattern, affecting the legs, arms, or face. The underlying tissues are often affected, which leads to functional and cosmetic problems. Linear scleroderma of the face is unilateral and may start in the midline, in which case it is called *en coup de sabre*. Localized scleroderma rarely evolves into SSc (1 of 750 cases⁵²).

Systemic sclerosis

SSc is very rare in children. It is divided into limited cutaneous SSc, in which the sclerosis is limited to the distal limbs (below the wrist or ankle) and the face; and diffuse cutaneous SSc, in which the sclerosis also involves the proximal limbs and the trunk. New classification criteria for juvenile SSc have been proposed. As with adult disease, the major criterion is skin thickening, with several minor criteria. The juvenile classification specifies that one major and two minor criteria must be met, whereas the adult classification specifies one major or two minor criteria (Box 105.1). SSc appears to be less severe in children, showing less visceral involvement and better long-term outcome, with renal crises reported in only 1 of 153 patients.⁵¹ Scleroderma can occur as an overlap syndrome with SLE, dermatomyositis, or juvenile idiopathic arthritis; however, patients with those disorders were excluded from these studies.

Management

Treatment is aimed at controlling inflammation; oral corticosteroids are commonly used,⁵¹ although care must be taken in SSc because corticosteroids can precipitate a renal crisis (seen in adult SSc). Second-line

BOX 105.1 PROPOSED CRITERIA FOR JUVENILE SYSTEMIC SCLEROSIS

Major criterion

Skin thickening/tightening/induration of the fingers proximal to the metacarpophalangeal or metatarsophalangeal joints

Minor criteria

Two of the following:

- Raynaud phenomenon
- Sclerodactyly
- Digital skin pitting/ulcers
- Nail-fold capillary abnormalities
- Dysphagia
- Gastroesophageal reflux
- Cardiac arrhythmias
- Cardiac failure
- Pulmonary fibrosis
- Reduced diffusion factor
- Pulmonary hypertension
- Renal crisis
- Hypertension
- Neuropathy
- Carpal tunnel syndrome
- Arthritis
- Myositis
- Tendon friction rubs
- Serologic autoantibodies such as anti-Scl-70

treatments include methotrexate, cyclophosphamide, D-penicillamine (although less since 1998), and mycophenolate mofetil. Vasodilators such as calcium channel blockers are used for Raynaud phenomenon and can help digital ulceration. Iloprost and bosentan are used for severe Raynaud phenomenon and pulmonary arterial hypertension. Physical therapy is important to maintain muscle strength (to counteract skin tightness) and to prevent restriction of movement. Many patients need psychological intervention because of the cosmetic problems, and once the disease is inactive, plastic surgery can be helpful.

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Rehabilitation and psychosocial issues in juvenile idiopathic arthritis

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- Rehabilitation for children with juvenile idiopathic arthritis (JIA) requires a multidisciplinary team approach focused on promoting maximal independent function and participation in activities of daily living, school, work, and leisure.
- Assessment in JIA addresses disease impact in terms of impairment, function, and involvement in life situations, as well as quality of life.
- Rehabilitative interventions use thermal and electrical modalities, therapeutic exercise, splinting and casting techniques, motor skill development, and gait and fitness training to help improve mobility and strength and to limit pain.
- Adaptive strategies and specialized equipment may be needed to favor maximal function at home, at school, and in the community. The presence of JIA has long-term physical and psychosocial implications felt well into adulthood.
- The psychosocial stresses can be addressed through education, self-management courses, counseling, camp experiences, and family retreats.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a complex disease that requires an interdisciplinary approach to treatment. Among the health care professionals typically caring for children with JIA are the pediatric rheumatologist, nurse, physical therapist, occupational therapist, and social worker. Other specialists such as orthopedic surgeons, ophthalmologists, and psychologists may also be consulted.

Rehabilitation professionals such as occupational therapists and physical therapists favor a family-centered approach in which child and parent may be involved in shaping meaningful treatment plans.¹ The goals of rehabilitation extend from improving adjustment to the physical limitations caused by the disease, to favoring functional abilities through daily exercises and adaptive equipment, to promoting the child's participation in life roles needed for proper development, well-being, and psychosocial integration.

In the following the authors have chosen to use the International Classification of Functioning, Disability, and Health (ICF),² which provides health care professionals with a conceptual framework for the description of functioning and disability, and is easily applicable to children with JIA.

In this chapter, JIA is described in terms of (1) impairment, which refers to the loss of body function or structure; (2) limitation in functioning, which refers to the difficulty an individual may experience in executing a particular activity; and (3) restriction in participation, which refers to the problems an individual may experience in involvement in life situations.^{2,3} The chapter first describes each of these disease components, then the measures most frequently used to assess them, and finally the evidence-based research supporting different interventions in rehabilitation.

IMPACTS

Children and adolescents with JIA often have chronic pain, joint tenderness and swelling, stiffness, decreased range of motion, joint deformity, decreased

muscle strength, poor cardiovascular endurance, increased fatigue, and headaches.⁴

Pain

Most children with JIA experience pain that fluctuates with changes in disease status. Sherry and associates showed that 86% of children with arthritis reported pain during routine clinical checkups when visiting their pediatric rheumatologist.⁵ Schanberg and coworkers⁶ found that the 41 children aged 8 to 18 years with polyarticular juvenile arthritis followed daily for 2 months reported pain on 73% of days. On average, participants rated their pain as mild to moderate, with 31% of children indicating they had severe pain.⁶

In response to articular pain, many children with JIA avoid tasks and activities that may be painful, which often leads to muscle and cardiovascular deconditioning.^{7,8} In the presence of regular inflammation, thresholds for afferent nociceptive fibers are decreased to below normal, which may result in higher-intensity and persisting pain that limits simple daily activities.⁹

Structural damage

In juvenile arthritis the number and symmetry of joint involvement differ depending on the different disease categories (oligoarthritis, polyarthritis, or systemic arthritis). Although any joint may be affected, it is the large joints that are most frequently involved. Joint involvement begins with swelling, stress pain at end of range, stiffness, and limited range of motion. The child may also have an enlarged joint caused by increased blood flow to the inflamed tissues.¹⁰ The acute and active phase of the disease is often characterized by morning stiffness, which may result in transient but significant range-of-motion loss.¹⁰

During the acute phase of active disease, intraarticular pressure is increased owing to inflammation. The enlargement of the articular capsule from increased synovial fluid causes stretching of the periarticular tissues. In response to this, to seek relief from pain, patients flex the involved joint, be it the wrist, elbow, or knee, which reduces the intraarticular pressure.¹¹ However, the long-term flexed position can shorten the flexor tendons and muscles, causing contractures and possibly deformity of the involved joints as well as malalignment of the adjoining bones (e.g., malalignment of the fingers when the wrist is involved).

Hand and wrist

Small-joint involvement of the hands is seen mostly in children with polyarticular arthritis. Joint involvement of the hand can range from a single joint to symmetric bilateral involvement. Clinical manifestations of arthritis in the hand include joint swelling, tenosynovitis, dactylitis, loss of range of motion, flexion contractures, joint deformities, and malalignment.⁴ In JIA, the wrist, metacarpophalangeal joints, and proximal interphalangeal joints can be involved. In a cross-sectional study of children with polyarticular JIA, abnormalities of the wrist related to periarticular osteoporosis, osteophytosis, narrowing of the joint space, and growth disturbances of the epiphysis were found in 21 of 23 children.¹¹ Malalignment of the wrist characterized by ulnar deviation and/or subluxation of certain carpal bones is a common deformity in children with JIA. The smaller joints of the hand are also vulnerable to deformity and loss of mobility, such as boutonnière deformities, flexion contractures, and swan neck deformities.¹²

Lower extremities

Children with JIA may also have a significant decrease in muscle strength.^{13,14} Broström and colleagues¹³ showed that young girls diagnosed with JIA who had active disease and lower-extremity involvement had weaker plantar flexor and dorsiflexor muscles than their age-matched peers. Klepper⁸ described children with JIA as having greater limitations in aerobic fitness and muscle strength compared with healthy children, presumably caused by decreased physical activity secondary to disease symptoms.

In addition to limited range of motion, children with JIA may be at risk of other musculoskeletal sequelae, such as leg-length and thigh circumference discrepancy.^{15,16} Clinical consequences of this may manifest as growth delays and premature stunting of the long bones, as well as the small bones of the hands.^{15,16} The reasons for the discrepancy in thigh circumference may be related to disuse or decreased load bearing of the leg due to capsular (or articular) damage, which could cause atrophy of the quadriceps of the involved leg.^{15,16}

Bone mineralization

Children with arthritis are at greater risk of developing osteopenia, that is, bone mineral density that is lower than expected for their age. Disease duration and severity, subtype of JIA (children with polyarthritis are at greater risk), use of corticosteroid treatment, growth retardation and limited physical activity may contribute to this risk.¹⁷ Other factors that may cause low bone mineral density are limited sun exposure, inadequate dietary intake of calcium and vitamin D, and low body mass (weight). Osteopenia can interfere with skeletal maturation and normal growth.¹⁸

Limitations in daily living

The impairments just described have an impact on function in everyday living and may require children to be dependent on family members for many of their activities of daily living, such as self-care and dressing.¹⁹ Children with JIA may have limited dexterity, which can limit their participation in writing activities and other school activities necessary for their development and social integration. Also, certain activities of daily living such as managing small fasteners and utensils may be hindered by finger joint tenderness and range-of-motion limitations. One in five adolescents rated twisting off a bottle or jar top, even if already loosened, and opening soft drink cans as the most problematic daily activities related to fine motor skills.⁴ Other problematic activities for older adolescents were pulling socks up, tying shoelaces, and putting on shoes.⁴ Ability to perform gross motor tasks, such as kneeling or sitting on heels for several minutes, standing for half an hour, and running two blocks, were also reported as limited.⁴ Younger adolescents (14-year-olds) reported problems participating in physical education classes and playing a favorite sport, with boys reporting this more often than girls.⁴ Some adolescents reported that driving was also a problem.⁴

Just over 40% of those diagnosed with JIA report persisting limitations well into adulthood, often as a result of joint deformity and destruction, and osteopenia.²⁰ They often have pain, reduced mobility, and difficulty with daily living.²⁰

PSYCHOSOCIAL IMPLICATIONS

Participation is defined by the World Health Organization as “the involvement of the person in life situations, which is influenced by both intrinsic and environmental factors.”² In children with JIA, increased daily symptoms of pain, stiffness, and fatigue were significant predictors of reduced participation in school and social activities.⁶ It has been shown that if participation remains limited on a long-term basis, children and adolescents may not have enough social contacts with peers, may be less able to make friends, may experience greater social isolation, and may be at greater risk of depression.²¹

Childhood

Children with JIA may also experience decreased participation in play due to pain and stiffness.²² Nevertheless, these children, with support from their families as well as community and health care professionals, may participate in activities with friends either by acting as spectators or by adapting the activity to suit their needs (e.g., walking instead of running).²² Unfortunately, when symptoms are significant children may retreat from certain activities, which affects not only their physical endurance but also their social integration.²²

Children may have to face being scrutinized by their peers in school because of their orthotics and their poor performance in writing activities,

and having to explain their disease to peers and teachers.²³ A qualitative study by Guell²³ explored the impact of JIA on the child's everyday life. Children reported adopting different management techniques to overcome the painful symptoms associated with their disease and to participate as fully as possible, albeit with limitations, in social and school activities.²³ Guell reviewed the notion of disease normalization, in which children and parents aspire for the child to have a normal life and eventually become a productive member of society.²³ Psychosocial issues (e.g., emotional distress, family functioning, mood, stress, coping with pain) can impact a child's participation in school and social activities. Although the global self-esteem of Dutch children with chronic juvenile arthritis did not differ from that of their healthy counterparts, they reported lower competency in athletics, possibly owing to the decreased opportunity to participate in sports compared with their healthy counterparts.¹⁹ Nevertheless, they still reported as many spontaneous social interactions as other children without JIA.¹⁹ With respect to body image, children with polyarticular juvenile chronic arthritis tended to view themselves as thinner compared with their classmates. Children with JIA have been shown to be at increased risk of psychosocial problems in comparison with healthy children.^{4,24} The effects of JIA on the child are felt well into adolescence and adulthood.

Adolescence

In a study of 308 adolescents with JIA, 30% reported frustration and 23% reported depression.⁴ These difficulties were particularly problematic for older adolescents, with 39% reporting frustration as one of their biggest problems and 64% reporting depression. Adolescents with greater disease activity, worse pain, worse general health, and greater functional disability were those most likely to rate frustration as one of their main problems. Similarly, adolescents described depression as their greatest problem when they experienced greater disease activity, worse pain, worse general health, and greater functional disability. Other frequently rated psychological problems included “interacted poorly with brothers and sisters” (19%), “felt sad” (19%), and “argued a lot” (17%).⁴ Thus social functioning and psychosocial adjustment appear to be directly related to the level of disease disability,^{4,21} and those with active or severe disease are at greater risk of social isolation, possibly psychosocial maladjustment, and depression.²⁵

Adulthood

Adults with a history of juvenile rheumatoid arthritis who had greater physical disability had more psychological difficulties.²⁶ Thirty percent were unemployed and believed that their arthritis was the reason for this.²⁶ A study in the United Kingdom confirmed that despite having a higher educational level, adults who had JIA had higher than average rates of unemployment.²⁷ However, a German study reported that of their cohort of patients who had had JIA for longer than 15 years, most demonstrated good social integration and had a lower rate of unemployment than their age-matched peers.²⁸

It is important to emphasize that body structure and function, activity, and participation are strongly linked, so that significant limitations in joint mobility, increased swelling, and pain of involved joints limit execution of daily activities and can hinder participation in age-appropriate roles.

EVALUATION

The impairments that children living with JIA must contend with are assessed using different measures and tools. In addition to the routine evaluation by the rheumatologist to assess the number of affected joints and erythrocyte sedimentation rate to determine disease classification and status,²⁹ other information on the child's function and participation must be collected to obtain a complete overview of the child's health status. Although rehabilitation professionals can also identify painful joints, they hold a key role in quantifying physical limitations in terms of pain, range of motion, and strength, as well as function, health-related quality of life, and participation. Using specific instruments rehabilitation clinicians can help determine change, progression of status, and effects of pharmacologic and rehabilitation interventions.

Pain scales

Pain is a frequent presentation among children and youth with arthritis and is most commonly assessed with self-report scales (Table 106.1).

Range of motion and muscle strength

Joint pain often limits movements and affects muscle strength. Range of motion is measured using different-sized goniometers to accommodate

TABLE 106.1
Pediatric pain measures

Scale	Content/purpose	Age	Reliability	Validity
Pain intensity visual analogue scale (VAS) ³⁰⁻³⁷	Self-report pain intensity visual analogue scale. 100-mm horizontal line anchored with terms "no pain" at left and "worst pain possible" at right. Respondent makes vertical mark on line to indicate his or her level of pain.	3 yr to adult; proxy report recommended for those younger than 8 yr	Fair to moderate test-retest reliability*: $r = 0.41-0.58$ Fair to good interrater reliability: $r = 0.28-0.72$	Moderate to excellent concurrent validity: $r = 0.61-0.90$
Wong-Baker Faces Pain Rating Scale ³⁸	Self-report pain intensity faces scale. Six line-drawn faces with descriptive terms from "no hurt" to "hurts worse."	3-18 yr	Fair interrater reliability: $r = 0.26-0.37$	Moderate to good concurrent validity: $r = 0.67-0.73$
The Oucher ^{33,34,39,40}	Self-report pain intensity scale. Two vertical pain scales: (1) Six-color photographic faces scale for younger children. (2) Numerical rating scale of 0 ("no hurt") to 10 ("the biggest hurt you could ever have") available for older children (8-12 yr).	3-12 yr	Good to excellent test-retest reliability: Photographic scale: $r = 0.88-0.91$ Numerical scale: $r = 0.91-0.99$	Moderate to excellent concurrent validity: $r = 0.62-0.98$
Varni-Thompson Pediatric Pain Questionnaire (PPQ) ^{30,41,42}	Self-report and parent/physician proxy assessing pain intensity, location, sensation, and affective impact. Intensity scale anchored by terms "No hurting, no discomfort, no pain" and "hurting a whole lot, very uncomfortable, severe pain."	5-18 yr	Fair test-retest reliability: $r = 0.29-0.41$ Fair to good interrater: $r = 0.40-0.85$	VAS scores were predictive of disability estimates ($P < .05$) Poor to moderate convergent validity: $r = 0.27-0.68$ with disease status; $r = 0.06-0.45$ with psychological functioning

*The stability of the measures is dependent on how the child recalls the pain.
 r , correlation coefficient

specific joints, whereas muscle strength can be assessed with dynamometers, vigorimeters, or via manual muscle testing (Table 106.2). Irrespective of the method of measurement, therapists must be cautious when assessing strength so as not to cause further pain.

Although it is necessary to assess impairments in body structures, new literature proposes that in addition to functional evaluations, quality of life and participation must be included in the clinical examination to assess health status and improvement accurately.⁵⁴

Function, quality of life, and health status

Although a physical evaluation can give rehabilitation professionals a good overall impression of disease severity, it does not provide enough information to thoroughly estimate the effects of disease activity in terms of the child's function. It has therefore become customary to question patients and family members regarding the limitations experienced by the child during daily activities. Also, results from functional, quality-of-life, and health status measures may be more meaningful to parents than physical measurements. These various measures are described in Tables 106.3 and 106.4.

Very little is known regarding the standardized and systematic evaluation of participation in different spheres of life (academic, social, leisure, and vocational) in children with juvenile arthritis. Different approaches can be used to evaluate participation. Daily diaries give a qualitative view of the person's participation in activities related to school, sports, and social activities.²³ The Child Behavior Checklist, a nonspecific questionnaire, describes the child's social functioning.¹⁹

Standardized assessments of participation for children with JIA need to be developed. A standardized generic assessment of participation, the Children's Assessment of Participation and Enjoyment (CAPE), has been administered to children with JIA.⁶⁸ The CAPE is a 55-item questionnaire designed to examine how children and youth participate in everyday activities outside of their school classes. The CAPE provides information about the following dimensions of participation: diversity (number of activities performed), intensity (frequency of participation measured as a function of the number of possible activities within a category), and enjoyment of activities. It also provides information about the context in which children and youth participate in these activities (e.g., with whom and where they participate).⁶⁹

Ideally, a disease-specific, standardized measure assessing participation related to communication, personal care, housing, mobility, fitness and nutrition, responsibility, recreation, education, community life, interpersonal relationships, attitudes, and beliefs toward involvement in different

activities may provide the health care professional with a comprehensive view of limitations in age-appropriate and meaningful life roles.

GOALS OF TREATMENT: EVIDENCE-BASED TREATMENT AND OUTCOME

Rehabilitation professionals have an important role to play in the care of children with JIA. Typical goals are to limit pain, prevent limitation, promote function, and improve range of motion in affected joints; maintain and improve muscle strength; increase and maintain endurance for activities of daily living; minimize the effects of inflammation; and promote normal growth, development, and participation in age-appropriate activities. Clinicians work closely with children to develop activity programs that suit their activity preferences, motivation, and interests in order to work toward the specified treatment goals. Examples of treatment interventions include home exercise programs; regular therapy sessions; inpatient hospital treatment; serial casting; night-time, serial, dynamic, or shoe splints; use of assistive devices for ambulation, school, and daily-living activities; joint protection; and the use of different therapeutic modalities, including heat, cold, ultrasound, and pool therapy (Table 106.5).

Physical therapists and occupational therapists also encourage and direct children with JIA to adopt healthier and more active lifestyles. In fact, there has been a shift in treatment strategies for children living with chronic conditions from recommending bed rest to now favoring the introduction of moderate exercise programs and promoting physical activity.⁷⁸ The danger that excessive inactivity will cause muscle weakness, joint contractures, and poor bone density is well recognized.⁷⁹⁻⁸¹ Table 106.6 describes the latest findings pertaining to more active treatment approaches. To promote better adherence to treatment, therapists review the importance and purpose of the different prescribed treatment regimens with parent and child.⁸⁷

Rehabilitation professionals may also be involved in treatments favoring the child's integration in school and the eventual workplace, as well as provision of relevant information pertaining to their arthritis, their treatment options, potential community services, and sources of support within the hospital and the community. They may need to consult with key players to help address contextual factors related to the family, school, and peers, including attitudes and perceptions impeding fulfillment of activities. To facilitate daily participation in school activities, health care professionals work with school officials (teacher, principal, physical education teacher)

TABLE 106.2

Tools and techniques for measuring range of motion and muscle strength

Measure	Description	Psychometric properties
Goniometer ⁴³⁻⁴⁵	Protractor with one axis that joins two arms (one stationary, the other movable). Angle of movement for a particular joint is measured by aligning goniometer arms with tested limb.	Excellent intrarater reliability: $r = 0.91-0.99$ Moderate to excellent interrater reliability: $r = 0.58-0.97$ Concurrent validity is established*
Paediatric Escola Paulista de Medicina Range of Motion Scale ⁴⁶	Range-of-motion scale assessing 10 movements: cervical spine rotation, shoulder abduction, wrist flexion and extension, thumb flexion (metacarpophalangeal), hip internal and external rotation, knee extension, and ankle dorsiflexion and plantar flexion. Four-point Likert scale (0 [no limitation] to 3 [severe limitation]). Final score is sum of mean scores for individual movements divided by 10.	Excellent test-retest reliability: $r = 0.96$ Excellent interrater reliability: $r = 0.98$ Moderate construct validity: $r = 0.55-0.65$
Jamar Hydraulic Hand Dynamometer ⁴⁷⁻⁵¹	Isometric grip strength is measured by asking participant to squeeze dynamometer handle. Maximal strength is recorded. During testing, patient sits with shoulders adducted and neutrally rotated, elbow flexed at 90 degrees, forearm in neutral position, and wrist between 0 and 30 degrees of dorsiflexion and between 0 and 15 degrees of ulnar deviation. Handle positions can be changed to accommodate child's hand size.	Excellent intrarater reliability: ICC = 0.90-0.97 Good to excellent interrater reliability: ICC = 0.80-0.95
Martin-type squeeze dynamometer-vigorimeter ⁵¹	Dynamic movement grip strength is measured by asking patient to apply pressure by squeezing a rubber bulb. Maximum force of the squeeze is registered on analogue dial. Various sizes are available to accommodate child's hand size.	Excellent intrarater reliability: ICC = 0.97 Excellent interrater reliability: ICC = 0.89-0.92 Concurrent validity ($r_s = -0.45$) with CHAQ's disability score
Hand-held dynamometer ⁵¹	Isometric force is measured by asking patient to push maximally against plate and piston of hand-held dynamometer with the muscle group being tested. Test limb is in a position not affected by gravity.	Excellent intrarater reliability: ICC = 0.92-0.97 Good to excellent interrater reliability: ICC = 0.80-0.93 Concurrent validity is established.
Pinch meter ^{48,49,51,52}	Pinch strength is measured for all pinch tests, that is, tip to tip, key, and palmar. Patient is simply asked to squeeze pinch gauge and maximal strength is recorded.	Excellent intrarater reliability: ICC = 0.92-0.97 Good to excellent interrater reliability: ICC = 0.80-0.95 Concurrent validity ($r_s = -0.33$) with CHAQ disability score
Manual muscle testing ⁵³	Isometric force is measured by asking patient to push maximally against examiner's hands with muscle group being tested. Test limb is in a position not affected by gravity. Both 0-5 point and 0-10 point scales have been used in clinical setting.	Excellent internal reliability: $r_s = 0.90-0.95$ Good internal consistency: ICC = 0.70-0.76 Moderate construct validity: $r_s = 0.47-0.70$

*The low measurement variability between goniometers supports concurrent validity, in that it would be unlikely that all three tools assessed measure range of motion inaccurately in the same way. Strong inter-rater reliability supports the goniometer as a measure of joint range of motion.

CHAQ, Childhood Health Assessment Questionnaire; ICC, intraclass correlation coefficient; r , correlation coefficient; r_s , Spearman's rank correlation coefficient.

TABLE 106.3

Pediatric functional measures used in juvenile idiopathic arthritis

Scale	Purpose/content	Administration	Time required	Scoring	Interpretation	Reliability	Validity
JAFAR ⁵⁵	Measures physical function by assessing child's ability to independently perform the activity in the past week. Twenty-three activities of daily function are included.	Parent proxy report and child self-report (ages 7-18 yr)	10-15 min	3-point scale (0 = all the time, 1 = some of the time, 2 = almost never). Total scores range from 0 to 46.	Higher scores indicate worse function.	Excellent internal consistency: parent report, Cronbach's $\alpha = 0.93$; child report, Cronbach's $\alpha = 0.85$	Good construct validity: $r = 0.69-0.75$
JAFAS ⁵⁶	Measures performance in completing 10 basic daily tasks.	Administered by physiotherapist or occupational therapist using simple equipment in clinical setting (ages 7-18 yr)	10 min	Participant performs 10 activities for which completion time is compared with a standard "criterion" time. Scores range from 0 to 20.	Lower scores indicate better function.	Good internal consistency: Cronbach's $\alpha = 0.85$	Fair to moderate convergent validity: $r = 0.32-0.59$
CHAQ ⁵⁷	Measures functional status for 30 activities in eight different domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, activities).	Parent proxy report (ages 1-18 yr) and child self-report (ages 8-18 yr)	10-15 min	Participant reports level of activity limitation. Total scores range from 0 (no limitation) to 3 (maximal limitation).	Lower scores indicate better function.	Excellent internal consistency: Cronbach's $\alpha = 0.94$ Good test-retest reliability: ICC = 0.8	Moderate to good construct validity: Kendall's tau-b = 0.54-0.77
JASI ^{58,59}	Part I: Measures activities of daily living and functional mobility; 100 functional items divided into five groups that include self-care, domestic, mobility, school, and extracurricular. Part II: Participants identify up to five tasks that are most problematic and these are reassessed at follow-up.	Child self-report (ages 8-18 yr)	45 min	Seven-point Likert scale of difficulty in performing tasks.	Higher scores indicate better function.	Part I: Excellent test-retest reliability: ICC ≥ 0.95 Part II: Moderate test-retest reliability: $\kappa = 0.57$	Moderate construct validity: $r > 0.50$

CHAQ, Child Health Assessment Questionnaire; JAFAR, Juvenile Arthritis Functional Assessment Report; JAFAS, Juvenile Arthritis Functional Assessment Scale; JASI, Juvenile Arthritis Status Index; ICC, intraclass correlation coefficient; Kendall's tau-b, Kendall's tau-b; Kendall's tau-b, Kendall's tau-b; κ , kappa statistic.

TABLE 106.4
Pediatric quality-of-life and general health measures used in juvenile idiopathic arthritis

Scale	Content/purpose	Administration	Time required	Scoring	Interpretation	Reliability	Validity
JAAQ ^{65,62}	Measures disease-specific health-related quality of life. Includes 74 items: gross motor function (17 items), fine motor function (16 items), psychosocial function (22 items), and general symptoms (19 items). Response options/scale.	Self-report	~20 min	Each item uses seven-point ordinal scale ranging from 1 (none of the time) to 7 (all of the time).	Higher score indicates poorer health-related quality of life.	Good internal consistency	Face, content, and construct validity established.
PedsQL ⁶³ (Core and Rheumatology modules)	Measures health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. Core module: 23-item scale measuring physical function. Items are distributed among four subcategories: emotional, social, and school functioning, physical functioning. Rheumatology module: 22-item scale. Items are distributed among four categories: pain and hurt, daily activities, treatment, worry and communication.	Parent proxy report and child (ages 5-7 and 8-12 yr) and teenager (ages 13-18 yr) self-reports	5 min	0-4 item scale for raw scores is reversed to a 0-100 scale.	Higher scores indicate better health-related quality of life.	Core module: Good to excellent internal consistency for child self-report: Cronbach's $\alpha = 0.86-0.91$ Internal consistency for parent proxy: Cronbach's $\alpha = 0.89-0.93$ Rheumatology module: Fair to excellent internal consistency for child self-report: Cronbach's $\alpha = 0.75-0.86$ Internal consistency for parent proxy: Cronbach's $\alpha = 0.0.82-0.91$	Construct validity established: PedsQL distinguished between healthy children and children with rheumatic diseases as a group.
CHQ-PF50 ^{64,65}	Measures parent-perceived functional health status. Fifty items divided into 13 single and multi-item scales: general health perceptions; physical functioning; general behavior; mental health; emotional or time impact on the parent; family cohesion; change in health; bodily pain; limitations in school, work, and activities with friends due to physical problems and emotional and behavioral difficulties; behavior; mental health and self-esteem; and limitations in family.	Parent proxy report (ages 5-18 yr)	10-15 min	Multi-item scales are transformed to range of 0-100, with 0 indicating poor health and 100 indicating excellent health.	Higher scores indicate better function.	Excellent internal consistency for parent report: Cronbach's $\alpha = 0.93$ Good internal consistency for child report: Cronbach's $\alpha = 0.85$	Construct validity established between child and proxy report ($r = 0.75$) as well as with the JAFAS ($r = 0.69$).
CAHP ^{66,67}	Attempts to measure a wide range of health statuses in disease-specific and generic disorders, including behavior, well-being, self-esteem, impact of disease on the family, and functioning in school.	Parent proxy report and child self-report (ages 7-18 yr)	15 min	Unknown.	Unknown.	Reliability coefficient* = 0.84-0.97	Internal and discriminant validity partially established.

CAHP, Childhood Arthritis Health Profile; CHQ-PF50, Child Health Questionnaire Parent Form 50 items; JAAQ, Juvenile Arthritis Quality of Life Questionnaire; PedsQL, Pediatric Quality of Life Questionnaire.

*Reliability coefficient was not specified.

TABLE 106.5

Therapeutic interventions

Type	Brief description	Therapeutic goal
Assistive devices	- Ambulation (cane, walker, wheelchair) - School writing aid (pencil grip) - Daily living (shoehorn, reacher, etc.)	- Promote independence and function in mobility, school activities, and daily living. - Limit pain.
Splinting ^{70*}		
Hand and wrist ^{11,71,72}	- Cock-up splint (Fig. 106.1) maintains wrist in pronation and 15-20 degrees of extension supported by forearm-based splint extending to middle of palm. - Hand-resting splint commonly worn at rest (Fig. 106.2) maintains wrist in pronation and 15-20 degrees of extension, as well as supporting fingers in slight flexion.	- Limits forced flexed position of the wrist and fingers.¹¹ - Limits pain. - May prevent further contractures. - Decreases ulnar deviation (joint deformity and misalignment).⁷⁴ - May improve grip strength and dexterity and decrease joint swelling.⁷⁵ - May increase function in fine motor tasks.
Elbow ¹¹	Splint is molded to fit anterior portion of arm and extends distally from elbow. Maintains elbow in maximal extension as tolerated by patient and is commonly worn at rest.	- Limits forced flexed position of elbow.¹¹ - May prevent further contractures.
Knee ^{11,73}	Splint is molded to fit behind child's knee to ensure maximal stretching in extension. Maintains knee in maximum extension as tolerated by patient and is commonly worn at rest (Fig. 106.3).	- Limits forced flexed position of the knee. - May prevent further contractures. - May help improve both passive and active range of motion.
Foot ⁷⁴	Custom-made semi-rigid foot orthotics with shock absorbing posts are fit in patient's shoe.	- Limits pain. - Improves speed of ambulation. - Reduces limitations.
Stretching ⁷⁵	Stretching should be maintained for 10 sec, released for 20 sec, and repeated 5-10 times in each session performed twice daily.	- May help improve passive range of motion. - May help prevent further contractures.
Therapeutic modalities ⁷⁵	- Heat is commonly applied for 15-30 min; however, heat should not be used on swollen active joints. - Cold may be applied for 20 min or according to child's tolerance. Cold therapy has an analgesic and vasoconstriction effect and is especially helpful for acute pain. - Ultrasound therapy. - Pool therapy.	- Relieve pain. - Relieve muscle tightness. - May decrease pain.
Massage therapy ⁷⁶	A 15-min massage comprised of two standardized phases given in a progressive sequence in both supine and prone positions, similar to that performed by massage therapists.	- Decreases anxiety levels of both child and parent. - Decreases child's levels of cortisol stress hormone.
Cognitive-behavioral approach by Walco ⁷⁷	- Teaches progressive muscle relaxation and meditation breathing exercises. - Instructs on the use of guided imagery.	Promotes pain management by helping to distract from pain.

*Splints are used in conjunction with regular stretching and pharmacologic treatment to promote treatment efficacy.



Fig. 106.1 A cock-up splint for night use supports the wrist in extension.



Fig. 106.2 A hand-resting splint for night use maintains the wrist in extension and fingers in slight flexion (safe position).



Fig. 106.3 A knee-extension splint is used to help counteract the effects of joint contractures.

TABLE 106.6
Exercise and physical activity interventions in juvenile idiopathic arthritis (JIA)

Intervention	Participants (age)	Study design	Outcomes
15-wk aquatic exercise program ⁸²	25 children with JIA (5-12 yr)	Pilot study (prospective)	Increase in health-related quality of life (general symptoms). No significant positive effects on functional ability, joint status, or physical fitness.
20-wk aquatic training program ⁸³	54 children with JIA (5-13 yr)	Randomized controlled trial	55% decrease in number of swollen and tender joints; results only tended toward statistical significance. No significant positive effects on functional ability, quality of life, and physical fitness.
12-wk circuit-training program including land- and water-based exercises ⁸⁴	9 children with JIA (8-11 yr)	Pilot study (prospective)	Increase in physical function, quality of life, fitness, and energy levels.
Vigorous or gentle exercise over 12-wk period ⁸⁵	80 children with JIA (8-16 yr)	Randomized controlled trial	Increase in physical function for both study groups equally. Better adherence in low-intensity group.
12-wk program including jumping, weight-bearing and muscle-strengthening exercises ⁸⁶	54 children and adolescents with JIA (9-21 yr)	Randomized controlled trial	Increase in bone mineral density. Increase in physical exercise in leisure time at 12-wk follow-up.



Fig. 106.4 Building up the pencil with a specialized grip helps alleviate symptoms of arthritis in fingers when writing.



Fig. 106.5 A thumb-splint can aid in stabilizing the child's thumb during writing activities.

to increase awareness of arthritis, as well as adapt the environment and curriculum as needed.

Occupational therapists may recommend adapted writing tools (Figs. 106.4 and 106.5) and workstations, as well as providing more time for completion of writing tasks and possibly the use of a keyboard to facilitate writing and tabletop activities and to limit pain in involved joints (fingers, wrist, neck).⁸⁸ The child's classes may also be moved to the first floor or the child may be granted access to the school elevator to facilitate mobility if lower extremity joints are affected. To assist the child's transition into adulthood, vocational rehabilitation can be provided and may have an impact on completion of higher levels of education and employment in patients with JIA.^{89,90}

The provision of health-related information through Web-based forums may facilitate accessibility of information regarding disease symptoms, treatment, and self-management techniques, as well as supplying links to community support.⁹¹ This information may help facilitate the child's transition to adult care. Furthermore, organized information programs or workshops provided through community or hospital-based services may favor parental coping, increase understanding of the disease's clinical and treatment implications, and improve the family's involvement in decision-making regarding the child's care and treatment management.⁹²⁻⁹⁴

CONCLUSION

This chapter has addressed aspects of the child's disability related to physical impairments and limitations in activities, and has explored the implications of disease on the child's involvement in social, school-based, and recreational activities. Much research has been completed on the assessment and treatment of biologic and musculoskeletal disease presentations; however, further studies are needed to assess the effectiveness of interventions favoring the child's participation in various age-appropriate roles. An interdisciplinary team approach, together with parent and child, is needed to help the child achieve optimal fulfillment in physical, academic, and social activities to favor health and well-being.

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INFECTION-RELATED
RHEUMATIC DISEASES

107

Infectious arthritis I:
bacterial arthritis

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- Staphylococci are the most common bacteria causing joint and osseous infections, and methicillin-resistant *Staphylococcus aureus* strains are an emerging problem.
- The risk of septic arthritis is increased in patients with rheumatoid arthritis, joint prosthesis, and immunocompromise; in the elderly; and in patients receiving anti-tumor necrosis factor therapy.
- Factors that predispose to prosthetic joint infection are older age, poor nutritional status, coexistence of joint diseases, obesity, diabetes, malignancy, remote infection, prior native joint infection, prosthesis revision surgery, and superficial surgical site infection.
- There is little evidence to guide the choice and duration of antibiotic treatment. The choice of antibiotics currently is based on the risk factors present and the organism considered most likely to be involved.
- The incidence of gonococcal arthritis has decreased, but it is the most common type of septic arthritis in patients younger than 30 years of age.
- The emergence of penicillinase-produced strains of *Neisseria gonorrhoeae* has changed the recommendations for the treatment of disseminated gonococcal infection.
- Musculoskeletal symptoms may appear in the congenital, secondary, or tertiary phases of syphilis but are most common in the secondary stage.

INTRODUCTION

Joint and bone infections are true rheumatologic emergencies because they may cause serious morbidity, permanent disability, or even death. The introduction of antibiotics has changed this course, but only when the drugs are active against the invading microorganism and are administered early. This emphasizes the two most significant problems: early diagnosis and prompt and effective treatment.

SEPTIC ARTHRITIS AND OSTEOMYELITIS

Epidemiology
Septic arthritis

Septic arthritis is an uncommon disease, with few studies large enough to provide robust estimates of incidence. The estimated incidence of acute septic arthritis in industrialized countries varies from 2 to 6 per 100,000 people per year,^{1,2} with the highest incidence occurring in those younger than 15 and older than 55 years of age.³ Thus in children the incidence is between 5 and 12 per 100,000 per year⁴; it is rare in children younger than 3 months of age.³ In patients with rheumatoid arthritis or joint prostheses, the incidence increases to 30 to 60 per 100,000 per year.^{5,6}

Prognosis

The prognosis of bacterial arthritis has not improved significantly, despite the availability of better treatment. Irreversible loss of joint function develops in 25% to 50% of patients,^{1,7} and the outcome depends on the types of microorganisms involved, type of disease, patient age, presence of comorbidities, and length of delay in the start of treatment. Total mortality rates were directly attributed to septic arthritis in 2% to 10% of cases,⁸ with polyarticular septic arthritis having a high mortality rate.²

Osteomyelitis

The incidence of osteomyelitis has been estimated at 2.4 cases per 100,000, with the incidence increasing with increasing age.⁹ Open fractures can lead to osteomyelitis depending on the fracture type, extent of soft tissue injury, and degree of microbial contamination. The incidence of hematogenous vertebral osteomyelitis is 0.5 to 2.4 per 100,000, increases with age,¹⁰ and most often results from hematogenous seeding, direct inoculation during spinal surgery, or continuous spread from adjacent tissues.⁹

Microbiology
Septic arthritis

The main causative organisms of septic arthritis are listed in Table 107.1.¹¹ In all age groups except neonates, *Staphylococcus*, mainly *Staphylococcus aureus*, is the primary cause and is responsible for 37% to 56% of cases. Methicillin-resistant *S. aureus* (MRSA) is an emerging problem, accounting for 25% of all septic arthritis cases in one urban area.¹² Group A and B streptococci are the next most common causative bacteria, mainly in the elderly. This is especially true in patients with chronic diseases such as diabetes, cirrhosis, or neurologic diseases.¹³ Most coagulase-negative staphylococci cultured from joints are contaminants, but they can become true pathogens after surgical arthroscopies, multiple procedures, and placement of a joint prosthesis.⁸ The two most frequent gram-negative organisms are *Neisseria gonorrhoeae* and *Neisseria meningitidis*, which account for up to 20% of cases. Gram-negative organisms such as *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*, and *Enterobacter* are seen infrequently and are more common in the elderly, in immunocompromised patients, and in intravenous drug abusers.¹⁴ Anaerobic organisms cause septic arthritis when there is a history of penetrating trauma. In intravenous drug abusers, *S. aureus* and gram-negative organisms are common along with more unusual microorganisms, including fungi.

Before immunization *Haemophilus influenzae* type b was a common cause of bacterial arthritis in children, but it is now rare. *Kingella kingae* is the most common gram-negative bacillus causing arthritis in children between 2 months and 5 years of age.¹⁵ Septic arthritis in infants younger than 2 months of age can be caused by *S. aureus*, *Streptococcus agalactiae*, or gram-negative enteric bacteria. *S. aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *K. kingae* are the predominant organisms affecting children between 2 months and 5 years of age. Children older than 5 years are more likely to have arthritis caused by *S. aureus* and *S. pyogenes*.¹⁶ *S. aureus* is the microorganism most frequently responsible for septic bursitis.¹⁷

No causative organism is identified in 20% to 50% of patients, most likely owing to initiation of antibiotic therapy before specimens were obtained, inadequate culture techniques, the changing patterns of the organisms, or failure to collect appropriate samples.^{3,9}

Osteomyelitis

Hematogenous osteomyelitis is almost always a monomicrobial infection, with *S. aureus* being the most frequently identified microorganism (see Table 107.1).⁹ Coagulase-negative staphylococci, anaerobic gram-negative bacteria, and *Peptostreptococcus* species can also be isolated. In children, *S. aureus* is the most common causative organism, and recently MRSA has become an increasingly common cause. Group A β -hemolytic streptococci, *S. pyogenes*, and gram-negative enteric bacteria are infrequently causes. Effective immunization against *H. influenzae* has virtually eliminated this cause, and its place has been taken by *S. pneumoniae* and *K. kingae*.^{4,15} Posttraumatic osteomyelitis is often a polymicrobial infection.

Pathogenesis

Septic arthritis

For septic arthritis to develop, pathogens must enter the synovial joint (Fig. 107.1), which occurs via the bloodstream in the majority of cases because synovium is highly vascular and lacks a protective basement membrane.¹⁴ In very young children with osteomyelitis, medullary infection may spread

to the epiphysis and joint cavity through capillaries that cross the growth plate (Fig. 107.2). The periosteum is also thin and does not adhere tightly to the underlying bone, and infection can spread into the surrounding tissues or can arise from contiguous spread.⁴ Finally, pathogens may enter the joint by direct inoculation or penetrating trauma. The risk factors for development of septic arthritis are shown in Box 107.1.^{1,18} The presence of combinations of independent risk factors substantially increases the risk.¹⁸

Osteomyelitis

Hematogenous osteomyelitis is the most frequent type and primarily affects the metaphysis because the bacteria travel through vascular tunnels and adhere to the bone matrix. Animal models show that bone infection becomes

BOX 107.1 RISKS AND PREDISPOSITION FACTORS FOR THE DEVELOPMENT OF SEPTIC ARTHRITIS

- Rheumatoid arthritis
- Prosthetic joints
- Low socioeconomic status
- Advanced age (>80 years)
- Intravenous drug abuse
- Alcoholism
- Diabetes mellitus
- Intraarticular injection
- Skin infections, cutaneous ulcers

TABLE 107.1
Usual causative organisms of septic arthritis and osteomyelitis

Septic arthritis	Osteomyelitis
<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>
<i>Streptococcus pyogenes</i>	<i>Streptococcus pyogenes</i>
<i>Streptococcus pneumoniae</i>	<i>Streptococcus pneumoniae</i>
Coagulase-negative staphylococci	Coagulase-negative staphylococci
<i>Haemophilus influenzae</i>	<i>Haemophilus influenzae</i>
<i>Kingella kingae</i>	<i>Kingella kingae</i>
<i>Mycobacterium tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
<i>Neisseria gonorrhoeae</i>	<i>Peptostreptococcus</i> species
<i>Neisseria meningitidis</i>	<i>Neisseria meningitidis</i>
<i>Escherichia coli</i>	<i>Escherichia coli</i>
<i>Proteus mirabilis</i>	Anaerobic bacilli
<i>Pseudomonas aeruginosa</i>	
<i>Klebsiella pneumoniae</i>	
<i>Salmonella</i> species	
Multiple species of microorganisms	
Fungi	

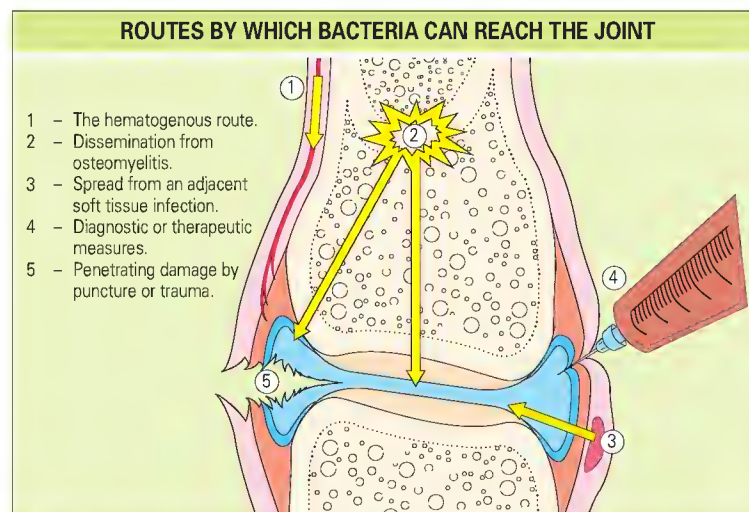


Fig. 107.1 Bacteria can reach the joint via hematogenous spread or by contiguity from nearby infections, open trauma, or directly inoculated by invasive techniques.

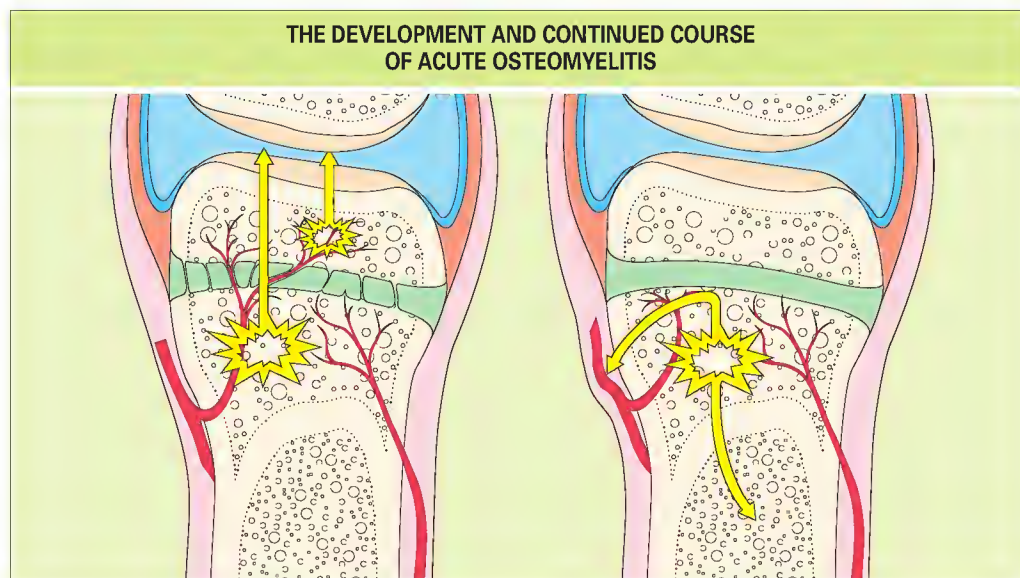


Fig. 107.2 The development and course of osteomyelitis differ with age. In infants younger than 1 year of age the epiphysis is nourished by arteries penetrating through the physis, which allows development of the condition within the epiphysis. In children up to 15 years of age the infection is restricted to below the epiphysis because of interruption of the vessels.

more likely after trauma.¹ Infection of the vertebrae and intervertebral disks is typically hematogenous. Infection occurs via the segmental arterial circulation of the vertebrae and spreads by extension through the endplate into the disk or the lateral plane, which may lead to paravertebral abscesses. Most patients with hematogenous osteomyelitis have underlying chronic diseases.⁹

The virulence of the infecting organism, the size of the bacterial inoculum, and the resistance of the host determine whether infection occurs. The virulence of *S. aureus*, the most prevalent pathogen, depends on the relative inefficiency of innate host defenses when dealing with extracellular toxins and enzymes, components of the cell wall, bacterial DNA, and the expression of a capsule, which is a major determinant of virulence.¹⁹ The process of bacteria interacting with host tissues is highly dynamic and subject to modulation by the regulatory mechanisms of the bacteria, environmental factors, host defense mechanisms, and antibacterial therapy.

Clinical features

Septic arthritis

Septic arthritis usually presents as the abrupt onset of a hot, swollen, and painful joint, but significant delays may occur with low-virulence organisms, tuberculosis, and prosthesis infection. Mild fever is common, but up to 40% of individuals have high fever.⁶ The knee is the most common site in adults and the hip is most common in children, followed by the shoulder, wrist, and ankle.²⁰ Infections of cartilaginous joints is frequent in intravenous drug users.²¹ Patients with sacroiliac septic arthritis have buttock pain, fever, and pain on maneuvers that stress the sacroiliac joint. Infection of the pubic symphysis presents as fever, suprapubic and hip pain, and an antalgic gait. Septic sternoclavicular arthritis can be a result of infected central lines. Septic arthritis usually affects only one joint but is polyarticular in 10% to 20% when comorbid systemic diseases or overwhelming sepsis occurs.²² In children, the pattern of acute septic arthritis is similar to that in adults.⁴ Septic arthritis does not appear to occur more often in patients with human immunodeficiency virus (HIV) infection than in other patients except in patients with advanced HIV infection, who may develop septic arthritis caused by *S. aureus* or opportunistic organisms.²³ Clinical experience suggests that elderly patients are more likely than others with septic arthritis to be afebrile. There may be evidence of an associated skin, urinary tract, or respiratory tract infection, which should provide a clue to the likely infecting organism.

Risk of septic arthritis is increased in patients with rheumatoid arthritis, and *S. aureus* is the microorganism most frequently responsible. Data from the British registries has shown that the use of anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis is associated with a doubling in the risk of septic arthritis, and the risk did not differ significantly between the three anti-TNF agents. The risk was highest in the early months of therapy, and the patterns of reported organisms differed in the cohort receiving anti-TNF treatment. Prior joint replacement surgery was a risk factor for septic arthritis in all patients.²⁴

Long-bone osteomyelitis

Acute osteomyelitis usually produces pain at the affected site and fever. Young infants and toddlers are the most frequently affected and may show irritability and refusal to bear weight and/or to use an extremity (Fig. 107.3). In very young patients, subperiosteal spread may lead to septic arthritis or local symptoms, such as symptoms similar to those that occur when osteomyelitis arises from a contiguous focus of infection. Chronic osteomyelitis usually presents as persistent pain, low-grade fever, and drainage. Subacute Brodie abscess is a chronic form of osteomyelitis that can present without inflammatory local signs (Fig. 107.4).

Vertebral osteomyelitis

Patients with vertebral osteomyelitis usually experience an insidious onset of local pain and tenderness, with fever occurring in fewer than half of cases. The most common site is the lumbar spine (58%), followed by the thoracic spine (30%) and the cervical spine (11%); neurologic impairment, such as sensory loss, weakness, or radiculopathy, is reported in one third of cases.⁹ Vertebral osteomyelitis is in most cases a secondary complication of a distant infection with hematogenous seeding, and the symptoms may initially be dominated by manifestations of the primary infection. The differential diagnosis of back pain in a febrile patient includes a viral syndrome, pyelonephritis, and pancreatitis, among other causes.⁹

Prosthetic joint infection

The rate of infection after primary implantation of a joint prosthesis is approximately 1% for hip prostheses and 2% for knee prostheses, whereas the rate after revision surgery it is somewhat higher. Factors that predispose



Fig. 107.3 An acute osteomyelitis in the proximal metaphysis of the left humerus. The child is not willing to move the affected limb. The roseola is consistent with a *Salmonella* infection, which was confirmed by fecal cultures.



Fig. 107.4 Subacute osteomyelitis (Brodie abscess). The well-defined oval lucency in the distal tibia shows fading sclerosis along its margins in a pattern typical of a bone abscess. Note the small projection of the upper pole of the lesion pointing to the medial metaphysis, where a subtle periosteal reaction is beginning to form (arrow). This identifies the site where this lesion may ultimately drain.

to prosthetic joint infection are older age, poor nutritional status, coexistence of joint diseases, obesity, diabetes, malignancy, remote infection, prior native joint infection, prosthesis revision surgery, and superficial surgical site infection.²⁵ Early infections (less than 3 months after surgery) are caused mainly by *S. aureus*, *Streptococcus*, or gram-negative bacilli, and patients typically have fever, malaise, and local signs of wound infection. Delayed infection (3 to 24 months) is usually caused by less virulent bacteria, such as coagulase-negative staphylococci, and general symptoms are less impressive. Persistent pain is present and local signs may be absent. Late infection (longer than 2 years after surgery) is almost always due to hematogenous seeding, such as from the skin, a dental origin, or a urinary tract infection, and is characterized by sudden local pain and general symptoms.

Differentiation of aseptic loosening from infection is important, because the associated treatments differ (Fig. 107.5). There are no accepted criteria

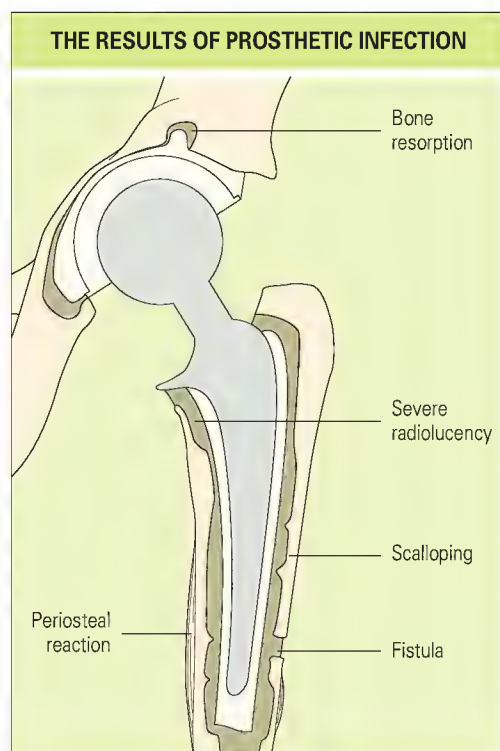


Fig. 107.5 Periosteal reaction, scalloping, severe radiolucency at the interface, fistula through the bone, and severe bone resorption are illustrated. All of these changes can also be seen in mechanical loosening but do not progress as rapidly as in infection.

to diagnose prosthetic joint infection, although it is strongly suggested by the presence of at least one of the following: growth of an identical organism in at least two cultures of synovial fluid or periprosthetic tissue, purulent synovial effusion, presence of granulocytes on periprosthetic tissue, or presence of a sinus tract communication.²⁵ Radiographic findings such as radiolucency, osteolysis, and migration can be present in both infection and aseptic loosening, although changes progress faster in prosthetic joint infection. The usefulness of computed tomography and magnetic resonance imaging (MRI) is limited by artifacts. Radionuclide imaging is the procedure of choice when leukocyte and bone marrow imaging are combined and has an overall accuracy in the range of 88% to 98% (Fig. 107.6).²⁶ New techniques such as positron emission tomography with fluorine-18–labeled fluorodeoxyglucose are not capable of distinguishing aseptic loosening from prosthetic joint infection.²⁷ Treatment of prosthetic joint infection requires a three-stage procedure that includes removal of the infected prosthesis, a long course of systemic antimicrobial therapy, and eventually a new arthroplasty.

Septic bursitis

S. aureus is the microorganism most frequently responsible for septic bursitis.¹⁷ Septic bursitis is more frequent in males and in the olecranon bursa (Fig. 107.7). Risk factors are trauma, alcoholism, preexisting bursal disease, and diabetes, but an absence of risk factors is more common in non-*S. aureus* septic bursitis. The usual pattern is a painful bursa that is hot with swelling and erythema, typically with some evidence of cutaneous injury. Joint function is typically not affected except in cases of severe inflammation. White blood cell counts are typically not as high as in septic arthritis.²⁸

Investigations

A definitive diagnosis should require identification of bacteria either by Gram stain or by culture; however, the gold standard for diagnosis of septic arthritis is the level of clinical suspicion of an experienced

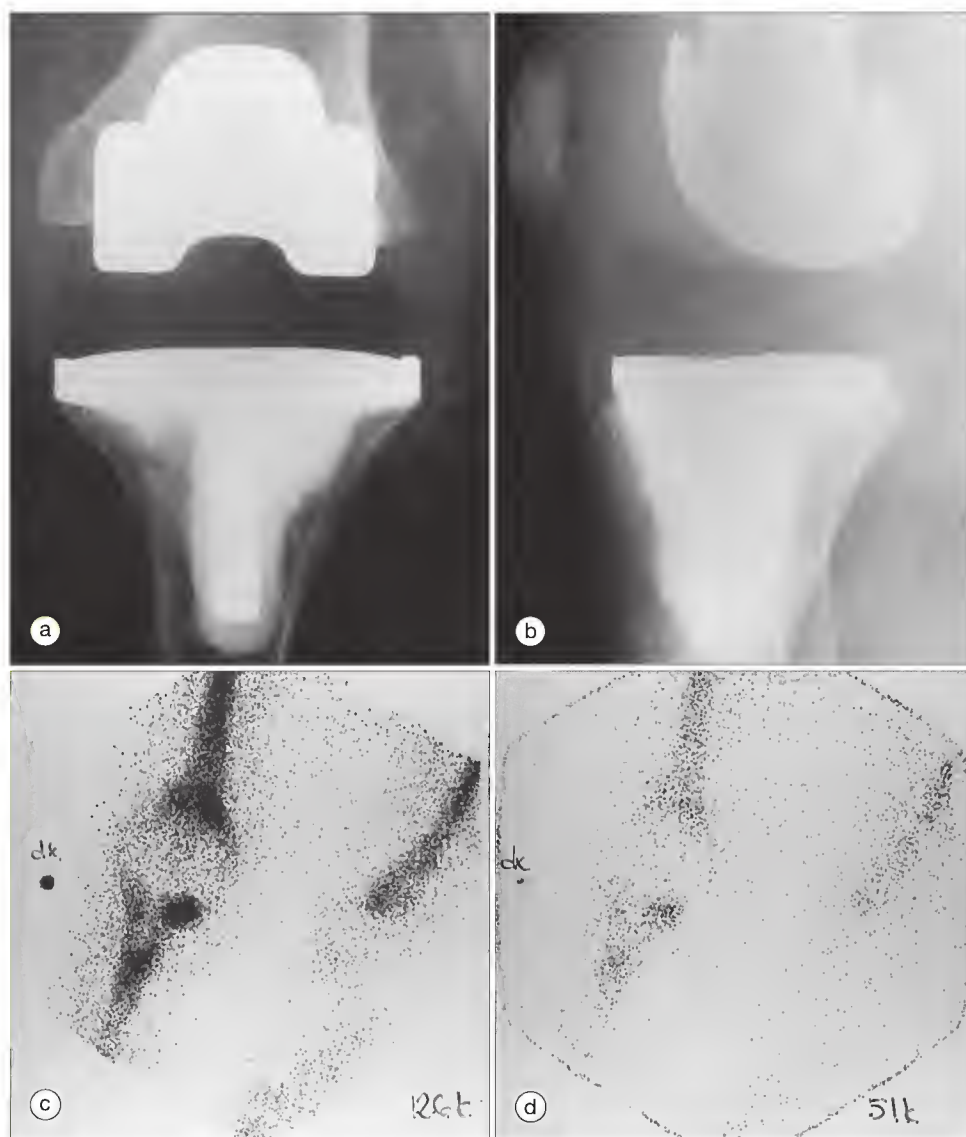


Fig. 107.6 A knee prosthesis 1 year after surgery in a patient with rheumatoid arthritis and severe pain at rest and on weight bearing. (a, b) The radiographs show no abnormalities and no radiolucency. (c) Technetium-99m–nanocolloid scintigraphy shows obvious increased uptake corresponding to the distal femur and proximal medial tibia. (d) The uptake with Indium-111–leukocyte scintigraphy was increased in a similar distribution.



Fig. 107.7 Bursitis symptoms are similar to those of arthritis, but a diagnostic puncture of the bursa containing purulent material in septic bursitis is easy to perform.

physician.²⁵ Clinical suspicion should prompt immediate synovial fluid aspiration by closed-needle aspiration, imaging guidance techniques, or surgical arthrotomy.

Laboratory features

Bacterial arthritis is part of the differential diagnosis of acute monoarthritis. No clinical or laboratory feature is specific for septic arthritis. A high synovial fluid white cell count increases the likelihood of a diagnosis of joint sepsis (Tables 107.2 and 107.3) and should be used in conjunction with clinical, imaging, and other laboratory findings.^{18,29} Infectious arthritis was diagnosed in 77% of patients with synovial white cell counts of more than 100,000/mm³, in 47% with counts in the range of 50,000 to 100,000/mm³, and in 5% with counts of less than 50,000/mm³. A majority of these infections were due to *S. aureus*, whereas infections associated with counts of less than 20,000/mm³ were associated with atypical organisms.³⁰

Synovial fluid glucose level is often depressed, although such values may also be observed in inflammatory diseases such as rheumatoid arthritis.⁸

Microbiologic testing

Prompt microscopic analysis and culture of synovial fluid are fundamental diagnostic tools in the evaluation of septic arthritis, enabling rapid diagnostic confirmation of both joint infection and microcrystalline arthritis.²⁶ In a review, synovial fluid Gram staining was found to yield positive results in only 50% of cases, and synovial fluid and blood cultures were positive for organisms in more than half of cases of nongonococcal bacterial arthritis.¹² One third of specimens from patients not receiving antibiotics and half of those from patients receiving antibiotics showed positive results on culture after inoculation of synovial fluid into blood culture bottles despite negative culture results when conventional solid media were used.³¹ However, a study of 94 synovial fluid cultures for 90 patients with acute joint effusions found no significant differences in the yield of positive culture results with the use of conventional agar plate culture, culture with lysis and centrifugation (Isolator) tubes, and broth-enriched blood culture bottles.²⁹ Blood culture results are positive in approximately 50% of cases in patients with suspected bacterial arthritis (even if fever is absent at the time of initial evaluation). Samples from other sites should be cultured if appropriate, including skin lesions, urine, or other suspected primary foci.

Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly measured in the early evaluation of patients with septic arthritis; the significance of the levels of these markers is uncertain. Elevations of CRP are usually present, although the sensitivity of the ESR test in patients with septic arthritis is inconsistent.³²

New techniques have emerged for the detection of bacteria in biologic fluids. DNA-based techniques, hybridization probes, polymerase chain reaction–based detection, and protein-based detection by mass spectroscopy provide quick results, but their usefulness in clinical practice needs to be proved.³³

Imaging

Conventional radiography should always be the first imaging technique, although it lacks sensitivity and specificity, and abnormalities indicates that

TABLE 107.2
Likelihood of a diagnosis of joint sepsis depending on the number of white blood cells in synovial fluid

Synovial fluid white blood cell counts	Likelihood of a diagnosis of joint sepsis
Fewer than 25,000/mm ³	0.32
More than 25,000/mm ³	2.9
More than 50,000/mm ³	7.7
More than 100,000/mm ³	28

Reproduced with permission from Margaretten ME, Kohlwe J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA 2007;297:1478-88.

TABLE 107.3
Sensitivities and specificities of some laboratory parameters in the diagnosis of septic arthritis

Laboratory parameter	Sensitivity	Specificity	Positive likelihood ratio
Blood white cell counts higher than 11,000/mm ³	75%	55%	1.7
Erythrocyte sedimentation rate higher than 20 mm/hr	75%	11%	0.84
Synovial white cell counts higher than 50,000/mm ³	50%	88%	4
All three together	100%	24%	1.3

Reproduced with permission from Li SF, Cassidy C, Chang C, et al. Diagnostic utility of laboratory tests in septic arthritis. Emerg Med J 2007;24:75-7.

the infection has been present for at least 2 to 3 weeks. In septic arthritis, osteopenia and progressive destruction of the joint and subchondral bone occur. In osteomyelitis, the initial finding is osteopenia, followed by cortical destruction and potentially periosteal new bone formation. Subacute and chronic forms of osteomyelitis have different characteristics on imaging, because marginal sclerosis and areas of osteopenia may be seen that indicate areas of healing. The most specific finding in chronic osteomyelitis is a sequestrum, a fragment of dead bone surrounded by inflammatory tissue that appears radiographically as a focal area of sclerotic bone within an area of lucency. Ultrasonography is very sensitive in detecting joint effusion. Two- or three-phase scintigraphic scans have been shown to be sensitive and somewhat specific; however, in the presence of previous joint or bone damage, the specificity is significantly reduced.³⁴ Indium-111 labeling of leukocytes combined with the use of technetium-99m improves the sensitivity and specificity, and results are considered positive if an uptake of leukocytes without uptake of sulfur colloid is observed.²⁶ MRI with contrast is the most powerful imaging technique for the evaluation of musculoskeletal infections, with a sensitivity of almost 100% and a specificity higher than 75%³⁴ (Fig. 107.8). Acute and chronic osteomyelitis can be differentiated with MRI, because acute infections do not show a sharp zone of transition between normal and abnormal bone marrow and do not have cortical thickening or sequestrum (Fig. 107.9).

Differential diagnosis

The differential diagnoses for bacterial arthritis include gout, pseudogout, reactive arthritis, rheumatoid arthritis, viral arthritis, and Lyme disease, each of which can present with acute involvement of one or a few joints.

Management
Septic arthritis

No randomized controlled studies have evaluated antibiotic regimens for bacterial arthritis. The initial choice of antimicrobial regimen is based on coverage of the most likely organisms to cause infection in this setting, the Gram stain results, the clinical presentation, and case series. Treatment of septic arthritis includes admission to the hospital and daily removal of purulent synovial fluid. Needle aspiration, if possible, is preferable to

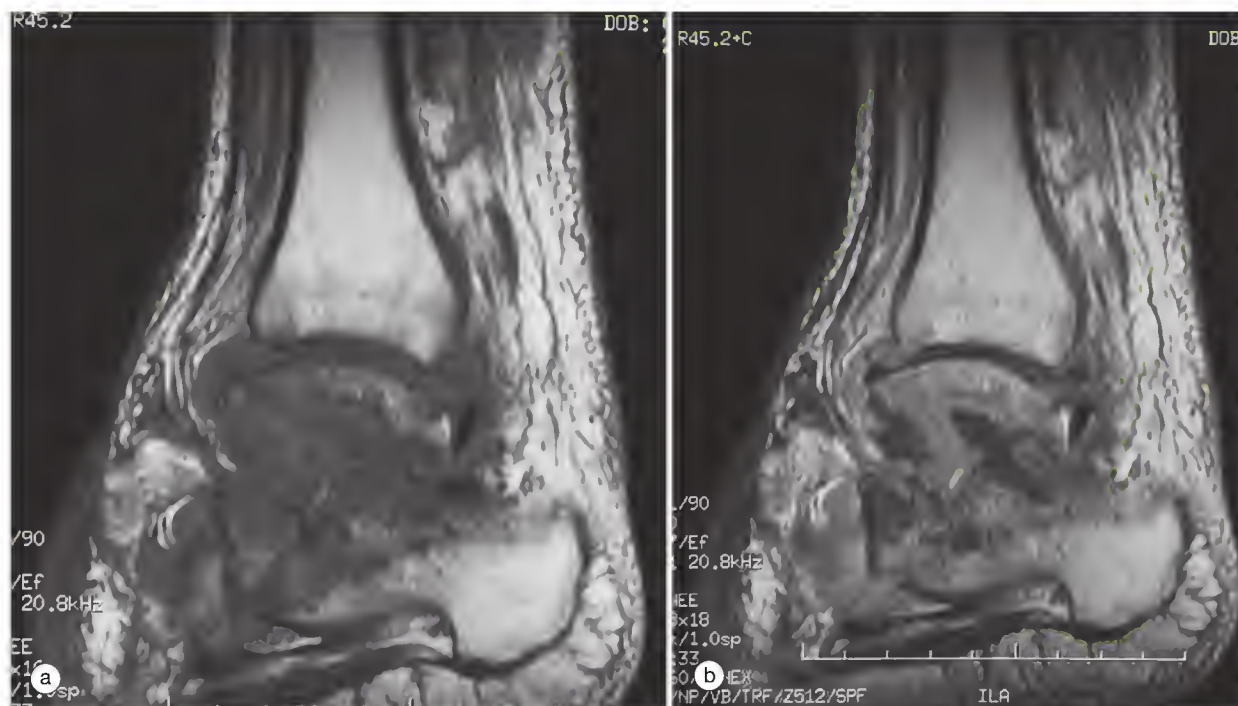


Fig. 107.8 Septic arthritis of the ankle complicated by osteomyelitis. (a) A sagittal T1-weighted spin-echo magnetic resonance image shows severe destruction of the subtalar joint with bone involvement. (b) Contrast-enhanced T1-weighted spin-echo magnetic resonance image shows generalized enhancement of both synovial and bone tissues and abscess formation into the talus and calcaneus.

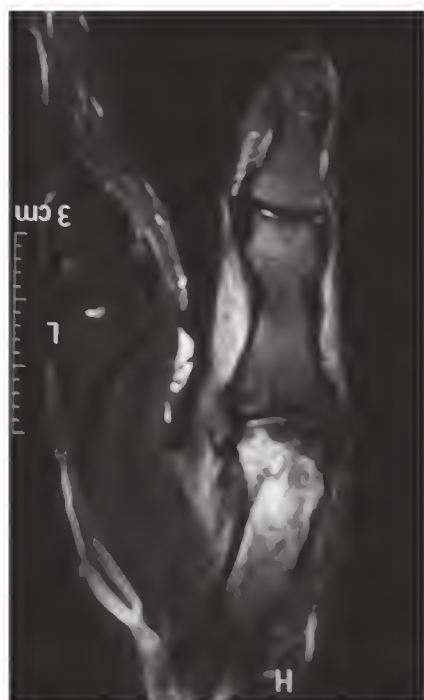


Fig. 107.9 Osteomyelitis. Coronal contrast-enhanced T1-weighted spin-echo magnetic resonance image with fat suppression of first metacarpophalangeal joint. Note bone marrow edema with soft tissue and capsular thickening with gadolinium enhancement.

arthroscopic drainage or surgical drainage.³⁵ It is not necessary to immobilize the infected joint, although weight bearing should be avoided. The joint should be maintained in a functional position, and active exercises can be started when inflammation has substantially subsided.⁶

There is little evidence on which to base the choice and duration of antibiotic treatment, and there are no randomized clinical trials addressing this issue. The usual course of therapy is 2 weeks for infection with streptococci or gram-negative cocci, 3 weeks for staphylococcal infection, and 4 weeks for infection with pneumococci or gram-negative bacilli.⁶ A summary of suggested empirical antibiotic treatment based on different patients groups and a review of the literature is presented in Table 107.4.

TABLE 107.4

Suggested empirical treatment of suspected septic arthritis

Patient group	Antibiotic choice
Patients with no risk factors for atypical organisms	Flucloxacillin, 2 g qid IV. Local policy may be to add fusidic acid 500 mg tid PO, or gentamicin IV. If the patient is allergic to penicillin, clindamycin 450-600 mg qid or second- or third-generation cephalosporin may be administered.
Patients at high risk of gram-negative sepsis (elderly, frail, recurrent UTI, recent abdominal surgery)	Second- or third-generation cephalosporin (e.g., cefuroxime 1.5 g tid). Local policy may be to add flucloxacillin. Discuss treatment of allergic patients with a microbiologist. Gram stain results may influence the choice of antibiotic.
Patients with MRSA risk (known MRSA, recent inpatient, nursing home resident, leg ulcers or catheters, or other risk factors determined locally)	Vancomycin plus second- or third-generation cephalosporin
Patients with suspected gonococcal or meningococcal infection	Ceftriaxone or similar drug, depending on local policy and drug resistance
Intravenous drug users	Discuss with a microbiologist
ICU patients, those with known colonization of other organs (e.g., cystic fibrosis patients)	Discuss with a microbiologist

Note: The choice of antibiotic will need to be modified in the light of the results of Gram staining and culture. It should also be reviewed locally by microbiology departments. ICU, intensive care unit; IV, intravenously; MRSA, methicillin-resistant Staphylococcus aureus; PO, orally; UTI, urinary tract infection. Reproduced with permission from Mathews CJ, Kingsley G, Field M, et al. Management of septic arthritis: a systematic review. Ann Rheum Dis 2007;66:440-5.

Depending on the initial Gram stain results the treatment may be as follows: If the Gram stain preparation shows gram-positive cocci, the recommended treatment is vancomycin (30 mg/kg daily intravenously [IV] in two divided doses, not to exceed 2 g/day).³⁶ If the Gram-stained specimen shows gram-negative bacilli, the recommended treatment is ceftazidime (1 to 2 g IV every 8 hours) or ceftriaxone (2 g IV once daily) or cefotaxime (2 g IV

every 8 hours). Ceftazidime should be given with an aminoglycoside such as gentamicin (3 to 5 mg/kg/day in two or three divided doses) when *Pseudomonas aeruginosa* is considered to be a likely pathogen (e.g., in patients who inject illicit drugs). In cephalosporin-allergic patients, we suggest treatment with ciprofloxacin (400 mg IV every 12 hours or 500 to 750 mg orally twice daily). If the initial Gram stain results are negative, we treat with vancomycin in immunocompetent patients and with vancomycin plus a third-generation cephalosporin in immunocompromised patients, injection drug users,³⁷ and patients with traumatic bacterial arthritis.

The major part of the destructive process is caused by the inflammatory response of the host directed at live organisms and their products, and thus killing of bacteria does not completely eliminate the destructive process.³⁸ Previous findings have shown a significant benefit of dexamethasone in combination with antibiotics in preventing disability in children with septic arthritis.³⁹ In experimental arthritis, the combination of corticosteroids, antibiotics, and bisphosphonates reduces inflammation and bone and cartilage destruction.

Osteomyelitis

Data from randomized controlled trials that were specifically focused on antimicrobial therapy for vertebral osteomyelitis are lacking, and information on cure rates is derived largely from observational studies.⁹ In a meta-analysis of 22 trials of antibiotic therapy for various types of bone and joint infections, with data on 1-year follow-up, the eradication rate was 79% (95% confidence interval, 66 to 94). With the exception of infections associated with orthopedic devices (for which regimens including rifampin appeared to be superior), there were no significant differences in the outcome related to the specific antibiotic therapy used.⁹

In acute hematogenous osteomyelitis, parenteral antibiotics are initially recommended, and abscesses, if present, need to be drained to prevent subsequent bone necrosis. If treatment has been delayed and necrosis of trabecular bone with sequestrum is present, surgical drainage is recommended. Chronic long-bone osteomyelitis in adults is usually treated with a combination of surgical debridement and specific antimicrobial therapy. Appropriate management of dead bone includes placement of a vascularized bone graft, placement of cancellous bone grafts, or temporary use of antibiotic-impregnated acrylic beads. The optimal duration and route of antibiotic administration is not known, but based on experimental animal studies, a duration of at least 4 to 6 weeks is necessary.⁴⁰ Intravenous administration of a β -lactam at high doses (nafcillin, oxacillin, or cefazolin in infections caused by *S. aureus* and vancomycin in MRSA infections) is initially used during the first 4 to 6 weeks,⁹ followed by oral antibiotics with high bioavailability in osseous tissue such as β -lactam antibiotics, quinolones, and rifampicin. In acute hematogenous osteomyelitis in children, 4 to 6 weeks of treatment is considered the standard therapy. There are no data from controlled trials that suggest the optimal duration of therapy. The recommended duration ranges from 4 to 6 weeks to 3 months.⁹

GONOCOCCAL ARTHRITIS

Gonorrhea is a sexually transmitted disease caused by the bacterium *Neisseria gonorrhoeae*. It usually affects the genital area, but it can also affect the throat, anus, or conjunctiva. It is easily transmitted during vaginal intercourse but it can also be transmitted during anal or oral sex and to a newborn during cervical parturition or from endometrial infection.

Epidemiology

The incidence of gonorrhea has declined significantly in developed countries. Disseminated gonococcal infection (DGI) develops in 0.5% to 3% of patients with untreated mucosal infection depending on the regional prevalence of specific strains. The incidence has now decreased, although it is still high in developing countries. In France and the United Kingdom, *N. gonorrhoeae* arthritis has been reported to be responsible for 1.6% and 0.06% of all cases of septic arthritis, respectively.⁴¹

Microbiology

N. gonorrhoeae is a small, gram-negative, nonmotile, and non-spore-forming bacterium that characteristically grows in pairs (diplococci) and exclusively infects humans. The biologic characteristics of gonococcal strains influence their virulence and the risk of disseminated infection. The ability of gonococci to disseminate has been associated with different factors, such as the presence of pili (see later); the serotypes of protein I (porin) and II (opacity-associated protein); different nutritional requirements for arginine,

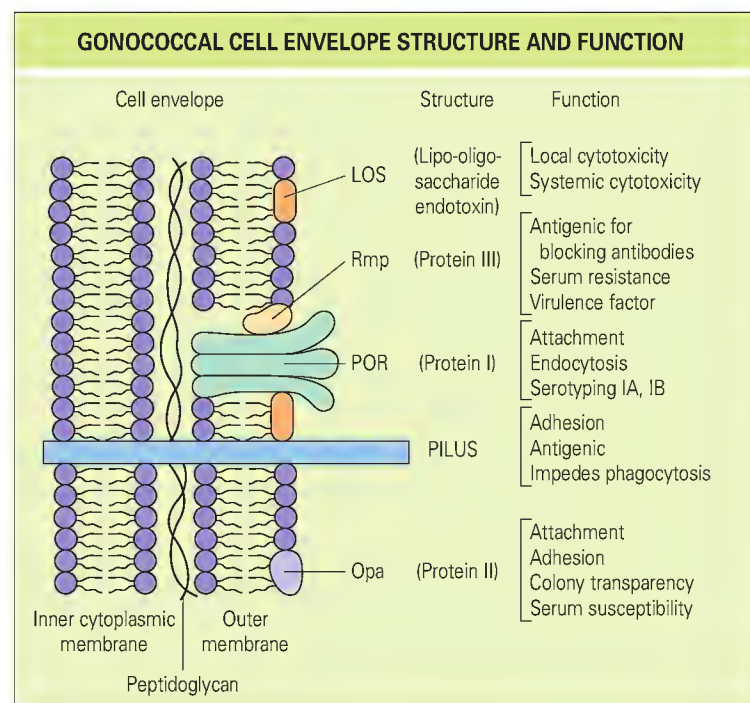


Fig. 107.10 Cell membrane structure of *Neisseria gonorrhoeae* and proteins related to infection pathogenesis. LOS, lipo-oligosaccharide; Opa, opacity-associated protein; POR, porin; Rmp, reduction-modifiable protein.

hypoxanthine, uracil, and proline; and the sensitivity to antibiotics. The cell membrane structure of *N. gonorrhoeae* is complex and closely related to the pathogenesis of infection and host defense (Fig. 107.10).

The pilus plays a critical role in forming an initial attachment to host cells. Piliated strains adhere better to epithelium, and the presence of pili is the major determinant of gonococcal morphology in culture and correlates with virulence. Porin, previously designated as protein I, is the most represented outer membrane protein that functions as a pore for the exchange of ions. Porins show stable interstrain antigenic variation and form the basis for gonococcal serotyping. Two main serotypes have been identified: Por.IA strains are usually found in DGI, whereas Por.IB strains cause local infection. These characteristics may be related to the interaction with components of the complement cascade.⁴⁰ Another surface protein that is important for virulence is opacity-associated protein, previously designated as protein II. This protein plays a major role in the formation of intimate associations between the plasma membrane of the host cell and the gonococcus and promotes the invasion of epithelial cells mediated by specific cell-surface receptor interactions.⁴²

Pathogenesis

Host factors also play a role in gonococcal infection and dissemination. Gonococcal infection of the lower female genital tract is typically asymptomatic, partially as a result of the ability of the gonococcus to subvert the alternative pathway of complement. Pregnancy and menses increase the risk of DGI as a consequence of associated changes in the gonococcal phenotype and endometrial exposure of submucosal vessels to the gonococci. In about half of affected women, symptoms of DGI begin within 7 days of the onset of menses. Gonococci have adapted multiple mechanisms by which they are able to evade the lytic action of the complement system, including C4b inactivation and the formation of a nonfunctional membrane attack complex on their cell surface. Inherited or acquired complement deficiency, mainly of the terminal components (C5 to C8), is therefore a risk factor, because serum bacterial activity becomes impaired.

Clinical features

The clinical manifestations of DGI have been classified into two stages: a bacteremic stage and a suppurative stage with infectious arthritis. Some patients, however, may possess features of both (Fig. 107.11).⁴¹

The most common symptoms of DGI are fever, polyarthralgia, tenosynovitis, and skin lesions that have been designated as *acute arthritis and dermatitis syndrome*.⁴³ Tenosynovitis is rare in other forms of septic arthritis and in the presence of skin lesions. Painful joints are also present and

usually include the knees, elbows, and ankles. Tenosynovitis with or without joint involvement occurs in up to 68% of cases. Polyarthralgia occurs in half of patients, and when arthritis is present, it usually involves several joints, with a mildly elevated inflammatory synovial fluid leukocyte count and negative culture results.

Septic arthritis is present in about 50% of cases and is usually monoarticular. Any joint may be affected, but the knees, wrists, ankles, elbows, and small joints of the hands are the most frequently involved.⁴³

Skin lesions are observed in about 75% of patients with DGI in the bacteremic stage (Fig. 107.12).⁴³ They are usually painless, nonpruritic, present in low numbers, and sometimes grouped and appear on the limbs and trunk, sparing the face and scalp. Small macules or papules with an erythematous base are the most common lesions, followed by pustules that sometimes have a hemorrhagic component. A wide variety of skin lesions can be present in DGI, including vesicles, bullae, erythema nodosum, and urticaria. Other unusual manifestations of DGI are gonococcal endocarditis, pericarditis, osteomyelitis, and central nervous system infection with meningitis.

Investigations

In symptomatic men, a rapid diagnosis of gonococcal infection can be obtained by Gram staining of urethral exudates (Fig. 107.13). The sensitivity and specificity of Gram staining are 90% and 95%, respectively, for urethral smears versus 50% to 70% sensitivity and over 90% specificity for endocervical smears.⁴² Only about one fourth of Gram-stained samples of synovial fluid from patients with septic joint arthritis are positive for *N. gonorrhoeae*. Most patients with DGI have no local mucosal symptoms. All potential sites of infection should be screened for gonococcal infection, regardless of the presence of local symptoms. Specimens should be collected with Dacron or rayon swabs, because calcium alginate may be toxic to gonococci and fatty acids inhibit gonococci growth. To minimize the inhibitory effects of unknown substances in the specimen, the swabs should be inoculated directly onto growth medium or placed in a swab transport medium immediately after sampling.⁴² Ideally, the specimens should be inoculated onto culture medium immediately after collection to preserve

the viability of gonococci for isolation. If long-distance shipping is required, the specimens should be inoculated onto media contained in a CO₂-generating system, should be incubated for 18 to 24 hours, and should display visible growth on the plate before shipping.⁴²

Until the late 1980s, laboratory diagnosis of gonorrhea was limited to Gram staining and bacterial isolation. Disadvantages of bacterial culture include the need for invasive collection of specimens that must be transported under appropriate conditions to maintain organism viability. The current recommendation of the Centers for Disease Control and Prevention is that only bacterial culture should be used to test for pharyngeal or rectal gonorrhea. Molecular detection methods allow for more rapid and specific diagnosis of pathogens that are fastidious or cannot be cultured. These methods permit the use of specimens that are unsuitable for culture, such as urine and vaginal swab samples, which can be obtained from patients without discomfort. The lower sensitivity of bacterial culture of specimens from extragenital sites may be attributed to the heavy colonization of these sites by a broad range of other organisms, including other *Neisseria* species, which may interfere with *N. gonorrhoeae* isolation.⁴⁴

In the early 1990s, nucleic acid amplification tests (NAATs) first became available for routine use. There are several advantages of *N. gonorrhoeae* NAATs. First, they offer greater sensitivity than bacterial culture. When compared with *N. gonorrhoeae* NAATs, gonococcal culture ranges in sensitivity from 85% to 95% for acute infections and may fall as low as 50% for females with chronic infection. The increased sensitivity of NAATs makes them particularly suitable for screening, which allows accurate diagnosis of both symptomatic and asymptomatic gonococcal infections, a critical factor in controlling the disease. Second, specimens collected for NAAT assays do not need to contain viable organisms to allow detection, so that transport conditions are less stringent than those for specimens collected for bacterial culture. Finally, NAATs can be used effectively on noninvasively collected specimens, such as urine and self-collected samples. A notable limitation of *N. gonorrhoeae* NAATs is the inability to provide data on antibiotic resistance, which is an emerging health concern given the increased reports of the antibiotic resistance of *N. gonorrhoeae*.⁴⁴

Management

DGIs require higher dosages and longer durations of therapy than uncomplicated infections. Penicillin resistance results either from the acquisition of plasmids that encode β -lactamase or from chromosomal mutations.⁴⁵ Quinolone-containing regimens are no longer recommended, because resistance to these drugs has been well documented. Hospitalization is indicated

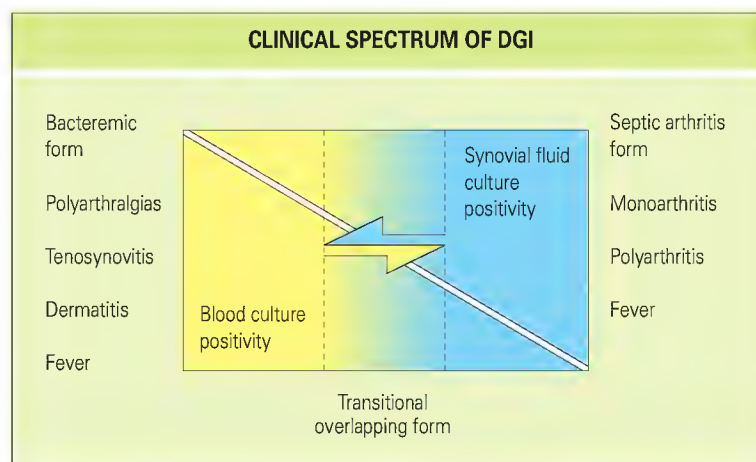


Fig. 107.11 Spectrum of the clinical manifestations of DGI. The bacteremic form is on the left and the suppurative form is on the right, with overlapping forms in the middle.

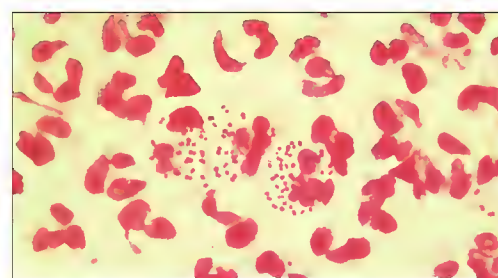


Fig. 107.13 *Neisseria gonorrhoeae*. Gram stain of urethral exudate in gonorrhea, showing intracellular gram-negative reniform diplococci. (Courtesy Dr. S.E. Thompson.)



Fig. 107.12 Skin lesions in disseminated gonococcal infection. (a) Macules, papules, and pustules over an ankle. (b) Hemorrhagic papules localized in the trunk. (c) Hemorrhagic vessel over a distal interphalangeal joint. (c, Courtesy Dr. Peter Schlessinger.)

if the diagnosis is uncertain, if there is a purulent arthritis that requires aspiration, or if the patient cannot be relied on to comply with the treatment regimen. A cephalosporin-based intravenous regimen is recommended for the initial treatment of DGI. This is particularly important when gonorrhea is detected at mucosal sites by nonculture tests. Daily ceftriaxone (1 g IV) is the first choice for antimicrobial therapy, although other third-generation cephalosporins, such as cefotaxime (1 g IV every 8 hours) or ceftizoxime (1 g IV every 8 hours), can also be prescribed. Patients who are allergic to β -lactam drugs can be treated with spectinomycin (2 g intramuscularly every 12 hours). Treatment should be continued for 24 to 48 hours after clinical improvement, at which time therapy may be changed to one of the following regimens (to be prescribed for at least 1 week of antimicrobial therapy): cefixime 400 mg orally twice daily, cefixime suspension 400 mg (200 mg/5 mL) twice daily, or cefpodoxime 400 mg orally twice daily.⁴⁶ Infected joints should be aspirated until the infection resolves, and open drainage is rarely necessary.

Because of the high rate of other sexually transmitted diseases, a diagnostic test for *Chlamydia trachomatis* should also be performed.

SYPHILITIC ARTHRITIS

Syphilis is a sexually transmitted chronic systemic infection caused by *Treponema pallidum* and is characterized by episodes of active disease followed by asymptomatic periods or latency. This is especially important in light of the increasing rates of syphilis, as well as the increasing recognition of concurrent syphilis and HIV infection. A systematic review of the literature found that between 2000 and 2004, the number of reported cases of primary and secondary syphilis increased by 33%.⁴⁷

Clinical features

Musculoskeletal symptoms may appear in the congenital, secondary, or tertiary phases of syphilis but are most common in the secondary stage.⁴⁸ The

most common manifestations of early congenital syphilis are bone changes, which include osteochondritis, osteitis, and periostitis. The symmetric destruction of the medial aspect of proximal tibial metaphyses (Wimberger sign) is usually pathognomonic for congenital syphilis. In 23% of patients, there is epiphyseal separation or fracture of the long bones, which prevents limb movement and results in pseudoparalysis.⁴⁹ Late congenital syphilis (more than 2 years) is usually subclinical. Joint complaints are characterized by painless bilateral effusion of the knees or elbows without local or systemic symptoms, often described as *Clutton joints*.⁴⁸ Neuroarthropathy due to tabes or Charcot joint, which affects the hips or knees, is the most common musculoskeletal manifestation of tertiary syphilis and is due to the loss of deep sensation and chronic trauma rather than direct infection of the joint.

Investigations

Laboratory diagnosis of syphilis is based on visualization of the *Treponema* species and/or demonstration of specific antibodies. Historically, screening for syphilis has involved the use of nontreponemal tests, such as the serum rapid plasma reagin or Venereal Disease Research Laboratory test. When results are positive, the disease is then confirmed using a more specific treponemal test, such as the *T. pallidum* hemagglutination test or the fluorescent treponemal antibody absorption test. In recent years, new diagnostic tests for syphilis such as the immunochromatography strip test, Western blot analysis, and use of nucleic acid amplification or molecular strain typing have been developed.

Management

Penicillin remains the drug of choice for the treatment of syphilis, but the doses and regimens vary with disease stage. Several studies have shown that azithromycin may have a similar clinical efficacy. Macrolide resistance has been documented among strains of *T. pallidum*, however, and treatment failures have been reported. Ceftriaxone is also effective for the treatment of syphilis when used in multiple-dose regimens.⁴⁹

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Infectious arthritis II: mycobacterial, brucellar, fungal, and parasitic arthritis

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- Human immunodeficiency virus infection and treatment with biologic agents are associated with an increased frequency of infectious musculoskeletal complications.
- Mycobacterial infections, especially infection with *Mycobacterium tuberculosis*, remain a concern.
- A good prognosis requires prompt and accurate diagnosis, which necessitates a high index of suspicion, particularly for rare infections.
- Novel molecular techniques are improving diagnosis, but careful clinical assessment is still mandatory.
- Effective antimicrobial therapies are available for most disorders, but resistance to these agents is an increasing concern.

INTRODUCTION

Musculoskeletal infectious disorders caused by mycobacterial, brucellar, fungal, and parasitic microorganisms are uncommon and difficult to diagnose. A resurgence of musculoskeletal infectious disorders is being seen triggered by a variety of factors, including the pandemic of human immunodeficiency virus (HIV) infection and increased use of immunosuppressive medications, including tumor necrosis factor- α (TNF- α) inhibitors.¹

TUBERCULOUS ARTHRITIS

Epidemiology

Tuberculosis remains a leading cause of morbidity and mortality. Cases of multidrug-resistant tuberculosis (resistance to isoniazid and rifampicin) and extensively drug-resistant tuberculosis are increasing.

In the United States, 10,521 cases of tuberculosis (3.4 cases per 100,000 inhabitants) were reported during 2011; this represents a 6.4% decrease compared with 2010. Despite a nationwide decline, foreign-born persons and racial and ethnic minorities continue to bear a disproportionate burden of tuberculosis disease. In 2011 the rate of tuberculosis in foreign-born individuals in the United States was 12 times higher than in the native population. The Asian populations had the largest number of cases.²

Pathophysiology

The genus *Mycobacterium* comprises several species. However, only two species of *Mycobacterium tuberculosis* complex (*M. tuberculosis* and *M. bovis*) are associated with significant human disease. Worldwide, *M. tuberculosis* is the most common cause of tuberculosis.

M. tuberculosis infection occurs through inhalation of aerosolized bacteria, ingestion of bacteria, or direct inoculation from infected individuals. The occurrence of *de-novo* infection depends on the number of organisms that survive phagocytosis and their ability to escape host defenses, such as alveolar macrophages (pneumocytes) and delayed hypersensitivity responses. Mycobacteria multiply intracellularly using Toll-like receptor 2 and receptors that bind complement, mannose, cholesterol-related receptors, and CD14, which leads to a burst of the pneumocytes. Released organisms are then phagocytized by other macrophages, and a chain reaction

ensues with cytokine production triggering an inflammatory response and eventually leading to hematogenous spread to distant organs. Microorganisms invading regional lymph nodes initiate the development of protective immunity that is mediated mainly by CD4+ lymphocytes with help from CD8+ cytotoxic lymphocytes and also B cells. Cytokines, such as interleukin-1 (IL-1), IL-2, IL-6, IL-12, interferon- γ (IFN- γ), and TNF- α , play a key role in protection against tuberculosis and also in formation and maintenance of granulomas (Ghon lesions). Tuberculosis related to anti-TNF inhibitors may be due to inhibition of a TNF-dependent chemokine gradient disrupting the cellular migration necessary to maintain the integrity of granulomas.³

Musculoskeletal manifestations

Bone and joint infections account for 1% to 3% of all forms of tuberculosis. Although 50% of patients have pulmonary tuberculosis, extrapulmonary disease accounts for up to 35% of cases. Musculoskeletal involvement (9% of cases) is considered the fifth most common extrapulmonary form, after lymphatic (27%), pleural (21%), genitourinary (16%), and miliary (10%) forms.

Skeletal tuberculosis has a tendency to involve weight-bearing joints, and several clinical patterns are described, including spondylitis, peripheral arthritis, reactive arthritis or Poncet disease, osteomyelitis, and soft tissue abscesses (Box 108.1).

Spondylitis (Pott disease)

Tuberculosis spondylitis may affect the vertebrae, intervertebral disks, paraspinal soft tissues, and epidural space. Unlike pyogenic osteomyelitis, tuberculosis spondylitis is characterized by a subacute course and lower disease activity.

Spondylitis comprises the most common form of osteoarticular tuberculosis and results from secondary hematogenous spread from a primary focus mainly localized in lungs, lymph nodes, and other tissues. The vertebral column is affected in 50% of cases of skeletal tuberculosis, and the thoracic and lumbar regions are the most frequent sites. Infection in the early stages is localized in the anterior subchondral bone of a vertebra adjacent to the intervertebral disk, resulting in narrowing of the disk space. In later stages, progression is evident 2 to 5 months after onset and first involves cancellous and, subsequently, cortical bone. Magnetic resonance imaging (MRI) findings have not significantly reduced the diagnostic delay.⁴

The characteristic form of presentation is back pain, localized in the thoracic and/or lumbar regions and accompanied by generalized malaise, low-grade fever, weight loss, and night sweats. Onset of symptoms has an average duration of approximately 1 year. It is usually insidious and varies from weeks to years. Vertebral collapse can occur, producing the classic radiologic picture of anterior wedging of two adjacent vertebral bodies with destruction of the intervening disk and the physical finding of a tender spinal prominence or gibbous deformity.

Radiologic findings suggestive of a tuberculosis cause include slow progression of lesions with preservation of disk space, involvement of several contiguous segments, the presence of large intraosseous and paraspinal abscesses containing calcifications, and body collapse with kyphotic deformity.⁵

Diagnosis is often delayed until signs of advanced disease occur, such as paraparesis and paraplegia, reported in 4% to 30% of cases. The most common findings are sensory deficit symptoms secondary to spinal cord or

BOX 108.1 CLINICAL PATTERN OF MUSCULOSKELETAL TUBERCULOUS INFECTION

- Spondylitis (Pott disease)
- Septic arthritis
- Osteomyelitis
- Tenosynovitis and bursitis
- Soft tissue abscess
- Reactive arthritis (Poncet disease)

nerve root involvement, which may appear before spinal deformity. Kyphosis is a late finding, and its combination with scoliosis produces the gibbous deformity.

Peripheral arthritis

Peripheral skeletal involvement is usually monoarticular, chronic, and insidious, but multiple joints may be involved. Any large joint can be affected, including hips (15%), knees (15%), and ribs (5%).⁶ In endemic areas, children and young adults are affected most often.

In a study in Taiwan of 51 adult patients with tuberculosis arthritis the mean duration of symptoms and signs before diagnosis was 25 months (range, 0 to 180 months).⁷ Joint pain (96%) and swelling (90%) were common. Forty-five patients (88%) had monoarthritis; arthritis of the knee (27%) was the most common. Twenty-six patients (51%) had radiologic evidence of pulmonary tuberculosis, and 43 patients (84%) had synovial fluid and/or tissue cultures positive for *M. tuberculosis*. One fourth of patients reported a history of previous trauma.

Osteomyelitis

Osteomyelitis occurs in children and adults and comprises 2% to 3% of osteoarticular tuberculosis. Any bone may be involved, but the femur and tibia are the most common, followed by short bones such as metacarpals, metatarsals, and phalanges.

Bony involvement is secondary to hematogenous dissemination of mycobacteria in the diaphysis with fusiform, painful swelling that clinically resembles inflammatory arthropathy, which causes a diagnostic dilemma. Tuberculous osteomyelitis outside the vertebral body presents as a cold abscess, with swelling and only modest erythema or pain.

Reactive arthritis (Poncet disease)

Reactive arthritis or Poncet disease is characterized by polyarthritis associated with extrapulmonary tuberculosis with no evidence of direct joint involvement. It affects young people and is slightly more common in women. Findings include fever, malaise, and polyarthritis of large joints such as knees, ankles, and, at times, wrists. The tuberculin test result frequently is positive, and the extrapulmonary site of tuberculosis is usually lymph nodes. Reactive arthritis responds well to nonsteroidal antiinflammatory drugs (NSAIDs).

Soft tissue abscess and panniculitis

Soft tissue abscesses are rare but may be associated with vertebral involvement (paravertebral abscess) and osteomyelitis. In contrast, panniculitis presenting as erythema nodosum is often seen with or without polyarthritis. Erythema induratum—a variety of panniculitis associated with vasculitis and at times with arthritis around the ankles, also known as *Bazin disease*—can be seen.

Cold abscesses (which develop slowly and with minimal inflammatory reaction and become painful only in the presence of pressure on the surrounding area) can appear after treatment has been initiated and in some cases are visible by only computed tomography (CT) or MRI in areas such as the spine, hips, lymph nodes, or genital region.

Diagnosis

The gold standard for diagnosis remains the identification of *M. tuberculosis* by microbiologic or histologic techniques. An elevated erythrocyte sedimentation rate (ESR) and C-reactive protein level may be present, but these indicators lack specificity. Culture is an important and sensitive diagnostic tool (80% positivity). More sophisticated techniques using polymerase



Fig. 108.1 Pott disease. Vertebral destruction with paraspinal soft tissue enlargement can be noted. (Courtesy Dr. Sergio Alvarez, Radiology Department, Hospital Pablo Tobon Uribe, Medellin, Colombia.)

chain reaction (PCR) or nucleic acid amplification tests that detect *M. tuberculosis* genetic material and amplify target sequences are even faster and may replace conventional procedures, and can be used in patients with negative smear results.

Skin testing with purified protein derivative and whole-blood IFN- γ -releasing assays are used to screen individuals and are discussed in detail in Chapter 65. Adenosine deaminase levels in serum or pleural fluid may provide a clue to a diagnosis of tuberculosis. Its levels increase in patients with tuberculosis independent of therapy with disease-modifying antirheumatic drugs or TNF- α inhibitors. Synovial fluid is nonhemorrhagic, turbid, and xanthochromic. White blood cell counts are moderately elevated to between 10,000 and 20,000 cells/mm³ with a predominance of polymorphonuclear leukocytes. Synovial tissue shows caseating granulomas in up to 80% of specimens.

Other diagnostic tests include the microscopic observation direct susceptibility assay, which allows for rapid detection of *M. tuberculosis* growth. Line probe assays for rapid drug susceptibility testing and urine tests for the diagnosis of tuberculosis are promising tools.⁸

Imaging

Radiologic techniques are useful to confirm the diagnosis. In addition, ultrasonography, CT, and MRI can be used to guide needle aspiration in sites that are difficult to access.

Spondylitis

Early abnormalities include resorption of the dense margins of the endplates and demineralization, narrowing or obliteration of the disk space, and soft tissue swelling (paravertebral abscess [Fig. 108.1]). Late-stage findings include lytic progressive destruction of the anterior vertebral body, vertebral collapse, and kyphosis.

CT reveals small abnormalities and paravertebral abscesses (which may occur in 50% of patients). MRI is the main diagnostic modality, provides higher soft tissue definition than CT, and is more specific for delineating swelling⁹ (see Fig. 108.1).

Peripheral arthritis

Soft tissue and joint swelling with effusion are seen in early stages. Later on, peripheral osseous erosions, articular destruction with narrowing of joint space, and juxtaarticular osteoporosis (Phemister triad) are evident. Bone involvement may be difficult to distinguish from pyogenic infection. Margin erosions are more common and the joint space is preserved for a longer period because tuberculosis progresses more slowly than pyogenic infection. CT, MRI, and scintigraphy are recommended to establish a diagnosis.

Osteomyelitis

Findings include cavity formation in 50% of cases, lytic lesions with blurred margins, and minimal or no reactive bone sclerosis. Bone sequestration



Fig. 108.2 Tuberculous osteomyelitis. There is soft tissue enlargement and the presence of air at the thigh with femur involvement. (Courtesy Dr. Sergio Alvarez, Radiology Department, Hospital Pablo Tobon Uribe, Medellin, Colombia.)



Fig. 108.3 Tuberculous osteomyelitis. A lytic bone lesion and blurred margin with cavitation of the femur can be seen. (Courtesy Dr. Sergio Alvarez, Radiology Department, Hospital Pablo Tobon Uribe, Medellin, Colombia.)

is rarely seen. However, subsequently, new subperiosteal bone develops, which produces the typical enlargement of the shaft¹⁰ (Figs. 108.2 through Fig. 108.4).

Treatment

Most recommended treatment regimens should be administered for at least 9 to 12 months. First-line drugs include 8 weeks of oral daily treatment with isoniazid 5 mg/kg (up to 300 mg), plus rifampin 10 mg/kg or 600 mg, plus pyrazinamide according to body weight 40 to 45 kg: 1000 mg, 56 to 75 kg: 1500 mg, 76 to 90 kg: 2000 mg, and ethambutol 15 mg/kg, or streptomycin 15 mg/kg or 1 g intramuscularly. Then, 28 to 36 weeks of treatment with isoniazid plus rifampin for 5 days/wk to complete 9 to 12 months of treatment. Pyridoxine 25 to 50 mg daily may be added to daily regimens that include isoniazid.

Other therapeutic modalities include the treatment of latent *M. tuberculosis* infection with isoniazid 5 mg/kg or 300 mg orally daily; or 15 mg/kg (up to 900 mg) twice weekly under supervision. The optimal duration of the therapy is 9 months, although in some situations a shorter course of 6 months may be considered for cost effectiveness. Alternatively, rifampin 600 mg/day given orally for 4 months is effective in HIV-infected and non-HIV-infected patients.

Treatment of multidrug-resistant tuberculosis includes regimens with combinations such as rifampin, ethambutol, pyrazinamide, quinolones, macrolides, and/or amikacin or streptomycin.

There are five principles in the treatment of multidrug-resistant tuberculosis: (1) Culture the bacilli and use drug sensitivity to guide therapy. (2) Never add a single drug to a failing regimen. (3) Use of four-drug regimens not administered previously is mandatory. (4) An injectable aminoglycoside should be added for at least 2 months. (5) A minimum treatment duration of 24 months is highly recommended.^{11,12}

In general, the clinical response to therapy is adequate, but patients should be monitored carefully for treatment-related toxicity. Other



Fig. 108.4 Computed tomographic scan with digital reconstruction showing involvement of the seventh rib by tuberculosis. (Courtesy Dr. Sergio Alvarez, Radiology Department, Hospital Pablo Tobon Uribe, Medellin, Colombia.)

therapeutic modalities, such as surgery, are indicated when large abscesses are present and in selected cases of vertebral tuberculosis (e.g., acute neurologic involvement or deterioration, paraparesis, or paraplegia) and/or spinal instability or deformity of more than 5 degrees. It is recommended that 1 to 4 weeks of drug therapy be administered to stabilize the general condition of patients before any surgical procedure is performed.

Prevention

Vaccination is a valuable tool and is widely employed in Latin America, Africa, Asia, and some European countries to prevent tuberculosis infection. Bacille Calmette-Guérin vaccine seems to be effective in some populations but not in others. Administration of repeated doses can increase its effectiveness.

Tuberculosis related to treatment with anti-tumor necrosis factor- α and biologic agents

Tuberculosis is a complication seen most commonly with anti-TNF therapy, but this infection has also occurred with other biologics (see Chapter 67).

LEPROSY AND OTHER ATYPICAL MYCOBACTERIAL INFECTIONS

Epidemiology

Leprosy has a low incidence and prevalence in developed countries. In 1998, 102 cases of leprosy were registered in the National Hansen's Disease Program in the United States. In 2010, according to the World Health Organization (WHO), the global figure reported for leprosy was 228,474 new cases, with the lowest rates seen in the Western Pacific region and the highest rates seen in Africa and Southeast Asia. India, with 126,800 patients, led the list of countries with the highest rates of incidence, followed by Brazil with 34,894 patients.¹³

Atypical mycobacterial infections may occur in healthy individuals with certain occupational exposures but are more common in immunocompromised individuals, including patients receiving corticosteroid therapy.

Microbiology

Despite significant efforts, *Mycobacterium leprae* cannot be cultured *in vitro*. *M. leprae* is a gram-positive and acid-fast rod-shaped organism. *M. leprae* and other atypical mycobacteria affect the musculoskeletal system. Infection usually derives from either hematogenous spread or percutaneous inoculation. *Mycobacterium avium-intracellulare*, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium haemophilum*, *Mycobacterium marinum* (in fish handlers), and *Mycobacterium kansasii* most commonly cause skeletal infections, usually through penetrating injuries.

Clinical features

The clinical spectrum is highly variable and depends on the causative agent. Leprosy is a chronic infection, and its features range from a nonsensitive or hypopigmented skin spot (tuberculous) to severe neuropathic and osteo-articular damage (lepromatous). Common to both types of lepra reaction are pain and swelling at sites of infection. Well-recognized musculoskeletal features of leprosy include neuropathic or Charcot joints, septic arthritis, acute polyarthritis of lepra reactions, and chronic/subacute rheumatoid-like polyarthritis (Box 108.2).

The Lucio phenomenon is an uncommon but severe form of reaction in multibacillary leprosy. It can manifest as bluish or violaceous and hemorrhagic plaques followed by large recurrent ulcerations in the lower extremities and may be fatal.¹⁴

Leprosy has a wide range of clinical manifestations, including infection of the nasal mucosa and cartilage, which may lead to saddle-nose deformity. *M. leprae* invades Schwann cells and the glial cells of the peripheral nervous system, and generally, thermal sensation is lost before the ability to sense pain and pressure. Leprosy tends to flare up either spontaneously or after the onset of treatment. In one study in 2004 involving 1257 leprosy patients at an outpatient clinic in the state of Amazonas, Brazil, 115 patients (9%) had articular involvement, 24 had arthralgias, and 55 had leprosy-related arthritis.¹⁵ Prevalence of arthritis was similar in both genders, and all patients had lepromatous or borderline disease type. Most patients had polyarticular and symmetric arthritis, and mean duration of articular

BOX 108.2 CLINICAL FEATURES OF LEPROSY

- Neuropathic or Charcot joints
- Septic arthritis
- Acute polyarthritis
- Rheumatoid arthritis-like involvement
- Cutaneous ulcerations (Lucio phenomenon)



Fig. 108.5 Leprosy involving the right foot with marked soft tissue edema, bone resorption, and diffuse phalangeal lytic lesions. (Courtesy Dr. Vanessa Garcia, Radiology Department, University of Antioquia, Medellín, Colombia.)

symptoms was 1 year (range, 5 days to 14 years). In all, 91% had erythema nodosum leprosum or reversal reactions. Most arthritis cases were considered reactive episodes, and the arthritis had a chronic course and was not responsive to conventional therapy.

The clinical picture of atypical *Mycobacterium* infection consists of constitutional symptoms such as malaise, weight loss, low-grade fever, and local pain. Musculoskeletal complications include tenosynovitis, soft tissue abscess, and osteomyelitis.

Diagnosis

Findings are nonspecific: an elevated ESR, anemia, and positivity for rheumatoid factor are seen in up to 30% of patients. Synovial fluid is usually a transudate. All infections, including infection with *M. leprae*, require histopathologic or bacteriologic demonstration of the organism in tissue samples, such as nasal swab specimens (leprosy) and/or biopsy specimens from soft tissue lesions, by conventional or newer techniques such as PCR assay. Radiographic features include multiple involved areas of the metaphysis and diaphysis of long bones, lytic areas with erosions in small joints, sclerosis, and osteoporosis (Figs. 108.5 and 108.6). Nerve involvement (three or more) and delay in treatment are significant markers of disability, with odds of 3.73 and 2.27 respectively.¹⁶

Treatment

Treatment of leprosy consists of specialized medications and physical rehabilitation to avoid joint contractures. The WHO recommends the use of multidrug therapy due to an increasing resistance to dapsone. Dapsone 100 mg orally daily and rifampin 600 mg once a month for 12 months are recommended for treatment of the paucibacillary form. Multibacillary infection should be treated with dapsone 100 mg daily, rifampin 600 mg monthly, plus clofazimine 50 mg daily for 2 years.

Combination therapy is needed for infection with *M. avium-intracellulare*, *M. chelonae*, *M. fortuitum*, and other atypical mycobacteria and includes macrolides (clarithromycin or azithromycin), ethambutol, and a third drug to be chosen from among rifampin (or rifabutin), ciprofloxacin, amikacin, cefoxitin, clofazimine, and tetracycline. Duration of treatment remains to be established and varies from 12 to 18 months.



Fig. 108.6 Leprosy involvement of the foot with phalangeal autoamputation and extensive bone tissue destruction, as well as Charcot-like neuroarthropathy. (Courtesy Dr. Lina Maria Cifuentes, Radiology Department, University of Antioquia, Medellín, Colombia.)

BRUCELLOSIS

Epidemiology

Brucellosis is a chronic granulomatous infection caused by intracellular bacteria that has public health implications. Transmission to humans occurs by consumption of contaminated food, mainly non pasteurized dairy products (cheese), associated with poor animal husbandry methods and hygiene standards. Populations in several countries in Europe are affected, including Spain, Greece, and Turkey. The Mediterranean region and the Arabian peninsula are endemic areas. India and Africa are also affected areas. In the Western Hemisphere, Mexico and Central and South America (particularly Brazil, Colombia, and Peru) are highly endemic areas. In the United States, brucellosis is considered a rare disease; approximately 100 cases are reported yearly. The incidence in endemic regions varies from 1 to 200 per 100,000 inhabitants, and the prevalence of the disease varies widely in these regions.

Microbiology

Brucellosis is caused by organisms of the genus *Brucella*, which is composed of at least 10 species.¹⁷ The *Brucella* organism is a small gram-negative coccobacillus.

Clinical features

Brucellosis is a systemic acute or insidious illness that usually follows a chronic course and is rarely fatal. Acute brucellosis presents as a flulike illness, including undulating fever, sweats, headaches, back pains, and weakness, whereas chronic brucellosis manifests as recurrent fevers, joint pain, fatigue, and complications of sacroiliitis, peripheral arthritis, spondylitis, osteomyelitis, and bursitis (Fig. 108.7, Box 108.3).

In a study of 195 patients no gender predisposition was seen, and individuals 15 to 45 years of age were most commonly affected.¹⁸ Sacroiliitis (55% of cases) was the most common manifestation, followed by peripheral joint involvement (54%) and spondylitic involvement (31%). Monoarthritis was the predominant pattern of peripheral involvement, with hips (58% of cases) and knees (22%) commonly affected.

Plain radiographs confirm axial involvement, although imaging studies such as MRI are helpful for the detection of early findings. Genetic



Fig. 108.7 Magnetic resonance imaging (MRI) scan of a 35-year-old Hispanic male with brucellar spondylitis. The patient had persistent fever, weight loss, and spondylodiskitis with intervertebral disk involvement and abnormal uptake of contrast agent in T7 and T8, and L2 and L3 on MRI. (Courtesy Dr. Luis F. Pinto, Rheumatologist, Hospital Pablo Tobón, Medellín, Colombia.)

predisposition may play a role, and HLA-B39 was found to be increased in patients with brucellosis who had musculoskeletal involvement.

In 231 Turkish patients the source of infection was unpasteurized milk and milk products (cheese). Thirty-seven percent of patients were classified as having an acute presentation (less than 3 months), 19% as having a subacute presentation (3 to 12 months), and 44% as having a chronic presentation (longer than 12 months).¹⁹ Fatigue, fever, anorexia, nausea, and diarrhea were significantly higher in the acute stage; weight loss and palpitations were significantly more frequent in the subacute stage; and osteoarticular manifestations were significantly more frequent in the chronic stage. Sacroiliitis was the most common complication, followed by spondylodiskitis, bursitis, and osteomyelitis. The lumbar spine was the most frequent site of spondylodiskitis (56%), and the cervical spine was least affected (4%).¹⁹

Other manifestations include intermittent or irregular fever of variable duration, malaise, malodorous perspiration, depression, weight loss, uveitis, hepatosplenomegaly, and lymphadenopathy. Relapses (first year) are relatively common (approximately 10%) and for the most part are caused by inadequate treatment. Childhood brucellosis tends to exhibit a more benign course and responds better to treatment.

BOX 108.3 RHEUMATIC MANIFESTATIONS OF BRUCELLOSIS

- Sacroiliitis, 40%-55%
- Peripheral arthritis, 30%-40%
- Spondylitis, 20%-30%
- Osteomyelitis, 5%-10%
- Bursitis, 2%-5%
- Reactive arthritis, ?

BOX 108.4 CHARACTERISTICS OF FUNGAL MUSCULOSKELETAL INFECTIONS

- Low incidence and occupation-related disease
- Occurrence in tropical or subtropical areas
- Occurrence in immunocompromised hosts
- Subacute or chronic course
- Pulmonary and/or cutaneous involvement important as extraarticular manifestations
- Definitive diagnosis requiring demonstration of fungi

Diagnosis

The diagnosis requires a high index of suspicion and isolation of the bacterium from blood or tissue samples. Elevations in ESR (49%) and C-reactive protein level (20% to 25%) may be seen but are nonspecific findings. Anemia (30%) and elevated transaminase levels (10%) are also found. Synovial fluid is inflammatory but sterile. Specific antibody titers may be detectable at presentation or will rise over 2 to 3 weeks. Titers above 1:160 in any of the agglutination tests in conjunction with typical clinical findings are considered diagnostic. High titers persist for up to 18 months, which makes it difficult to use these tests for follow-up. Blood culture yields a positive result in 50% to 80% of cases, even in afebrile patients.

Treatment

The intracellular character of *Brucella* infection associated with an acidic environment requires treatment with antibiotics that can penetrate macrophages and reach adequate concentration—preferably used in combination. The WHO recommends two regimens, both of which use doxycycline orally (100 mg every 12 hours) plus rifampin 900 mg/day for a 45-day period. Or the same dose of doxycycline for 45 days in combination with streptomycin IM (1 g daily) for 2 weeks. In general, the response to treatment and outcome are excellent.

Alternative drug combinations may be used, such as other aminoglycosides (e.g., gentamicin and netilmicin), trimethoprim-sulfamethoxazole, and quinolones (especially in patients with spondylitis and for a minimum of 3 to 6 months). Rifampin is the drug of choice during pregnancy. Brucellosis in children is treated with combinations that include rifampin, trimethoprim, and aminoglycosides.

Prevention

Vaccination of uninfected animals and culling of infected animals have successfully eradicated brucellosis from most of the United States; however, there are countries without resources to implement effective eradication programs.

FUNGAL MUSCULOSKELETAL INFECTIONS

Based on the study of some genetic and immunologic disorders known to predispose to invasive fungal infections, defects in phagocyte effector function, abnormalities in IL-12, IFN- γ signaling, and mutations in GATA2 have been identified as playing important roles. These advances translate into new powerful and specific antifungals.²⁰

Patients at risk include immunocompromised hosts with systemic underlying diseases such as HIV infection, systemic lupus erythematosus, rheumatoid arthritis (RA), and malignancies, as well as patients receiving immunosuppressive therapy, including corticosteroids and biologic agents. In addition, residence in endemic areas such as tropical and subtropical regions, as well as some occupations, may also be associated with a higher incidence.

Definitive diagnosis requires demonstration of the fungi. Clinical findings, serologic test results (Box 108.4, Table 108.1), and tissue biopsy samples play an important role. The gold standard in diagnosis is culture.

Treatment includes a combination of antimycotic drugs, with or without surgery.²¹ Amphotericin B remains the cornerstone of treatment.

Histoplasmosis

Histoplasmosis is a worldwide mycosis, although it is highly endemic in Ohio and Mississippi in the United States and Central and West African countries. The incidence of endemic mycoses (number of cases per 100,000 person-years) among a cohort of Medicare beneficiaries from 1999 to 2008

TABLE 108.1

Serologic fungal tests

Fungi	Antibodies				Antigens
	CF	ID	ELISA	Other	LA
<i>Histoplasma</i>	+++	++	IgG		
<i>Blastomyces</i>	++	+++	IgG		
<i>Paracoccidioides</i>	++	++			
<i>Coccidioides</i>	+++	++	IgG		
<i>Cryptococcus</i>				IF	+++
<i>Aspergillus</i>	++	+++			
<i>Candida</i>	++	+++	IgG, IgM, IgA		++
<i>Sporothrix</i>				LA	

CF, complement fixation; ELISA, enzyme-linked immunosorbent assay; ID, immunodiffusion; IF, immunofluorescent; Ig, immunoglobulin; LA, latex agglutination.

was as follows: histoplasmosis, 357; coccidioidomycosis, 345; and blastomycosis, 74; the Midwest was the most common location.²²

Histoplasma capsulatum is a dimorphic fungus that is found in soil. Infection occurs after the spores are inhaled and phagocytized by *in situ* pneumocytes. Direct inoculation in the skin has been reported in rare cases. Although histoplasmosis remains a rural disease, occupational hazards are encountered by individuals exposed to the droppings of urban-living birds and by cave explorers in contact with bat and bird guano after disturbance of contaminated soil.

Macrophages and dendritic cells are the principal effectors in host resistance, whereas T cells contribute to host defense with the production of cytokines to activate mononuclear phagocytes. TNF- α , IFN- γ , and IL-12 play a role in controlling primary infection. Histoplasmosis may be an important complication of treatment with TNF- α inhibitors. The clinical presentation of histoplasmosis (pulmonary, extrapulmonary, or disseminated) may mimic that of some rheumatic diseases, which may delay recognition and treatment.

H. capsulatum infection is frequently asymptomatic and self-limited in the healthy host. Migratory polyarthralgias/arthritis involving large joints (knees, ankles, and wrists), tenosynovitis, myalgias, and erythema nodosum are the most common musculoskeletal manifestations (Fig. 108.8). Patients may also exhibit fever, headaches, and cough. Disseminated histoplasmosis can occur in as many as 1 per 2000 cases of infection. Risk factors include immunosuppression, age older than 54 years, renal transplantation, and use of anti-TNF- α inhibitors. Chest radiographs are mandatory to rule out lung involvement. Serologic or urinary tests are also useful techniques. Tissue biopsies and/or culture are mandatory.

Treatment

Most cases of acute histoplasmosis do not require specific treatment. Symptomatic management with NSAIDs may suffice. Severe, persistent, or progressive disease in an immunocompromised host requires specific antifungal drugs. New antifungal agents, including several azoles such as voriconazole, caspofungin, and lipid-based preparations of amphotericin B, are available.

Mild to moderate disease in progressive disseminated histoplasmosis should be treated with itraconazole 200 mg orally 3 times a day for 3 days, then 200 mg twice daily for at least 12 months. However, for severe and/or life-threatening infections such as meningitis, amphotericin B is the choice. Severely immunocompromised hosts can be treated with liposomal amphotericin B 3 mg/kg/day intravenously for 1 to 2 weeks followed by suppressive therapy with itraconazole. Surgical débridement is often required.²³



Fig. 108.8 Forty-one-year-old Hispanic female who developed dermatomyositis while taking steroids, complicated by biopsy-confirmed histoplasmosis-induced panniculitis. She was treated successfully with amphotericin B.

Blastomycosis

Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis* and has a widespread distribution. It is endemic to central and southeastern regions of the United States but is also seen in Mexico, the Middle East, Africa, and India. The fungus is acquired by inhalation, and dissemination occurs from lungs to skin (80%) and to bones (60%), where osteolytic lesions exhibit a mild periosteal reaction and no sequestra formation, resembling a neoplasm.

Onset of illness is usually abrupt (but may be insidious). Lungs are the major targets, and complaints include cough, headaches, chest pain, weight loss, fever, abdominal pain, night sweats, chills, and anorexia. Cutaneous involvement is the most common extrapulmonary feature, followed by bone and joint manifestations.

In a Canadian study of 45 patients with blastomycosis there were 41 cases of osteomyelitis and 12 cases of septic arthritis. The majority were men (35 patients [78%]) and non-Aboriginal (32 patients [71%]). Cutaneous disease was present in 33 patients (73%) and lung involvement in 29 (64%). The most common sites of osseous involvement were the lower limbs and axial skeleton. Features included bone pain in 42 patients (78%), swelling in 32 patients (59%), and soft tissue abscesses in 21 patients (39%). Joint infection occurred in 12 patients and manifested as a monoarthritis presenting with effusion in 9 patients (75%), pain in 8 patients (67%), and decreased range of motion in 5 patients (42%).²⁴

Delay in diagnosis is common, and the differential diagnoses include endemic fungal infections and bone tumors. Histopathologic evidence of broad-based budding yeast and serologic evidence of *B. dermatitidis* infection confirms the diagnosis.

Less than 5% of cases of disseminated infection involve the central nervous system, the meninges, or the brain itself.

Serologic tests are not helpful, but enzyme-linked immunosorbent assay (ELISA) seems to have greater sensitivity than other tests; however, immunodiffusion and complement fixation tests have better specificity. Synovial fluid examination or tissue biopsy should be performed whenever possible. The fungus grows slowly in culture. Radiographs may show an eccentric lucency in the distal end of large bones and osteopenia in the involved location.

Treatment

Blastomycosis is managed with itraconazole oral solution 200 mg administered 3 times a day for 3 days, then 200 mg once or twice a day for 12 months. Surgical débridement or drainage is helpful to accelerate healing. In refractory or life-threatening disease, liposomal amphotericin B (5 mg/kg/day) or amphotericin B 0.7 to 1 mg/kg/day for a total dose of 1.5 g or more may be useful and previously was considered first-line therapy for all forms of the disease. Fluconazole 400 to 800 mg/day for 6 to 12 months and ketoconazole are alternatives, although the relapse rate may be high. In general, response to treatment is excellent.²³

Paracoccidioidomycosis

Paracoccidioidomycosis (PCM), caused by *Paracoccidioides brasiliensis*, is an endemic disease in the south of Venezuela and Brazil, and armadillos are the natural reservoir.

The disease has a restricted distribution and has been reported only in Latin America from Mexico to Argentina; it does not occur in the Caribbean or any region of the United States, except in travelers to those endemic areas. The primary foci of infection are the lungs through the inhalation of airborne spores, but the disease may affect the skin, colon, genital tract, and central nervous system. This disorder can be classified into an acute/subacute (or juvenile) variety, which accounts for 3% to 5% of all cases, and a chronic (adult) variety, which can be unifocal. The prevalence of bone lesions ranges from 2% to 30%, and articular and muscular involvement are very rare. Osteoarticular involvement is the primary presentation of PCM in up to 42% of cases.

The clinical picture is highly variable. The disease shows a male predominance; affects mostly manual workers, which suggests that exposure is occupation dependent; and ranges from an asymptomatic state to malaise, low-grade fever, lymph node enlargement, and oral ulcers with inflamed lips and deformity (tapir mouth). Pharyngeal, laryngeal, and tracheal involvement may occur. Severe lymphadenitis with swelling and neck deformity (buffalo neck) may be seen. Adrenal insufficiency is occasionally noted, as is involvement of the spleen, liver, gastrointestinal tract, eyes, male genitourinary tract, and central nervous system. Bones commonly affected include the scapula, acromion, clavicle, rib, humerus, radius, and phalanges. Bony lesions produce mild but slowly progressive pain. Most patients have pulmonary involvement (tuberculosis-like infection); therefore, differential diagnoses include other granulomatous conditions such as tuberculosis, sarcoidosis, fungal infections, and malignancies (lymphoma). Radiologic findings include osteolytic lesions, as well as metaphyseal or meta-epiphyseal osteomyelitis of the long bones, which can be solitary or multifocal.²⁵

Diagnosis is difficult, and PCM should be considered in immunocompromised patients from endemic areas. Detection of antigen in cerebrospinal fluid and in bronchoalveolar lavage fluid increases the sensitivity for diagnosis and facilitates monitoring of the response to treatment.

Treatment

Treatment of mild to moderate disseminated PCM infection requires administration of itraconazole 200 mg orally daily for 6 months, or ketoconazole 200 to 400 mg/day orally for 6 months, or sulfadiazine 25 to 50 mg/kg (maximum 1 to 1.5 g/dose) orally in 2 to 4 divided doses daily for 6 to 12 months, as well as surgical intervention if needed. Successful treatment of skeletal disease with trimethoprim-sulfamethoxazole administered for a prolonged period (1 to 4 years) has been reported.

Coccidioidomycosis

Coccidioidomycosis is a self-limited disease caused by *Coccidioides immitis* and *Coccidioides posadasii* present in the soil. Endemic areas have been identified in the southwestern United States (San Joaquin fever, desert rheumatism, and Posada disease), northern Mexico, and Central and South America.

Coccidioidomycosis is primarily a lung disease. Systemic dissemination occurs in about 1% of cases. Risk of infection is related to residence in endemic areas and occupations requiring the frequent aerosolization of soils, such as construction, agriculture, archaeology, and excavation. In addition, high incidence has been reported in Filipinos and African Americans.

The clinical picture in coccidioidomycosis of subacute onset is characterized by cough, shortness of breath, fatigue, pleuritic chest pain and fever (Valley fever), arthralgias, myalgias, rash, erythema nodosum, and erythema multiforme. Musculoskeletal involvement includes monoarthritis (more often the knee) or oligoarthritis in the early stages or osteomyelitis in late stages involving large joints. The spine may also be affected.

One practice reported an incidence rate of coccidioidomycosis of 1.9% and a rate of 3.1% to 3.6% in patients with RA. The annual incidence was 1% in patients recently diagnosed with RA and 2% in patients with recently initiated infliximab treatment.²⁶

Diagnosis requires the presence of an illness consistent with *Coccidioides* infection and one of the following: (1) culture recovery of the organism from an affected site or blood; (2) direct microscopic or histopathologic demonstration of the organism; or (3) demonstration of coccidioidal antibody in cerebrospinal fluid or a two-dilution rise measured in two consecutive blood samples tested.

C. immitis grows readily in culture, and synovial fluid analysis and examination of biopsy tissue samples are also excellent ways to identify the fungus.

Treatment

Symptomatic management for 1 to 2 weeks suffices to control complaints in most patients. Drugs of choice are itraconazole solution 200 mg twice daily orally for 3 to 6 months or fluconazole 400 mg/day orally or IV for many months to years in duration. Extensive or severe disease may require treatment with amphotericin B followed by itraconazole or fluconazole. Surgery may also be required.

Prophylaxis is limited to laboratory workers and those at high risk of inoculation as well as selected patients receiving transplanted organs from donors with known coccidioidal infection.²⁷

Cryptococcosis

Cryptococcosis is worldwide in distribution and is caused by *Cryptococcus neoformans*, which resides in the soil and typically infects via the respiratory tract. Frequent contact with urban-living birds (pigeons, chickens, and parrots), guano, and rotten wood appears to be the mode of infection. More recently, *Cryptococcus gattii* is emerging as an important pathogen in several parts of the world.²⁸

Dissemination is rare and is usually associated with immunosuppression, either iatrogenic or HIV related. Other conditions linked to cryptococcosis include diabetes mellitus, corticosteroid use, malignancies, sarcoidosis, and liver cirrhosis.

The clinical picture of infection is variable and lacks specificity. Mild fever, nonproductive or slightly productive cough, and malaise are frequently seen. Often the disease is restricted to the respiratory tract (90% of cases) with a variety of features, including pulmonary nodules, interstitial pneumonitis, pleural effusions, adenopathy, and acute respiratory distress syndrome. However, any organ, muscle, eye, bone, skin, or mucosa can be affected; the organism has a particular affinity for the central nervous system, and meningitis is the most common clinical manifestation in HIV-associated cryptococcosis.

Musculoskeletal manifestations, including arthritis and osteomyelitis with paravertebral abscess, resemble tuberculosis. Diagnosis is made by isolation of the microorganism from synovial fluid, cerebrospinal fluid obtained by lumbar puncture (with India ink staining), or tissue samples. Recently advances have been made in the use of ELISA, antigen detection (titers), and the random amplified polymorphic DNA technique to detect the fungi. Skeletal radiographs typically show lytic lesions without periostitis.

Treatment

Management requires débridement or drainage. In addition, fluconazole 400 mg/day intravenously or orally for 8 weeks to 6 months in nonmeningeal or non-HIV-associated cryptococcosis is needed. For more severe disease or HIV-related infection, the recommended treatment is amphotericin B 0.5 to 0.8 mg/kg/day intravenously plus flucytosine 37.5 mg/kg every 6 hours orally until the patient becomes afebrile and culture results are negative, and then continuation with fluconazole lifelong therapy.

Aspergillosis

Despite progress in early diagnosis and treatment of aspergillosis, mortality rate remains high. Aspergillosis is caused by several (more than 150) species of ubiquitous and opportunistic fungi. In the United States, *Aspergillus* infection has been estimated to occur at a rate of 12 per 1 million inhabitants per year.

Invasive *Aspergillus* infection is the most common cause of mortality due to invasive mycosis in the United States, with mortality rates ranging from 80% to 95% without treatment and 29.2% and 42.1% after 12 weeks of treatment with voriconazole or amphotericin B, respectively. Stem cell and solid organ transplantation, hematologic malignancy, and intraarticular steroid injection are risk factors.²⁹ The clinical picture may range from a relatively rapid course with inexorable progression to a very slow

and surprisingly indolent course, with the infection appearing to improve temporarily even without treatment. Cough, fever, sinusitis, and asthmalike features are characteristics of allergic pulmonary manifestations. Hemoptysis is noted when an aspergilloma occurs in the lung.

Dissemination is acute and life threatening and usually occurs by (1) contiguous spread from an adjacent involved organ, most commonly the lung; (2) hematogenous spread from a distant focus; and (3) iatrogenic inoculation. Fungi embolism (20% to 50% of cases) allows infection of any organ, including bones, where lytic lesions may be seen. Involvement of the central nervous system (meningitis and abscess) and skin (papules, abscess, plaques, or ulcers) are often related. Musculoskeletal involvement is quite rare, although osteomyelitis and/or vertebral involvement may occur. The knee is the most affected joint, followed by the shoulder. Synovial fluid analysis may show elevated cell count with a predominance of polymorphonuclear neutrophils.³⁰

Diagnosis is difficult to establish, but mycelia can be visualized at times, and the fungus may be cultivated in standard media. Most cases, however, require examination of tissue biopsy samples to identify the fungi. Serologic tests for circulating antigen or antibody using immunodiffusion or ELISA yield positive results in 50% to 70% of cases. Testing for *Aspergillus* galactomannan antigens in serum and PCR testing of serial blood samples in patients at high risk have been suggested.

Treatment

Management varies according to the severity of the infection and includes medical and surgical débridement if aspergilloma is present. Voriconazole 6 mg/kg intravenously twice daily for a day, then 4 mg/kg intravenously for at least 7 days followed by the maintenance dose of 200 mg orally for 8 weeks, is the standard therapy. The second choice is lipid-based amphotericin B, which may be as effective and less nephrotoxic than standard amphotericin B but is much more expensive. There are also other antifungal therapies available, including caspofungin.

Candidiasis

Candidiasis is the fourth most common cause of nosocomial bloodstream infections in the United States and results from disseminated *Candida* infection. There are more than 190 *Candida* species but only eight are important human pathogens: *C. albicans*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. stellatoidea*, *C. tropicalis*, *C. pseudotropicalis*, and *C. glabrata*.

C. albicans remains the species most commonly associated with candidemia (50% of cases), followed by *C. glabrata* and *C. parapsilosis*, which are normal commensal organisms in humans, and most disseminated infections are endogenous and originate from the gastrointestinal tract. Colonized indwelling central venous catheters may also serve as a conduit for organisms into the bloodstream.

Neutropenic patients, organ transplant recipients, postsurgical patients, and patients receiving parenteral alimentation, and patients receiving broad-spectrum antibiotics are at higher risk of disseminated candidiasis. Clinical features include fever, malaise, and skin and mucosal involvement. Bone, joint, and cartilage involvement may also occur. *Candida*-associated osteomyelitis occurs most commonly in the spine in adults and the long bones in children. Pain is the most significant complaint.

An isolated monoarthritis may occur caused by direct inoculation of fungi that inhabit the skin, or inoculation by injection or during surgery. The second syndrome is the development of a monoarthritis or polyarthritis as a complication of hematogenous disseminated candidiasis. Costochondral joint involvement may be seen in intravenous drug users. Synovial fluid is inflammatory, with predominantly polymorphonuclear cells. Radiographs or bone scans are used to demonstrate osteomyelitis. MRI is more sensitive and can reveal earlier lesions.

The current gold standard is blood culture (results are negative in 50% of cases). However, combined mannan antigen and antimannan antibody detection assays have demonstrated a sensitivity of 71% to 100% and a specificity of 86% to 93%. In the United States, there is more experience with (1→3)-β-D-glucan detection as a broad-spectrum assay for fungal pathogens. Optimized PCR assays have sensitivities and specificities for candidemia and documented or probable invasive candidiasis that exceed 90%.³¹

Treatment

Intravenous amphotericin B is the drug of choice, 0.6 to 0.7 mg/kg per day IV treatment duration may last 3 to 6 months. Frequent joint aspiration may be needed. Prosthetic joint infections are refractory to treatment and often require removal of the prosthesis.

The mortality from systemic infection has been reported to be as high as 56%. Refractory vertebral osteomyelitis may be treated with antifungal

combinations, and caspofungin, micafungin, or anidulafungin have been recently introduced as alternatives.

Prevention measures are very important to decrease the incidence of this infection, especially diabetes control, surveillance of peripheral catheters, and oral prophylaxis with fluconazole or nystatin in selected immunocompromised patients to avoid gastrointestinal dissemination.

Sporotrichosis

Sporotrichosis is caused by *Sporothrix schenckii*, a dimorphic fungus. Sporotrichosis occurs worldwide. Decaying vegetation, soil, wood, and hay are ideal growth environments for this fungus. Traumatic inoculation (skin injury) is the main portal of entry. The disease occurs more frequently in farmers, gardeners, miners, forestry workers, and immunosuppressed hosts. Zoonotic transmission may occur through scratches or bites from rodents, cats, dogs, horses, and armadillos.

Clinical manifestations occur in the skin at the site of inoculation, typically the extremities and more often the hands (fingers) or face, but can be localized on any (exposed) part of the body. Small nodules enlarge progressively and become red, pustular, and ulcerative with release of purulent material. The lymphocutaneous form occurs in 65% to 82% of patients and produces a chain of ulcerative (chancrous) and nodular skin lesions. Typically, the older distal lesions exhibit more ulcerations than younger proximal lesions, with bridges of normal skin between them.

Systemic disease results as a consequence of hematogenous dissemination after spread from a pulmonary focus, the primary inoculation site, or regional lymph nodes. Large joints and large bones may be affected, including the tibia, fibula, knee, elbow, ankle, or wrist. The most common complaints are pain and gradual onset of stiffness. Osteomyelitis is a major concern, with bone destruction and draining fistulas from which the organism is readily cultivated. Erythema nodosum–like lesions may occur as well as tenosynovitis, periostitis, synovial effusion, and osteolysis.

Demonstration of *S. schenckii* is needed for a definitive diagnosis. Serologic agglutination tests are useful for the diagnosis of extracutaneous manifestations. Radiographic findings are nonspecific. Osteopenia, joint space narrowing, or lytic lesions may be seen.

Treatment

The management of sporotrichosis often requires surgical débridement. Itraconazole is the drug of choice for skin, musculoskeletal, or meningeal involvement. A dosage of 200 mg orally twice daily for at least 12 months is needed.

Potassium iodide 1 to 3 g orally three times a day for 2 to 4 months may be successful for cutaneous manifestations. Trimethoprim/sulfamethoxazole, fluconazole, or liposomal amphotericin B also may be used. Prevention measures include avoiding scratches from vegetation or pets and washing and disinfecting wounds immediately.

PARASITIC ARTHRITIS

Musculoskeletal involvement secondary to parasitic infection is an important cause of arthritis in certain geographic areas of the world. This zoonotic disorder is closely related to cultural and dietary habits, such as ingestion of undercooked food containing parasitic agents. Risk factors include immunocompromised states, residence in or travel to an area of epidemic parasitosis, or poor hygienic conditions. Primary parasitic musculoskeletal involvement is rare, and in most cases concomitant involvement of gastrointestinal organs and lungs is seen. Parasites may produce symptoms by direct invasion or induction of autoimmune-mediated reactions. The spectrum of disease is highly variable, ranging from asymptomatic infection to vasculitis, reactive arthritis, large abscesses, or polymyositis. Diagnosis requires a high degree of suspicion in individuals at high risk, those with atypical clinical manifestations, and those with poor response to conventional treatment (Box 108.5).

Diagnosis is facilitated by clinical history and the presence of peripheral eosinophilia, which often correlates with the degree of musculoskeletal involvement. Diagnostic tests should include parasitic, serologic, and molecular assays, with confirmation by histopathologic examination. Radiologic studies are helpful (Table 108.2).

Parasitic infections may be grouped into four subsets: protozoan, cestode, nematode, and trematode.

BOX 108.5 CHARACTERISTICS OF PARASITIC RHEUMATISM

- Inflammatory arthropathy
- Association with residence in or travel to an area of epidemic parasitosis
- Eosinophilia
- Absence of radiologic findings
- No response to antirheumatic treatment
- Identification of parasite
- Response to antiparasitic medications

TABLE 108.2 Musculoskeletal associations and treatment of parasitic infections

Parasite	Musculoskeletal associations	Diagnostic workup	Treatment
Protozoans			
<i>Ameba</i> species	Arthritis: knee, reactive arthritis	Trophozoites and cysts in stool	Metronidazole
<i>Cryptosporidium</i>	Reactive arthritis	Oocysts in stool specimens	TMP/SMX
<i>Giardia intestinalis</i>	Children: polyarthritis related to HLA-B27	Trophozoites and cysts in stool, duodenal biopsy and aspirates, ELISA	Metronidazole or albendazole
<i>Plasmodium</i> species	Myalgia, RA-like manifestations	Blood smear, ELISA, PCR	Chloroquine
<i>Toxoplasma</i> species	Myositis, vasculitis, RA-like manifestations	Tissue biopsy, PCR	Pyrimethamine
<i>Trypanosoma</i> species	Myositis	Blood smear, ELISA	Sulfadiazine
Cestodes			
<i>Echinococcus granulosus</i>	Bone cyst	Bone radiograph, ELISA, Western blot, histopathologic examination	Albendazole, praziquantel
<i>Taenia</i> species	Muscle weakness, palpable nodules	Eggs and proglottids in stool	Praziquantel, niclosamide
Nematodes			
<i>Strongyloides</i> species	Oligoarthritis, vasculitis	Larvae in stool, sputum, or other body fluid	Ivermectin
<i>Dracunculus</i> species (Guinea worm)	Monoarthritis, arthralgias	Calcified worms on radiograph	Mebendazole
<i>Filaria</i> (<i>Loa loa</i>)	Arthralgias, RA-like manifestations	Serologic testing, tissue biopsy	Diethylcarbamazine
Trematodes			
<i>Schistosoma</i> species	ReA-like manifestations, oligoarthritis, RA-like manifestations, sacroiliitis	Schistosome eggs in feces, urine, or biopsy specimen	Praziquantel

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; RA, rheumatoid arthritis; ReA, reactive arthritis; TMP/SMX, trimethoprim-sulfamethoxazole.

Protozoans

A variety of protozoans may cause musculoskeletal manifestations, including *Amoeba* species, *Cryptosporidium parvum*, *Cyclospora cayetanensis*, *Isospora belli*, *Sarcocystis* species, *Giardia intestinalis*, *Leishmania* species, *Plasmodium* species, *Microsporidia* species, *Pneumocystis jiroveci*, *Toxoplasma gondii*, *Trypanosoma* species, and *Trichomonas* species.

A wide spectrum of clinical manifestations may occur. *T. gondii* induces a mononucleosis-like illness characterized by fever, cervical adenopathy, myalgias, and malaise. *Trypanosoma cruzi* favors involvement of smooth and striate muscles and causes severe autonomic disturbances in the cardiovascular and gastrointestinal systems. *Microsporidia* and *Entamoeba* infections produce precipitate diarrhea, keratoconjunctivitis, genitourinary infections, hepatitis, and myositis. *Plasmodium* infection commonly causes myalgias and myositis and rarely rhabdomyolysis. Visceral leishmaniasis or kala-azar syndrome manifests with fever, severe cachexia, hepatosplenomegaly, and pancytopenia, and a few cases of myositis or cutaneous dermatomyositis-like lesions have occurred in patients with acquired immunodeficiency syndrome patients.

Musculoskeletal involvement includes polyarthritis or oligoarthritis, RA-like joint involvement, reactive arthritis, polymyositis- or dermatomyositis-like features, and bone cysts. Large bones or joints are often affected, and diarrhea or other gastrointestinal manifestations may occur.

Diagnosis

ELISA and indirect fluorescent antibody testing have been used to establish diagnosis. PCR-based assay and real-time PCR are new tools with a high degree of accuracy. Refractoriness and/or unresponsiveness of diseases to standard therapies should raise suspicion of parasitic infection in endemic areas. Clinical manifestations, serologic tests, and radiologic imaging studies are all useful in identifying parasitosis. However, the diagnosis should be confirmed only by direct identification of the parasitic agent in synovial fluid or biopsy specimens.

Cestodes

Cysticercosis is the most important cestode infection. *Taenia solium* (pork tapeworm), the causative agent, belongs to the intestinal tapeworm group. Musculoskeletal involvement is characterized by muscle weakness and/or palpable nodules. Over 75% of patients with neurocysticercosis also have affected muscles with dot-shaped or ellipsoidal calcifications in the muscle bundle in thighs or arms. Other organisms are *Diphyllobothrium latum* (fish tapeworm), *Hymenolepis nana* (dwarf tapeworm), and *Taenia saginata* (beef tapeworm). In addition, tissue tapeworms such as *Echinococcus granulosus* may infect muscle and large bones.

Musculoskeletal involvement is variable, and symmetric arthritis of the wrists and metacarpophalangeal and proximal interphalangeal joints has been described. Cystic lesions of bone may be seen as manifestations of hydatidosis, in which the spine (30%), pelvis/hip (20%), and femur and tibia (15%) are commonly affected sites.

Diagnosis

Diagnosis of *T. solium* infection requires detection of eggs or proglottids in stool specimens. ELISA can detect live parasites and can be used to guide therapeutic decisions. Infections with *Echinococcus* species (hydatid disease) are a common cause of musculoskeletal involvement. Radiographic findings of bone cysts may support the diagnosis.

Serologic antibody testing and histopathologic examinations (subcutaneous nodules can be excised) are complementary tools to reach a final diagnosis.

Nematodes

A wide spectrum of complaints may be seen with infection by nematodes. Dracunculiasis is caused by *Dracunculus medinensis* and may induce

asymptomatic disease until the worm migrates to the subcutaneous tissue, usually in the lower extremities, where it may induce chronic ulcers with parasitic discharge. Knee monoarthritis (Ibadan knee) and septic and destructive arthritis are seen. Lymphatic filariasis (caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*) and tissue filariasis (dirofilariasis, loiasis, and infection with *Onchocerca volvulus*, which also cause blindness river in Africa and Central and South America) are characterized by a variety of manifestations ranging from acute lymphatic inflammation or chronic lymphatic obstruction—leading to elephantiasis of the extremities, arthritis resembling septic arthritis, swelling, and localized subcutaneous edema—to migratory arthritis.

Infection with *Trichinella* species may involve the muscles, and symptoms are related to the number of larvae ingested (fewer than 10 larvae per gram are often asymptomatic, whereas more than 50 larvae per gram are associated with muscular symptoms) as well as host characteristics such as age, size, and underlying health conditions. Muscle invasion is manifested by myalgias, swelling, and weakness. Myositis of any striate muscle (which may begin with extraocular muscle involvement and diplopia) can develop 5 to 6 weeks after infection, but only 2% of cases are life threatening (due to heart dysrhythmias, pneumonitis, or brain involvement).

Diagnosis

Diagnosis depends on the detection of microfilaria in blood collected at midnight. ELISA and PCR assays are excellent indicators of active nematode infection, but sometimes muscle or tissue biopsy is needed to confirm the diagnosis.³²

Trematodes

Toxocariasis (visceral larva migrans) may also affect muscle or bone tissue; polyarthralgias, monoarthritis or oligoarthritis, and dermatomyositis-like and vasculitis-like features are the major complaints. Infection with *Schistosoma mansoni* and *Schistosoma haematobium* can be associated with arthritis, enteritis, and, occasionally, diffuse myopathy. Katayama syndrome occurs 4 to 8 weeks after exposure to fresh water contaminated with schistosomes and is seen mainly in Africa, South America, and the Arabian peninsula. A serum sickness-like illness with fever, cough, headache, abdominal tenderness, and urticaria are the most remarkable findings. In addition, there can be loss of muscle mass, muscle weakness, involvement of the pelvic diaphragm with rectal prolapse, and reduced physical activity.

Diagnosis

A diagnosis of *Schistosoma* infection is suggested by travel to endemic areas, eosinophilia, and possibly a history of swimmer's itch. Microscopic visualization of eggs in a stool smear, antigen detection by ELISA, and rectal biopsy are very specific diagnostic methods.

A high index of suspicion is needed to diagnose nematode and trematode infection in the setting of musculoskeletal involvement. Serologic tests, radiographic studies, tissue biopsy, and examination of stool specimens are all useful to establish a diagnosis. Furthermore, isolation or demonstration of the specific agent is mandatory to initiate the most effective and specific treatment.

Treatment

Management of parasitic complaints depends on the causal agent. Specific treatment is required most of the time, and symptoms improve following eradication of the parasite. In addition, NSAIDs and surgical intervention may be needed (see Table 108.2). It is important to become familiar with antiparasitic agents and their dosages and potential adverse effects. The Mazzotti reaction (arthralgias, rash, fever, lymphadenopathy, tachycardia, and hypotension) is a relatively common complication related to the treatment of active filariasis and is seen after the use of diethylcarbamazine.

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109 Lyme disease

■ ALLEN C. STEERE

- Lyme disease is a tick-borne infection caused by the spirochete *Borrelia burgdorferi* sensu lato leading to a multisystem illness primarily in the skin, joints, nervous system, and/or heart.
- Peak onset of early infection is the summer months in endemic areas in North America, Europe, and Asia.
- The first clinical sign is usually a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite.
- Disseminated infection is often associated with characteristic manifestations in the skin, joints, nervous system, and/or heart.
- In the United States, arthritis in one or a few joints, especially the knee, is the most common late disease manifestation.
- Diagnosis is usually based on characteristic clinical findings and a positive result on an immunoglobulin G serologic test for *B. burgdorferi* by ELISA and Western blot.
- Treatment with oral antibiotic therapy for 1 month is usually successful, but some patients with arthritis or neurologic involvement require intravenous antibiotics.

HISTORY

Lyme disease was recognized as a separate entity in 1976 because of the geographic clustering in Lyme, Connecticut, of affected children, who were thought to have juvenile rheumatoid arthritis.¹ However, parts of the illness were recognized previously in Europe and were given different names, including *erythema chronicum migrans*, *Bannwarth syndrome*, and *acrodermatitis chronica atrophicans*.² These syndromes were linked conclusively in 1982 and 1983 with recovery of a previously unrecognized spirochete from the tick vector³ and from infected patients.⁴ The basic outlines of the disease are similar worldwide, but there are regional variations.⁵ Arthritis is a prominent feature of late infection in the United States.

EPIDEMIOLOGY

Lyme disease occurs in North America, Europe, and Asia (Fig. 109.1). In the United States, the disease is located primarily in three geographic areas: in the northeastern and mid-Atlantic states, in the upper Midwest, and in northern California. However, the infection is spreading to new geographic locations; it is increasing in frequency; and it is epidemic in certain locations in the northeastern states.⁶ Currently, about 30,000 cases are reported yearly to the Centers for Disease Control and Prevention (CDC), but the actual number may be closer to 300,000 cases annually.⁷ The disease may also be acquired in locations throughout Europe, particularly in central Europe, and in Russia, China, and Japan.

The vectors of Lyme disease are 14 closely related ixodid tick species that are part of the *Ixodes ricinus* complex: *Ixodes scapularis* in northeastern and upper Midwestern states, *Ixodes pacificus* on the West coast, *Ixodes ricinus* in Europe, and *Ixodes persulcatus* in Asia.⁶ Ticks of the *I. ricinus* complex have larval, nymphal, and adult stages. In North America and Europe, it is the tiny nymphal tick that is primarily responsible for transmission of the disease during the late spring or early summer months. The tick must usually be attached for at least 24 hours before transmission of the spirochete occurs.

ETIOLOGIC AGENT

The *Borrelia* are loosely coiled, spiral, microaerophilic bacteria (Fig. 109.2). *Borrelia burgdorferi* sensu lato (i.e., *B. burgdorferi* in the general sense) consists of 14 closely related genospecies.⁶ However, the human infection is caused primarily by three genospecies. In the United States, *B. burgdorferi* sensu stricto (*B. burgdorferi* in the strict sense), hereafter referred to as *B. burgdorferi*, is the sole cause of the disease, whereas *Borrelia afzelii* and *Borrelia garinii* are the primary causes in Europe and Asia.

Strains of *B. burgdorferi* have been subdivided according to several typing schemes: one based on sequence variation in outer-surface protein C (OspC), a second based on the 16S-23S ribosomal RNA intergenic spacer region (RST), and a third called *multilocus sequence typing*.⁸ From these typing systems there is emerging evidence that strains of *B. burgdorferi* differ in pathogenicity. OspC type A (RST1) strains, which account for 30% to 50% of the infections in the northeastern United States, are particularly virulent.^{8,9} These strains are thought to have played an important role in the emergence of Lyme disease in epidemic form in the United States in the late 20th century.¹⁰

PATHOGENESIS

To maintain its complex enzootic cycle, *B. burgdorferi* must adapt to two markedly different environments: the tick during the fall, winter, and spring, and the mammalian host during the summer months, where it meets its nutritional requirements.⁶ The spirochete expresses a different set of proteins on its outer membrane in the tick and in the mammalian host. For example, outer-surface protein A (OspA) is expressed primarily in the midgut of the tick, whereas OspC is upregulated as the organism travels to the tick salivary gland. There, OspC binds a tick salivary gland protein (Salp15), which is required for infection of the mammalian host.¹¹

Once in the mammalian host, the spirochete downregulates OspC, and upregulates the VlsE lipoprotein, which undergoes extensive antigenic variation during the course of the infection.¹² Some *Borrelia* strains bind host complement regulator proteins to their surface, which help protect spirochetes from complement-mediated lysis.¹³ During hematogenous dissemination, *B. burgdorferi* surface proteins attach to host integrins, glycosaminoglycans, and glycoproteins.⁶ Finally, spirochetal decorin-binding proteins bind decorin, a glycosaminoglycan on collagen fibrils.¹⁴ This binding may explain why the organism is commonly aligned with collagen fibrils in the extracellular matrix of the heart, nervous system, or joints.

To control and eradicate *B. burgdorferi*, the host mounts both innate and adaptive immune responses, resulting in macrophage- and antibody-mediated killing of the spirochete. Cells at affected sites release potent proinflammatory cytokines, including interleukin-6, tumor necrosis factor- α , interleukin-1 β , and interferon- γ .⁶ Patients who are homozygous for a TLRI (Toll-like receptor 1) polymorphism (1805GG), particularly when infected with highly inflammatory *B. burgdorferi* RST1 strains, have exceptionally high levels of proinflammatory cytokines.¹⁵ The purpose of the adaptive immune response seems to be the production of specific antibodies, which opsonize the organism. This process helps greatly in phagocytosis and effective spirochetal killing.

Within several weeks to months, innate and adaptive immune mechanisms, even without antibiotic treatment, control widely disseminated infection, and generalized systemic symptoms wane. In the absence of antibiotic therapy, however, spirochetes may survive in localized niches for several more years. For example, *B. burgdorferi* infection in the United States may cause persistent arthritis or, in rare cases, a subtle encephalopathy or

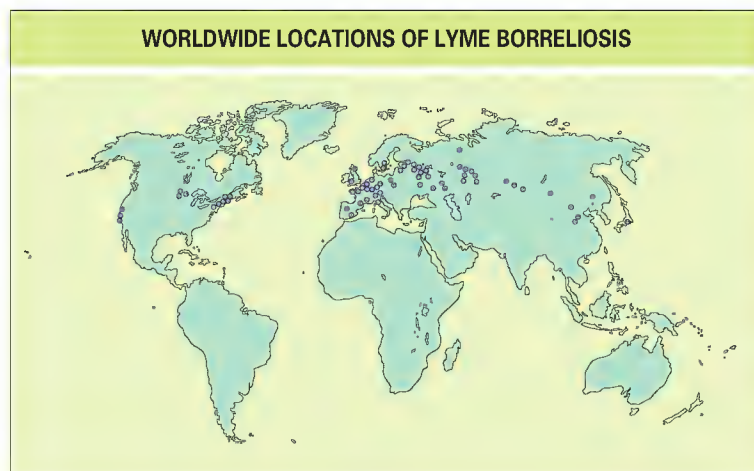


Fig. 109.1 The dots show locations affected by Lyme disease in North America, Europe, and Asia.

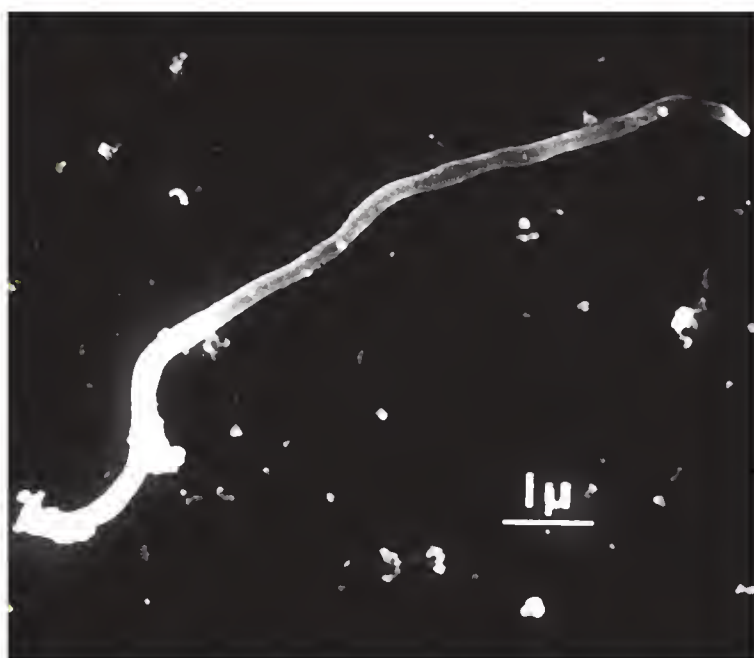


Fig. 109.2 Scanning electron micrograph of *Borrelia burgdorferi*. The *Borrelia* species are longer and more loosely coiled than the other spirochetes. Of the *Borrelia* species, *B. burgdorferi* is the longest (20 to 30 μm) and narrowest (0.2 to 0.3 μm).

polyneuropathy. Eventually, immune mechanisms seem to succeed in the near or total eradication of *B. burgdorferi* from selected niches, including the joints or nervous system, and in most patients, symptoms resolve.

CLINICAL MANIFESTATIONS

Natural infection, without antibiotic therapy, generally occurs in stages, with different clinical manifestations at each stage.² Early infection consists of stage 1 (localized erythema migrans), followed within days to weeks by stage 2 (disseminated infection, particularly affecting the nervous system or heart), followed within months by late infection (stage 3, persistent infection, particularly affecting joints). However, early infection may be asymptomatic, and the illness may present with stage 2 or 3 manifestations. A complete list of possible manifestations at each stage is given in Table 109.1.

Skin

In approximately 80% of American patients, Lyme disease begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite.¹⁶ As the area around the center expands, most lesions



Fig. 109.3 Erythema migrans. (a) The site of the tick bite is visible near the center of the lesion. (b) Typical bull's-eye lesion. (From Huppertz H-I, Dressler F. Lyme Disease. In: Cassidy J, Petty R, Laxer R, et al, editors. Textbook of pediatric rheumatology. 6th ed. Philadelphia: Saunders; 2011.)

develop bright red outer borders with partial central clearing (Fig. 109.3).^{2,5} The centers of early lesions sometimes become intensely erythematous and indurated, vesicular, or necrotic. In America, erythema migrans is frequently accompanied by nonspecific flulike symptoms such as headache, neck stiffness, myalgias, arthralgias, malaise, or fatigue, and these symptoms, without erythema migrans, may be the presenting picture of the illness.¹⁷ Fever, if present, is typically low grade, except in young children. Malaise and fatigue may be debilitating.

Patients with erythema migrans may be coinfecting with other infectious agents transmitted by the same tick, including *Babesia microti* (a red cell parasite) and *Anaplasma phagocytophilum* (which infects granulocytes).^{18,19} As in early Lyme disease, each of these pathogens may cause nonspecific flulike symptoms during summer, and coinfection with one or both of these agents may lead to more severe, acute illness. However, neither *A. phagocytophilum* nor *B. microti* is known to cause chronic infection, as with untreated *B. burgdorferi* infection.

Erythema migrans is also the most common feature of Lyme borreliosis in Europe.²⁰ In addition, in Europe the infection is associated with several other dermatologic manifestations that may occur later in the illness.²⁰ Borrelia lymphocytoma is a subacute lesion, typically on the ear or breast, that eventually resolves. Acrodermatitis chronica atrophicans is a slowly progressive lesion located on the extensor (acral) surfaces of the extremities, which may result in persistent spirochetal infection over a period of years.

Nervous system

Within weeks, during or shortly after spirochetal dissemination, about 15% of untreated patients in the United States develop objective signs of acute neuroborreliosis.^{2,5} Possible manifestations include lymphocytic meningitis with episodic headache and mild neck stiffness, subtle encephalitis with difficulty with mentation, cranial neuropathy (particularly unilateral or bilateral facial palsy), motor or sensory radiculoneuritis, mononeuritis multiplex, cerebellar ataxia, or myelitis. Particularly in Europe, the first neurologic sign is often radicular pain, which is followed by the development of a pleocytosis in cerebrospinal fluid, but meningeal or encephalitic signs are more often absent.²¹ In children, the optic nerve may be affected because of inflammation or increased intracranial pressure, which may lead to blindness.²² Even in untreated patients, acute neurologic symptoms typically improve or resolve within weeks to months.

TABLE 109.1

Manifestations of Lyme disease by stage*

System [†]	Early infection		Late infection
	Localized, stage 1	Disseminated, stage 2	Persistent, stage 3
Skin	Erythema migrans	Secondary annular lesions Malar rash Diffuse erythema or urticaria Evanescent lesions Lymphocytoma	Acrodermatitis chronica atrophicans Localized scleroderma-like lesions
Musculoskeletal		Migratory pain in joints, tendons bursae, muscle, bone Brief arthritis attacks Myositis Osteomyelitis Panniculitis	Prolonged arthritis attacks Chronic arthritis Peripheral enthesopathy Periostitis or joint subluxations below lesions of acrodermatitis
Neurologic		Meningitis Cranial neuritis, Bell palsy Motor or sensory radiculoneuritis Subtle encephalitis Mononeuritis multiplex Myelitis Chorea Cerebellar ataxia	Chronic encephalomyelitis Subtle encephalopathy Chronic axonal polyradiculopathy
Lymphatic	Regional lymphadenopathy	Regional or generalized lymphadenopathy Splenomegaly	
Heart		Atrioventricular nodal block Myopericarditis Pancarditis	
Eyes		Conjunctivitis Iritis Choroiditis Retinal hemorrhage or detachment Panophthalmitis	Keratitis
Liver		Mild hepatitis	
Respiratory		Nonexudative sore throat	
Kidney		Microscopic hematuria or proteinuria	
Genitourinary		Orchitis	
Constitutional symptoms	Minor	Severe malaise and fatigue	Fatigue

*The staging system provides a guideline for the expected timing of the different manifestations of the illness, but this may vary in an individual case.

[†]The systems are listed from the most to the least commonly affected.From Steere AC. Lyme disease. *N Engl J Med* 1989;321:586-96.

In perhaps 5% or fewer of untreated patients, *B. burgdorferi* may cause chronic neuroborreliosis, sometimes following long periods of latent infection.⁵ In the United States, the typical picture is a subtle axonal polyneuropathy manifested primarily as spinal radicular pain or distal paresthesias²³ and/or a subtle encephalopathy manifested primarily by mild cognitive disturbances.²⁴ Systemic symptoms are minimal, if present at all. In patients with polyneuropathy, electromyograms typically show diffuse involvement of both proximal and distal nerve segments, and those with encephalopathy often have intrathecal production of antibody to the spirochete.

Cardiac system

Within several weeks after disease onset, about 5% of untreated patients have acute cardiac involvement, most commonly fluctuating degrees of atrioventricular block, occasionally acute myopericarditis or mild left ventricular dysfunction, and rarely cardiomegaly or fatal pancarditis.^{2,5} The duration of cardiac abnormalities is usually brief (between 3 days and 6 weeks), and insertion of a permanent pacemaker is not necessary. In Europe, *B. burgdorferi* has been isolated from endomyocardial biopsy specimens of several patients with chronic dilated cardiomyopathy,²⁵ but this complication has not been observed in America.²⁶

Joints

Months after the onset of illness, often following a latent period, about 60% of untreated patients in the United States have intermittent or persistent attacks of joint swelling and pain, primarily in one or a few large joints, especially the knee, during a period of several years (Fig. 109.4).²⁷



Fig. 109.4 The swollen knee of a 9-year-old child with Lyme arthritis. In the United States, affected knees may be very swollen and warm, but not particularly painful. In Europe and Asia, the amount of joint swelling is often less.

TABLE 109.2

Joint and periarticular sites affected in 28 untreated patients with Lyme arthritis

Joints	No. of patients (N = 28)	Periarticular sites	No. of patients (N = 28)
Knee	27	Tendons	
Shoulder	14	Back	9
Ankle	12	Neck	6
Elbow	11	Bicipital	4
Temporomandibular	11	Lateral epicondyle	2
Wrist	10	Lateral collateral	1
Hip	9	De Quervain tenosynovitis	1
Metacarpophalangeal	4	Bursae	
Proximal interphalangeal	4	Prepatellar	4
Distal interphalangeal	4	Subacromial	2
Metatarsophalangeal	4	Infraspinatus	2
Sternoclavicular	1	Olecranon	2
		Sausage digits	2
		Heel pain	2

From Steere AC, Schoen RT, Taylor E. The clinical evolution of Lyme arthritis. *Ann Intern Med* 1987;107:725-31.

However, particularly in earlier episodes, other large or small joints, the temporomandibular joint, or periarticular sites are sometimes affected (Table 109.2). Affected knees may be very swollen and warm (see Fig. 109.4) but not particularly painful. Baker cysts may form and rupture early. Joint involvement may be milder in young children than in older children or adults.²⁸ Joint fluid white cell counts usually range from 10,000 to 25,000 cells/mm³, but cell counts as low as 500 or as high as 100,000 cells/mm³ have been noted.²⁷ Although tests for rheumatoid factor or antinuclear antibodies typically yield negative results, antinuclear antibodies in low titer may be detected.

Although most patients with Lyme arthritis respond to recommended antibiotic therapies, a small percentage of patients have persistent synovitis for months or several years after receiving oral and intravenous antibiotic therapy for 2 or 3 months, called *antibiotic-refractory arthritis*.²⁹ Rather than persistent infection, infection-induced autoimmunity,³⁰ retained spirochetal antigens,³¹ or both may play a role in this outcome. Antibiotic-refractory arthritis is associated with specific HLA-DR alleles (such as the DRB1*0101 and 0401 alleles),³² a TLR1 polymorphism (1805GG) that leads to exceptionally high levels of cytokines and chemokines in affected joints,¹⁵ and low frequencies of FoxP3+ regulatory T cells in synovial fluid, which correlate with longer posttreatment durations of arthritis.³³ A novel human autoantigen, endothelial cell growth factor, was recently identified as a target of T- and B-cell responses in patients with Lyme disease, which provides the first direct evidence for autoimmune T- and B-cell responses in this illness.³⁰ Synovial histologic findings in these patients, which include synovial hypertrophy, vascular proliferation, and mononuclear cell infiltration, are similar to those in all forms of chronic inflammatory arthritis, including rheumatoid arthritis.³⁴ However, synovial tissue from patients with antibiotic-refractory arthritis often shows obliterative microvascular lesions, which are not found in other types of arthritis.

DIAGNOSIS

Culture of *B. burgdorferi* from patient specimens permits definitive diagnosis.³⁵ However, positive culture results have been obtained mainly early in the illness, primarily from biopsy specimens from erythema migrans skin lesions. Although it is almost impossible to culture *B. burgdorferi* from synovial fluid in patients with Lyme arthritis, polymerase chain reaction testing of synovial fluid for *B. burgdorferi* DNA often yields positive results before antibiotic therapy.³⁶ Even at that time, however, *B. burgdorferi* in synovial fluid appear to be moribund or dead, yet *B. burgdorferi* DNA may also persist after spirochetal killing with antibiotics. For these reasons, detection of *B. burgdorferi* DNA in joint fluid is not an accurate test of active

BOX 109.1 DIAGNOSIS OF LYME DISEASE

- Recognition of a characteristic clinical picture
- Positive antibody response to *Borrelia burgdorferi* determined by a two-test approach using enzyme-linked immunosorbent assay and Western blot analysis, except in patients with erythema migrans
- Interpretive criteria of the Centers for Disease Control and Prevention for Western blot results:
First 30 days of symptoms—two of the following three immunoglobulin M bands: 23, 39, 41 kDa
At any time in the illness—five of the following ten immunoglobulin G bands: 18, 23, 28, 30, 39, 41, 45, 58, 66, 93 kDa

Adapted from recommendations made by the Centers for Disease Control and Prevention.³⁷
From Steere AC. Lyme disease. *N Engl J Med* 2001;345:115-25.

joint infection in Lyme disease and cannot be used reliably to determine the adequacy of antibiotic therapy.

Because of the limited utility of microbiologic techniques, diagnosis is usually based on recognition of a characteristic clinical picture and, except in patients with erythema migrans, a positive antibody response to *B. burgdorferi*. For serologic testing in the United States, the CDC currently recommends a two-test approach in which samples are first tested by enzyme-linked immunosorbent assay (ELISA) and those with equivocal or positive results are tested by Western blotting, with findings interpreted according to the CDC criteria (Box 109.1).³⁷

During the first several weeks of infection, only 20% to 30% of patients with erythema migrans have positive responses in tests of acute-phase samples, usually of the immunoglobulin M (IgM) isotype, but by convalescence 2 to 4 weeks later, 70% to 80% show IgM reactivity, even after antibiotic therapy.^{38,39} After 4 to 8 weeks, patients with active infection have IgG antibody responses to five or more spirochetal proteins, which is required for a positive test result.^{39,40} In persons with infection of longer than 4 to 8 weeks' duration, a positive IgM test result alone is likely to be a false-positive response or one indicative of previous, early infection, and thus a positive IgM response by itself should not be used to support the diagnosis of Lyme arthritis or other late disease manifestations. Patients with Lyme arthritis typically have the highest IgG antibody responses seen in the infection, with expansion of the response to many spirochetal proteins.³⁹ When microarrays of more than 1200 spirochetal proteins were used, 120 proteins, primarily outer-membrane lipoproteins, were found to be immunogenic, and patients with Lyme arthritis had IgG reactivity to as many as 89 of these proteins.⁴¹

The most promising second-generation serologic test is an IgG ELISA that employs a 26-mer peptide of the sixth invariant region of the VlsE lipoprotein of *B. burgdorferi*, called the *C6 peptide ELISA*.^{39,42} Similar results were obtained with this test and the standard two-test approach of sonicate IgM and IgG ELISA and Western blot, and therefore the C6 ELISA has been considered for use as a stand-alone test.⁴³ The principal advantage of the C6 peptide ELISA is the early IgG response, and therefore determination of an IgM response is not necessary. However, the C6 ELISA is not quite as specific as sonicate Western blotting.^{43,44} Therefore, with current methods, a two-test approach that employs sonicate and VlsE ELISAs⁴⁴ or that uses an ELISA and Western blot analysis^{39,40} remains valuable for specificity, and blotting can be helpful in assessing the duration of current or past disease.

After successful antibiotic treatment, antibody titers decline slowly, but responses may persist for many years after treatment,⁴⁵ including responses to the VlsE C6 peptide.¹⁹ Moreover, not only the IgG but also the IgM response may persist for years after therapy. Therefore even a positive IgM response cannot be interpreted as showing recent infection or reinfection unless the appropriate clinical picture is present. Reinfection may occur in patients who were treated for erythema migrans,⁴⁶ but in patients who previously had Lyme arthritis, this seems to occur rarely, if at all. Thus the expanded immune response of late infection appears to protect against reinfection, whereas the incompletely developed immune response of early infection does not.

Differential diagnosis

Lyme arthritis typically causes marked joint swelling and pain in one or a few joints at a time with minimal systemic symptoms.²⁷ This clinical picture is most like reactive arthritis in adults or pauciarticular juvenile idiopathic arthritis in children. Lyme arthritis does not cause chronic, sym-

metric polyarthritis, and therefore distinguishing Lyme arthritis from rheumatoid arthritis is not difficult.

Fibromyalgia and chronic fatigue syndrome are sometimes misdiagnosed as Lyme disease.⁴⁷⁻⁴⁹ In contrast with Lyme arthritis, which causes minimal systemic symptoms, patients with fibromyalgia often have marked fatigue, severe headache, diffuse musculoskeletal pain, stiffness and pain in many joints, diffuse dysesthesias, difficulty with concentration, and sleep disturbance. On physical examination, such patients have multiple symmetric tender points in characteristic locations, but they lack evidence of joint inflammation.

TREATMENT

All manifestations of Lyme disease are usually treated successfully with oral or intravenous (IV) antibiotic therapy for 2 to 4 weeks, depending on the manifestation, as recommended by the Infectious Diseases Society of America (Box 109.2).^{50,51} For early localized or disseminated infection, doxycycline for 14 to 21 days is recommended in persons older than 8 years of age, except in pregnant women. Amoxicillin, the second-choice alternative, should be used in children or pregnant women. Because maternal-fetal transmission of *B. burgdorferi* seems to occur rarely, if at all,⁵² standard

therapy for the manifestation of the illness is recommended in pregnant women.

For patients with objective neurologic abnormalities, 2- to 4-week courses of IV ceftriaxone are most commonly given.⁵⁰ Objective evidence of relapse is rare after a 4-week course of therapy. In Europe, oral doxycycline is often adequate therapy for acute neuroborreliosis,^{53,54} but in the United States, patients with neuroborreliosis may require IV antibiotic therapy for successful treatment of the infection. In patients with high-degree atrioventricular nodal block (PR interval of longer than 0.3 sec), IV therapy for at least part of the treatment course and cardiac monitoring are recommended.⁵⁰ Once the patient's condition has stabilized, the course may be completed with oral therapy.

Lyme arthritis can often be treated successfully with a 30-day course of oral doxycycline or amoxicillin.⁵⁵ However, some patients require 2 to 4 weeks of IV antibiotics for successful treatment of the infection.²⁹ Despite therapy with 2 months or more of oral antibiotics and 1 month or more of intravenous antibiotics, a small percentage of patients in the United States have persistent, proliferative synovitis, primarily in one knee, for months or several years after antibiotic therapy.²⁹ After oral and IV antibiotic therapy, the authors treat such patients with nonsteroidal antiinflammatory agents and/or disease-modifying antirheumatic drugs, such as hydroxychloroquine or methotrexate. If the response to these agents is incomplete, arthroscopic synovectomy may be successful. An algorithm for the treatment of Lyme arthritis is shown in Figure 109.5.

BOX 109.2 TREATMENT AND VACCINATION REGIMENS FOR LYME DISEASE*

Early infection (local or disseminated)

Adults

Doxycycline 100 mg orally twice daily for 14 to 21 days

Amoxicillin 500 mg orally 3 times daily for 14 to 21 days

Alternatives in case of doxycycline or amoxicillin allergy:

Cefuroxime axetil 500 mg orally twice daily for 14 to 21 days

Erythromycin 250 mg orally 4 times daily for 14 to 21 days

Children (age 8 and younger)

Amoxicillin 250 mg orally 3 times daily or 50 mg/kg/day in 3 divided doses for 14 to 21 days

Alternatives in case of penicillin allergy:

Cefuroxime axetil 125 mg orally twice daily or 30 mg/kg/day in 2 divided doses for 14 to 21 days

Erythromycin 250 mg orally 3 times daily or 30 mg/kg/day in 3 divided doses for 14 to 21 days

Neurologic abnormalities (early or late)

Adults

Ceftriaxone 2 g IV once daily for 14 to 28 days

Cefotaxime 2 g IV every 8 hr for 14 to 28 days

Na penicillin G 3.3 million U IV every 4 hr for 14 to 28 days

Alternative in case of ceftriaxone or penicillin allergy:

Doxycycline 100 mg orally 3 times daily for 30 days, but this regimen may be ineffective for late neuroborreliosis

Facial palsy alone: oral regimens may be adequate

Children (age 8 and younger)

Ceftriaxone 75 to 100 mg/kg/day (maximum, 2 g) IV once daily for 14 to 28 days

Cefotaxime 150 mg/kg/day in 3 or 4 divided doses (maximum, 6 g) for 14 to 28 days

Na penicillin G 200,000 to 400,000 U/kg/day in 6 divided doses for 14 to 28 days

Arthritis (intermittent or persistent)

Oral regimens listed above for 30 to 60 days or

IV regimens listed above for 14 to 28 days

Cardiac abnormalities

First-degree AV block: oral regimens, as for early infection

High-degree AV block (PR interval of >0.3 sec): IV regimens and cardiac monitoring

Once the patient's condition has stabilized, the course may be completed with oral therapy.

Pregnant women

Standard therapy for manifestation of the illness. Avoid doxycycline.

AV, atrioventricular; IV, intravenously.

*Antibiotic recommendations are based on the guidelines of the Infectious Diseases Society of America.⁵⁰

POST-LYME DISEASE SYMPTOMS

After antibiotic therapy, some patients have persistent subjective symptoms—primarily pain, neurocognitive symptoms, or fatigue.⁵⁰ Although the frequency of such symptoms decreases with time, perhaps 10% of patients with erythema migrans have symptoms for at least 6 months after treatment,⁵⁶ and the frequency may be greater after disease with neurologic involvement.⁵⁷ Patients with Lyme arthritis usually have minimal, if any, associated symptoms, and subjective symptoms occur rarely after treatment of this manifestation.

Regardless, these subjective symptoms do not appear to respond to further antibiotic therapy. In the largest study of antibiotic therapy for post-Lyme disease symptoms, patients received IV ceftriaxone for 30 days followed by 60 days of oral doxycycline or IV and oral placebo for the same duration.⁵⁸ Six months after starting therapy, the numbers of patients who worsened, stayed the same, and improved were similar in both study groups, which suggests that such symptoms were not a result of persistent infection.

This issue has become more complicated because of patient-advocacy groups that promote months or years of antibiotic therapy for “chronic Lyme disease.” Moreover, chronic Lyme disease has become a common diagnosis for medically unexplained pain or fatigue symptoms, even when there is little or no evidence of previous *B. burgdorferi* infection.^{59,60} Even so, these patients are said to have persistent infection that can be suppressed only with months or years of antibiotic therapy. Although *B. burgdorferi* infection may persist for years in untreated patients, the weight of evidence is against persistent infection as the explanation for persistent symptoms in antibiotic-treated patients with Lyme disease.^{50,51}

PREVENTION

Personal protective measures against tick bites, particularly during the late spring and early summer, may help in the prevention of Lyme disease. Insecticides containing DEET (*N,N*-diethyl-*meta*-toluamide) effectively deter ticks, and tick checks after outdoor exposures are important. Because 24 to 72 hours of tick attachment is necessary before transmission of the spirochete occurs, removal of a tick within 24 hours of attachment is usually sufficient to prevent Lyme disease. However, if an engorged nymphal *I. scapularis* tick is found, a single 200-mg dose of doxycycline usually prevents Lyme disease when given within 72 hours after the tick bite occurs.⁶¹

For people living in areas where Lyme disease is endemic, it has been difficult to keep up these personal protective measures throughout the tick transmission season. For these individuals, vaccination would probably be the most effective approach for prevention of the infection. A safe and effective vaccine was marketed for Lyme disease from 1998 through 2002,³⁵ but it was removed from the market, primarily because of the risk of lawsuits. Nevertheless, experience gained in the 1990s proved the feasibility of this approach.

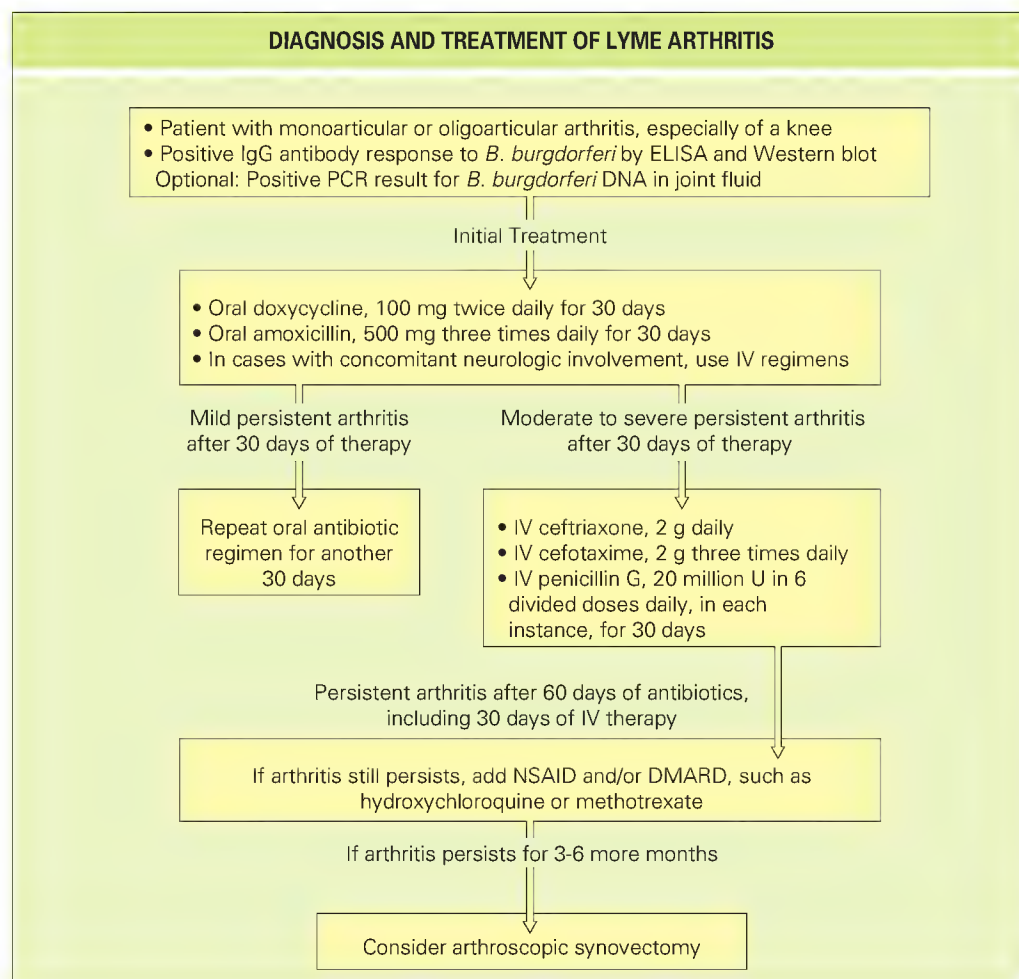


Fig. 109.5 Algorithm for the diagnosis and treatment of arthritis associated with Lyme disease. DMARDs, disease-modifying antirheumatic drugs; ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; IV, intravenous; NSAIDs, nonsteroidal antiinflammatory drugs; PCR, polymerase chain reaction.

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Rheumatologic aspects of viral infections

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HUMAN IMMUNODEFICIENCY VIRUS

- A variety of autoimmune-like and rheumatic manifestations, including arthritis, myositis, Sjögren-like syndrome, vasculitis, and low bone mineral density (BMD), have been described in patients with human immunodeficiency virus (HIV) infection.
- Arthritic syndromes that may be associated are reactive arthritis, psoriatic arthritis, and idiopathic articular disease.
- Associated myopathies includes polymyositis, noninflammatory myopathies, and drug-induced muscle disease.
- Vasculitic disease represents the spectrum of vascular inflammation.
- Sjögren-like disease is characterized by sicca symptoms, diffuse lymphocytic infiltration in the absence of specific autoantibodies.
- Low BMD and fragility fractures are increasingly recognized in aging HIV-infected patients.

OTHER VIRUSES

- A host of different viruses may cause arthritis through various pathogenetic mechanisms, including direct infection of synovial cells, immune complex formation, disruption of cell homeostatic mechanisms, and others.
- The most common arthritogenic viruses in North America and Western Europe are parvovirus B19, and hepatitis B and C viruses, whereas a variety of mosquito-borne viruses (mainly alphaviruses) cause epidemics of polyarthritis in Africa, the western Pacific, and South America.
- The majority of virally caused arthritides are acute, self-limiting illnesses, usually accompanied by fever, distinctive cutaneous manifestations, hematologic abnormalities (especially in parvovirus B19 infection), and other clinical features.
- Chronic polyarthritis mimicking rheumatoid arthritis may occur, especially in patients with chronic hepatitis C infection.
- Diagnosis requires knowledge of the epidemiology of these viral infections and the specific laboratory tests required for the detection of the specific arthritogenic virus.

INTRODUCTION

Despite the high frequency of acute and chronic viral infections worldwide, clinically significant rheumatic manifestations including arthritis and systemic rheumatic disorders occurring during the course of such infections are relatively rare. Viruses can cause either acute self-limited inflammatory polyarthritis (hepatitis B virus [HBV], parvovirus B19, rubella virus) or chronic arthritis (hepatitis C virus [HCV], human immunodeficiency virus [HIV], human T-cell lymphotropic virus type I [HTLV-I]). More recently, epidemics of virus-associated arthritides have been reported in certain areas of the world (Southeast Asia) as well as in travelers from these areas (alphavirus infections), which emphasizes their significance from a public health perspective.

Virus-associated rheumatic syndromes can be challenging both diagnostically and therapeutically. Diagnostically, certain virus-associated rheumatic syndromes can mimic rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or Sjögren syndrome. Therapeutically,

administering immunosuppressive therapy to patients with certain chronic viral infections such as HBV or HIV infection can be detrimental to the host.

HUMAN IMMUNODEFICIENCY VIRUS

Since the early 1980s rheumatic complications of HIV infection have been well described (Box 110.1). A number of discrete rheumatic syndromes have been reported,¹⁻³ including reactive arthritis, psoriatic arthritis (Fig. 110.1), HIV-associated arthritis (Fig. 110.2), and others, as well as a number of connective tissue diseases such as diffuse infiltrative lymphocytosis syndrome (DILS) and vasculitis. Since the introduction of active antiretroviral therapy (ART) in 1997, there has been a remarkable transformation not only in the natural history of HIV infection itself but also the attendant rheumatic complications. By contrast, in much of the developing world, access to ART is nonexistent or minimal, and thus HIV and its rheumatic complications have continued unabated.

Rheumatic manifestations in the era before active antiretroviral therapy

In the early 1980s a number of groups described an array of nonsuppurative rheumatic complications in HIV infection, including severe forms of reactive arthritis, psoriatic arthritis, and several nosologically unclear articular syndromes, all of which were clinically challenging (see Box 110.1).³ A variety of connective tissue diseases were described, including numerous forms of vasculitis, inflammatory myopathies, and DILS. The pathogenesis of these disorders has remained unclear with regard to their relationships to the underlying retroviral infection, the immunodeficiency state, or some opportunistic infective complication. Longitudinal studies of HIV-infected patients with inflammatory arthritis demonstrated an increased incidence of arthritis in those with severe or progressive disease.^{3,4} Patients with highly symptomatic rheumatic complications posed profound challenges in management because these complications often occurred in the setting of advanced immunodeficiency in the absence of any effective forms of treatment. The early experience with such patients documented rapid progression to end-stage HIV disease with antirheumatic therapy such as methotrexate. Similarly, clinical anecdotes described patients with idiopathic forms of connective tissue disease such as RA or SLE who experienced spontaneous remission with advancement of the underlying immunodeficiency.⁵

Rheumatic complications in global areas without access to active antiretroviral therapy

Since the early phases of the epidemic in areas such as sub-Saharan Africa, an increased incidence of a number of rheumatic syndromes, including reactive arthritis, spondyloarthritis, and enthesopathies, have been well described. This is particularly interesting because of the nearly complete lack of HLA-B*27 in these African populations. Investigations have demonstrated alternative genetic risk markers. In a series of studies in Zambia, HLA-B*5703 has been demonstrated to be a protective allele against the progression of HIV infection while possibly influencing the increased incidence of spondyloarthritis observed in this population.^{6,7}

A unique vasculopathy involving extracranial (carotid, aorta, and their branches) or intracranial (branches of the circle of Willis) blood vessels has been described in HIV patients over the last decade, initially in South Africa but recently in other areas of the world, and has been termed *HIV-associated vasculopathy*.⁸⁻¹¹ The vasculopathy is characterized by fusiform aneurysms that frequently lead to vascular occlusion and to a number of clinical syndromes such as stroke or ischemia of the upper or lower limbs.¹¹ Although

BOX 110.1 RHEUMATIC SYNDROMES IN THE SETTING OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION**Articular syndromes**

- Arthralgias
- HIV-associated arthritis
- Spondyloarthritis (reactive arthritis, psoriatic arthritis, undifferentiated spondyloarthritis)
- Septic arthritis
- Osteonecrosis
- Osteoporosis

Connective tissue disorders

- Sjögren-like syndrome, diffuse infiltrative lymphocytosis syndrome
- Myopathy (inflammatory/noninflammatory)
- Vasculitis
- Lupuslike syndrome



Fig. 110.1 Hands of a patient with psoriatic arthritis and human immunodeficiency virus infection.



Fig. 110.2 Hands of a 35-year-old man with advanced human immunodeficiency virus infection fulfilling the American College of Rheumatology criteria for rheumatoid arthritis.

in certain cases arterial wall inflammation has been documented (especially in the periadventitial or vasa vasorum vessels), in other cases no evidence of vasculitis has been found.^{9,11} The diagnosis of HIV-associated vasculopathy is usually made by imaging studies of the affected vessels (computed tomographic angiography, magnetic resonance angiography, invasive angiography) after opportunistic infections or neoplasms of the blood vessels

have been excluded.¹¹ It should be emphasized that patients with HIV infection have also a higher risk of accelerated atherosclerosis of the large vessels, which could be due to the HIV infection itself, traditional cardiovascular risk factors (e.g., dyslipidemia, smoking, diabetes, insulin resistance), or certain antiretroviral drugs.^{12,13}

Rheumatic manifestations in the era of active antiretroviral therapy

Since 1997 with the introduction of ART the frequency of opportunistic infections and many other attendant complications has diminished dramatically. Many of the nonsuppurative rheumatic manifestations and certain connective tissue diseases, including DILS,¹⁴ that were relatively common in HIV patients in the pre-ART era have nearly disappeared.^{2,15}

At the same time, other complications have arisen as a consequence of ART, including numerous metabolic disorders such as lipodystrophy, osteomalacia, and osteonecrosis.³ Low bone mineral density and fragility fractures are increasingly diagnosed in HIV-infected patients.¹⁶ The cause of osteoporosis is multifactorial and includes uncontrolled HIV infection (low CD4 count and/or high HCV RNA levels), antiretroviral therapy (during the first year of treatment, mainly with tenofovir),¹³ and traditional osteoporosis risk factors such as low body mass index, low vitamin D levels, and tobacco and alcohol use.¹⁶ The population of HIV patients is gradually aging, so primary care providers should be aware of this association and screen and treat these patients appropriately in collaboration with HIV specialists.^{16,17}

A peculiar nonsuppurative immune reconstitution syndrome has also been described in patients with advanced immunodeficiency, who, when started on ART, experience either an exacerbation of a previously quiescent or occult rheumatic disease or the *de-novo* appearance of a new rheumatic disease. Disorders that have been described as immune reconstitution syndromes include RA-like disorders, SLE, autoimmune thyroid disease, inflammatory myopathy, and sarcoidosis.¹⁵ Unlike patients in the pre-ART era who demonstrated intolerance to immunosuppressive drugs, patients receiving ART with good CD4 cell counts and well-controlled viral loads appear to tolerate aggressive immunosuppressive therapy, including treatment with biologic agents such as tumor necrosis factor (TNF) inhibitors.^{18,19} Given that even in the industrialized West an estimated one-third of HIV-infected patients remain undiagnosed, clinical vigilance appears warranted, and more widespread testing even in the absence of defined high-risk status has been recommended.²⁰

PARVOVIRUS B19

Virology

Parvovirus B19 was discovered in 1975 and is a member of the Parvoviridae family. Parvovirus B19 is among the smallest viruses known to infect mammalian cells; it is 22 to 24 nm in diameter and consists of an unencapsulated single strand of DNA of 5596 nucleotides.²¹ Parvovirus B19 replicates in erythrocyte precursors after binding to its cognate receptor, the blood group P antigen or globoside. The P antigen is expressed by a variety of cells, including erythrocytes, erythroblasts, megakaryocytes, endothelial cells, hepatocytes, and cardiac cells. The presence of the P antigen alone is not adequate for infection, and a coreceptor is required in the form of $\alpha_5\beta_1$ integrin, which provides an explanation for specific patterns of infectivity.²²

Parvovirus B19 infections occur in outbreaks and are transmitted by respiratory secretions, often in the late winter and spring. Serologic evidence of immunologic memory of parvovirus B19 is common in the form of specific immunoglobulin G (IgG) antibodies and is present in 50% to 70% of the population.²¹ Among immunologically naive individuals, schoolteachers, day care workers, pediatric nurses, and those proximate to small children are highly susceptible.²¹ During outbreaks the household transmission rate of parvovirus B19 can be as high as 50%.

Clinical manifestations

Parvovirus B19 is responsible for a number of clinical syndromes, including the common childhood exanthema erythema infectiosum, or fifth disease, with its classical presentation of a febrile child with a “slapped cheek” appearance and a maculopapular or reticular rash.²¹ Infection during early pregnancy results in the syndrome of fetal hydrops. In adults, parvovirus B19 infection may result in a transient aplastic crisis with chronic anemia as observed in immunocompromised individuals.²¹

The rheumatic manifestations of parvovirus B19 infection are numerous.^{21,23} Articular manifestations of parvovirus B19 infection are uncommon

in children but quite common in adults. Symptoms begin in a few joints and may spread in additive fashion, giving an RA appearance, and often include prominent morning stiffness. Synovitis is minimal, and frank joint effusion is rare. Articular manifestations are most prominent in the early stages of the infection coinciding with the appearance of IgM antibodies during the intense phase of viremia, which suggests an immune complex mechanism. Further complicating the clinical presentation is the documented ability of parvovirus B19 to induce a spectrum of autoantibodies, often transient, including rheumatoid factor (RF), antinuclear antibodies (ANAs), anti-DNA, anti-ENA, antiphospholipid antibodies, and others. In the presence of polyarthritis, autoantibodies, and cytopenias the infection can mimic SLE. The pathogenic mechanism of autoantibody formation is not clear, but recent evidence has provided strong evidence for molecular mimicry.²² Parvovirus B19 has also been associated with a variety of other autoimmune syndromes, including systemic vasculitis, reactive arthritis, Sjögren syndrome, idiopathic inflammatory myopathies, and scleroderma.^{21,23} Systematic search strategies for serologic or *in situ* evidence of parvovirus B19 in patients with RA and vasculitis have revealed no difference in detection rates compared with control subjects without autoimmune disease.²²

Laboratory investigation

The laboratory detection of parvovirus B19 infection depends on identification of specific IgM antibodies with or without the presence of IgG anti-B19. The presence of IgG alone is common and consistent with past infection. IgM antibodies may persist for weeks to months. The virus can also be detected early by polymerase chain reaction assay, although this is not clinically necessary. The critical clinical point regarding parvovirus B19 infection is not to confuse it with idiopathic autoimmune disease and thus to spare the patient unnecessary immunosuppression, because treatment for parvovirus B19 infection is generally supportive. The diagnosis of parvovirus B19 infection must start with a high index of suspicion in an immunologically vulnerable host and must be confirmed by appropriate serologic testing. Routine screening of patients with early inflammatory arthritis is not recommended in the absence of clinical suspicion, because parvovirus B19 is an uncommon cause (0.25% of cases in a recent French study).²⁴

HEPATITIS B VIRUS

Virology

Chronic HBV infection remains one of the most common chronic viral infections, with approximately 350 million people infected worldwide.^{25,26} It is caused by HBV, a hepatotropic, enveloped, double-stranded DNA virus that is transmitted parenterally, sexually, or vertically (mother to child). Chronic HBV infection is most often the result of vertical, perinatal, or early childhood transmission; in adults exposure to the virus after parenteral or sexual transmission most frequently leads to acute hepatitis and viral clearance.^{25,26}

Clinical manifestations

Arthritis in patients with HBV infection can be seen in two different settings: as arthritis related directly to the viral infection (polyarthritis during acute hepatitis B or arthritis in patients with HBV-associated medium-vessel vasculitis or polyarteritis nodosa [PAN]) and as a coexisting arthropathy like RA, SLE, and so on, in patients with chronic HBV infection.⁵

HBV-related rheumatic manifestations are attributed to the deposition of immune complexes containing viral antigens (hepatitis B surface antigen [HBsAg], hepatitis B e antigen [HBeAg]) and antibodies directed against these antigens (anti-HBs, anti-HBe) in the synovium or in vessel walls, which results in arthritis or vasculitis (affecting small or medium-sized vessels).

During the preicteric phase of acute hepatitis B, a small proportion of patients develop a symmetric polyarthritis resembling RA that affects mainly the proximal interphalangeal joints, knees, and ankles.²⁷ Associated symptoms include rash (maculopapular, urticarial, petechial), fever, malaise, and myalgias. In 25% of cases RF is present, whereas C3 and C4 levels are low in approximately 40%. The presence of HBsAg, highly elevated levels of aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), and IgM anti-HBe antibodies provide the definitive diagnosis of HBV-associated polyarthritis and differentiate it from other forms of acute inflammatory polyarthritis. No treatment is needed because the arthritis resolves spontaneously after 2 to 3 weeks.

HBV-associated PAN is a rare form of vasculitis of medium-sized vessels the frequency of which is gradually decreasing worldwide.²⁸ Usually HBV-associated PAN develops during the first 6 months after acute HBV infection, and its clinical presentation and course do not differ significantly from those of classical PAN.²⁸ The most common musculoskeletal manifestations are arthralgias (approximately 50% of cases) and myalgias, whereas frank arthritis, affecting predominantly large joints (knees, ankles, wrists), is observed only in a small proportion of patients.²⁸ HBV-associated PAN has a more severe course with more frequent nerve, gastrointestinal, and heart involvement than non-HBV-associated PAN, but skin involvement appears to be less frequent (approximately 35%). The management of HBV-associated PAN includes treatment with immunosuppressive drugs (corticosteroids, cyclophosphamide in severe cases) and antiviral agents (oral nucleoside or nucleotide analogues). The overall long-term mortality rate of HBV-associated PAN is high (approximately 34%) with a 10-year survival rate of 54%.²⁸ For patients who achieve remission after therapy, however, the overall prognosis is favorable with only 10% of patients experiencing relapse.²⁸

Over the last decade HBV reactivation has been described in patients with chronic rheumatic diseases and coexisting HBV infection after the use of biologic agents such as TNF inhibitors, rituximab, and abatacept in the absence of appropriate antiviral prophylaxis.²⁶ Therefore screening for HBV infection (HBsAg, anti-HBc, anti-HBs) is recommended in patients with rheumatic diseases before the initiation of immunosuppressive therapies, especially treatment with biologic agents. Patients with chronic HBV infection (HBsAg+) should receive oral antiviral therapy (preferably with the newer antiviral agents like tenofovir and entecavir) for the duration of immunosuppressive therapy.²⁶ Patients with past HBV infection (HBsAg−/anti-HBc+) should be monitored regularly with measurement of ALT, HBsAg, and HBV DNA levels and treated with antivirals if there is evidence of HBV reactivation (HBsAg+ and/or HBV DNA+).²⁶

HEPATITIS C VIRUS

Chronic HCV infection is another common chronic viral infection, with more than 180 million people affected worldwide. HCV is an RNA hepatotropic virus that is transmitted parenterally, mainly through injection drug use.^{26,29} Patients who received blood transfusions before 1992 and persons with multiple sexual partners are also at increased risk.^{26,29} In contrast to HBV exposure, the majority of adults exposed to HCV (60% to 85%) develop chronic infection.^{26,29}

Clinical manifestations

The rheumatic manifestations in patients with chronic HCV infection can be divided into four groups (Box 110.2): a coexistent arthritis (not related to HCV infection), arthritis in the setting of HCV-associated cryoglobulinemic vasculitis, arthritis directly related to HCV infection (HCV-associated arthritis), and arthritis induced by antiviral therapy (interferon- α [IFN- α]).³⁰

Coexistent arthropathy

Coexistent arthropathy probably is the most common cause of rheumatic manifestations in patients chronically infected with HCV.⁵ The coexistence of another inflammatory (RA, SLE, Sjögren syndrome, etc.) or noninflammatory (fibromyalgia) arthropathy in this setting creates diagnostic as well as therapeutic problems. These coexisting rheumatic disorders can present with clinical and laboratory features that are also seen in chronic HCV infection, such as sialadenitis, fatigue, positivity for RF and/or ANAs, cytopenias, or low levels of complement (particularly C4). The presence of characteristic laboratory results (anti-cyclic citrullinated peptide [anti-CCP] for RA, anti-double-stranded DNA for SLE, anti-Ro/La for Sjögren syndrome) or radiologic findings (erosive changes in RA) are extremely helpful for the differential diagnosis.

BOX 110.2 ARTHRITIS IN THE SETTING OF HEPATITIS C VIRUS (HCV) INFECTION

- Coexistent arthropathy (rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, fibromyalgia)
- HCV-associated arthritis
- Arthritis in the setting of HCV-associated cryoglobulinemic vasculitis
- Arthritis induced by antiviral therapy (interferon- α)



Fig. 110.3 Cutaneous manifestations in hepatitis C virus–associated cryoglobulinemic vasculitis. (a) Palpable purpura. (b) Confluent purpura. (c) Necrotic ulcers. (From Vassilopoulos D, Calabrese LH. Hepatitis C virus infection and vasculitis. Implications of antiviral and immunosuppressive therapies. *Arthritis Rheum* 2002;46:585-97.)

In terms of treatment of the coexistent rheumatic disorder, especially when long-term immunosuppressive therapy with potentially hepatotoxic medications (methotrexate, leflunomide) is planned, a thorough baseline assessment of the underlying liver disease in collaboration with an experienced hepatologist is imperative.³¹ In patients with advanced liver disease (advanced fibrosis in liver biopsy specimens or decompensated cirrhosis [ascites, encephalopathy, coagulopathy]), medications such as methotrexate or leflunomide should be avoided.³² In patients with less advanced disease and stable liver function, these medications can be used with close monitoring of liver function. With regard to biologic agents such as TNF inhibitors and rituximab, a number of recent studies have demonstrated their short-term safety in rheumatic patients chronically infected with HCV.²⁶

Hepatitis C virus–associated arthritis

In rare cases (less than 5%), patients with chronic HCV infection can develop an inflammatory arthritis that has been directly attributed to HCV infection.³³ The arthritis is a symmetric, nondeforming, nonerosive polyarthritis that involves small joints of the upper and lower extremities (metacarpophalangeal joints, proximal interphalangeal joints, ankles). Monoarthritis or oligoarthritis can be seen in 20% of cases. RF and cryoglobulin can be found in these patients, which makes the differential diagnosis from early RA or HCV-associated mixed cryoglobulinemia challenging.³³ The presence of anti-CCP antibodies and erosive changes on radiographs are helpful for excluding the diagnosis of RA. Analgesics, low-dose corticosteroids (less than 10 mg/day), and in severe cases disease-modifying antirheumatic drugs or anti-TNF agents can be used after appropriate evaluation and monitoring of hepatitis C.³³

Arthritis in hepatitis C virus–associated cryoglobulinemic vasculitis

Circulating cryoglobulins are a common laboratory finding in patients with chronic HCV infection (40% to 50% of cases), but less than 5% of patients develop the distinct syndrome of mixed cryoglobulinemia manifested by purpura, polyneuropathy, membranoproliferative glomerulonephritis, and other features.^{34,35} The clinical and laboratory manifestations of the syndrome are thought to be induced by monoclonal RF or immune complexes containing RF and polyclonal IgG, with or without associated HCV antigens, that are deposited in small-vessel walls in different tissues (skin, nerves, synovium, glomeruli).³⁴ The most common musculoskeletal complaints are intermittent nonspecific polyarthralgias involving the hands and knees, whereas less than 10% of patients develop inflammatory arthritis (nonerosive).

The diagnosis of arthritis in this setting is easier because patients have the typical clinical picture (purpura, skin ulcers, membranoproliferative glomerulonephritis, peripheral neuropathy), and laboratory findings (type II or III serum cryoglobulins, low C4 levels, RF, active urine sediment) of mixed cryoglobulinemia (Fig. 110.3).

The treatment of HCV-associated cryoglobulinemic vasculitis is guided by the severity and pattern of organ involvement. In patients with mild to severe disease, antiviral treatment (pegylated IFN- α plus ribavirin) with or without the addition of low-dose corticosteroids (prednisone at less than 10 mg/day) can lead to viral clearance and resolution of the mixed cryoglobulinemia syndrome.²⁶ In more severe cases, high-dose corticosteroids, cyclophosphamide, rituximab, and/or plasmapheresis followed by antiviral treatment have been used with very good success rates.^{36,37} In cases in which antiviral therapy has failed, is contraindicated, or is not tolerated, rituximab monotherapy has been used with success and without significant adverse effects.^{38,39}

Interferon- α -induced arthritis

IFN- α is an immunomodulatory cytokine with pleiotropic properties, and its use has been associated with a number of autoimmune manifestations, including autoimmune thyroiditis, arthritis, and lupuslike syndrome.³⁰ Arthritis is rare, and when it appears the decision to continue treatment depends on the severity of the IFN- α -induced arthritis as well as the likelihood of viral clearance with IFN- α therapy.

CHIKUNGUNYA AND OTHER ALPHAVIRUSES

Although alphavirus infections have long been associated with various forms of inflammatory arthritis, for Western rheumatologists these have not been infections of practical concern.⁴⁰⁻⁴² Table 110.1 lists the alphaviruses linked to arthritis, all of which are arboviruses.⁵

Over the past decade this pattern of limited spread has changed with the emergence of one alphavirus, namely chikungunya virus (CHIKV), which is no longer restricted to tropical developing countries and now poses a global public health problem. CHIKV, a single-stranded RNA virus, like other members of the genus, is a mosquito-borne virus that in the past has been responsible for significant epidemics in Asia and Africa.⁴¹ In 2006 an outbreak of CHIKV infection swept over several islands in the Indian Ocean and parts of India proper, and appeared most recently in Singapore. During this same time increasing numbers of cases were reported in travelers returning to Europe and the United States.⁴³ A major reason for this epidemiologic shift appears to be a single adaptive mutation enhancing CHIKV's ability to be carried by *Aedes albopictus*, a mosquito linked to urbanization and international transport.⁴⁴ Evidence of this threat is now documented by way of an outbreak of CHIKV in northwestern Italy, where more than 200 cases were described and traced to an infected traveler returning home with subsequent spread of the virus by *A. albopictus*.⁴¹

Clinical manifestations

Nearly all patients infected with CHIKV develop an inflammatory polyarthritis that, although generally short-lived, is clinically severe and may

TABLE 110.1

Alphavirus-related arthritis and geographic distribution

Alphavirus distribution	Geographic	Clinical manifestations	Comments
Ross River	Australia Oceania	Polyarthritis Fever Rash	Reported in travelers and visiting U.S. military personnel
Sindbis	Russia Finland Sweden	Arthritis Rash	Transmitted by mosquitoes from birds to humans
Mayaro	South America	Arthritis Fever	
O'nyong-nyong	Africa	Polyarthritis Fever Rash	Similar clinical picture to chikungunya virus
Igbo-ora	Central Africa	Arthralgias Fever Myalgias	
Chikungunya	Southeast Asia Africa	Polyarthritis Fever	Reported in travelers from endemic areas (e.g., Northern Italy, France)



Fig. 110.4 Chronic arthritis involving wrist and metacarpophalangeal and interphalangeal joints in a patient with chikungunya virus infection. (From Khasnis AA, Schoen RT, Calabrese LH. Emerging viral infections in rheumatic diseases. *Semin Arthritis Rheum* 2011;41:236-46).

BOX 110.3 CLINICAL AND LABORATORY FINDINGS OF CHIKUNGUNYA VIRUS INFECTION

A. Early phase (0-10 days)

Clinical

- Fever
- Symmetric polyarthritis (wrists, hands, ankles, toes)
- Rash
- Conjunctivitis

Laboratory

- Cytopenias (leukopenia, thrombocytopenia)
- Transaminasemia (aspartate aminotransferase, alanine aminotransferase)
- Detection of virus (virus isolation methods) or viral RNA (reverse transcriptase-polymerase chain reaction)

B. Late phase (>10 days)

Clinical

- Arthritis/tenosynovitis of hand joints (lasting up to 6 months)

Laboratory

- Detection of specific immunoglobulin M or immunoglobulin G antibodies (fourfold increase in paired samples)

mimic more serious and persistent forms of noninfectious arthritis. The disease has been reported to run through two consecutive phases (Box 110.3).⁴¹⁻⁴³ During the early phase (less than 10 days), manifestations include fever, transient rash (macular, papular, or generalized erythematous, located on the trunk), conjunctivitis, myalgias, and symmetric polyarthralgias and/or polyarthritis involving mainly the wrists, hands, ankles, and toes.^{40,41,43} Edema of the face and periarticular tissues is common in these patients. Axial pain is also common, affecting almost half of patients. During this phase, elevation of liver enzymes (AST, ALT, γ -glutamyltransferase) and muscle enzymes (creatinine phosphokinase, lactate dehydrogenase) have been documented in 50% of patients, often accompanied by cytopenias (thrombocytopenia, leukopenia). In some cases, petechial hemorrhages are also

noted. During the second stage of the disease (longer than 10 days), most patients have persistent joint pain in the form of tenosynovitis involving wrists and fingers and/or proximal finger joint arthritis. At this stage fever and rash have generally abated. Almost half of patients continue to have articular symptoms 6 months after the onset of disease, but laboratory results are normal during this phase. Rarely, the disease can follow a chronic course reminiscent of RA (Fig. 110.4).⁴⁵ Only symptomatic treatment with analgesics and nonsteroidal antiinflammatory drugs (NSAIDs) is given throughout the entire course of the disease, because no specific therapy is available. In certain cases, corticosteroids or methotrexate has been administered.^{40,45}

The diagnosis of CHIKV infection is based on clinical features (fever and arthralgias/arthritis), epidemiologic factors (residence in or return from an endemic area within 15 days of the onset of symptoms), and laboratory findings (virus isolation, detection of viral RNA, detection of specific IgM antibodies, fourfold increase in IgG titers).⁴¹ During the first week of febrile illness, virus isolation or detection of CHIKV RNA by reverse transcriptase-polymerase chain reaction assay is used, but later on the detection of antibody response (IgM antibodies) by indirect immunofluorescence or ELISA is necessary for diagnosis.⁴¹

HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE I

HTLV-I infection, which is endemic in certain geographic areas such as southern Japan and the Caribbean, has been associated with an inflammatory arthropathy resembling RA.⁴⁶ The virus, a human retrovirus, is transmitted perinatally, sexually, and through contaminated blood transfusions. HTLV-I-associated arthropathy commonly affects elderly women and takes the form of a seropositive (RF+), symmetric, inflammatory arthritis. Radiographs of the affected joints usually reveal mild erosive changes. NSAIDs, DMARDs, and low-dose prednisolone have been used for its treatment.⁴⁶

OTHER VIRUSES

Rarely, other viruses have been implicated as causes of acute self-limited arthritis, including rubella virus,⁴⁷ Epstein-Barr virus,⁴⁸ and coxsackievirus.⁴⁹

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Acute rheumatic fever

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- Acute rheumatic fever (ARF) is a systemic autoimmune disease triggered by cross-reactive immune responses between group A β -hemolytic streptococci (GAS) and host tissue epitopes.
- There is a 2- to 3-week latency period between the inciting GAS infection and ARF symptoms with the exception of chorea, for which the latency period is typically 4 to 8 weeks.
- ARF is most common among 5- to 15-year-old individuals, with a declining incidence in adults. This condition is rare in children younger than age 3.
- The acute form of the illness is characterized by all or a subset of the following symptoms: fever, arthritis, carditis, Sydenham chorea, erythema marginatum, and subcutaneous nodules.
- Chronic rheumatic heart disease is the primary cause of death in rheumatic fever and may be largely prevented by adequate antibiotic prophylaxis.

INTRODUCTION

The composer Wolfgang Amadeus Mozart (1756-1791) was tormented by frequent attacks of arthritis and appears to have been ultimately killed by heart failure (and renal dysfunction). The artist Andy Warhol (1928-1987) and the German poet Bertolt Brecht (1898-1956) both had St. Vitus' dance and died of heart failure. Rheumatic fever (RF) was once so common throughout Europe, the United States, and the rest of the world that the medical specialty of rheumatology owes its name to the disease referred to as *Rhumatism* by the 16th-century French Hellenistic doctor Guillaume de Baillou. The incidence of acute rheumatic fever (ARF) declined dramatically in the developed world throughout the 20th century, being restricted primarily to sporadic outbreaks. However, the disease remains a major medical and social problem in the developing world and so-called hotspots, where it still causes approximately 230,000 deaths annually.¹

EPIDEMIOLOGY

Denmark has the best historical records regarding the incidence of ARF, and this nation can be used as an example of what occurred in what is now referred to as the developed world. In 1862, this country recorded 250 cases per 100,000 inhabitants. However, in 1962, the incidence had dropped to 100 per 100,000. Between 1860 and 1945, when antibiotics became available, the disease incidence decreased by approximately 75%. By 1980, the incidence of ARF was approximately what it is currently, which is 0.3 per 100,000 inhabitants.² The reasons behind this dramatic decline in incidence before the use of antibiotics are incompletely understood but include improvements in living conditions and possibly changes in the infecting bacteria.

In the mid-1980s, ARF outbreaks were observed in Utah, Pennsylvania, Ohio, and military bases in San Diego and Missouri in the United States. The annual incidence at that time was as low as 0.23 to 1.88 per 100,000 among children and adolescents but increased approximately 10-fold in specific epidemic areas. The affected children in the Utah outbreak were primarily from upper-middle-class families who had full access to medical facilities, which highlights the role of factors other than poverty and overcrowding in the pathogenesis of this disease.³

Presently, the incidence of ARF in most developed countries remains below 5 per 100,000 inhabitants (Fig. 111.1). Australia and New Zealand are exceptions due to a high incidence of ARF in communities of individuals of Aboriginal and Polynesian descent. Such individuals do not have the same standard of living as those of European ancestry. Higher incidences of ARF are observed in the Aboriginal population of Australia, which exhibits annual rates above 300 per 100,000 inhabitants.⁴ The developing world has also witnessed a clear decline in the incidence of ARF, but the disease is still endemic in South America, Africa, and Asia, and in the less affluent communities of Australasia and the Pacific islands. Based on the few data that are available, the annual global incidence of ARF has been estimated to be approximately 471,000 cases, leading to a worldwide prevalence of rheumatic heart disease (RHD) of at least 15.6 million cases, with 282,000 new cases and 233,000 deaths due to RHD each year. Given that the progression of carditis is silent in most cases and that arthritis can be mild and easily controlled by regular use of antiinflammatory drugs, these numbers may be underestimates. In addition, fewer data are available from the areas in which the disease is more prevalent.¹

Relationship between group A streptococci and rheumatic fever

Consistent data strongly support a relationship between pharyngitis caused by group A β -hemolytic streptococci (GAS) and ARF⁵: (1) streptococcal sore throats or scarlet fever epidemics precede outbreaks of RF; (2) adequate treatment of streptococcal pharyngitis markedly decreases the incidence of subsequent RF; (3) secondary antimicrobial prophylaxis prevents the recurrence of ARF; and (4) antistreptococcal antibody titers are high in most patients with ARF, even if the patients do not recall preceding pharyngitis.

The laboratory and epidemiologic data that have been gathered over more than 60 years suggest that, in contrast to nephritis, RF is associated with pharyngeal but not skin infections. Moreover, GAS strains have been characterized as either "rheumatogenic" or "nephritogenic" based on their phenotypic and genotypic properties. ARF almost never occurs following outbreaks of impetigo. Although impetigo strains do colonize the pharynx, they do not appear to elicit a strong immunogenic response to the bacterial M protein. The pharynx is largely supplied with lymphoid tissue, a fact that is most likely important with respect to the initiation of the anomalous cross-reactive immune response. Nevertheless, the epidemiology of ARF in the Aboriginal populations of central and northern Australia runs counter to this view. Although this population has some of the highest reported rates of ARF and RHD, GAS throat carriage rates are low and symptomatic GAS pharyngitis is rare.⁴ In these high-risk populations pyoderma is the major manifestation of GAS infection, typical rheumatogenic strains do not occur,⁴ and a distinction cannot easily be made between the strains that cause ARF and those that cause glomerulonephritis based on genotype and the site of recovery. A possible causal link between GAS skin infection and RF in the tropics has been suggested and has been the subject of investigation in Australia⁶; however, the question of whether such a correlation exists remains open. In endemic settings, there is an increased genetic transfer of virulence factors between organisms, an effect that blurs the classic genotypic and phenotypic traits of the strains.⁴ Group C and G streptococci are more commonly observed in the throats of Aboriginal children and have been demonstrated to exchange key virulence determinants with GAS. It has been proposed that these strains may be involved in the pathogenesis of RF in such communities.⁶ An alternative explanation is that certain ethnic groups are predisposed to RF so that even the low observed pharyngeal GAS carriage rates are sufficient to cause higher rates of ARF and RHD.

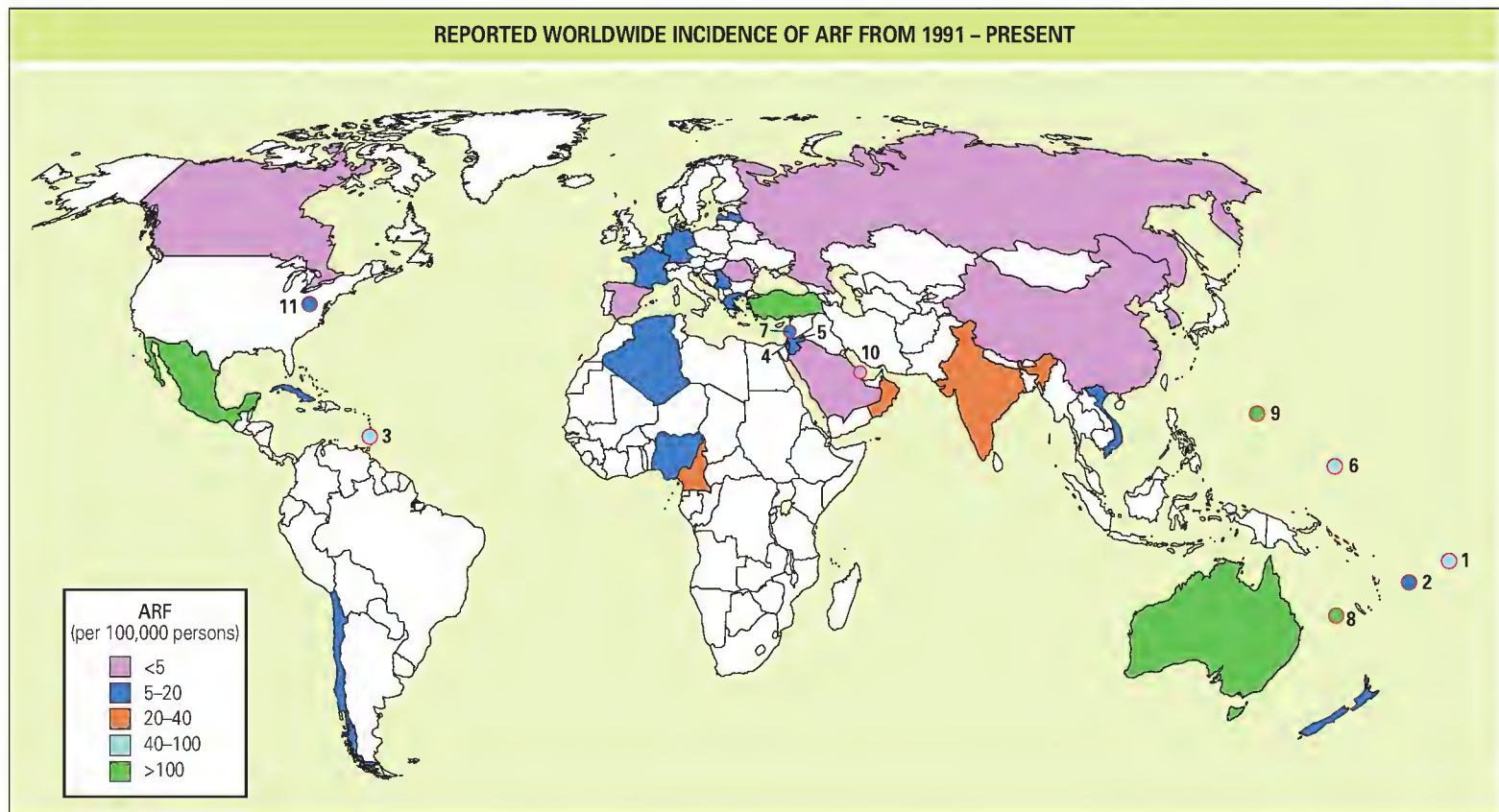


Fig. 111.1 The circles and numbers represent areas too small to be depicted in their true forms. (1) American Samoa, (2) Fiji, (3) Grenada, (4) Israel, (5) Jordan, (6) Kosrae, Federated States of Micronesia, (7) Lebanon, (8) New Caledonia, (9) Northern Mariana Islands, (10) Qatar, (11) West Virginia. (Adapted with permission from Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin Epidemiol* 2011;3:67-84.)

Streptococcal factors

Streptococcus pyogenes, or GAS, is an anaerobic, facultative, gram-positive coccus that grows in chains and causes numerous infections in humans. Phenotypic and genotypic characteristics of the bacteria are determinants of its virulence and immunogenicity. The surface layer of the bacterial cell wall contains the M protein, a major virulence factor. It exhibits a great deal of variation in its N-terminal molecular structure, which allows GAS to be further differentiated into more than 130 M-serotypes. The abundant production of M protein may confer a mucoid appearance to colonies in blood-agar plates. The M protein binds to the Fc portion of immunoglobulin G and immunoglobulin A molecules, creating a human immunoglobulin shield with the Fab portion facing outward that prevents phagocytosis and immune recognition. Within the M protein lies a domain that binds to one of the complement regulatory proteins (factor H), inhibiting antibody binding and complement-derived opsonin deposition. The M protein has a helical and coiled structure that has structural homology with cardiac cytoskeletal tropomyosin and myosin and many other coiled structures, including vimentin, keratin, DNA, and lamin. T-cell clones from the heart valves of patients with RHD can be reactive to the epitopes of type 5 M protein.⁷ Cross-reactivity between the endothelium and sarcolemma antigens with M-protein structures have also been described.⁷ In the 1960s, 3 of 21 patients enrolled in an M-protein vaccine early trial developed ARF, which further indicates the pathophysiologic role of this structure.⁸ Nontypeable strains of GAS may express small quantities of M protein, express an entirely novel M protein that is not recognized by the current typing techniques, or completely lack M proteins. New M-types are frequently described, which poses a great challenge to bacteriologists. Several different M-serotypes and nontypeable GAS strains, both mucoid and nonmucoid, have been associated with RF. Moreover, different M serotypes have been linked to RF in different populations. Because GAS strains are able to transfer genetic material horizontally, it is believed that any GAS can potentially acquire the ability to cause RF. Although GAS organisms have many structures that may cross-react with joints, the heart, the skin, the kidneys, and the brain, the role of each specific antigen in RF pathogenesis remains unclear.

The decline of RF in the 20th century could possibly be linked to alterations in *Streptococcus*. Some experts believe that there has been a decline in the incidence of streptococcal infections, but there are no data that

document this hypothesis. Scarlet fever has become a much milder disease than in previous decades, and its incidence appears to have declined. The incidence of poststreptococcal acute glomerulonephritis also has declined, although not as markedly as has the incidence of RF.⁹ Changes in bacterial virulence were proposed to be a possible mechanism for this observed decline in incidence. The M protein is considered to be the major streptococcus virulence factor, but there are no data indicating that the percentage of non-M-typeable strains (i.e., strains lacking M protein) are increasing in prevalence.⁹

Environmental factors

RF is a disease of poverty. The influence of socioeconomic status on its prevalence is supported by the near disappearance of ARF in industrialized countries since the mid-20th century, which began before the introduction of antibiotics. In a study in the Congo, the prevalence of RHD, based on clinical examination, was 22.2 per 1000 among children who lived in slums but only 4 per 1000 among children who attended schools.¹⁰ The exact poverty-related factors that lead to RF susceptibility are incompletely understood. Crowding is associated with lower social indices and is a facilitating factor for the spread of streptococcal infection. In early U.S. military studies, the acquisition of pharyngeal GAS was inversely proportional to the distance between barrack beds.¹¹ Nevertheless, not all authors have been able to demonstrate an association between crowding and ARF. Maternal unemployment and treatment noncompliance have also been associated with both low socioeconomic status and ARF.¹²

Host factors

During the U.S. military base outbreak in the 1950s, only approximately 3% of individuals infected with the rheumatogenic *Streptococcus* strains developed ARF. During the Utah epidemic in the 1980s, the majority of affected children, as noted earlier, were from upper-middle-class homes with access to medical facilities, which suggests that individual factors are important in the pathogenesis of this disease. Additionally, only a very small percentage of patients develop all of the associated symptoms,¹³ and only one to two thirds develop chronic rheumatic heart disease (CRHD).¹⁴ Individual factors are determinants of the disease pattern but are poorly understood. Familiar

aggregation, the similarity of disease patterns in siblings and identical twins, and HLA correlation studies provide evidence for a genetic influence on RF susceptibility and manifestation; however, this influence does not appear to be single-gene/mendelian in nature.¹⁴ The pooled probandwise concordance risk for acute rheumatic fever was 44% in monozygotic twins and 12% in dizygotic twins, and the association between zygosity and concordance was strong (OR 6.39; 95% confidence interval, 3.39 to 12.06; $P < 0.001$), with no significant study heterogeneity ($P = 0.768$). The estimated heritability across all the studies was 60% and RF was considered an autoimmune disorder with a high heritability.^{14a}

Given the evidence for a genetic component of RF susceptibility, several genes have been examined for a possible role, the majority of which are in some manner involved in the regulation of the immune system. These proposed genetic factors include genes that encode HLA antigens and B-cell alloantigens, as well as polymorphisms within immune system-related genes.

HLA class II antigens

Different HLA class II antigen associations have been observed in several populations, chiefly those encoded by the DR and DQ genes. The HLA class II gene most consistently associated with RF/RHD was HLA-DR7, observed in Brazilian, Egyptian, Latvian, and Turkish patients. The combination of HLA-DR7 with certain HLA-DQB or HLA-DQA alleles was associated with multiple valvular lesions in patients with RHD in Egypt and Latvia.⁷ The HLA class II genes encode cell-surface proteins that present outer antigens to the T-cell receptor (TCR). It is the HLA-antigen complex that is recognized, not the antigen alone; it is therefore plausible that the HLA type has a direct influence on RF pathophysiology. Accordingly, the M5 immunodominant epitope was preferentially presented to T cells in the context of specific HLA class II molecules (DR7 and DR53).⁷ Because different strains of GAS with different immunogenic properties cause RF in different countries, it is unsurprising that diverse HLA class II associations have been reported. The HLA gene complex may also be in linkage disequilibrium with the actual RF susceptibility genes and may thus serve only as a marker.

B-cell alloantigen

In 1979, it was observed that the serum from a multiparous woman reacted with RF patients' blood with a higher frequency than with control serum. The alloantigen was demonstrated to be at the B cells' surface and was not associated with any specific major histocompatibility complex. A monoclonal antibody (D8/17) was subsequently produced by immunizing mice with B cells from patients with RF. The B-cell antigen was highly expressed on 100% of B cells from RF patients in several ethnic groups but in only 10% of samples from controls.¹ The D8/17 target antigen shares antigenic determinants with heart and streptococcal membrane cross-reactive antigens. This monoclonal antibody also reacted with cells of the Aschoff bodies, which express HLA-DR molecules. This result suggests that these cells act as antigen-presenting cells and elicit a delayed immune reaction.¹⁵ However, the D8/17 marker was absent in one third of North Indian patients. Using the same technique, a novel monoclonal antibody (PGI/MNII) was developed for this population and also exhibited a high sensitivity (identifying 86% of patients with RF and 94% of patients with RHD).¹ These results suggest that different epitopes are presented to the adaptive immune system in the two populations, perhaps in the context of different class II HLA molecules.

Gene polymorphisms

The innate immune response provides a direct defense against infection, recruits immune cells to the site of infection, and activates the adaptive immune system via antigen presentation, the production of cytokines, and initiation of the complement cascade. Variations within the genes involved in the innate immune response could influence an individual's predisposition to GAS infection, ARF, or its sequelae. It follows that polymorphisms in the genes that code for proteins involved in the innate immune response have been associated with RF and/or its manifestations. These genes include mannose-binding lectin, Toll-like receptor 2, and ficolin-2, which is a receptor for the Fc fragments of immunoglobulin G (FcγRIIA) and a macrophage migration inhibitory factor.

The agent primarily responsible for the maintenance and expansion of the inflammation that leads to the tissue damage observed in RHD is the adaptive immune system. To date, the genes or genomic regions that have been associated with RF and/or its manifestations include interleukin-1 (IL-1) receptor antagonist, tumor necrosis factor- α (TNF- α), the IL-10 gene promoter, transforming growth factor- β , and cytotoxic T-lymphocyte antigen 4.⁷

HUMORAL IMMUNE RESPONSE

Several antibodies that are capable of cross-recognizing human and streptococcal molecules have been described.¹⁴ Antibodies against the streptococcal wall component GlcNAc display cross-reactivity against laminin, which is present in the extracellular matrix of both the myocardium and heart valves. Cardiac myosin and vimentin are other chief target antigens in RF. Cunningham and colleagues¹⁶ identified a five-amino-acid residue epitope of the streptococcal N-terminal M5 and M6 proteins that cross-reacts with cardiac myosin. Sydenham chorea is believed to be mediated by antibodies that bind to neurons. Antibodies against streptococcal GlcNAc cross-react with lysoganglioside GM1 from neurons, producing an effective signal transduction pathway that prompts dopamine release from neurons.¹⁴ It is clear that not all autoantibodies mediate disease, and a subset of these may even have a protective role in the clearing of circulating antigens. Nevertheless, Cunningham's group demonstrated that RF patients' antimyosin and antilaminin antibodies upregulate the expression of the vascular adhesion molecule VCAM-1 after binding to the endothelial surface and promote immune cell infiltration, inflammation, and valve scarring.¹⁴

CELLULAR IMMUNE RESPONSE

The heart lesions that are observed in patients with RHD are primarily mediated by CD4+ lymphocytes.¹⁴ The peripheral and intracardiac T cells of patients with RF are able to cross-recognize several self and streptococcus epitopes, specifically cardiac myosin, laminin, and tropomyosin as well as certain bacterial M5 protein.¹⁴ These M5 epitopes preferentially recognize peripheral T lymphocytes from patients with RHD over those from healthy individuals.⁷ There is evidence that a cross-reactive T-cell population migrates from the periphery to the heart, where it expands in an oligoclonal manner.⁷ Several intralesional T-cell clones present the same amino acid sequences in the CDR3 region of the TCR, which indicates degeneracy in antigen recognition.⁷ Together, these data support the idea that antigen-specific peripheral T-cell populations migrate to the heart tissue, expand locally, and become capable, via an epitope-spreading mechanism, of recognizing novel self-antigens that are distinct from the initial pathogen antigen.⁷

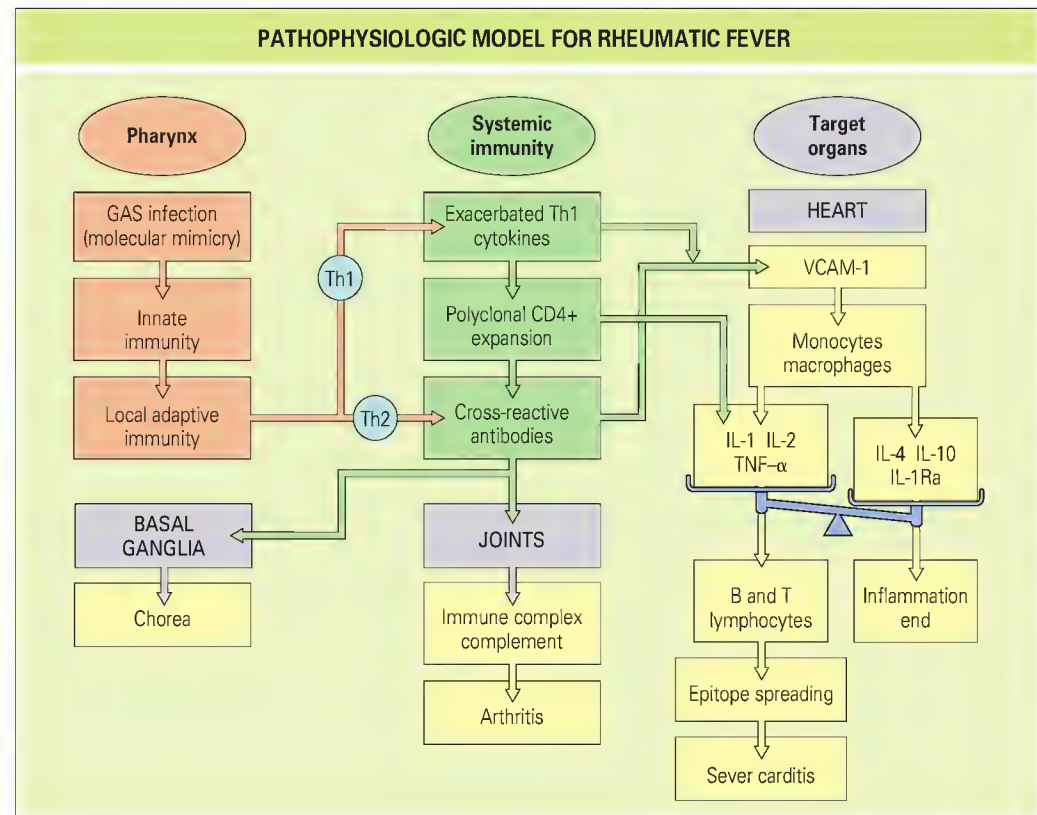
CYTOKINES IN RHEUMATIC FEVER

Transient and mild carditis, like Sydenham chorea and arthritis, are believed to be mediated primarily by humoral immunity (i.e., the helper T cell 2 [Th2]-type immune response),¹⁴ whereas severe and persistent carditis is mediated by cellular immunity (i.e., the Th1-type immune response).¹⁴ Antigen-activated CD4+ T cells become polarized toward a Th1 or Th2 phenotype based on the cytokines they secrete. In the classic 1951 Bland and Jones series of 1000 patients, those with chorea had a better prognosis (less severe carditis),¹⁷ which suggests that a trend toward a Th2-type immune response somewhat diminishes the likelihood of Th1-mediated involvement. The same finding was observed in other series but is not consistently reported.⁷

Several results suggest that RF patients exhibit a more severe and longer-lasting immune reaction than unaffected individuals. Compared with the lymphocytes of patients with acute poststreptococcal glomerulonephritis, the lymphocytes of patients with ARF exhibit exacerbated *in-vitro* cellular reactivity that peaks after 1 to 6 months and lasts for a minimum of 2 years after onset.¹⁴ Stimulated peripheral blood mononuclear cells from patients with ARF produce higher levels of IL-1, IL-2, and IL-2 receptors (CD25) than peripheral blood mononuclear cells from normal control subjects or patients with streptococcal pharyngitis or CRHD. The observed IL-2 overproduction persisted following 48 weeks of throat infection. IL-1 stimulates IL-2 and CD25 production; thus IL-1 was considered to be primarily responsible for the persistent inflammatory process.¹⁴ Another study also observed higher IL-1 and IL-2 concentrations in patients with ARF than in patients with streptococcal pharyngitis, patients with CRHD, and healthy control subjects. In this study, the production of IL-2 in patients with ARF and CRHD was correlated with altered proportions of CD4+ (Th) and CD25+ cells in the peripheral blood.¹⁸

In the heart tissue (i.e., the myocardium and heart valves) of patients with RHD, large numbers of mononuclear cells secrete inflammatory mediators (TNF- α , interferon- γ , IL-1, and IL-2) and regulatory mediators (IL-10, IL-4, and IL-1 receptor antagonist [IL-1Ra]). The analysis of the cytokine profile of these cells suggested that Th1-type cytokines are involved in the mediation of chronicity and that the regression of myocardial inflammation

Fig. 111.2 Pathophysiologic model for rheumatic fever. GAS, group A streptococci; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; Th1, Th2, type 1 and 2 helper T cells; TNF- α , tumor necrosis factor- α ; VCAM-1, vascular cell adhesion molecule 1. (Modified with permission from Azevedo PM, Pereira RR, Guilherme L. Understanding rheumatic fever. *Rheumatol Int* 2012;32[5]:1113-20.)



depends on the regulatory function of IL-10 and, most importantly, IL-4. Only small numbers of IL-4-producing cells were observed in the valves of patients with CRHD, and the lack of this cytokine was implicated in the perpetuation of valvular inflammation.⁷ Another lineage of CD4+ T cells that produce IL-17 and IL-23 has been recently described in the myocardium and valvular infiltrating cells. This result indicates that Th17 cells are important effectors of the inflammatory process in RHD heart lesions.

A protective association was suggested between the IL-1Ra genotype that is classically associated with a milder immune response and the development of severe carditis in 84 Brazilian patients with RF.¹⁴ IL-1Ra production acts as a major stop signal for inflammation in the Th1 immune response and could diminish the possibility of chronification and epitope spreading. Ongoing inflammation in children that progressed to RHD was documented through the persistence of elevated levels of both C-reactive protein (CRP)¹⁹ and proinflammatory cytokines.²⁰

In summary, molecular mimicry and autoimmunity are not sufficient to explain RF. RF patients exhibit a more severe and longer-lasting cytokine-mediated immune reaction than unaffected individuals. Genetic variation, particularly in the genes involved in immune system regulation, help explain the prevalence of RF-related dyscrasias (Fig. 111.2).

PATHOLOGY

Cardiac involvement in RF is loosely classified as acute and chronic. The pericardium, myocardium, and endocardium can be affected (i.e., pancarditis) in RF.

Myocarditis

In the acute phase, a dilation of the chambers may be observed; the autopsy may reveal a pale, flabby, and edematous myocardium. The initial histologic alterations consist of nonspecific myocarditis with edema of the muscle fibers and focal collections of inflammatory cells in the interstitium. Subsequently, a more specific granulomatous myocarditis may occur, occasionally with the presence of distinctive Aschoff nodules. Fully developed Aschoff nodules are composed of a central area of fibrinoid change that is surrounded by lymphocytic infiltration (occasionally of plasma cells), specialized histiocytes that are referred to as *Aschoff giant (multinucleated) cells*, and *Anickov cells* (also known as *caterpillar cells* due to the appearance of their chromatin). Stollerman^{20a} defined three phases in the progression of Aschoff nodules: (1) the early stage, which is characterized by central fibrinoid necrosis, edema, and an infiltrate of lymphocytes and plasma cells (nonspecific stage

or exudative-degenerative phase); (2) the specific granulomatous stage, which is characterized by the accumulation of characteristic Aschoff giant cells and Anickov cells; (3) the late stage, which is characterized by the diminution of the cellular infiltrate and its replacement by scar tissue.

Significant inflammation is relatively uncommon in CRHD. Histologically, neovascularization, fibrosis, and relatively mild calcification are typical. Histiolympocytic reactivity, lymphocytic infiltrate, and Aschoff nodules are rarely observed.²¹

Endocarditis

In its early stages, endocarditis is associated with edema of the valves and possibly vegetations along the free borders of the cusps. These minute vegetations are platelet-rich microthrombi (marantic vegetations), which do not become dislodged and hence do not produce emboli. During healing, vascularization and fibrosis occur. In the majority of cases, fibrosis does not affect the function of the valve. In other cases, the scarring is progressive over years and may affect the subendocardial tissue as well as the annulus, cusp, and chordae tendineae. These changes can cause a contraction of the cuspid or thickening and stiffening of the cusp, resulting in valvular incompetence or the fusion of the commissures and leading to stenosis. Why a subset of patients exhibit progressive scarring whereas others do not is incompletely understood. Recurrent *Streptococcus* infection is a clear cause, but an unfavorable progression is occasionally observed in patients with only one documented ARF episode. The intensity of the inflammatory process in each attack is most likely a factor. A jet of blood that squirts through the incompetent mitral valve can in rare cases produce a patch of endocardial thickening where the jet hits the atrial wall (jet lesion); this indicates that constant blood turbulence can cause endocardial fibrosis, which is one of the mechanisms of scarring progression. This scarring may be mediated by the release of growth factors from platelets and other components of small mural thrombi. Tissue from valve and papillary muscles, which are collected during valve replacement procedures in CRHD patients, occasionally exhibits some mononuclear or lymphocytic infiltrates, and Aschoff nodules are rarely observed, even in patients whose disease was considered to be in remission based on laboratory and clinical findings.^{22,23} These results indicate that subclinical recurrent or persistent inflammation plays a role in the progression of valve destruction.

Pericarditis

Pericarditis affects both the fibrous and serous pericardium layers, which are potentially thickened and covered by a fibrin-rich exudate. A

serosanguineous pericardial effusion is occasionally observed. Pericarditis resolves completely with fibrosis and adhesions, but constriction does not occur.

Arthritis

In RF-related arthritis, the synovial fluid is sterile and shows inflammatory features. There may be a reduction in the levels of complement components C1q, C3, and C4, which suggests their consumption by immune complexes.

Chorea

Neuropathologic autopsy studies of patients with Sydenham chorea have reported neuronal degeneration and vascular alterations in the cerebral cortex, basal nuclei, and cerebellum. Antibodies against antigens in the cerebral cortex and caudate and subthalamic nuclei have been observed via immunofluorescence. Imaging case series have revealed acute changes in the caudate nucleus and subcortical white matter; some of these changes were persistent after a year.²⁴

Pathophysiologic model of disease

The information presented earlier implies a model of RF pathophysiology in which throat infection by a GAS strain that bears epitopes similar to human antigens (molecular mimicry) is initially fought by the innate immune system (see Fig. 111.2). The locally activated adaptive immune response then overproduces proinflammatory cytokines and antibodies, a subset of which are capable of cross-reacting with human and bacterial epitopes. The cytokines act systemically, activating and expanding multiple lymphocytes clones. At the joints, these antibodies precipitate in the form of an immune complex and activate the complement system, inducing arthritis. Certain antibodies may recognize basal ganglia neurons and induce dopamine secretion, which leads to Sydenham chorea and most likely obsessive-compulsive disorder in certain patients. It is possible that a trend toward Th2-type systemic immune response implies a less exacerbated Th1 response, conferring some cardioprotective effects. Certain autoantibodies against heart structures, primarily those derived from myosin, laminin, and tropomyosin, promote the expression of adhesion molecules such as VCAM-1, which initially induces the recruitment of monocytes and macrophages. These mononuclear cells produce a large number of cytokines, which act locally with proinflammatory and antiinflammatory properties. The balance between these cytokines determines the magnitude of the attraction of peripheral lymphocytes to the heart and the severity of the local inflammation. Degeneracy in antigen recognition and epitope spreading may occur, leading to persistent and intense inflammation and heart damage. If antiinflammatory cytokines have a greater effect, the inflammation ends and little, if any, heart damage occurs. In this model, possible points at which the host genetic background may have an influence are the exacerbated initial immune response, HLA/TCR epitope presentation (and thus molecular mimicry and adaptive system activation), systemic Th1/Th2

balance, and local cytokine balance, which determines whether inflammation continues or ends.¹⁴

CLINICAL MANIFESTATIONS

ARF manifestations vary greatly among individuals and among patients of different ages. Differences are also observed in the findings of prospective and retrospective studies (Table 111.1).

RF is rare before the third year of life and is infrequent in individuals who are older than 15 years of age; the majority of cases occur in individuals between the ages of 4 and 9 years. Small children tend to exhibit fever and carditis more frequently, whereas arthritis is more common in adults. If fever is present, it may be high or low. Arthritis is the most common of the major manifestations, followed by carditis and chorea. The symptoms generally begin 2 to 3 weeks after the GAS infection (average, 18.6 days; 4 to 6 weeks in cases of chorea). However, approximately one third of patients cannot remember having an airway infection. The period between the infection and the onset of ARF is free of clinical and laboratory evidence of inflammation.

Arthritis

Arthritis is generally the earliest major symptom of ARF, although carditis occasionally may occur first. Arthritis is more severe and more common in young adults (nearly 100% of cases) than in teenagers (82%) and children (66%). The traditional term *migratory* does not necessarily indicate that the inflammation disappears in one joint and appears in another. The affected sites generally overlap in time, and the progression may also be additive. Monoarticular involvement was described in only 17% to 25% of the patients in older series. However, since nonsteroidal antiinflammatory drugs (NSAIDs) alter the natural course of the arthritis and potentially abort the migratory pattern, monoarthritis is now more common. Untreated patients typically exhibit 6 to 16 involved joints. Large joints such as the knees, ankles, elbows, and wrists are the most frequently involved, and the lower limbs are normally the first to be affected. The hip, shoulder, and phalangeal joints are less frequently involved. The inflammation lasts for a few days to a week for each articulation²⁵; however, the entire articular picture is intense for approximately 1 week and may linger for another 1 to 2 weeks. If joint swelling persists after 4 weeks, it is necessary to reconsider the diagnosis. Joint pain may be sufficiently severe to limit movement significantly and is generally disproportional to the objective signs of inflammation. Radiographic findings are normal, except for occasional effusion. No erosion is observed.

Jaccoud arthropathy, or chronic post-RF arthropathy, is a rare manifestation of RF that may occur following repeated attacks of arthritis. This condition results from recurrent inflammation of the fibrous articular capsule that leads to ulnar deviation of the fingers, particularly the fourth and fifth fingers; flexion of the metacarpophalangeal joints; and hyperextension of the proximal interphalangeal joints. The deformities are generally correctible but may become fixed in later stages. A similar form of arthropathy is observed in patients with systemic lupus erythematosus.

■ TABLE 111.1 Percentages of patients meeting major and minor criteria by WHO region and for all reported studies

WHO region	Males	Recurrences	Major criteria					Minor criteria				
			Carditis	Arthritis	EM	Chorea	Nodules	Arthralgia	Fever	↑PR	↑ESR	↑ASO
The Americas	54.7	22.0	52.8	64.4	7.8	15.3	3.8	40.9	63.9	23.3	84.2	79.4
Europe	54.7	7.9	62.0	65.7§	5.5	12.3	8.0	43.1	68.9	26.3	81.5	78.3
Africa	50.0	17.9	63.3	48.9	1.7	8.8	4.8	55.5	35.4	22.7	52.9	48.7
Eastern Mediterranean	54.4	27.9	60.3	63.5	2.8	8.0	1.6	35.4	74.8	20.3	90.5	86.9
Western Pacific	48.2	22.6	67.5	54.3	11.7	11.7	35.1	35.1	68.4	24.7	91.0	72.3
Southeast Asia	57.4	33.9	66.0	46.0	0.8	15.4	45.5	45.5	71.3	28.9	71.9	60.9
All	53.7	21.9	59.5	59.3	5.9	12.9	40.7	40.7	65.6	24.1	81.4	75.3

Note: Percentages are restricted to patients with acute rheumatic fever. ↑ASO, elevated antistreptolysin O titer; EM, erythema marginatum; ↑ESR, increased erythrocyte sedimentation rate; ↑PR, prolonged PR interval on electrocardiogram; WHO, World Health Organization. Used with permission from Seckler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol 2011;3:67-84.

Carditis

Acute rheumatic carditis

Heart murmurs, cardiomegaly, and congestive heart failure are all signs and symptoms of acute rheumatic carditis, although a subset of patients are asymptomatic. Pleuritic chest discomfort or pain and pericardial friction rub are indicators of pericarditis, which is present in approximately 10% of patients. The pericardial effusion may be large, but cardiac tamponade is rare. Valvular inflammation and deformity cause new or changing organic murmurs, most commonly mitral regurgitation. Aortic regurgitation and systolic ejection murmurs are occasionally observed. The classical Carey Coombs mid-diastolic murmur is rare and is caused by a rapid overflow of the mitral valve.

Mitral regurgitation is the most common early valvular finding and may be accompanied by aortic regurgitation. Isolated aortic regurgitation is less frequent. Mitral regurgitation can be caused by a prolapsed mitral valve, which chiefly involves the anterior leaflet, with minimal leaflet redundancy. This presentation is in contrast with that in myxomatous disease, which more commonly involves the posterior leaflet and is associated with prominent leaflet redundancy. Valve prolapse is due to annular dilation and chordal elongation. Aortic or mitral stenosis is atypical at presentation. Congestive heart failure is the most life-threatening feature of ARF and can develop if severe valvular damage occurs in addition to cardiac dysfunction. Congestive heart failure occurs in 5% to 10% of initial ARF episodes and is more frequent during recurrences. This complication must be treated rapidly and aggressively with diuretics and antiinflammatory drugs. Myocarditis in the absence of valvulitis is unlikely to be rheumatic. Varying degrees of heart blockage can be observed on electrocardiography. Second- and third-degree blockage may require short-term use of a pacemaker if it is associated with congestive heart disease.

The incidence of carditis during the initial ARF attack varies from 40% to 91%, depending on the selection of patients and whether the diagnosis is made on a clinical basis or in combination with echocardiography (see Table 111.1).

Transition from acute to chronic heart disease

In the series reported by Bland and Jones,¹⁷ signs of rheumatic valvular disease had disappeared in 17% of the patients after 20 years. However, 44% of the patients who did not exhibit clinical carditis at presentation later developed overt signs of valvular heart disease. In total, 70% of the patients eventually developed CRHD. A more modern prospective study of 258 Brazilian children with ARF revealed that 72% of the patients developed chronic valvular disease based on echocardiographic findings, and 37% exhibited this condition based on a clinical assessment. Forty-one children (16%) eventually developed severe aortic and/or mitral disease. The risk factors for progression to severe chronic valvular disease were moderate or severe acute carditis, recurrences of ARF, and a low educational level of the mother.²⁶

Subclinical indolent carditis

Although clinically evident recurrences of ARF are associated with the development and severity of CRHD, this outcome is also possible in patients with a history of only one⁵ or no ARF attacks. Subclinical cases of carditis comprise a substantial portion, perhaps the majority, of CRHD cases.²⁷

Chronic rheumatic heart disease

CRHD is the single greatest cause of acquired valvular disease in the world and is responsible for approximately one in four cases of heart failure in endemic countries. In the majority of cases, the valvular disease occurs 10 to 20 years following the original ARF episode. Patients who are younger than age 30 generally have pure mitral regurgitation, whereas middle-aged adults develop mitral stenosis. Mixed mitral valve disease becomes more prevalent in patients who are older. Mitral valve involvement is nearly universal; the aortic valve is involved in approximately 20% to 30% of cases. The tricuspid valve is frequently affected, but this involvement is often subclinical until surgery is required. The pace of progression of mitral stenosis varies among geographical areas. In developed countries, the stenosis normally progresses slowly over 20 to 40 years until the onset of symptoms. In developing countries, mitral stenosis may progress rapidly, and symptoms are possible in patients who are younger than 5 years of age. There is normally a long period during which RHD remains asymptomatic and, if new ARF episodes do not come to the attention of a physician, frequently goes unnoticed. In a survey of 12,000 black schoolchildren in South Africa, 82.5% of the children found to be affected were previously undiagnosed.²⁸ Sixty percent of patients who are asymptomatic or minimally symptomatic

at the time of diagnosis will not experience any progression of the symptoms over 10 years, and survival is over 80% in such cases. Once limiting symptoms (New York Heart Association functional class III or IV) develop, survival without surgery is estimated to be between 0% and 15% over 10 years. Survival falls to less than 3 years in the presence of severe pulmonary hypertension.²⁵

Sydenham chorea

Sydenham chorea (also known as *St. Vitus dance* and *chorea minor*) is a neurologic condition characterized by abrupt, nonrhythmic, jerky, and purposeless movements; muscular weakness; and emotional disturbances. The movement abnormalities affect the hands, arms, shoulders, feet, legs, face, and trunk. These movements are frequently more striking on one side, are occasionally unilateral (hemichorea), and cease during sleep. Other symptoms include dysarthria, gait disturbance, the loss of fine and gross motor control, headache, slowed cognition, facial grimacing, and hypotonia. Moreover, there may be tongue fasciculations ("bag of worms") and "milkmaid's sign," which is a recurring grip characterized by alternate increases and decreases in handgrip tension, as if hand milking.²⁵ It may initially be possible for the patient to suppress these movements voluntarily, but they potentially intensify to the point of seriously impairing daily activities. Handwriting generally becomes clumsy and provides an opportune manner of following the patient's course. The latency period between the streptococcal infection and the development of chorea is generally 6 to 8 weeks but may extend to 8 months. In the series of 1000 patients described by Bland and Jones, 51.8% had chorea, and the condition was associated with less severe carditis and a better prognosis.^{17,25} More recently, chorea has been reported to occur in 20% to 30% of patients with ARF. Females are more often affected than males, and most of the patients are children. Sydenham chorea is relatively rare in adults and, in most cases, patients also had the condition during childhood. Approximately 50% of patients with acute Sydenham chorea recover spontaneously after 2 to 6 months, although symptoms can persist for up to 2 years. Chorea may be the only manifestation of ARF, but all patients should undergo echocardiography to exclude silent carditis. The emotional disturbances may precede the motor symptoms and are characterized by outbursts of inappropriate behavior, including crying, restlessness, and irritation. Psychological manifestations may be severe and, in rare cases, result in transient psychosis.

PANDAS

PANDAS is an acronym for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. It was observed that in the years following a chorea attack, a subset of patients exhibit behavioral disturbances, such as tics and obsessive-compulsive disorders (OCDs). This finding, together with the presence of antibodies against neurons in the sera of patients with Sydenham chorea, led to the hypothesis that a prior streptococcal infection may cause these behavioral alterations. A strong association between the D8/17 cell marker and OCD was described.^{29,30} Although it is largely accepted that a streptococcal infection can worsen OCD symptoms in a subset of patients, the PANDAS hypothesis is controversial, and the question remains open.

Erythema marginatum

Erythema marginatum, which is also referred to as *erythema annulare* because of its ringlike appearance, is an infrequent RF manifestation that affects the limbs and trunk but spares the face. It is an evanescent, pink (or faintly red), nonpruritic, and nontender rash that extends centrifugally while the center returns to normal—hence the term *marginatum*. The border is irregular, serpiginous, and sharp on the outside edge, whereas the border is diffuse on the inside edge. A hot shower may reveal discrete lesions that may appear, disappear, and reappear in a matter of hours. Erythema marginatum is strongly associated with carditis and may occur at any time in the course of RF, occasionally in the chronic heart disease phase.

Subcutaneous nodules

Subcutaneous nodules in RF resemble those in rheumatoid arthritis but are smaller and last for a shorter period of time. In both diseases, these nodules occur over bony surfaces or near tendons (e.g., the occiput, elbows, knees, ankles, Achilles tendons), with a predilection for the elbows; however, in RF these nodules are generally observed 3 to 4 cm distal to the olecranon. The nodules are firm, painless, and not anchored

to the adjacent surfaces; the overlying skin is not inflamed. The size of the nodules varies from a few millimeters to 2 cm, and the duration does not exceed 1 month. The number of nodules varies from one to a few dozen (with an average of four), and they tend to occur in crops with a symmetric distribution when abundant. Subcutaneous nodules were described in 8.8% of patients in the Bland and Jones series¹⁷ but in only 1.5% of patients in a more recent series of 786 patients.³¹ Nodules are more common in patients with a history of prolonged active carditis than those in the early stages of the disease, and the appearance of multiple crops of nodules may be related to the severity of the RHD.

INVESTIGATIONS

The evaluation of a patient with suspected ARF involves searching for evidence of streptococcal infection, documenting the presence or persistence of an inflammatory process, and diagnosing and following the course of carditis.

Throat cultures

By the time the symptoms of RF appear, approximately 75% of patients have negative throat culture results.²⁵ A positive throat culture finding may be due to convalescent carriage of the original rheumatogenic strain or a new infection.

Streptococcal antibody tests

The available antibody tests are directed against the extracellular products of streptococci and include the anti-streptolysin O (ASO), anti-DNAse B, antihyaluronidase, anti-NADase (anti-diphosphopyridine nucleotidase), and antistreptokinase tests. Antibody titers peak at approximately 4 to 5 weeks following the infection, which normally coincides with the second or third week of RF. The titers then decline relatively rapidly over the next several months and more slowly after 6 months. Asymptomatic pharyngeal streptococcus carriers generally exhibit titers just above the limits of detectability; a high titer therefore indicates a true infection. To confirm a recent infection, however, a significant increase in the titer should be documented in a sample that is collected when the diagnosis of ARF is first suspected and in another sample obtained 2 weeks later. Patients with documented ARF will exhibit raised titers of ASO, which is the most widely used test, in approximately 80% of cases. Approximately 90% of them will exhibit positive test results if two antigens are evaluated, and approximately 95% will exhibit positive results if three antigens are used.

Rapid streptococcus antigen test

The rapid streptococcus antigen test (RSAT) has a specificity of 95% or higher and a sensitivity that varies between 65% and 90%.³² A positive RSAT finding is useful in establishing the diagnosis of GAS pharyngitis, but a negative RSAT result does not exclude this diagnosis.

Acute-phase reactants

The erythrocyte sedimentation rate and CRP levels increase during an ARF attack, except in situations in which chorea or erythema marginatum are the only manifestations. Salicylates or antiinflammatory drugs may mask the results of these tests, which are particularly useful in monitoring rebounds of rheumatic inflammation when treatment is being discontinued. If the test results are normal a few weeks following the cessation of therapy, the ARF attack is likely over, unless chorea appears. Erythrocyte sedimentation rate may remain elevated for up to 2 months following an episode of inflammation, whereas CRP levels normalize within days.

Other laboratory tests

A mild normochromic normocytic anemia may be present during ARF, but red cell counts generally normalize following the cessation of inflammation. The D8/17 monoclonal antibody test (mentioned earlier) is helpful in differentiating ARF from other disorders but is not commercially available.

Chest radiography

An enlarged heart silhouette may be present on the chest radiograph secondary to myocardial dilatation and/or pericardial effusion.

Electrocardiography

Tachycardia and prolongation of the PR interval are features of myocarditis. In rare cases, third-degree heart block may be observed. Pericarditis can induce diffuse elevation of the ST segments. Electrocardiographic abnormalities are present in approximately 21% of patients, with 60% of these patients exhibiting some degree of heart block.

Echocardiography

Echocardiography is approximately 10-fold more sensitive than auscultation in identifying valvular involvement.²⁵ Echocardiography confirms the clinical diagnosis of valvular lesions and aids in the exclusion of nonrheumatic causes of valvular damage. This technique is therefore used extensively in clinical practice. Nevertheless, echocardiographic indicators were not included in the 2002-2003 World Health Organization (WHO) RF/RHD criteria. This decision was made primarily (1) to avoid hindering the diagnosis when echocardiography is unavailable and (2) because most cases of subclinical carditis exhibit a benign evolution.²⁵ The echocardiographic documentation of isolated mitral and/or aortic regurgitation is not diagnostic of rheumatic valvulitis. Physiologic valve regurgitation is a common finding in healthy individuals and may be present in viral myocarditis and other conditions. The World Heart Federation recently proposed criteria for the echocardiographic diagnosis of RHD.³³

Echocardiographic population screening efficiently identifies asymptomatic patients with RF, who can then be enrolled in secondary prevention programs. These screenings may therefore be justified and cost effective in high-prevalence areas.^{34,35}

DIAGNOSIS

No single clinical or laboratory finding is diagnostic of ARF except perhaps the presence of Sydenham chorea. Therefore a set of diagnostic criteria was developed in 1944 by Jones and colleagues.^{35a} These criteria were modified in 1956 and revised in 1965. In 1988, WHO developed a new set of criteria, which was updated in 1992 by the American Heart Association.³⁶ More recently, a WHO 2002-2003 Expert Consultation Report modified the previous diagnostic criteria²⁵; these updated criteria are provided in Table 111.2. Each change of the Jones criteria is made to improve specificity at the expense of sensitivity, largely in response to the falling incidence of ARF in the USA. As a result, the criteria may not be sensitive enough to pick up disease in high incidence populations. Important circumstances where ARF can be diagnosed without fulfilling the Jones criteria include chorea and carditis of insidious onset and slow progression as the only manifestations of ARF. RF should be diagnosed even in the absence of evidence of a preceding GAS infection in these patients, and as well in those with chronic valve lesions of RHD. Doppler echocardiographic examination should be performed if the facilities are available and are currently integrated in the RF guidelines of countries with high incidence as Australia and New Zealand.^{36a}

PRIMARY PREVENTION (PHARYNGITIS TREATMENT)

In 2009, the American Heart Association released a statement regarding the prevention of RF and the diagnosis and treatment of acute streptococcal pharyngitis.³⁷

Antibiotic treatment of streptococcal pharyngitis diminishes the duration and intensity of streptococcal antigen exposure and can prevent most cases of ARF.²⁵ Streptococcal pharyngitis should be treated with antibiotics, and penicillin is the drug of choice because it is bactericidal. This drug can be given as a single intramuscular injection of benzathine benzylpenicillin G (600,000 units in children who weigh less than 27 kg, and 1.2 million units in those who weigh over 27 kg) or as 10 days of oral penicillin V (phenoxymethylpenicillin 40 mg/kg per 24 hours, given in three equal doses, not to exceed 750 mg for those weighing <27 kg, and 500 mg two to three times daily in adolescents and adults).³⁷ Oral administration has the disadvantage of noncompliance. Patients who are allergic to penicillin should be given a 10-day course of oral erythromycin (erythromycin estolate 20 to 40 mg/kg/day in two to four divided doses, or erythromycin ethylsuccinate 40 mg/kg/day in two to four divided doses, with a maximum dosage of 1 g/day).³⁷

According to a 2009 Cochrane review, a 3- to 6-day course of oral antibiotics (azithromycin, clarithromycin, and cefuroxime) is similar to 10-day

TABLE 111.2
2002-2003 WHO criteria for the diagnoses of rheumatic fever and rheumatic heart disease

Diagnostic categories	Criteria
Primary episode of rheumatic fever ^a	Two major* or one major and two minor** manifestations, plus evidence of a preceding group A streptococcal infection***
Recurrent attack of rheumatic fever in a patient without established rheumatic heart disease ^b	Two major or one major and two minor manifestations, plus evidence of a preceding group A streptococcal infection
Recurrent attack of rheumatic fever in a patient with established rheumatic heart disease	Two minor manifestations, plus evidence of a preceding group A streptococcal infection ^c
Rheumatic chorea and insidious onset of rheumatic carditis ^b	Other major manifestations or evidence of group A streptococcal infection are not required
Chronic valve lesions of rheumatic heart disease (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease) ^d	No other criteria required for diagnosis of rheumatic heart disease

*Major manifestations: carditis, polyarthritis, chorea, erythema marginatum, and subcutaneous nodules.

**Minor manifestations: clinical findings—fever, polyarthralgia; laboratory findings—elevated acute-phase reactants (erythrocyte sedimentation rate or leukocyte count).

***Supporting evidence for a preceding streptococcal infection within the last 45 days: prolonged PR interval on electrocardiogram; elevated or rising antistreptolysin-O or other streptococcal antibody; positive throat culture results; positive result on rapid antigen test for group A streptococci; recent scarlet fever.

^aPatients may have polyarthritis (or only polyarthralgia or monoarthritis) and several (three or more) other minor manifestations, together with evidence of recent group A streptococcal infection. Some of these cases may later turn out to be rheumatic fever. It is prudent to consider them as cases of “probable rheumatic fever” (once other diagnoses are excluded), and regular secondary prophylaxis is advised. Such patients require close follow-up and regular heart examinations. This cautious approach is particularly suitable for patients in vulnerable age groups in high-incidence settings.

^bInfective endocarditis should be excluded.

^cCertain patients with recurrent attacks may not fulfill these criteria.

^dCongenital heart disease should be excluded.

WHO, World Health Organization.

From Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation. World Health Organ Tech Rep Ser 2004;923:1-122.

course of oral penicillin for treatment of streptococcal pharyngitis and may be an alternative in countries with a low incidence of RF.³⁸

Clinical clues are not sufficient to differentiate viral from streptococcal pharyngitis, even for experienced clinicians. If the means are available, the streptococcal infection should be confirmed using a throat culture or rapid diagnostic antigen-detection test. The American Heart Association recommends that a negative antigen test result be confirmed by throat culture. This strategy is not appropriate in developing countries, where throat culture and serologic testing are not readily available. The elimination of positive throat culture results as a prerequisite for prescribing antibiotics for throat infections was followed by a significant reduction in the incidence of RF in Costa Rica, although a causal association could not be confirmed.³⁹ Although it is clear that all streptococcal pharyngitis should be treated with antibiotics and that the population in question and medical awareness regarding RF are fundamental for the prevention of the disease, there are conflicting data on whether school-based systematic screening and treatment of sore throats are cost effective, even in endemic areas.^{40,41} This uncertainty is explained in part by the fact that as many as one third of throat infections are asymptomatic.

TREATMENT OF ACUTE RHEUMATIC FEVER

Bed rest

Bed rest is traditionally advised in cases of ARF, although this recommendation is not based on clinical trial results. Once the symptoms subside, the patient should be progressively mobilized.

Antibiotic therapy

Patients with ARF should receive antibiotic therapy to eradicate GAS, regardless of whether pharyngitis is present at the time of diagnosis. Close associates and household contacts should be tested for streptococcus carriage and treated if positive.

Arthritis, fever, and rash

Most inflammatory ARF symptoms, including arthritis and fever, respond promptly to nonhormonal antiinflammatory agents. Aspirin (80 to 100 mg/kg/day in children and 4 to 8 g/day in adults) is the traditional choice and should be continued until all of the symptoms subside and levels of inflammatory markers normalize. Other NSAIDs can be used instead of aspirin, and naproxen has been reported to be effective and well tolerated. Erythema marginatum does not require treatment, although antihistamines may help alleviate pruritus.

Acute carditis

Patients with congestive heart failure and third-degree heart block must receive treatment for these complications. A 2003 Cochrane meta-analysis, updated in 2012, involving eight randomized controlled trials that involved 996 individuals with ARF observed no significant difference in the risk of cardiac disease between corticosteroid-treated and aspirin-treated groups at 1 year.⁴² Similarly, administration of intravenous immunoglobulin did not alter the evolution of ARF.⁴² There are no evidence-based treatment options for patients with acute carditis, and steroids are occasionally used in severe cases. The preference is to delay valve surgery until the carditis is inactive, but surgery may be necessary during the acute phase when heart failure due to regurgitant lesions cannot be managed with medications alone.

Sydenham chorea

Chorea is frequently mild and self-limiting, not requiring specific therapy. For prolonged or incapacitating cases, haloperidol, diazepam, and carbamazepine have all been reported to be effective. In one study, a group of 22 children with Sydenham chorea treated with prednisone exhibited a more rapid resolution of symptoms than 15 children given a placebo.⁴³

SECONDARY PREVENTION

The risk of a new ARF attack following a GAS infection is between approximately 25% and 75% for those with a history of previous RF. Thus patients with RF are at a high risk of recurrences and increased severity of the manifestations, including RHD. Recurrences can occur at any time but are most common in the first 2 years following the initial attack. Because streptococcal pharyngitis is often asymptomatic, secondary prevention requires continuous antimicrobial prophylaxis rather than treatment of the acute episodes of GAS pharyngitis. This treatment is indicated for any patient with a documented history of ARF or Sydenham chorea, or convincing evidence of RHD. Intramuscular penicillin appears to be more effective than oral penicillin in preventing recurrences.⁴⁴ Intramuscular injection of benzathine benzylpenicillin G is the regimen of choice (1.2 million units for children and adults weighing >27 kg and 600,000 units for those weighing <27 kg).²⁵ Alternative treatments are penicillin V (250 mg twice daily, orally) and sulfadiazine (0.5 g once daily, orally, for those weighing <27 kg and 1 g/day for those weighing >27 kg). Patients allergic to penicillin and sulfadiazine should be treated with 250 mg of erythromycin orally twice daily.²⁵ Several factors can influence the risk of RF recurrences, including patient age, the presence of RHD, the time elapsed from the previous attack, the number of previous episodes, the degree of crowding in the family, a family history of RF/RHD, the socioeconomic and educational status of the individual, the risk of streptococcal infection in the area, and the patient's occupation and place of employment (e.g., schoolteachers, physicians, and employees who work in crowded areas may be at higher risk). For high-risk patients and in high-risk areas, intramuscular penicillin G should be administered every 3 weeks or less, given that the levels of penicillin are low in the fourth week. Similarly, the duration of secondary prophylaxis should be individualized. The 2004 WHO guidelines for the duration of secondary prophylaxis are summarized in Table 111.3.

In a prospective study of 59 patients with ARF judged to be at a low risk of recurrence, secondary prophylaxis was not indicated and patients were closely followed during 3349 patient-months. Only two ARF episodes were observed in the study group, result suggesting that discontinuing ARF

TABLE 111.3
WHO guidelines for duration of secondary prophylaxis

Patient category	Duration of prophylaxis
No proven carditis	For 5 years following the previous attack or until 18 years of age (whichever is longer)
Carditis (mild mitral regurgitation or healed carditis)	For 10 years following the previous attack or until 25 years of age (whichever is longer)
More severe valvular disease	Lifelong
Following valve surgery	Lifelong

Note: These are only recommendations and must be modified as individual circumstances warrant.
 WHO, World Health Organization.
 Data from Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation. World Health Organ Tech Rep Ser 2004;923:1-122.

prophylaxis may have a favorable risk-benefit ratio in patients who are at a low risk of recurrence and are kept under careful prospective surveillance.⁴⁵

The efficacy of secondary prophylaxis programs depends completely on patient compliance with the prescribed drug regimen. A prospective international study that involved 1790 patients demonstrated a prevalence of new ARF attacks of 0.45% among the patients who regularly received benzathine benzylpenicillin G compared with 11.5% in noncompliant patients.⁴⁶

Unfortunately, noncompliance is far from exceptional. In the Aboriginal communities of Australia, only one in five individuals with a history of ARF or RHD receives 80% or more of the scheduled doses.⁴⁷ The reasons for noncompliance include the painfulness and high frequency of injections, the long period of treatment, and the low socioeconomic and educational level of the patients.

Endocarditis prophylaxis

Patients with RHD should receive prophylactic antibiotics to prevent infective endocarditis when they undergo surgical procedures of the mouth (e.g., dental extractions), eyes, ears, nose, throat, or gastrointestinal and genitourinary tracts.⁴⁸

Vaccines

Efforts to produce an effective vaccine against streptococcal infections have been ongoing for more than three decades. Despite the advances that have been made in this field, no ideal vaccine is available. The major difficulties for researchers are the following: (1) The vaccines should not trigger autoimmunity or exacerbate the disease. (2) More than 130 GAS M-serotypes have been described, and nontypeable strains of GAS are equally capable of causing infection. New M-types are constantly emerging, and their association with disease varies greatly among regions. (3) The vaccine's epitope should be equally effective and safe in all HLA class II contexts. (4) The vaccine should produce lasting immune protection.

The increasing immunity to streptococcal infections that normally occurs with age indicates that the development of a vaccine is possible, and such a vaccine hopefully will be available in the future.

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Reactive arthritis

■ ROBERT D. INMAN

- Reactive arthritis is the paradigm of a rheumatic disease in which genetic susceptibility interacts with an environmental trigger.
- Genetic elements that predispose to reactive arthritis include polymorphisms in class I MHC molecules and toll-like receptors.
- Reactive arthritis has microbial and immunologic features that suggest it is a *forme fruste* of septic arthritis.
- New concepts in the management of reactive arthritis—including antibiotics and biologics—are developing.

INTRODUCTION

Reactive arthritis (ReA) became operationally defined as a nonseptic arthritis that followed an extraarticular infection.¹ Although rheumatic fever itself would qualify for this definition, the concept became clinically associated with antecedent infections of the gastrointestinal and genitourinary tracts. In cases in which *Salmonella* or *Chlamydia* organisms were cultured from the respective sites, this construct provided a useful framework for understanding pathogenesis. But much of the clinical research in this area was hampered by uncertainties in disease definition. If the triggering pathogen could not be isolated from the gastrointestinal or genitourinary tract, would antecedent diarrhea or urethritis be sufficient for the diagnosis? Would there be antibody profiles with sufficient specificity to be considered as inclusion criteria for ReA? Would proliferation of immunoreactive cells from synovial fluid (in response to candidate bacterial antigens) carry diagnostic specificity? Challenges to these studies were also compounded by poorly defined diagnostic criteria for ReA and by changing nomenclature as the older term *Reiter syndrome* came to be replaced by *reactive arthritis*.

Extrapolating from rheumatic fever, a number of investigations addressed molecular mimicry as the basis of ReA. These studies sought to operationalize the recent discovery of HLA-B27 as a risk factor not only for ReA but also for ankylosing spondylitis (AS). Approaches to linking infection to disease included demonstration of sequence homology between B27 and arthritogenic pathogens, as well as the characterization of monoclonal antibodies and T-cell clones reacting with both B27 and the putative inciting organism.^{2,3} Some experimental models suggested that *Chlamydia* could break tolerance of self-B27.⁴ But rigorous proof that autoreactivity is the underlying mechanism in ReA remained difficult to obtain, and ReA remained a charter member of *seronegative* spondyloarthritis.

The report that phlogistic components of *Yersinia* and *Salmonella* could be recovered from synovial fluid of ReA patients suggested that, rather than autoimmunity acting as the operational event in chronic ReA, local persistence of microbial fragments could be the true culprit. The presence of such foreign material was demonstrated by immunofluorescence studies of synovial fluid and synovial tissues.⁵ These findings shifted the focus of investigators to address the structural basis of arthritogenicity. It was found that certain glycosylation patterns of foreign antigen appeared to correspond with the ability to induce experimental ReA by virtue of lingering as non-biodegradable fragments in the joint.⁶ Gas chromatography and mass spectrometry analysis of organisms can identify such patterns, but this approach has yet to be transferred into clinical practice.

INNATE IMMUNITY AND REACTIVE ARTHRITIS

For all the sophistication of adaptive immunity, with specificity and memory as its pinnacle achievements, it was recognized that the time required to

expand the T-cell and B-cell responses in the setting of acute infection could place the host at great peril. The concept of innate immunity as the first line of host defense was the province of students of leukocyte biology. The discovery of Toll-like receptors (TLRs) as the quintessential recognition elements of the innate immune system created an intense interest in defining the role of this family of receptors in infectious disease. There were, however, some conceptual hurdles in the path of linking TLRs to rheumatic diseases.

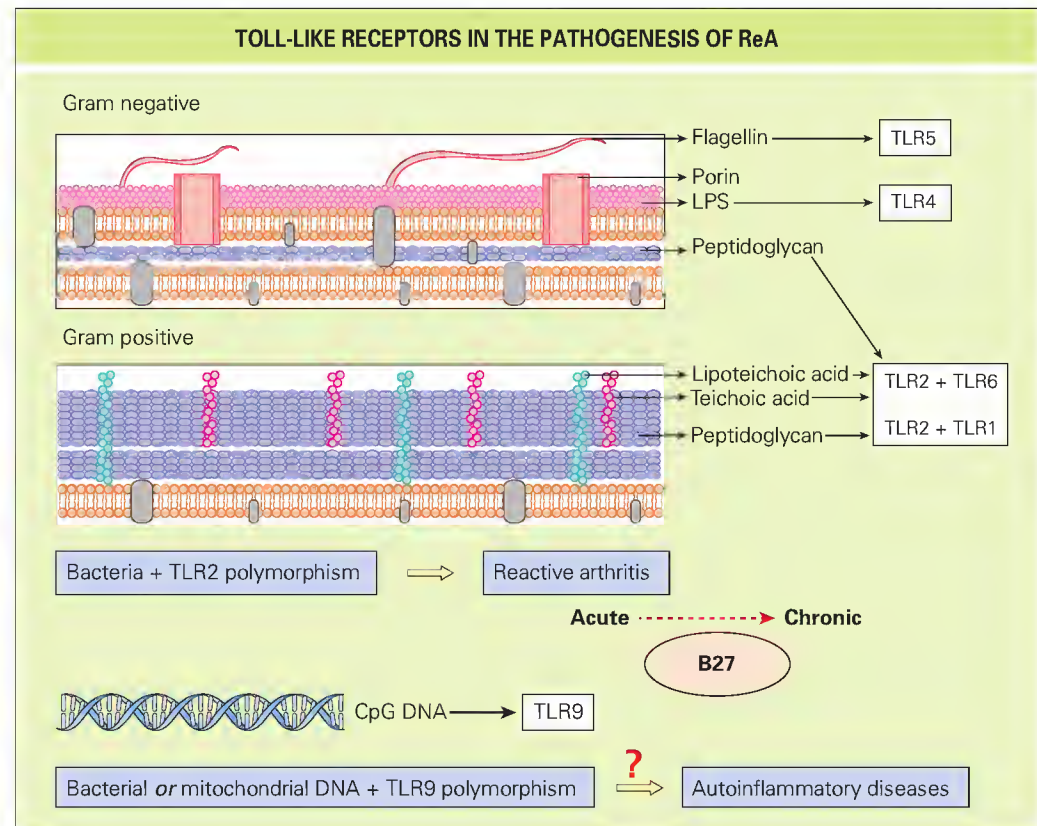
The first of these hurdles related to the apparent nonpolymorphic nature of the TLR, which posed a significant challenge in explaining the heterogeneity of susceptibility to ReA in target populations. The second was that self-nonsel self discrimination by the innate immune system was proposed to be perfect, unlike its forever failing counterpart in adaptive immunity. Both of these concepts have needed significant revision. There are, in fact, significant polymorphisms in the TLR families, and recent studies of epidemic ReA have demonstrated that nonsynonymous single nucleotide polymorphisms (SNPs) in TLR2 confer susceptibility to post-*Salmonella* ReA.⁷ The notion that TLRs are specific only for foreign determinants has been replaced by the recognition that mammalian nucleic acids, among other molecules, are ligands for certain TLRs; indeed, this concept has proved to be pivotal in current concepts of lupus pathogenesis.

These findings have broadened the landscape linking infection to arthritis. The hypothesis of microbial pathogenesis began from the conceptual starting line that disease mediated by infection resulted from viable microbes in the target organ. The discovery of the complex tango of receptor-ligand interactions involving TLRs led to the recognition that the inflammation arising as a consequence of infection requires neither a viable pathogen nor even the intact organism. Signaling events that can usher in damaging inflammation call only for fragments of the pathogen, such as lipopolysaccharide or peptidoglycan, to interact with TLRs on host cells. This has been borne out in several experimental models of arthritis. The B27 transgenic rat expresses a number of features that recapitulate spondyloarthritis (SpA) in patients, including arthritis, dermatitis, and enteritis.⁸ These features are dramatically attenuated if the animal is raised in a germfree environment.⁹ Reestablishing the clinical features of SpA in this model does not require a gut infection in the usual sense. Rather, the animal need only be challenged with a gut commensal, *Bacteroides*, which normally would not be counted among the arthritogenic pathogens.

Thus the gut's being populated, not infected, with commensal organisms creates the immunologic platform on which arthritis can proceed. The mouse deficient in interleukin-1 receptor antagonist (IL-1Ra) is genetically programmed to develop an aggressive polyarthritis. This propensity, too, is completely abrogated if the animal is raised germ free.¹⁰ But to reestablish the arthritis in the germfree setting requires no intact organism at all. A TLR ligand alone will do quite nicely. These studies have also demonstrated that TLR signaling at the gut level can have very disparate effects on arthritis, with TLR4 signaling playing an exacerbating role and TLR2 signaling playing a modulatory role.

When viewed in the context of concurrent genetic polymorphisms not only in TLR but also in class I major histocompatibility complex and IL-23R, the infectious link between gut and joint has become intriguingly complex. This situation has become clinically relevant with the recognition that TLR2 genetic polymorphisms predispose to post-*Salmonella* ReA. The importance of the gut as the site of triggering events has been supported not only by the recognition that the same genetic variants confer susceptibility to AS and to Crohn disease (CD) but also that subclinical inflammation and upregulation of IL-23 expression is present in gut tissues of AS patients.^{11,12} Hematologists in search of the cause of pernicious anemia might have probed the bone marrow ad infinitum without realizing that the answer lay in the gut. Are rheumatologists destined to learn the same lesson?

Fig. 112.1 Toll-like receptors in the pathogenesis of reactive arthritis (ReA). LPS, lipopolysaccharide; TLR, Toll-like receptor. (From Inman RD. *Reactive arthritis—back to the future. Rheumatologist* 2010;4:24-33.)



Too much immunity or too little?

The underlying assumption in the molecular mimicry theories, exemplified by the studies of rheumatic fever, is that the host immune response to infection is *overactive* in nonseptic sequelae like ReA. But there are intriguing clues that host defenses might be diminished rather than amplified in patients with ReA. The cytokine profiles of ReA patients suggest downregulation of proinflammatory cytokines rather than upregulation.¹³ These changes include a decrease in levels of tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), cytokines normally thought to be deleterious rather than beneficial cytokines with respect to arthritis. The role of cytokine dysregulation in disease etiology is borne out in experimental ReA.¹⁴ Animals that are susceptible to *Chlamydia*-induced arthritis have *diminished* rather than enhanced production of TNF- α and IFN- γ within the joint. This appears to relate to impaired capacity of host clearance of the organism in susceptible strains of animals. Of interest, this genetically defined cytokine signature can be dramatically altered by exposure to heavy metals, which suggests that other environmental factors may come into play in the dynamics of ReA in the clinical setting.¹⁵

Recent studies in CD have supported the role of defective host immune response to foreign organisms in immunopathogenesis. Genetic susceptibility to CD has been related to polymorphisms in the *CARD15* gene, but the implicated SNPs suggest a loss-of-function process that would predict diminished, not enhanced, elaboration of TNF- α . This situation seems counterintuitive in a disease that is marked by TNF-mediated inflammation and that is responsive to anti-TNF agents. Recent studies have shed light on this paradox.¹⁶ Macrophage function in CD is indeed diminished, with impaired generation of proinflammatory cytokines, because of lysosomal degradation of precursor molecules, which impairs their egress to the secretory pathways of the macrophage. The net effect of this cytokine signature is diminished inflammatory response to pathogens, with persistence of the organism being the consequence. Thus the model for CD, as that for ReA, is undergoing a conceptual change that suggests therapeutic enhancement, rather than diminution, of host immune responses as a strategy for intervention.

Have we thus come full circle in considering the role of infection in ReA? With the expanded knowledge of innate immunity in arthritis and autoimmunity, and the recognition that TLRs function as gatekeepers of adaptive immunity by upregulation of costimulatory molecules, the microbial aspects of ReA and CD have begun to be clarified. The genetic complexity of CD revealed in recent genomewide association studies suggests that modulation of host-microbial interactions is a complex and changing story. But more pieces of this challenging jigsaw puzzle are now in place.

Self-nonspecific complexities arising

In the original formulation of the underlying principles of the innate immune response, perfect self-nonspecific discrimination was proposed as the one of the cardinal features since the pathogen-associated molecular patterns (PAMPs) recognized by host innate immune receptors were so different from endogenous host ligands that a case of mistaken identity was never allowed. A PAMP was the molecular passport of an alien. But what happens in the event that an alien not only has invaded our home and native land, but has become enculturated and fully assimilated into the society? Such is the case with the bacterial symbionts of antiquity that invaded eukaryotic cells, set up distinct societies, and in time became mitochondria. But a genetic footprint of this event has been left behind: our mitochondrial DNA retains significant sequences of bacterial DNA.¹⁷ With respect to immune recognition, this is far more profound, and more unnerving, than molecular mimicry of host and microbial determinants. This is molecular *identity* of host and microbial determinants.

What, then, would transpire if the DNA were released systemically, as might occur following trauma? This might occasion a response that is indistinguishable from sepsis, which seems unlikely. Yet that is precisely what occurs. The binding of mitochondrial DNA to TLR9 on the surface of neutrophils initiates activation of neutrophils and release of IL-8 in a way that looks just like an infection.¹⁸ Indeed, infusion of mitochondrial DNA alone initiates an intense pneumonitis similar to that seen in the systemic inflammatory response syndrome that occurs after trauma. This recognition is changing the landscape of the concept of infection. Perhaps the enemy has been lurking within all along. With respect to host immune response, perhaps we have met the enemy and it is us (Fig. 112.1).

Because our thinking of self-nonspecific proved in retrospect to be simplistic, and the gap between infection and trauma begins to narrow, potential new scenarios arise in the pathogenesis of inflammatory joint disease. Could exacerbation of AS after trauma reflect such processes? Could chronic inflammatory events in the skin, with local tissue injury, set the stage for psoriatic arthritis? Could the mucosal injury of *Salmonella* gastroenteritis or *Chlamydia* urethritis invoke these pathways? Could all arthritis be reactive?

CHLAMYDIA-INDUCED REACTIVE ARTHRITIS

As stated earlier, ReA is operationally defined as an inflammatory arthritis preceded by an extraarticular infection, most commonly with the enteric pathogens *Salmonella*, *Yersinia*, and *Campylobacter* or the oculogenital pathogen *Chlamydia*.¹⁹ By virtue of HLA-B27 association, pattern of joint

involvement, and the absence of rheumatoid factor, ReA is classified as a part of the spectrum of SpA. However, there are distinct differences between ReA and the classical spondyloarthritis such as AS, notably a lower association with HLA-B27²⁰ and an established link between a prior infection with the aforementioned bacteria and the onset of arthritis. Moreover, it is becoming clear that post-enteritis and post-*Chlamydia* ReA are distinct entities in that viable organisms can be detected in the joints of patients with *Chlamydia*-induced ReA (CiReA), but not those of patients with post-enteritis ReA.²¹ CiReA represents the majority of cases of ReA. Between 4% and 15% of those with genital chlamydial infections subsequently develop arthritis, which accounts for over half of all ReA cases. Given the high prevalence of chlamydial genital tract infections, it has been proposed that the incidence of CiReA may rival that of rheumatoid arthritis.²² Furthermore, many undifferentiated spondyloarthritis have been proposed to be undiagnosed ReA. Thus CiReA represents a significantly understudied disease with a measurable physical and economic burden.²³

Reactive arthritis: the noncanonical septic arthritis

The term *reactive arthritis* describes how this disease was traditionally viewed as a nonseptic, autoimmune reaction occurring in the joint in response to an extraarticular bacterial infection.^{24,29} This notion was based on the fact that no pathogen could be cultured from the arthritic joint despite detection of arthritis-associated bacteria at other sites in the body. Surprisingly, extensive searching for the bacterial antigens responsible for adaptive immunity-mediated pathology has not yielded conclusive results to date. To further confound the autoimmunity-mediated hypotheses for ReA, it was discovered that *Chlamydia* organisms are present in the joint, albeit in an aberrant but viable state, through the use of nucleic acid detection methods and electron microscopy.

The possibility that CiReA is driven not by a reactive autoimmune process but rather by the infection of nonimmune cells *in situ* has paralleled a paradigm shift establishing the mechanism of tissue damage during chlamydial infections in general. Initially the immunologic paradigm proposed that tissue damage results from the aberrant activation of the adaptive immune system through delayed-type hypersensitivity or autoimmunity.²⁵ An alternative cellular paradigm postulates that chlamydial pathogenesis is driven by an inflammatory response propagated by sustained infection of nonimmune cells whereby ongoing release of inflammatory mediators and subsequent recruitment of inflammatory cells causes tissue damage.²⁶ Since *Chlamydia* is known to infect fibroblast-like synoviocytes,²⁷ could the cellular paradigm hold true in CiReA?

With the identification of viable *Chlamydia* organisms in the joint, a contradiction arises regarding the classification and nomenclature of CiReA in terms of underlying clinical and pathologic features. Figure 112.2

illustrates this concept, with ReA holding a midpoint between SpA and septic arthritis. In support of the concept of CiReA as a septic arthritis, a recent clinical trial demonstrated that combination antibiotics could alter the course of ReA.²⁸ In addition, the immunopathogenesis of CiReA recapitulates that seen in experimental septic arthritis with regard to mediators of susceptibility and the role of the immune system^{29,30} (see Fig. 112.2).

The classification of CiReA as a septic arthritis necessitates a better understanding of bacterial colonization of the joint. After primary infection in both humans and animals, *Chlamydia* is known to spread throughout the body via monocytic cells³¹ to a diverse group of tissues, including spleen, liver, peritoneum, and lungs.³² In many of these tissues *Chlamydia* is cleared, so why is it that organisms are found in the joint long after initial infection? The traditional hypothesis suggests that the joint provides an immunoprivileged site; however, immune cells can be found in the joint in either the healthy or the arthritic state. One extension of this theory proposes that it is the hypoxic environment of the inflamed joint³³ that creates an immunoprivileged microenvironment. This idea stems from the fact that the natural site of infection for *Chlamydia*, the genital tract, is relatively hypoxic and that *Chlamydia* thrives under hypoxic conditions.³⁴ It appears that *Chlamydia* may have adapted to growth under such conditions, because the organism actively manipulates hypoxia-inducible factor 1 (HIF-1).³⁵ Additionally, both bacteriocidal cytokines such as IFN- γ and antibiotics³⁶ have reduced efficacy under hypoxic conditions, which provides the rationale for chlamydial escape from these mechanisms of control within the joint.

Chlamydial persistence: pathogenicity or symbiosis?

Another incompletely explained aspect of host-pathogen interaction during CiReA is the observation that *Chlamydia* adopts an atypical, persistent state within the joint. *Chlamydia* is an obligate intracellular pathogen that exist in two distinct states during its life cycle: the extracellular, infectious elementary body and the intracellular, replicative reticulate body. When appropriate stress is applied during the intracellular stage, such as IFN- γ exposure, antibiotic treatment, or infection of monocytic cells, *Chlamydia* enters a nonreplicative and unculturable but viable persistent state.³⁷ The persistent state differs from the normal intracellular state in that *Chlamydia* organisms fail to divide or differentiate into infectious particles, have a reduced metabolism, and are immunoevasive.³⁸

Persistent *Chlamydia* organisms in CiReA were originally detected through microscopy or polymerase chain reaction (PCR) analysis and could not be cultured from synovial biopsy specimens.³⁹ It is now possible to accurately identify *Chlamydia* with a persistent phenotype in CiReA using quantitative PCR analysis, because these cells display a unique gene expression profile.⁴⁰ The recognition of persistent *Chlamydia* in ReA represents an important advance in our understanding of this disease but leaves unanswered key questions with respect to pathogenesis.

Is persistent *Chlamydia* the cause of ReA or the effect of host-pathogen adaptation? A mechanistic hypothesis to address *Chlamydia* as the instigator of ReA postulates that persistent *Chlamydia* organisms provide a continuous source of bacterial components to stimulate the immune system, which results in chronic inflammation and tissue damage.⁴¹ These components could be PAMPs that stimulate host innate receptors or adaptive immune responses against microbial antigens. On the other hand, it is equally plausible that persistence represents the host's best attempt at controlling *Chlamydia*, which has developed specialized mechanisms to avoid the immune response, especially through the establishment of the immunoevasive persistent state. In support of this theory, chronic chlamydial infection elicits little immune stimulation relative to that seen during acute infection.⁴² This latter theory also provides the rationale for the arthritic flares seen commonly in ReA because chlamydial escape from persistence could result in an acute inflammatory event. The basic understanding of chlamydial persistence is in its early stages, and an emphasis needs to be placed on understanding the role of this phenomenon in the pathogenesis of CiReA. Thus clinical ReA studies need to address chlamydial state concurrently with joint inflammation, and animal models need to address the temporal relationship between persistence and arthritis.

Mediators of susceptibility to *Chlamydia*-induced reactive arthritis

Up to 80% of chlamydial infections are asymptomatic.⁴³ This poses significant hurdles in attempting to link clinical evidence of infection with subsequent ReA, but clearly only a few infected individuals go on to develop ReA, for reasons not yet defined. Factors that contribute to the increased virulence of an infection include pathogen, host, and environmental variation.

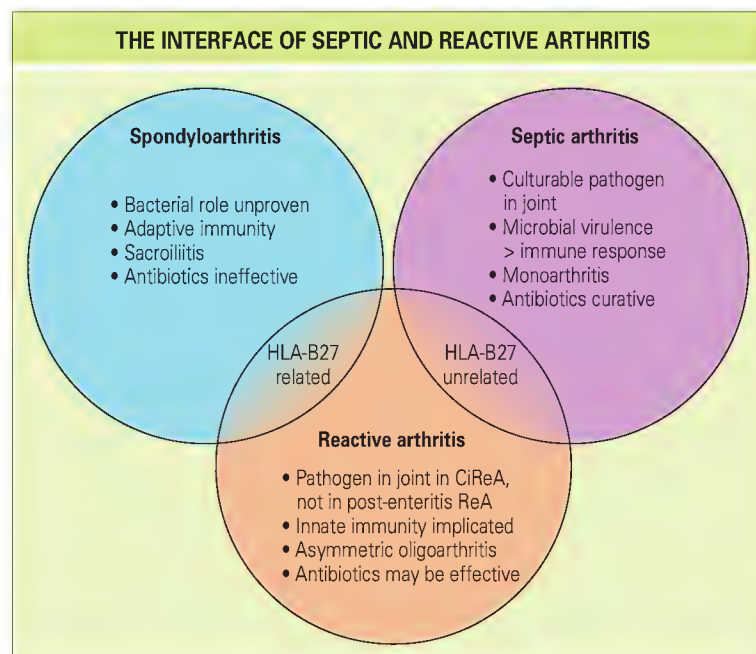


Fig. 112.2 The interface of septic and reactive arthritis (ReA). CiReA, *Chlamydia*-induced reactive arthritis. (From Gracey E, Inman RD. *Chlamydia-induced ReA: immune imbalances and persistent pathogens*. *Nat Rev Rheumatol* 2011;8:55-9.)

The most commonly observed variability in *Chlamydia* relates to the outer membrane proteins that dictate chlamydial biovar. This variation is associated with tissue tropism rather than virulence; however, one study did detect ocular biovars more commonly than genital biovars in ReA.⁴⁴ A limited number of studies have addressed non-biovar-related variance as a determinant of pathogenicity,⁴⁵ yet the effect of this variance on human infection or CiReA remains to be determined. From a broader perspective, a stable host-pathogen interaction is indicated by the consistent rates of *Chlamydia*-related disease⁴⁶ compared with the fluctuating temporal incidence of diseases caused by highly mutable pathogens such as influenza virus. This suggests that alterations in chlamydial pathogenicity are uncommon. Environmental factors are also known to affect chlamydial infections. Clinically, repeated chlamydial infections have been associated with increased genital tract abnormality,⁴⁷ but whether repeated infections are required for the development of CiReA remains unknown. In practice this issue is rarely addressed because diagnostic tests for *Chlamydia* do not distinguish between repeat infections and chronic infections with the same pathogen.⁴⁸ Another potential environmental factor is heavy metal exposure. Experimentally, it has been shown that exposure to heavy metals sensitizes otherwise-resistant animals to CiReA.⁴⁹ Heavy metal-induced sensitization correlates with the suppression of the inflammatory cytokines IFN- γ and TNF- α , which raises the question of an immune imbalance as a mediator of susceptibility to CiReA.

Most studies examining mediators of susceptibility to chlamydial sequelae focus on host genetic variability—in particular, differences in the genes determining immune response. A robust type 1 (classical) inflammatory response is crucial for the control of *Chlamydia*, whereas an enhanced type 2 (alternative) inflammatory response is associated with susceptibility to infection (Fig. 112.3). This has been demonstrated in animal models in

which deficiency of type 1 cytokines, such as IL-12 or IFN- γ , influences susceptibility to chlamydial infection, whereas deficiency of type 2 cytokines, such as IL-10, influences resistance.⁵⁰

Furthermore, it has been shown that high synovial IFN- γ and TNF- α levels correlate with resistance to experimental induction of CiReA.⁵¹ The protective effect of a type 1 response during chlamydial infection of animals has been recapitulated in human studies in which sequelae are associated with higher type 2 cytokine responses.⁵² Additionally, an attenuated type 1 response is seen in patients with SpA,⁵³ manifested as an impaired IFN- γ -induced gene expression profile.⁵⁴ Although there are few studies in CiReA, the trends appear to be consistent, with patients who experience prolonged ReA expressing lower IFN- γ than those who rapidly overcome ReA.⁵⁵ Another study demonstrated the IL-10/IL-12 balance to be crucial in preventing ReA.⁵⁶

Importance of innate immunity in *Chlamydia*-induced reactive arthritis

If susceptibility to CiReA is determined by a disruption in the yin-yang balance of type 1 and type 2 inflammatory responses, then at which point during an inflammatory response does such an imbalance have an effect? The immune system is comprised of two distinct arms, the germline-encoded, rapidly responding innate immune response, and the delayed but highly specific adaptive immune response. Both systems can be polarized during a type 1- or type 2-dominant response. CD4⁺ T cells can be polarized into the well-defined helper T 1 (Th1) and Th2 phenotypes, which have traditionally defined type 1 and type 2 responses. Th1 cells are crucial for eliminating chlamydial infections⁵⁷; however, an effective immune response to *Chlamydia*, and resistance to CiReA, is associated

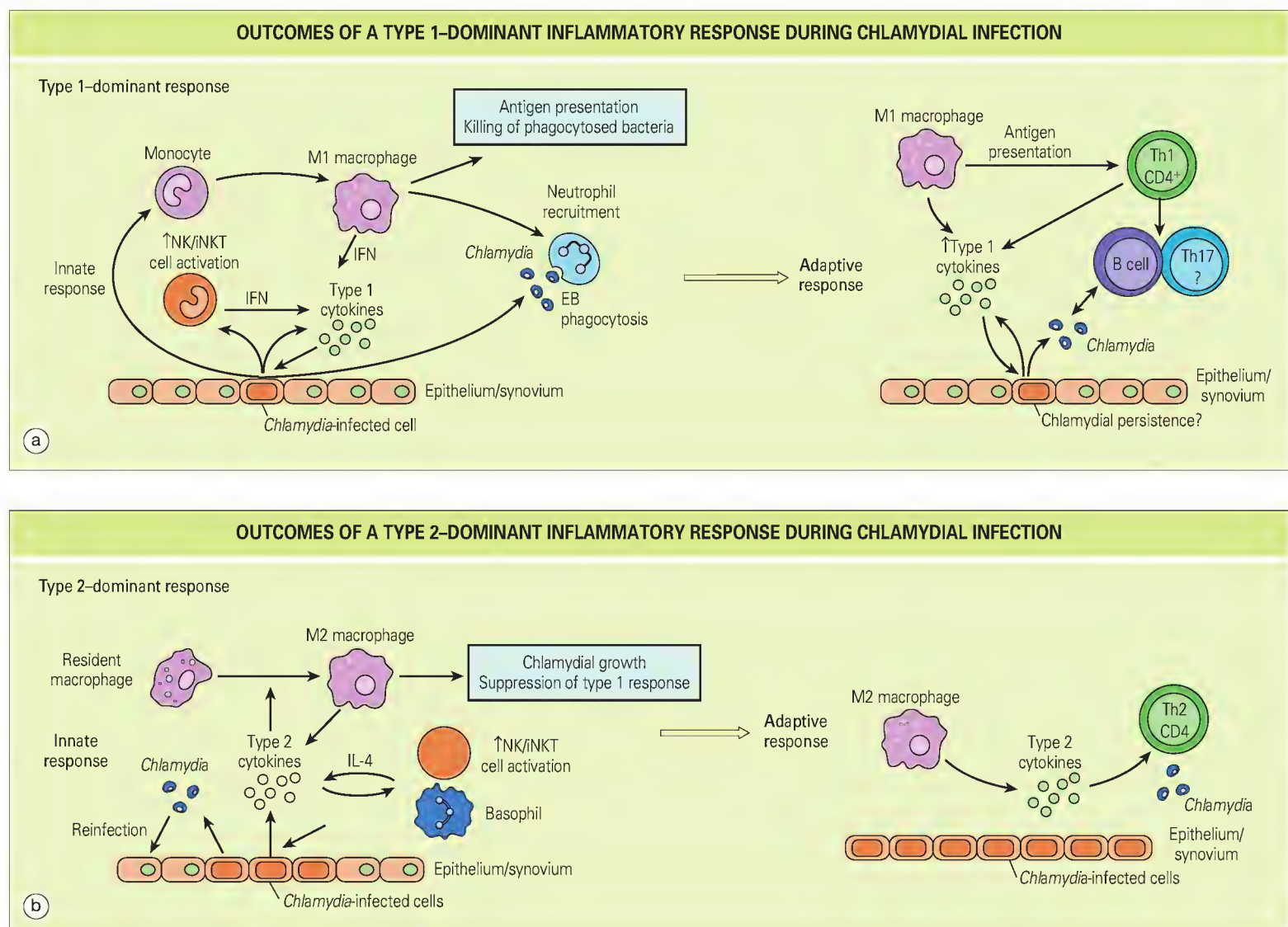


Fig. 112.3 The role of macrophages in *Chlamydia*-induced arthritis. IFN, interferon; Th, helper T cell. (From Gracey E, Inman RD. Chlamydia-induced ReA: immune imbalances and persistent pathogens. *Nat Rev Rheumatol* 2011;8:55-9.)

with a robust type 1 cytokine response as early as 3 days after infection.^{50,58} These temporal kinetics exclude the adaptive immune system as the defining process in early resistance versus susceptibility to *Chlamydia*. But which cells of the innate immune response might cause a disrupted inflammatory balance and how might such cells be affected by this alteration?

Research into the innate immune response during *Chlamydia* infection has been somewhat neglected because the primary focus in chlamydial research has been on vaccine development. Yet many innate immune cells have been shown to play important roles. NK cells have been implicated in providing an early protective effect though IFN- γ release,⁵⁹ an effect that is also mediated by NKT cells during CiReA.⁶⁰ Neutrophils, on the other hand, appear to have a dual role in that they reduce early excessive chlamydial growth,⁶¹ yet excessive activation can itself contribute to tissue damage, including CiReA.⁶² Another innate cell type shown to be important in chlamydial infection is the macrophage, and macrophage depletion greatly enhances infection progression.⁶³

Macrophages are a heterogeneous group of related cells ranging from aggressive proinflammatory macrophages to passive tissue-resident macrophages. Tissue-resident macrophages comprise up to 15% of all cells in healthy tissue and up to 20% of synovocytes.⁶⁴ Thus the primary role of the macrophage should be viewed as that of a homeostatic local resident cell rather than an aggressive innate immune effector. Tissue-resident macrophages tend to be antiinflammatory and have recently been shown to maintain their numbers through proliferation of tissue-resident macrophages.⁶⁵ Inflammatory macrophage populations, on the other hand, rarely exist in healthy tissue and appear on the scene through recruitment and activation of blood monocytes.⁶⁵

A classification system has been devised to delineate polarized macrophages based on phenotype and function, encompassing a spectrum ranging from the classically activated or inflammatory (M1) macrophage to the homeostatic or alternatively activated (M2) macrophage.⁶⁶ This classification system was based on analogy with the Th1/Th2 paradigm in which polarization to M1 is induced by a type 1 inflammatory environment, such as by IFN- γ , and M2 is induced by an IL-10- or IL-4-containing environment. Furthermore, the existence of Foxp3+ regulatory macrophages has recently been demonstrated, akin to the identification of Foxp3+ regulatory T cells.⁶⁷ A key distinction exists between macrophage and Th-cell polarization in that macrophage polarization is highly plastic whereas the differentiation of T cells is somewhat rigid.⁶⁸ This plasticity serves host defense when one considers the role of the innate immune system, which is to respond rapidly to alterations in the immediate environment.

In many biologic systems a dynamic balance exists between opposing mechanisms, as is the case with macrophage polarization. Alterations in this balance, either endogenous or exogenous, are associated with certain pathologic processes, but often it can be hard to ascertain whether the polarized state is cause or effect. Differential macrophage polarization can be demonstrated in rheumatic diseases, with rheumatoid arthritis associated with an M1 dominance and SpA with an M2 dominance.⁶⁹ Further, a robust M1 response is essential for the control of intracellular pathogens, and it is recognized that a deficient M1 response facilitates uncontrolled acute intracellular bacterial infections.⁷⁰ Certain intracellular bacteria, such as *Francisella*, have been shown to induce M2 polarization in macrophages, which results in prolonged bacterial survival.⁷¹ *Chlamydia* is known to infect macrophages, but how *Chlamydia* can survive in differentially polarized macrophages or whether *Chlamydia* is capable of such immune subversion remains unknown (see Fig. 112.3).

Macrophages as key players in *Chlamydia*-induced reactive arthritis

Given the importance of the macrophage in chlamydial infections and susceptibility correlating with a deficient early type 1 response, it is surprising that more is not known about macrophage polarization in the setting of chlamydial infections, especially in the microenvironment of the joint during CiReA. There are, however, indicators that M1 macrophages control *Chlamydia*⁷² and that M2 may be permissive to chlamydial growth⁷³; yet control of *Chlamydia* has traditionally been measured as a reduction in culturable organisms, which is also the hallmark of persistence. An important goal is to validate the observation of M2 macrophage dominance in SpA and to determine if this alteration in macrophage phenotype is also present in CiReA. It is conceivable that individuals with an M2 dominance are less able to control chlamydial infections and thus are more susceptible to *Chlamydia*-associated inflammation of the joints. Additionally, it is plausible that joints are particularly sensitive to M2 polarization given that IFN- γ has reduced activity under hypoxic conditions.

BOX 112.1 PRELIMINARY CLASSIFICATION CRITERIA FOR REACTIVE ARTHRITIS

Major criteria

1. Arthritis, with two of three of the following findings:
 - Asymmetric
 - Monoarthritis or oligoarthritis
 - Affecting predominantly lower limbs
2. Preceding symptomatic infection, with one or two of the following findings:
 - Enteritis (diarrhea for at least 1 day, 3 days to 6 weeks before the onset of arthritis)
 - Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)

Minor criteria (at least one of the following)

1. Evidence of triggering infection
 - Positive nucleic acid amplification test in the morning urine or urethral/cervical swab for *Chlamydia trachomatis*
 - Positive stool culture for enteric pathogens associated with reactive arthritis
2. Evidence of persistent synovial infection (positive result on immunohistologic analysis or polymerase chain reaction assay for *Chlamydia*)

Definition of reactive arthritis

Definite reactive arthritis: Both major criteria and one relevant minor criterion

Probable reactive arthritis: Both major criteria but no relevant minor criteria or major criteria and one or more minor criteria

Exclusion criteria

Other causes for acute arthritis

Modified from Braun J, Kingsley G, van der Heijde D, et al. On the difficulties of establishing a consensus on the definition of and diagnostic investigations for reactive arthritis: results and discussion of a questionnaire prepared for the 4th International Workshop on Reactive Arthritis, Berlin, Germany, July 3-6, 1999. *J Rheumatol* 2000;27:2185-92.

CLASSIFICATION CRITERIA

Early approaches to the development of criteria for ReA relied on clinical symptoms such as preceding symptomatic infection or extraarticular manifestations. Proposed criteria for “Reiter syndrome” that address arthritis in association with urethritis or cervicitis may not apply to ReA occurring after other infections such as enteritis. Specifying a duration of arthritis of at least 1 month excludes the mildest forms of ReA. The need to include inflammatory axial pain and to identify ReA-triggering microbes was emphasized.^{74,75} A consensus was achieved in 1999 that use of the term *reactive arthritis* should be confined to patients who have clinical features and in whom the preceding infection is caused by a microbe that commonly associates with ReA, and this yielded preliminary, but not validated, classification criteria for ReA (Box 112.1).

The primary focus of infection is through the mucosal membrane, usually in the gut or in the urogenital tract. *Chlamydia trachomatis* is by far the most common cause of genital infection, but infections with other organisms such as *Ureaplasma urealyticum* are associated.^{76,77} *Neisseria gonorrhoeae* can cause septic and sterile arthritis, but its role as a triggering agent of ReA is not well established. Infection with *Mycoplasma genitalium* is connected with urethritis, but its role as an independent trigger (in the absence of *Chlamydia* infection) is not settled. *Chlamydia (Chlamydophila) pneumoniae*, a respiratory pathogen, can be involved in about 10% of patients.⁷⁸

In the gastrointestinal tract, the common microbes that are associated with ReA include *Yersinia*, *Salmonella*, *Shigella*, and *Campylobacter*. Previously, *Shigella flexneri* was the only *Shigella* species that had been associated with ReA. However, according to a large epidemiologic survey in Finland, *Shigella sonnei* and *Shigella dysenteriae* can also trigger ReA.⁷⁹ Other infections less frequently diagnosed in association with ReA are infections with *Campylobacter lari*, *Chlamydia psittaci*, and *Clostridium difficile*.⁸⁰

The list of potential triggering agents in ReA is gradually growing (Box 112.2). Bacteria belonging to the normal gut flora (e.g., *Escherichia coli*) have only occasionally been connected with ReA. However, epidemiologic data from Denmark^{81,82} show that a considerable number of patients (1% to 16%) report arthralgia and even arthritis in association with gut infection caused by diarrheagenic strains of *E. coli* identified in the stools.

GENETIC FACTORS

HLA-B27 is the hallmark of the genetic component of spondyloarthritides, and about 90% of patients with AS carry this antigen. The first

BOX 112.2 BACTERIA ASSOCIATED WITH THE DEVELOPMENT OF REACTIVE ARTHRITIS**Enteric infections***Salmonella*

Various serovars

*Shigella**S. flexneri**S. dysenteriae**S. sonnei**Yersinia**Y. enterocolitica* (especially O:3 and O:9)*Y. pseudotuberculosis**Campylobacter**C. jejuni**C. coli**Clostridium difficile**Escherichia coli*

Diarrheagenic strains

Urogenital infections*Chlamydia trachomatis**Ureaplasma urealyticum**Mycoplasma genitalium***Respiratory infections***Chlamydia pneumoniae*Group A β -hemolytic *Streptococcus**

*Typically causes acute rheumatic fever but has been described to cause "reactive-like" arthritis.

hospital-based reports of patients with ReA showed 60% to 80% positivity for HLA-B27. HLA-B27 is associated with a more severe arthritis and the occurrence of extraarticular features and predicts a prolonged disease course.⁸³⁻⁸⁵ By contrast, in population-based studies, the disease is usually mild, oligoarticular, or polyarticular in patients with only a slight or no increase in HLA-B27.⁸⁶ Polymorphisms of TLR2 were reported to be associated with post-*Salmonella* ReA, which suggests that genetic alterations in innate immunity may set the stage for late sequelae of enteric infections.⁷

EPIDEMIOLOGY

The data on the incidence and prevalence of ReA are influenced by the prevalence of triggering infections in the community, genetic susceptibility (frequency of the HLA-B27 gene) in the population, and the criteria applied to diagnose ReA. Much of the epidemiologic data concern the incidence of ReA after infection and estimate that 1% to 15% of patients with ReA are found to have a prior infection. Enterically triggered ReA occurs most commonly after outbreaks caused by gastroenteritis, whereas sexually acquired ReA is endemic.⁸⁷ In epidemiologic studies, nationwide laboratory registers of pathogenic microbial isolations have proved to be helpful.

In California the Foodborne Diseases Active Surveillance Network (FoodNet), covering a population of 2.2 million, collects data on laboratory-confirmed infections with enteric pathogens. Of the 1454 infections reported from 1998 to 1999, 52% were due to *Campylobacter*; 22% due to *Salmonella*, 15% due to *Shigella*, 2% due to diarrheagenic *E. coli* O157:H7, and 2% due to *Yersinia*.⁸⁸ According to results of a questionnaire, newly developed musculoskeletal symptoms were reported by 2.1% of the individuals, most of whom had *Campylobacter* infection.

Epidemiologic data from both the United States⁸⁹ and Denmark⁹⁰ show that 10% to 23% of patients report arthralgia and 13% report arthritis in association with gut infection, most frequently in association with *Yersinia* and *Salmonella* infections. These figures are applicable only to the Western world, in which background rates of gastrointestinal tract infections are low. Microbial contamination of drinking water is a common problem and a major source of microbial pathogens in developing countries, where about half of asymptomatic patients can carry enteric pathogens in the stools. Despite the microbial load, a prevalence study in rural western India disclosed no cases of well-defined ReA in the population of 4092 adults examined.⁹¹

There are only a few population-based studies examining the annual whole-population incidence of ReA, most conducted in Scandinavia. The total incidence has been estimated to be 10 to 30 per 100,000.^{89,92,93}

Campylobacter is the most important infective organism to cause gastroenteritis. In Finland and the United States, the annual incidences of ReA due to *Campylobacter* infection were 4.3 and 2.1 per 100,000, respectively.^{89,94} The U.S. data suggested an incidence of 1.4 per 100,000 after *Salmonella* infections. Tourism can change the epidemiologic data. In the West, *Shigella* infections are uncommon and are usually imported. The incidence of *Shigella*-induced ReA in Finland was 1.3 per 100,000,^{79,84} and all infections were acquired abroad.

Single-source epidemics, which give better information regarding the spectrum and severity of the diseases, have been reported in association with



Fig. 112.4 A patient with a swollen knee.



Fig. 112.5 A patient with acute reactive arthritis in the feet. Stool culture was positive for *Campylobacter jejuni*.

Yersinia enterocolitica, *Yersinia pseudotuberculosis*, *Campylobacter jejuni*, *Shigella flexneri*, and *Salmonella enterica* infections.^{95,96} The frequency of ReA varies greatly among these studies (from 0% to 29%) with low proportions associated with HLA-B27 positivity.⁹⁵ The clinical picture of ReA at the population level is milder, and only a minority of patients visit their physicians.

CLINICAL FEATURES

Infection may be the cause of acute joint symptoms in 9% to 18% of patients with inflammatory joint disease of less than 6 months' duration.⁹⁷ (see Box 112.1). Thus patients with ReA comprise about 10% of those who come to early synovitis clinics.⁹⁸ The clinical features of ReA are those of SpA, with arthritis the most frequent single manifestation. The patients are usually young adults (mean age, 30 to 40 years); in children the disease is uncommon and generally preceded by gastroenteritis. Male and female patients have a similar risk of ReA induced by gastrointestinal tract infection, whereas ReA triggered by *C. trachomatis* is more frequent in males. There is usually a lag of 1 to 4 weeks from the start of infection to the onset of musculoskeletal symptoms. The triggering infection can also be asymptomatic and hence go unrecognized.

Arthritis

The typical clinical feature of arthritis is asymmetric oligoarthritis, often in large joints of the lower extremities (Fig. 112.4). About 50% of patients have upper limb arthritis, and mild polyarticular small joint arthritis (Fig. 112.5) also occurs. Patients can also have dactylitis (Fig. 112.6). About 30% of patients have acute inflammatory low back pain, typically worse during the night, that radiates to the buttocks.

Extraarticular features

Patients frequently have extraarticular inflammatory symptoms and signs (Table 112.1).^{83,99} Enthesitis or bursitis can occur either in association with arthritis or as the only reactive complication. Other extraarticular features, common to other spondyloarthritides, include eye symptoms, usually conjunctivitis and less frequently acute anterior uveitis, and various skin symptoms, such as pustular eruption erythema nodosum (Fig. 112.7) and keratoderma blennorrhagicum, which is a pustular skin lesion usually observed on the soles of the feet. Circinate balanitis is most frequently associated with *Chlamydia* arthritis but can also occur in ReA from another cause. Erythema nodosum is usually associated with *Yersinia* infection and is more frequent in women. In addition to gut symptoms directly associated with gut infection, patients can have (often asymptomatic) chronic gut inflammation, mostly an aphthous colitis or terminal ileitis or microscopic gut inflammation. In most cases these conditions are benign, but they can herald the chronicity of arthritis.

LABORATORY TESTING

Presence of the typical clinical picture suggests the diagnosis of ReA, but the diagnosis is most confidently made if the triggering infection can be demonstrated by isolation of the microbe. Most of the genital infections are asymptomatic,¹⁰⁰ with a high suspicion of *Chlamydia* infection leading to the first test to detect *C. trachomatis* in the urogenital tract. The test of choice is examination of the first portion of the morning urine by nucleic acid amplification, because it is more convenient and results are comparable to

those with urogenital swab testing. Evidence of *Chlamydia* in the joint by PCR assay is diagnostic, but the methods used to test synovial samples have not been validated.

During the acute phase of enteric infections isolation is usually possible from the stools. However, by the time arthritic complications appear the patient may have already recovered from the gastroenteritis and the microbe may no longer be detectable in the feces. *Salmonella* and *Yersinia* infections are usually associated with a strong antibody response that suggests a diagnosis of ReA. There are no international standards for these tests, and the techniques vary greatly. Serologic methods include the classic agglutination tests (by the Widal technique), immunoblotting, hemagglutination, radioimmunoassay, and immunofluorescence tests. None of these techniques has gained general acceptance in clinical practice. The use of serologic testing (complement fixation, microimmunofluorescence, enzyme immunoassay) for the diagnosis of *C. trachomatis* infection is useful in upper genital tract infections and seroepidemiologic studies but not in lower urinary tract infections, which do not necessarily elicit a systemic antibody response. A degree of serologic cross-reactivity between *C. trachomatis* and *Chlamydia pneumoniae* complicates application of these tests, as well does the



Fig. 112.6 Dactylitis in a patient with reactive arthritis induced by *Chlamydia trachomatis*.



Fig. 112.7 Erythema nodosum in a patient with *Yersinia*-induced arthritis.

■ TABLE 112.1
Clinical features of reactive arthritis in hospital-based studies

Feature	Triggering infection				
	<i>Yersinia</i>	<i>Salmonella</i>	<i>Shigella</i>	<i>Campylobacter</i>	<i>Chlamydia</i> /chlamydial urethritis
Number of affected joints: mean (range)	6 (1-22)	6 (0-22)	4 (2-11)	3 (1-10)	7 (1-24)
Low back pain: mean (range) (%)	30 (16-45)	37 (18-67)	3 (2-50)	24	47
Radiographic sacroiliitis: mean (range) (%)	19 (11-20)	11	NA	NA	25
Urethritis: mean (range) (%)	15 (4-23)	14	69 (50-69)	NA	93
Conjunctivitis: mean (range) (%)	6 (6-7)	13 (6-18)	72 (17-78)	NA	41
Iritis: mean (range) (%)	7 (6-17)	3	4 (3-17)	NA	4
Skin lesions: mean (range) (%)	5 (4-7)	2 (2-6)	17	NA	14
Duration of arthritis in months: mean (range)	3 (1-13)	5 (0-30)	1	0	5 (1-16)
Chronic course (>12 mo): mean (range) (%)	4 (1-24)	19 (0-30)	1	0	14
HLA-B27+: mean (range) (%)	71 (56-72)	77 (0-94)	83 (83-85)	59	81

NA, not available.
Data from Leirisalo M, Skylv G, Kausa M, et al. Followup study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. *Arthritis Rheum* 1982;25:249-59; Leirisalo-Repa M, Skylv V, Kousa M. Follow-up study of Reiter's disease and reactive arthritis: factors influencing the natural course and the prognosis. *Clin Rheumatol* 1987;6(Suppl 2):73-82; Leirisalo-Repa M: Enteric infections and arthritis: clinical aspects. In: Calin A, Taugog J, editors. *Spondylarthritides*. Oxford: Oxford University Press; 1985. p. 59-67.

persistence of antibodies, which prevents distinction between past and present infection. Microimmunofluorescence serologic analysis, which is commonly used for diagnosis of *C. pneumoniae* infection, is not optimal because false-negative and false-positive results are frequently obtained. In only about 60% of patients with clinically diagnosed ReA can evidence of previous infection be detected by means of serologic testing and appropriate culture of urogenital or stool samples.¹⁰¹

A substantial proportion of infections are asymptomatic or associated with only minor symptoms, which can hinder the diagnosis. It is also not uncommon for the symptoms of the infection to have subsided when the patient comes to the physician. There are also infections—for example, those due to *Shigella*—for which no reliable serologic detection methods exist. Among the routine laboratory tests, erythrocyte sedimentation rate and C-reactive values are usually elevated. Synovial fluid leukocyte count can range between 2000 and 64,000/mm³. None of these laboratory tests is specific for ReA. HLA-B27 testing has little value, with a low posttest probability.¹⁰² Synovial fluid should always be cultured as the definitive test to distinguish between septic arthritis and ReA. Other rheumatic conditions, such as Lyme arthritis, gout, rheumatoid arthritis, viral arthritides, and osteoarthritis, should be excluded on the basis of the clinical picture and relevant laboratory test results.

NATURAL HISTORY

The average duration of acute ReA is 3 to 5 months, and about 15% of patients develop chronic sequelae (lasting longer than 6 months) or proceed into chronic SpA.⁸³ In about 4% of patients with *Yersinia* arthritis, 19% of those with *Salmonella* arthritis, 19% of those with *Shigella* arthritis, and 17% of those with *Chlamydia* arthritis, the disease extends longer than a year.⁸⁰ In some studies, chronicity has been reported in a vast majority of patients with the arthritis–urethritis–eye symptom triad.⁸⁰

After the acute episode, mild joint pain or enthesopathy is common. Also, one third of patients have occasional attacks of low back pain. Recurrent episodes of acute ReA seldom occur in patients with previous *Yersinia* arthritis but are more frequent in patients with previous *Salmonella*-, *Shigella*-, or *Chlamydia*-induced arthritis. Depending on the triggering infection and the follow-up time, chronic arthritis is observed in 2% to 18%, sacroiliitis in 14% to 49%, and definite AS in 12% to 26% of patients (Table 112.2).

Factors determining the progression of acute ReA to chronic SpA are not completely known, but they include the type of infection, the presence of HLA-B27, a family history of SpA or AS, and the presence of chronic gut inflammation. Patients with ReA triggered by urogenital infection seem to be more vulnerable to recurrent urethritides and, consequently, recurrent episodes of ReA. It is still uncertain to what extent ReA contributes to the development of sacroiliitis or AS or whether sacroiliac changes would have been proceeding in a patient with genetic predisposition to axial SpA even in the absence of intervening ReA (see Table 112.2).

ATYPICAL ASPECTS OF REACTIVE ARTHRITIS

SAPHO

One ongoing controversy in the field of ReA is whether SpA should include the clinical syndrome called SAPHO—synovitis, acne, pustulosis, hyperostosis, and osteitis.¹⁰³ The terms from which the acronym SAPHO is derived accurately describe its clinical features. In addition to synovitis, both hyperostosis and osteitis are seen. The most common sites of involvement are on the anterior chest wall—in particular, the clavicles, sternum, and sternoclavicular joints. Symptoms consistent with an SpA include a lower extremity oligoarthritis including the knees, hips, and ankles. Furthermore, sacroiliitis is present in 52% of patients with SAPHO.¹⁰⁴ Its classical dermatologic features include both severe acne and palmoplantar pustulosis. On both histopathologic and radiographic analysis, SAPHO initially can be indistinguishable from osteomyelitis. Radiographic lesions are typically seen in the sternoclavicular joints.

Because of its overlap with SpA, it has been suggested that SAPHO is not a unique entity but rather one component along a spectrum of disease.¹⁰⁵ Not only does it have clinical and radiographic features similar to those of SpA, but infection may also play a role in its pathogenesis. A review of the results of several smaller studies proposed a possible link between *Propionibacterium acnes* infection and SAPHO.¹⁰⁶ Sixty-nine patients underwent bone biopsy, and *P. acnes* was isolated from 24 specimens. Furthermore, intraarticular injection of inactivated *P. acnes* in the knees of laboratory rats can cause joint lesions, including bony erosions and proliferation of the synovial lining.¹⁰⁷ Also suggestive of an infectious cause is the observation that SAPHO may be responsive to antibiotics. In one case improvement in magnetic resonance imaging findings, decrease in skin disease activity, and improvement in osteitis occurred after completion of a 4-month course of azithromycin.¹⁰⁸ By three months after the completion of antibiotic treatment, however, the benefits had disappeared.

These findings raise the possibility that SAPHO is a reactive osteitis that mechanistically is along the same spectrum as ReA. We have previously proposed a classification system to address this issue.¹⁰⁹ If the traditional definition of ReA is used, SAPHO does not meet its diagnostic criteria, but there are several features which suggest that SAPHO has an infectious trigger and may be a variant of ReA (Fig. 112.8).

Clostridium difficile and Giardia lamblia

Classically, *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* have been implicated as the pathogens responsible for the infections preceding ReA. However, there are a number of reported cases of *C. difficile*-associated ReA. In these cases knees and wrists are the most common sites of involvement. Although the temporal relationship is clear, *C. difficile* has not been isolated from the joint itself, and the infection is not associated with *C. difficile* bacteremia. A retrospective analysis in Canada demonstrated that the incidence of *C. difficile* infection had increased 4-fold from 1991 to 2003, with

TABLE 112.2 Long-term prognosis of reactive arthritis

	Preceding infection					
	Solmonello		Yersinio enterocolitico		Shigello	Urogenital infection
	(n = 27)	(n = 50)	(n = 58)	(n = 107)	(n = 100)	(n = 129)
Follow-up time (yr)	5	11	4-5	10	20	5
HLA-B27+ (%)	22	88	NA	78	NA	81
Recovered (%)	33	40	19	49	20	NA
Arthralgia (%)	NA	20	32	19	NA	NA
Low back pain (%)	30	44	NA	37	NA	41
Recurrent arthritis (%)	37	22	NA	5	18	10
Chronic arthritis (%)	52	16	16	2	18	16
Ankylosing spondylitis (%)	NA	12	9	16	14	44
Radiologic sacroiliitis (%)	NA	12	9	30	32	44
Erosions in peripheral joints (%)	15	NA	3	0	12	16

NA, not available.
Data from Hannu T, Inman R, Granfors K, et al. Reactive arthritis or post-infectious arthritis? Best Pract Res Clin Rheumatol 2006;20:419-33; Leirisala M, Skytå G, Kausa M, et al. Followup study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. Arthritis Rheum 1982;25:249-59.

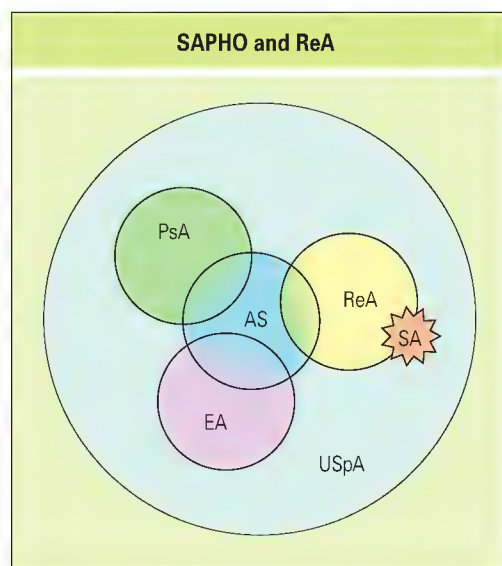


Fig. 112.8 Proposed classification of spondyloarthritis. Note that SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) is on a spectrum with reactive arthritis (ReA). AS, ankylosing spondylitis; EA, enteropathic arthritis; PsA, psoriatic arthritis; SA, SAPHO; USpA, undifferentiated spondyloarthritis. (From Rohekar G, Inman RD. *Conundrums in nosology: synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome and spondylarthritis*. *Arthritis Rheum* 2006;55:665-9.)

a 10-fold increase in individuals older than 65 years.¹¹⁰ Given this marked increase in incidence, rheumatologists should expect to encounter an increasing number of patients with *C. difficile*-associated ReA. Perhaps with more clinical exposure a more uniform approach to treatment will evolve. In the 40 documented cases, a variety of treatment modalities were used; however, on average, cases resolved in 68 days with treatment of the underlying *C. difficile* colitis.¹¹¹

Like *C. difficile*, *Giardia* is a gastrointestinal pathogen that has been associated with ReA, albeit rarely. It is typically acquired by drinking water in rural areas. In a case series of patients with nonoutbreak *Giardia* infections it was demonstrated that 11.7% of patients experienced joint pain, most commonly affecting the knee, and 13.6% experienced ocular symptoms.¹¹² Although this study did not include sacroiliac involvement in the analysis, previous case reports have documented its occurrence.¹¹³

It is clear that atypical pathogens can lead to a clinical presentation consistent with ReA. For this reason, the traditional definition of ReA needs to be revisited to include these and other atypical pathogens that have yet to be identified.

Streptococcal infections

According to the current definition of ReA, only infections with pathogens that affect the gastrointestinal or genitourinary tract lead to a diagnosis of ReA. However, group A streptococci and *C. pneumoniae*, both implicated in respiratory tract infections, have been associated with ReA. Although *C. pneumoniae* is far less commonly linked to ReA, PCR analysis has recovered its DNA from synovial tissue of patients with ReA.¹¹⁴ Poststreptococcal ReA can present as a predominantly lower extremity oligoarthritis and may have an associated enthesitis or tendonitis.¹¹⁵ One review concluded that poststreptococcal ReA is a heterogeneous group of disorders, some of which share features of SpA and others of which are more like acute rheumatic fever (ARF).¹¹⁶ The consensus is that ARF and poststreptococcal ReA are distinct clinical entities. Poststreptococcal ReA is characterized by a longer interval between infection and symptom onset and does not respond as readily to salicylates. The pericardial disease and valvular heart disease characteristic of ARF are not recognized as a feature of poststreptococcal ReA.

TREATMENT

Triggering infection

All patients with acute *C. trachomatis* infection should receive the routine treatment (e.g., azithromycin 1 g as a single dose or a 7-day course of

doxycycline 200 mg/day, with partners treated as well). If a diarrheal episode associated with ReA is self-limited, it is not treated with antimicrobial agents.

Acute arthritis

The use of nonsteroidal antiinflammatory drugs (NSAIDs), often in a full dose, is usually of major benefit and should be first-line treatment for the acute arthritis. Intraarticular glucocorticoid injections are usually of benefit in patients with monoarticular or oligoarticular disease. Enthesitis may also respond to local corticosteroid injections. Systemic use of corticosteroids may be instituted if there is severe polyarthritis, if systemic inflammation is high, or if the patient is severely disabled. The starting dosage of prednisone is usually 20 to 40 mg/day.

Extraarticular symptoms

Acute anterior uveitis needs a prompt diagnosis and treatment with topical glucocorticoids and mydriatics. The outcome is usually good, but in about 5% of the patients the inflammation progresses to chronic uveitis. In severe cases, TNF-blocking agents have been used in uncontrolled fashion for the treatment of uveitis.

Skin and mucosal lesions

Keratoderma and pustular lesions mimic psoriasis and can be treated in the same way with topical glucocorticoids. In severe cases, methotrexate may be used and may have some benefit for more prolonged arthritis. Circinate balanitis and oral mucosal lesions usually respond to mild topical glucocorticoids.

Chlamydia-induced reactive arthritis

C. trachomatis represents the most common pathogen to trigger ReA, with 4% to 15% of infected individuals developing ReA. Recent studies have shown that both *C. trachomatis* and *C. pneumoniae* are able to disseminate from their site of primary infection to distant sites, such as synovium, and establish residence in the tissues. At these distant sites, the pathogens enter into a persistent yet aberrant state at which point the organisms are unable to be cultured; however, they are detectable by electron microscopy and nucleic acid detection methods. These features seem specific for CiReA, and it is noteworthy that in post-enteritis ReA, controlled studies examining the introduction of antibiotics during ongoing ReA have shown no effect on the course of the arthritis. In 2010 a clinical trial demonstrated that combination antibiotics could alter the course of CiReA.¹¹⁷ Patients were randomly assigned to receive placebo, doxycycline plus rifampin, or azithromycin plus rifampin. After 6 months of treatment, 63% of patients assigned to receive combination antibiotic therapy versus 20% of patients assigned to receive placebo experienced clinical improvement as measured by swollen joint count. Furthermore, 70% of patients who received antibiotics demonstrated clearance of *Chlamydia* as measured by PCR assay of peripheral blood mononuclear cells. Although several previous studies had used antibiotics in treating ReA, this is the first that demonstrated clinical improvement and examined clearance of *Chlamydia*. This trial was unique in that it enrolled only patients with blood or synovial tissue that tested positive for *Chlamydia* by PCR analysis. Other studies using antibiotics have enrolled patients with heterogeneous causes of ReA. Furthermore, they have often employed antibiotic monotherapy, which may not be effective in treating infections with aberrant pathogens. These findings lead to a reconsideration of the definition of ReA as a nonseptic arthritis (Table 112.3).

Disease-modifying antirheumatic drugs

Because about 50% of patients recover from ReA within the first 3 to 4 months, use of disease-modifying antirheumatic drugs (DMARDs) often is not considered. Sulfasalazine, if started during the first 3 months of ReA, may induce clinical remission more rapidly compared with placebo. Sulfasalazine or methotrexate may also be effective in chronic ReA when NSAID therapy has proved ineffective in controlling the arthritis or enthesitis, but there are few prospective trials to determine efficacy in this setting.

Biologic agents in the treatment of reactive arthritis

Traditionally the treatment of ReA involves an initial trial of NSAIDs and local corticosteroid injections with the addition of a DMARD should the individual continue to be symptomatic. As stated, limited evidence exists

TABLE 112.3
Randomized, double-blind, placebo-controlled studies of the effect of antimicrobial chemotherapy on reactive arthritis

Cause	No. of patients	Duration of therapy (mo)	Treatment	Result compared with placebo
<i>Chlamydia</i>	21	3	Lymecycline	Lymecycline effective
Enteric infections	19	3	Lymecycline	No difference
<i>Yersinia</i>	36	3	Ciprofloxacin	No difference
Various triggers	55	3	Ciprofloxacin	No difference
Various triggers	71	3	Ciprofloxacin	No difference
Clinical suspicion of reactive arthritis	152	3	Azithromycin	No difference
<i>Chlamydia trachomatis</i>	37	4	Doxycycline	No difference

Data from Hannu T, Inman R, Granfors K, et al. Reactive arthritis or post-infectious arthritis? *Best Pract Res Clin Rheumatol* 2006;20:419-33; Putschky N, Patt H-G, Kuipers JG, et al. Comparing 10-day and 4 month doxycycline courses for treatment of *Chlamydia trachomatis*-reactive arthritis: a prospective, double-blind trial. *Ann Rheum Dis* 2006;65:1521-4.

TABLE 112.4
Trials of biologic agents in reactive arthritis (ReA)

Study	No. of patients	Treatment	Clinical infection	Microbial infection	Efficacy
Oili et al (2003) ¹²¹	2	IFX	Diarrhea	<i>Yersinia</i>	Yes
Gaylis (2003) ¹²²	1	IFX	HIV	HIV	Yes
Flagg et al (2005) ¹¹⁹	16	ETA	6 wk before ReA	6 wk before ReA	56%
Gill & Majithia (2008) ¹²³	1	IFX	Urethritis	None	Yes
Abdelmoula et al (2008) ¹²⁴	1	IFX	None	<i>Chlamydia</i>	Yes
Schafanski (2010) ¹²⁵	1	IFX	Urethritis	<i>Chlamydia</i>	Yes
Meyer et al (2011) ¹²⁰	10	IFX, ETA, ADA	4 wk before ReA	4 wk before ReA	Yes

ADA, adalimumab; ETA, etanercept; IFX, infliximab; HIV, human immunodeficiency virus.

regarding the use of DMARDs, in part because of the relative infrequency of their use since approximately 50% of patients recover from ReA within the initial 6 months and only 4% to 19% of patients go on to develop a protracted ReA lasting longer than 1 year.¹¹⁸ Unlike the other clinical subsets of SpA, no guidelines exist for ReA with respect to more aggressive treatment should the initial therapy fail. Because there are no guidelines and most patients respond to NSAIDs, there are a limited number of reports of cases in which patients were given biologic agents.

There is limited experience with the use of anti-TNF agents in ReA (Table 112.4). In the largest reported experience with biologic therapy in ReA, the efficacy and safety of etanercept (25 mg subcutaneously twice weekly) was examined in 16 patients with ReA in a 6-month open-label trial.¹¹⁹ Synovial biopsies with PCR analysis of specimens were performed before and after treatment with etanercept. Ten of 16 patients completed the trial. Six patients withdrew, but none had a worsening of arthritis or infection. Of the 10 who completed the study, 9 could be classified as treatment responders, including 3 who showed evidence of bacterial organisms on PCR analysis before initiation of etanercept therapy; PCR results became negative in 2 patients while they were taking etanercept. Five of 6 patients in whom adequate synovial biopsy specimens were obtained showed improvement but not normalization of histologic findings.

The most recent study to examine the efficacy of anti-TNF agents in ReA was a retrospective analysis of data for 10 patients.¹²⁰ Ten patients with ReA previously refractory to treatment with NSAIDs and DMARDs received anti-TNF therapy at a median of 6 months (range, 2 to 12 months) from the

onset of ReA to the initiation of treatment. The median follow-up was 20.6 months. Anti-TNF therapy was rapidly effective in nine patients (90%), as shown by the swift effect on visual analogue scale pain score, tender joint count, swollen joint count, and extraarticular manifestations as well as the corticosteroid-sparing effect. The relatively short disease duration in this study raises the issues of generalizability and cost effectiveness. Given the self-limited nature of ReA in most cases, it is unclear whether the resolution of disease was secondary to the anti-TNF treatment or simply its spontaneous resolution. Understandably, there is a theoretical concern in administering an anti-TNF agent to someone who is harboring a potential pathogen, but in the studies conducted to date this does not seem to be an issue. In the study described earlier no adverse events, including severe infection, were documented.¹²⁰ Only mild infections were reported, none of which was associated with the triggering infection.

PROPHYLAXIS

There is no controlled evidence that chemotherapy initiated to treat urethritis can diminish the risk of recurrent ReA. Nevertheless, because a recurrent attack is often preceded by an infection, it is logical to tell patients how to prevent the potential triggering infections in the future. Avoidance of unprotected sex is sound advice with respect to *C. trachomatis* infection. When visiting regions where the risk of foodborne infections is high, the traveler should adopt caution in consumption of uncooked foods. Tap water and ice cubes should be considered contaminated. If the patient develops diarrhea, a fluoroquinolone (e.g., ciprofloxacin 750 mg as a single dose or 500 mg twice a day for 3 days) is effective for traveler's diarrhea and is also effective against most strains of *Salmonella*, *Shigella*, and *Yersinia*. In a patient with previous ReA, the treatment should be continued until the results of a stool culture are available. Fluoroquinolone resistance is an increasing problem in *Campylobacter* isolates from travelers returning from Asia, Africa, and Latin America.¹²⁶ Therefore, if there is a risk of *Campylobacter* infection (e.g., visit to a farm, consumption of poultry or egg-containing food), azithromycin (1 g as a single dose or 500 mg once daily for 3 days) is more preferable for traveler's diarrhea.¹²⁷ In rare cases, initial treatment with the combination of azithromycin and a fluoroquinolone may be considered to cover the major agents causing traveler's diarrhea, including fluoroquinolone-resistant *Campylobacter*. If the patient develops community-acquired pneumonia, treatment with the combination of a macrolide and a β -lactam drug covers both pneumococcal pneumonia and *C. pneumoniae* infection.

Preventing a recurrence of ReA is influenced more by advice than by antibiotic treatment. "Practice safe sex" is sound advice for all sexually active individuals. In patients with a history of ReA following a genitourinary tract infection, such advice should be reinforced. Similarly, patients who have had episodes of ReA following enteric infections should exercise extra precaution with regard to local food and hygiene when traveling to locales where enteric pathogens are common.

FUTURE DIRECTIONS IN REACTIVE ARTHRITIS

With the advent of improved methods of detecting pathogens in the synovium and the recognition of an expanding number of pathogens implicated in ReA, there remains a challenge to create a practical and more generalized definition of ReA. Presently, inclusion and exclusion criteria are not well defined, and clinicians are often left to treat ReA based on clinical experience. Current evidence suggests that ReA is a variant of septic arthritis in which the pathogen cannot be cultured. This should direct future research efforts toward therapies targeted at eradication of the intraarticular pathogens. But before such initiatives can be taken, more reliable methods for detecting these pathogens in the joints need to be developed. With increased use of biologic agents for the treatment of SpA, defined guidelines need to be formulated that balance both the risk and cost of these agents in the treatment of ReA.

SUMMARY: KEY ELEMENTS OF THE CLINICAL APPROACH TO REACTIVE ARTHRITIS¹²⁸

(Box 112.3)

Monoarthritis in a young adult should raise the possibility of ReA. ReA most often affects adults between 18 and 40 years of age and presents as a monoarthritis or oligoarthritis. The knee, ankle, or one of the metatarsophalangeal joints is usually affected first. Septic arthritis must be always be considered and excluded in any monoarthritis. Culture of

BOX 112.3 CLINICAL HIGHLIGHTS OF REACTIVE ARTHRITIS (ReA)

- In ReA, exposure to an infectious agent leads to the development of an inflammatory arthritis and other characteristic clinical findings.
- Approximately 50% of cases of ReA and undifferentiated oligoarthritis can be attributed to a specific pathogen by a combination of culture and serologic testing. The predominant organisms are *Chlamydia*, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* species.
- The frequency of ReA following exposure to potential etiologic agents is between 3% and 10%.
- ReA characteristically involves the joints of the lower extremities in an asymmetric, oligoarticular pattern. Dactylitis in the feet is typical of ReA.
- The presence of HLA-B27 increases disease susceptibility but is neither sufficient nor necessary for ReA to occur. Individuals who are HLA-B27+ tend to have more severe and longer episodes of ReA.
- Cutaneous manifestations of ReA include (1) oral ulcers, typically painless; (2) keratoderma blennorrhagicum, a papulosquamous rash on palms and soles; and (3) circinate balanitis, characterized by shallow ulcers on the penis.

synovial fluid is the only definitive method of differentiating septic arthritis from ReA.

Dysuria and a genital rash can follow infections of the gastrointestinal tract as well as the genitourinary tract. When genitourinary complaints occur concurrently with an inflammatory arthritis, clinicians may assume that a sexually transmitted disease has been the inciting event. However, genitourinary symptoms and signs are perfectly compatible with the syndrome of ReA that follows a gastrointestinal tract infection. A sexually transmitted disease need not be invoked to explain genitourinary features.

The enthesitis of ReA can be the dominant feature of the disease. Enthesitis, particularly Achilles tendonitis and plantar fasciitis, can be profoundly

disabling in the acute phase. Enthesitis overshadows inflammatory joint symptoms in some patients.

The uveitis of ReA is anterior, unilateral, and highly symptomatic. ReA is associated with an anterior uveitis that tends to affect one eye at a time. The finding of concurrent bilateral disease or disease in the posterior pole of the eye strongly suggests other diagnoses. Patients with the anterior uveitis of ReA have pronounced photophobia, eye pain, ocular erythema, and tearing. In addition to topical glucocorticoid eye drops, a mydriatic agent is essential to dilate the involved eye and prevent the formation of synechiae between the pupil and the lens.

Recurrence of ReA associated with sexually acquired infection is not uncommon. Approximately 50% of such patients experience subsequent episodes. In contrast, recurrence after enteric infection is uncommon. Patients should be advised about the risk that reinfection will lead to recurrence of arthritis and about specific precautions for avoiding reinfection. The precise role of repeated infections in precipitating recurrences of ReA is not clear. Additional genital tract infections have been associated with recurrent ReA, but reinfection with enteric bacteria—even the same species that caused the initial episode—does not always lead to a recurrence of ReA.

The interval between antecedent infection and ReA may extend to 4 weeks, although an interval of 1 to 2 weeks after the inciting infection is typical for the appearance of ReA. Patients with joint symptoms and other clinical features compatible with ReA therefore must be questioned closely about more remote occurrences of infection.

Postdiarrheal arthritis should always occasion a search for gastrointestinal pathogens as well as consideration of inflammatory bowel disease. The new onset of joint pain in the setting of diarrhea may indeed herald a case of inflammatory bowel disease with accompanying arthritis. However, infectious diarrhea caused by bacteria, parasites, or their toxins must be excluded definitively as the first priority. Examination of stool specimens for leukocytes, ova, and parasites as well as *C. difficile* toxin assays are critical in this evaluation.

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SPONDYLOARTHRITIS

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Classification and epidemiology of spondyloarthritis

■ MARTIN RUDWALEIT

- Ankylosing spondylitis (AS), reactive arthritis, undifferentiated spondyloarthritis, and arthritis associated with psoriasis or inflammatory bowel disease constitute spondyloarthritis (SpA), a group of interrelated inflammatory disorders with overlapping clinical manifestations and shared genetic markers.
- Clinical manifestations of the spondyloarthritides include axial manifestations such as inflammatory back pain and peripheral manifestations such as peripheral arthritis, enthesitis, dactylitis, and uveitis. HLA-B27 is the major contributing gene in SpA.
- The entire group of spondyloarthritides has a prevalence of 0.5% to 1.9%. AS, the largest subgroup, has a prevalence of 0.1% to 1.4%, which depends to some degree on the frequency of HLA-B27 in the population.
- Classification criteria were established for AS, for the entire group of spondyloarthritides, and recently for axial and for peripheral SpA.
- In the Assessment of SpondyloArthritis international Society classification criteria for axial SpA, sacroiliitis on magnetic resonance images is as important as sacroiliitis on radiographs, so that not only AS but also early axial SpA is captured.

CLASSIFICATION OF SPONDYLOARTHRITIS

The evolutionary concept of spondyloarthritis

Although anatomic and clinical descriptions of patients with advanced ankylosing spondylitis (AS) date back to the 16th century, it was not until the 1930s that the German radiologist Krebs reported that radiographic sacroiliitis is present in nearly all AS patients and that sacroiliitis occurs early in the course of the disease.¹ These findings were subsequently confirmed by Forestier in France and Scott in England, and formed the basis for the central role of radiographic sacroiliitis in criteria for AS. The Rome criteria² formulated in 1961 were the first set of criteria developed to classify AS. Modifications led to the New York criteria³ and eventually to the modified New York criteria for AS in 1984.⁴ Accordingly, a patient can be classified as having definite AS if one clinical criterion plus the radiologic criterion (radiographic sacroiliitis grade 2 or higher bilaterally or grade 3 or higher unilaterally) are fulfilled (Table 113.1). The modified New York criteria are the most widely used criteria for both classification and diagnosis of AS. However, it takes on average 6 to 8 years from the onset of inflammatory back pain until a definite diagnosis of AS is made because of the relatively late appearance of definite radiographic sacroiliitis on plain radiographs,⁵ a requirement of the modified New York criteria.

In the 1970s, Moll and Wright established the concept of a group of interrelated disorders termed *seronegative spondyloarthritides* that initially included AS, psoriatic arthritis, reactive arthritis, arthritis with ulcerative

colitis or Crohn disease, Whipple disease, and Behçet syndrome.⁶ These disorders were termed *seronegative* because patients with these conditions typically tested negative for rheumatoid factor. These conditions were considered interrelated because of the absence of subcutaneous nodules (as found in rheumatoid arthritis); the presence of similar clinical manifestations such as involvement of the sacroiliac joints and spine as well as peripheral joints and skin and mucosal involvement; and a presumed similar genetic background. The discovery in 1973 of the strong association of human leukocyte antigen B27 (HLA-B27) with AS and, to a lesser extent, with other spondyloarthritis (SpA) subgroups strongly supported this concept. As a result of subsequent research findings, including the lack of a genetic association of HLA-B27 with Behçet syndrome and identification of *Tropheryma whippelii* as the causative microbe in Whipple disease, both Behçet syndrome and Whipple disease were excluded from the spondyloarthritides.

In the 1990s the Amor criteria⁷ and the European Spondylarthropathy Study Group (ESSG) classification criteria⁸ were established as classification criteria for the entire group of spondyloarthritides (Table 113.2). The Amor and ESSG criteria took into consideration the fact that some patients have clinical features typical of SpA but cannot be assigned to any one of the specified SpA subgroups (i.e., AS, psoriatic arthritis, reactive arthritis, and arthritis with ulcerative colitis or Crohn disease). This subgroup of patients with so-called undifferentiated SpA became part of the SpA concept and were then classifiable by either set of criteria. Moreover, both the Amor and ESSG criteria underlined the typical characteristics of peripheral arthritis in SpA, which often is asymmetric, oligoarticular, and involves the lower extremity. Although in the 1980s and 1990s the term *spondyloarthropathy* was used, François and colleagues proposed in the mid-1990s that the term *spondyloarthritis* be adopted instead, based on pathologic findings.⁹ The term *spondyloarthritis* underlines the inflammatory nature of these conditions more strongly than does the term *spondyloarthropathy* and is therefore preferred.

Diagnosis and classification of axial spondyloarthritis

The introduction of magnetic resonance imaging (MRI) has revolutionized the imaging of patients with sacroiliitis and has led to new criteria for the diagnosis and classification of SpA. By the use of MRI, acute inflammation of the sacroiliac joints with or without signs of structural damage can be accurately visualized. Active sacroiliitis on MRI has been shown to predict the later appearance of sacroiliitis on radiographs,^{10,11} which adds validity to the finding of inflammation on MRI in early disease. Thus a patient at an early stage of AS typically has clinical symptoms suggestive of AS, such as inflammatory back pain, but may not show sacroiliitis on radiographs.³ In such a patient sacroiliitis may be reliably detectable on MRI, which facilitates earlier diagnosis. Since definite structural damage is not yet visible on radiographs at this stage, it has been proposed that this disease stage be referred to as *nonradiographic axial SpA* (nr-axSpA) rather than *early AS*

(Fig. 113.1).¹² Thus axial SpA encompasses AS and nr-axSpA, and the evolution from nr-axSpA to AS depends on time and on disease severity factors. The concept of axial spondyloarthritis (axSpA) also implies that not all patients will progress to AS. The precise proportion of patients with nr-axSpA who experience disease progression is currently unknown, as are the factors determining the rate of progression. Male gender, the extent of inflammation on MRI, disease duration, and other still-unknown factors play a role. Attempts have been made to provide some guidance on how to establish a diagnosis of nr-axSpA. These include a diagnostic algorithm¹³ as well as a probability approach based on likelihood ratios.¹² Of importance, a combination of typical SpA symptoms and findings is necessary to arrive at a diagnosis. Age at onset in axSpA is usually during the third decade of life. Back pain is the leading symptom, and many but not all patients have the symptom of inflammatory back pain, for which several definitions are available (Table 113.3).¹⁴⁻¹⁶ However, inflammatory back pain alone does not

suffice for making a diagnosis of axSpA because of the low specificity of the symptom (75% to 80%) and the fact that axSpA accounts for no more than 5% of cases of chronic low back pain. The presence of inflammatory back pain alone results in an estimated likelihood of the presence of axSpA of around 16%, regardless of which set of criteria for inflammatory back pain¹⁴⁻¹⁶ is used (see Table 113.3). Rather, a combination of clinical, laboratory (HLA-B27), and imaging (MRI) findings is necessary to arrive at a high enough disease probability.^{12,13} Some patients with nr-axSpA have high disease activity (signs and symptoms) comparable to that of patients with established AS¹⁷ and require effective treatments, including nonsteroidal antiinflammatory drugs and anti-tumor necrosis factor agents, just as do patients with established AS. To better standardize the conduct of clinical trials in patients with nr-axSpA, the Assessment of SpondyloArthritis international Society (ASAS) has developed and validated new classification criteria for axSpA.^{18,19} According to the ASAS classification criteria for axSpA, a patient with chronic back pain and age at onset of less than 45 years can be classified as having axSpA if sacroiliitis is apparent on imaging (radiographs or MRI scans) plus at least one additional SpA feature is present, or, in the absence of sacroiliitis on imaging, if HLA-B27 positivity plus at least two additional SpA features are present (Fig. 113.2). Thus sacroiliitis on MRI scans has been given as much weight as sacroiliitis on radiographs. A preliminary definition of sacroiliitis on MRI scans has also been elaborated based on consensus and will be refined as necessary.²⁰ The new ASAS classification criteria encompass the entire spectrum of SpA patients with predominantly axial manifestations, from nr-axSpA to AS. Of note, the new ASAS classification criteria are intended to be used as classification criteria for clinical trials and are not intended to be used as diagnostic criteria.

Classification of peripheral spondyloarthritis

For peripheral SpA, both the Amor⁷ and ESSG criteria⁸ have been used in the past. New classification criteria for predominantly peripheral SpA were also developed by the ASAS.²¹ The peripheral SpA criteria focus on peripheral arthritis of the SpA type, enthesitis, or dactylitis as entry criterion and are fulfilled if in addition either one or two other SpA features are present (Fig. 113.3). In the original study the new ASAS criteria showed a

TABLE 113.1
Modified New York Criteria for ankylosing spondylitis

Clinical criteria:
1. Low back pain and stiffness for > 3 mo that improves with exercise but is not relieved with rest
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes
3. Limitation of chest expansion relative to normal values corrected for age and sex
Radiologic criterion:
Sacroiliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally
Definite ankylosing spondylitis:
■ The radiologic criterion is associated with at least one clinical criterion.
From van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. <i>Arthritis Rheum</i> 1984;27:361-8.

TABLE 113.2
Criteria for spondyloarthritis (SpA)

Amor criteria ⁷	ESSG criteria ⁸
A. Past or current clinical manifestations	Inflammatory back pain or synovitis
1. Back pain at night and/or back stiffness in the morning (1 point)	■ Asymmetric or
2. Asymmetric oligoarthritis (2 points)	■ Predominantly lower limb
3. Gluteal pain without other details (1 point) or alternating gluteal pain (2 points)	AND
4. Sausage-like digit or toe (2 points)	One or more of the following:
5. Heel pain or other enthesopathy (2 points)	■ Positive family history
6. Iritis (2 points)	■ Psoriasis
7. Nongonococcal urethritis within 1 mo before the onset of arthritis (1 point)	■ Inflammatory bowel disease
8. Acute diarrhea within 1 mo before the onset of arthritis (1 point)	■ Urethritis, cervicitis, or acute diarrhea within 1 mo before arthritis
9. Past or current psoriasis and/or balanitis and/or inflammatory bowel disease (2 points)	■ Buttock pain alternating between right and left gluteal areas
B. Radiographic changes	■ Enthesopathy
10. Sacroiliitis grade 2 or more if bilateral, grade 3 or more if unilateral (3 points)	■ Sacroiliitis (radiography)
C. Predisposing genetic factors	
11. Presence of HLA-B27 antigen and/or family history of ankylosing spondylitis, Reiter syndrome, psoriasis, uveitis, or chronic bowel disease (2 points)	
D. Responsiveness to treatment	
12. Improvement within 48 hours after initiation of a nonsteroidal antiinflammatory drug and/or recurrence within 48 hours after discontinuation of a nonsteroidal antiinflammatory drug (2 points)	
Definite SpA if ≥6 points, probable SpA if 5 points.	
ESSG, European Spondylarthropathy Study Group.	

Fig. 113.1 The concept of axial spondyloarthritis (SpA) comprises nonradiographic axial SpA and ankylosing spondylitis. Note that all patients with AS start as nonradiographic axial SpA but not all patients with nonradiographic axial SpA progress to ankylosing spondylitis. MRI, magnetic resonance imaging. (Adapted with permission from Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005;52:1000-8.)

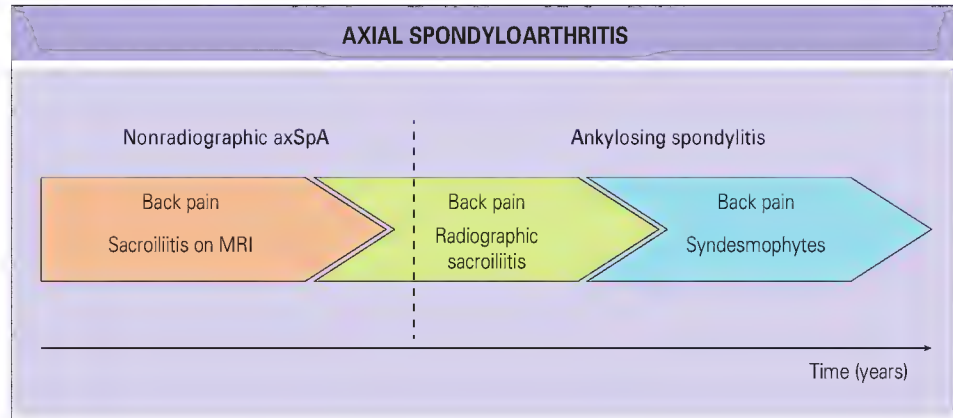


TABLE 113.3
Criteria for inflammatory back pain (IBP)

Calin criteria ¹⁴	Berlin criteria ¹⁵	IBP according to ASAS experts ¹⁶
Age at onset < 40 yr Duration of back pain > 3 mo Insidious onset Morning stiffness Improvement with exercise (at least four of five present)	Morning stiffness > 30 min Improvement with exercise, not with rest Awakening at second half of the night because of pain Alternating buttock pain (at least two of four present)	Age at onset < 40 yr Insidious onset Improvement with exercise No improvement with rest Pain at night (with improvement on rising) (at least four of five present)

ASAS, Assessment of SpondyloArthritis international Society.

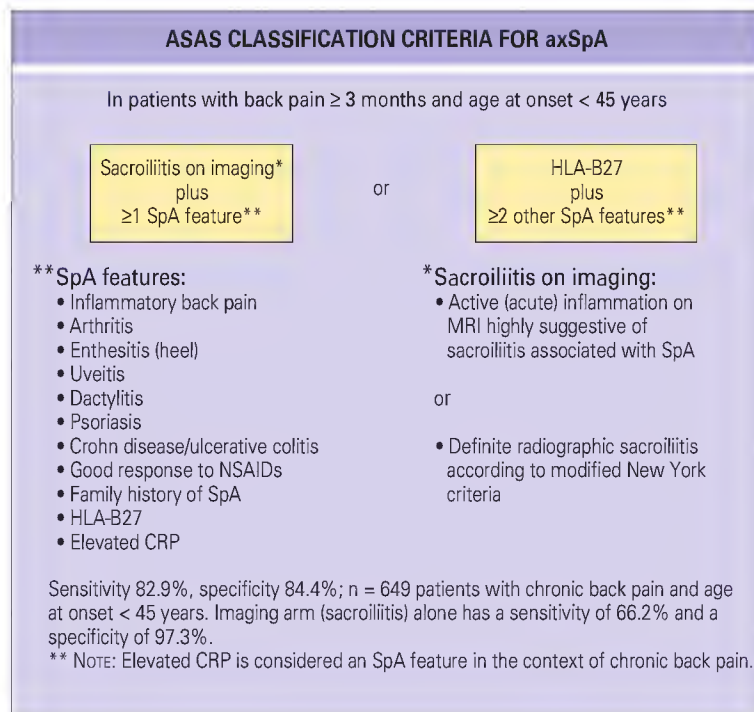


Fig. 113.2 Assessment of SpondyloArthritis international Society (ASAS) endorsed criteria for classifying patients with axial spondyloarthritis (SpA). To be applied in patients with a diagnosis of axial SpA, age at onset less than 45 years and chronic back pain. Patients can be classified either by the imaging arm with sacroiliitis on radiographs or MRI, plus at least one further SpA feature, or by the clinical arm with positivity for HLA-B27 plus at least 2 further SpA features. CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs. (Modified with permission from Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.)

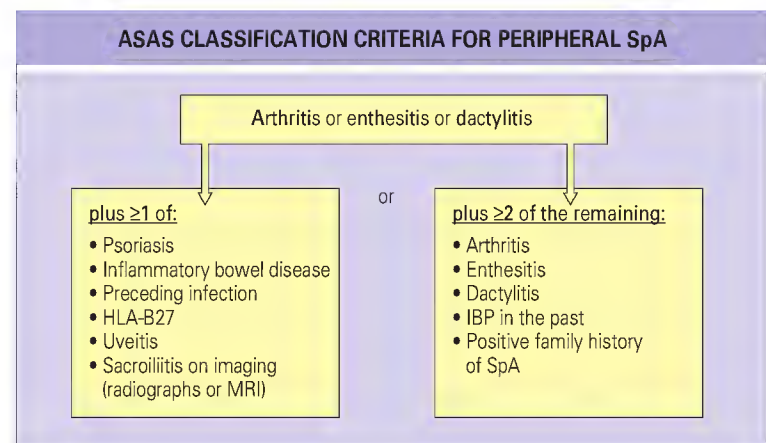


Fig. 113.3 Assessment of SpondyloArthritis international Society (ASAS) endorsed criteria for classifying peripheral spondyloarthritis (SpA). Patients have either peripheral arthritis, enthesitis, or dactylitis with at least one of SpA features shown in the left box or at least two SpA features shown in the right box. IBP, inflammatory back pain; MRI, magnetic resonance imaging. (Modified with permission from Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25-31.)

good balance between sensitivity and specificity and performed better than the Amor and ESSG criteria, particularly with regard to sensitivity, which implies better performance in early disease. Although results from a first validation study²² are clearly promising, further studies in other settings are warranted.

PREVALENCE OF SPONDYLOARTHRITIS

The prevalence of AS has been reported from population studies to vary between 0.1% in the Netherlands and 1.1% to 1.4% in Norway.^{23,24} A blood donor study in Germany estimated a prevalence of AS of 0.55%, taking into account the male-female ratio in AS of 2:1 to 3:1.^{25,26} The incidence of AS

has been reported to be approximately 7.2 per 100,000 adults in the United States, 6.9 per 100,000 adults in Finland, and 7.26 per 100,000 in Norway and appears to have been stable over the past 50 years.²⁷ The incidence and prevalence of AS generally mirror to some extent the frequency of HLA-B27 in the population, which explains the virtual absence of AS in southern Africa, low rates of AS in Japan, higher rates in Norway than in other European countries, and very high rates among the native peoples of the circumpolar arctic and subarctic regions of Eurasia and North America.²⁷ The risk of development of AS in healthy HLA-B27+ subjects has been studied in North America, European countries including Scandinavia, Siberia, and Asia and has been reported to be approximately 6% in various populations (range, 1% to 8%).^{23,24,27} Estimates of the prevalence of the entire group of spondyloarthritides in North America, Germany, France, Greece, and Lithuania range from 0.3% to 1.9%, and therefore are as high as those reported for rheumatoid arthritis.²³⁻³⁰ Again, higher prevalence rates of 2.5% for the entire group of spondyloarthritides have been reported for Alaskan Eskimos.³¹ Within the group of spondyloarthritides it appears that AS and undifferentiated SpA are the two most common subgroups.²⁵

GENETIC FACTORS

The precise etiopathogenesis of AS is still unknown despite extensive research. The role of genes is undisputable, however, because AS has been long known to be highly familial. A family history of AS or other SpA is reported by 7% to 36% of AS patients.¹³ In first-degree relatives of AS patients the risk of developing AS is around 10%. The risk increases to 20% if the relative is HLA-B27+ but decreases to less than 1% if the relative is HLA-B27-.²³ Twin studies have revealed a high degree of heritability with concordance rates of 63% among monozygotic twins and 12% among dizygotic twins, the latter increasing to 23% if both twins are HLA-B27+. From these family studies it has been estimated that more than 90% of the risk of developing AS is genetically determined.³² The strong association of HLA-B27 has been known for more than 40 years; HLA-B27 is found in 80% to 95% of AS patients compared with 6% to 9% of the general populations of Central Europe and North America. Yet the molecular mechanism underlying the strong association between HLA-B27 and AS has not been elucidated. Many of the more common HLA-B27 subtypes such as B*2705, B*2704, and B*2702 are strongly associated with AS. However, two subtypes are less strongly associated with AS: HLA-B*2706, which occurs commonly in Southeast Asia, and HLA-B*2709, which can be found in Sardinia. Again, the mechanism behind this differential association is unclear but may relate to peptide binding and/or recognition characteristics. HLA-B27 is associated with a younger age at onset¹⁷ and predisposes to axial involvement in SpA because the frequency of HLA-B27 is highest in AS, whereas in peripheral SpA, such as reactive arthritis or undifferentiated SpA, the frequency of HLA-B27 ranges from 20% to 70%. In addition to HLA-B27 two other major AS-related genes have been recently identified and replicated: those for the

interleukin-23 receptor and endoplasmic reticulum aminopeptidase-1 (ERAP1), formerly known as *type 1 tumor necrosis factor receptor-shedding aminopeptidase regulator-1* (ARTS1). Both genes are of great pathophysiologic interest because they encode proteins involved in inflammatory pathways and/or peptide presentation.^{33,34} Of note, ERAP1 appears to be involved in peptide handling in a HLA-B27 dependent fashion.³⁵

IMPACT OF GENDER

Previously, AS was considered a predominantly male disease with a male-female ratio of 9:1. In more recent studies, this ratio has been found to be 2:1 to 3:1, which may be due to higher awareness of the occurrence of the disease in females and better access to diagnostic tests in general. Large epidemiologic studies revealed that females with AS are slightly younger at disease onset by 1 to 2 years, on average, but are diagnosed later than males, again on average, by 1 to 2 years.³⁶⁻³⁸ Moreover, females with AS have, on average, less ankylosis of the spine as assessed by radiography in long-term follow-up studies and therefore less damage.^{36,39,40} It is thus assumed that females with AS on average have a milder form of the disease than their male counterparts.

In epidemiologic studies of undifferentiated SpA/nr-axSpA a male-female ratio of 1:1 is usually found,^{17,41,42} which obviously contrasts with the male-female ratio of 2:1 to 3:1 in AS. These findings suggest that male gender predisposes to structural damage, including ankylosis of the sacroiliac joints and spine as detected by radiography. This view is supported by recent data from an inception cohort of patients with axSpA, including patients with nr-axSpA and patients with AS, which clearly showed that male gender was significantly associated with the presence of radiographic sacroiliitis.¹⁷ Along this line, an earlier study in Alaskan Eskimos with SpA revealed that males were more likely to have ankylosis of the sacroiliac joints and advanced spinal mobility restrictions.³⁸ Clearly, more research is needed to study the role of gender and other factors for progression from nr-axSpA to AS in axSpA.

CONCLUSION

In various populations the entire group of spondyloarthritides occurs in 0.3% to 1.9% of the population and is as frequent as rheumatoid arthritis. Genes, in particular HLA-B27, have an important role in SpA. The presence of HLA-B27 is associated with an early age at onset and involvement of the axial skeleton. Great advances have been made in better characterizing the early stage of AS. The term *axial spondyloarthritis* is meant to function as an umbrella for all SpA with predominantly involvement of the axial skeleton, independent of the presence of structural damage on radiographs. The new ASAS classification criteria for axSpA are applicable not only to patients with AS but also to patients with active sacroiliitis on MRI without definite structural damage, which facilitates studies and clinical trials in early axSpA.

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Clinical features of axial spondyloarthritis

■ LIANNE S. GENSLER

- Axial spondyloarthritis is a chronic systemic inflammatory rheumatic disorder with a predilection for axial skeletal involvement and inflammation at sites of bony insertions of tendons and ligaments (enthesitis).
- Sacroiliitis is the hallmark of the disease. There is a strong genetic predisposition associated with HLA-B27.
- Clinical manifestations include chronic inflammatory low back pain and stiffness as well as limitation of spinal mobility and chest expansion. Acute anterior uveitis or other less common extraarticular manifestations occur in some patients.
- There is an association with psoriasis, chronic inflammatory bowel disease, and reactive arthritis in some patients.
- Radiographic findings are characteristic of the disease, though this can take years to show up.
- Generally there is good symptomatic response to antiinflammatory doses of nonsteroidal antiinflammatory drugs.

INTRODUCTION

Ankylosing spondylitis (AS), perhaps the best known and characterized of the spondyloarthritis (SpA) family, is a chronic inflammatory disease affecting the axial skeleton, the entheses, and occasionally the peripheral joints. The hallmark of AS is inflammatory back pain (see later) associated with radiographic sacroiliitis and often spondylitis. In addition to the axial, enthesal, and appendicular skeletal involvement, AS can also be associated with extraarticular manifestations, especially uveitis and, less commonly, cardiac, pulmonary, and renal disease. AS can occur as a primary disorder or can complicate other types of SpA, especially in the setting of psoriasis and inflammatory bowel disease (IBD). A broader term, *axial spondyloarthritis*, has been adopted to describe all forms of SpA that affect the axial joints. This includes not only AS that meets the 1984 modified New York criteria¹ but also nonradiographic disease.²

CLINICAL FEATURES

Inflammatory back pain

The first symptoms of AS usually appear in adolescence to early adulthood and almost invariably start before the age of 45.³⁻⁶ The most characteristic presentation is that of inflammatory back pain, which accounts for about 15% of all types of chronic low back pain (Table 114.1).⁷⁻¹⁰ This is dull chronic low back pain (lasting longer than 3 months), insidious in onset, usually in the buttocks (or hips, as interpreted by the patient). It is worse in the early part of the morning, when it is associated with morning stiffness lasting at least 30 minutes; is relieved with exercise or activity (i.e., limbering up) and/or a hot shower; is worsened by rest; and usually is improved by the use of nonsteroidal antiinflammatory drugs (NSAIDs).⁸ In fact, a good response of back pain to NSAIDs within 48 hours is a good predictor of the presence of inflammatory low back pain and of axial SpA, with a sensitivity of 75%.^{5,11} Although the pain may be unilateral or intermittent at first (in

fact, alternating buttock pain is a cardinal feature of the disease), it usually becomes persistent and bilateral in the lower lumbar area.⁷⁻¹⁰

Occasionally, the first symptom comes from extraarticular sources, such as acute anterior uveitis or enthesitis; in fact, with disease onset in childhood, peripheral joint and enthesal manifestations figure prominently.²⁻⁵ Bone tenderness, especially over enthesal points (e.g., Achilles tendon insertion into the calcaneus), may also be a complaint in some AS patients.² Neck pain and stiffness is characteristic of advanced disease, although it can be a dominant feature in early AS in women.² In later disease, these gender differences in cervical spine involvement do not appear to be maintained.¹¹

Hip and shoulder involvement

The shoulders and hips are considered axial joints, and their involvement occurs in up to 50% of patients and is more common than involvement of the peripheral joints.²⁻⁴ In the hips, there may be progressive flexion deformity and eventual destruction of the joint.¹² Destructive changes in the hips are slowly progressive and are associated with marked deformity of the femoral head before the development of ankylosis. More commonly, however, nondestructive symmetric loss of the hip joint space is associated with a fairly characteristic osteophytic collar that forms at the junction of the femoral head and the neck.¹² Hip disease in AS is a marker of more severe disease in adults.¹³ There is a higher prevalence of hip involvement and greater need for hip arthroplasty in juvenile-onset AS.¹⁴ In the shoulders, joint space narrowing and erosive changes in the superolateral aspect of the humeral head, with eventual ankylosis, can occur. Chronic rotator cuff tears can also be seen in AS patients.¹⁵

Peripheral arthritis

Peripheral arthritis in joints other than the hips and shoulders is less common in AS, but when it occurs, it is usually an asymmetric oligoarthritis presenting predominantly in the lower extremities.¹⁶ When it develops early in the disease course, it is a predictor of more aggressive disease.¹⁶ It appears to be more common in women¹¹ and juvenile-onset AS.¹⁴

Chest wall involvement

With involvement of the thoracic spine (including costovertebral joints) and occurrence of enthesopathy at the costosternal and manubriosternal joints, patients may experience chest pain especially on coughing or sneezing, which sometimes is characterized as “pleuritic.”³⁻⁵ Occasionally, chest pain may be the presenting symptom of AS. Subsequently the costovertebral joints may fuse, which diminishes chest expansion and can lead to restrictive lung disease of a mechanical nature.

Enthesitis

The enthesitis is the insertion of a tendon, ligament, capsule, or fascia into bone. Enthesitis is inflammation of the origin and insertion of ligaments, tendons, aponeuroses, annulus fibrosis, or joint capsules and is a characteristic feature of SpA.²⁻⁶ Inflammation may occur at any enthesitis in AS, although it is most common in the entheses of the lower limbs, especially in the calcaneus at the insertion of the Achilles tendon and the plantar fascia. Pathologic examination of enthesitis in AS demonstrates local inflammation, fibrosis, erosion, and ossification.¹⁷⁻¹⁹ Bursitis and synovitis may also occur adjacent to the entheses, and it has been postulated that the entheses may be the initial site of joint inflammation in AS.¹⁷⁻¹⁹

TABLE 114.1
Differentiation of inflammatory versus mechanical low back pain (LBP)

	Inflammatory LBP	Mechanical LBP
Age of onset	<40 yr	Any age (usually later)
Type of onset	Insidious	Acute
Symptom duration	>3 mo	<4 wk
Morning stiffness	≥30 min	<30 min
Nocturnal pain	Common	Absent
Effect of exercise	Improvement	Exacerbation
Sacroiliac joint tenderness	Frequent	Absent
Back mobility	Loss in all planes (late finding)	Abnormal flexion
Chest expansion	Often decreased	Normal
Neurologic deficits	Unusual	Possible

Physical examination findings

The main finding on physical examination in patients with AS is loss of spinal mobility; however, this can be a late finding.² Limitation of flexion and extension of the lumbar spine as well as chest expansion is seen. Sacroiliac joint pain can also be elicited with direct pressure or movement and may be elicited in the acute phase of the disease; however, this finding lacks sensitivity.² Peripheral joint or enthesal inflammation can also be observed. Lumbar lordosis may be lost, atrophy of the buttocks can be present, exaggerated kyphosis may be observed, and the neck may stoop forward.² Resulting flexion contractures of the hips and knees may occur, with significant morbidity and disability.^{2,4} Mild to moderate reduction of chest expansion is often detectable in an early stage of AS.^{2,4}

Three physical measurements have been validated and recommended by the Assessment of SpondyloArthritis international Society (ASAS) as useful for evaluating patients with AS specifically and those with inflammatory back pain in general.²⁰⁻²² A modification of the Schober test is measured as the increase in distance upon maximal forward spinal flexion with extended knees of a 10-cm segment drawn on the patient's back with the inferior mark at the level of the superior aspect of the dimples of Venus. The measured distance should increase from 10 cm to at least 13.5 cm in an adult; however, this value has been recently brought into question in at least two studies suggesting that the normal reference range is actually lower (see Fig. 118.4d).^{23,24} Chest wall expansion with inspiration is measured with a tape measure placed circumferentially around the chest wall at the 4th intercostal space in men or the xiphisternum in women. Normal chest expansion in an adult has been reported to be more than 5 cm, although this may vary with age and gender. A more recent population-based study suggests lower normative values.²³ To measure the occiput-to-wall distance (a measure of kyphosis), the patient stands with heels and buttocks touching the wall behind and with the knees straight. The patient is asked how far back he or she can move the head while keeping the chin in the normal, tucked position. The distance between the posterior convexity of the occiput and the wall is measured to the nearest 0.1 cm. The better of two attempts is recorded. Any value greater than zero is regarded as abnormal. This does not appear to be true in patients older than age 50.²³ Tragus-to-wall distance is also a measure of kyphosis and is used as part of the composite Bath Ankylosing Spondylitis Metrology Index (BASMI) but is problematic because there is variation in tragus location across individuals.

Another measure that is used more and more commonly is the degree of lumbar lateral bending. Here the patient stands with the heels and back against the wall. There is no flexion of the knees nor bending forward. The distance between the patient's middle fingertip and the floor is measured. The patient then bends sideways, keeping the back against the wall without bending the knees or lifting the heels. A second reading is taken and the difference between the two is recorded. The best of two tries is recorded for left and right. The mean of left and right values gives the final result (in centimeters to the nearest 0.1 cm). Normal value is more than 10 cm.

Extraarticular manifestations
Uveitis

The anterior portion of the uvea consists of the iris and ciliary body, whereas the posterior portion is known as the *choroid*. Inflammation of the anterior

TABLE 114.2
Comparison of ankylosing spondylitis and related disorders

Feature	Ankylosing spondylitis	Psoriatic arthritis	Reactive arthritis	Enteropathic arthropathy
Gender (male:female)	2-3:1	1:1	1:1	1:1
Age of onset	<40 yr	35-55 yr	20-40 yr	Any age
Sacroiliitis or spondylitis	100%	~20%	~40%	<20%
Symmetry of sacroiliitis	Symmetric	Asymmetric	Asymmetric	Symmetric
Peripheral arthritis	~25%	95%	90%	5%-20%
Distribution	Axial and lower limbs	Variable	Lower limbs	Variable
HLA-B27 positivity	85%-95%	25%-60%*	30%-70%	7%-70%†
Uveitis	0%-40%	~20%	~50%	<15%

*60% when spondylitis present.
†70% when spondylitis present.

uveal tract is known as *anterior uveitis* or *iritis*. When the adjacent ciliary body is also inflamed, the process is known as *iridocyclitis*. Acute anterior uveitis (AAU) is the typical uveitis associated with AS.

AAU occurs in about 30% to 40% of patients with AS,²⁵⁻³⁰ of whom approximately 90% are HLA-B27 positive. Of patients with recurrent unilateral AAU, 50% are HLA B27 positive and most of these have some form of SpA (Table 114.2).²⁵⁻³⁰ Typically, AAU presents unilaterally with sudden onset and may be recurrent. Symptoms may include redness, pain, blurred vision, increased lacrimation, photophobia, and miosis. The diagnosis is characteristically confirmed by slit-lamp examination, which is also useful in monitoring response to treatment.

Prognosis is favorable in AAU, with resolution of symptoms within a few weeks. If treatment is delayed or inadequate, however, complications can occur; these include anterior synechiae (adherence of the iris to the cornea) and posterior synechiae (adherence of the iris to the lens), which can lead to cataracts and cystoid macular edema.^{29,30} Increased intraocular pressure can be seen. Macular edema has been shown to be the main factor that determines visual outcome in cases of uveitis.^{29,30} Although AAU is the most common uveitis associated with AS, posterior uveitis has been reported and tends to be more severe, especially in those with coexistent IBD.³⁰

Gastrointestinal manifestations

Up to 50% of patients with AS have both macroscopic and microscopic ileal and cecal inflammation seen on ileocolonoscopy.^{31,32} Moreover, two thirds of patients with undifferentiated SpA have histologically determined gut inflammation. Gut inflammation in AS appears to be immunologically related to that seen in Crohn disease. Those with chronic inflammatory lesions tend to have more severe erosive peripheral and hip arthritis.³³ Risk factors for evolution to overt IBD include the presence of chronic inflammatory gut lesions, persistence of elevated levels of inflammatory serum markers, and absence of HLA-B27 in the presence of sacroiliitis.³³ Patients with established IBD can have asymptomatic sacroiliitis, and HLA-B27 status has less predictive value in this group of patients.³²

Cardiac manifestations

The classic cardiac abnormalities in AS are aortitis, aortic regurgitation (AR), and conduction abnormalities (especially first-degree atrioventricular block).³⁴⁻³⁸ HLA-B27 appears to be an important genetic risk factor for cardiac conditions.³⁵ AR is well characterized and distinguished from aortic valvular dysfunction in other disorders.³⁵ Three factors contribute to the development of incompetent aortic valves: dilation of the aortic root, fibrotic thickening and downward retraction of the bases of the cusps, and inward rolling of the edges or margins of the cusps.³⁵ AR is present in 2% to 10% of patients with AS and increases in likelihood with longer disease duration.

Cardiac conduction abnormalities, including atrioventricular and intra-ventricular blocks, have been regarded as the most common cardiac complication in patients with AS.³⁵ Complete heart block has been found in 1%

to 9% of patients with AS.³⁵ Electrophysiologic studies show that the preferential level of block is in the atrioventricular node itself, in contrast with most cases of acquired complete heart block, in which 80% are within or below the bundle of His.³⁵

More common in AS is ischemic heart disease, peripheral vascular disease, and congestive heart failure with prevalence ratios of 1.2, 1.6, and 1.8, respectively, compared with control subjects matched for age, gender, and geographic location.³⁷ In a population study, both cerebrovascular and cardiovascular events were more common in AS. The excess risk was attributable to the younger AS patients.³⁸

Pulmonary manifestations

Involvement of the lung parenchyma is a well-recognized manifestation of AS.³⁹⁻⁴² The reported prevalence of pleuropulmonary involvement in AS is variable depending on the technique used to assess it. It is rare when assessed by plain radiography (1% to 2% of cases) but common when assessed by high-resolution computed tomography (HRCT).³⁹⁻⁴² The most frequently recognized manifestations are upper lobe fibrosis, mycetoma formation, and pleural thickening. Fusion of the costovertebral joints caused by inflammation and ankylosis of the thoracic spine can lead to restrictive ventilatory impairment on pulmonary function testing.⁴²

Pulmonary abnormalities on chest radiography consist mainly of irregular linear or reticulonodular opacities and cyst formation. The upper lobe fibrosis tends to be progressive. Another common finding is the presence of bilateral symmetric apical pleural thickening. The most common findings described on HRCT are linear opacities and bronchial wall thickening. The clinical implications of these observations remain unclear because lung involvement in AS is usually asymptomatic. Cigarette smoking in the setting of pulmonary fibrosis may increase the risk of spontaneous pneumothorax in AS.⁴³ There appears to be a higher prevalence of obstructive sleep apnea in AS patients compared with the general population.⁴⁴

Renal manifestations

Renal involvement in AS may include secondary amyloidosis (AA type), NSAID nephropathy, and glomerulonephritis.⁴⁵⁻⁴⁷ Renal amyloidosis is the most common cause of renal involvement in AS, occurring in 4% to 9% of AS patients; it is usually a complication of long-standing untreated disease and is associated with peripheral joint involvement, elevated erythrocyte sedimentation rate (ESR), and hypergammaglobulinemia.⁴⁶ Immunoglobulin A (IgA) nephropathy has been well described, although its true prevalence is unknown.⁴⁵⁻⁴⁷ It has been suggested that IgA nephropathy in AS patients is part of the disease spectrum and may indicate a common pathogenic mechanism.^{45,46} NSAID nephrotoxicity may result in interstitial nephritis with nephrotic-range proteinuria and/or acute renal failure.^{45,46} These manifestations usually occur in older individuals after long-term NSAID therapy and seem to be reversible with discontinuation of the NSAID.⁴⁶

Osteoporosis

Measurement of bone mineral density (BMD) in patients with spondylitis is complicated by false increases in spinal BMD from ossification, which has led some to recommend the use of quantitative computed tomography over standard dual energy x-ray absorptiometry (DEXA) for BMD measurements in AS patients. Others have suggested that lateral and volumetric DEXA may be more sensitive.⁴⁸ Nevertheless, up to half of patients with long-standing AS have been reported to have low BMD or osteoporosis.^{49,50} Decreases in BMD can be seen not only in the spine but also in the femoral neck by DEXA (which may be a more reliable measure).⁴⁹⁻⁵² It has been noted that osteoporosis is related to disease activity as measured by ESR, C-reactive protein (CRP) level, and BASDAI.⁵⁰ It has also been associated with older age, longer disease duration, limited metrology, and low body mass index.⁴⁹ Even in studies of disease of short duration (less than 10 years), low BMD is prevalent.⁵² The cause of osteoporosis in AS is still not completely understood, although treatment factors and decreased mobility or physical activity may lead to its development.⁴⁹ Histologic examinations point to an osteoclast-osteoblast imbalance.⁵⁰ It has also been shown that the vitamin D receptor gene may be involved in BMD differences, bone metabolism, and inflammatory processes in AS.⁵⁰

Spondylodiskitis and spinal fractures

An uncommon but well-recognized complication of AS is spondylodiskitis, a destructive diskovertebral lesion also called *Andersson lesion*. Typically, these lesions are more common in the thoracic and lumbar spine, sometimes with multilevel involvement⁵³⁻⁵⁵; however, cervical spondylodiskitis has been reported.⁵⁶ Pain and tenderness localized to the affected disk are the most common presenting features of spondylodiskitis, although it can be

asymptomatic and only detected on routine radiographic examination many years later.⁵³⁻⁵⁵ Spondylodiskitis usually occurs at an advanced stage of AS in the form of an erosive condition related to both mechanical factors and osteoporosis.^{54,55} However, early spondylodiskitis can occur as a result of the inflammatory process.⁵³⁻⁵⁵ Patients may or may not give a history of preceding trauma.⁵³⁻⁵⁶

The histologic appearance of these lesions can vary depending on the phase of the disease process.⁵⁶ During the initial inflammatory phase, there is marked lymphocytic infiltration. During the healing phase, reactive new bone formation with less inflammation is seen. Advanced lesions may show pseudoarthrosis with hemorrhage, fibrous tissue, callus formation, and sclerosis of the adjacent vertebral bone with few inflammatory cells.⁵⁶

Even trivial falls can be catastrophic for AS patients, who are at risk of spinal fractures due to their spinal rigidity and osteoporosis. The estimated prevalence of vertebral fractures in AS varies from 4% to 18%.⁵⁷ Fractures through the disk space, the weakest point in the ankylosed spine, are most common, with the cervical spine being the most frequently affected region, followed by the thoracolumbar junction.⁵⁸ Fractures may or may not be complicated by injury to the spinal cord, which can range from mild sensory loss to quadriplegia.^{57,59,60} One study found spinal fractures to be more frequent in AS patients with peripheral arthritis than in patients with only axial involvement.⁵⁸

Atlantoaxial subluxation

Spontaneous atlantoaxial subluxation is a well-recognized complication affecting about 2% of patients with AS, presenting with and without signs of spinal cord compression.^{61,62} The causes of atlantoaxial subluxation may be multifactorial, including transverse ligament damage by a periodontoid proliferative pannus or sequelae of ossification of the anterior and posterior longitudinal ligaments, associated inflammatory lesions (cervical spine osteoarthritis, atlantodental synovitis, erosions of the dens and adjacent ligaments), and physical stresses (kyphosis of the dorsal spine and weight of the head at the C1-C2 level).⁶¹

Neurologic manifestations

Neurologic involvement in AS is most often related to spinal fracture, atlantoaxial subluxation, or cauda equina syndrome. The cauda equina syndrome in AS is characterized by a slow, insidious progression and a high incidence of dural ectasia, although a rapid onset secondary to an event has been reported.^{63,64} It tends to be a late manifestation of AS, often when the disease is no longer active.⁶⁴ The prevalence of neurologic findings in cauda equina syndrome in AS is very high, and it presents with a prodrome of sensory, motor, or reflex loss before the progression to sphincter disturbance.⁶³ About half of patients have pain in the rectum or lower limbs that is presumably neurogenic in origin.⁶⁴ The pathophysiology is thought to include arachnoiditis and chronic inflammatory reaction, which may result in formation of dural ectasias and a slow progression of neurologic deficits.^{63,64} Another possible mechanism is reduced compliance and expansibility of the caudal sac resulting in excessive cerebrospinal fluid pulse pressure that over the years leads to a capacious caudal sac, enlarging arachnoid diverticula, secondary erosion into bone, and potential lumbosacral nerve root injury.⁶⁴ Tumor necrosis factor inhibitors have been used with success according to case reports.⁶⁵ Case reports have also been published describing the occurrence of AS with a multiple sclerosis–like syndrome and transverse myelitis, although the association is not conclusive.^{66,67}

Fatigue and psychosocial manifestations

Fatigue is a common problem in patients with AS and seems to be associated with more severe disease.^{68,69} Sleep disturbance has also been reported to occur in as many as nearly 81% of female AS patients and 50% of male AS patients. The disturbance is closely related to pain during the night characteristic of active disease.⁶⁸ A high level of depressive symptoms has been reported in approximately one third of patients with AS, with women reporting more depression than men.^{68,69} Pain was found to be a major determinant of depression in women but was of lesser importance in men.⁷⁰ In one study, self-reported measures of disease activity and mental health contributed significantly to explain fatigue, whereas clinical measures of inflammation and joint mobility did not.⁶⁹

Ankylosing spondylitis in women

AS may not be as severe in women as it is in men and may present with isolated neck pain in the absence of typical back pain.³ There tends to be a greater delay in the diagnosis of AS in women compared with men.³ Women tend to have less severe involvement of the spine with peripheral joint involvement.¹¹ After adjustment for degree of radiographic damage, women

appear to have worse functional outcomes than men.¹¹ A large review of the impact of AS on reproductive events in women concluded that AS did not adversely affect the ability to conceive, pregnancy outcome, or neonatal health. The disease did have an adverse effect, however, on the ability of the AS patient to cope as a mother and caregiver. Active disease at conception was a predictor of a postpartum flare.

INVESTIGATIONS

The most useful investigation in AS is musculoskeletal imaging, which is described in detail in Chapter 40, although some laboratory tests can be informative.

Data on the correlation of ESR and CRP level with disease activity in AS show ambiguous results, although most studies suggest that CRP performs better. A literature review examining the validity of ESR and CRP in AS concluded that ESR and CRP level do not comprehensively represent the disease process and thus do not have the same content validity as in rheumatoid arthritis. Generally speaking, it is felt that AS patients with peripheral joint involvement or with IBD, rather than those with axial disease, tend to have elevated ESR and CRP levels.^{71,72} However, a normal ESR and/or CRP level do not exclude the presence of clinically active AS.

A mild normochromic normocytic anemia may be detected.³ In severe disease alkaline phosphatase level may be elevated.³ Elevated serum IgA levels are common.³ Synovial fluid does not differ in appearance or cytologic findings from that in any inflammatory joint disease.³

DIAGNOSIS AND CLASSIFICATION

In most cases, AS is largely diagnosed, or at least initially suspected, on clinical grounds. There are no diagnostic criteria for AS, although there are recommended diagnostic algorithms.^{73,74} Classification criteria for AS and the larger category of SpA are reviewed in Chapter 113.^{1,75-77}

Natural history

Although AS is a chronic condition, it can have a variable course. Poor prognostic factors include hip disease, and risks of progression include elevation of inflammatory markers, smoking, and radiographic damage in the spine.^{78,79}

MEASURES OF ANKYLOSING SPONDYLITIS ACTIVITY AND SEVERITY

A number of measures have been developed to assess disease status in AS and are summarized in Box 114.1, including measures of disease activity, functional impairment, and quality of life. These instruments have been extensively validated, are easy to administer in clinical practice, and have been shown to perform well in clinical trials.

DISABILITY AND SOCIOECONOMIC IMPACT

Significant risk factors for work disability identified in several studies include older age, longer disease duration, lower level of education, reduced physical functioning, pain, and employment in more physically demanding

BOX 114.1 MEASURES OF DISEASE IN ANKYLOSING SPONDYLITIS

Disease activity

Bath Ankylosing Spondylitis Disease Activity Index⁸⁶

Ankylosing Spondylitis Disease Activity Score⁸⁷

Patient and physician global assessments

Function

Bath Ankylosing Spondylitis Functional Index⁸⁸

Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S)⁸⁹

Physical examination

Modification of the Schober test (lumbar flexion)⁹⁰

Chest expansion⁹⁰

Occiput-to-wall distance or tragus-to-wall distance⁹⁰

Lateral bending⁹⁰

Bath Ankylosing Spondylitis Metrometry Index⁹⁰

Cervical rotation⁹⁰

Intermalleolar distance⁹⁰

Quality of life

Medical Outcome Study Short Form-36 (MOS-SF-36)

Ankylosing Spondylitis Quality of Life Index⁹¹

jobs.^{3,80-83} Prolonged standing at work or exposure to cold conditions are risk factors for disability.³ Patients with peripheral joint involvement are more likely to take sick leaves than those with only axial manifestations.³

Patients with AS have an overall frequency of disability and economic costs similar to those of patients with rheumatoid arthritis.⁸⁰⁻⁸³ The impact of agents such as anti-tumor necrosis factor drugs on the natural history of this disease appears promising, but their benefit remains to be confirmed.

LIFE SPAN

Survival may be reduced among patients with AS compared with the general population, and the standardized mortality ratio is higher in men than in women.⁸⁷ Causes of death include heart disease, cerebrovascular disease, malignancy, renal failure, pneumonia, suicide, and alcohol-related death, but the most common cause of death is cardiovascular disease.⁸⁴ Mortality risk appears to correlate with disease activity.⁸⁵

CONCLUSION

Axial spondyloarthritis and ankylosing spondylitis are regarded as the prototype and perhaps the most common type of SpA and are best characterized by the presence of chronic inflammatory back pain in the setting of radiographic sacroiliitis and frequently spondylitis and spinal limitation. In addition, common features of other types of SpA, both musculoskeletal (enthesitis and peripheral arthritis) and nonmusculoskeletal (uveitis and, less commonly, mucocutaneous, gastrointestinal, pulmonary and cardiac disease), are seen. Overall, it appears to be as disabling as rheumatoid arthritis, although advances in assessment as well as in imaging and treatment (detailed elsewhere) may greatly affect how and when it is diagnosed and treated and, ultimately, its natural history.

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Etiology, pathogenesis, and pathophysiology of ankylosing spondylitis

■ DOMINIQUE BAETEN

- The etiopathology of ankylosing spondylitis (AS), the prototypic form of axial spondyloarthritis (SpA), may overlap only partially with that of peripheral SpA.
- HLA-B27 is the major susceptibility factor and is directly involved in the pathogenesis of disease, although it contributes only 20% to 30% of the entire genetic risk.
- HLA-B27 may contribute to disease pathogenesis through different mechanisms, including antigen presentation to CD8 T cells, direct stimulation of natural killer cells by HLA-B27 heavy-chain homodimers, and induction of an unfolded protein response in myeloid cells.
- Emerging evidence, including data on the non-antigen-dependent roles of HLA-B27 and the therapeutic failure of T- and/or B-cell-targeted therapies in AS, argues for a prominent role of innate immune cells rather than (autoreactive) lymphocytes.
- The role of bacterial and mechanical stress in disease induction and tissue predilection is consistent with a prominent autoinflammatory component.
- Tumor necrosis factor, interleukin-1 (IL-1), and IL-23/IL-17 are the major proinflammatory cytokine axes in SpA, with innate immune cells serving as the major source of these cytokines.
- Histopathologic examination of axial and peripheral lesions identifies specific changes in both innate and stromal cell populations, and a combination of bone destruction and new bone formation.
- Progression of new bone formation, an essential structural feature of AS, is partially disconnected from inflammation and bone destruction. Both BMP and Wnt signaling are important molecular pathways of osteoproliferation, but the factors leading to abnormal activation of these pathways remain unknown.

INTRODUCTION

The concept of spondyloarthritis (SpA) includes a number of associated disorders with common genetic, radiologic, and clinical features. Accordingly, the phenotypic presentation of SpA is diverse, which has led to a clinical subclassification into different subgroups depending on the symptoms that prevail: (1) ankylosing spondylitis (AS), in which spinal inflammation is predominant; (2) psoriatic arthritis, in which patients have cutaneous psoriasis together with spinal inflammation and/or arthritis; (3) reactive arthritis, in which an episode of acute infection of the gastrointestinal or urogenital tract is followed by spondylitis and/or arthritis; (4) inflammatory bowel disease-associated SpA, in which overt gastrointestinal inflammation is accompanied by spondylitis and/or peripheral arthritis; and (5) undifferentiated SpA, in which patients have SpA without any other specific symptoms that would allow a classification into the previously mentioned categories.

Although this phenotypic subclassification has obvious advantages in clinical practice and clinical research, one can question the degree to which it reflects different pathologic and pathogenic entities. First, the different conditions can occur consecutively in the same patient. Second, there are

often overlapping syndromes in which it is impossible to discriminate one specific subtype. Third, the different subtypes often affect different members of the same family. This familial aggregation can be explained largely by an important genetic component in the pathogenesis of the disease apart from the presence of similar environmental factors. This is illustrated by the fact that first-degree relatives of SpA patients have a risk of developing SpA that is 40-fold higher than that in the general population. Genetic studies in multiplex families have indicated that the clinical subclassification of SpA is not related to the underlying pathogenic mechanisms of the disease. More specifically, there is a random presentation of different clinical subtypes within multiplex families, which indicates that the genetic background does not account for the clinical subtypes but for SpA as a whole. The only exception to this rule is inflammatory bowel disease-associated SpA.¹

More recently, it has been proposed that SpA be subdivided based on the predominant musculoskeletal manifestation.^{2,3} In this classification, patients with symptoms arising primarily from inflammation of the axial skeleton are separated from patients in whom peripheral arthritis is the prevailing symptom. There is also evidence that the pathophysiologic mechanisms underlying peripheral SpA are distinct from those involved in exclusively axial SpA. First, patients with peripheral arthritis were found to be clustered in specific families in a study that included 329 SpA patients belonging to multiplex families.⁴ Because this was independent of the HLA-B27 status of the family members and disease duration, it strongly suggested that the development of peripheral synovitis is linked to the specific genetic background of the patients. Second, immunopathologic studies showed differences between axial and peripheral SpA. For example, matrix metalloproteinase-3 levels are specifically elevated in peripheral SpA⁵ and interleukin-17 (IL-17) is expressed mainly by myeloperoxidase (MPO)-positive cells in axial disease but by mast cells in peripheral synovitis.^{6,7} Third, therapeutic studies demonstrated a differential effect of non-steroidal antiinflammatory drugs (NSAIDs)⁸ and sulfasalazine⁹ in axial and in peripheral SpA.

In keeping with this genetic, pathophysiologic, and therapeutic evidence, the discussion here emphasizes the pathologic and pathophysiologic features of axial and peripheral SpA rather than using the phenotypic subclassification.

HLA-B27 AND THE ROLE OF T LYMPHOCYTES

The most important genetic risk factor for SpA is HLA-B27. The pathogenic role of this molecule has been formally demonstrated by the fact that overexpression in the rat leads to spontaneous SpA-like disease characterized by colitis, peripheral arthritis, spondylitis, uveitis, skin lesions, and orchitis.¹⁰ In support of the concept that SpA is one single disorder with different phenotypic manifestations, these rats display all the different features of human SpA, and the precise phenotype of the disease can be modulated by either environmental factors or additional genetic modifications. For example, the rats do not display colitis and peripheral arthritis in germfree conditions¹¹ and have more pronounced arthritis and spondylitis, but not colitis, in the presence of additional β_2 -microglobulin overexpression.¹²

Despite almost 40 years of intensive research, however, the precise role of HLA-B27 in SpA pathogenesis is still unknown. Three major hypotheses have been suggested (Fig. 115.1). The first and most logical explanation is the arthritogenic peptide hypothesis. This hypothesis is related to the antigen-presenting function of the HLA molecules and proposes that a specific peptide is presented in the context of HLA-B27, but not other HLA

molecules, and is presented to cytotoxic T lymphocytes, and that these cytotoxic T cells drive the pathologic process in SpA. This peptide could originate from bacteria, as suggested by the facts that gastrointestinal infections precede arthritis in the reactive arthritis subform of SpA and that May and associates¹³ demonstrated the clonal expansion of the same T-cell clones in the gut and joint of a patient with reactive arthritis. This suggests that the bacterial antigen-specific T-cell clones may recirculate to the joint and eventually be triggered by cross-reactive self-peptides derived, for example, from cartilage.¹⁴ The arthritogenic peptide hypothesis has been severely challenged, however, by two different studies demonstrating that CD8⁺ T cells do not appear to be crucial players in the HLA-B27 transgenic rat model.^{15,16} Moreover, recent observations indicate that antigen-presenting cells from HLA-B27 transgenic rats in fact show defective stimulation of naive helper T cells because of impaired engagement of the costimulatory molecules.^{17,18} In more general terms, a series of observations questions the role of T cells and the acquired immune system in SpA. First, individuals with SpA lack common genetic risk factors for classical autoimmune diseases such as polymorphisms in protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) and cytotoxic T-lymphocyte antigen 4 (*CTLA4*) genes. Second, SpA lacks the female predominance seen in most if not all autoimmune diseases. Third, individuals with SpA do not display disease-specific autoantibodies. And fourth, T- and/or B-cell-directed therapies are poorly effective or ineffective in at least the AS subform of SpA.¹⁹ Taken together, these data strongly suggest that SpA is not a classical autoimmune disease driven by self-reactive lymphocytes like rheumatoid arthritis (RA) or systemic lupus erythematosus.

ALTERNATIVE INNATE ROLES OF HLA-B27

Two alternative hypotheses have been proposed to explain the role of HLA-B27 in SpA (see Fig. 115.1). Both hypotheses relate to the presence of a cysteine residue in the β pocket of HLA-B27 that may lead to disulfide bonds and thereby abnormal structural organization of the HLA-B27 molecule. The first hypothesis proposes that HLA-B27 can form heavy-chain homodimers expressed on the surface of the cells.²⁰ These HLA-B27 homodimers can be recognized directly (i.e., independently of the antigen loaded on the major histocompatibility complex molecule) by killer-immunoglobulin-like receptors²¹ and thereby lead to activation of natural killer (NK) cells and T cells.²²⁻²⁴ The second alternative hypothesis is that HLA-B27 easily misfolds in the endoplasmic reticulum, which leads to the induction of unfolded protein response (UPR) and subsequent activation of a proinflammatory response program.^{25,26} It has now been established that the UPR induced by high HLA-B27 overexpression in bone marrow-derived rat macrophages²⁷ as well as by chemical agents in human dendritic cells²⁸ leads to abnormal production of cytokines, in particular IL-23, that could play a major role in SpA. Two key questions, however, remain to be answered in this context. First, it remains unknown whether physiologic expression of HLA-B27 as seen in SpA patients rather than nonphysiologic overexpression as observed in rats is sufficient to drive this proinflammatory program. Indeed, a recent report indicates that the increased production of cytokines, including but not restricted to IL-23, by peripheral blood monocyte-derived macrophages in AS is not related to manifest UPR.²⁹ Second, it remains to

be established whether the newly discovered susceptibility polymorphisms in the *ARTS1* gene have an influence on HLA-B27 misfolding, homodimer formation, and UPR. *ARTS1* codes for endoplasmic reticulum-associated aminopeptidase-1 (ERAP-1), a proteolytic enzyme that tailors peptides for presentation by class I molecules. ERAP-1 regulates both the amount of surface expression of class I molecules and the peptide repertoire presented by these molecules. Thus ERAP-1 polymorphisms could certainly play a key role in antigen presentation, as proposed in the arthritogenic peptide hypothesis, but may also influence the abnormal structural behavior of HLA-B27 as proposed in the two alternative hypotheses.

Although the exact, and not mutually exclusive, contributions of these different potential roles of HLA-B27 remains to be clearly established in human SpA, it is important to note that antigen-specific interactions with T cells are not central in either alternative hypothesis. Direct effects on NK and myeloid cells are thus compatible with a more central role for innate immune cells in the pathogenesis of SpA. Accordingly, SpA has now been proposed to be an autoinflammatory rather than autoimmune disease.^{30,31} A key feature of autoinflammatory diseases is that tissue-specific chronic inflammation is triggered by cellular stress. This concept fits well with (1) the role of gut luminal bacteria in the HLA-B27 transgenic rat model as well as human reactive arthritis and (2) the predilection of SpA for tissues subjected to intensive mechanical stress. The latter includes not only weight-bearing joints but also the enthesis and the underlying bone marrow. For this reason, an autoinflammatory theory of SpA may reconcile the role of HLA-B27, the anatomic predilection of the disease for tissues exposed to bacterial or mechanical stress, and, as is discussed in the next paragraphs, the role of specific innate cytokines and cell types.

INFLAMMATORY CYTOKINES IN SPONDYLOARTHRITIS

Additional insights in the pathophysiology of inflammation in SpA come from genetic and functional studies of specific cytokines or cytokine axes. An overview of the most important genetic risk factors for AS and SpA in general (Table 115.1) highlights the importance of three cytokine axes. First, the tumor necrosis factor (TNF) signaling pathway is genetically associated with AS. Obviously, the major pathogenic role of TNF in AS and SpA has now been very firmly established by the widespread use of TNF

TABLE 115.1
Major genetic susceptibility factors in ankylosing spondylitis (AS) and psoriatic arthritis (PsA),* ordered by chromosomal location

Genetic factor	Locus	AS	PsA
IL23R	1p31.3	Present	Present
RUNX3	1p36	Present	Absent
KIF21B	1q32.1	Present	Absent
IL1R2	2q11.2	Present	Absent
IL1A	2q13	Present	Present
ANTRX2	4q21	Present	Absent
PTGER4	5p13	Present	Absent
ERAP1	5q15	Present	Absent
IL13	5q31.1	Absent	Present
TNIP1	5q33.1	Absent	Present
IL12B	5q33.3	Present	Present
HLA-B	6p21.3	Present	Present
HLA-C	6p21.3	Absent	Present
HLA-DRB1	6p21.32	Possible	Doubtful
TRAF3IP2	6q21	Absent	Present
CARD9	9q34	Present	Absent
TNFRSF1A	12p13	Present	Absent
IL23A	12q13	Absent	Present
STAT3	17q21.2	Present	Absent
TBKBP1	17q21.32	Present	Absent

*Large genetic analyses have not been performed in other spondyloarthritis subtypes.

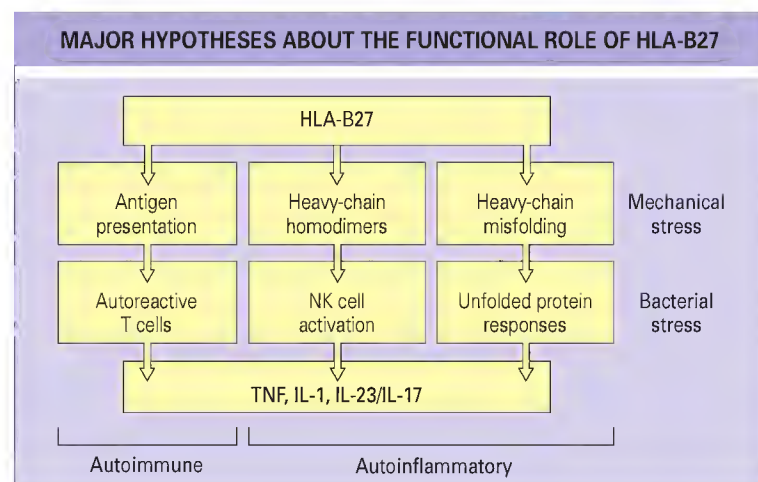


Fig. 115.1 Pathogenesis of spondyloarthritis and the role of HLA-B27. IL, interleukin; NK, natural killer; TNF, tumor necrosis factor.

inhibition in human patients. Intriguingly, however, the biology of TNF in SpA remains very poorly understood. Only very few if any data are available on which cells are the primary producers of TNF, whether TNF is produced mainly in its transmembrane or soluble form, which cells respond to TNF, and which receptor is crucial in this response in the context of SpA inflammation. One study demonstrated that, although SpA and RA show similar levels of overall inflammation, soluble TNF is lower in SpA than in RA, which indirectly suggests that TNF may act in its transmembrane rather than its soluble form in SpA.³² Using a TNF overexpression model in which mice develop severe colitis and destructive polyarthritis, another study elegantly demonstrated that expression of TNF receptor 1 on stromal cells was required for disease,³³ which suggests that stromal cells are one of the primary targets of TNF in SpA. Intriguingly, however, there is currently no clear indication that TNF blockade in human SpA significantly alters stromal remodeling and new bone formation, as is discussed in more detail later.

A second important cytokine is IL-1. Genetic studies now consistently indicate that IL-1 α is a susceptibility gene for AS.³⁴ In contrast to IL-1 β , IL-1 α is mainly an intracellular cytokine. The potential function of IL-1 α in SpA remains completely unexplored, but it is important to note that the IL-1 pathway is crucial to a large set of autoinflammatory diseases.

The third and most intensively studied cytokine axis is IL-23/IL-17. AS is genetically associated with IL-23 receptor (IL-23R) polymorphisms that are also linked to Crohn disease and psoriasis.³⁵ Taken together with the previously discussed upregulation of IL-23 by endoplasmic reticulum stress and the functional data indicating that the protective polymorphisms in the IL-23R gene are associated with impaired function of helper T 17 (Th17) cells,^{36,37} these data point toward a central role of IL-23/IL-17 in SpA. Although this role of IL-17 in the pathogenesis of AS has now been formally established in a still unpublished proof-of-concept trial using an anti-IL17A monoclonal antibody, the data on IL-23 and IL-17 expression in human SpA remain difficult to interpret. Systemic IL-23 serum levels are not markedly elevated and do not correlate with disease activity in SpA.³⁸ As for IL-17, reliable detection of serum levels remains a challenge. Studies measuring Th17 cells in peripheral blood have yielded mixed results, with most data indicating that the increase in circulating Th17 cells in AS is not specific and is also observed in other inflammatory conditions.³⁹ Two approaches have contributed here to our general understanding of IL-17-producing cells in SpA. First, analysis of very specific cellular subsets turned out to be more informative than a crude analysis of total numbers of IL-17-producing T cells. Among KIR3DL2-expressing T cells, which can be activated directly by the previously discussed HLA-B27 homodimers, the fraction expressing IL-17 is specifically increased in SpA.²³ Moreover, this fraction also shows a trend toward an increase in healthy HLA-B27+ individuals, which suggests that HLA-B27 may contribute to a proinflammatory, IL-17-oriented milieu. Another study carefully measured the IL-23R-expressing circulating leukocytes and found a specific increase in IL-17+ $\gamma\delta$ T cells in AS.⁴⁰ Second, the fact that inflammation in SpA is highly restricted to specific tissue environments prompted an analysis of IL-17 expression in axial and peripheral joints. Analysis of facet joints in patients with long-standing AS revealed IL-17 expression by CD15+ neutrophils, MPO+ innate immune cells, and, to a lesser degree, mast cells but not T cells.⁴¹ In peripheral SpA synovitis, IL-17 is mainly expressed by mast cells and, to a lesser extent, neutrophils.⁴² These data are in agreement with recent reports involving psoriasis.⁴³ Although it remains to be established whether neutrophils and mast cells really can produce IL-17 themselves, there is increasing evidence that they can at least release the protein and thereby contribute to local inflammation.^{42,44} The concept that innate immune cells rather than canonical CD4+ Th17 cells are the main cellular source of IL-17 is in agreement with the autoinflammatory rather than autoimmune nature of the disease. This concept is also further reinforced by a recent study showing that IL-23-responsive CD4–CD8– innate lymphoid cells present at enthesal sites drive localized tissue inflammation.⁴⁵ In this model, disease could be significantly ameliorated by both IL-17 blockade and IL-22 blockade. IL-22, however, appeared to play a more prominent role than IL-17, especially in the new bone formation program activated by IL-23 overexpression in these animals.

IMMUNOPATHOLOGY OF SPONDYLOARTHRITIS

A series of studies have assessed the histopathologic features of axial and peripheral SpA lesions. The resulting knowledge of cellular infiltration and inflammation helps to frame the pathogenic concepts in the context of human tissue inflammation.

In axial disease, one should distinguish the inflammation of the sacroiliac joints, the vertebral bodies, and the zygapophyseal joints. The sacroiliac joint is the most typical disease site in SpA. A detailed histomorphologic

study by François and colleagues of the sacroiliac joints of AS patients described the presence of inflammatory cells in the subchondral bone marrow as well as the synovial membrane, which can even form a small pannus.⁴⁶ In comparison with normal sacroiliac joints, there was significantly more superficial cartilage erosion, bone marrow edema, new bone formation, and bony ankylosis in the diseased joints. In analyzing the kinetics of the histopathologic changes, these authors described the presence of synovial inflammation and bone marrow edema as the earliest changes. This was followed by the formation of strings of connective tissue and new bone that eventually led to complete bony ankylosis of the joints. The presence of membranous as well as enchondral new bone formation was described. A second study used tissue obtained from the sacroiliac joint by computed tomography-guided needle biopsy.⁴⁷ Although it remains unclear whether the biopsy specimens represent genuine synovium because the characteristic intimal lining layer was not described, examination showed that the inflammatory infiltrate consisted of both T cells (CD4+ as well as CD8+) and macrophages.

Studies of vertebral bodies and intervertebral spaces in human AS are limited and indicate that the inflammatory cells are seen mostly in the annulus fibrosus, in association with erosion of the bone that makes contact with the annulus and a prominent neovascularization.^{48,49} The articulation between the vertebral bodies is formed by the zygapophyseal or facet joints. These synovial joints are frequently affected in SpA, with both the synovium and the subchondral bone marrow heavily infiltrated with inflammatory cells.⁴⁸ Identification of these inflammatory cells in the subchondral marrow space showed a predominant infiltration with T cells (CD4+ as well as CD8+) but also B lymphocytes.⁵⁰ Organized lymphocyte aggregates were present in 6 of 16 samples that were studied. In addition to bone marrow edema, there was also a prominent neovascularization in these samples. Unfortunately, the synovial membrane was not investigated in this study.

In peripheral SpA, an immunohistochemical study of femur heads of AS patients focused on the bone abnormalities, describing a pronounced infiltration of the subchondral bone marrow by T lymphocytes, with a predominance for CD4+ cells over CD8+ cells.⁵¹ In all samples, lymphocytic aggregates were present. Interestingly, the presence of T lymphocytes as well as osteoclasts was closely associated with the presence of cartilage in the close vicinity. Unfortunately, the presence of B cells and macrophages was not investigated in these samples. Although the synovial tissue was not investigated in this study of postsurgical femur heads, a series of studies has detailed the immunopathologic features of knee and ankle synovitis using synovial biopsy sampling in active disease. The inflamed synovium in both psoriatic and nonpsoriatic SpA contains a mixed inflammatory infiltrate that consists of macrophages, T lymphocytes, B lymphocytes, plasma cells, and a few neutrophils.^{52,53} The macrophages are the most prominent cellular population, and the majority of these cells express CD163, a scavenger receptor for heme-haptoglobin complexes.⁵⁴ An important role of these CD163+ macrophages in the local inflammatory process is suggested by the close correlation between the number of these cells and disease activity, both cross-sectionally and during effective treatment.^{55,56} These cells have now been identified as alternatively activated macrophages, and increasing evidence indicates that macrophage polarization is indeed biased toward this phenotype in SpA, whereas classical macrophage activation is seen in RA.^{32,57-59} The concept that specific innate immune cell populations are central to the immunopathologic characteristics of synovitis in SpA is further reinforced by the specific increase in mast cell infiltration and the specific upregulation of expression of Toll-like receptors 2 and 4 in SpA compared with RA.^{42,60}

Besides osteitis and synovitis, peripheral SpA is also characterized by enthesitis. There are two kinds of entheses: fibrous and fibrocartilaginous. Fibrocartilaginous entheses, which contain fibrocartilage, develop at the insertion of ligaments on bones that arise by enchondral osteogenesis, for instance, the calcaneum. Fibrous entheses develop at the insertion of ligaments on bones that arise by membranous osteogenesis, for instance, the iliac bone. In SpA, inflammation can occur in both types of entheses. Immunophenotyping of the infiltrate in SpA enthesitis was performed by two groups. McGonagle and associates sampled fibrocartilaginous tissue from the entheses of SpA patients by needle biopsy.⁶¹ CD68+ macrophages were the predominant cellular population in the inflammatory infiltrate in these samples. Laloux and associates sampled the entheses from the crucial ligaments and vastus lateralis of SpA patients by open surgery and focused on the changes in the subentheseal bone marrow.⁶² They described the presence of bone marrow edema together with an inflammatory infiltrate that consisted predominantly of CD8+ T lymphocytes. There was no increase in the numbers of macrophages in this tissue. Interestingly, both studies of enthesitis as well as most synovial studies described a pronounced neovascularization in the tissues.

JOINT REMODELING IN SPONDYLOARTHRITIS

A peculiar pathogenic feature of axial and peripheral SpA is that, unlike in RA, the chronic disease process leads not only to extensive bone and cartilage destruction but also to new tissue formation and even ankylosis. The previously mentioned histopathologic studies of the spine and the sacroiliac joints have confirmed that SpA structural abnormality is characterized by a combination of destruction and new bone formation. For example, the formation of bony bridges can be observed both in the granulation tissue, which penetrates into the joint from the bone marrow space after erosion of the bony endplate, and in the periarticular capsule of the facet joints in SpA. The exact nature of this bone formation process is unclear, however; some studies describe a predominance of membranous or reactive new bone formation, which is the direct transdifferentiation of fibroblastoid cells into osteoblasts, whereas other studies describe a predominance of endochondral bone formation, which is the formation of bone out of cartilage.

A number of important cellular and molecular insights into structural damage have started to emerge over the last years. First, it is now clearly established that the structural phenotype of SpA cannot be explained by the absence of destruction. In contrast, histologic, radiologic, and experimental evidence converge to indicate that bone erosions as well as the molecular and cellular machinery underlying these erosions are present and operative in SpA.⁶³⁻⁶⁶ Second, a number of molecular pathways have been identified that may drive osteoproliferation in SpA, in particular the BMP and Wnt signaling pathways.⁶⁷⁻⁶⁹ Although both pathways have been studied in animal models, it is interesting to note that biomarkers related to Wnt signaling are also associated with structural damage in human AS.^{70,71} Third, clinical and experimental studies have started to clarify the complex relationship between inflammation and structural damage in SpA. One hypothesis proposed that osteoproliferation in SpA is a repair mechanism triggered by an initial but transient inflammatory and destructive insult.⁷² Data from experimental models, however, indicate that complete prevention of early bone erosions does not impact osteoproliferation and, moreover, that osteoproliferation occurs simultaneously with pronounced inflammation and destruction (Fig. 115.2).^{66,73,74} Accordingly, radiologic data from clinical trials indicate that TNF blockade does not halt but also does not accelerate new bone formation. A second hypothesis proposes that the tissue remodeling and ankylosis is initiated by a common trigger but, once initiated, is completely uncoupled from inflammation.^{56,75} This hypothesis, however, is hard to reconcile with the fact that new bone formation is observed only in the presence of pronounced inflammation in experimental SpA.⁶⁶ Additionally, the genomewide association studies do not suggest primary genetic alterations in the bone formation pathways in AS. A third alternative hypothesis starting to emerge is that, in contrast to TNF-mediated inflammation, which promotes destruction and inhibits new bone formation, other types of inflammation may in fact drive osteoproliferation. This view is supported by recent data indicating a role of IL-22 in new bone formation in enthesitis⁴⁵ and by the observation that continuous and adequate NSAID treatment slows down osteoproliferation in AS.⁷⁶ Deciphering the exact mechanisms and interactions of joint remodeling and inflammation has become the major pathogenic and clinical challenge in the field of SpA research because it has crucial consequences for the timing and type of treatment.

INTERACTION BETWEEN INFLAMMATION, BONE DESTRUCTION, AND OSTEOPROLIFERATION

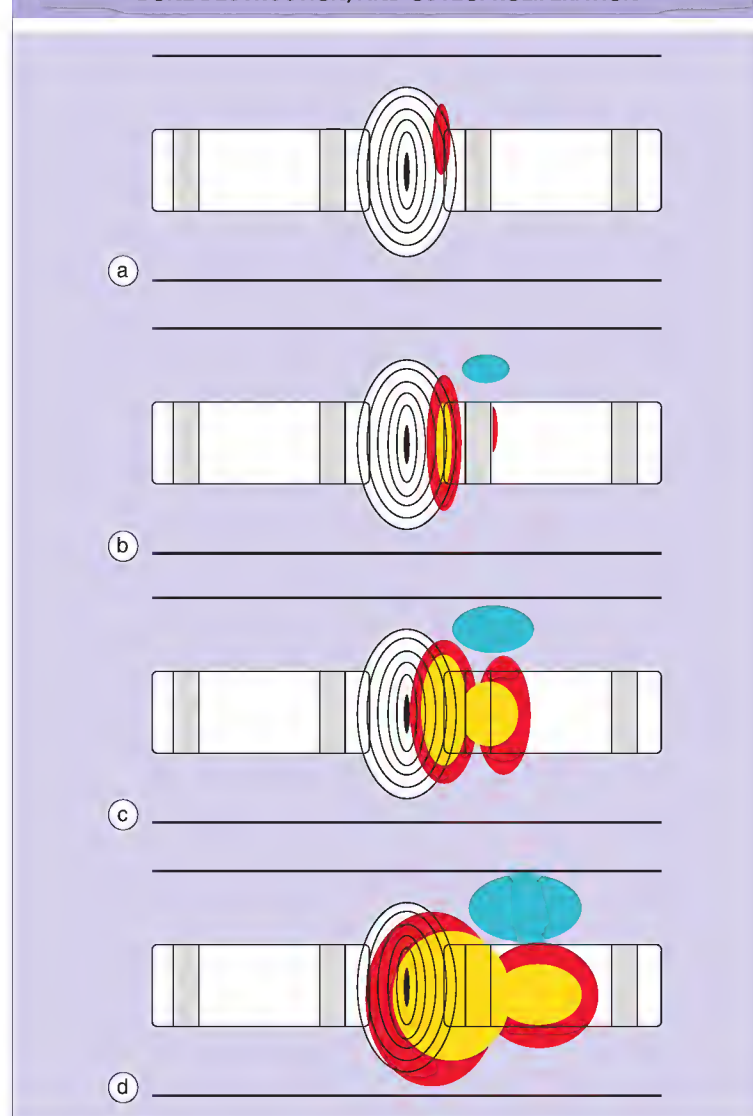


Fig. 115.2 Schematic representation of the interaction between inflammation, bone destruction, and osteoproliferation as observed in the spine of an HLA-B27/ β_2 -microglobulin transgenic rat model of spondyloarthritis. (a) Inflammation starts at the junction between vertebrae, intervertebral disk, and the enthesis. (b) Inflammation progresses toward the entire space between the cartilage endplate and annulus fibrosus; some inflammatory cells appear within the bone marrow. At this stage, the first signs of destruction (osteoclast-like cells and bone erosions) and remodeling (hypertrophic chondrocytes) appear. However, the remodeling process occurs at a distance from the site of inflammation. (c) Both inflammation, destruction, and remodeling become more pronounced over time. (d) Even when the joint is completely destroyed and normal anatomic structures have completely disappeared, the processes of inflammation, destruction, and remodeling is still ongoing. Red indicates inflammation; yellow indicates tissue destruction; and blue indicates bone remodeling.

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Genetics of axial spondyloarthritis

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- Susceptibility to and severity of ankylosing spondylitis, the prototypic axial spondyloarthritis, are highly heritable.
- Although HLA-B27 is the main genetic variant associated with axial spondyloarthritis, many other genes are involved in both HLA-B27+ and HLA-B27–disease.
- In particular, genes in the interleukin-23 response pathway and genes encoding aminopeptidases involved in peptide processing before HLA class I presentation are overrepresented among ankylosing spondylitis–associated variants.

GENETIC EPIDEMIOLOGY OF ANKYLOSING SPONDYLITIS

For more than 40 years, ankylosing spondylitis (AS) has been known to run in families. Familiality occurs because of shared susceptibility factors among family members, which may be environmental (random or common) or genetic.

Twin studies confirm that susceptibility to AS is almost entirely genetically determined, with two studies now formally estimating heritability as greater than 90%.^{1,2} Heritability of clinical manifestations of disease is also significant, with age of symptom onset, disease activity measured by the widely employed Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Functional Index (BASFI) questionnaires, and radiographic severity being 40%, 51%, 76%,^{3,4} and 62% heritable,⁵ respectively.

The association of HLA-B27 with AS is among the strongest genetic associations in any common disease, and yet studies in families suggest that less than 50% of the overall genetic risk is due to HLA-B27 and that it is likely that several other genes are involved. First-degree relatives of AS patients have a 5 to 16 times greater risk of developing AS than HLA-B27+ individuals in the general population, which implies the existence of factors modifying the risk of AS apart from HLA-B27.^{6,7} The most likely models of the disease suggest that genes modifying the effect of HLA-B27 determine the risk of getting the disease in HLA-B27 carriers.⁸ It is likely that, in addition to HLA-B27, there are a small number of genes with moderate effect and a large number of genes with small effect. Certainly, large multicausal families, which are typical in diseases with a monogenic cause, are extremely rare in AS. The risks of developing AS in different degrees of relatives to a proband with the condition are given in Table 116.1.

MAJOR HISTOCOMPATIBILITY COMPLEX GENES

The major histocompatibility complex (MHC) on chromosome arm 6p is strongly linked and associated with AS.^{9–15} Although most of the genetic association of this locus is driven by the association of AS with HLA-B27, the association is clearly more complex than that.

HLA-B27 and B27 subtypes

HLA-B27 is more common in Northern Europeans and is rare in Africans and Australian Aboriginals. The prevalence of AS generally follows the frequency of HLA-B27 in that population. In most studies, 80% to 95% of AS patients are HLA-B27+; thus in white Europeans the odds ratio for AS in HLA-B27 carriers is more than 50.^{16–18} Homozygous HLA-B27 carriers are

at an increased risk of AS compared with heterozygotes (odds ratio, 2.07; $P = .0025$).^{18–21} Despite that, only a minority of HLA-B27 carriers develop AS, and thus HLA-B27 has not been found useful in population screening. However, in patients with inflammatory low back pain, HLA-B27 testing is a useful component of the diagnostic workup (Fig. 116.1). This testing is further facilitated by the discovery of single nucleotide polymorphisms (SNPs) that accurately tag the HLA-B27 allele (rs116488202, sensitivity and specificity for HLA-B27 of 98.5% to 100% in white Europeans and East Asians), so that a cheap and robust SNP assay can be used rather than the more expensive and complex HLA-B27 assays.

There is strong evidence in specific populations that different subtypes of HLA-B27 have different strengths of association with AS. Over 90 HLA-B27 subtypes have now been reported (see the Anthony Nolan Trust database at <http://hla.alleles.org/class1.html>), with a rapid increase in the number of subtypes occurring over the past 5 years related to increased use of DNA-based HLA typing. In most cases the subtypes involved have been reported in only a few unaffected individuals, and therefore it is not possible to say whether or not they are associated with AS. However, some subtypes are sufficiently prevalent that the relative strengths of their association with AS can be compared.

AS (not just undifferentiated spondyloarthritis) has been reported to occur with the following subtypes of HLA-B27: *2702, *2703, *2704, *2705, *2706, *2707, *2708, *2710, *2714, *2715, and *2719. Until recently, no case of AS had been reported with B*2709, and this subtype is protective for the disease, relative to B*2705.²² Six cases with spondyloarthritis have now been reported in B*2709 carriers, although only two of these had classical axial AS, and in each case there were other potential explanations for the development of AS.^{23,24} These cases confirm that B*2709 is not absolutely protective for AS, although it is underrepresented in cases in Sardinia, due to its weaker association with disease than B*2705.

B*2706 similarly has been shown to be less strongly associated with AS than B*2704 in Southeast Asia, although these studies are complicated by ethnic differences in B*2704 and *2706 carriers, because B*2704 carriers are more likely to be of Chinese descent, whereas B*2706 carriers are more likely to be of Malay descent.^{24–27} There is increasing evidence that B*2704 is more strongly associated with AS than B*2705. A recent study in Taiwanese of Han Chinese descent supported this conclusion and also reported cases of AS in carriers of B*2706, confirming that the protective effect of this B27 subtype is not absolute.²⁸

Other major histocompatibility complex genes

The MHC, situated on chromosome arm 6 (6p21.3), extends over 3.6 megabases and contains about 220 genes, many of which have immunoregulatory functions. Although compelling evidence has been published suggesting that the HLA-B allele HLA-B60 is associated with AS, this finding was not supported by the large International Genetics of Ankylosing Spondylitis Consortium study, perhaps because of difficulties imputing HLA alleles using single SNPs rather than direct genotyping.¹⁸ This study did show that HLA-A*0201 is significantly associated with AS, although with a much smaller effect size than HLA-B27 (odds ratio of 1.21 in HLA-B27+ cases, 1.36 in HLA-B27– cases, compared with an odds ratio of 46 for HLA-B27 itself).

NON-MAJOR HISTOCOMPATIBILITY COMPLEX GENES

Association with the MHC explains less than half of the familiality of AS. Major advances have occurred in the last several years in identifying the

TABLE 116.1
Risk of ankylosing spondylitis in relatives of patients given HLA-B27 status

	B27 status unknown	B27+	B27–
Grandparent	1%	5%	0%
Parent/sibling	10%	15%	0%
Identical twin	60%	60%	?

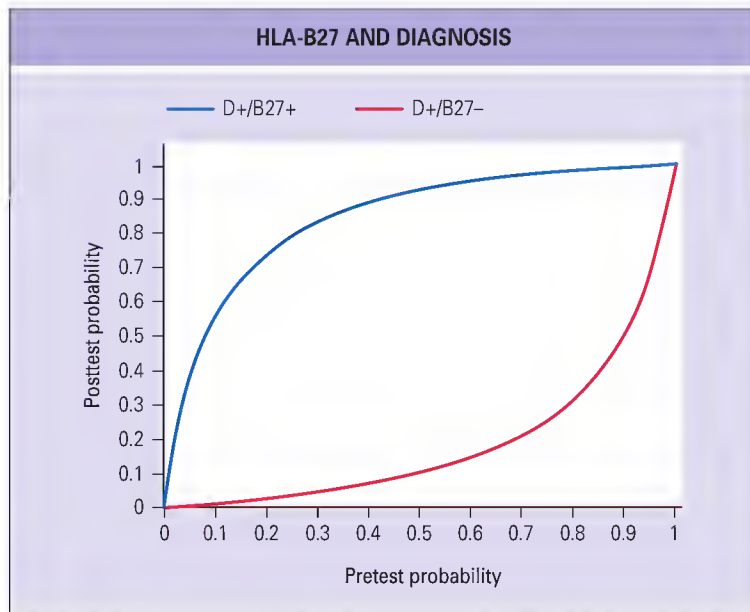


Fig. 116.1 The x-axis shows the probability of ankylosing spondylitis (AS) before the HLA-B27 status is known. The likelihood of AS in the general population is approximately 0.5%; in a patient coming to a general practice with low back pain, the likelihood of spondyloarthritis is 5%. The posttest probability is the likelihood of AS given the prior probability of disease and the HLA-B27 status. The blue line represents the likelihood of disease (D) if the patient tests positive for HLA-B27, and the red line represents the likelihood if the HLA-B27 test result is negative.

non-MHC genes involved in AS. Starting with the discovery of the association of *IL23R* and *ERAP1* with AS,⁴ there have now been 31 loci reported to be associated with AS at genome-wide significance, and because at some loci more than one haplotype is disease associated, a total of 41 haplotypes have been identified. The current known replicated genes in AS are listed in Table 116.2, along with their relative contribution to the heritability of AS and putative functions.

In 2007 the first large-scale genome-wide association study to be performed in AS was reported by the Wellcome Trust Case Control Consortium (WTCCC) and the Australo-Anglo-American Spondyloarthritis Consortium (TASC).²⁹ The study identified and confirmed the association of SNPs in the genes *IL23R* and *ERAP1* with AS.

IL23R has also been demonstrated to be associated with both inflammatory bowel disease (IBD) and psoriasis. The three conditions AS, IBD, and psoriasis are closely related clinically. When cases with no history of either psoriasis or IBD are analyzed, the *IL23R* association with AS remains unchanged in the WTCCC/TASC data set, which indicates that AS itself is primarily associated with *IL23R* variants and is not secondary to the association of *IL23R* with IBD or psoriasis. Since this study the association of *IL23R* has been replicated in multiple white European populations, and findings in non-European populations are awaited. Fine-mapping and transethnic studies have confirmed that rs11209026 is the key associated SNP in white Europeans and that there is a second haplotype tagged by the SNP rs11209032, which lies between *IL23R* and the neighboring gene *IL12RB2*. In Behçet disease, an association is seen only at this second haplotype. In Asians, rs11209026 is nonpolymorphic, but another low-frequency protective allele with deleterious effects on interleukin-23 receptor (IL-23R) protein function is associated with AS (rs76418789, G149R).

In Crohn disease and ulcerative colitis, associations have also been reported with *STAT3*, *JAK2*, and *TYK2*, the genes encoding the signaling kinases and transcription factors associated with IL-23R signaling.^{30,31} This is in contrast to the findings in autoimmune diseases, in which strong association has been reported with *STAT4* in rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis.^{32,33} *STAT3* is critical in the development of type 17 helper T lymphocytes (Th17), and individuals with monogenic conditions causing loss of *STAT3* have no Th17 lymphocytes and are extremely prone to extracellular infections.³⁴

The *IL23R* association with AS was the first suggestion that the IL-23-responsive and likely IL-17-producing lymphocyte pathways may be involved in the disease (see Chapter 115 for a discussion of the pathophysiology of AS). Although *IL23R* is also expressed on a number of other immunologic cell types such as macrophages, microglia, NK cells, NK T cells, and $\gamma\delta$ T cells, and it is not yet clear which cell type is primarily affected by the *IL23R* disease-associated variant (reviewed by Kenna and Brown³⁵). AS risk variants at *IL23R* have been shown to have greater function than protective variants, and it has been shown that IL-23 treatment induces enthesitis and psoriasiform skin lesions.³⁶ Many other genes in the IL-23R pathway have been found to be associated with AS, including *CARD9*, *TYK2*, *IL6R*, *PTGER4*, and *IL27*, which highlights the significance of this pathway to AS.¹⁷

Inhibition of IL-23 pathway activity is being investigated as a possible therapeutic approach for autoimmune disease. Antibodies to the IL-12p40 subunit (the shared IL-23/IL-12 subunit) have been studied with successful results in psoriasis³⁷ and Crohn disease,³⁸ and there are preliminary data to suggest that such therapies are effective in AS.³⁹

The other major finding of the WTCCC/TASC study²⁹ was the association of the gene *ERAP1* (formerly known as *ARTS1*), which is an aminopeptidase, the function of which is still being clarified. Since this original finding, the International Genetics of Ankylosing Spondylitis Consortium study has identified associations with loci harboring three other aminopeptidases, including *ERAP2*, *LN-PEP*, and *NPEPPS*, which indicates that this class of gene is critically involved in AS etiopathogenesis.¹⁸ The *ERAP1*-associated variant was associated only with HLA-B27+ AS, which indicates that it interacts with HLA-B27 to induce disease. The *ERAP2/LN-PEP* and *NPEPPS* associations are not HLA-B27 restricted. Interestingly, *ERAP1* variants have now been shown to be associated with HLA-Cw6+ psoriasis,⁴⁰ which suggests that HLA-Cw6 is involved in psoriasis pathogenesis by a mechanism similar to that by which HLA-B27 induces AS. *ERAP2* but not *ERAP1* has recently been associated with IBD; whether it interacts with any HLA variants is unknown.^{32,41}

The main associated variants at *ERAP1* and *ERAP2* are loss-of-function variants, which have been shown to reduce peptide trimming before HLA class I antigen presentation. The downstream effects of this reduction in trimming on peptide handling, HLA-B27 folding, and cell surface stability are still being elucidated, and it is possible that these *ERAP1* and *ERAP2* variants influence the peptide repertoire being presented by HLA-B27 either quantitatively or qualitatively.

ERAP1–/– mice are more prone to infection with *Toxoplasma gondii*, a vacuolar parasite, due to defective presentation of parasite antigen by the murine HLA class I system to CD8 T cells.⁴² This confirms a functional role of *ERAP1* in HLA class I-mediated immunity.

ERAP1 is expressed primarily in the endoplasmic reticulum, with two main functions reported. First, it may be involved in cleavage of cytokine cell surface receptors including IL-1R2, TNFR1 and IL-6R, downregulating their function,^{43–45} although *in-vivo* studies of this reported function have not confirmed this effect. Second, there is strong evidence that *ERAP1* is a key component of the peptide processing pathway before peptide loading into nascent HLA-class I molecules,^{46,47} such as HLA-B27. The crystal structure of *ERAP1* protein has now been determined, and it has been shown that the AS-protective variants either prevent closure of the catalytic domain by effects on its hinge regions or impinge on the catalytic site's capacity to engage with peptides.⁴⁸ The *ERAP2* protective haplotype carries a variant that causes nonsense-mediated decay of *ERAP2* messenger RNA and so is also a loss-of-function variant. The mechanisms underlying the genetic associations of *NPEPPS* and *LN-PEP* with AS remain to be determined. It also is not known whether the *ERAP1* and *ERAP2* variant associations operate by quantitative or qualitative effects on peptide handling. Whichever it is, it is clear that these associations are helping greatly in determining the mechanism of association of HLA-B27 with AS.

ANKYLOSING SPONDYLITIS IN EAST ASIANS

The prevalence of AS in Chinese populations is not dissimilar to that in white Europeans (0.2% to 0.54%), but the prevalence of the disease is low

TABLE 116.2

Genetic associations of ankylosing spondylitis (AS) and likely mechanism of action in the disease

Candidate gene	Gene locus	Contribution to genetic variance in AS (%)*	Putative functional significance
<i>IL23R</i>	1p31	0.352	Acts on IL-23R-expressing cells
<i>RUNX3</i>	1p36	0.138	Transcription factor involved in control of T-lymphocyte differentiation
<i>IL6R</i>	1q21	0.151	Th17 lymphocyte differentiation and multiple other effects
<i>FCGR2A</i>	1q23	0.08	Low-affinity receptor for immunoglobulin G Fc fragment; unclear role in AS
<i>GPR25-KIF21B</i>	1q32	0.162	Unknown
Intergenic region	2p15	0.407	Unknown
<i>IL1R2-IL1R1</i>	2q12	0.055	Response to IL-1
<i>UBE2E3</i>	2q31	0.062	Ubiquitin-conjugating enzyme; unknown role in AS
<i>GPR35</i>	2q37	0.06	Unknown
<i>ANTXR2</i>	4q21	?	Unknown
<i>PTGER4</i>	5p13	0.047	Promotes IL-23 expression in response to physical stress at entheses
<i>ERAP1</i>	5q15	0.411	Peptide trimming before antigen presentation
<i>ERAP2</i>	5q15	0.147	Peptide trimming before antigen presentation
<i>IL12B</i>	5q33	0.066	Acts on IL-23R-expressing cells
HLA-B*27	6p21	20.089	Antigen presentation
<i>BACH2</i>	6q15	0.064	Transcription factor; unknown role in AS
<i>CARD9</i>	9p34	0.082	Innate immune system activation, leading to IL-23 production
<i>ZMIZ1</i>	10q22	0.059	Transcription factor, unclear role in AS
<i>NKX2-3</i>	10q24	0.136	Transcription factor, unclear role in AS
<i>LTBR-TNFRSF1A</i>	12p13	0.092	Protective allele increases level of soluble tumor necrosis factor in serum
<i>SH2B3</i>	12q24	0.06	Involved in T-cell receptor signaling
<i>GPR65</i>	14q31	0.086	Unknown
<i>IL27-SULT1A1</i>	16p11	0.064	Influences Th17 lymphocyte differentiation
<i>NPEPPS-TBKBP1-TBX21</i>	17p21	0.111	<i>NPEPPS</i> : peptide trimming before antigen presentation
<i>NOS2</i>	17q11	0.074	Produces nitric oxide, multiple inflammatory effects
<i>TYK2</i>	19p13	0.08	IL-23R signaling
Intergenic region	21q22	0.407	Unknown
<i>ICOSLG</i>	21q22	0.052	Inducible T-cell costimulator ligand

*Contribution to genetic variance determined from International Genetics of Ankylosing Spondylitis Consortium Immunochip Study.

IL, interleukin; IL-23R, interleukin-23 receptor; Th17, type 17 helper T cell.

Data from International Genetics of Ankylosing Spondylitis Consortium (IGAS); Cortes A, Hodler J, Pointon JP, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013;45:730-8.

in Japan, where HLA-B27 is rare. As in whites, AS in Chinese has a strong genetic background. However, the genetic association with AS in Chinese individuals has unique features. As in other ethnic populations, AS in Chinese is strongly associated with the class I MHC allele HLA-B27, which is found in more than 80% of Chinese AS patients compared with approximately 3% to 5% of healthy Chinese. Unlike the situation in many white populations, where B*2705 is largely predominant, in Chinese the main subtype is B*2704, with the majority of the remaining individuals carrying B*2705. Moreover, B*2704 appears to be the ancestor of a group of less frequent subtypes found in the Chinese population, including B*2715, which differs from B*2704 by a single amino acid changed at position 163.

In China, only 1% to 5% of HLA-B27 carriers develop AS, which suggests that although HLA-B27 plays a large role in disease susceptibility, there are other genetic factors responsible for modifying disease penetrance. So far, other genes that have been shown to be associated with AS in Chinese population include HLA-B60, *IL1A/B*, *STAT3*, *TNFRSF1A*, and *ERAP1*. As mentioned earlier with regard to *IL23R*, the actual associated allele at specific loci may differ among ethnic groups, although in most cases it is the same, consistent with a common ancestor origin of the disease-associated variant(s). The extent of genetic sharing between Chinese and Europeans is highlighted by a recent large-scale association study in which, of the 23 loci achieving genomewide significance in white Europeans, 13 showed at least nominal levels of association in East Asians (Chinese, Koreans, Taiwanese).¹⁸

One genomewide association study has been performed in Han Chinese alone, reporting the identification of two novel non-MHC loci at chromosome band 5q14 (between *HAPLN1* and *EDIL3*) and chromosome band 12q12 (*ANO6*).⁴⁹ Neither of these associations has been replicated in very large independent confirmation studies in either East Asians or white Europeans, and thus it seems likely that they are not AS associated.¹⁸

The common and unique genetic features of Chinese AS have shown the value of exploring the genetic diversity among different ethnic groups for gene mapping. These differences among various ethnic groups may possibly be used to distinguish true associations from artifact effects. Furthermore, identification of new susceptibility genes in Chinese may provide additional information on the pathogenesis of AS in white Europeans. This will make further gene mapping studies in East Asian populations very valuable in improving our understanding of the genetic basis of disease.

ANKYLOSING SPONDYLITIS IN AFRICANS

AS is rare in Africa, largely because of the rarity of HLA-B27, although even in rural African populations where HLA-B27 is prevalent, AS is rare.^{50,51} This is not due to differences in the HLA-B27 subtypes present because AS has a lower prevalence even in Africans carrying the European subtype HLA-B*2705.⁵² African Americans do get AS, which indicates that the rarity of the disease in Africa is likely to have an environmental component, in addition to the effect of the low prevalence of HLA-B27. Little has been reported

about the clinical or genetic manifestations of AS in African Americans. A recent case series reported more severe disease and a lower prevalence of HLA-B27 in African American than in white AS cases (62% vs. 84%, respectively),⁵² consistent with previous reports.⁵³

SUMMARY AND CONCLUSIONS

The field of the genetics of AS is progressing rapidly and has already contributed much to our understanding of the disease etiopathogenesis, in particular implicating the IL-23-responsive lymphocyte subset as being

important in the development of the AS. A significant proportion of the overall genetic risk in AS has yet to be determined, and no genes have yet been identified that contribute to the clinical manifestations of the disease. Identifying genes involved in these processes will assist in the development of novel therapies for AS, for which no treatment is currently available that has been shown to alter the natural history of the disease.

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Imaging in spondyloarthritis

■ JUERGEN BRAUN ■ XENOFON BARALIAKOS

- MRI is the gold standard for assessment of inflammatory changes in the sacroiliac joints and the spine of patients with axial spondyloarthritis.
- Conventional radiographs are still the gold standard for assessment for chronic/postinflammatory changes but the knowledge about the use and interpretation of these changes by MRI is increasing.
- Definitions for a positive MRI of the sacroiliac joints and the spine for use in the Assessment of SpondyloArthritis international Society classification criteria have been recently published.

INTRODUCTION

Axial spondyloarthritis (axSpA)—a new term that covers both “classical” ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis¹—is a chronic inflammatory rheumatic disease that affects mainly the axial skeleton, whereas patients with predominantly peripheral spondyloarthritis (SpA) have mainly arthritis, enthesitis, and dactylitis.¹ The pathognomonic findings of axSpA are inflammatory, osteodestructive, and osteoproliferative changes in the sacroiliac joints (SIJ) and spinal structures, many of which are enthesal in nature. Clinically, these pathologic changes lead to chronic inflammatory back pain, although some patients report only increasing spinal stiffness.^{2,3} The whole group of spondyloarthritides shares other characteristic clinical symptoms caused by extraarticular manifestations such as acute anterior uveitis, psoriasis, and inflammatory bowel disease. Rare but typical manifestations of AS are aortic valve disease and cauda equina syndrome. Frequent comorbidities are osteoporosis and cardiovascular disease.

Sacroiliitis, spondylitis, spondylodiskitis, and spondyloarthritis are the main inflammatory manifestations in the axial skeleton⁴ and may lead to new bone formation occurring as syndesmophytes and ankylosis in the vertebral column; about 15% of AS patients even develop bamboo spine.⁵ Peripheral manifestations are found mainly in the root joints, the hips, and the shoulders but also are seen at many entheses such as the heel (Achilles tendon, plantar fascia), the knee (pes anserinus) and the elbow (epicondyle).

These characteristic changes may occur during the course of the disease in many patients. However, the frequency of these manifestations as well as the velocity of disease progression and severity vary among patients.⁶ The complex pathogenic process involving inflammation and transformation to structural changes in axSpA is still incompletely understood. One important aspect in this regard is the parallel occurrence of inflammatory, osteodestructive, and osteoproliferative but also osteoporotic changes in the vertebral column.⁷ Although the effect on the spine consists largely of new bone formation, the involvement of the peripheral joints clearly is erosive.

Different imaging techniques are relevant for diagnosis, classification, assessment of disease activity and structural damage, and prognosis in patients with axSpA. The capacity of the various techniques to detect potential pathologic processes clearly is different. Conventional radiographs currently are still considered the gold standard for assessment of structural changes in the axial skeleton of patients with axSpA.^{4,5} Computed tomography (CT) is useful for the detection of structural changes in the SIJ because of its superior sensitivity and specificity compared with conventional radiography, especially when the absence of structural changes needs to be documented. However, both methods are unable to visualize active inflammation. The best method to detect inflammatory changes is magnetic

resonance imaging (MRI). The use of scintigraphy is not recommended because of the very low specificity of this technique.⁸

Peripheral joints affected by the disease increasingly are assessed using ultrasound techniques, and the knowledge in this field has grown remarkably in the last decade.⁹ Therefore the different imaging techniques currently available for evaluation of axSpA should be used in complementary fashion and according to individual indications (Table 117.1).

Only changes in the SIJ are considered relevant in the current classification criteria for axSpA and AS. Nevertheless, some patients may show spinal involvement in the absence of abnormalities in the SIJ.⁴

The magnitude of the pathologic changes in the axial skeletons of patients with axSpA is used to quantify inflammatory and structural outcomes in clinical trials involving axSpA. Different scoring systems have been proposed for the assessment of inflammatory and structural changes in axSpA.¹⁰⁻¹²

The prognostic relevance of structural changes (presence of syndesmophytes by radiography) and of the degree of inflammatory changes in the SIJ (by MRI, in combination with HLA-B27 testing) has been well demonstrated.¹³

TECHNICAL ASPECTS OF IMAGING IN AXIAL SPONDYLOARTHRITIS

For imaging of the SIJ, different orientations are used depending on the imaging technique. For conventional radiography, the orientation used is the anteroposterior (AP) view. This is the most common view for assessing the SIJ, in combination with either the lumbar spine, including the thoracolumbar junction (Fig. 117.1a), or the pelvis and hip joints (see Fig. 117.1b), depending on the location of the patients' symptoms. In addition, the Barsony technique (patient in the supine position, AP projection, the tube angled at 10 to 25 degrees toward the head; see Fig. 117.1c and d) or the Ferguson technique (patient in the prone position, posteroanterior projection, the tube angled at 25 to 30 degrees toward the head) is used for imaging solely of the SIJ. However, a clear advantage of these views has not been established to date.

Imaging with CT and MRI has the general advantage of providing multidimensional images through a technique in which the anatomic region of interest is cut into slices and digital processing of the data is performed. Pathologic processes can then be visualized in different orientations and planes. The most commonly used orientation in the case of the SIJ is the semicoronal plane (parallel to a line tangent to the upper posterior portion of S1 and S3), but a semiaxial view (perpendicular to the semicoronal orientation) can also be produced to provide additional information.^{14,15}

In the evaluation of the spine, the sagittal orientation is most frequently used in all imaging techniques. In conventional radiography the AP view is also frequently used to increase the sensitivity for detecting syndesmophytes. In CT and MRI the slices should cover the whole vertebral body, including the posterior elements (spinous processes) as well as the lateral elements (facet joints). Because of the digital nature of these techniques, coronal or axial (transverse) views can also be generated but do not need to be produced on a routine basis.

Technical aspects of magnetic resonance imaging

For the assessment of bone marrow edema as a sign of inflammation in axSpA, the short tau inversion recovery (STIR) sequence, the T2 fat-suppressed sequence, and the T1-weighted sequence performed after administration of intravenous contrast agent (gadolinium–diethylenetriamine pentaacetic acid [T1/Gd-DTPA]), with or without additional fat-suppression



sequences, are recommended.³⁵ For routine imaging, the STIR sequence (see Fig. 117.4a) is usually sufficient because of the strong suppression of the fat signal, which leads to very good fat-water contrast.⁷

Soft tissue involvement around the SIJ such as synovitis, capsulitis, and enthesitis is better detected using T1/Gd-DTPA sequences. However, such changes are not considered highly specific for axSpA, and the use of gadolinium is more expensive, is time consuming, and is contraindicated in

patients with impaired renal function, which makes this technique less feasible for routine practice.

There is some evidence that STIR is 90% compatible with imaging techniques using post-gadolinium T1-weighted sequences in imaging of the SIJ.⁷ The use of dynamic MRI of the SIJ, as proposed earlier,³⁷ is no longer recommended because it produced too many positive but nonspecific results.

For the assessment of structural lesions, the T1-weighted turbo spin-echo sequence, a standard technique that is usually performed before the administration of a contrast agent, is frequently used, but gradient-echo techniques also have been recommended because of their ability to show cartilage abnormalities.⁷

Protocols for MRI examination of the SIJ currently are based on the use of a 1- to 1.5-T superconducting whole-body magnet with a body phased-array coil. For STIR sequences the following parameters are most frequently used: TR/TE/TI: 4000/60/150 ms, slice thickness 3 or 4 mm. The parameters for a T1 sequence are TR/TE: 500/10 ms; for a T1 with fat suppression (T1 FS): TR/TE: 660/16 ms; and for a T2-weighted gradient-echo sequence: TR/TE 180/7.15 ms.

■ TABLE 117.1

Overview of imaging techniques available for use in axial spondyloarthritis

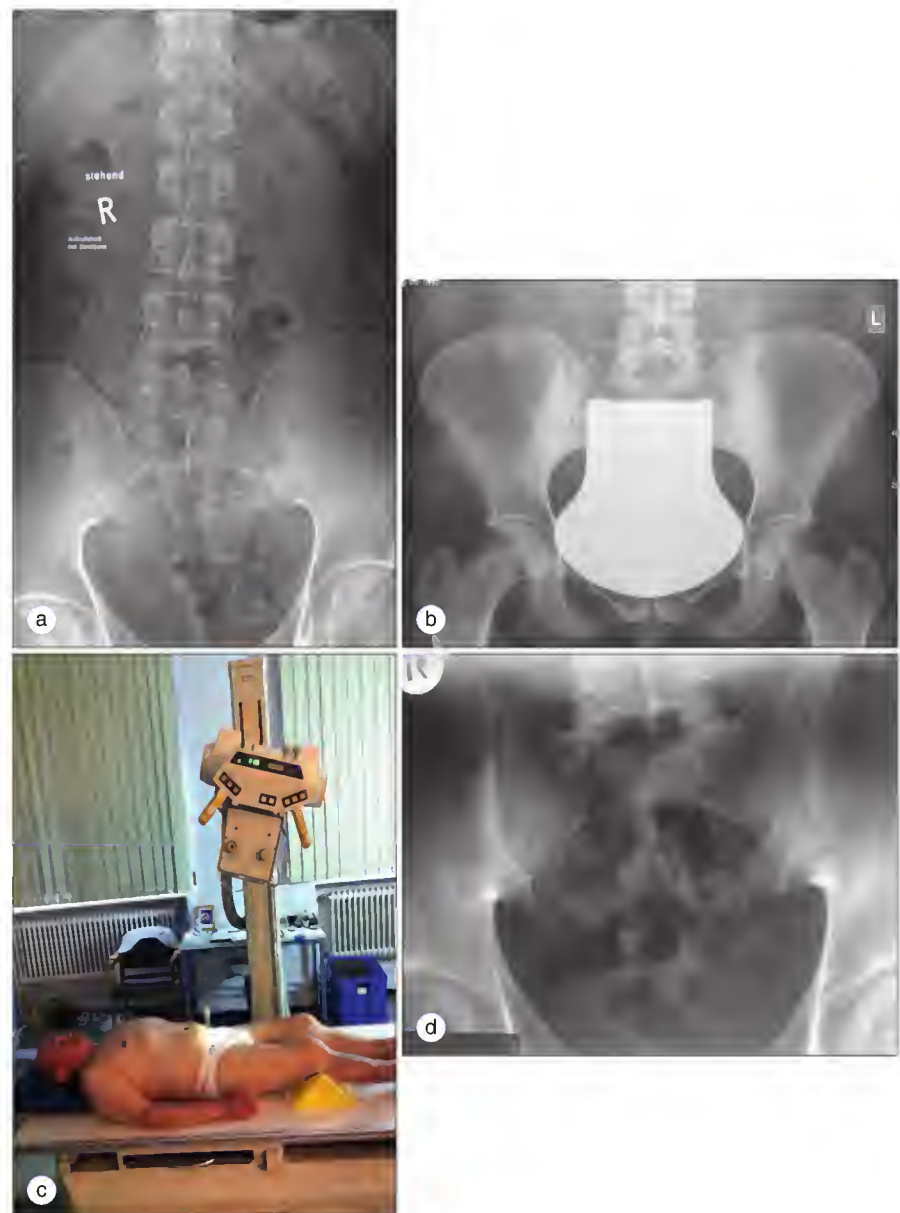
Technique	Inflammatory/acute changes	Structural/chronic changes
Conventional radiography	(+)	+
Computed tomography	(+)	+
Scintigraphy	+	—
Magnetic resonance imaging		
T1 weighted	(+)	+
STIR, T1/Gd-DTPA, T2	++	(+)
Ultrasonography	+	(+)

Gd-DTPA, gadolinium diethylenetriamine-pentaacetic acid; STIR, short tau inversion recovery; +, useful; (+), useful only in combination with other imaging techniques or MRI sequences; —, not useful.

IMAGING OF THE SACROILIAC JOINTS IN AXIAL SPONDYLOARTHRITIS

Imaging of the SIJ is critically important for diagnosis and classification in axSpA because the vast majority of patients with axSpA show involvement of this part of the axial skeleton, especially in early stages of the disease. For example, a certain degree of structural changes in the SIJ is a prerequisite for the classification of AS according to the 1984 modified New York

Fig. 117.1 (a) Conventional radiograph of the sacroiliac joints and the thoracolumbar junction in a patient with established ankylosing spondylitis. (b) Conventional radiograph of the sacroiliac joints and the hips in a patient with established ankylosing spondylitis. (c, d) Barsony technique for imaging of the sacroiliac joints in ankylosing spondylitis.



criteria¹⁶ and for classification of axSpA according to the Assessment of SpondyloArthritis international Society (ASAS) criteria published in 2009.¹

Conventional radiography

As the initial approach in a patient suspected of having axSpA, radiographs are the gold standard for assessment of structural changes in the SIJ. Typical findings are sclerosis, erosions or pseudodilation, and/or bony bridges (Fig. 117.2). The method used for quantification of structural changes in the SIJ in clinical practice¹⁷ has been derived from the modified New York criteria for classification of AS.¹⁶ Importantly, for this evaluation, the age of the patient needs to be taken into account, because bony changes in the SIJ frequently may be found in the elderly population as a feature of osteoarthritis. For a diagnosis of axSpA in early disease stages conventional radiography has limited value because of its poor sensitivity due to the inability of the method to detect active inflammation.¹⁸ Routine imaging of patients with low back pain to detect chronic SIJ changes did not provide substantial additional information in one study,¹⁹ but results may be different in younger patients who have inflammatory back pain and in whom the suspicion of axSpA is high.⁴ There is some evidence that structural changes in the SIJ may develop rather rapidly.²⁰

Computed tomography

For the detection of structural changes in the SIJ, CT (Fig. 117.3) has proven more useful than conventional radiography because it provides superior multidimensional imaging of anatomic structures by cutting the SIJ into slices.²¹⁻²³ This is advantageous because of the complicated anatomy of the SIJ caused by the irregular S-shaped orientation and the partly overlapping structures of the sacral and iliac joints.²⁴

With CT, however, as with radiography, findings of sclerosis, joint space narrowing, erosions, and ankylosis may be misleading in elderly patients,²⁵ since subchondral sclerosis of the SIJ, especially in the iliac portion, is a phenomenon of aging, as is joint space narrowing.⁷

CT-guided techniques to biopsy and inject the SIJ²⁶ have been used in experienced centers with some success.²⁷

One general note is that the radiation exposure associated with CT needs to be taken into account when a decision is made regarding imaging method. This radiation exposure is the reason that CT is not recommended for the evaluation of patients with low back pain and suspected SpA in daily practice.

Scintigraphy

The nuclear-medical method of scintigraphy takes advantage of the physical behavior of the radionuclide technetium-99, which enriches in areas of increased metabolism or inflammation. Therefore scintigraphy of the SIJ frequently was used in the past to detect sacroiliac and/or spinal inflammation in patients suspected having of axSpA.²⁸⁻³² However, because the sensitivity and specificity of other imaging techniques such as MRI were shown to be superior, its use has decreased substantially in recent years.^{8,33} The results of scintigraphy of the SIJ seem to be more reliable if there is unilateral involvement consistent with clinical symptoms. Therefore, since scintigraphy as a tool to detect sacroiliitis has clear limitations, it is not suitable for the diagnosis of axSpA. Whether scintigraphy can be of use as a more general tool for detecting enthesal inflammation in different regions at a time remains to be elucidated. As with CT, the radiation exposure needs to be taken into account when young patients with low back pain are being evaluated.

Magnetic resonance imaging

One of the major advantages of MRI is the detailed anatomic and pathologic imaging it affords in connection with the information provided on the location of inflammation. MRI is especially useful for detecting bone marrow edema as a sign of osteitis in the axial skeleton in patients with axSpA (Fig. 117.4a). MRI is also able to visualize the complicated anatomy of the region of the SIJ; this includes characteristic abnormalities of the periarticular soft tissue, which are only indirectly visible by other methods (Table 117.2). Sacroiliac inflammation as detected by MRI ("water signal") has been shown to correlate with conventional histologic and immunohistologic findings and to some degree with clinical symptoms of axSpA as well.¹⁴ MRI has also been used to detect more chronic structural changes of bone and joints. The typical structural changes in patients with axSpA are periarticular fat deposition, subchondral erosions, sclerosis (see Table 117.2, Fig. 117.4b), and



Fig. 117.2 Typical radiographic findings of sacroiliac joints involvement in a patient with ankylosing spondylitis, showing extensive sclerosis (left arrow), pseudodilation (right arrow), and partial ankylosis (asterisk).

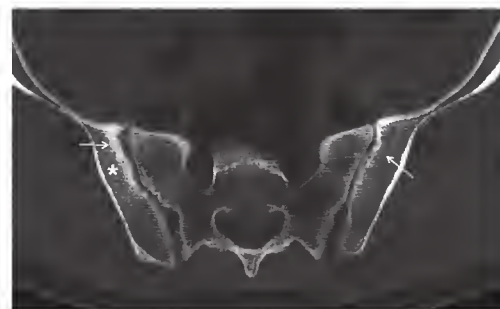


Fig. 117.3 Computed tomographic scan of the sacroiliac joints of a patient with ankylosing spondylitis. Note the areas with erosions (arrows) and sclerosis (asterisks), which represent characteristic signs of the disease.

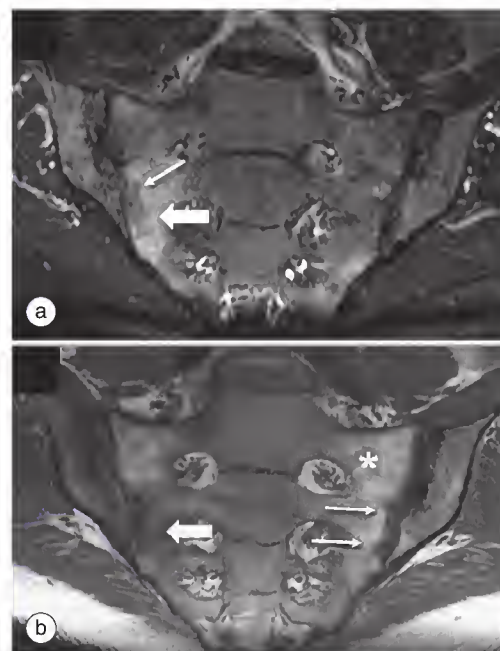


Fig. 117.4 Magnetic resonance image (MRI) of the sacroiliac joints of a patient with ankylosing spondylitis. Bone marrow edema (osteitis) is visible as hyperintense signal in the short tau inversion recovery (STIR) sequence (a) and as hypointense signal (thick arrows) in the T1-weighted sequence (b). Postinflammatory changes such as fat deposition are visible as hyperintense signal in the T1-weighted sequence and hypointense signal in the STIR sequence (asterisk). Structural changes (erosions) are seen in both sequences (thin arrows). In cases where more than one inflammatory lesion or a large periarticular lesion is present on one slice, this MRI finding is highly suggestive of axial spondyloarthritis.

TABLE 117.2

Characteristic lesions in the sacroiliac joints of patients with ankylosing spondylitis as revealed by magnetic resonance imaging

Tissue	Inflammatory changes	Structural changes
Bone marrow	Sacroiliitis (bone marrow edema, osteitis) in one or both parts of the sacroiliac joint (sacral or iliac). Bone marrow edema related to spondyloarthritis is located periarticularly.	Subchondral sclerosis Erosions Fatty deposition
Synovium	Synovitis. Shown only by T1/Gd-DTPA sequences. STIR sequences cannot differentiate between synovitis and physiologic joint fluid. Synovitis is a rare lesion.	Bony bridges/ankylosis
Joint capsule	Capsulitis. Comparable to synovitis. Both anterior and posterior joint capsule can be affected.	Bony bridges/ankylosis
Ligaments	Enthesitis, seen in the junction of ligaments and tendons with the bone.	Degeneration of ligament

Gd-DTPA, gadolinium diethylenetriamine-pentaacetic acid; STIR, short tau inversion recovery.

bony bridges or ankylosis. The fat signal in particular has raised interest because this element cannot be detected by conventional radiography.³⁴

Even though structural changes in the SIJ as demonstrated by MRI are not included in the current ASAS classification criteria¹ and the definition of positive findings on MRI,³⁵ there is some evidence that lesions such as fatty changes and erosions may contribute to the diagnostic usefulness of MRI in axSpA.³⁴ However, it is not clear whether MRI can substitute for radiography to optimize the diagnosis of chronic changes, and an international agreement on clear-cut definitions has not been achieved to date (see later).

Importantly, and in contrast to other imaging techniques, MRI is not associated with radiation exposure. This makes the technique especially useful in young women, children, and patients with a suspected future risk of relevant radiation exposure. However, routine access to MRI, optimal technical equipment, and skilled staff is not widely available, and the costs of MRI are still higher than those of other imaging techniques.³⁶ Furthermore, patients with claustrophobia, pacemakers, or metal implants cannot be examined by MRI. In addition, because of the long duration of the procedure (approximately 20 to 30 minutes) use of the technique is not feasible in some patients because of intolerable pain and stiffness in the supine position.⁷

Definition of a positive finding on magnetic resonance imaging of the sacroiliac joint in axial spondyloarthritis

According to the ASAS definition, the hyperintense/inflammatory signal in the bone marrow near the SIJ should preferably be located in the periarticular region. The MRI finding for the SIJ in patients with axSpA is considered positive when more than one lesion is present on a single MRI slice or, if there is only one lesion, it is present on at least two consecutive slices³⁵ (see Figs. 117.4 and 117.5).

Differential diagnoses for involvement of the sacroiliac joint

Bone marrow edema is not a specific feature of axSpA and may also occur in other diseases. The most important differential diagnoses for active changes in the SIJ are septic sacroiliitis, osteitis condensans, and pelvic fractures, and those for chronic changes are extensive sclerosis or structural changes caused by degenerative conditions.

In the case of septic sacroiliitis, conventional radiographs usually show normal findings in the first weeks of disease,⁷ whereas MRI is capable of demonstrating the pathologic process much earlier.^{38,39} Therefore MRI is considered the gold standard for a diagnosis of septic sacroiliitis. The major differential diagnostic criterion is that the infection passes the mark of anatomic borders, so that the proximal parasacroiliac structures, including

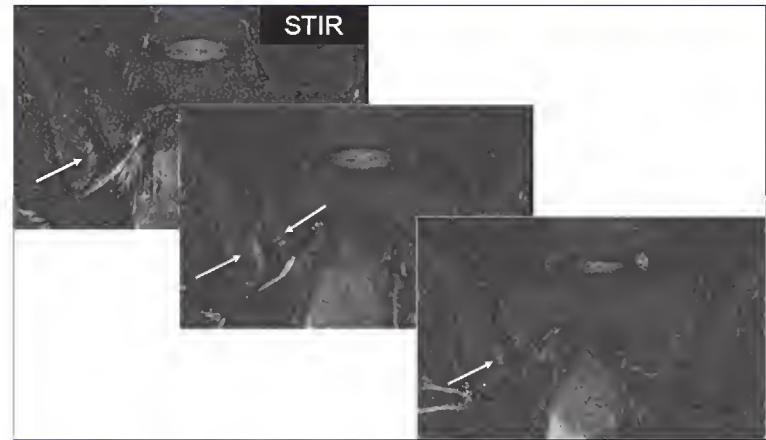


Fig. 117.5 Example of a positive finding on magnetic resonance imaging of the sacroiliac joints in axial spondyloarthritis. When only one lesion is seen, this lesion must be present in at least two consecutive slices (arrows).

the iliopsoas muscle, may be infiltrated. Fractures are mainly seen as insufficiency fractures and are characterized by a bone marrow edema that may be similar to that seen in sacroiliitis.

The MRI finding of extensive sclerosis, especially at the iliac side of the SIJ, may also be misleading. Osteitis condensans ilii, characterized by a triangular sclerosis, is found most often in women after pregnancy, but it may rarely occur in men as well. In diffuse idiopathic skeletal hyperostosis (Forestier disease), the typical findings are an irregularly shaped SIJ, including sclerosis, ossification of the joint capsule, and bony bridges, many of which may be difficult to differentiate from axSpA. However, such changes usually do not occur in young patients.

IMAGING OF THE SPINE IN AXIAL SPONDYLOARTHRITIS

Spinal changes, usually representing more advanced stages of the disease, may be clinically relevant for a diagnosis of axSpA, but they have never been part of the classification criteria for AS or axSpA. One reason is that only 3% to 5% of patients with AS were reported not to have unequivocal structural changes in the SIJ.⁴⁰ The other reason is the similarity of syndesmophytes to spondylophytes of a degenerative nature, especially in patients with disease of longer duration.

Therefore the current clinical significance of syndesmophytes is to support a diagnosis of axSpA in individual patients with indefinite SIJ findings. Furthermore, syndesmophytes have definite prognostic value, since the presence of one syndesmophyte has been shown to increase significantly the risk of development of more such changes.⁵ How much time is required for structural lesions of the spine to develop is not clearly known. Within the first 16 years of AS, bony changes have been reported to be present in more than 50% of patients.⁴¹

Both inflammatory and structural spinal changes play an important role in the evaluation of medical interventions, since the effect of anti-inflammatory agents such as non-steroidal anti-inflammatory drugs or tumor necrosis factor blockers on spinal inflammation (bone marrow edema) and new bone formation (syndesmophytes) are relevant objective outcomes in clinical studies in axSpA patients. However, clinical symptoms, including pain, stiffness, and decreased function, are considered even more important.

Conventional radiography

As for the SIJ, conventional radiography has a low sensitivity in detecting inflammation of the spine such as spondylitis, SpA, or spondylodiskitis.⁴² Nevertheless, conventional radiographs are the gold standard for the assessment and quantification of structural spinal changes. The visualization of osteodestructive and osteoproliferative processes in the vertebral bodies (Fig. 117.6) is useful to assess the course of the disease and the damage that has already occurred. Pathologic spinal changes related to axSpA can be differentiated in osteodestructive changes (erosions) and hyperproliferative changes (enthesophytes, vertebral squaring, disk calcifications, spondylophytes, syndesmophytes, bony bridging, vertebral ankylosis). Syndesmophytes are characterized by their typical vertical growth, which may lead to



Fig. 117.6 Typical osteodestructive changes seen as erosion (asterisk) and osteoproliferative changes seen as syndesmophytes (arrows) on a radiograph of the cervical spine of a patient with ankylosing spondylitis.



Fig. 117.7 Next to the vertebral bodies, also facet joints are frequently affected in ankylosing spondylitis, showing hyperproliferation and ankylosis (arrows).

bridging phenomena in the prediskal region between the intervertebral disk and the anterior intervertebral ligament.⁴³⁻⁴⁵

Furthermore, the lateral parts of the vertebral bodies and the facet joint area deserve attention, since they are frequently affected in AS (Fig. 117.7). Because these areas are difficult to assess by most imaging procedures, involvement of the facet joints is frequently underdiagnosed. Ankylosis of the facet joints may be discordantly associated with the presence of bridging syndesmophytes in established AS,⁴⁶ which suggests that these joints are involved primarily and early in the course of the disease.

Magnetic resonance imaging

For the spine as for the SIJ, MRI is considered the most sensitive method for the detection of inflammatory lesions related to axSpA.^{47,48} Assessment of spinal inflammation on MRI can be used as an indicator of disease activity, as a tool for evaluating response to biologic treatment, and also as a possible predictor of response to therapy.⁴⁹ Overall, spinal MRI performs best in the identification and quantification of active spinal lesions (Table 117.3, Figs. 117.8 and 117.9), for which it has proved superior compared with other

TABLE 117.3

Characteristic lesions in the spines of patients with ankylosing spondylitis as revealed by magnetic resonance imaging

Tissue	Inflammatory changes	Structural changes
Vertebral body	Inflammation (spondylitis) in the bone marrow, mainly in the corners	New bone formation (syndesmophytes, ankylosis), eventually erosions or destruction of the vertebral body (e.g. fracture) Fatty degeneration
Intervertebral disk	Inflammation (spondylodiskitis)	Ossification of the disk
Facet and costovertebral joints	Inflammation with or without involvement of the vertebral body	New bone formation and ankylosis in advanced stages
Ligaments	Enthesitis, mainly of the supraspinal and interspinal ligaments	Degeneration of ligaments

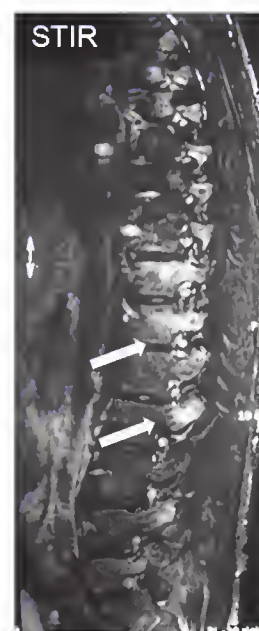


Fig. 117.8 Magnetic resonance images showing (posterior) spondylitis and inflammation of the facet joints (arrows).

imaging techniques.^{47,50} T1-weighted MRI has also been used successfully to assess structural changes (see Table 117.3, Fig. 117.10a).⁵⁰

Typical findings of disease activity when using spinal MRI in patients with axSpA are spondylitis, inflammation of the facet joints, and spondylodiskitis (see Fig. 117.8).

Spondylitis is a pathognomonic sign of bone marrow edema related to axSpA and has been considered as an early sign of spinal involvement in the disease (see Fig. 117.8). It represents an active osteitis and enthesitis at the junction of the annulus fibrosus and the longitudinal ligaments with the anterior ligament, the vertebral body, and the intervertebral disk. When MRI is used, spondylitis is typically seen as a hyperintense signal in STIR or T1/Gd-DTPA sequences with a corresponding hypointense signal in T1-weighted sequences. In later stages, the pathologic signal is inverted as a sign of a healing process and local tissue metaplasia with occurrence of fatty lesions, which shows as hyperintensity in T1-weighted images and hypointensity in STIR (or T1/Gd-DTPA) sequences. There is evidence that the posterior vertebral edges are more frequently involved in early stages of AS.⁵¹

Inflammatory lesions in the *facet joints* are also characterized by hyperintense signal in MRI sequences sensitive to depiction of inflammation (see Fig. 117.8) and hypointense signals in T1-weighted sequences. Active and structural changes of the facets and especially of costosternal and costovertebral joints in AS may lead to reduced chest expansion—a relatively frequent finding even in young AS patients. If clearly pathologic (age does have

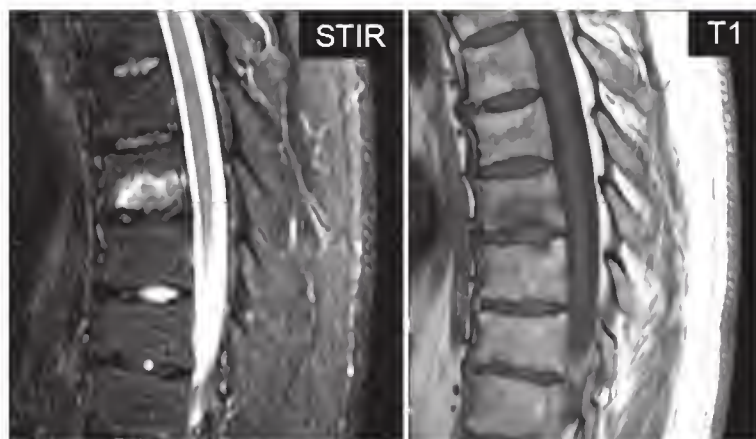


Fig. 117.9 (Abacterial) spondylodiskitis (formerly known as Andersson lesion) in established AS, typically recognized by a circumscribed hemispherical erosive lesion surrounded by bone marrow edema in STIR and the corresponding hypointense signal in T1-weighted MRI.



Fig. 117.10 “Positive MRI” of the spine for inflammatory changes, highly suggestive for axial SpA, with three vertebral corners being affected by bone marrow edema (a). Positive MRI of the spine for chronic changes, highly suggestive for axial SpA, with several vertebral corners being affected by fatty degenerative changes (b).

an influence on thoracic excursion), it can even be used as a diagnostic sign in AS.¹⁶

Spondylodiskitis is characterized by a circumscribed hemispheric erosive lesion, which is often surrounded by an area of bone marrow edema in one of two adjacent vertebral bodies. In contrast to conventional radiography, in which only the consequences of spondylodiskitis are visible in later disease stages as areas with sclerosis, MRI is able to detect such changes even in early phases^{52,53} (see Fig. 117.9). Accordingly, negative radiographic findings are sometimes accompanied by positive MRI findings indicative of spondylodiskitis.^{52,53} Asymptomatic spondylodiskitis occurs in multiple spinal segments in approximately 8% to 15% of patients with AS,^{42,54} whereas such findings are apparent in up to 31% of patients with enteropathic SpA.⁵⁵

Definition of a positive finding on magnetic resonance imaging of the spine in axial spondyloarthritis

According to the ASAS definition of a positive finding on MRI of the spine in axSpA,⁴⁸ bone marrow edema preferably should be located in the corner of the vertebral bodies. Evidence of anterior-posterior spondylitis in three or more vertebral corners is considered to be highly suggestive of axSpA (Fig. 117.10a), especially in patients of younger ages at which degenerative



Fig. 117.11 Spinal radiograph showing degenerative changes (arrows) in a patient with ankylosing spondylitis. Such changes are differentiated by syndesmophytes due to their horizontal growth. Ankylosis of the facet joints is also visible (asterisks).

changes play a minor role in the differential diagnosis. As for chronic changes, fatty deposition at several vertebral corners also may be indicative of axSpA (Fig. 117.10b). Detection of fatty deposition at vertebral corners, particularly if present at several sites, increases the likelihood of axSpA, especially in younger patients. There is limited information on the appearance of bone changes in early phases of diffuse idiopathic skeletal hyperostosis.

Differential diagnoses for involvement of the spine

As with the SIJ, bone marrow edema of spinal structures is not specific for axSpA but may also occur in other diseases. The most important differential diagnoses are degenerative changes, blood vessels and hemangioma, fractures, bacterial infection, and hyperproliferative changes due to other conditions.

Degenerative changes are seen on radiographs as osteophytes that grow in a horizontal direction (spondylophytes)⁵ (Fig. 117.11). The most typical degenerative changes on MRI are so-called erosive osteochondrosis or Modic lesions, which are a frequent finding in association with chronic back pain in patients of every age. These changes are recognized by the presence of bone marrow edema of the vertebral endplate accompanied by decreased disk height (Fig. 117.12). Similarly, Scheuermann disease starting in childhood is characterized by irregularities in the upper or lower part of the vertebral endplates and erosive changes on the vertebral surface, which often are not recognized before adulthood.

Diffuse idiopathic skeletal hyperostosis (DISH, Forrester's disease; Fig. 117.13) is characterized by bulky osteophytes, which often exceed the length of the anterior longitudinal ligament. Differentiating between the typical ankylosing processes in AS and DISH is sometimes difficult. Nevertheless, a radiographic differentiation between AS and DISH is possible because the shape of the spinal osteophytes differs. Typical syndesmophytes are much more frequent in AS, whereas DISH is characterized by degenerative spondylophytes and spondylosis.⁵⁶

Blood vessels are visualized by hyperintense signals in STIR sequences and hypointense signals in T1-weighted sequences, and they appear mainly in the posterior part of the vertebral body (Fig. 117.14). A hemangioma (see Fig. 117.14) is defined as an accumulation of blood vessels typically located within the vertebral body. Although its MRI appearance is similar to that of inflammatory bone marrow edema, these findings represent physiologic abnormalities and not inflammatory changes. In contrast, the most important feature for the inflammatory differential diagnosis is the extension of the hyperintense signal into the surrounding soft tissue across anatomic borders, which is typical of bacterial spondylodiskitis. Finally, because of underlying osteoporosis in association with a rigid stiffness of the spine, an increase in the risk of spinal fractures has been reported in patients with established AS, especially in patients with long disease duration and a high

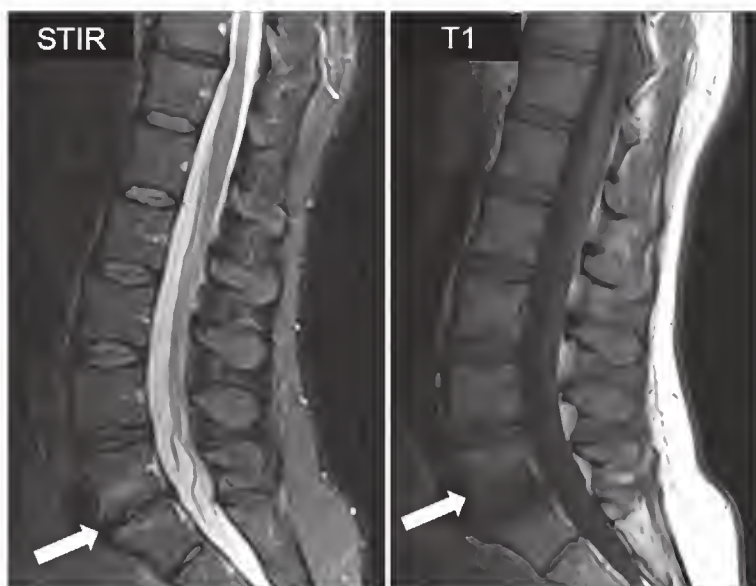


Fig. 117.12 Modic 1 lesion (arrows) characterized by bone marrow edema in the area of the vertebral endplates on short tau inversion recovery (STIR) magnetic resonance image and by hypointense signal on T1-weighted image, accompanied by a decrease in disk height and degeneration of the intervertebral disk.



Fig. 117.14 Magnetic resonance image showing blood vessels (thin arrows), appearing mainly in the posterior and middle part but also extending to the anterior part of the vertebral body, sometimes forming a hemangioma (thick arrow).

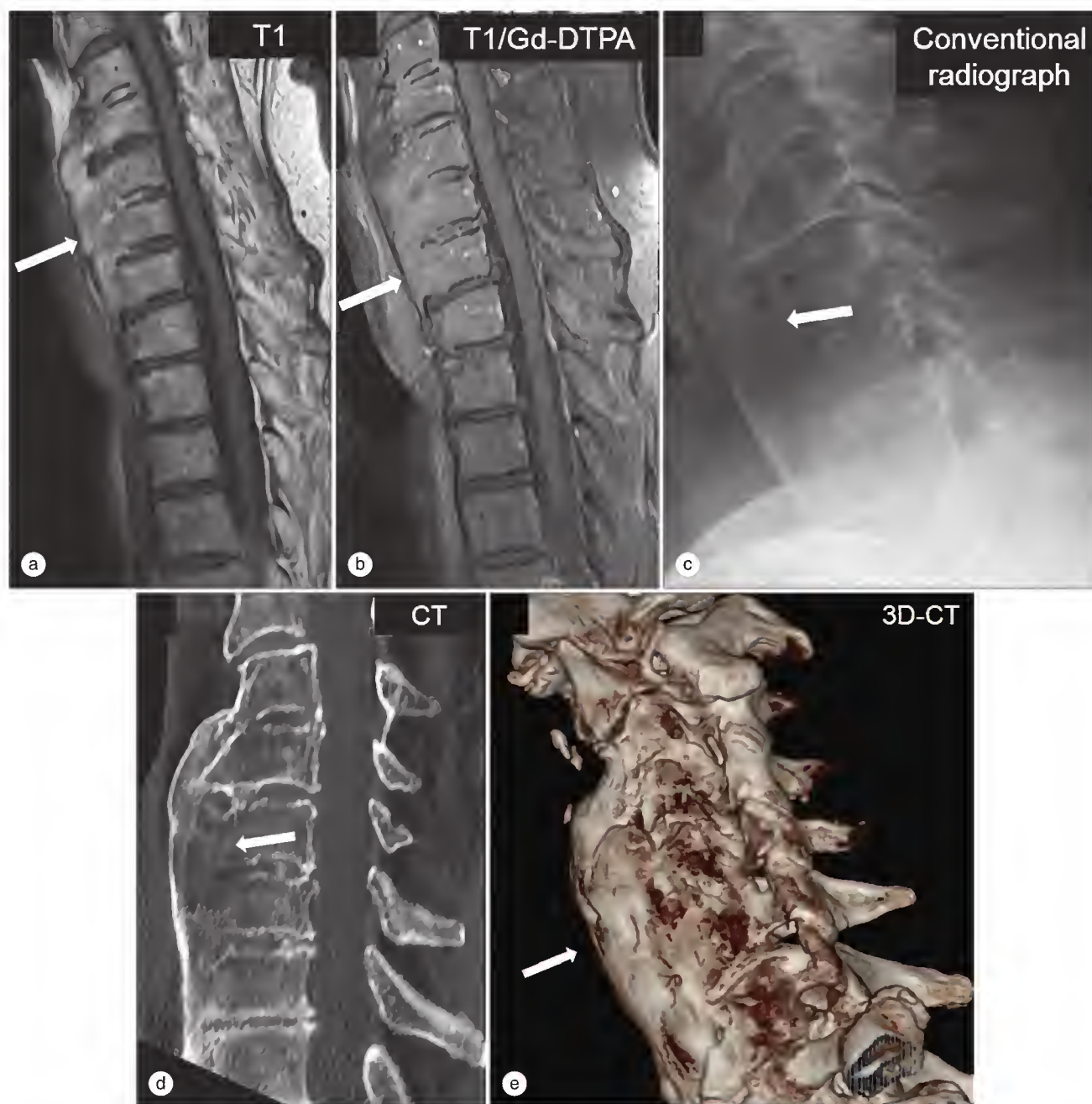


Fig. 117.13 Diffuse idiopathic skeletal hyperostosis (DISH) in the cervical spine as imaged by magnetic resonance imaging (a, b), conventional radiography (c), and computed tomography (d, e). DISH is characterized by bulky osteophytes that exceed the length of the anterior longitudinal ligament.

Fig. 117.15 Nondisplaced spinal fracture in the anterior part of the vertebral body. Because of the low bone mineral density, these fractures are not apparent on conventional radiographs (left panel). On magnetic resonance images (right panel), they are characterized by hyperintense signal on T1-weighted sequences with gadolinium diethylenetriamine-pentaacetic acid contrast (T1/Gd-DTPA) or short tau inversion recovery (STIR) sequences and by hypointense signal on T1-weighted sequences.



Fig. 117.16 Magnetic resonance images showing subarachnoid cysts, which are the pathophysiologic basis for the development of cauda equina syndrome, a rare but characteristic feature in patients with ankylosing spondylitis.

degree of spinal involvement.^{57,58} Spinal fractures in AS occur most frequently in the cervical spine^{59,60} but also may be seen in the cervicothoracic and thoracolumbar spine, often due to hyperextension injuries.^{54,61} Because of low bone mineral density and severe ankylosis, nondisplaced spinal fractures may not be diagnosed easily by conventional radiography (Fig. 117.15). The shear forces resulting from spinal movements may lead to dislocation of the injured spinal segment.⁵⁹ Spinal CT is necessary to diagnose a possible dislocation in patients with persistent or progressive symptoms after injury. Acute fractures show an increased signal intensity on STIR-weighted MRI and variable enhancement in T1/Gd-DTPA MRI, which indicates the location of the fracture line⁶² (see Fig. 117.15). On T1-weighted MRI the fractures display a decreased signal intensity⁶¹ (see Fig. 117.15). Finally, a disruption of the anterior longitudinal ligament is detected as a discontinuation and step-off of the low-signal-intensity structure along the anterior side of the vertebral body.⁶²

Cauda equina syndrome

Cauda equina syndrome (CES) is a rare but characteristic feature in patients with AS that occurs mainly in patients in advanced disease stages.⁶³ The pathophysiologic basis is cysts of the dural sack (Fig. 117.16). Clinically, these cysts may cause nerve compression symptoms such as irradiating pain

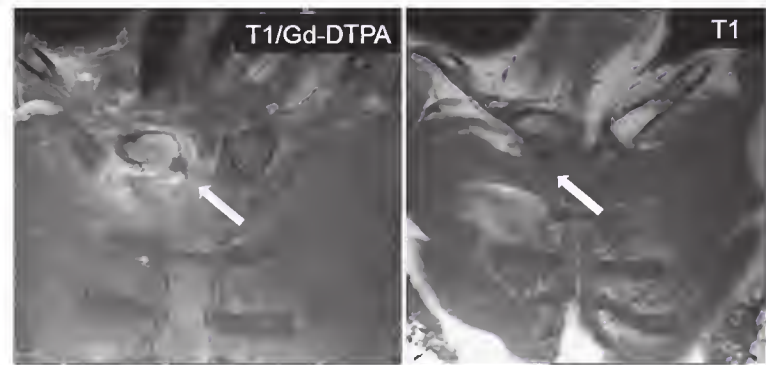


Fig. 117.17 Magnetic resonance images showing costochondritis (arrow) in a patient with ankylosing spondylitis.

and limb numbness. The ultimate cause of CES in AS is not completely known, but arachnoiditis due to inflammation of the posterior facet joints leading to adhesions within the thecal sac seems to be a likely explanation.⁶⁴ CES is characterized by slow and progressive sensorimotor loss possibly resulting in sphincter disturbances and incontinence. The overall prevalence of neurologic symptoms in AS patients is in the range of 2.1%,⁶⁵ and CES is not an infrequent cause of these.⁶⁶

Since diagnosis of CES by conventional radiographs is impossible, CT and MRI, which both are able to show enlargement of the caudal sac and the dorsal arachnoid diverticula, must be performed⁶⁷ (see Fig. 117.16).

IMAGING OF EXTRAVERTEBRAL MANIFESTATIONS OF AXIAL SPONDYLOARTHRITIS

Peripheral or extravertebral inflammatory manifestations of SpA may present clinically as involvement of the soft tissue (enthesitis, bursitis). However, when MRI is used, bone marrow edema (sympphysitis, costochondritis) may be found.

Involvement of the pubic symphysis may be seen in up to 25% of patients with axSpA. In most cases this is detected only in later stages of the disease when advanced abnormalities in the SIJ have already occurred.⁶⁸ In earlier stages of disease, symphysitis may be detected by MRI sequences sensitive for inflammation and appears as subcortical, anteriorly located bone marrow edema, indicating either enthesitis or pelvic instability, with a correspondingly decreased signal on T1-weighted sequences. However, involvement of the symphysis generally is not pathognomonic nor specific for a diagnosis of axSpA. Costochondritis (Fig. 117.17) is also a frequent extravertebral manifestation and can occur in up to 26% of axSpA patients.⁶⁹ Interestingly, many patients show no association between imaging assessments of

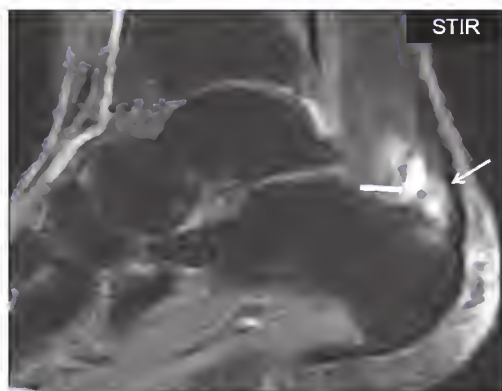


Fig. 117.18 Magnetic resonance image showing enthesitis (right arrow) and bursitis of the subachilleal bursa (left arrow) in a patient with peripheral spondyloarthritis.

costochondritis or anterior chest wall involvement and clinical signs of the disease.⁶⁹

Enthesitis (Fig. 117.18) and bursitis are clinical hallmarks of the spondyloarthritides. Frequently affected sites of enthesitis in SpA are the major trochanter, the pes anserinus, the Achilles tendon (see Fig. 117.18), and the retrocalcaneal bursa. Peripheral enthesitis may appear clinically as arthritis, but a differentiation can be achieved by MRI.⁷⁰ However, enthesitis is also well detected by ultrasonography.^{71,72} Both the longitudinal and the transversal axes need to be scanned to detect pathologic changes. In B mode (two-dimensional, real-time sequence), the presence of anechoic areas within the tendon sheath, especially in association with decreased echogenicity or synovial thickening, is considered to represent tenosynovitis.⁷³

Bursitis is seen as an enlarged bursa with a central hypoechoic zone.⁷³ Power Doppler ultrasonography is especially useful for visualization of vascularization at the cortical bone, the insertion of entheses, the junction between tendon and entheses, the body of tendons, and bursae. On ultrasonographic examination, most patients with SpA are found to have peripheral enthesitis, mostly in the distal portion of the lower limbs, irrespective of SpA subtype and other clinical symptoms.⁷² Inflammation of the tarsus⁷⁴ may occur as a first symptom earlier than manifestations at the axial skeleton and may develop into a chronic disease state characterized by ankylosis.⁴²

FUTURE PERSPECTIVES IN THE IMAGING OF SPONDYLOARTHRITIS

One important area of research in the field of imaging in spondyloarthritis is the potential of MRI to detect areas in the axial skeleton that will present any type of metabolic activity in order to predict those lesions which are going to show bone progression in the future. At the moment, more advanced techniques are being developed and tested in pilot studies, some of them also having the potential to be included in future research projects or maybe also in daily clinical routine. Preliminary studies with stronger MRI fields such as 3 Tesla MRI scanners or fusion imaging techniques such as positron emission tomography (PET)-CT and PET-MRI (Figure e117.1a and b) have shown that the sensitivity of the MRI scanners used in daily practice (1.0-1.5 Tesla) can be improved.⁷⁵ This suggestion is supported by studies analyzing biopsies of the facet joints⁷⁶ and the sacroiliac joints⁷⁷ of patients with clinical symptoms for SpA but negative MRIs, still showing areas with clear-cut inflammation detected histologically. The research on the diagnostic utility and clinical feasibility of such highly sensitive imaging techniques will lead to improved understanding of the processes underlying the development and the course of this disease but also lead the therapeutic research and clinical decisions in the future.

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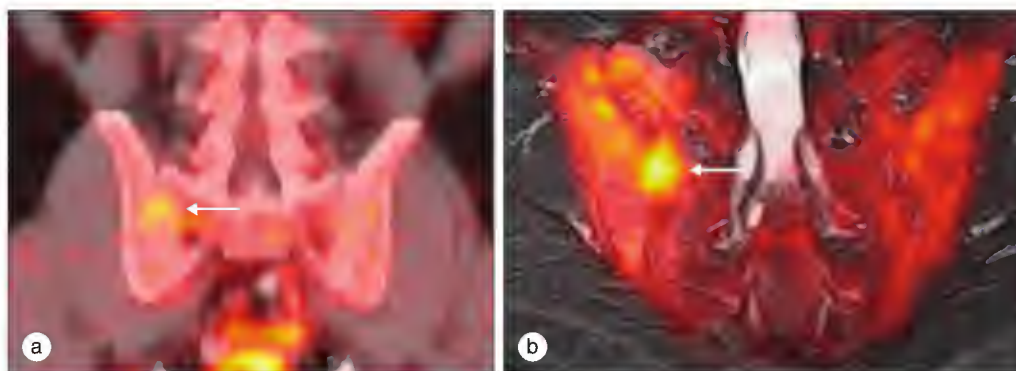


Fig. e117.1 Positron emission tomography of a 51-year-old patient with ankylosing spondylitis (a) fused with computer tomography scan and (b) with a 3-tesla magnetic resonance imaging scan. The arrows indicate the metabolic active region in the left sacroiliac joint of the patient.

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Management of ankylosing spondylitis/axial spondyloarthritis

■ JOACHIM SIEPER

- Early diagnosis, patient education, and physical therapy are essential for the successful management of ankylosing spondylitis (AS).
- The goals of physical therapy are to restore and maintain posture and movement to as nearly normal as possible.
- Self-management with exercises must be continued on a lifelong basis.
- Nonsteroidal antiinflammatory drugs (NSAIDs) and anti-tumor necrosis factor- α (anti-TNF- α) drugs are the only effective drugs available for the axial manifestations of AS.
- NSAIDs relieve pain and stiffness and facilitate physical therapy and might even be effective in preventing radiologic progression.
- Sulfasalazine and methotrexate have some effect on peripheral joint disease.
- Anti-TNF- α therapy is very effective in relieving symptoms and seems to have the potential for true disease modification.

HISTORICAL PERSPECTIVE

Until recently, rheumatologists have been much less interested in studying ankylosing spondylitis (AS) than other rheumatic diseases such as rheumatoid arthritis (RA) and lupus. This is despite the former's relatively high prevalence of between 0.2% and 1.0%¹ and the initial occurrence of symptoms early in life. The limitation of treatment options can probably be regarded as one important reason for this lack of interest.

The analgesic properties of salicylates and opioids led them to be among the first treatments that were offered to AS patients. Aspirin, a salicylate with less toxicity than salicylic acid, was developed in 1899. However, this drug was not as effective for AS as it was for other inflammatory rheumatic diseases. Beginning in the 1920s, radiation therapy was used to treat spinal inflammation with good results, including improvement of pain and stiffness. However, this type of treatment was discontinued once the serious long-term side effects such as leukemia and other hematologic malignancies became evident.

In 1949, phenylbutazone was introduced into clinical practice and showed very good efficacy in reducing pain and inflammation in patients with AS. It was the first drug for which the term *nonsteroidal antiinflammatory drug* (NSAID) was applied. However, because phenylbutazone causes serious side effects, notably aplastic anemia and hepatic injury, its use became restricted. It was largely replaced by indomethacin and, subsequently, other NSAIDs. Corticosteroids, despite being very effective in treating diseases such as RA, proved to be less effective for the treatment of AS.

The so-called disease-modifying antirheumatic drugs (DMARDs), including gold salts, antimalarial drugs, D-penicillamine, sulfasalazine, methotrexate, and various other immunosuppressive agents, were found to be effective for the treatment of RA but are either much less effective or not effective at all for the treatment of AS.

Current perspectives

The recently established efficacy of tumor necrosis factor (TNF)-blocking agents in treating patients with active AS, in contrast to the disappointing results from the agents just mentioned, has transformed treatment of this chronic inflammatory, frequently disabling disease.

Recently, an international group of experts from the Assessment of SpondyloArthritis international Society (ASAS) published recommendations for

the management of AS, which form part of the European League Against Rheumatism (EULAR) recommendations for various rheumatic diseases.² These recommendations are summarized in 11 bulleted statements in [Box 118.1](#) and in a flowchart in [Figure 118.1](#). It can easily be seen that NSAIDs and TNF blockers are regarded as the most important and possibly the only relevant part of the pharmacologic treatment that has to be combined with nonpharmacologic treatment during the entire course of the disease.

New classification criteria were published in 2009 for the entire group of axial spondyloarthritis (SpAs); the criteria apply not only to patients with AS and radiographic sacroiliitis according to the modified New York criteria³ but also to patients with nonradiographic axial SpA (nr-axSpA)—those in whom structural damage visible on radiographs has not yet developed⁴ (see also Chapter 113). These criteria allow clinical trials to be performed not only in AS patients but also in those with nr-axSpA only and the whole group of patients with axSpA.

ASSESSMENT OF EFFICACY OF TREATMENT OF ANKYLOSING SPONDYLITIS

To judge the efficacy of certain treatments, instruments for the measurement of improvement during therapy are needed, both for clinical trials and for daily clinical practice. In parallel with the limited effective pharmacologic therapies for AS, until recently there were only poorly defined tools available to assess outcome in clinical trials.

Pooled indices

Assessment of SpondyloArthritis international Society criteria

In 1995 the ASAS was formed and established a core set of domains and individual instruments for the evaluation of AS ([Table 118.1](#)).⁵ Subsequently, the ASAS developed criteria for the short-term improvement of AS patients treated with symptom-modifying drugs by analyzing treatment trials involving NSAIDs. According to these criteria, improvement in AS is defined as both relative improvement of at least 20% and actual improvement of at least 10 units on a scale of 0 to 100 in each of three domains, with no worsening in the fourth domain of more than either 20% or 10 units ([Table 118.2](#)). Partial remission was defined as a low level of disease activity below 20 units on a scale of 0 to 100 in each of the four domains (see [Table 118.2](#)).^{5,6} Once the dramatic therapeutic effects of TNF-blocking agents became evident, higher levels of response, such as ASAS40 improvement (see [Table 118.2](#)), were defined in these domains. In addition, ASAS5/6 criteria were proposed and based on a 20% improvement in at least five of six domains, including the same four domains defined in the ASAS20 criteria with the addition of acute-phase reactants and spinal mobility (see [Table 118.2](#)). Most recently, an AS Disease Activity Score has been developed by taking into account total back pain (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] question 2), patient global evaluation, peripheral joint pain or swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6), and C-reactive protein (CRP) (or erythrocyte sedimentation rate [ESR] if CRP is not available).⁵ This disease activity score differentiated better between responders and nonresponders in treatment trials than did the other scores.

Bath criteria

Apart from this ASAS core set, a number of measures of AS were developed by the Bath group in the United Kingdom. The BASDAI combined the level of pain in the spine, peripheral joints, and entheses, the level of fatigue, and the intensity and duration of morning stiffness and is frequently used as a

BOX 118.1 FIRST UPDATE OF THE ASAS/EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF AS**Overarching principles of the management of AS**

- AS is a potentially severe disease with diverse manifestations that usually requires multidisciplinary treatment coordinated by a rheumatologist.
- The primary goal of treating patients with AS is to maximize long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation or normalization of function, and social participation.
- Treatment of AS should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
- Optimal management of patients with AS requires a combination of nonpharmacologic and pharmacologic treatment modalities.

1. General treatment

Treatment of patients with AS should be tailored according to

- Current manifestations of the disease (axial, peripheral, enthesal, extraarticular symptoms and signs)
- Level of current symptoms, clinical findings, and prognostic indicators
- General clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors)

2. Disease monitoring

Monitoring of disease in patients with AS should include

- Patient history (e.g., questionnaires)
- Clinical parameters
- Laboratory tests
- Imaging

All monitoring should be conducted according to the clinical findings, as well as the ASAS core set. The frequency of monitoring should be decided on an individual basis depending on the

- Course of symptoms
- Severity
- Treatment

3. Nonpharmacologic treatment

- The cornerstone of nonpharmacologic treatment of patients with AS is patient education and regular exercise.
- Home exercises are effective. Physical therapy with supervised exercises, land or water based and individually or in a group, should be preferred because these are more effective than home exercises.
- Patient associations and self-help groups may be useful.

4. Extraarticular manifestations and comorbid conditions

- Frequently observed extraarticular manifestations, such as psoriasis, uveitis, and IBD, should be managed in collaboration with the respective specialists.
- Rheumatologists should be aware of the increased risk for cardiovascular disease and osteoporosis.

5. Nonsteroidal antiinflammatory drugs

- NSAIDs, including coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness.
- Continuous treatment with NSAIDs is preferred for patients with persistently active, symptomatic disease.
- Cardiovascular, gastrointestinal, and renal risks should be taken into account when prescribing NSAIDs.

6. Analgesics

- Analgesics, such as paracetamol and opioid (like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, or are poorly tolerated.

7. Glucocorticoids

- Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered.
- The use of systemic glucocorticoids for axial disease is not supported by evidence.

8. Disease-modifying antirheumatic drugs

- There is no evidence for the efficacy of DMARDs, including sulfasalazine and methotrexate, in the treatment of axial disease.
- Sulfasalazine may be considered in patients with peripheral arthritis.

9. Anti-tumor necrosis factor therapy

- Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
- There is no evidence to support the obligatory use of DMARDs before or concomitant with anti-TNF therapy in patients with axial disease.
- There is no evidence to support a difference in efficacy of the various TNF inhibitors in treating the axial and articular/enthesal disease manifestations, but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
- Switching to a second TNF blocker might be beneficial, especially in patients with loss of response.
- There is no evidence to support the use of biologic agents other than TNF inhibitors for AS.

10. Surgery

- Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age.
- Spinal corrective osteotomy may be considered in patients with severe disabling deformity.
- In patients with AS and an acute vertebral fracture, a spinal surgeon should be consulted.

11. Changes in disease course

- If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor.

parameter of disease activity (Fig. 118.2).⁵ The Bath Ankylosing Spondylitis Function Index (BASFI), which is based on a questionnaire filled out by the patient, is the most frequently applied instrument for the measurement of function.⁵

Specific clinical and laboratory markers**Laboratory tests**

ESR and CRP values are lower in patients with AS than in those with RA, are elevated in only 50% to 60% of patients, and often do not correlate very well with disease activity. However, it was recently shown that elevated CRP is a risk factor for radiographic progression in both the sacroiliac (SI) joint⁶ and the spine.⁷

Spinal mobility

Limitation of spinal mobility and ankylosis of the spine are the major long-term adverse outcomes of AS, and any effective treatment should, besides improving the signs and symptoms, also be judged by its capacity to preserve spinal mobility and prevent or retard the occurrence of ankylosis in the spine. The Bath Ankylosing Spondylitis Metrology Index (BASMI) is a

combined tool for assessing spinal mobility and hip function. The BASMI 10 (Table 118.3) or the linear BASMI is recommended instead of the BASMI 3-point answer scale for clinical trials and in daily clinical practice because they are more sensitive to change.⁵ Measurement of chest expansion is often used as a stand-alone measure.

Imaging

In contrast to RA, for which radiographic change is an important endpoint and several validated scoring methods are available, radiographic change in AS is not a well-established measure of outcome. Only recently have scoring methods for radiologic change in the spine been evaluated. The best method currently seems to be the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), which has the highest reliability and the best sensitivity to change.⁵ This score ranges from 0 to 72 and scores 24 vertebral units (two opposing vertebral bodies of the anterior cervical and lumbar spine) as 0 (normal), 1 (erosion, sclerosis, or squaring), 2 (syndesmophyte), or 3 (bridging syndesmophyte).

In contrast to radiographic imaging, which may take several years to detect the consequences of inflammation (and not inflammation itself), magnetic resonance imaging (MRI) detects acute inflammation of the

ASAS/EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF AS

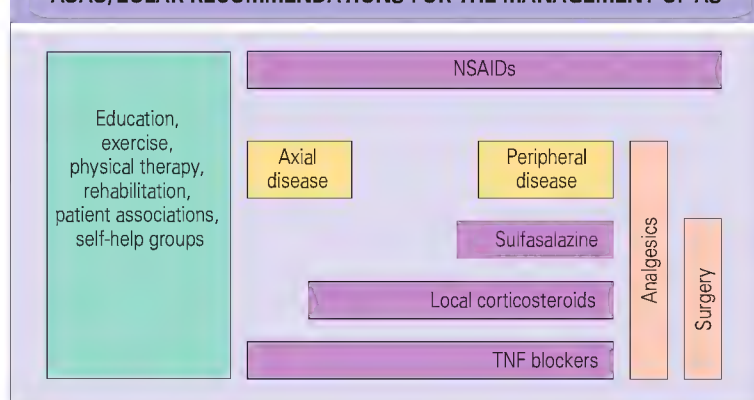


Fig. 118.1 Flowchart summary of the Assessment of SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) recommendations for the management of ankylosing spondylitis (AS). NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor. (From Zochling J, van der Heijde D, Burgos-Vargas R, et al. Assessment in AS international working group: European League Against Rheumatism. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;65:442-52.)

TABLE 118.1

Assessment of disease in patients with ankylosing spondylitis

Domain	Instrument
Physical function	BASFI
Pain	VAS*—last week, spine, at night, attributable to AS; and VAS—last week, spine, attributable to AS
Spinal mobility	Chest expansion test, modified Schober test, and occiput-to-wall distance test
Patient global	VAS—last week
Stiffness	Duration of morning stiffness—spine, last week
Peripheral joints	Number of swollen joints (44-joint count)
Entheses	No preferred instruments yet available
Fatigue	First question of the BASDAI
Acute-phase reactants	ESR or CRP
Radiographs of spine and pelvis	Lateral lumbar spine, lateral cervical spine, and pelvis (sacroiliac and hip joints)

*Instead of a VAS (0 to 100), a numeric rating scale (0 to 10) can also be used and is easier to apply in daily clinical practice (see Fig. 118.2).

AS, ankylosing spondylitis; BASFI, Bath Ankylosing Spondylitis Function Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale.

As proposed by the Assessment in Ankylosing Spondylitis (ASAS) Working Group and with modification from van der Heijde D, Bellamy N, Calin A, et al. Preliminary core sets for endpoints in ankylosing spondylitis. *Assessments in Ankylosing Spondylitis Working Group. J Rheumatol* 1997;74:4225-9.

entheses, bone, and synovium. Acute inflammation is best detected by applying contrast with gadolinium or diethylenetriamine pentaacetic acid (DTPA) or by using fat suppression techniques (i.e., short tau inversion recovery [STIR]). Scores for the quantification of acute lesions in the spine and SI joint have recently been proposed.⁸

PHYSICAL THERAPY

Physical therapy was for a long time the most important strategy in managing AS and remains the most important nonpharmacologic approach. Its aims are primarily to prevent or slow restriction of spinal mobility and the development of disability and also to improve the symptoms of pain and stiffness. Once the diagnosis of AS is made, the patient should be referred to a physical therapist to teach the patient the exercises to perform regularly.

TABLE 118.2

ASAS Working Group criteria for response*

A. Domains and instruments relevant for ASAS response criteria (4 domains)	
Patient global assessment	VAS (0-100)
Back pain	VAS (0-100)
Function	BASFI
Inflammation	Mean of duration and severity of morning stiffness (questions 5 and 6 of the BASDAI)
B. ASAS improvement criteria in 3 of 4 domains (on a scale of 0-100)	
ASAS20	≥20% and ≥10 units (on a scale of 0-100) in 3 of 4 domains with no worsening ≥20% and ≥10 units in the remaining domain
ASAS40	≥40% and ≥20 units with no worsening at all in the 4th domain
Partial remission	≤20 units (on a scale of 0-100) in all 4 domains
C. ASAS 5/6 improvement criteria: improvement (≥20%) in any 5 of the following 6 domains	
Patient global assessment	VAS (0-100)
Back pain	VAS (0-100)
Function	BASFI
Inflammation	Mean duration and severity of morning stiffness (questions 5 and 6 of the BASDAI)
C-reactive protein	
Spinal mobility	Measured by either spinal lumbar flexion or the BASMI (see Table 118.3)

*ASAS 20% (ASAS20) improvement and partial remission criteria have been developed based on NSAID studies.⁵ ASAS 40% improvement (highlighted in Fig. 118.3b) and 5 of 6 criteria (see Fig. 118.3c) differentiated best between placebo and drug response in anti-tumor necrosis factor- α trials.⁶ Instead of a VAS (0-100), a numeric rating scale (0-10) can also be used.

ASAS, Assessment of SpondyloArthritis international Society; BASFI, Bath Ankylosing Spondylitis Function Index; VAS, visual analogue scale.

Because the main long-term outcome to be prevented is flexion deformity of the spine, exercises concentrate on extension and rotation of the spine.² An exercise sequence for AS patients is shown in Figure 118.3.

Patients should be advised to exercise daily at home and to attend weekly group physical therapy sessions. The patient's own efforts are the key to future success, and patients have to be convinced that a daily exercise program should become a normal part of their day. In the long term many patients do not need to continue attendance, but some mechanism should exist to ensure that patients are seen and assessed regularly by their physical therapist. If patients are symptomatic and complain about pain or stiffness, they should also be treated with NSAIDs (see later) or other effective drugs to permit full mobilization during the exercises. Furthermore, patients should be encouraged to participate in moderate sport activities such as swimming and cycling.

Although the clear benefit of regular physical therapy has long been recognized at an individual level by patients and physicians, these impressions are supported by results from controlled trials. Thus in one study, a program combining physical therapy with patient education significantly improved function after 4 months in comparison to a control group.⁹ Another study comparing group physical therapy and daily home exercise with home exercise alone showed only a small advantage for group exercise.

Hydrotherapy might be of additional benefit in producing the appropriate environment in which movement can be maximized. Normal spa therapy seems to have at least as good a short-term effect as weekly group physical therapy plus daily home exercise, but its long-term effect is less certain.⁹ Other specific physiotherapy interventions such as pulsed shortwave, local ultrasound therapy, local heat or cold therapy, and transcutaneous nerve stimulation are used for the treatment of AS, but their additional potential value has not been well established.

Patient education is an essential part of nonpharmacologic therapy and should include information on pathogenesis, clinical manifestations, and course of the disease; information on physiotherapy (including advice about posture) and how to cope with the disease; and counseling on the socioeconomic consequences of the disease.²

BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX (BASDAI)

Please tick the box which represents your answer (for example, ☒ 10).
All questions refer to **last week**.

1. How would you describe the overall level of fatigue/tiredness you have experienced?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
none very severe

2. How would you describe the overall level of AS **neck, back, or hip** pain you have had?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
none very severe

3. How would you describe the overall level of pain/swelling in joints **other than** the neck, back, or hips you have had?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
none very severe

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
none very severe

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
none very severe

6. How long does your morning stiffness last from the time you wake up?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
0 hr 1 hr 2 hr or more

Fig. 118.2 In the original version a visual analogue scale was used, whereas here a numeric rating scale is shown. The BASDAI is evaluated by computing the mean of questions 5 and 6, calculating the sum of the values of questions 1 to 4 and the mean of questions 5 and 6, and dividing the result by 5. (Modified from Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286-91.)

TABLE 118.3

Bath Ankylosing Spondylitis Metrology Index for the measurement of spinal mobility

	0	1	2	3	4	5	6	7	8	9	10
Lateral flexion	≥20	18-20	15.9-17.9	13.8-15.8	11.7-13.7	9.6-11.6	7.5-9.5	5.4-7.4	3.3-5.3	1.2-3.2	<1.2
TTW	<10	10-12.9	13-15.9	16-18.9	19-21.9	22-24.9	25-27.9	28-30.9	31-33.9	34-36.9	≥37
Modified Schober	≥7.0	6.4-7.0	5.7-6.3	5.0-5.6	4.3-4.9	3.6-4.2	2.9-3.5	2.2-2.8	1.5-2.1	0.8-1.4	≤0.7
IMD	≥120	110-119.9	100-109.9	90-99.9	80-89.9	70-79.9	60-69.9	50-59.9	40-49.9	30-39.9	<30
Cervical rotation	≥85	76.6-85	68.1-76.5	59.6-68	51.1-59.5	42.6-51	34.1-42.5	25.6-34	17.1-25.5	8.6-17	<8.5

Eleven-point scale or linear function recommended by the Assessment of SpondyloArthritis international Society.

IMD, intermalleolar distance; TTW, trochanter to wall.

From Jones SD, Porter J, Gorrett SL, et al. A new scoring system for the Bath Ankylosing Spondylitis Metrology Index (BASMI). *J Rheumatol* 1995;22:1609.

NONBIOLOGIC PHARMACOLOGIC THERAPY

Nonsteroidal antiinflammatory drugs

NSAIDs are regarded as the cornerstone of pharmacologic intervention for AS; they reduce pain and stiffness rapidly after 48 to 72 hours.

The first NSAIDs used for the treatment of AS were phenylbutazone and indomethacin, which were shown to be effective in controlled trials. Subsequently, many others have been shown to be effective, including diclofenac, naproxen, ibuprofen, piroxicam, meloxicam, ketoprofen, and aceclofenac, among others (Table 118.4).¹⁰⁻¹⁷ More recently, efficacy in treating AS has also been demonstrated for the cyclooxygenase-2 (COX-2)-selective



Fig. 118.3 An exercise sequence used in patients with ankylosing spondylitis. Cervical spine exercises include full extension (a) and rotation (b). A sequence of back extension (c and d) is followed by rotation in the lying (e and f) and upright kneeling (g) positions. Finally, breathing with the thoracic muscles is practiced (not shown).

TABLE 118.4

Overview of nonsteroidal antiinflammatory drugs that have been studied for treatment of ankylosing spondylitis

Drug	Half-life (hr)	Approved maximum daily dosage (normally for arthritis)	Investigated for ankylosing spondylitis	Efficacy for ankylosing spondylitis	Ref
Aceclofenac	4.0-4.3	200 mg	Aceclofenac 100 mg twice daily vs. tenoxicam 20 mg daily	Equally effective	10
Celecoxib	8-12	400 mg	Ketoprofen 100 mg twice daily vs. celecoxib 100 mg twice daily vs. placebo	Celecoxib and ketoprofen equally effective, both superior to placebo	11
Etoricoxib	≈22	90 mg	Etoricoxib 90 mg daily vs. etoricoxib 120 mg daily vs. naproxen 1000 mg daily vs. placebo	Etoricoxib in both dosages superior to naproxen, naproxen superior to placebo	12
Ibuprofen	1.8-3.5	2400 mg	Ketoprofen 100 mg twice daily vs. ibuprofen 400 mg three times daily	Ketoprofen superior to ibuprofen	13
Indomethacin	2	150 mg	Aceclofenac 200 mg daily vs. indomethacin 100 mg daily	Equally effective	14
Diclofenac	≈2	150 mg	Diclofenac 75, 100, 125 mg daily vs. indomethacin 75, 100, 125 mg daily	Equally effective	15
Ketoprofen	1.5-2.5	200 mg	Ketoprofen 100 mg twice daily vs. celecoxib 100 mg twice daily vs. placebo	Ketoprofen and celecoxib equally effective, both superior to placebo	11
Naproxen	10-18	1000 mg	Etoricoxib 90 mg daily vs. etoricoxib 120 mg daily vs. naproxen 1000 mg daily vs. placebo	Etoricoxib in both dosages superior to naproxen, naproxen superior to placebo	12
Meloxicam	≈20	15 mg	Piroxicam 20 mg daily vs. meloxicam 15 mg daily vs. meloxicam 22.5 mg daily vs. placebo	Equally effective in all 3 treatment groups, superior to placebo	16
Piroxicam	30-60	20 mg	Piroxicam 20 mg daily vs. meloxicam 15 mg daily vs. meloxicam 22.5 mg daily vs. placebo	Equally effective in all 3 treatment groups, superior to placebo	16
Phenylbutazone	50-100	600 mg	Flurbiprofen 200 mg 3 times daily vs. phenylbutazone 300 mg	Equally effective	17

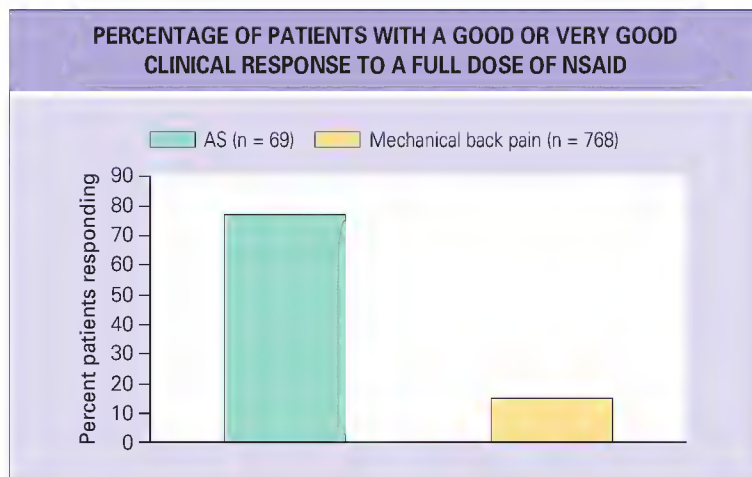


Fig. 118.4 Percentage of patients with ankylosing spondylitis (AS) versus those with mechanical back pain who exhibit a good or very good clinical response to a full dose of a nonsteroidal antiinflammatory drug (NSAID). (Modified from Amor B et al.¹⁸)

inhibitors celecoxib and etoricoxib (see Table 118.4). When AS patients are asked about the level of efficacy when treated with NSAIDs, 70% to 80% report good or very good improvement in their symptoms.^{12,18} In contrast, this level of response is reported by only about 15% of patients with chronic low back pain of noninflammatory etiology (Fig. 118.4).¹⁸ Furthermore, a good response to NSAID treatment can be used as a helpful diagnostic approach to differentiate chronic back pain attributable to AS from other causes.¹⁸ Major improvement can occur with NSAIDs, with up to 15% of active AS patients treated with a full dose of an NSAID reaching the ASAS criteria for partial remission.¹⁸

In AS patients with active disease, the highest tolerated dose of a single NSAID might be necessary to achieve an optimal effect, although a dose plateau may be reached. Thus in a recent study, 120 mg/day of etoricoxib was not superior to 90 mg/day.¹² Normally, the optimal effect of an NSAID is reached in about 2 weeks, but sometimes a longer duration of treatment is necessary to determine the optimal dose. In some patients a full dosage

is needed to cover the entire day, whereas if morning stiffness and pain at night are the predominant symptoms, a long-acting nighttime dose might be sufficient. The treating physician should be familiar with the optimal dose of at least three different NSAIDs, such as diclofenac, indomethacin, and naproxen, and at least one coxib because patients often respond to one NSAID but not another.

A recent study in which different NSAIDs were compared for the treatment of AS found that the level of improvement was higher in AS patients with axial manifestations only than in AS patients with axial symptoms plus peripheral arthritis.¹⁹ The reason for this difference is unknown.

Nonsteroidal antiinflammatory drugs as disease modifiers

One interesting question is whether NSAIDs are effective only in reducing symptoms or whether they might have an additional effect on the long-term outcome of AS. One earlier study reported a reduction in spinal ossification after prolonged and continuous use of phenylbutazone in patients with AS.²⁰ Similar findings have been reported for treatment with indomethacin. The issue has therefore been raised whether NSAIDs should be given continuously or, in the light of their potential toxicity, should be administered only during disease flare-ups. A recent study allocated a total of 215 patients to receive treatment with NSAIDs either continuously or only on demand for a period of 2 years. All patients began treatment with celecoxib at a starting dosage of 100 mg twice daily; patients could increase the dosage to 200 mg twice daily or could change to another NSAID. Most interestingly, significantly less radiographic progression was found in the continuous-treatment group than in the on-demand group (Fig. 118.5),²¹ thus suggesting that NSAIDs may have disease-controlling properties. In this study no increased toxicity was noted in the continuous-treatment group. Intriguingly, the overall level of clinical disease activity was not clearly different between the groups during the 2-year treatment period. A subsequent analysis of the study showed that only patients with elevated acute-phase reactants (CRP, ESR, or both) benefited from continuous NSAID therapy, not patients with normal CRP.²² It was indeed recently confirmed in another AS cohort that radiographic progression was slowed in patients with elevated time-averaged CRP or the presence of syndesmophytes at baseline when treated with higher cumulative doses of NSAIDs over a 2-year period.²³ These data raise the question whether such a possible disease-controlling effect is due to the antiinflammatory action of these drugs or whether these agents have additional actions. Furthermore, treatment with NSAIDs caused a significant decrease in serum CRP levels, either in comparison to baseline²⁴ or in comparison to placebo-treated patients.²⁵ More data are needed to confirm these exciting findings and to address these questions.

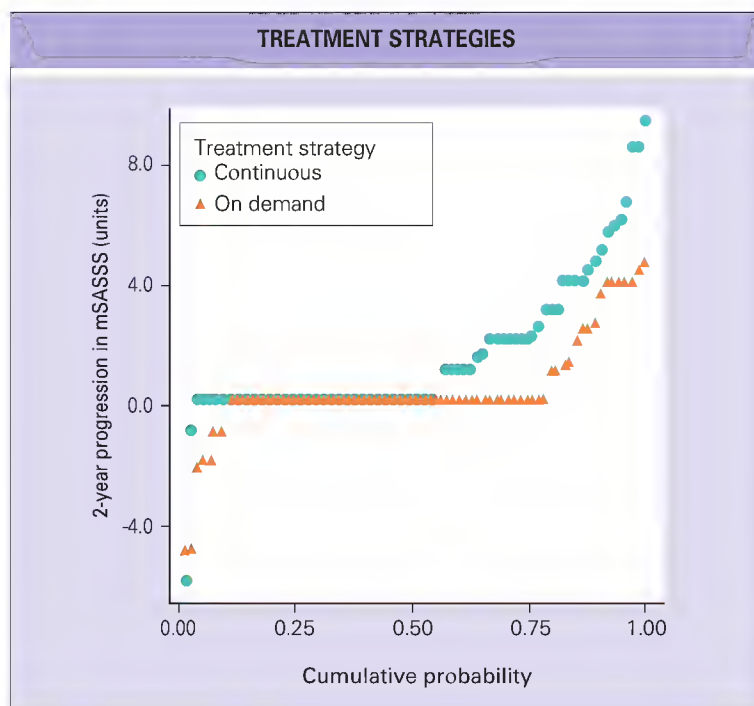


Fig. 118.5 Patients from a previous placebo-controlled trial were randomized to receive continuous ($n = 111$) or on-demand ($n = 104$) treatment with celecoxib 2×100 mg/day, which could be increased to 2×200 mg/day or could be changed to another NSAID. Radiographs of the spine were scored at baseline and after 2 years of treatment according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) without information on the order of the films. Each symbol represents one single patient. The slower radiologic progression in the continuous than in the on-demand group was significant ($P = .002$). (From Wanders A et al,²¹ with permission from John Wiley & Sons, Inc.)

It still needs to be determined whether NSAIDs should be used continuously even if patients are free of symptoms.²⁶

A key factor is the known toxicity of NSAIDs, which must be taken into account when using such a treatment strategy. The toxicity of nonselective and COX-2-selective NSAIDs is now better understood than ever before. Severe gastrointestinal side effects can be expected in 1% to 3% of patients per year treated continuously with nonselective NSAIDs, whereas severe cardiovascular thrombotic side effects occur in 1% to 2% per year if either COX-2-selective inhibitors or traditional NSAIDs are chosen for treatment. These side effects are dose dependent and more frequent in patients with gastrointestinal or cardiovascular risk factors, respectively.²⁶

Patients who still have active disease despite treatment with NSAIDs or who do not tolerate such treatment should then be considered candidates for other therapies (see below).

Corticosteroids

Systemic corticosteroids

In contrast to other inflammatory rheumatic diseases such as RA, systemic corticosteroids do not play a major role in the treatment of AS.²⁷ This judgment is based on clinical experience because no studies have investigated the efficacy of oral corticosteroid therapy. Even though peripheral arthritis often improves if patients are treated with moderate doses of prednisolone (20 to 30 mg/day), the axial manifestations improve only slightly, if at all, at such a dose.

Some uncontrolled open trials and one double-blind randomized trial demonstrated good short-term efficacy of intravenous pulsed methylprednisolone (1 g/day for 3 days) in patients with AS refractory to therapy. However, there is no evidence of a long-term effect of such treatment.

Intraarticular corticosteroids

Intraarticular corticosteroid injections into the SI joints have been shown to be effective. Usually, 40 mg of triamcinolone is injected; intraarticular positioning of the needle should be guided by computed tomography (CT) (Fig. 118.6a) or, if available, by open low-field MRI. An improvement in symptoms and a reduction in inflammation as detected by MRI (see Fig.

118.6b and c) have been demonstrated for up to 6 months and sometimes even longer. Non-CT- or non-MRI-guided local injections of the SI joint (most of them probably periarticular) have also been reported to occasionally be effective, although no formal study is available. Local corticosteroid injections are likewise recommended for peripheral joint manifestations² and particularly for enthesitis.²⁸

Conventional disease-modifying antirheumatic drugs

In general, conventional DMARDs, which play such a dominant role in the treatment of RA, have no proven efficacy for the axial manifestations of AS and limited efficacy for the peripheral manifestations.

Sulfasalazine

Sulfasalazine is the best-investigated DMARD for the treatment of AS. A recent Cochrane review analyzed the published studies of AS.²⁹ The pooled analysis, based on 11 studies, showed that the difference between intervention groups was significant only for ESR and morning stiffness, with sulfasalazine favored over placebo, but not for the other variables. One trial investigating patients with a relative short disease duration (<6 years) showed a benefit in the primary outcome parameters, including back pain, spinal mobility, and well-being. Another reported no effect in patients with axSpA and a symptom duration of less than 5 years,³⁰ including patients with nr-axSpA.⁴ By contrast, several trials showed higher efficacy of sulfasalazine than placebo in patients with peripheral arthritis. Based on these results, sulfasalazine is not recommended for treatment of the axial manifestations of AS but may be used for peripheral arthritis in AS patients (see Box 118.1).² Normally, treatment at a dosage of 2 g/day, which can be increased to 3 g/day, for a duration of up to 4 months is necessary before treatment failure can be assumed.

Methotrexate

Given the efficacy of methotrexate for the treatment of RA, the lack of good studies of methotrexate for AS is surprising. Three randomized controlled trials have been published in which patients with AS were treated with methotrexate at a dosage of between 7.5 and 10 mg/wk versus placebo and a treatment duration of 12 to 24 weeks. Methotrexate was not superior to placebo in two of these studies. In the third study, a high percentage of patients in the methotrexate-treated group with concurrent peripheral arthritis had a better response in some of the outcome variables. In all three trials the subgroups were too small to differentiate between the effect in patients with axial manifestations only and the effect in those with additional peripheral arthritis. A more recent trial did not find any efficacy of 20 mg methotrexate given subcutaneously once a week for up to 16 weeks.³¹ Therefore, methotrexate is not recommended for either the axial or the peripheral manifestations of AS.

The lack of clear evidence of the efficacy of sulfasalazine and methotrexate for the treatment of AS contrasts with the fact that up to 20% to 30% of patients with AS are treated with one of these two drugs, probably because of the lack of alternative therapies.

Other disease-modifying antirheumatic drugs

There is no evidence that any of the other DMARDs often used for the treatment of RA play a role in the treatment of AS patients.²⁷ Recently, leflunomide was tested in two trials with negative results. In the first study, 20 AS patients were treated with 100 mg/day leflunomide for the first 3 days followed by 20 mg/day for 6 months. No change was observed in several of the outcome parameters, including the BASDAI. Only in a subgroup of 10 patients with peripheral arthritis was a decrease in the number of affected joints found.³² This beneficial effect restricted to peripheral arthritis was also shown in psoriatic arthritis. However, a larger number of patients would be necessary to confirm these results. In the second randomized controlled study, 45 patients with AS were treated with either the same dosage of leflunomide or placebo, also for 6 months, and no significant difference was shown between the two groups.³³ Again, the number of patients with peripheral arthritis in this study was too small to allow any further conclusions to be derived in this subgroup.

Thalidomide has also been tested for the treatment of AS patients in open uncontrolled trials, mainly because of its assumed anti-TNF- α potential. In the largest study, 30 patients with AS were treated with 200 mg thalidomide daily (increased slowly to reach this final dosage) given at night over a 12-month period. Twenty-six patients completed the study, with 80% showing at least 20% improvement in several variables starting after 3 to 6 months of therapy and 9 patients becoming free of symptoms. A similar result was reported by the same group in another smaller open study.

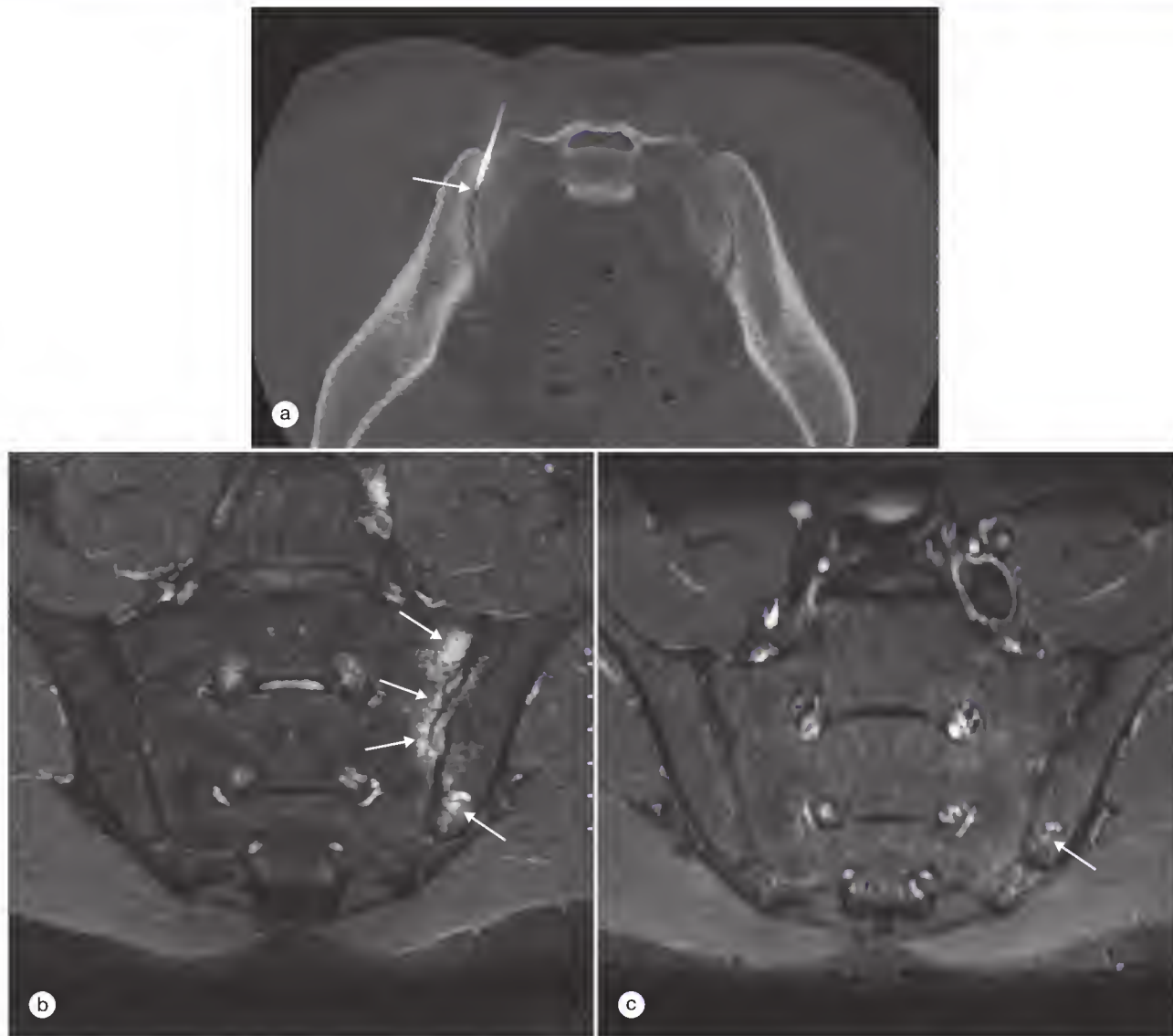


Fig. 118.6 Intraarticular corticosteroid injection into the sacroiliac joints. (a) Computed tomography-guided intraarticular injection of 40 mg triamcinolone acetonide. The tip of the needle (arrow) is located deep in the joint space. (b) Magnetic resonance imaging (MRI) of the sacroiliac (SI) joints (short tau inversion recovery [STIR] sequence) of a 37-year-old patient with ankylosing spondylitis shows osteitis at the left SI joint (arrows) before injection. A small intraosseous cyst is seen at the dorsal part of the iliac bone (arrow on bottom right). (c) MRI (STIR sequence) of the SIJs 4 months after the injection shows complete resolution of the osteitis. As expected, no change is seen at the intraosseous iliac cyst (arrow). (Courtesy K.G. Hermann, Berlin.)

However, the side effects, especially sedation, are thought to be considerable, which will probably prevent widespread use and the performance of controlled studies for this drug.

Pamidronate, a bisphosphonate, has been tested in patients with rheumatic diseases because of its possible antiinflammatory and inhibiting effect on osteoclasts. In a 6-month randomized controlled trial, 60 mg pamidronate given intravenously once a month was superior to a small placebo-like dosage of 10 mg pamidronate, with significant improvement being demonstrated in function and pain.³⁴ Such an effect became evident only after 3 months of treatment. A positive effect was not observed in another open trial in which AS patients were treated with the same dosage over a period of 3 months. Further studies are needed before bisphosphonates can be recommended.

Biologic Agents

Besides TNF- α inhibitors, other biologic agents have been investigated for the treatment of AS. The interleukin-1 (IL-1) receptor antagonist anakinra given as a 100-mg daily subcutaneous injection for 6 months did not show any efficacy in 20 active TNF blocker-naïve patients with AS in an open-label trial.³⁵ Abatacept (10 mg/kg) was administered intravenously on days 1, 15, and 29 and every 28 days thereafter up to week 24 to 15 TNF- α inhibitor-naïve patients and 15 with an inadequate response to TNF- α inhibitors; no clear improvement in signs and symptoms was noted in the two groups.³⁶ Similarly, the IL-6 receptor antagonist tocilizumab administered at a dose of 8 mg/kg body weight every 4 weeks over a 3-month

period was not superior to placebo in TNF blocker-naïve patients with active AS.³⁷ Interestingly, rituximab given as two 1000-mg infusions 2 weeks apart resulted in a clinically relevant improvement in a small-label study in TNF-naïve patients but not in those with active AS who failed TNF therapy.³⁸ However, this result needs to be further investigated in a placebo-controlled trial design. Thus, at the moment there is no clear evidence for a role of any other non-TNF blocker in the treatment of AS.

Anti-tumor necrosis factor- α blocking agents

The limited treatment options available for AS patients discussed earlier mean that the demonstration of good or very good efficacy of TNF blockers in treating active AS can be regarded as a breakthrough in the treatment of AS.² These drugs improve the signs and symptoms of AS rapidly in a high percentage of patients. Whether they are also capable of stopping structural damage of the bone, as has already been shown in RA, still has to be demonstrated.

Biologic basis

Inflammation at the interface of cartilage and bone has convincingly been demonstrated by MRI and immunohistologic techniques³⁹ in SI joint biopsy specimens. Abundant TNF- α mRNA has been found in the inflamed SI joint,³⁹ thus clearly demonstrating that AS is an inflammatory disorder. TNF- α is a proinflammatory cytokine produced by monocytes, macrophages, and activated T cells. TNF- α induces the release of other cytokines such as IL-1 and IL-6, as well as metalloproteinases and prostaglandins; it

is involved in the activation of lymphocytes, as well as in osteoclastogenesis. Furthermore, TNF- α induces the expression of endothelial adhesion molecules (e.g., E-selectin, intracellular adhesion molecule 1, and vascular adhesion molecule 1). Thus TNF- α plays a central role in inflammation.

Using enzyme-linked immunosorbent assays, elevated serum levels of TNF- α and IL-6 have been found in patients with AS.

Today, there are five main biologic agents that target TNF- α : the chimeric ($\frac{1}{4}$ murine and $\frac{3}{4}$ human) monoclonal IgG1 antibody infliximab, the recombinant 75-kDa TNF receptor IgG1 fusion protein etanercept, and the fully humanized monoclonal antibodies adalimumab and golimumab, and the PEGylated Fc-free anti-TNF certolizumab. All five TNF inhibitors have already been approved for the treatment of AS in the European Union, the United States, and other parts of the world. Infliximab is administered as an intravenous infusion over a 2-hour period, whereas etanercept, adalimumab, golimumab, and certolizumab are injected subcutaneously.

Infliximab

Short-term efficacy

Efficacy is based on the results of two pivotal placebo-controlled, randomized controlled trials in which infliximab was administered intravenously at a dosage of 5 mg/kg body weight at weeks 0, 2, and 6 and thereafter every 6 to 8 weeks. In contrast to treatment of RA, infliximab was given in both studies as monotherapy without concomitant treatment with DMARDs or corticosteroids.

In the first study, patients were treated with either infliximab ($n = 34$) or placebo ($n = 35$) for 3 months.⁴⁰ After this time all patients were treated with infliximab and monitored long-term. In the second study, which used the same dosage and treatment intervals, 201 patients were treated with infliximab and 78 with placebo for 6 months.⁴¹ Patients had to have a BASDAI score of 4 or higher despite treatment with NSAIDs. Continuation of NSAID therapy was permitted in both studies. The crucial endpoint in both these studies was a 50% improvement in disease activity (BASDAI) (see Fig. 118.2) or in a composite clinical score (ASAS percent improvement; see Table 118.2).⁵ This endpoint was reached by about 50% of infliximab-treated patients in the placebo-controlled trials, with about 10% or less of the placebo group attaining this level of response (Fig. 118.7). This endpoint was also reached in up to 60% to 70% of patients in the open-label studies. Interestingly, between 20% and 25% of these patients with active AS even fulfilled the criteria for partial remission. In addition, the number of entheses sites, the number of affected peripheral joints, function, and spinal mobility improved (some reaching statistical significance) during the placebo-controlled phase.

Long-term efficacy

In the German randomized controlled trial,⁴⁰ 69 patients were treated continuously with infliximab for 3 years, with the same dose given every 6 weeks. After 54 weeks, 78% of the patients were still being treated; after 2 years, 70%; and after 3 years, 69%. The intention-to-treat primary efficacy analysis at week 54 showed that almost 50% of the patients achieved a 50% improvement in disease activity (BASDAI score). In the completer analysis, the pretreatment mean BASDAI score of 6.5 decreased further from 3.3 at week 12 to as low as 2.5 at week 54 and remained low until week 156. NSAIDs could be reduced in 70% of patients and discontinued in 59%.

When infliximab was discontinued after 3 years of therapy, patients experienced a relapse between weeks 7 and 45, and by week 52 all but one patient had active disease. When treatment with infliximab was begun again, all except one patient responded similar to the first time, and the drug was well tolerated. Thus, for this group of patients with very active, long-standing disease (mean disease duration >10 years), infliximab needs to be administered long-term. After 8 years of treatment, 48% of the initial patients were still taking the drug, with a similar level of improvement in the completers.⁴²

In the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) study, 166 of the initial 201 patients were still taking infliximab after 2 years of treatment, with a continuously good response (Fig. 118.8).

Combination treatment with infliximab and methotrexate or other disease-modifying drugs

Reports of the treatment of RA and Crohn disease suggest that combining infliximab with methotrexate, glucocorticoids, or another immunosuppressive agent such as azathioprine (mostly for Crohn disease) might reduce side effects such as allergic reactions. However, two randomized controlled trials could not find a significant difference in efficacy or side effects in AS patients treated with infliximab alone or with a combination of infliximab and methotrexate.

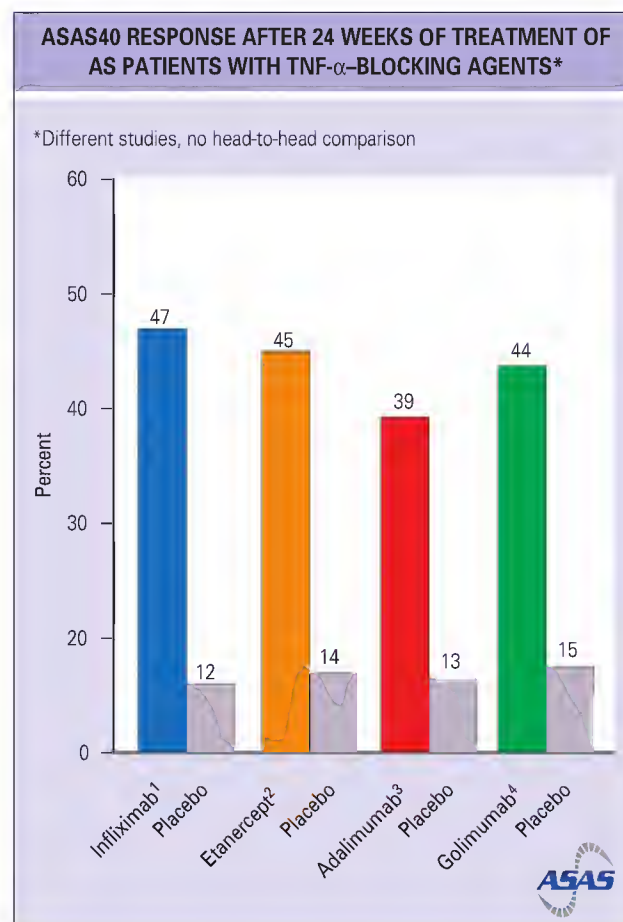


Fig. 118.7 Assessment of SpondyloArthritis international Society 40% (ASAS40) response after 24 weeks of treatment of ankylosing spondylitis patients with (left to right): (1) infliximab, (2) etanercept, (3) adalimumab, or (4) golimumab. (Data from [1] van der Heijde D et al.⁴¹; [2] Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005;64:1557-62; [3] van der Heijde D et al.⁴⁸ with permission from ASAS [www.asas-group.org]; and [4] Inman, et al.⁵¹)

Impact of infliximab on active inflammation as seen on magnetic resonance imaging

MRI has proved to be a powerful tool for detection of acute inflammation in the SI joints and spine. Therefore, MRI should also be used for follow-up of these inflammatory lesions during treatment since it provides an objective outcome parameter for efficacy of a given therapy. Serial MRI studies performed in patients from the German randomized controlled trial demonstrated that after 3 months of treatment, active inflammatory lesions in the spine regressed significantly by 60% versus 20% deterioration in the placebo group.²³ As mentioned earlier, these patients from both groups were then treated in open-label studies continuously for up to 3 years. When MRI data at baseline and after 2 years of continuous treatment were analyzed, a persistent improvement in spinal inflammation was seen (Fig. 118.9), with a mean score for acute spinal lesions of 4.6 versus 15.2 at baseline. Data are also available from the other placebo-controlled trial⁴³ and showed a significant reduction in spinal inflammation but no reduction in the placebo group.

Etanercept

Short-term efficacy

Four double-blind placebo-controlled trials have been published that demonstrate the efficacy of etanercept in treating AS to be similar to that with infliximab. In the first study, 40 patients were treated with either etanercept 25 mg subcutaneously twice per week (20 patients) or placebo (20 patients). DMARDs and corticosteroids were allowed to be continued during the study in 40% and 25% of patients, respectively. The main outcome parameters of morning stiffness and nocturnal spinal pain improved significantly in the etanercept but not in the placebo group after 4 months of treatment. In a second single-center trial, 30 AS patients with active disease (BASDAI score ≥ 4) were randomized to therapy with etanercept or an initial

LONG-TERM (2-YEAR) EFFICACY OF THE TNF- α ANTAGONISTS IN PATIENTS WITH ANKYLOSING SPONDYLITIS*

*Different studies, no head-to-head comparison

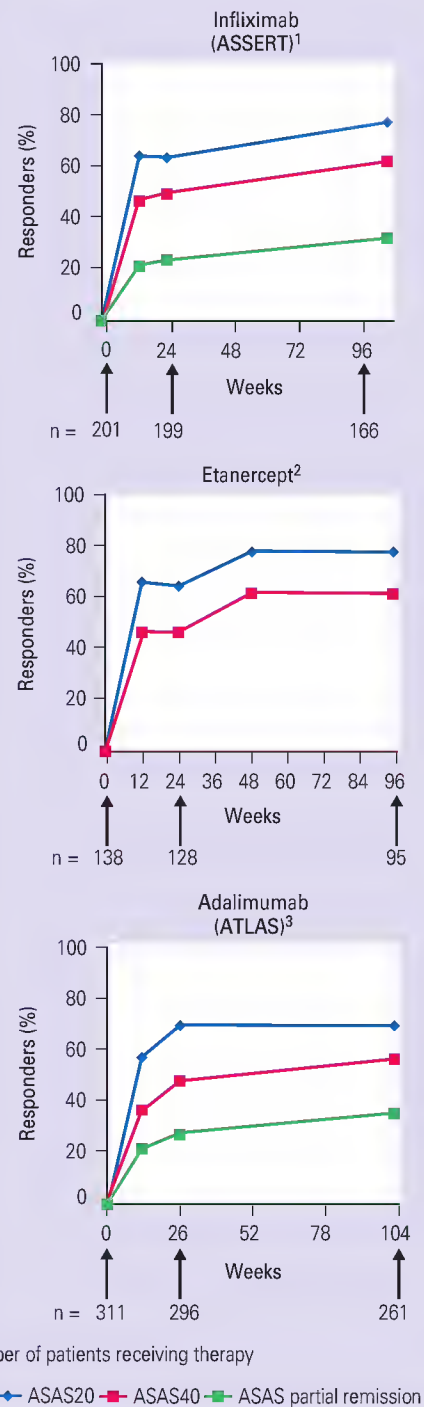


Fig. 118.8 Long-term (2-year) efficacy of tumor necrosis factor- α (TNF- α) antagonists (infliximab [1], etanercept [2], and adalimumab [3]) in patients with ankylosing spondylitis. (Data from [1] Braun J, Deodhar A, Dijkmans B, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. *Arthritis Rheum* 2008;59:1270-8; [2] Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005;64:1557-62; and [3] van der Heijde D, Schiff MH, Sieper J, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009;68:922-9, with permission from ASAS [www.asas-group.org].)

placebo-controlled period of 6 weeks, followed by an observational phase lasting 24 weeks. The placebo group was switched to etanercept after 6 weeks, and both groups were treated with etanercept for 3 months. Treatment with etanercept was significantly better than placebo, with at least 50% regression of disease activity in 57% of these patients at week 6 versus only 6% in the placebo group. No severe adverse events, including major infections, were observed during this trial.

Subsequently, two further placebo-controlled international trials were performed with the same dosage of etanercept. In the first, 277 patients were treated with either etanercept ($n = 138$) or placebo ($n = 139$) for 24 weeks.⁴⁴ An ASAS50 response was seen at week 24 in 45% of the etanercept group versus 10% of the placebo group (see Fig. 118.7). In a second study consisting of 84 patients, very similar results were obtained.

Long-term efficacy

To date, three studies have been published with long-term follow-up data from the original randomized controlled trials. In one of the studies, 277 patients were enrolled over a 24-week period, and subsequently all were treated with etanercept and observed in an open-label extension trial for a further 72 weeks. After 2 years, 200 of the patients (72%) were still being treated with the drug. Fifty percent of patients showed an ASAS50 response at week 48, and 54% of the patients reached this level of response at week 96 (see Fig. 118.8). Recently, a 4-year follow-up of this study reported similar safety and efficacy over this period. The other long-term trial was a 2-year open-label extension study of another randomized controlled trial.⁴⁴ Overall, 21 of 30 patients (70%) completed year 2. In the intention-to-treat analysis, 54% of the patients were BASDAI 50% responders. In the completer analysis, 43% (9 of 21 patients) fulfilled the ASAS criteria for partial remission. The BASDAI score decreased from 6.3 at baseline to 2.7 after 1 year and 2.6 after 2 years. However, when treatment with etanercept was stopped after 3 months, relapse occurred at a mean of 6.2 ± 3 weeks, and at week 35 all 30 patients had relapsed. However, when treatment was started again, the response rate was similar to that at the initial treatment.

A 63% drug survival rate was reported in another study after 5 years of treatment of AS patients with etanercept.⁴⁵

Impact of etanercept on active inflammation as seen on magnetic resonance imaging

MRI results during treatment were also reported in two of these studies. In the larger study, MRI of the spine was available at baseline and weeks 12, 24, and 48.⁴⁶ After 12 weeks spinal inflammation regressed by 54% in the etanercept group but worsened by 13% in the placebo group. After switching to etanercept, placebo patients improved similarly. In the second study, significant regression of spinal inflammation was already seen after 6 weeks in patients treated with etanercept but not in patients given placebo. Continuous treatment with etanercept for 24 weeks resulted in a 69% reduction in active spinal changes, as well as a reduction of inflammation in the SI joints.⁴⁷

Adalimumab

Short-term efficacy

Adalimumab 40 mg subcutaneously given as monotherapy every other week for 52 weeks was first shown to be effective in 15 patients with active AS in an open-label trial. This effectiveness was subsequently confirmed in two placebo-controlled randomized trials. In the Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS (ATLAS) trial, 58.2% (121 of 208) of adalimumab-treated patients achieved an ASAS20 response as compared with 20.6% (22 of 107) in the placebo group at week 12. A BASDAI 50 response was reached by 45.2% of the patients in the adalimumab group versus 15.9% in the placebo group (see Fig. 118.7).⁴⁸

Long-term efficacy

In the ATLAS trial, 65% (202 patients) of the original 311 patients still participated in the trial at year 5.⁴⁹ The level of response was maintained over the 5 years of treatment; 70%, 77%, and 51% of the completers achieved ASAS40, BASDAI 50, and ASAS partial remission, respectively (see also Fig. 118.8 for the 2-year data).

Impact of adalimumab on active inflammation as seen on magnetic resonance imaging

Acute inflammation decreased in both the spine and SI joints as detected on MRI in the open-label trial. In one of the placebo-controlled trials, active inflammation of the spine and the SI joints, as shown on MRI, was scored at weeks 12 and 52. The applied score for the spine increased by 9.4% in the placebo group versus a mean decrease of 53.6% in the adalimumab-treated patients. Similarly, the SI joint score decreased by a mean of 12.7%



Fig. 118.9 Reduction of acute spinal inflammation as seen on magnetic resonance imaging (short tau inversion recovery technique) during infliximab treatment over a period of 2 years. No change in acute inflammation versus baseline (a) could be seen after 12 weeks (b) of treatment with placebo; however, inflammation disappeared after 2 years (c). (From Sieper J, Baraliakos X, Listing J, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. *Rheumatology [Oxford]* 2005;44:1525-30.)

in the placebo group but by 52.9% in adalimumab-treated patients. This response was maintained at week 52 in the adalimumab group and reached a similar level of reduction after the placebo group was switched to adalimumab at week 12.⁵⁰

Golimumab

Golimumab, another fully humanized monoclonal antibody against TNF- α , is administered subcutaneously every 4 weeks. It showed good efficacy in a randomized placebo-controlled trial over a 24-week period,⁵¹ comparable to the other TNF-blocking agents.

Certolizumab

Certolizumab, a PEGylated Fc-free anti-TNF, is administered subcutaneously in doses of 200 mg every 2 weeks or 400 mg once every 4 weeks. It showed good efficacy in a randomized, placebo-controlled trial over a 24-week period in patients with axial spondyloarthritis, including a subgroup of patients with ankylosing spondylitis.^{51a}

Treatment of nonradiographic axial spondyloarthritis with tumor necrosis factor blockers

The AS patients treated in all the TNF blocker trials had a mean disease duration of longer than 10 years, which can be explained partly by the fact that the presence of radiographic sacroiliitis was a necessary inclusion criterion. Several studies have now been performed with TNF blockers either in the entire group of patients with axSpA or in patients with nr-axSpA only. To date, five controlled TNF blocker trials have been published. In all studies patients either retrospectively or prospectively fulfilled the new ASAS classification criteria for axSpA. In the first study, patients with nr-axSpA were treated with adalimumab or with placebo for 12 weeks; all patients were then switched to adalimumab and treated until week 52.⁵² An ASAS40 response was reached by 54.5% of patients in the adalimumab group versus 12.5% in the placebo group, efficacy being similar to that in the AS trials. The mean symptom duration in this trial was 7 to 8 years; patients with a shorter duration of symptoms had a better response than did patients with a longer duration. In another trial, patients with axSpA were included only if the duration of symptoms was less than 3 years, if patients showed active inflammation of the SI joints on MRI, if they were positive for HLA-B27, and if they suffered from the clinical symptom of inflammatory back pain.⁵³ Only about 12% of these patients also had radiographic evidence of sacroiliitis and fulfilled the modified New York criteria. More

than half the patients (55.6%) reached the ASAS criteria of partial remission versus only 12.5% in the placebo group. Active inflammation as seen on MRI improved significantly better in the infliximab-treated than in the placebo-treated group. In the third trial, patients with axSpA and a symptom duration of less than 5 years were treated in a randomized prospective trial for 1 year with either etanercept or sulfasalazine.⁸ A significantly higher number of patients in the etanercept group showed improvement in active subchondral bone marrow inflammation in the SI joints, the spine, and the peripheral entheses on whole-body MRI. Furthermore, 50% of the patients reached the ASAS criteria for partial remission in the etanercept group versus 19% in the sulfasalazine group after 1 year of treatment. Fifty-one percent of these patients had radiographic sacroiliitis at inclusion in the trial; the treatment effect was very similar in patients with nonradiographic and radiographic sacroiliitis.⁸ A phase 3 placebo-controlled trial of adalimumab in patients with nr-axSpA resulted in an ASAS40 response in 36.3% of the adalimumab-treated patients versus 14.9% of the placebo group.⁵⁴ Disease duration was rather long at a mean of 10 years, and patients in whom the duration of symptoms was less than 5 years had a better ASAS40 response, with 49% reaching the criteria for response. Finally, certolizumab showed a good efficacy for the treatment of nonradiographic axial SpA in a placebo-controlled 24-week trial, similar to the efficacy shown for the AS subgroup in the same trial.^{51a} Thus patients with nr-axSpA have an at least a similar response to TNF blocker treatment as do patients fulfilling the modified New York criteria for AS.

Currently, adalimumab and certolizumab are the first TNF blockers approved by the European Medicines Agency for patients with active nr-axSpA who either have an elevated CRP or active inflammation of the SI joint or spine on MRI.

Can radiographic damage or progression be prevented by tumor necrosis factor blocker treatment?

When radiographs of the spine were scored for growth of syndesmophytes over a follow-up period of 2 years, it was shown that all four TNF blockers—etanercept,⁵⁵ infliximab, adalimumab, and golimumab—did not stop radiographic progression over a treatment period of 2 years in comparison to a historical control group of AS patients not treated with TNF blockers. This raises the question of how inflammation and new bone formation are linked in AS. Based on an analysis of the available histologic and imaging literature, it was proposed that the structural damage in AS occurs in two steps.⁵⁶ First, inflammation causes erosive structural damage that results in bony defects

being filled with fibrous repair tissue. This would not be that much different from RA. Second, the repair tissue becomes ossified, which is made easier if inflammation is no longer present. This is probably typical for any damage in the spine. Thus, if inflammation is treated early enough before structural damage has occurred, TNF blockers might prevent new bone formation in the long term. However, TNF blockers will not prevent ossification of already damaged bone because these agents do not have an effect on osteoblast activity. Future studies need to show whether this assumption about the sequence of events is correct.

Tumor necrosis factor blockers for peripheral arthritis and enthesitis

Peripheral arthritis and enthesitis are frequent manifestations that are also characteristic of the whole group of SpAs and occur in 30% to 40% of patients with AS,⁴ normally in transient or relapsing form (or both), but chronic manifestations are also possible. TNF blockers have thus far been investigated mostly in studies addressing improvement in these peripheral manifestations as secondary outcome parameters. Both peripheral arthritis and enthesitis improved when patients were treated with TNF blockers in these studies. Enthesitis of the heel was the primary outcome measure in one placebo-controlled, 12-week trial of etanercept in patients with peripheral SpA, with significantly better improvement being shown in the etanercept group.⁵⁷

Tumor necrosis factor blockers for the treatment of psoriasis and inflammatory bowel disease in patients with ankylosing spondylitis

Psoriasis is present in about 10% and inflammatory bowel disease (Crohn disease or ulcerative colitis) in about 5% of patients with AS. Thus a relevant question is how these diseases are affected by treatment with TNF blockers. Most data available are derived from studies that have tested infliximab, etanercept, or adalimumab for the treatment of psoriasis or psoriatic arthritis (see also Chapter 122) and Crohn disease. All TNF blockers are effective for the treatment of psoriasis.

In Crohn disease, infliximab and adalimumab were shown to be highly effective for different manifestations of active disease, whereas etanercept failed to be superior to placebo in a controlled trial. There were even single reports of flares or new manifestations of Crohn disease in AS patients treated with etanercept. Infliximab and adalimumab are also effective for ulcerative colitis. Infliximab was more effective in preventing flares of inflammatory bowel disease in AS patients treated with TNF blockers than were adalimumab, etanercept, and placebo in an analysis of all published AS studies.⁵⁸

Tumor necrosis factor blockers for the treatment of juvenile spondyloarthritis

The first symptoms of AS occur in 15% to 20% of patients before the age of 20 years and in a considerable number of patients even 16 years or younger. Although juvenile forms normally occur initially with a predominance of peripheral manifestations (enthesitis and peripheral arthritis), the full picture of typical AS develops later in many juvenile patients. In two small open-label studies both infliximab and etanercept showed good efficacy in patients with juvenile SpA or enthesitis-related arthritis. One recent double-blind placebo-controlled trial showed highly significant improvement in a variety of clinical parameters in the infliximab-treated group in comparison to the placebo group.

Adverse events associated with anti-tumor necrosis factor therapy

Adverse events in AS patients treated with TNF blockers do not differ from those seen in patients with other diseases such as RA and Crohn disease. However, patients with AS are normally younger than those with the other two diseases and less frequently have been treated with glucocorticoids or immunosuppressive drugs. Thus the number and severity of side effects can be expected to be at least no higher than in other chronic inflammatory diseases and might even be lower. Comparative data on this issue are not available at this time. However, implementation of the usual precautions for and contraindications to biologic therapy should be followed. Infections, including opportunistic infections, can occur in a small percentage of patients, and a small increase in risk for the development of lymphoproliferative disorders cannot be excluded at this stage. Allergic reactions occur, and neurologic events and congestive heart failure have been reported occasionally.

Which patients with ankylosing spondylitis should be treated with tumor necrosis factor blockers?

Recommendations on which AS patients should be treated with TNF blockers are required, especially on the background of possible side effects and the relatively high cost of these drugs. Thus patients with the best

ASAS RECOMMENDATIONS FOR THE START OF TREATMENT OF AXIAL SPONDYLOARTHRITIS PATIENTS WITH TNF BLOCKERS

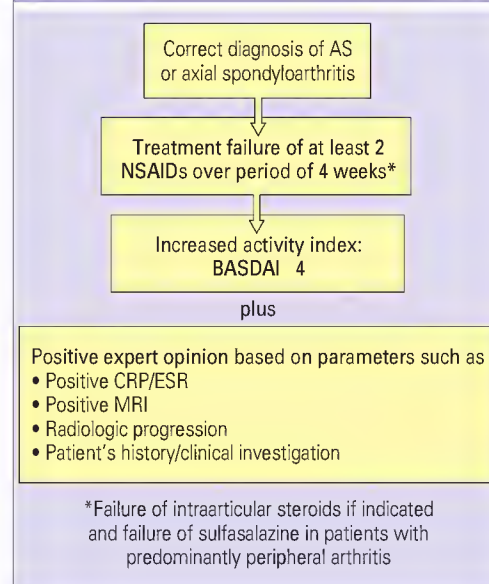


Fig. 118.10 Assessment of SpondyloArthritis international Society (ASAS) recommendations for the start of treatment of axial spondyloarthritis patients with tumor necrosis factor (TNF) blockers.⁵⁹ BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs.

benefit-to-risk ratio should be treated preferentially. An international ASAS consensus statement on the use of anti-TNF agents in AS patients was just recently updated⁵⁹ (Fig. 118.10). According to these recommendations, the following criteria should be fulfilled for the initiation of anti-TNF- α therapy:

1. A diagnosis of axSpA made by fulfilling either the modified New York criteria for AS³ or the ASAS criteria for axSpA.⁴
2. The presence of active disease for at least 4 weeks as defined by both a sustained BASDAI score of at least 4 (on a scale of 0 to 10) and an expert opinion based on clinical features, acute-phase reactants, and imaging modalities. The expert will normally be a rheumatologist, and in addition to the patient's symptoms, the rheumatologist will make a judgment by taking into account the objective parameters of activity or inflammation.
3. The presence of refractory disease as defined by the failure of at least two NSAIDs during a 4-week period, failure of intraarticular corticosteroids if indicated, and failure of one DMARD, preferably sulfasalazine, in patients with peripheral arthritis. These recommendations are also in accordance with the ASAS/EULAR recommendations for the management of AS,³ which do not see a role for DMARDs in treating the predominant axial manifestations of AS (see Box 118.1 and Fig. 118.1).
4. The usual precautions for and contraindications to biologic therapy should be applied.
5. For monitoring of anti-TNF- α therapy, both the BASDAI and the ASAS core set for clinical practice should be followed regularly. Discontinuation of anti-TNF- α therapy should be considered strongly in nonresponders after 12 weeks of treatment (Fig. 118.11). Response is defined as improvement of at least 50% or 2 units (on a 0 to 10 scale) of the BASDAI in addition to an expert opinion that treatment should be continued, again not only relying on the patient's subjective symptoms.

Similar recommendations have been published by national societies such as the Canadian Rheumatology Association and the British Society of Rheumatology and from the United States; they follow the reasoning of the ASAS recommendations with only slight modifications.

Can a good response to tumor necrosis factor blockers be predicted?

The good results in axSpA patients treated with TNF blockers early in their disease raised the question of whether a shorter symptom duration is a

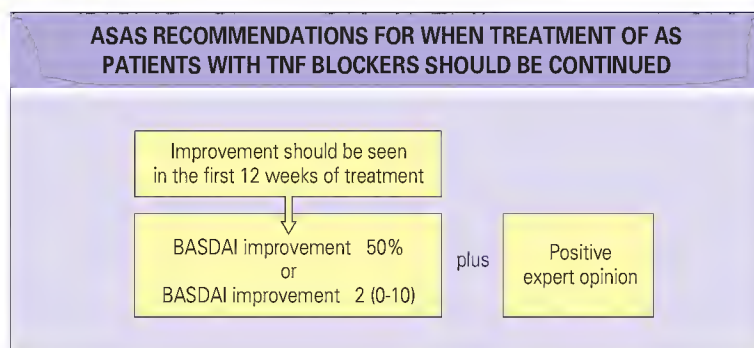


Fig. 118.11 Assessment of SpondyloArthritis international Society ASAS recommendations for when treatment of ankylosing spondylitis (AS) patients with tumor necrosis factor (TNF) blockers should be continued. If these criteria are not met, discontinuation should be considered.⁵⁹ BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

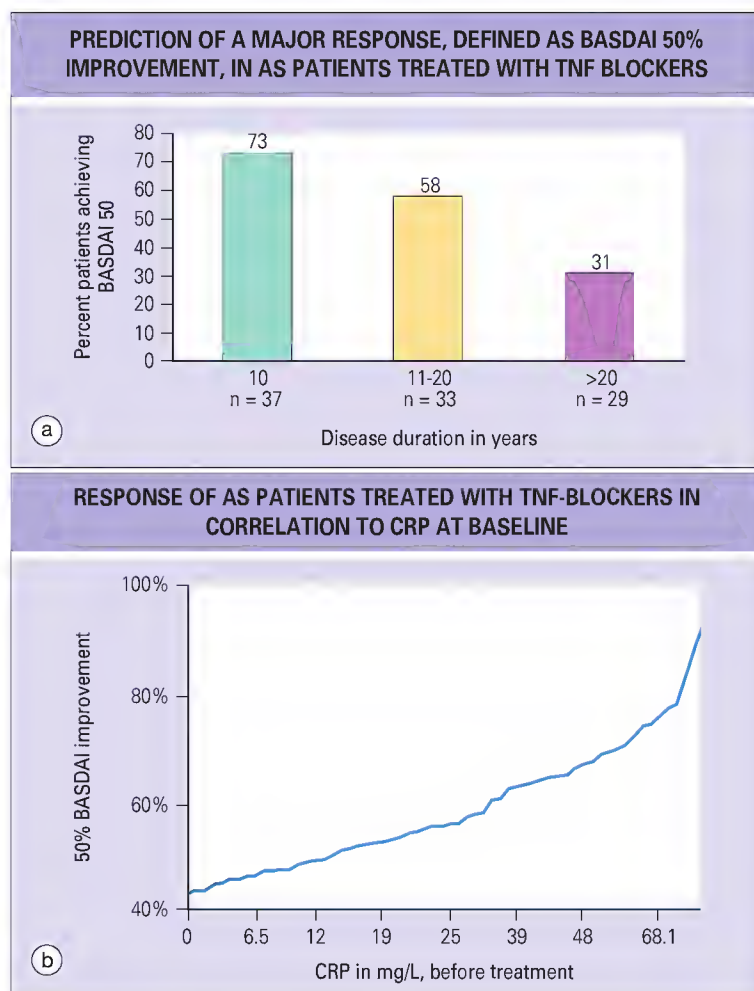


Fig. 118.12 Prediction of a major response, defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50% improvement in patients with ankylosing spondylitis (AS) ($n = 99$) treated with tumor necrosis factor (TNF) blockers. The response of AS patients treated with TNF blockers is shown in correlation to disease duration (a) or the level of C-reactive protein (CRP) (b) at baseline. A short disease duration and high CRP predict a good response. (a, from Rudwaleit M et al,⁶⁰ with permission from the BMJ Publishing Group; b, modified from the same source.)

prognostic factor for a good treatment response for the entire group of axSpA patients, including those with AS. Based on analysis of the early AS trials it was shown that a symptom duration of less than 10 years was associated with a better response to TNF blocker therapy than was a longer duration of disease⁶⁰ (Fig. 118.12). Indeed, such an association was also found in the two adalimumab trials in patients with nr-axSpA, for which symptom duration was not limited.^{52,54} There was always a large overlap between short symptom duration and young age as predictors of a good treatment response. In one AS trial of adalimumab, 50% of patients reached ASAS partial remission if younger than 30 years as opposed to 39% of patients between 30 and

39 years of age and about 18% older than 40 years. In the first trial of adalimumab for patients with nr-axSpA, 87% reached the ASAS40 criteria if they were 30 years or younger versus only 16.7% if older than 40.⁵² Such a better response in patients with a shorter duration of disease was also confirmed in the second adalimumab study in patients with nr-axSpA.⁵⁴ The second predictor of a good response in nearly all analyses was an elevated CRP level at inclusion. Positive HLA-B27, active bony inflammation on MRI, and good function were not consistently associated with a favorable treatment response. Thus, patients with younger age, a short disease duration, or objective signs of inflammation—elevated CRP seems to be a better predictor than active inflammation on MRI—do respond especially well to TNF blocker therapy.

These analyses were based on the presence or absence of predictive factors at baseline. A more recent analysis of a 5-year follow-up of AS patients treated with adalimumab looked for parameters predicting sustained remission over several time points or predictors of the presence of remission after 5 years.⁴⁹ Besides baseline parameters, the response after 12 weeks was also taken into account. The best predictor was achieving remission at week 12. Taken together, an elevated CRP, short duration of symptoms, and good response to a TNF blocker in the first 3 months seem to be the best predictors of long-term response to TNF blocker therapy in patients with axSpA.

Switching from one tumor necrosis factor blocker to another in case of treatment failure

In patients with primary or secondary failure of treatment with a TNF blocker, switching to another can be effective, although the response rate is lower. In one study, an ASAS40 response was found in 38% of patients versus 59% of those with no previous exposure to TNF blockers. Patients respond better if the response is lost over time (secondary failure) than if they have no response to the initial course of treatment. In another report, a decrease in the BASDAI score by 2 points was still observed in patients who switched to a second and third TNF blocker, as opposed to a decrease of 3 BASDAI points in patients treated with their first TNF blocker. Secondary failure of treatment with a TNF blocker might be due to the induction of antidrug antibodies, which can occur in AS patients treated with TNF blockers, especially if treated with the monoclonal antibodies.

MANAGEMENT OF EXTRAARTICULAR MANIFESTATIONS

Anterior uveitis

Anterior uveitis is the most frequently occurring extraspinal manifestation in AS patients, with 30% to 40% experiencing isolated or recurrent attacks. It is typically unilateral, but relapses frequently affect the contralateral eye. Patients should seek immediate medical help if a painful eye occurs to avoid the formation of synechiae (adhesions to the back of the iris) with the possible consequence of secondary glaucoma. Local treatment with glucocorticoid eye drops and mydriatics is sufficient in most instances. In more severe cases, glucocorticoids given either orally or as an intraocular injection might be necessary. Results from controlled trials suggest that sulfasalazine can prevent attacks.

Experience in the treatment of anterior uveitis with TNF blockers is currently limited. In one study, 16 patients, 14 of whom received etanercept and 2 infliximab for either inflammatory eye disease or associated joint disease, were studied retrospectively. Although all 12 patients with active arthritis showed improvement in joint disease, only 6 (38%) experienced improvement in their eye disease. Inflammatory eye disease even developed for the first time in five patients while taking etanercept. Therefore, conclusions from this report regarding AS-associated uveitis are limited.

A beneficial effect of infliximab administered in a single dose of 10 mg/kg was reported in seven patients with an acute onset of HLA-B27-associated anterior uveitis. These patients were monitored for a mean period of 17 months. Total resolution of anterior uveitis was achieved with infliximab as the only antiinflammatory drug in all but one patient. Relapse occurred in four patients after a median of 5 months.

Recently, data from four placebo-controlled trials of TNF blockers for the treatment of AS (two with etanercept and two with infliximab) were analyzed for the incidence of reported flares of anterior uveitis during treatment.⁶¹ The calculated frequency of flares of anterior uveitis in the placebo group was 15.6 per 100 patient-years, whereas patients treated with TNF blockers had significantly fewer flares (mean of 6.8 flares per 100 patient-years). Flares occurred less frequently in patients treated with infliximab (3.4 per 100 patient-years) than in those treated with etanercept (7.9 per 100 patient-years), although this difference was not significant. A more



Fig. 118.13 Radiograph of a 23-year-old man with ankylosing spondylitis and arthritis in the right hip joint. Depending on the symptoms and progression of the arthritis, this patient could become a candidate for hip replacement.

recent analysis of all published trials of AS patients treated with etanercept confirmed that the rate of uveitis flares could be reduced from 19.3 per 100 patient-years in the placebo-treated group to 8.6 in the etanercept-treated patients, a rate not significantly different from the 10.7 found in AS patients treated with sulfasalazine. A similar reduction was reported in an open-label trial of AS patients treated with adalimumab: from 15 flares per 100 patient-years before treatment to 7.4 after treatment.

Thus, although treatment with TNF blockers can reduce the frequency of anterior uveitis, the exact role of TNF blocker for severe treatment-refractory cases of anterior uveitis still has to be defined.

Osteoporosis

Osteoporosis is a frequent manifestation of AS, most probably as a consequence of limited mobility and local and general inflammation. Recently it was shown that treatment of active AS with TNF blockers induces a rather rapid improvement in bone mineral density after 6 months of treatment with infliximab or etanercept but not with placebo.

SURGICAL INTERVENTION IN ANKYLOSING SPONDYLITIS

Hip replacement

Hip arthritis (Fig. 118.13) occurs in up to a third of AS patients, most often early in the disease (first 10 years), and is more common if the disease starts



Fig. 118.14 Severe Andersson lesion (diskovertebral erosions and destruction) (a, arrow) of the thoracic spine in a patient with ankylosing spondylitis resulting in instability and severe pain, which was treated with a fusion operation (b).

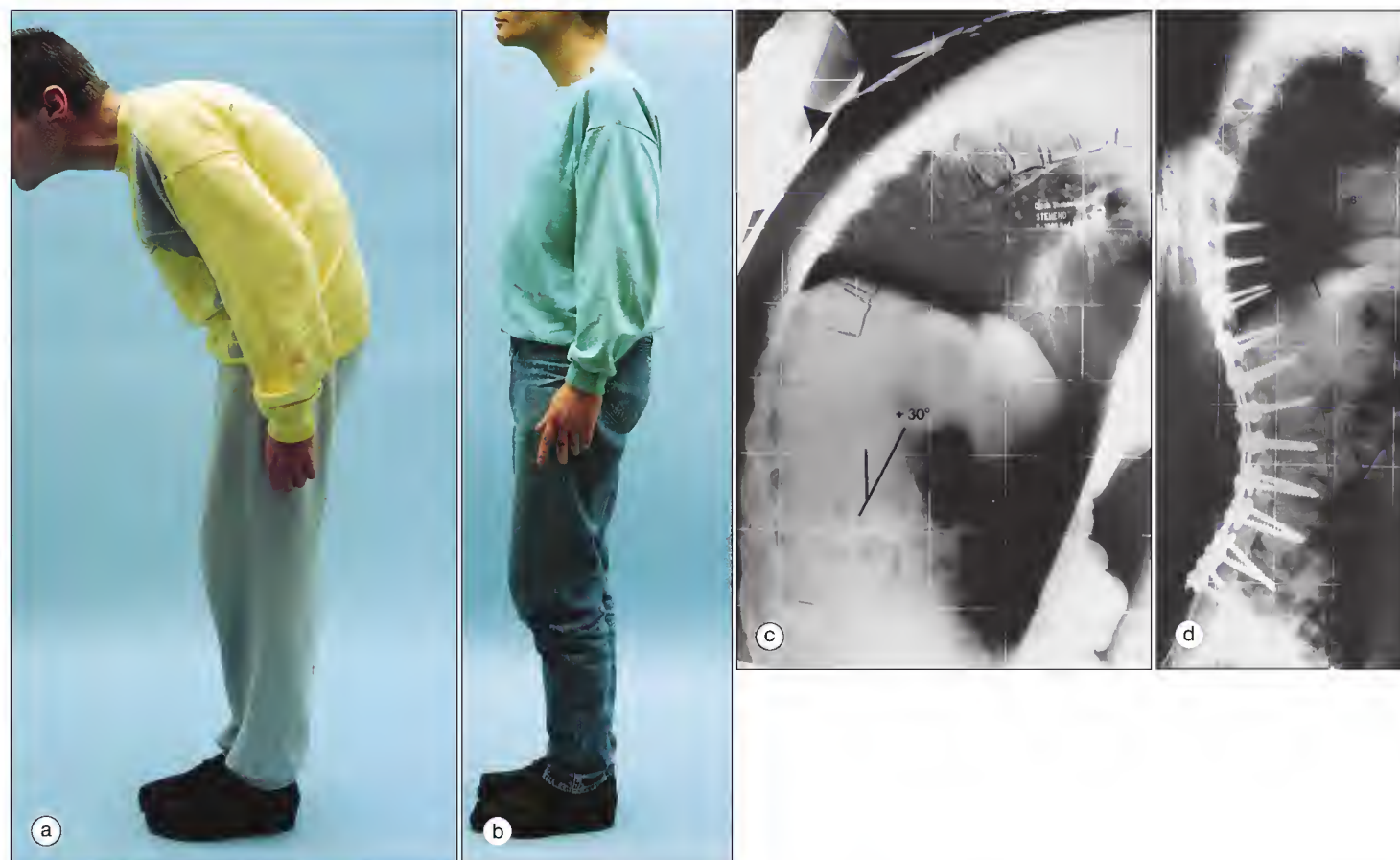


Fig. 118.15 Patient with ankylosing spondylitis before (a) and after (b) correction of severe kyphosis by polysegmental wedge osteotomy. Radiographs before (c) and after (d) correction are shown. (Courtesy P. Metz-Stavenhagen, Bad Wildungen, Germany.)

early in life. Total hip replacement (THR) may be necessary in about 5% of all AS patients.² Although AS patients are normally younger than others undergoing hip replacement, the revision rate is not higher. No major difference in durability or complications is seen between cemented and non-cemented hip prostheses, but noncemented THR is regarded to be preferable in younger patients because revision is technically easier.²

Two larger studies described the results of THR in patients with AS. The first analyzed 24 young AS patients with an average age of 28.8 years at the time of surgery. Eighty-eight percent of patients became completely free of pain. After an average follow-up of 22.7 years, 88% of the original femoral components and 74% of the original acetabular components remained *in situ*. The second study reported on 340 THRs; 276 were primary and 64 were revisions. The mean age of AS patients at disease onset was 19.5 years (vs. 24.4 years for all AS patients at this center), and the mean age at the first THR was 40.0 years. Overall, 85% of patients considered the outcome to be very good. The survival rate of the original THR after 10, 15, and 20 years was 90%, 78%, and 64%, respectively, and the survival rate of revisions was 73%, 55%, and 55%, respectively.

Thus, the long-term outcome of THR in AS patients, including young ones, is good, and it should be considered an option in those with severe pain or loss of function. Although no controlled trials have investigated THR, the ASAS/EULAR experts recommended this treatment with a high level of confidence.² To avoid heterotopic bone formation and

redevelopment of ankylosis after THR, NSAID treatment should be started in AS patients (if not so treated already) before the operation and be continued for some days after.

Spinal surgery

Ankylosis of the spine results in obvious limitation of movement and elasticity. The reduced flexibility in combination with osteoporosis of the spine as a consequence of lack of movement and local and systemic inflammation renders the spine susceptible to a variety of complications, including fracture and dislocation, sometimes even after minor trauma. Spinal instability can also occur as a consequence of a severe Andersson lesion (diskovertebral erosions and destruction). Pain and neurologic involvement are indications for fusion operations (Fig. 118.14). A severe kyphotic deformity can be an indication for surgery to improve posture and forward vision, with the average correction ranging from 37 to 40 degrees. The three commonly performed procedures are opening-wedge osteotomy, polysegmental wedge osteotomy, and closing-wedge osteotomy. Severe complications such as neurologic effects occur in only 2% to 4%. Figure 118.15 shows a patient before and after correction of severe kyphosis by polysegmental wedge osteotomy of the lumbar spine, which is the location most frequently used. Atlantoaxial and atlantooccipital subluxation and spinal stenosis can be other reasons for surgical interventions.²

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119

Classification and epidemiology of psoriatic arthritis

■ M. ELAINE HUSNI

- Psoriatic arthritis is a chronic inflammatory disease of both the skin and joints, as well as extraarticular features such as enthesitis and dactylitis.
- Five different subtypes are generally recognized; however, some overlap may occur within individual patients:
 - Distal interphalangeal joint–predominant arthritis
 - Asymmetric oligoarticular arthritis
 - Symmetric polyarticular arthritis
 - Axial disease predominant with spondylitis, sacroiliitis, and hip and shoulder involvement
 - Arthritis mutilans
- There has been a consensus to develop new classification criteria, which has led to development of the CASPAR criteria (Classification Criteria for the Study of Psoriatic Arthritis). Improved definition of the epidemiology and classification criteria for psoriatic diseases may lead to early detection and improve clinical outcomes.
- Individuals with psoriasis or psoriatic arthritis have a higher prevalence of comorbid disease, particularly cardiovascular risk factors, metabolic disorders, and other immune-mediated inflammatory issues.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with cutaneous psoriasis. It has many diverse characteristics that can be distinguished from the more common form of inflammatory arthritis—rheumatoid arthritis (RA). In PsA, not only the joints but also the surrounding structures, such as tendons and ligaments, can be involved and be manifested clinically as dactylitis and enthesitis. In addition, PsA can affect the nails and cause pitting, ridging, and distal onycholysis. There is increasing evidence on many levels, including molecular, cellular, and tissue evidence, that PsA is a distinctive form of arthritis that includes new bone formation and inflammation. Prompt diagnosis and treatment can alleviate both pain and inflammation and possibly help prevent progressive joint involvement and damage.

The focus in this chapter is on the epidemiology and classification criteria for PsA. Some of the key features distinguishing PsA from other inflammatory disorders are also reviewed to highlight the complexity of this condition. Furthermore, it is important to recognize that the proposed categorizations of PsA may be inadequate to some degree when referring to early versus late changes, classic versus atypical manifestations, or clinical/therapeutic trials versus bedside diagnosis. It is also clear that the study of PsA has lagged behind that of other inflammatory joint diseases such as RA because to date there is no universally agreed or thoroughly validated criteria for PsA. We anticipate that as our understanding of the pathogenesis of PsA increases, the diagnostic and classification criteria will be refined to assist in earlier diagnosis of the disease.

DIAGNOSIS

A clinical diagnosis of PsA is established mainly by the presence of characteristic signs and symptoms in both the skin and joints and by the process of elimination of more common inflammatory arthritides such as RA. However, these clinical features are not confined to PsA, and both PsA and

RA share many common characteristics. The diagnosis may be easier to confirm if psoriasis coexists with symptoms of arthritis. However, in as many as 15% of cases, symptoms of PsA appear before signs of psoriasis (called “psoriatic arthritis sine psoriasis”). A careful medical history, physical examination, blood tests, and imaging of the involved joints along with dermatologic evaluation are used to diagnose PsA.

The earliest reports by Wright of inflammatory arthritis associated with psoriasis described the characteristic involvement of the distal interphalangeal (DIP) joints with erosive and terminal digital absorptive changes at the distal phalanges, concurrent sacroiliitis, and arthritis mutilans.^{1,2} The first paper from the American College of Rheumatology that identified PsA as a distinct clinical entity was published in 1964.³ More than 40 years later, we are still gathering a great deal of new information about patients with PsA, including distinct pathophysiologic mechanisms in the entheses and bone, revisions of the classification criteria, and the efficacy of novel immunologic targets.

PsA can develop at any age. However, in most people it appears between the ages of 30 and 50 years. Unlike other types of inflammatory arthritis with a large female preponderance, PsA seems to affect men equally or even at a slightly higher rate. The onset of PsA symptoms may vary in patients with psoriasis. In the majority, skin changes occur before the involvement of joints. However, this is not always a consistent feature. A subset of patients can have skin and joint symptoms concurrently. More rarely, inflammatory joint symptoms occur before skin changes. Typically, PsA is initially a mild, oligoarticular disease but can become polyarticular with time and progresses to a severe, erosive condition in at least 20% of patients. The aggressive form is seen more commonly in patients who exhibit polyarticular or erosive PsA at initial evaluation. The discovery of rheumatoid factor (RF) and, more recently, anti-citrullinated peptide antibodies has helped distinguish PsA from other inflammatory arthritides. Nevertheless, PsA is still differentiated from other inflammatory conditions predominately via clinical assessment by a physician rather than with a serologic test or widely accepted classification criteria. In general, patients with PsA are seronegative, whereas other patients with PsA can also have an increased prevalence of cardiovascular disease and its associated risk factors.

Patients with psoriasis are at increased risk for the development of PsA during their lifetime.⁴ Risk factors for the development of inflammatory arthritis in patients with psoriasis are the subject of current research, both in the area of predicting the more severe forms of PsA and in early detection/recognition, especially in nonrheumatology practices such as general internal medicine and dermatology. Given that PsA can have an indolent and progressive course, a delay in diagnosis and treatment may lead to erosive arthropathy and irreversible joint damage. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has led an effort to develop and validate three PsA screening tools.⁵ To aid clinicians in screening for PsA, consensus on a well-designed screening tool can help increase detection in general and specialty clinics. It can also help in determining the prevalence of PsA in a given population, recording clinical data for genotype-phenotype studies, and tracking response to therapy. Furthermore, all patients with psoriasis should be screened for signs and symptoms of inflammatory joint disease to ensure early diagnosis and treatment of PsA. In a more recent population-based study, a psoriasis incidence cohort of 1633 patients demonstrated psoriatic features associated with a higher likelihood of PsA that included nail dystrophy, scalp lesions, and intergluteal or perianal psoriasis.⁶

Additional factors can also be predictive of a worse prognosis for psoriatic patients, including more extensive skin involvement, strong family history of psoriasis, and disease onset at an age younger than 20 years. The aggressive form is seen more commonly in those who exhibit polyarticular or erosive PsA at diagnosis.

EPIDEMIOLOGY

The ability to precisely define the epidemiology of PsA has been hampered by the lack of widely accepted classification criteria (see below). Although the exact prevalence of PsA is unknown, estimates vary from 0.3% to 1% of the U.S. population, with a reported prevalence of 7% to 42% in patients with psoriasis.^{7,8} The wide variation in estimates of prevalence stems from several factors: the large heterogeneity of the disease, lack of a precise case definition, and the diversity of cohorts being studied, which makes direct comparisons difficult. Interestingly, for the first time a recent study has shown that the incidence of PsA may be rising. A population-based incidence cohort in Olmsted County, Minnesota, demonstrated that the incidence of PsA (using the Classification Criteria for the Study of Psoriatic Arthritis [CASPAR]; see below) has been rising over a period of 30 years (1970 to 2000) in both men and women (Fig. 119.1).⁶ The results showed that the age- and sex-adjusted incidence of PsA per 100,000 increased from 3.6 (95% confidence interval [CI], 2.0 to 5.2) to 9.8 (95% CI, 27.7 to 11.9).

In a more recent review by Alamanos and associates,⁹ a total of 13 epidemiologic studies of PsA patients were systematically examined. Wide variation in the incidence and prevalence of PsA was observed in several countries and areas around the world, thus suggesting significant geographic variation in patients with PsA. For example, the prevalence of PsA in Japan is 1 case per 100,000 versus 420 cases per 100,000 in an Italian study. Pedersen and Junker¹⁰ carried out a population-based study of the

prevalence of PsA according to both the Moll and Wright criteria and CASPAR. This study found the point prevalence to be 0.15%, with an incidence of 6 per 100,000 person-years.^{9,10} A more recent population-based study of 1633 subjects with psoriasis found that PsA developed in less than 10% of the patients during the 30-year period.⁶ Two additional studies performed in Italy and Germany showed a much higher prevalence of PsA, 20.6% and 36%, respectively. Although these studies demonstrated a much greater prevalence than the 10% reported in a U.S. population-based study, all have added to our understanding of the epidemiology of PsA worldwide. A more recent study of the incidence and prevalence of PsA was performed in Buenos Aires by Soriano and colleagues.¹¹ The incidence of PsA was found to be 6.3 cases per 100,000 person-years and the prevalence was 79 cases per 100,000, which is similar to that reported in other European and U.S. studies.¹¹ Potential differences in these geographic variations could be due to secular trends, genetic factors, and study design such as differences in case ascertainment, methodology, or environmental exposure. Box 119.1 presents the methodologic challenges seen across many epidemiologic PsA studies that make it difficult to find the true prevalence and incidence of the disease.

CLASSIFICATION

Because no pathognomonic test for PsA is available to establish a definitive diagnosis, the development of well-validated and widely adopted criteria for classification has been of great interest to rheumatologists. From a historical standpoint, the main classification criteria for PsA were presented by Moll and Wright.¹² Published observations of a large cohort of patients in Leeds, England, during the early 1970s led to development of the Moll and Wright criteria (Table 119.1).^{12,13} They have been the most concise criteria and, until recently, the most widely used. The Moll and Wright criteria were based on having established inflammatory arthritis (either peripheral arthritis and/or axial involvement with sacroiliitis or spondylitis) along with the presence of psoriasis and a negative test for RF. The limitation of this classification is the fact that it was not validated with patient data or tested in diverse populations.

PsA patients have historically been classified into five different subtypes with some overlap (Box 119.2): (1) distal interphalangeal joint–predominant

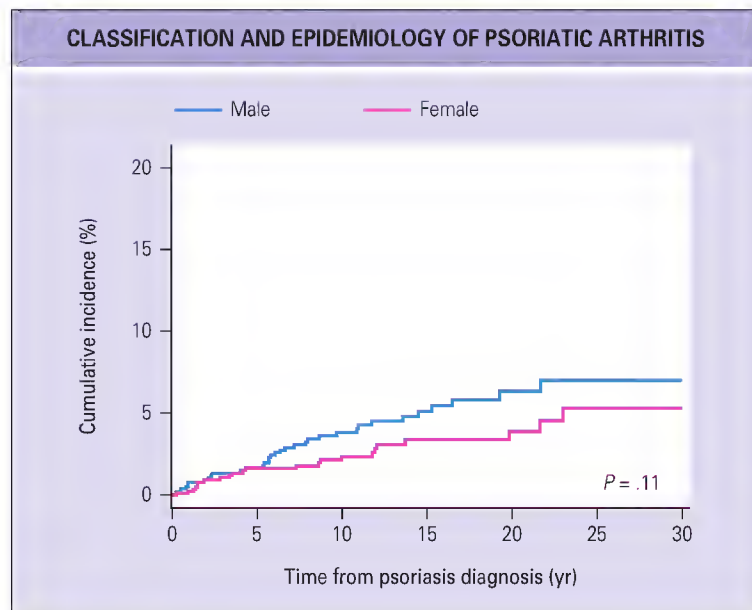


Fig. 119.1 Psoriatic arthritis: epidemiology and classification.

BOX 119.1 METHODOLOGIC CHALLENGES IN EPIDEMIOLOGIC STUDIES OF PSORIATIC ARTHRITIS

- Variations in case identification or definition
- Lack of validated, widely accepted criteria for classification or diagnosis
- Different methods of case ascertainment
- Different age adjustment methods
- Small cross-sectional cohorts
- Selective study populations
- Limited follow-up period
- Lack of sensitivity of the classification criteria

TABLE 119.1

Classifications of psoriatic arthritis

Moll and Wright ¹²	CASPAR ¹³ (CLASSification criteria for Psoriatic ARthritis)*		
	Points	Category	Description
Presence of psoriasis and an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) The (usual) absence of serologic tests for rheumatoid factor (RF)	2	Current psoriasis	Psoriatic skin or scalp disease confirmed by a dermatologist or rheumatologist;
	1	Personal or family history of psoriasis	history of psoriasis from the patient, family physician, dermatologist, rheumatologist, or other qualified practitioner; patient-reported history of psoriasis in a first- or second-degree relative
	1	Psoriatic nail dystrophy on current physical examination	Includes onycholysis, pitting, and hyperkeratosis
	1	Negative test for RF	Enzyme-linked immunosorbent assay or nephelometry preferred (no latex) using the local laboratory reference range
	1	Current dactylitis or history of dactylitis documented by a rheumatologist	Swelling of the entire digit
	1	Radiographic evidence of juxtaarticular new bone formation	Ill-defined ossification near joint margins in the hand or foot, excluding osteophyte formation on plain radiographs

*Psoriatic arthritis is diagnosed when 3 or more points are assigned in the presence of inflammatory articular disease (joint, spine, or entheses).

BOX 119.2 SUBTYPES OF PSORIATIC ARTHRITIS

- Distal interphalangeal joint—predominant arthritis (10%)
- Symmetric polyarthritis—predominant arthritis (5% to 20%)
- Asymmetric oligoarthritis or monoarthritis (70% to 80%)
- Axial disease—predominant (spondylitis and/or sacroiliitis) (5% to 20%)
- Arthritis mutilans (rare)

arthritis, (2) asymmetric oligoarticular arthritis, (3) symmetric polyarticular arthritis (RA-like picture), (4) axial disease predominant (spondylitis, sacroiliitis, and/or hip and shoulder involvement), and less commonly, (5) arthritis mutilans. Arthritis mutilans is a very rare, painful, and rapidly destructive type of PsA that is characterized by deforming arthritis, especially of the hands, and resorption of phalangeal bones. Other distinctive clinical features include dactylitis, or swelling of the fingers and toes suggestive of a “sausage-like” appearance, and inflammation of the tendon sheath (tenosynovitis) and entheses (enthesitis). *Enthesis* is the term used to describe the insertion of tendons or ligaments into bone. Inflammation of the eye such as conjunctivitis and uveitis can also be associated with PsA. Because PsA is clinically and genetically heterogeneous, it has been difficult to develop comprehensive classification criteria.

Validated criteria such as those developed for RA have not yet been fully implemented for patients with PsA. More recently, several reports have highlighted specific modifications of the Moll and Wight subgroups.¹⁴⁻¹⁶ A more recent and unified effort of expert investigators has led to development of CASPAR.¹³ Considered one of the largest international endeavors, it established a consensus based on 32 centers worldwide. The study evaluated 588 patients with definite PsA versus 536 controls (patients with other forms of inflammatory arthritis) to collect standardized data. This very thorough effort culminated in CASPAR, which yielded a sensitivity of 98.7% and specificity of 91.4% for the diagnosis of PsA. The new classification criteria incorporated musculoskeletal, dermatologic, and radiographic features. The main limitation of the CASPAR study cohort is the long-standing (>12 years' duration), well-established diagnosis of PsA in the participants, thus possibly losing generalizability to those with early disease. Chandran and colleagues¹³ undertook a study to determine the sensitivity of CASPAR

in patients with early PsA (duration of disease < 1 year) and found these criteria to have very high sensitivity for both early and late PsA disease. We need to realize, however, that this study was undertaken in a specialty clinic of a tertiary referral center without a control group, thus possibly leading to overestimation of the sensitivity of the criteria. An additional limitation of CASPAR is the complexity of the principal qualification for inflammatory arthritis (peripheral, spinal, or enthesal disease), which may be difficult for a nonrheumatology health care provider to confirm. Performance of CASPAR has not been studied in cohorts with early disease. Van den Berg and colleagues¹⁷ demonstrated that CASPAR was 88.7% sensitive and that the Assessment of SpondyloArthritis international Study (ASAS) and European Spondylarthropathies Study Group (ESSG) criteria reached 48.7% in an early-spondyloarthritis cohort.

It is important to remember that fulfilling classification criteria is not equivalent to making a diagnosis in an individual patient.¹⁸ It is appropriate to have separate criteria for classification and diagnostic purposes. The use of validated classification criteria for various inflammatory chronic diseases such as RA has been demonstrated to be critical for rigorous research. The development of new therapies, particularly biologic disease-modifying antirheumatic drugs, has highlighted this shortfall and created a need for more sensitive and specific criteria and for standardized outcome and response. The situation is made more complex in PsA by the existence of several clinical subgroups, for which precise definition has been the subject of some debate, as well as by the considerable overlap of the subgroups. The problem is not so critical with the classic manifestation of PsA—oligoarthritis, DIP joint involvement, calcaneal enthesitis, and dactylitis—but becomes more problematic with the group of patients who have seronegative polyarthritis and psoriasis.

During the past decade the overall prognosis of patients with PsA has steadily improved. However, for optimal treatment and best practice outcomes, further attention must be given to classification criteria for the entire spectrum of psoriatic disease. Psoriatic diseases should not be thought of as a condition limited to the skin and joints but also as a systemic inflammatory condition.¹⁹ Evidence is increasing that individuals with psoriasis or psoriatic arthritis have a higher prevalence of comorbid disease, particularly cardiovascular risk factors, metabolic disorders, and other immune-mediated inflammatory issues.²⁰ As we better define the epidemiology and classification criteria for psoriatic diseases, the ability to detect patients with psoriatic diseases earlier may assist in improving clinical outcomes in these patients.

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Clinical features of psoriatic arthritis

■ IAN N. BRUCE ■ PAULINE Y.P. HO

- Psoriatic arthritis is an inflammatory arthritis associated with psoriasis; tests for rheumatoid factor are usually negative.
- In 15% of patients psoriasis develops after the onset of arthritis.
- Nail changes have the strongest association with arthropathy; the distal interphalangeal joints are particularly affected.
- Typical clinical features include the following:
 - Distal interphalangeal joint involvement
 - Asymmetric sacroiliitis/spondylitis
 - Dactylitis
 - Enthesitis
- The number of joints involved can increase with disease duration.
- Patients with polyarticular involvement tend to have poorer long-term outcomes.

HISTORY

Psoriatic arthritis can be defined as “an inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor.”¹ Alibert first described the association between psoriasis and arthritis in 1818, although the term *psoriasis arthritique* was first used by Bazin in 1860. Bourdillon developed a more detailed description of the condition in 1888.¹ In the 1950s, Wright² formally described psoriatic arthritis and pointed out the low frequency of rheumatoid factor (RF) positivity, its predilection for distal interphalangeal (DIP) and sacroiliac joint involvement, the asymmetric nature of the arthritis, and its tendency to result in severe joint destruction (arthritis mutilans). In 1964 the American Rheumatism Association recognized psoriatic arthritis as a distinct entity.

CLINICAL FEATURES

Classification criteria

Psoriatic arthropathy is classified within the group of seronegative spondyloarthritis (see Chapter 113) on the basis of work by Moll and Wright¹ and others. Psoriatic arthritis is also included within the European Spondylarthropathies Study Group (ESSG) criteria. To facilitate further research on psoriatic arthritis, a new criteria set has been developed and validated. The CASPAR (CLASsification criteria for Psoriatic ARthritis) criteria³ have been shown to have high sensitivity and specificity for the diagnosis of psoriatic arthritis and provide a more consistent framework on which to base case ascertainment for future clinical and basic research on this condition (Box 120.1).

Articular involvement

Joint involvement in psoriatic arthritis can vary considerably, from isolated monoarthritis to extensive destructive arthritis, and can involve peripheral joints and the axial spine. The most widely used descriptive classification is that proposed by Moll and Wright,¹ which identifies five major subtypes of psoriatic arthritis (Box 120.2). Many further attempts have been made to revise and modify this system, but they have not been widely adopted. Categories within these subtypes have a high degree of overlap; for example,

spondyloarthritis may be the dominant feature in only a minority of patients, whereas clinical and radiologic involvement of the spine can be detected in approximately a third of cases.⁴ Similarly, exclusive involvement of the DIP joint is less common than involvement of this joint as part of a general peripheral arthritis.^{5,6} Many series have therefore shown quite marked differences in the relative frequencies of these subtypes. This is partly related to the criteria for entry into these cohorts and differences in the definitions used for each subgroup and the duration of disease at the time of the study (Table 120.1 and Fig. 120.1).⁵ For example, Jones and associates⁵ found that although the majority of patients described monoarticular or oligoarticular disease at onset, after a mean follow-up of 12.1 years, 63% of patients had polyarthritis. Marsal and coworkers⁷ also found that the median number of joints affected at the onset of disease was 2 (range, 0 to 8), as compared with a median of 10 (range, 2 to 19) after a follow-up period of 8 years. Arthritis mutilans is also a feature of prolonged disease,⁵ and the frequency of spinal involvement tends to increase with time. A more pragmatic classification based simply on peripheral or axial involvement has therefore been suggested and may be justified.⁷ This more pragmatic classification also seems to be generally true of other forms of spondyloarthritis inasmuch as the Assessment of SpondyloArthritis international Society (ASAS) published classification criteria for both axial and peripheral spondyloarthritis.

Symmetry of involvement in psoriatic arthritis

Wright² identified asymmetry as a common feature of psoriatic arthritis, particularly with the oligoarticular pattern,¹ a finding supported by other investigators.^{4,5} In contrast, the majority of patients with polyarticular disease have symmetric involvement.^{3,8} Symmetry may in part reflect the total number of joints involved. In a comparison of patients with early and late rheumatoid arthritis (RA) and psoriatic arthritis, after correction for the total number of involved joints, no difference was found in the degree of joint symmetry observed between these conditions.

Distal interphalangeal joint involvement

Involvement of the DIP joints in psoriatic arthritis is considered a distinctive feature of this condition (Fig. 120.2). These joints are involved more frequently in psoriatic arthritis than in inflammatory arthritis without psoriasis.⁹ In a community-based survey of early inflammatory arthritis, a DIP-predominant pattern at onset was found in 3.9% of patients with psoriasis versus 0.3% of those without psoriasis.¹⁰ Several large clinic series have noted involvement of the DIP joints in up to 54% of patients as part of polyarthritis,^{4,6} whereas the DIP-predominant subgroup represented a much smaller proportion of cases (1% to 16%) and its presence was often confined to early disease.^{1,6} DIP joint involvement is also associated with dactylitis^{4,6} and nail dystrophy.² Recent studies using magnetic resonance imaging (MRI) have noted a close association between involvement of the DIP joint and the nail–distal phalanx complex, which may explain this clinical association.¹¹

Monoarticular and oligoarticular arthritis

The frequency of these subtypes is highly variable across series and ranges in prevalence from 11% to 70%.^{1,4} In a community-based study of psoriatic arthritis in the United States, 90% of patients with psoriatic arthritis had an oligoarticular pattern at onset.¹² As pointed out earlier, monoarthritis and oligoarthritides are the most common patterns seen initially.^{5,7,12} A high proportion will, however, progress to additional joint involvement.⁵ In addition to involvement of the lower limb joints, this pattern of arthritis can fre-

quently affect the small joints of the hands, including the proximal interphalangeal and DIP joints. This pattern also has a male preponderance.⁶

Symmetric polyarthritis

Symmetric polyarthritis involves the small joints of the hands and feet, in addition to larger joints (Fig. 120.3). It has a female preponderance^{4,6,13} and can be clinically indistinguishable from RA.^{2,8} The exact frequency of this pattern is again controversial. Shbeeb and coworkers¹² described a 3% prevalence of polyarthritis at onset, whereas in hospital series polyarthritis may affect 15% to 61% of individuals.^{1,4,12} Patients with polyarticular disease tend to have a longer duration of disease than do those with other more discrete patterns.^{5,6} Regardless of the precise frequency of polyarthritis, it is patients with this condition who have more evidence of erosive joint damage.^{6,7}

Arthritis mutilans

Arthritis mutilans is a commonly used term with no clear definition. In general, it describes the end stage of a destructive erosive arthritis, with disorganization of joints leading to subluxation, “flail” joints, and digital telescoping—the so-called *doigt en lorgnette* (opera glass finger) (Figs. 120.4 and 120.5).² In most series its prevalence is lower than 5%.^{1,5,6} *Arthritis mutilans* is associated with long-standing disease and a female preponderance.^{5,7} An association with sacroiliac joint involvement has also been described.^{1,7}

BOX 120.1 CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS (CASPAR)

- Inflammatory articular disease (joint, spine, or enthesitis)
- AND at least 3 points from the following:
 - Current psoriasis (2 points), a personal history of psoriasis (1 point), or a family history of psoriasis (1 point)
 - Typical nail dystrophy (1 point): onycholysis, pitting, hyperkeratosis
 - Negative rheumatoid factor test (1 point): enzyme-linked immunosorbent assay or nephelometry preferred
 - Dactylitis (1 point): current dactylitis or a previous episode noted by a rheumatologist
 - Juxtaarticular new bone formation (1 point) on hand or foot radiographs

From Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665-73.

BOX 120.2 MOLL AND WRIGHT CLASSIFICATION OF PSORIATIC ARTHRITIS

- Arthritis with predominant distal interphalangeal joint involvement
- Arthritis mutilans
- Symmetric polyarthritis—indistinguishable from rheumatoid arthritis
- Asymmetric oligoarticular arthritis
- Predominant spondylitis

From Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55-78.

Spondyloarthritis

The spondyloarthritis of psoriatic arthritis is uncommon as a predominant feature and accounts for only approximately 5% of cases.^{1,4} Careful clinical and radiologic assessment, however, reveals involvement of the axial spine in 20% to 40% of cases,^{4,6,13} a figure that increases to as high as 51% at long-term follow-up. Involvement of the sacroiliac joints can be symmetric or asymmetric. Patients with bilateral sacroiliitis have a stronger association

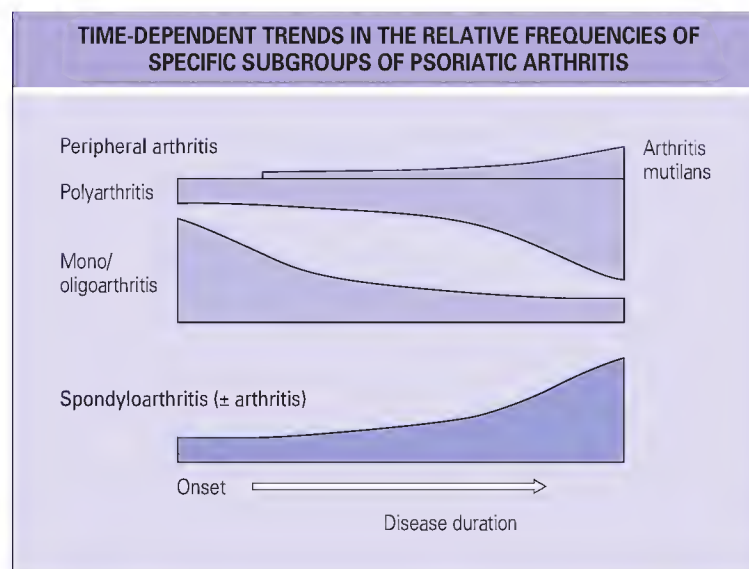


Fig. 120.1 Time-dependent trends in the relative frequencies of specific subgroups of psoriatic arthritis.



Fig. 120.2 Psoriatic arthritis with predominant involvement of the distal interphalangeal joints. (© University of Manchester.)

TABLE 120.1

Relative frequency of various subtypes of psoriatic arthritis in selected clinic series displayed according to duration of disease in the cohort studied

First author	Disease duration	DIP predominant	Oligoarticular	Polyarticular	Spondyloarthritis	Arthritis mutilans
Jones ⁵	Onset	2%*	63%†	25%	10%	0%
Veale ⁶	4 yr (median)	16%	43%	33%	4%	2%
Gladman ^{4†}	9 yr (mean)	12%	14%	40%	2%	16%
Jones ⁵	12 yr (median)	10%*	26%	63%	6%	4%

Note: Jones and colleagues⁵ described patterns at onset and follow-up.

*Defined as DIP only in this series.

†This includes monoarticular and oligoarticular onset.

‡The balance in this series had overlapping patterns.

DIP, distal interphalangeal.



Fig. 120.3 Symmetric polyarthritis resembling rheumatoid arthritis.



Fig. 120.4 Arthritis mutilans. Note the shortening of the thumbs and the left index finger (the right fifth finger has been amputated). (© University of Manchester.)

with HLA-B27.¹³ In contrast to ankylosing spondylitis, this form of spinal disease carries a better prognosis,¹⁴ which may partly reflect the random nature of spinal involvement, as well as a lower frequency of zygapophyseal joint fusion than seen in psoriatic arthritis. Cervical spine involvement in psoriatic arthritis can occur as part of more widespread axial disease or as the sole site of axial involvement and becomes more frequent with time. Two main types of cervical spine changes are described: an ankylosing type, similar to that seen in ankylosing spondylitis, and an erosive or inflammatory type, which can result in atlantoaxial or subaxial instability. Because cervical spine involvement can be clinically silent, patients with psoriatic arthritis, particularly those with long-standing disease, should have cervical spine radiographs taken and evaluated before receiving general anesthesia.

Other musculoskeletal features

Dactylitis

Dactylitis, or “sausage digit,” represents complete swelling of a single digit in the hand or foot. Dactylitis occurs in 30% to 40% of patients during the course of their disease.^{4,6} It most commonly involves one or two digits at a time, and the feet are affected more commonly than the hands (Fig. 120.6).¹⁵ There is an association with involvement of the DIP joint,^{4,6} and erosive damage more frequently develops in patients with dactylitis.^{7,15} MRI has revealed dactylitis to be strongly associated with flexor tenosynovitis, soft tissue edema, bone edema, and synovitis.^{16,17}

Enthesitis

Inflammatory lesions at the insertion of tendon into bone are a hallmark clinical feature of spondyloarthritis, and indeed, it has been postulated that this inflammatory lesion is the key central pathogenic process in all forms of seronegative spondyloarthritis.¹⁸ Symptomatic enthesitis occurs in 20%



Fig. 120.5 (a and b) Digital telescoping in arthritis mutilans. (© University of Manchester.)



Fig. 120.6 Dactylitis of the second toe.

to 40% of patients with psoriatic arthritis.^{18,19} It has been reported to be an initial feature in 4%.¹⁹ Common sites of enthesitis include the Achilles tendon (Fig. 120.7), the plantar fascia insertion into the calcaneus, and ligamentous insertions into the pelvic bones. With the advent of ultrasound, patients with psoriasis and more extensive nail involvement have also been noted to have higher systemic enthesopathy scores.²⁰

Peripheral edema

In contrast to the remitting seronegative symmetric synovitis with peripheral edema (RS3PE) syndrome, the distal extremity swelling in psoriatic arthritis is frequently asymmetric and preferentially affects the lower limbs. It can occur at any time and may be an initial feature of the disease. Peripheral edema is associated with extensor tenosynovitis and local enthesitis, and the edema is often found along the course of the involved tendon. Peripheral edema is usually responsive to oral corticosteroids. Several cases of lymphedema associated with psoriatic arthritis have also been reported. Though generally less painful, lymphedema can become more extensive and has been associated with progression of erosive damage. The response to corticosteroids and disease-modifying antirheumatic drugs varies, and it can be an additional source of disability in these patients.

Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome

The syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) is an uncommon but recognized subgroup of psoriatic arthritis. Clinically, less than 3% of patients with psoriatic arthritis are found to have SAPHO syndrome at initial evaluation. Nevertheless, at least 67% of all patients with SAPHO syndrome have psoriasis vulgaris or palmoplantar pustulosis.²¹ Scintigraphy suggests that involvement of the anterior chest wall may occur at a much greater frequency in patients with psoriatic arthritis than is clinically recognized.⁸



Fig. 120.7 Enthesitis involving the insertion of the right Achilles tendon.

Psoriatic onychopachydermoperiostitis

The key features of this rare manifestation include severe involvement of one or more terminal phalanges with associated severe nail dystrophy, soft tissue swelling, and marked periosteal reaction of the distal phalanx noted radiologically. Involvement of the DIP joint appears to be variable but is difficult to assess because of the marked local inflammation.²² Involvement of the great toe in particular had been described in this condition, and marked periostitis may eventually result in the radiologic phenomenon of the “ivory phalanx.” This entity appears to reflect the previously mentioned close association between the DIP joint, distal phalanx, and nail insertion as an extended enthesal complex.¹¹

Associated nail and skin changes

Skin changes

There is a suggestion that patients with psoriatic arthritis may have more extensive psoriasis than those with uncomplicated psoriasis only and that severe skin disease may increase the risk for development of psoriatic arthritis.²³ However, in general, most patients with psoriatic arthritis have only mild to moderate skin disease.²⁴ There is also no correlation between the extent of skin disease and total joint scores in patients with psoriatic arthritis.^{3,24} Nevertheless, 30% to 40% of patients with psoriatic arthritis report synchronicity of flares of their joint and skin disease, although the validity of this observation has not been formally tested.^{2,4} In a recent community-based psoriasis cohort, the pattern of psoriasis was found to be associated with future risk for psoriatic arthritis. In particular, scalp or intergluteal/perianal involvement is associated with increased risk for the development of arthritis.²⁵ With regard to specific psoriatic arthritis subtypes, an association between palmoplantar pustulosis and the SAPHO syndrome has been described.

Nail involvement

In contrast to skin disease, there is a close association between nail and joint involvement in psoriatic arthritis. Nail involvement is a risk factor for the future development of psoriatic arthritis²⁵; although onset of the skin disease may precede onset of the arthropathy by an average of 7 to 10 years, onset of the nail changes often occurs only 1 to 2 years before the onset of arthropathy.² Nail involvement occurs in 20% to 40% of patients with uncomplicated psoriasis, whereas 60% to 80% of patients with psoriatic arthritis have nail involvement.⁴⁻⁶ Anatomically, the nail is closely related to the distal phalanx by Sharpey fibers that insert into the bone in a manner similar to an enthesis. In addition, the extensor tendon entheses insert into the area adjacent to the nail root.¹¹ All the typical nail changes of psoriasis can be observed in psoriatic arthritis, including pitting, ridging, hyperkeratosis, and onycholysis.¹ The association between nails and joints is particularly marked in the presence of DIP joint arthritis, and 80% to 100% of such patients have nail involvement that frequently occurs at the adjacent nail (Fig. 120.8).^{2,5,6} Patients with DIP joint involvement also have more severe nail changes,^{5,9} and patients with nail disease have more DIP joint involvement.²⁴ There is also closer synchronicity between flares of DIP joint disease



Fig. 120.8 Involvement of the joint and adjacent nail in the right hand (a) and in the foot (b). Note the lack of involvement of the right fourth finger and nail. (© University of Manchester.)

and worsening of nail involvement than is reported for flares of skin and joint disease.²

Other extraarticular features

The extraarticular features observed in psoriatic arthritis overlap with those of the other forms of seronegative spondyloarthritis. Ocular inflammation can occur and is most frequently manifested as conjunctivitis. However, iritis has also been described in 7% of those affected by psoriatic arthritis.⁴ Additional uncommon complications such as oral ulceration, urethritis, and aortic valve disease have likewise been reported.²⁶

JUVENILE PSORIATIC ARTHRITIS

Psoriatic arthritis in those younger than 16 years is relatively uncommon and appears to account for less than 10% of chronic arthritis cases in childhood.²⁷ In contrast to adult-onset psoriatic arthritis, in juvenile-onset psoriatic arthritis the arthropathy precedes psoriasis in up to 50% of cases.²⁸ Careful attention therefore needs to be paid to examination of the nails and taking an accurate family history in children with arthritis (Table 120.2).²⁸ Juvenile psoriatic arthritis has a female preponderance of 2:1 to 3:1.²⁸ It is frequently manifested as monoarthritis or oligoarthritis, and the knee is often the first joint affected. Progression to polyarthritis occurs in a significant proportion of those affected, and involvement of the small joints of the hands and feet occurs commonly during the course of disease.²⁸ The other typical musculoskeletal features of adult psoriatic arthritis, such as dactylitis, enthesitis, and DIP joint involvement, are all recognized. In addition, chronic uveitis is reported in 10% to 15% of patients and may be associated with antinuclear antibodies.²⁸ There is also evidence of two subgroups of juvenile psoriatic arthritis. The first subgroup has an onset around 2 years of age and predominantly consists of females. This population has a very low prevalence of actual psoriasis and tends to have a more oligoarticular disease with less axial involvement but a very high prevalence of dactylitis; in one study, 60% of this cohort was antinuclear antibody positive. In the second subgroup, psoriatic arthritis is diagnosed at a median age of 9.5 (range, 6.2 to 11) years, and such children are more likely to have axial disease, enthesitis, and polyarticular arthritis. Interestingly, uveitis had a similar prevalence in both populations. The prognosis of children with juvenile psoriatic arthritis is good. It can, however, persist into adulthood, and 10% to 15% of those affected have significant residual disabilities.²⁹

INVESTIGATIONS

Laboratory investigation

No laboratory tests are diagnostic of psoriatic arthritis. Several studies have shown that the acute-phase reactants display typical inflammatory changes when the disease is active. In particular, anemia of chronic disease, hypoalbuminemia, and an increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and fibrinogen levels are described.³⁰ Hypergammaglobulinemia with increased IgG and IgA is observed.⁴ Increased IgA is

especially associated with spondyloarthritis.¹³ Monoclonal gammopathy has also been reported in 9.7% of patients with psoriatic arthritis in one series and is associated with older age, longer disease duration, more active disease, and less intensive therapy.³¹ Overall, the ESR and CRP show good correlation with inflammatory disease activity, particularly in polyarticular disease.^{8,13} Because in most series positive RF is not taken as an absolute exclusion criterion for the case definition of psoriatic arthritis, RF-positive status has been reported in 5% to 10% of patients.^{4,13} In a community cohort of patients with recent-onset inflammatory polyarthritis, those with psoriasis were significantly less likely to be RF positive than were those without psoriasis (13% vs. 31%).¹⁰ Anti-citrullinated peptide antibodies (ACPAs) have also been reported to have a low prevalence of 6% to 10% in psoriatic arthritis.³²⁻³⁵ Like RF positivity, there is an association with female gender and polyarticular disease.³³⁻³⁵ It has also been noted, however, that other typical psoriatic features such as DIP involvement and enthesitis are likewise observed in ACPA-positive patients.^{32,33} Positivity for antinuclear antibody is also found in 10% to 14% of patients with psoriatic arthritis.^{4,13} Hyperuricemia is present in up to 20% of patients with psoriatic arthritis.³⁶ A prospective study of patients with psoriatic arthritis found that the best predictors of hyperuricemia were renal impairment and increased total cholesterol. No correlation with the extent or severity of skin involvement was found, so hyperuricemia does not primarily reflect increased epidermal cell turnover.³⁶ Hyperuricemia should therefore alert the physician to assess the patient for other components of metabolic syndrome, such as abdominal adiposity, higher blood pressure, and dyslipidemia.

Radiographic changes

Peripheral joint features

Many radiologic features reflect the clinical distribution of psoriatic arthritis described earlier. Therefore, involvement of the DIP joints (Fig. 120.9) and an asymmetric distribution when few joints are affected are well described. In addition, involvement of enthesal sites can result in proliferative new bone formation at sites of predilection, such as the plantar fascia and Achilles tendon insertions. With regard to the onset of erosive changes in peripheral joints, in a community survey of early inflammatory arthritis, the risk for development of erosions at 1 year was lower in patients with psoriasis than in those without psoriasis.¹⁰ This reduced risk was explained by the lower incidence of RF positivity in the psoriasis group. Nevertheless, 22% of patients with psoriasis and early arthritis had evidence of erosions at 1 year.¹⁰ In more established hospital cohorts, the prevalence of erosions can range from 35% to 70%.^{4,6,7} Erosions are most frequent in patients with polyarthritis and in those with a longer disease duration, as well as in those

■ TABLE 120.2

Proposed criteria for diagnosis of juvenile psoriatic arthritis

Diagnosis	Criteria
Definite psoriatic arthritis	Onset of arthritis before 16 years of age <i>and either</i> Typical psoriasis <i>or</i> Three or four minor criteria: Dactylitis Nail pitting Psoriasis-like rash Family history of psoriasis (first- or second-degree relative)
Probable psoriatic arthritis	Onset of arthritis onset before 16 years of age <i>and</i> Two minor criteria

After Southwood TR, Petty RE, Malleon PN, et al. Psoriatic arthritis in children. *Arthritis Rheum* 1989;32:1007-13.



Fig. 120.9 Radiograph of the hands showing erosive changes at the distal and proximal interphalangeal joints with sparing of the metacarpophalangeal joints and wrists. (© Dr. R. Whitehouse.)



Fig. 120.10 Arthritis mutilans. (a and b) Marked osteolysis and “penciling” have resulted in complete disorganization of the metatarsophalangeal (MTP) joints. There is also a “pencil-in-cup” deformity of the right fifth MTP joint (b). (© Dr. R. Whitehouse.)

with dactylitis.^{6,7} Patients with psoriatic arthropathy also tend to have a lower prevalence of erosions at the wrist and more erosions at the DIP joints than RA patients do.³⁷ In addition to erosions, soft tissue swelling can be seen around sites of active inflammation, although periarticular osteopenia is not a feature of psoriatic arthritis.³⁸ The other peripheral joint radiographic features can be broadly grouped into destructive and proliferative changes.

Destructive changes

Osteolysis may result in whittling or penciling of a phalanx. This can occur alone or in association with erosion at the base of the adjacent phalanx, which causes the classic “pencil-in-cup” deformity.³⁹ Such destruction is typical of the arthritis mutilans pattern of disease (Fig. 120.10).

Proliferative changes

In periostitis, proliferative new bone formation can occur along the shaft of the metacarpal and metatarsal bones (Figs. 120.11 and 120.12a). When this change occurs adjacent to an erosion, the term *whiskering* is often used (see Fig. 120.12b).³⁹

An ivory phalanx (see “*Psoriatic onychopachydermoperiostitis*,” earlier) can be noted, as can bony ankylosis and joint fusion (Fig. 120.13).

Spinal changes

Asymmetric sacroiliitis is more common in psoriatic arthritis than in ankylosing spondylitis (Fig. 120.14). Many of the classic features of ankylosing spondylitis can be observed in psoriatic arthritis, but patients with psoriatic arthritis tend to have less frequent involvement of the zygapophyseal joint and less severe and extensive involvement of the lumbar spine. Overall, the spinal involvement in psoriatic arthritis tends to be more “spotty” and asymmetric, with frequent involvement of the cervical spine. An additional feature in the spine is paravertebral ossification or “chunky” syndesmophytes.⁴⁰ These bony outgrowths appear to be distinct from the classic “marginal” syndesmophytes observed in ankylosing spondylitis. The chunky syndesmophytes again occur in a patchy and asymmetric fashion throughout the axial spine (Fig. 120.15).



Fig. 120.11 Asymmetric involvement of the hands. Soft tissue swelling and a periosteal reaction are evident in the right second and third fingers in the typical “ray” distribution. (© Dr. R. Whitehouse.)

Other imaging modalities

MRI studies have demonstrated that in psoriatic arthritis, extraarticular tissues such as ligaments, periarticular soft tissue and tendon sheaths, and bone are frequently involved (Fig. 120.16).^{16,41} In addition to delineating clinical joint involvement, MRI has demonstrated evidence of “subclinical” musculoskeletal changes in a significant proportion of patients with apparently uncomplicated psoriasis. Scintigraphy in patients with psoriatic

Fig. 120.12 Examples of periosteal reactions. (a) Along the shaft of the proximal phalanx. (b) Adjacent to a large erosion and producing “whiskering.” (© Dr. R. Whitehouse.)

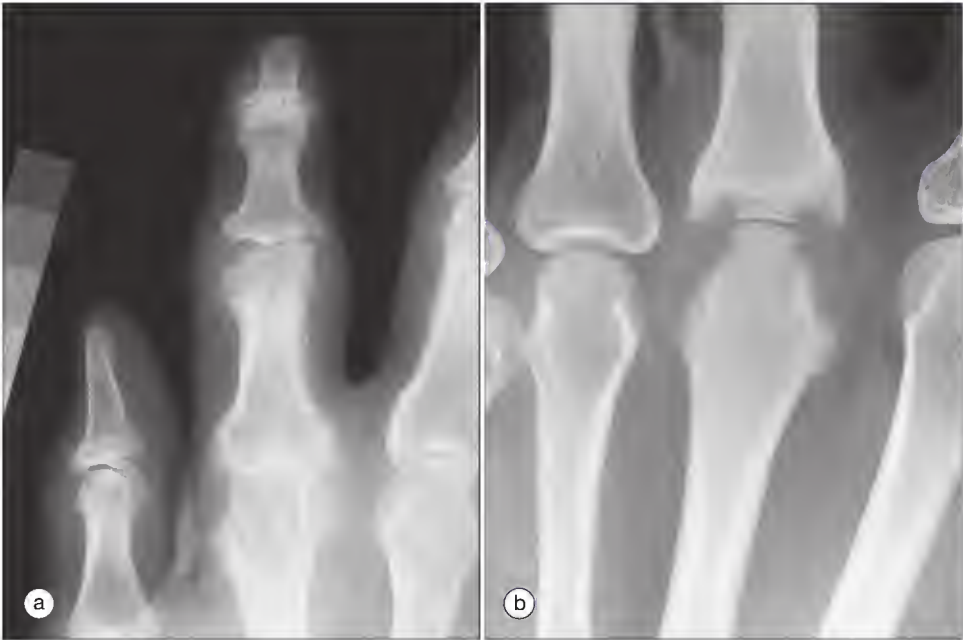


Fig. 120.13 Bony ankylosis of the distal interphalangeal joint. (© Dr. R. Whitehouse.)



Fig. 120.14 Early asymmetric sacroiliitis with erosion and sclerosis of the left sacroiliac joint. (© Dr. R. Whitehouse.)

arthritis has also demonstrated more extensive involvement than is appreciated clinically, particularly in the anterior chest wall and large peripheral joints.⁸ Such techniques can therefore facilitate clinical evaluation of patients with psoriasis and articular complaints.

DIFFERENTIAL DIAGNOSIS AND CLINICAL EVALUATION

Differential diagnosis

Psoriatic arthritis poses an important diagnostic challenge, and the wide range of clinical manifestations described earlier means that the differential diagnosis is extensive. Given the frequency of hyperuricemia, crystal arthropathies also need to be excluded, and accordingly, joint fluid analysis may need to be performed. The distinctions between psoriatic arthritis and RA or psoriatic arthritis and ankylosing spondylitis have been discussed and are summarized in [Tables 120.3](#) and [120.4](#). In patients without any clinical

TABLE 120.3
Key features that help distinguish between psoriatic arthritis (PsA) and rheumatoid arthritis (RA)

Feature	PsA	RA
Gender (M:F)	1:1	2:1
Rh factor	<10%	80%
DIP joints	30%-50%	Uncommon
Pattern of joint involvement	Asymmetric “ray” pattern	Symmetric “row” pattern
Sacroiliac joints/axial spine	35%—any level	Cervical spine in late disease
Other musculoskeletal disorders	Enthesitis Dactylitis Periarticular erythema	
Extraarticular	Skin Nail dystrophy	Nodules Sicca Vasculitis
Radiology	Erosion (distal interphalangeal joints) Periostitis/bony proliferation	Periarticular osteopenia Erosion (wrists)



Fig. 120.15 Nonmarginal “chunky” syndesmophytes.

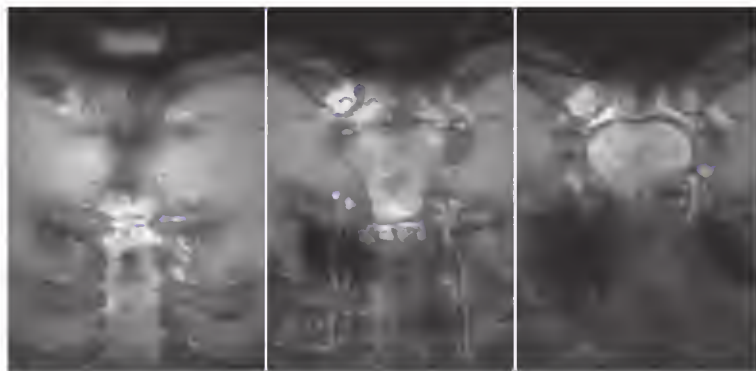


Fig. 120.16 Involvement of extraarticular tissues in psoriatic arthritis. Magnetic resonance images (coronal fat suppressed, proton density weighted) show osteitis and bone edema as high signal in the clavicles, manubrium, and upper part of the sternum in a patient with the syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO). (© Dr. R. Whitehouse.)

TABLE 120.4
Key features that help distinguish between psoriatic arthritis (PsA) and ankylosing spondylitis (AS)

Feature	PsA	AS
Gender (M:F)	1:1	9:1
Sacroiliac joints/axial spine	35%	100%
Spinal movements	↓	↓↓
Peripheral joint involvement	90%-95%	40%
Peripheral joint pattern	Upper and lower limbs Large and small joints	Lower limbs Large joints
Dactylitis	Common	Uncommon
HLA-B27	10%-25%	90%
Spinal radiology	Random distribution Asymmetric “chunky” syndesmophytes	Contiguous involvement Symmetric classic syndesmophytes



Fig. 120.17 Flexural psoriasis in the gluteal cleft, a typical “hidden” site for psoriasis.

evidence of skin or nail disease—“psoriatic arthritis sine psoriasis”—distinguishing psoriatic arthritis from other arthropathies, including erosive or inflammatory osteoarthritis, is particularly difficult.

Clinical evaluation

Patients with psoriatic arthritis can be less tender over affected joints than patients with RA, and effusions can be more difficult to detect. It is therefore easy to underestimate the extent of joint involvement in psoriatic arthritis. Examination for other musculoskeletal features such as enthesitis, tenosynovitis, and axial spine involvement is also necessary. Limitations in spinal movement may not follow the classic pattern observed in ankylosing spondylitis and may be confined to the neck or thoracic spine in the absence of lumbar spine or sacroiliac joint involvement. Radiologic evaluation complements the clinical examination in that joint damage from previous involvement may be detectable radiologically in the absence of current symptoms. Similarly, previous or current inflammatory back symptoms suggest spondylitis and require radiologic examination. Finally, detailed examination of the skin and nails to include “hidden areas” such as the scalp, perineum, and periumbilical area is important (Fig. 120.17). The choice of therapeutic agent or agents is determined by the extent and severity of the skin and joint disease and by estimation of the risk for progression of disease.

PROGNOSIS

Functional impairment

Only a few prospective studies of prognosis in patients with psoriatic arthritis have been conducted. The general impression is that the condition is associated with less long-term disability than is observed with RA.¹ Several hospital clinic series have, however, shown that between 11% and 42% of patients with psoriatic arthritis have American College of Rheumatology grade III or IV functional impairment at the time of study.^{4,6,7,13} Direct comparison between patients with psoriatic arthritis, RA, and ankylosing spondylitis also shows a comparable burden of illness across these conditions.⁴² All studies are in agreement that there is an association between polyarthritis and functional disability. One study found that patients with at least five joint effusions at initial evaluation in the clinic were significantly more likely to exhibit progressive joint deformity at follow-up. Additional predictive factors include the presence of HLA-B27, HLA-B39, or HLA-DQw3.⁴³

Mortality

A community-based study in Olmsted County, Minnesota, showed no difference in survival of patients with psoriatic arthritis and members of the general population.¹² In contrast, in a hospital cohort, an increased mortality rate in comparison to the general population was observed, with an overall standardized mortality ratio of 1.36 (95% confidence interval, 1.12 to 1.64)⁴⁴; this probably reflects the spectrum of disease with long-term follow-up in hospital clinics. Interestingly, there was also evidence that the standardized mortality rate has improved with calendar year such that in the 1996-2004 cohort, no excess mortality was noted.⁴⁴ The most common

causes of mortality in patients with psoriatic arthritis included cardiovascular disease, neoplasia, and respiratory disease.^{44,45} Others have also shown an excess burden of cardiovascular disease in those with psoriatic arthritis.⁴⁶⁻⁴⁸ Significant predictors of mortality in patients with psoriatic arthritis include radiologic damage, increased ESR, and previous use of disease-modifying

antirheumatic drugs, with nail lesions being identified as a “protective factor.”⁴⁹ From these studies one can conclude that patients with polyarthritides are most likely to have functional impairment and progression of disease. In addition, extensive and progressive disease may also be associated with excess mortality.

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Etiology and pathogenesis of psoriatic arthritis

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- Psoriatic arthritis (PsA) is an inflammatory arthropathy associated with psoriasis, but not all patients with the characteristic arthropathy have skin disease.
- The heterogeneity in expression of PsA with diverse skeletal patterns of involvement is a hallmark of the disease not observed in rheumatoid arthritis (RA). Whereas RA is considered an autoimmune-mediated peripheral synovitis that leads to bone destruction, the phenotype of PsA is strikingly different, with characteristic features of florid bone destruction (including erosion and osteolysis) and new bone formation that encompasses periostitis, joint ankylosis, and syndesmophyte formation.
- This heterogeneous pattern of pathobiology in PsA is best conceptualized in relation to inflammation at “the entheses organ,” which includes the soft tissue structures adjacent to the insertion, regional trabecular bone, and the associated synovium, all of which form a musculoskeletal assembly called the synovial/enthesal complex. As yet poorly defined, immune dysfunction at the entheses organ probably contributes to much of the local skeletal inflammation in PsA.
- Nail disease, including matrix and nail bed involvement, is characteristic of PsA but less common in psoriasis. Recent evidence indicates that neither nail disease nor joint disease shares the strong HLA-Cw06 genetic association noted in early-onset psoriasis. Moreover, inflammation at the entheses may be a link between distal joint arthritis and nail involvement in PsA.
- Imaging studies have convincingly demonstrated that psoriasis without clinical arthritis is strongly associated with subclinical abnormal signals in entheses and bone. These studies, coupled with the association of PsA with a wide array of extraarticular features, including uveitis, inflammatory bowel disease, obesity, metabolic syndrome, cardiovascular disease, and frequent nail inflammation, support the emerging concept of a wide spectrum of disease that can be viewed as psoriatic disease.
- The entire spectrum of skeletal and cutaneous inflammation associated with PsA is remarkably responsive to blockade of tumor necrosis factor (TNF) in the majority of patients, which underscores the pivotal role of this cytokine in disease pathogenesis. Recent studies have indicated that blockade of p40, the common subunit of interleukin-12 (IL-12) and IL-23, is effective for both skin and joint inflammation as well.
- Genome-wide association studies have confirmed several genetic associations with psoriasis. The B8, B27, B38, and MICA alleles of HLA are significantly associated with PsA as opposed to psoriasis. Other associated risk alleles include molecules involved in signaling through the IL-23, IL-17, and TNF receptors.

INTRODUCTION

The first definitive description of the link between psoriasis and arthritis was elucidated in a seminal paper published by Wright in 1956.¹ In a landmark paper published in 1973, Moll and Wright² described the characteristic features of psoriatic arthritis (PsA) in more detail and emphasized the diversity of its clinical manifestations, such as asymmetry, arthritis mutilans, enthesitis, dactylitis, and nail disease, findings not generally observed in rheumatoid arthritis (RA).³

Over the past 35 years, scientific and translational studies have supported the concept that PsA has distinct disease mechanisms that contrast sharply

with the key pathophysiologic events associated with RA, although some parallels exist. In this chapter, genetic and environmental factors are discussed, and a comprehensive review of the alterations that take place in the skin, synovium, entheses, cartilage, and bone is presented. In addition, relevant observations obtained from the study of animal models are highlighted, and both human and preclinical data are incorporated into a working model of disease pathogenesis.

GENETIC FACTORS

Epidemiologic reports, association studies, and genome-wide association scans (GWAS) indicate that PsA is a highly heritable disease mediated by multiple genes with low-risk effects.⁴ Heritability as measured by λ s (risk to siblings vs. risk in the general population) was greater than 27, as compared with 4 to 7 for psoriasis.⁵⁻⁷ Of note, one twin study did not find the concordance rate to be higher in dizygotic twins than in monozygotic twins, but the study was underpowered.⁸ The recent development of classification criteria⁹ may help improve diagnostic precision, and larger sample sizes that include subjects with well-characterized psoriasis and PsA should facilitate better understanding of the genetic factors associated with the two disorders.

Genome-wide association scans have shown that IL-23R and HLA-Cw06, along with molecules involved in NF- κ B gene expression (TNIP1) and signaling (TNFAIP3), and tumor necrosis factor (TNF) polymorphisms are observed with greater frequency in PsA subjects than in controls (Table 121.1). Association studies and GWAS have also identified risk alleles in patients with both psoriasis and PsA, including interleukin-12A (IL-12A), IL-12B, IL-23 receptor (IL-23R), genes that regulate nuclear factor κ B (NF- κ B), TNIP1, and the class I major histocompatibility complex (MHC), particularly HLA-Cw6 and HLA-B27 (see Table 121.1).¹⁰⁻¹⁷ Closer examination of the association with HLA-Cw06, however, revealed that the presence of the allele primarily relates to the early onset of psoriasis and not arthritis¹⁸ and, likewise, that the IL-23R association appears to be more strongly linked to psoriasis than to arthritis.¹¹

TRAF3IP3 or Act1 is an adaptor protein in the IL-17R complex that is essential for type 17 helper T cell (Th17)-mediated inflammatory responses. It is now apparent that a variety of other cells, including monocytes and epithelial cells, can also release IL-17.¹⁹ The mutation in Act1 is associated with increased production of IL-22, a cytokine linked to keratinocyte proliferation in the skin and bone formation, as discussed later.²⁰ Of note are recent findings showing an increased frequency of HLA-B27 in PsA, and the presence of this allele is associated with a short interval between the onset of skin and joint disease.¹⁶ Other studies have found an association with MHC class I chain-related gene A (MICA) alleles that are situated centromeric to the HLA-B locus, and this susceptibility was independent of HLA-Cw6.^{21,22} Overall, the MHC associations have the strongest relative risk, but defining specific alleles is complicated by the strong linkage disequilibrium characteristic of this region.⁴ The association with killer immunoglobulin-like receptor (KIR) alleles is particularly fascinating because these receptors bind MHC class I molecules with locus and allele specificity and this interaction can result in both activating and suppressive signals to natural killer cells and lymphocytes that are dependent on the ligand-receptor interaction.²³

A recent high-density GWAS study in individuals with inflammatory bowel disease showed a remarkably strong genetic overlap with both psoriasis and ankylosing spondylitis, thus adding further support to the presence of PsA within the spondyloarthritis concept.²⁴ One recent discovery in the field of familial psoriasis involves the disease association with CARD14, which implicates cutaneous innate disease immune responses.²⁵ The extent of involvement of CARD14 in PsA awaits elucidation. Although the CARD14

TABLE 121.1
Loci linked to psoriatic arthritis from association studies

Gene	Study	Cases	Controls	Odds ratio	Strength of association
IL-12B	Liu et al. ¹⁰	576	480	1.1	$P = .0013$
	Huffmeier et al. ¹¹	748	937	1.5	$P = 4.72 \times 10^{-7}$
IL-23R	Liu et al. ¹⁰	576	480	1.70	$P = 8 \times 10^{-4}$
	Huffmeier et al. ¹¹	748	937	1.59	$P = .002$
TRAF3IP2	Ellinghaus et al. ¹³	1919	8037	1.57	$P = 4.6 \times 10^{-12}$
IL-2/IL-21	Liu et al. ¹⁰	576	480	1.37	$P = .002$
TNFAIP3	Nair et al. ¹⁴	1755	5942	1.18	$P = .0003$
TNIP1	Nair et al. ¹⁴	1755	5942	1.78	$P = 2 \times 10^{-14}$
TNF	Reich et al. ¹⁵	375	376	1.96	$P = .0025$
HLA-Cw6	Liu et al. ¹⁰	576	480	2.4	$P = 6.9 \times 10^{-11}$
HLA-Cw6	Liu et al. ¹⁰	576	480	3.2	$P = 1.9 \times 10^{-10}$
HLA-B27	Winchester et al. ¹⁶	359	1000	3.18	$P < .0001$
KIR ligands	Martin et al. ¹⁷	366	299	NR	$P < .0001$

IL, interleukin; KIR, killer inhibitory receptor; NR, not reported; TNF, tumor necrosis factor.

Modified with permission from Nogroles KE, Brosington RD, Bowcock AM. New insights into the pathogenesis and genetics of psoriatic arthritis. *Not Clin Pract Rheumatol* 2003;5:83-1.

mutation has an autosomal dominant pattern of inheritance, a second discovery of an autosomal recessive mutation in the IL-36 receptor antagonist has been described in both psoriasis and PsA.²⁶ This molecule is associated with pustular psoriasis and plays a pivotal role in the regulation of IL-8 and other cytokines known to be involved in psoriasis.

ENVIRONMENTAL FACTORS

Infection

The classic environmental association with psoriasis is the link with post-streptococcal tonsillitis and subsequent guttate psoriasis. This skin eruption typically affects younger patients and is associated with the presence of the HLA-Cw6 antigen. Based on restricted use of T-cell receptor expression in the tonsils and skin, a case for molecular mimicry between streptococcal and cutaneous antigens has been proposed, but the alternative possibility that the inflammatory process is driven by superantigens is likewise valid.²⁷ The importance of chronic carriage of the inciting streptococcus is also supported by data showing improvement in psoriasis when patients undergo tonsillectomy, and the degree of clinical response correlated with the decrease in frequency of peptide-reactive (streptococcal M proteins, keratin) cutaneous lymphocyte antigen (CLA+) skin-homing T cells in the circulation.²⁸ Although streptococcal infections have been associated with post-streptococcal arthritis that is totally independent of the psoriasis phenotype, no definitive evidence linking a specific infectious agent to PsA joint disease has been reported.

A role of bacterial colonization of psoriatic skin plaques and associated dysregulation of the skin barrier has also been hypothesized. Abnormal mucosal permeability of the large intestine has been reported in about 20% of PsA cases. Whether this is environmental or genetic in origin and the implications of access of bacteria or their constituent macromolecules to the circulation and the effect that this might have on expression of the skin disease remain unknown.²⁹

Trauma, obesity, and severity of psoriasis

A well-recognized association between psoriasis and trauma known as the Koebner phenomenon is widely appreciated. Koebner responses are generally greater in HLA-Cw6 positive psoriasis cases. Analogous to the skin, several studies have shown that the intriguing relationship between trauma and the presence of PsA is stronger than that between trauma and RA.³⁰ If trauma is important in PsA, the target entheses, which are sites of high mechanical stress, might exhibit signs of microdamage. Of particular relevance is that these structures often have prominent alterations, including bone microfracture, repair, and altered vascularity in normal cadaveric tissue.³¹ Intriguingly, these sites of damage may be associated with microscopic inflammatory changes.³² Thus, even in the absence of recognizable

clinical trauma, the normal physiologic responses associated with joint locomotion may lead to deep Koebner-type responses that could trigger joint inflammation.

An association between psychological stress and the development of psoriasis has been reported.³⁰ Unfortunately, accurate and scientific measurement of psychological stress remains difficult.

Obesity and severity of psoriasis have been associated with increased risk for PsA.^{33,34} In a cohort study of The Health Improvement Network (THIN), PsA incidence rates correlated with increasing body mass index. In another study performed on a cohort of patients with psoriasis, the extent of psoriasis correlated with a new diagnosis of PsA. Nail disease has also been associated with psoriasis.

IMMUNOPATHOLOGY

Any understanding of the mechanisms that underlie PsA must consider the association with psoriasis, the marked impact of local factors that account for the diversity of joint involvement, and the predilection for axial, enthesal, and tendon inflammation (Fig. 121.1a). The key sites of inflammation include not only the synovium but also the bone (osteitis), entheses (enthesitis), and tendons (dactylitis). Even though these different anatomic sites of disease were historically considered distinct unrelated entities, it has become increasingly evident in the past decade that a common anatomic biomechanical thread may connect the diverse pathologic processes.

The pattern of asymmetric arthritis has been recognized to be one of simultaneously occurring opposite phenotypes with new bone formation and bone destruction occurring in adjacent joints. These changes range from frank osteolysis (arthritis mutilans) and eccentric erosions to fluffy periostitis or frank bone erosion (see Fig. 121.1b). After the initial inflammatory insult to the joint, it appears that both osteoclastic-mediated joint damage and osteoblastic-mediated joint repair and remodeling can take place (Fig. 121.2). It is fair to say that these responses remain somewhat enigmatic beyond the fact that the local joint environment at each involved site critically influences disease expression.

Dissociation is often observed between the extent of skin and joint involvement in an individual patient. In fact, this observation has crystallized with the advent of numerous trials of biologic agents for both psoriasis and PsA, in which it became evident that the Psoriasis Area and Severity Index (PASI) score may be just minimally elevated in subjects with advanced polyarticular PsA.

Psoriatic plaque

A brief summary of the immunopathology of psoriasis is the key to setting the stage for an understanding of PsA. The events that lead to formation of the raised, scaly, erythematous plaques of psoriasis arise as a result of interactions between the innate and acquired immune responses.³⁵ Intradermal



Fig. 121.1 (a) Ray diversity in psoriatic arthritis. Note the marked differences in pathologic changes in the various rays of the hand. (b) On radiography, marked bony resorption, early “pencil-in-cup” deformities, and bony ankylosis are evident. (Reproduced with permission from the American College of Rheumatology.)

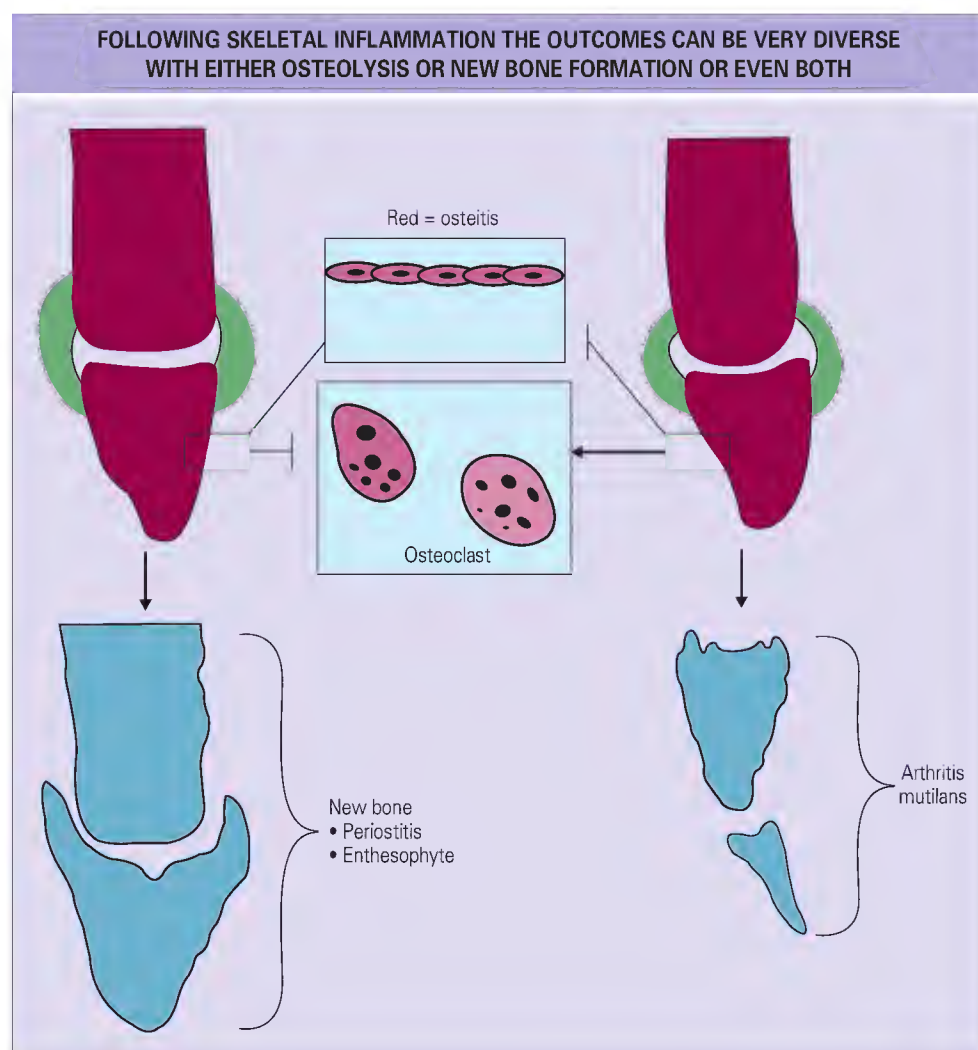


Fig. 121.2 After diffuse digital osteitis (top left), tissue repair responses may dominate and lead to new bone formation at insertions and periostitis or even bony sclerosis (bottom left). This suggests a response that is ultimately dominated by osteoblastic and mesenchymal stem cell-mediated tissue repair responses. However, after diffuse osteitis the disease processes may be dominated by osteoclastic-mediated catabolic responses, with diffuse bone destruction leading to osteolysis and other characteristic radiographic changes, including bone whittling (bottom right). (Blue bone denotes bone after resolution of the active osteitis phase. Red bone denotes the active osteitis phase.)

injection of interferon alfa (IFN- α) can precipitate psoriasis, and nucleic acids, including DNA and RNA, can lead to the upregulation of an array of “interferon signature” genes. Stressed or apoptotic keratinocytes release DNA that binds to cathelicidin LL-37, an antibacterial peptide produced by keratinocytes. This LL-37/DNA complex binds to Toll-like receptor 9 (TLR9) in the endosomes of plasmacytoid dendritic cells, which in turn promotes the release of IFN- α .³⁶ Dermal dendritic cells activated by IFN- α migrate to skin-draining lymph nodes and promote naive T-cell

differentiation to Th1 and Th17 cells. These Th1 and Th17 cells migrate to the dermis via lymphatics and blood vessels. In the dermis, INF- γ and TNF are released by Th1 cells, whereas Th17 cells produce IL-17, TNF, IL-1, and IL-22. IL-22 stimulates keratinocyte proliferation and additional cathelicidin production. Keratinocytes produce large quantities of the cytokines IL-1, IL-6, and TNF and an array of chemokines.³⁷ Dermal dendritic cells also induce autoprolieration of T cells and release IL-23, which enhances the proliferation and survival of Th17 cells. Additionally, crosstalk between

keratinocytes, fibroblasts, and endothelial cells results in tissue remodeling and deposition of matrix molecules. Marked angiogenesis is observed in the dermis where tortuous, leaky vessels form, but it remains unclear whether such changes are driving events or represent a secondary remodeling response to inflammation.

Nail disease

Although the nail is generally of limited clinical relevance to rheumatologists beyond its use in confirming the presence of PsA in a patient with inflammatory arthritis, it has nevertheless contributed greatly to a better understanding of psoriatic disease. The entheses of the distal interphalangeal joint, including the extensor tendon and lateral collateral ligaments, are intimately anchored to both the nail and adjacent periosteum.³⁸ Although the nail may be derived ectodermally, it is functionally integrated into the joint. Recent high-resolution ultrasound studies of the extensor tendons have shown that enthesopathy is observed more frequently at this site in psoriasis patients with nail disease. These subjects had no clinical arthropathy, so these findings further strengthen the link between nail disease and psoriasis. What is also intriguing is that nail disease, like joint disease, is not associated with carriage of the HLA-Cw6 antigen.³⁹

Links between skin and musculoskeletal inflammation

Epidemiologic evidence suggests that musculoskeletal involvement will develop in 13% to 25% of patients with psoriasis, but the mechanisms that underlie joint inflammation are not well understood.³⁵ Various imaging modalities, including scintigraphy, magnetic resonance imaging (MRI), and Doppler ultrasonography, have consistently demonstrated skeletal abnormalities, including periostitis, osteitis, and enthesitis, in psoriasis patients with no musculoskeletal symptoms or objective findings.⁴⁰⁻⁴² These data suggest ongoing subclinical joint inflammation in more than a third of psoriasis subjects. In a recent study, PsA was found to have developed in about 10% of patients with psoriasis over a period of 2 decades. Based on these data, it would appear that overt skeletal inflammation may not develop in the majority of patients with subclinical disease, but this finding awaits confirmation.⁴³

Several conceptual models can be envisioned to explain the links between psoriasis and joint inflammation (Fig. 121.3), and it is entirely possible that several of these mechanisms are operative in a parallel manner or in different subgroups of patients. T lymphocytes, dendritic cells, or activated monocytes may leave the skin and enter subsynovial vessels in the joint and promote inflammation. Local factors that arise in the entheses or joints, such

as trauma, stress, or infectious pathogens, could promote an innate immune response that rapidly expands to acquired immunity in the setting of pre-existing T-cell expansion in the skin and secondary lymph organs.

The skin and joint inflammation may not be linked by circulating cells but by an underlying aberrant response to injury in the skin and the joint (localized Koebner or pathergy reaction).⁴⁴ Indeed, the skin and joint entheses share some common microanatomic features, including different degrees of mechanical stress across different tissue layers and a sharp interface between vascular and nonvascular tissue.⁴⁵ Alternatively, inflammation in the gut may initiate an immune response in the skin and the joint, and the finding of subclinical bowel inflammation in up to a third of patients with PsA provides evidence for this model.⁴⁶

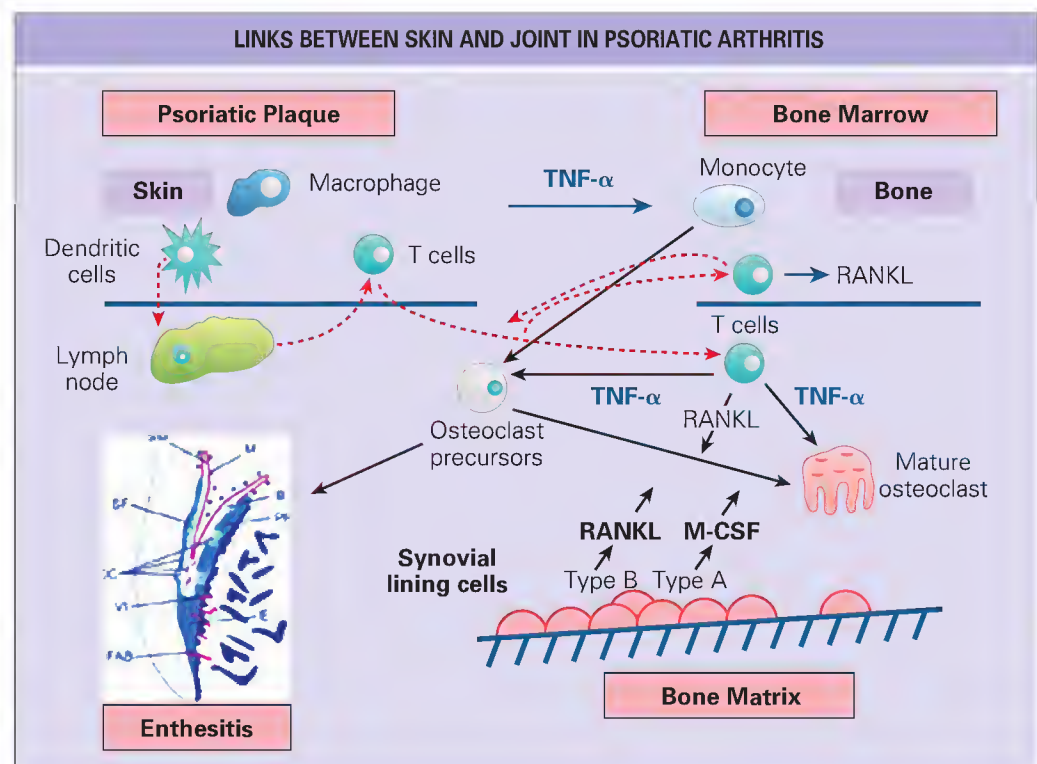
Synovium

One of the most intriguing aspects of joint inflammation in psoriasis is the prominent and striking vascular changes. Early studies showed changes in endothelial cells on both light and electron microscopy that consisted of swelling accompanied by inflammatory cell infiltration and marked thickening of the vessel wall.⁴⁷ Quantitative histopathologic analysis has shown that vessel numbers are higher in PsA than in RA, and arthroscopic studies have shown that PsA synovial tissue has more tortuous vascularity whereas in RA the vascular tissue takes on a more linear morphology.⁴⁸ Subsequent studies have revealed that RA tissue blood vessels can manifest linear, mixed, or tortuous patterns, although PsA synovial vasculature is almost always tortuous or bushy in appearance.⁴⁹

Histologic studies reveal an inflammatory tissue that is very similar to RA in appearance, with lining-layer hyperplasia and a subsynovial infiltrate of T cells, B cells, and monocytes. Digital image analysis of biopsied tissue has revealed that PsA tissue has a lower number of infiltrating T and plasma cells but that TNF- α , IL-1 β , IL-6, and IL-18 protein expression is similar in the two diseases. Activated T cells have been identified in the skin and joints of patients with PsA; T cells in the epidermis and joint fluid are predominantly CD8+, although more recent studies have uncovered a prominent Th17 response in psoriatic plaque.⁵⁰ Th17 cells were identified in psoriatic synovium, and mast cells in the joint tissue were also noted to express IL-17.^{51,52}

Expression of matrix metalloproteinases (MMPs), adhesion molecules, and vascular markers was also found to be comparable in PsA and RA.⁵³ In another report, PsA tissue vascularity and neutrophil infiltration were increased in PsA in comparison to RA, but antibodies to the shared epitope were observed only in RA (Fig. 121.4).⁵⁴ Most importantly, the synovial pathology of PsA resembled the features observed in spondyloarthritis more than those observed in RA. A somewhat surprising finding was the presence

Fig. 121.3 Pathogenesis of psoriatic arthritis. Infection, danger signals, or an autoimmune response leads to the overproduction of tumor necrosis factor (TNF) and other proinflammatory molecules such as interferon- α , as recently described in psoriatic plaque. It is envisioned that the response to these environmental events is strongly influenced by genetic factors. The site of the original event may take place in the skin, bone marrow, or bowel. Both the innate and the acquired immune type 1 helper T cell (Th1) and Th17 pathways are triggered, which results in the release of interleukin-23 (IL-23), IL-17, TNF, and other cytokines. In response to these cytokines and other inflammatory mediators, monocytes and T cells undergo activation and circulate to the entheses, joints, and soft tissues, where inflammation unfolds in response to local factors. G-CSF, granulocyte colony-stimulating factor; RANKL, receptor activator of nuclear factor κ B ligand.



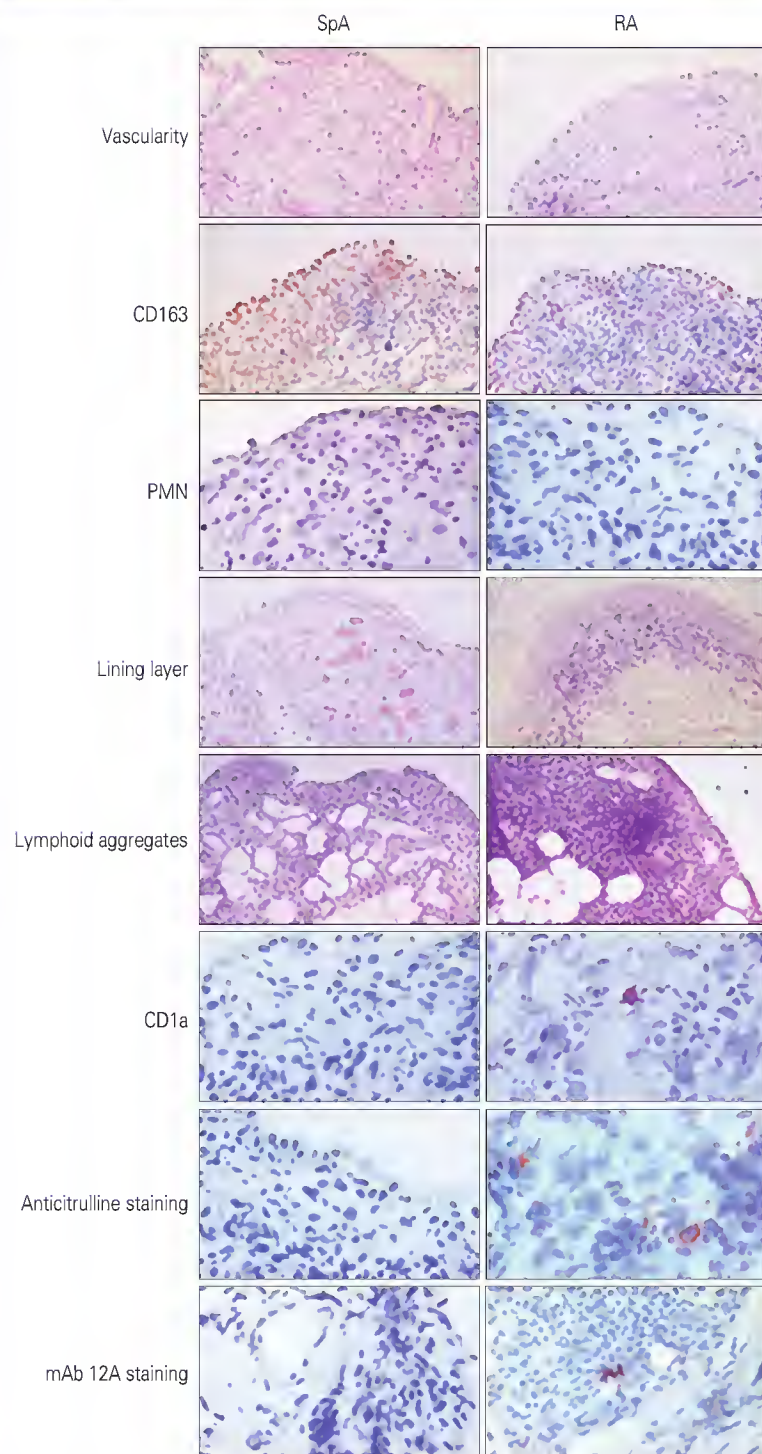


Fig. 121.4 Distinct synovial features in spondyloarthritis (SpA) and rheumatoid arthritis (RA). Vascularity, CD163+ macrophages, and polymorphonuclear leukocytes (PMNs) were significantly increased in SpA, whereas lining-layer hyperplasia, lymphoid aggregates, CD1a+ dendritic cells, and intracellular citrullinated antibodies were higher in RA. mAb, monoclonal antibody. (From Kruithof E, Baeten D, Van den Bosch F, et al. *Histological evidence that infliximab treatment leads to downregulation of inflammation and tissue remodelling of the synovial membrane in spondyloarthropathy*. *Ann Rheum Dis* 2005;64:523-36.)

of lymphoid aggregates in the synovium that were similar in prevalence and appearance to those observed in RA tissue.⁵⁵ Taken together, the histopathologic studies indicate the presence of marked vascularity with fewer T lymphocytes but greater infiltration of neutrophils in psoriatic than in rheumatoid synovium.

Enthesis

The importance of enthesitis as a key pathologic lesion in the seronegative spondyloarthritides, including PsA, has recently been elucidated (see

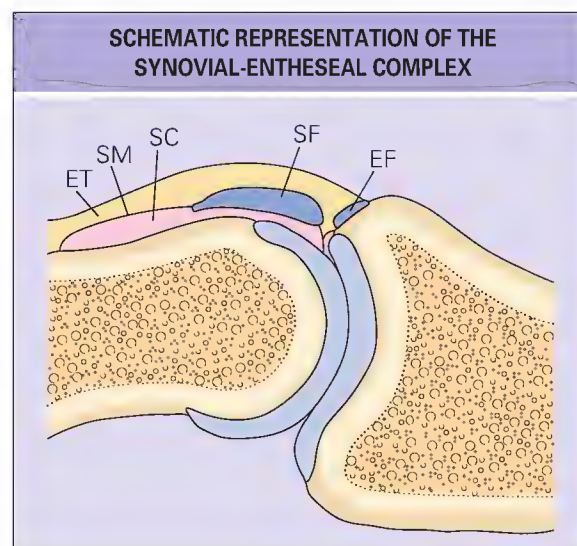


Fig. 121.5 Synovial-entheseal complex of an extensor tendon (ET) in an interphalangeal joint, as seen in a sagittal section of a finger. Synovium lines the deep surface of the tendon except in the region of the sesamoid fibrocartilage (SF), which in a flexed finger is compressed against articular cartilage. EF, entheses fibrocartilage; SC, synovial cavity; SM, synovial membrane. (From McGonagle D, Tan AL, Benjamin M. *The biomechanical link between skin and joint disease in psoriasis and psoriatic arthritis: what every dermatologist needs to know*. *Ann Rheum Dis* 2008;67:1-4.)

Chapter 123). The enthesis is an organ that dissipates mechanical stress over a wide area, including the adjacent bone and soft tissues; consequently, the immunopathology associated with enthesitis is similarly distributed over a wide area. Of particular importance is that the enthesis may be closely integrated with the adjacent synovium, bursae, and fibrocartilage, which together form a structure termed a **synovial-entheseal complex** (Fig. 121.5).

The insertion point in bone is fibrocartilaginous and normally avascular, which minimizes stress and risk for injury at the sites of highest impact. Despite these anatomic adaptations, stress forces can lead to injury and microscopic inflammation in normal insertions. When compared with the synovium, the molecular basis for human enthesitis has been very difficult to study, largely because of the relative inaccessibility of the enthesis tissue. The limited histologic data on enthesitis show destruction of fibrocartilage, vascular changes, and the presence of predominantly inflammatory cells. However, imaging of acute enthesitis shows a diffuse inflammatory reaction with sparing of the avascular fibrocartilage (Fig. 121.6). This does not support the concept that autoimmunity against fibrocartilage antigens underlies the enthesitis in PsA.

Dactylitis

The pathophysiologic events that are responsible for dactylitis, a defining feature of PsA, are not well understood, but imaging studies have provided some intriguing clues.⁵⁶ MRI studies of dactylitis show flexor tenosynovitis, circumferential soft tissue inflammation, synovitis, and bone marrow edema. Of note is the fact that erosions are more commonly seen in digits with dactylitis, and joint fusion is also observed.⁵⁷ One possibility is that the diffuse tissue inflammation begins at the attachment of the capsule onto the phalanx and represents a form of enthesitis.⁵⁸ However, enthesitis does not explain the widespread tissue inflammation and the predilection for involvement of the second digit of the hand and the fourth digit of the foot. An additional hypothesis is that the process begins in the entheses but spreads to the soft tissues and bone in response to trauma and represents a deep form of the Koebner phenomenon.

PATHOLOGIC CARTILAGE RESORPTION AND ALTERED BONE REMODELING

Cartilage resorption

Loss of cartilage, manifested radiographically as joint space narrowing, is a common finding on plain radiographs of joints in patients with PsA. Based on the radiographs, it is not unexpected that matrix metalloproteinases



Fig. 121.6 Magnetic resonance image of acute psoriatic arthritis–associated Achilles enthesitis. Thickening and edema of the Achilles tendon are evident in proximity to the insertion (black arrow). This is associated with prominent inflammation in the retrocalcaneal bursa (arrowhead). The avascular cartilage at the insertion point appears black (white arrow).

(MMPs) and their specific tissue inhibitors (TIMPs) are increased in the lining and subsynovial lining cells in psoriatic joints.⁵⁹ Immunohistochemical studies have revealed that MMP-9 is upregulated in the vasculature and that MMP-1, MMP-2, and MMP-3 and the inhibitors TIMP-1 and TIMP-2 are present in the synovial lining cells. Once again, the levels of MMP-1, MMP-3, and TIMP-1 and TIMP-2 messenger RNA were similar to those observed in RA. Moreover, after therapy with anti-TNF agents, serum MMP-3 levels dropped rapidly and MMP-13 staining declined in psoriatic synovial tissue. Based on these findings, it is likely that the immunopathogenetic mechanisms that dictate cartilage destruction in psoriatic joints are shared with RA and other forms of spondyloarthritis.

Altered bone remodeling

Bone involvement in PsA is heterogeneous both between and within patients. Unlike RA, in which synovitis leads to secondary diffuse osteoporosis and periarticular erosion, and ankylosing spondylitis, in which new bone formation is characteristic; in PsA bone involvement is diverse and encompasses the features of both ankylosing spondylitis and RA. Additionally, patients with PsA are prone to the development of mutilating arthritis in the distal interphalangeal joints; synovitis, acne, palmopustular pustulosis, hyperostosis, and osteitis (SAPHO syndrome); sterile osteomyelitis; and rare variants, including palmopustular psoriasis.⁶⁰

Abnormal bone remodeling and new tissue formation, including joint ankylosis and syndesmophyte formation, typically develop at sites of soft tissue inflammation at the enthesis. The common denominator for this osseous pathology relates to the functional integration of the enthesis to bone and the complex mechanical stress patterns in the bone adjacent to fibrocartilage. Diffuse skeletal inflammation at joints, including the sacroiliac, sternoclavicular, and distal interproximal joints, thus have a unifying biomechanical basis. The essence of these diffuse skeletal pathologic processes became evident not from pathologic studies but from MRI evaluation of early PsA at a stage when the radiographic findings were still normal. Basically, every site of bone or joint involvement in PsA is associated with the presence of diffuse bone marrow edema, which histologically represents osteitis.

Based on the high prevalence of bone marrow edema in the distal interproximal joint coupled with evidence from MRI studies of RA,⁶¹ it is reasonable to speculate on an association between osteitis and subsequent joint destruction. Baseline MRI has been demonstrated to have prognostic value in predicting joint destruction in the sacroiliac joint in patients with

ankylosing spondylitis, but its ability to show arthritis mutilans awaits confirmation.

Although the precise origins of bone marrow edema and osteitis in PsA remain somewhat enigmatic, there have been some tantalizing studies from animal models. Diffuse osteitis is seen in several TNF transgenic models, and the lesions are not dependent on adaptive immunity because pathology is evident in RAG double knockout mice. Also, the earliest lesions may develop in the stromal compartment of the enthesis in TNF transgenic models. MRI and histopathologic studies of arthritic TNF transgenic mice have revealed that bone marrow edema represents expansion of monocytes into the bone marrow, which corresponds to bone marrow edema signals on MRI.⁶² Similar histologic findings from rheumatoid joints have been reported in regions that manifested bone marrow edema preoperatively.⁶³ Collectively, these models underscore the potential importance of “tissue-specific” factors that are independent of adaptive or even innate immune cells as potential drivers in the genesis of entheseal-related disease because the earliest inflammatory changes occur in stromal cells at the insertion.⁶⁴

Altered bone remodeling, captured in psoriatic radiographs as large eccentric bone erosions, “pencil-in-cup” deformities, and tuft resorption, is often accompanied by features of new bone formation manifested as periostitis and ankylosis in the peripheral joints and enthesophytes in the spine. Surgical samples of psoriatic bone and adjacent synovium have revealed large multinucleated osteoclasts in deep resorption pits at the bone-pannus junction.⁶⁵ The details of osteoclast generation are discussed in Chapter 22. Briefly, two cytokines, macrophage colony-stimulating factor (M-CSF) and receptor activator of NF- κ B ligand (RANKL), bind to RANK on the surface of osteoclast precursors (OCPs) derived from circulating CD14+ monocytes and on mature osteoclasts. This ligand-receptor interaction triggers proliferation and differentiation of OCPs and osteoclast activation, respectively. Because permissive quantities of M-CSF are present in the bone marrow microenvironment, it is likely that the relative expression of RANKL and its natural antagonist osteoprotegerin (OPG) ultimately controls osteoclastogenesis, although TNF- α can synergize with RANKL and M-CSF and potentiate osteoclast formation. Interestingly, RANKL is also expressed by infiltrating Th17 lymphocytes and by synovial fibroblastoid cells in the synovial lining of inflamed joints.⁶⁶ In psoriatic synovium, marked upregulation of RANKL protein and low expression of its antagonist OPG were detected in the adjacent synovial lining (Fig. 121.7).⁶⁵ Osteoclasts were also observed in the cutting cones traversing subchondral bone, thus indicating a bidirectional attack on bone (see Fig. 121.3). Moreover, OCPs derived from circulating CD14+ monocytes were markedly elevated in the peripheral blood of PsA patients versus healthy controls. Treatment of PsA patients with anti-TNF agents significantly decreased the level of circulating OCPs, a finding that supports a central effect of TNF in the generation of precursor formation.⁶⁷

Recent advances in osteoimmunology have provided new insight into the mechanisms that are probably involved in pathologic new bone formation. Of particular relevance was the finding that two molecules, dickkopf-1 (DKK-1) and sclerostin, can inhibit the Wnt signaling pathway, as discussed in Chapter 22.⁶⁸ Activation of the Wnt pathway results in bone formation, so the finding that sclerostin levels were low in the osteocytes of bone from patients with ankylosing spondylitis supports the view that osteoid formation, mediated through Wnt signaling, is important in spondyloarthritis.⁶⁹ Additional molecules such as transforming growth factor- β (TGF- β), also expressed in synovial tissue in patients with ankylosing spondylitis,⁷⁰ can synergize with vascular endothelial growth factor (VEGF) to induce bone formation, as shown in an animal model.⁷¹

Lories and colleagues⁷² showed that bone morphogenetic protein-2 (BMP-2) and BMP-7 are upregulated in regions of pathologic new bone formation, and of particular interest was the finding that anti-TNF therapy blocked joint inflammation but not new bone formation in the DBA/1 mouse model. Phosphorylation of Smad1 and Smad5, important molecules in the downstream BMP signaling pathway, was markedly upregulated in regions of new bone formation on a calcaneal bone biopsy sample obtained from a patient with ankylosing spondylitis. These studies provide important clues about the interactions between the Wnt signaling pathway, BMPs, TGF- β , and VEGF in pathologic new bone formation, but additional studies are needed to determine the importance of these molecules in psoriatic disease.

CYTOKINE PATHWAYS INVOLVED IN SKIN AND JOINT TISSUE INFLAMMATION

The most compelling evidence for a central role of cytokines in skin and joint diseases comes from studies that show remarkable efficacy of anti-TNF agents for both skin and joint involvement. The prevailing evidence

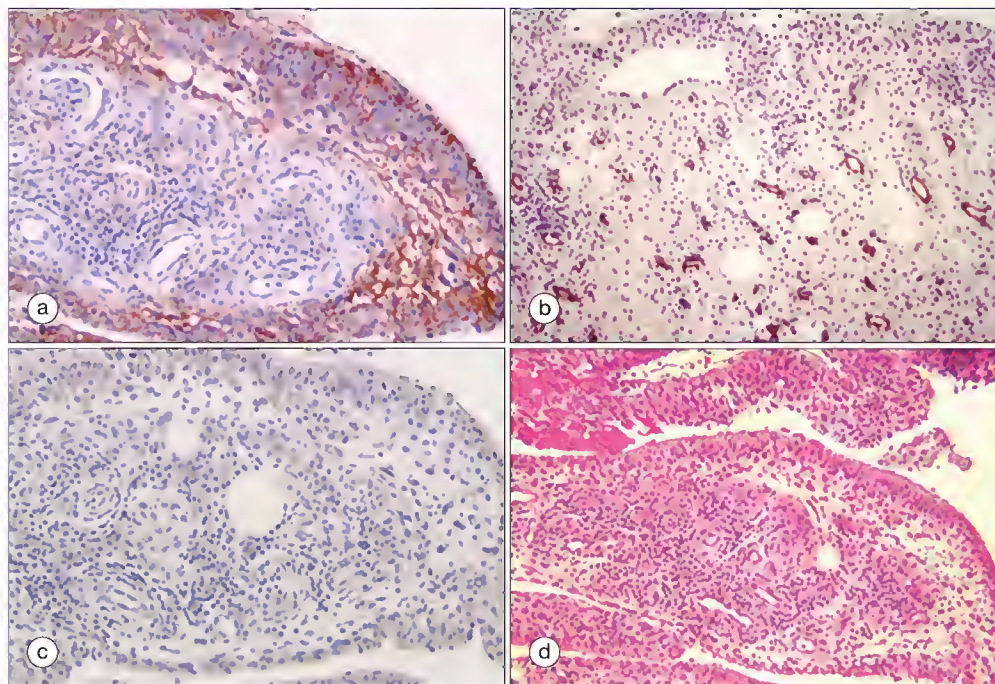


Fig. 121.7 Receptor activator of nuclear factor κ B ligand (RANKL) and osteoprotegerin (OPG) expression in synovium affected by psoriatic arthritis (PsA). Retrieved tissues containing synovium from patients with PsA were processed for immunohistochemistry with antibodies specific for RANKL and OPG. A representative synovial membrane from a patient with PsA stained with anti-RANKL antibody (a), anti-OPG antibody (b), secondary antibody only (c), and hematoxylin-eosin (d) are shown photographed at 20 $\times$. Of note is the very specific and intense RANKL staining by synovial lining cells and OPG staining restricted to endothelial cells below the synovial lining. (Reproduced with permission from Ritchlin CT, Haas-Smith SA, Li P, et al. Mechanisms of TNF- α - and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003;111:821-31.)

supports the concept that an imbalance in proinflammatory and antiinflammatory cytokines is a dominant factor responsible for the downstream events that result in joint destruction.⁷³ Similar to RA, the cytokines TNF and IL-1 are elevated in explanted tissues from the skin, synovial tissue, and joint fluid of patients with PsA.^{74,75} A similar pattern of cytokine production in psoriatic synovium was noted by immunohistochemistry.⁷⁶

Evidence to support the importance of TNF in PsA comes from several findings. TNF transgenic mice exhibit joint destruction similar to that observed in patients with PsA.⁷⁷ In one clinical trial, subjects with the TNF- α 308 allele, which is associated with higher levels of TNF, had more erosions than did subjects without the allele,⁷⁸ and analysis of synovial tissue in PsA subjects after treatment with TNF antagonists showed decreased vascularity, synovial lining thickness, and mononuclear inflammation.^{79,80} A central question that remains to be addressed is whether Th17 effector cells are important in the musculoskeletal inflammation and matrix destruction in PsA. The answer to this question awaits definitive histologic analysis of psoriatic synovial tissue, but reports of increased levels of circulating Th17 cells in PsA in comparison to RA, along with elevated quantities of IL-17 in the synovial fluid of patients with PsA, provides support for the presence of an activated IL-23/Th17 pathway in PsA.^{81,82} Clinical trials of agents that block different molecules in the IL-17 pathway (anti-IL-17, anti-IL-17R) have proven to be markedly effective in psoriasis,^{83,84} and several studies examining the efficacy and safety of these agents in patients with PsA are under way. Moreover, a recent phase 3 trial of ustekinumab, a molecule that blocks IL-12 and IL-23, showed efficacy in PsA.⁸⁵ Together, the data indicate that psoriatic skin and joint inflammation results from a combination of innate and acquired immune interactions with a prominent role for TNF and Th1 and Th17 cells.

PSORIATIC DISEASE

Scarpa and colleagues⁸⁶ put forth the concept of “psoriatic disease” in which psoriasis is viewed as a systemic disorder that can involve multiple different tissues and organ systems such as the gut (colitis), eye (uveitis), vasculature (atherosclerosis), cardiovascular (atherosclerosis and myocardial infarction) and endocrine systems (diabetes, metabolic syndrome), in addition to musculoskeletal structures. It has been known for some time that patients with psoriasis are considerably heavier than matched controls, and a well-designed epidemiologic study by Setty and associates⁸⁷ demonstrated that obesity is a risk factor for the development of psoriasis.

Obesity is associated with a low-grade inflammatory state, and a growing body of evidence has shown that both macrophages and T cells with a proinflammatory phenotype are present in adipose tissue. Moreover, the chronic inflammation in adipocytes may promote a systemic inflammatory response.^{88,89} In fact, the presence of low-grade inflammation in adipose tissue has the potential to activate monocytes and immunocytes, which could initiate skin inflammation via mechanisms outlined earlier.⁹⁰ These

activated cells could also home to the skin, joints, eyes, bowel, and vasculature and initiate a chronic inflammatory state that is responsible for the heterogeneous disease features observed in psoriasis.

ANIMAL MODELS OF PSORIATIC ARTHRITIS

Insight into disease pathogenesis is often derived from preclinical models, but until recently PsA models had not been identified. Over the past several years, however, a number of rodent models have provided clues regarding disease mechanisms (Table 121.2).⁹¹⁻⁹⁹ The finding that an inducible keratinocyte deletion of the transcription factors JunB and c-Jun resulted in both psoriasiform skin lesion and inflammatory erosive arthritis with periostitis has generated considerable interest because of the possible link between cutaneous inflammation and arthritis.⁹¹ After the epidermal deletion, chemokine production increased, followed by the infiltration of granulocytes and macrophages. Functional B and T cells and signaling through the TNFR1 receptor were required for the full arthritis phenotype, but psoriasiform lesions were still present in mice (albeit to a lesser extent) without lymphocytes or intact TNF signaling pathways. Thus, in this model, targeted deletion of a key keratinocyte transcription factor resulted in arthritis with several features reminiscent of PsA that was in part dependent on a functional acquired immune response.

Two murine models have been described in which prominent distal joint inflammation develops. In the first, extensive resorption of the distal phalangeal bones along with pitting and frequent nail loss with hyperkeratosis and parakeratosis spontaneously developed in transgenic mice lacking endogenous MHC class II molecules.⁹⁴ Peripheral or axial arthritis did not develop in the mice, and the skin findings were localized to the affected toes. In the second model, arthritis and nail abnormalities developed in male DBA/1 mice from different litters that were caged together.⁹⁶ These mice behaved aggressively toward each other, and it is conceivable that the joint inflammation was induced by repetitive trauma. They also manifested dacrylitis and onychopariostitis in the distal phalanx. Interestingly, these findings did not develop if the mice were reared in a germfree environment.

Two additional models of arthritis that develop spontaneously with skin and joint lesions have been described besides the erosive arthritis model that was previously mentioned in the TNF transgenic animals. Gut lesions, peripheral mild nonerosive arthritis, psoriasiform skin lesions, and alopecia without thickening or shortening of the distal joints developed in the HLA-B27/ β_2 -microglobulin transgenic rat.⁹² The mice manifested only the skin lesions when raised in a germfree environment. In addition, paw swelling, joint ankylosis, nail changes, and hair loss were noted in transgenic mice lacking β_2 -microglobulin.⁹⁷ In these mice, the frequency of disease was highly influenced by non-MHC background genes. Collectively, these models suggest that alteration of MHC expression combined with microbial interaction plays a dominant role in the pathogenesis of skin and joint disease, although the precise mechanisms remain to be elucidated. An

TABLE 121.2
Animal models of psoriatic arthritis

Author	Species	Genetic alteration	Phenotype
Zenz et al. ⁹¹	Mouse	Inducible deletion of JunB and c-Jun	Psoriasiform skin lesions, erosive arthritis, periostitis
Yanagisawa et al. ⁹²	Rat	HLA-B27/ β_2 transgene	Psoriasiform nail lesions, peripheral arthritis, gut and nail lesions
Khare et al. ⁹³	Mouse	β_2 -Microglobulin knockout	Paw swelling, joint ankylosis, nail changes
Bardos et al. ⁹⁴	Mouse	Lacks endogenous MHC class II molecules	Psoriasiform skin lesions, resorption of distal phalanges, nail changes
Rothschild et al. ⁹⁵	Baboon	None	30% of baboons exhibit radiographic changes similar to those in psoriatic arthritis
Lories et al. ⁹⁶	Mouse/DBA/1 strain—males only	None	Ankylosing enthesitis, dactylitis, onychopariostitis
Cook et al. ⁹⁷	Mouse, FVB/NCrIBR strain	Amphiregulin expression under control of INV-AR	Psoriasiform skin lesions, mild knee synovitis
Ruutu et al. ⁹⁸	SKG mouse injected with mannan or curdlan	ZAP70 mutation	Enthesitis, sacroiliitis, dactylitis, plantar fasciitis, vertebral inflammation, ileitis, unilateral uveitis
Sherlock et al. ⁹⁹	Mouse	Passive collagen-induced arthritis or IL-23 minicircle injection	Enthesitis, heart valve and aortic inflammation with bone erosion and new bone formation

IL-23, interleukin-23; MHC, major histocompatibility complex.
Modified from Ritchlin C, Fitzgerald O. Pathogenesis of psoriatic arthritis. In: Ritchlin C, Fitzgerald O, editors. *Psoriatic and reactive arthritis*. Philadelphia: Mosby; 2007.

intriguing model with cutaneous features reminiscent of psoriasis in which systemic overexpression of IL-23 leads to an enthesitis-centered inflammatory arthritis and aortic root disease has recently been reported.⁹⁹ This disease has been tentatively linked to a novel population of hitherto poorly characterized lymphocytes at the enthesitis and opens up novel ways for exploring the disease process experimentally. The new paradigm has particular translational credence since it follows the description of the genetic association with the IL-23 pathway in humans and also the successful treatment of PsA with anti-IL-23 therapies.

Features of spondyloarthritis have been noted in a variety of primate species, but psoriasiform lesions have not been reported. In baboons, the prevalence of spondyloarthritis reaches 30%.⁹⁵ The distribution of erosive disease and axial involvement in Old World primates is quite similar to that observed in PsA. Thus, these primates may be a more appropriate model for the study of disease mechanisms in spondyloarthritis, but the absence of psoriasis suggests a disease pattern different from that observed in PsA.

LESSONS FROM CLINICAL TRIALS

The availability of targeted biologic molecules allows the physician scientist to directly observe human disease rather than infer from comparatively imprecise animal models. Based on insight from these studies, the spectrum of psoriasis seems to be more dependent on innate than on adaptive immunity because blockade of the innate cytokine TNF leads to powerful suppression of disease, although new bone formation remains relatively unaffected.¹⁰⁰ Efalizumab and alefacept have shown some efficacy in the skin but much less efficacy in the joints, and indeed, efalizumab may be associated with worsening of joint disease.^{101,102} The anti-TNF agents seem to exhibit differential efficacy, and in general, higher doses are needed to control skin disease than to control joint disease. Use of the anti-P40 antibody directed against a shared subunit of the cytokines IL-12 and IL-23 for the treatment of psoriasis and PsA has proved to be extremely effective, although results in the skin are more impressive than those in the joint. Moreover, several studies examining the efficacy of agents that inhibit IL-17

and its receptor in PsA are in progress.^{83,85,103} Interestingly, IL-17 blockade has not proven to be an effective strategy in RA. Recently PDE4 inhibition with a compound called apremilast has shown promise in PsA. This second messenger inhibitor appears to have wide-ranging effects on the modulation of proinflammatory responses.

The differential efficacy of several agents in RA and PsA provide invaluable insight into disease mechanisms. For example, PsA patients show significant improvement in psoriasis and joint inflammation in PsA, but joint responses were not observed in RA.¹⁰⁴ In contrast, methotrexate, a cornerstone of treatment in RA, is considerably more effective for psoriatic skin inflammation but not for the joint disease.¹⁰⁵ Also, some agents, including the retinoids, work solely in the skin and have no value in the joints. Finally, rituximab and abatacept are effective treatments in RA patients with inadequate responses to anti-TNF agents, but they show less efficacy for PsA and do not lead to improvement of psoriasis.^{106,107} Collectively, these contrasting findings from clinical trials support the presence of divergent mechanisms underlying rheumatoid and psoriatic arthritis and the pathophysiologic pathways that lead to psoriatic skin and joint disease.

CONCLUSION

The model that the pathophysiologic processes underlying PsA can be understood as an autoimmune response to a common skin or synovial antigen is not supported by the evidence. In the case of psoriasis, the LL-37/DNA complex with the subsequent release of IFN- α represents a novel autoimmune pathway, but in PsA, immune system activation triggered by events in the local joint environment appear to play a pivotal role in the regional expression of psoriatic disease. The multiple varied interactions between microbes and musculoskeletal structures promote vascular injury and release of cytokines and initiate pathways of cell activation that lead to tissue injury. A detailed genotype-phenotype correlation in the coming years will elucidate the complex nature of psoriatic joint inflammation and ultimately lead to a better understanding of the skin and joint subsets observed in psoriatic disease.

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Management of psoriatic arthritis

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- Psoriatic arthritis is a systemic disorder that causes chronic pain, altered physical appearance, and loss of function. The clinical features are diverse, but the core manifestations are psoriasis, peripheral arthritis, axial arthritis, enthesitis, and dactylitis.
- Multicenter randomized controlled trials of psoriatic arthritis that incorporate outcome measures for the core manifestations have been performed. The data from these trials allow us to make evidence-based therapeutic choices.
- Clinical trial data support the marginal efficacy of methotrexate, sulfasalazine, leflunomide, and cyclosporine for peripheral arthritis that is unresponsive to nonsteroidal agents.
- The tumor necrosis factor antagonists (etanercept, infliximab, adalimumab, golimumab, certolizumab) have proved to be efficacious and relatively safe for the treatment of peripheral arthritis and psoriasis and inhibit structural damage. Infliximab and golimumab are efficacious for dactylitis and enthesitis.
- Ustekinumab, an antibody to the common p40 subunit of interleukin-12 and interleukin-23, is efficacious in the management of psoriasis, peripheral arthritis, enthesitis, and dactylitis.
- Potential new therapies for psoriatic arthritis include biologic agents that inhibit T lymphocytes and proinflammatory cytokines.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease that affects some 30% of patients with psoriasis.¹ A number of domains have been recognized, including peripheral arthritis, skin and nail psoriasis, axial arthritis, enthesitis, and dactylitis.² Psoriatic arthritis is unique among the inflammatory forms of arthritis in that it usually follows the development of skin psoriasis. Thus, patients with psoriasis are the individuals in whom PsA is most likely to develop. Management of PsA begins with early diagnosis, followed by assessment of disease activity and damage and evaluation of therapy. Effective treatment of PsA involves therapies that have the capability of improving all these clinical domains, either by using a treatment that can benefit all domains or by using combinations of therapies that can affect all domains and be used safely together.³ Because the severity of disease in each domain will vary from patient to patient, therapy should be customized accordingly.⁴ Factors that influence the choice of treatment include patient preference regarding mode and frequency of administration, potential adverse events, contextual elements such as age and comorbid conditions, and practical issues such as medical insurance coverage. In addition to controlling the signs and symptoms, a further purpose of control of multiple-domain disease activity is to improve function and quality of life (QoL), decrease progressive structural damage in joints to avoid disability, and reduce significant comorbid conditions such as cardiovascular disease to improve life expectancy.

Although PsA had been considered a mild disease, evidence has accumulated in the past 20 years that it may be a severe form of arthritis in a significant proportion of patients. Even early in the course of the disease, at an average of 10 months from the onset of symptoms, 27% of patients had erosions, and by 2 years of follow-up, at least one erosion had developed on radiographs in 47% of patients.⁵ Thus, a majority of the patients will have erosive disease during follow-up. Predictors of the development of joint damage include previous inflammation and previous damage, both as

a global measure and in an individual joint.^{6,7} Damage accumulates over time in a linear fashion.

It is most important to identify patients with PsA early and treat them appropriately because it has been shown that patients who are identified early fare better than those identified later in the course of their disease.⁸ Identification may be made easier by some of the features of PsA, including the common occurrence of distal joint inflammation, an asymmetric distribution, the presence of axial disease, and inflammation of the entire digit (dactylitis) and at the insertion of ligaments and tendons into bone (enthesitis) (see Chapter 120). In addition, a number of screening questionnaires have been developed to identify PsA in patients with psoriasis or in the general population.⁹ However, even though these screening tools functioned very well during their initial validation, recent studies comparing the instruments in other clinics have demonstrated that they do not have as high sensitivity and specificity as previously reported.¹⁰ Further work is therefore necessary to identify the best screening tool that can be completed by patients and help primary care providers refer appropriate patients for rheumatologic assessment. Several groups are trying to identify genetic or other biomarkers that can predict the development of PsA.¹¹ Levels of high-sensitivity C-reactive protein (hsCRP), matrix metalloproteinase-3 (MMP-3), and osteoprotegerin (OPG) and the ratio of the C-propeptide of type II collagen (CPII) to the type II collagen neoepitopes Col2-3/4C long mono (C2C) (CPII/C2C) have been identified as independent biomarkers for PsA in patients with psoriasis.¹² Several HLA alleles associated with the development of PsA in patients with psoriasis have also been identified.¹³ Thus biomarkers, genetic, soluble, and cellular, together with clinical features may be used to identify patients with psoriasis in whom PsA is destined to develop.

Clinical predictive factors of a more severe course include polyarticular disease, elevated levels of acute-phase reactants, evidence of disability and erosive joint disease, and demonstration of lack of response to initial therapeutic agents.¹⁴ Historically, systemic treatments of psoriasis have not prevented the onset of PsA. It is not yet known whether current use of more effective biologic agents for psoriasis will delay or prevent the appearance of PsA.

Although this chapter focuses on pharmacotherapy for PsA, it must be recognized that optimal therapy also comprises nonpharmacotherapeutic approaches, including patient and family education about the disease process and therapy, exercise, nutrition, psychological counseling, physical and occupational therapy, and orthopedic surgery. Few studies of these modalities have been conducted for PsA *per se*, although their value and utility in the management of arthritis in general and rheumatoid arthritis (RA) specifically have been investigated extensively, from which we can extrapolate their value and utility for PsA. A key role for the rheumatology team is to serve as a central triage point for these types of therapies by working closely with dermatologists in the comanagement of patients with PsA.¹⁵ The relationship between the rheumatologist and dermatologist in the management of patients with PsA is important. In some settings, typically academic, shared rheumatology-dermatology clinics have arisen for optimal coevaluation and management of both patients with psoriasis and patients with PsA. In standard clinical practice, such shared clinics may not be practical for logistic or economic reasons, but close working relationships between rheumatologists and dermatologists characterized by shared electronic records and other documents, phone discussions, and evaluation of patients in both offices on a regular basis can facilitate optimal management from the perspective of both disciplines. In general, if the primary problem is skin disease and the arthritis is mild, the subject may be managed by a dermatologist after complete assessment by a rheumatologist. Periodic assessment by a rheumatologist in such cases would be ideal. On the other hand, if the primary problem is joint disease, the rheumatologist should

primarily manage the patient, with the dermatologist confirming the diagnosis of psoriasis and providing input if the skin disease remains inadequately controlled.

ASSESSMENT OF DISEASE ACTIVITY AND OUTCOME OF PSORIATIC ARTHRITIS

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), working with OMERACT (Outcome Measures in Rheumatology Clinical Trials), has developed a core set of clinical domains of PsA to be assessed in clinical trials (Fig. 122.1).¹⁶ Outcome measures for these domains have generally been adapted from similar measures used for the assessment of RA, such as the American College of Rheumatology (ACR) 20/50/70 scoring system, the Health Assessment Questionnaire (HAQ), and the modified Sharp–van der Heijde radiographic score, and for the assessment of psoriasis, such as the Psoriasis Area and Severity Index (PASI), as well as more general measures, such as the 36-item Short-Form Health Survey (SF-36) (Box 122.1). These measures have been used in clinical trials and clinical registries of PsA patients and have been shown to effectively assess peripheral joint and skin symptoms and signs, function, QoL, and radiographic damage. Various measures of enthesitis, dactylitis, and spinal involvement are being used in clinical trials and registries.^{17–19} Composite disease activity measures, including the psoriatic arthritis disease activity score (PASDAS), arithmetic mean of desirability functions (AMDF), Composite Psoriatic arthritis Disease Activity Index (CPDAI) and Disease Activity for Psoriatic Arthritis (DAPSA), have recently been developed.²⁰ Determination of which measures are optimal is still at a research stage. Several studies have documented the effectiveness of ultrasonography and magnetic resonance imaging in detecting inflammation in the joints and enthesal sites of patients with PsA, as well as the extent of structural damage.²¹ As these tools become more refined and widely accessible, they will enhance our ability to diagnose PsA earlier and assess the effectiveness of therapy in treating inflammation and inhibiting the progression of joint damage both in clinical trials and in clinical practice.

Drug therapies for PsA may be divided into those that provide symptomatic relief, primarily nonsteroidal antiinflammatory drugs (NSAIDs);

traditional disease-modifying antirheumatic drugs (DMARDs); and biologic agents.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND GLUCOCORTICOIDS

NSAIDs are useful in the treatment of PsA and provide relief of symptoms such as pain and stiffness, although published evidence of their effect on PsA is limited.²² NSAIDs have been found to be efficacious in treating the spinal pain in ankylosing spondylitis, on which evidence it is reasonable to extrapolate efficacy in management of axial PsA. However, NSAIDs do not prevent disease progression and may worsen skin lesions. They may be used as sole therapy in treating mild PsA. NSAIDs other than naproxen, however, should be used with caution in patients with PsA because their use is associated with increased risk for cardiovascular thrombotic events and patients with PsA are already at higher risk for cardiovascular events. Naproxen, therefore, may be preferable. If the symptoms persist or if more joints become involved after adequate trials with two different NSAIDs, DMARDs should be considered.

Glucocorticoid therapy in the form of intraarticular injections of corticosteroids (triamcinolone, methylprednisolone) is often used when only one or a few joints are affected. This form of therapy has proved effective for PsA.²³ Oral corticosteroids are used occasionally for relief of symptoms in patients with polyarthritis or an inadequate response to NSAIDs and significant disability. However, glucocorticoids do not work as well for patients with PsA as they do for patients with RA. Moreover, glucocorticoids need to be used with extreme caution and a slow taper because psoriasis worsens in many instances and could occasionally evolve into more severe forms such as pustular psoriasis. Treatment with oral steroids is usually resorted to as short-term therapy until other longer-acting drugs take effect and for situations in which an entire hand is swollen. Long-term steroid therapy is associated with significant toxicity such as high blood pressure, cataracts, weight gain, diabetes, osteoporosis, and avascular necrosis of bone.

TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

A paucity of clinical trials have been conducted on treatment of PsA with traditional DMARDs.²² Systematic reviews of the efficacy and toxicity of

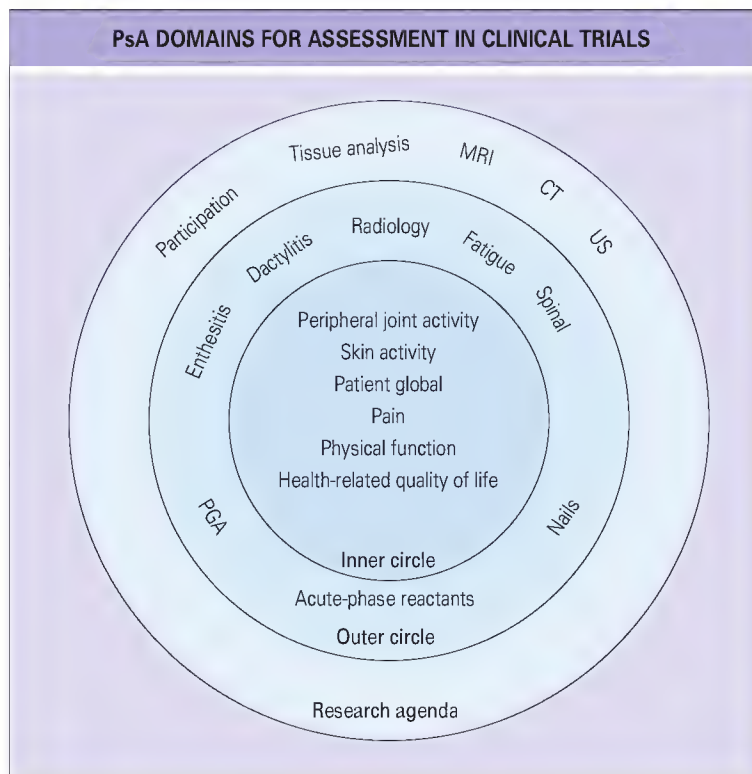


Fig. 122.1 This concentric circle diagram reflects the hierarchy of domains of psoriatic arthritis (PsA) that may be assessed in clinical trials. The inner circle includes the core set of domains to be assessed in all clinical trials of PsA. The second concentric circle includes the set of domains to be assessed in some but not all PsA trials. The outermost circle includes the domains on the research agenda that may or may not be included in PsA trials. CT, computed tomography; MRI, magnetic resonance imaging; PGA, physician global assessment; US, ultrasound.

BOX 122.1 PSORIATIC ARTHRITIS OUTCOME MEASURES USED IN CLINICAL TRIALS

Arthritis

- American College of Rheumatology (ACR) response criteria
- Disease Activity Score (DAS, DAS44, DAS28)
- Psoriatic arthritis response criteria (PsARC)

Radiographic

- Modified van der Heijde–Sharp

Skin

- Psoriasis Area and Severity Index (PASI)
- Target lesion score
- Physician global assessment (PGA) of psoriasis

Quality of life/function

- Short-Form 36-Item Health Survey (SF-36)
- Health Assessment Questionnaire (HAQ) Disability Index
- Dermatology Life Quality Index (DLQI)
- Functional Assessment of Chronic Illness Therapy (FACIT)—Fatigue

Enthesitis

- Leeds
- SpondyloArthritis Research Consortium Canada (SPARCC)
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

Dactylitis

- Presence or absence
- Leeds dactylitis score

Spine

- Assessment of SpondyloArthritis international Society (ASAS) measures

DMARDs and biologic agents for PsA have shown that treatment is more effective than placebo, though more toxic.²²

Methotrexate

Methotrexate (MTX) is one of the most commonly used systemic medications for PsA despite limited evidence of efficacy in controlled trials. Only three published randomized controlled trials (RCTs) have compared MTX with placebo. The first used parenteral MTX, and though effective, it resulted in two deaths.²⁴ The second was underpowered because only 37 patients were recruited but the sample size called for 45, and the dose given was 7.5 to 15 mg/wk. Although MTX significantly improved physician global assessment, no significant effects on tender and swollen joint scores, patient global assessment, and the erythrocyte sedimentation rate were noted.²⁵ The third was a large multicenter RCT from Britain.²⁶ Patients were randomized to receive 15 mg MTX once per week versus placebo. No evidence of response was found with use of either the PsA response criteria (PsARC) or analysis of the individual components. As in the previous trial, the only benefits of MTX were reductions in patient and assessor global scores and skin scores at 6 months. MTX has not been effective in reducing progression of joint damage. Despite these results, MTX is still considered the first-line drug in all treatment recommendations for PsA, partly because the above mentioned studies have several limitations, and thus the lack of evidence is not necessary evidence of lack of efficacy.

Patients being treated long-term with MTX must undergo regular blood monitoring (blood cell counts, liver function tests, and serum creatinine) at least every 3 months. Significant elevation of liver function test results or a decrease in blood cell counts should lead to adjustment of the dose or cessation of therapy. The occurrence of liver fibrosis and cirrhosis, even in the absence of abnormal liver function test results, seems to be more frequent in patients with psoriasis than in those with RA, as reflected in the different recommendations for liver biopsy in rheumatology and dermatology. Patients with psoriasis treated with MTX who have risk factors for liver disease, especially type 2 diabetes or obesity, are at higher risk for the development of liver fibrosis than are those without such risk factors, even when lower cumulative MTX doses are given.²⁷ These risk factors are important for nonalcoholic steatohepatitis. Thus in clinical practice it is prudent to obtain serial liver biopsy specimens after a cumulative MTX dose of 1.5 g, especially in patients with risk factors for fibrosis and cirrhosis, such as obesity, metabolic syndrome, type 2 diabetes, a history of viral hepatitis, and significant alcohol use.

Sulfasalazine

Five RCTs have evaluated sulfasalazine (SSZ) for the treatment of PsA. In the largest of these, 221 patients with PsA were treated with 2 g/day of SSZ for 36 weeks.²⁸ The PsARC developed specifically for this study showed statistically significant improvement in the treatment group (57.8% for SSZ vs. 44.6% for placebo, $P = 0.05$). However, the only individual measure within the responder index to do so was patient global assessment, and longitudinal analysis showed only a trend favoring SSZ treatment. A systematic review revealed that the effect size for SSZ was less than 0.2, the level required to confirm response.²⁹ SSZ has not been demonstrated to prevent progression of joint damage. Despite the paucity of data, SSZ is also recommended as a first-line drug for patients with PsA.

Leflunomide

The efficacy of leflunomide was evaluated in one RCT, and it was shown to have a modest benefit over placebo.³⁰ In this study of 188 patients with PsA, PsARC were achieved by 59% of leflunomide-treated patients versus 29.7% of placebo-treated patients ($P < .0001$). An ACR20 response was achieved by 36.3% and 20%, respectively ($P = .01$). A PASI75 response was seen in 17.4% and 7.8%, respectively ($P = .048$). Leflunomide was found to be an effective and well-tolerated option for PsA in daily clinical practice with beneficial effects on peripheral arthritis and other PsA manifestations, including pain, fatigue, dactylitis, and skin disease.³¹ Unfortunately, radiographs were not included in the study; therefore, the effect of leflunomide on progression of joint damage has not been studied. Monitoring of leflunomide toxicity is similar to that for MTX.

Cyclosporine

Cyclosporine (CsA) is effective in controlling psoriasis. A three-arm RCT comparing CsA 3 mg/kg/day added to standard therapy, SSZ 2 g/day added to standard therapy, and standard therapy alone showed that CsA plus

standard therapy was well tolerated and more efficacious than both standard therapy alone and standard therapy plus SSZ.³² In the most recently published RCT, CsA was compared with placebo as an add-on treatment in patients with PsA who had an incomplete response to MTX monotherapy. Significant improvement was noted at 12 months in the swollen joint count, C-reactive protein, PASI score, and synovitis as detected by high-resolution ultrasound in the group that received CsA. No difference, however, was found in the HAQ or pain scores.³³ Thus, CsA has a role in the management of PsA either on its own or as an add-on treatment with MTX. Nonetheless, it is not well tolerated, with particular concern regarding hypertension and renal dysfunction. Its effect on joint damage has not been assessed.

Small molecules

Apremilast

Apremilast is a new potent, orally active phosphodiesterase 4 inhibitor that suppresses multiple proinflammatory mediators and cytokines. A phase 2 RCT of apremilast in 204 subjects randomized to 20 mg twice daily, 40 mg daily, or placebo reported an ACR20 response in 43.5%, 35.8%, and 11.8%, respectively, at 12 weeks.³⁴ Common adverse events were nausea, diarrhea, headache, nasopharyngitis, and fatigue. Similar observations were documented in a phase 3 trial, which suggested that a dose of 30 mg twice daily may be more effective than 20 mg twice daily but may also be more toxic.

BIOLOGIC RESPONSE MODIFIERS

Management of PsA was greatly facilitated when anti-tumor necrosis factor (TNF) agents became available. Additional medications directed at T cells were also introduced primarily for the treatment of psoriasis, although two were recently withdrawn from the market. Other anticytokine therapies have been developed as well.

Tumor necrosis factor- α inhibitors

Etanercept

Etanercept is a soluble receptor for TNF that is typically administered subcutaneously at a dose of 50 mg once per week. In the placebo-controlled portion of the phase 3 trial for PsA ($n = 205$), an ACR20 response was achieved by 59% of the etanercept-treated patients versus 15% in the placebo group (42% and 41% receiving background MTX, respectively) ($P < .0001$).³⁵ Skin response, as measured by the PASI score in patients with body surface area (BSA) involvement greater than 3%, showed a 75% improvement in 23% and 3%, respectively, at 24 weeks ($P = .001$). Measures of function and QoL improved significantly. Significant inhibition of progression of joint space narrowing and erosions was shown. In the open-label extension of this study, effectiveness was maintained in joint response and skin response at 2 years, and 38% improved further to a PASI75 response.³⁶ The drug was well tolerated, with the most common adverse events being injection site reactions and infections.

The Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA) trial assessed 752 patients with highly active PsA and psoriasis (average BSA involvement, 31%); the patients were randomized to a standard dose of etanercept approved for PsA, 50 mg/wk (group 1), versus a dose approved for psoriasis, 50 mg twice a week for 12 weeks, followed by 50 mg/wk thereafter (group 2).³⁷ ACR and enthesitis scores similarly improved in both dosage arms at 12 and 24 weeks. An ACR20 response was achieved in 61% and 72% at each time point, respectively, in group 1 and in 66% and 69% in group 2. Of patients with enthesitis as assessed by Achilles tendon and plantar fascia insertion tenderness, 65% and 66% in groups 1 and 2, respectively, had no enthesitis at week 12 and 76% and 75% had none at week 24. Thus, the increased initial dose offered no advantage for the musculoskeletal domains. Substantial improvement in the skin lesions occurred, with a PASI75 response at week 12 seen in 55% and 36% ($P < .001$) in groups 2 and 1, respectively, and 70% and 62% at week 24 ($P < .05$). When the Composite Psoriatic Disease Activity Index (CPDAI) was used to analyze the results, the twice-weekly dose demonstrated an advantage over the once-weekly dose at 12 weeks.³⁸ Thus, consideration might be given to initially higher dosing in patients with severe skin disease, followed by standard dosing, an approach commonly used for psoriasis with other biologic agents.

In a recent serial skin biopsy study of patients with psoriasis treated with etanercept, transcripts of cytokines in the type 17 helper T-cell (Th17) pathway were diminished, presumably because of decreased stimulation of interleukin-23 (IL-23) by TNE.³⁹ Traditionally, anti-TNF agents have been thought to affect Th1 pathway cells and cytokines, so these results demonstrate the immunologic crosstalk that occurs among various inflammatory

cell pathways. Another study showed that the addition of MTX to etanercept could improve skin responses over those achieved with etanercept monotherapy.⁴⁰

Infliximab

Infliximab is a chimeric monoclonal anti-TNF antibody. A phase 3 study of infliximab in 200 patients with PsA (Infliximab Multinational Psoriatic Arthritis Controlled Trial II [IMPACT II]) showed significant benefit.⁴¹ Baseline demographic and disease activity characteristics were similar to those of the etanercept phase 3 trial. At week 14, 58% of infliximab-treated patients and 11% of placebo patients achieved an ACR20 response ($P < .001$). The presence and severity of dactylitis and enthesitis improved significantly in the infliximab group. At 24 weeks, a PASI75 response was achieved by 64% of the infliximab group and 2% of the placebo group ($P < .001$). Infliximab-treated patients showed inhibition of radiographic disease progression at 24 weeks.⁴² Function and QoL improved significantly. The long-term PsA data with infliximab (up to 98 weeks in the IMPACT II study) also showed persistent benefit on PsA.⁴³

Adalimumab

Adalimumab is a fully human anti-TNF- α monoclonal antibody. The standard dose approved for PsA is 40 mg administered subcutaneously every other week. It was studied in a phase 3 study ($n = 313$), the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).⁴⁴ At 12 weeks, 58% of the patients receiving adalimumab achieved an ACR20 response versus 14% of those receiving placebo ($P < .001$). This response rate did not differ between patients taking adalimumab in combination with MTX (50% of patients) and those taking adalimumab alone, similar to observations made in the etanercept and infliximab trials. A PASI75 response was achieved by 59% in the adalimumab-treated group and by 1% in the placebo group ($P < .001$) in those evaluable for PASI scoring. Radiographic progression of disease was significantly inhibited by adalimumab.⁴⁵ Function, QoL, and fatigue measures improved significantly. A 2-year extension study showed sustained ACR and PASI responses and persistent inhibition of radiographic progression. Adalimumab also demonstrated improvement in work productivity.

Golimumab

Golimumab is a fully human, anti-TNF- α monoclonal antibody that is approved in a 50-mg once-a-month subcutaneous dose for PsA based on a study of 405 patients.⁴⁶ At the primary endpoint of 14 weeks, this dose resulted in an ACR20 response in 51% versus 9% in the placebo group ($P < .001$) and an ACR50/70 response in 30% and 12%, respectively. A PASI75 response was achieved by 40% at week 14 and by 56% at week 24 in the 109 and 102 patients with at least 3% BSA involvement who were evaluable for PASI. Of those with enthesitis, significantly more patients showed resolution with golimumab than with placebo. Nail changes also significantly improved, as did measures of physical function. These improvements were sustained at 104 weeks in an open extension phase of this trial.⁴⁷ The safety of golimumab in patients with PsA was commensurate with that of other anti-TNF agents.

Certolizumab

Certolizumab pegol, another anti-TNF- α agent, is a subcutaneously administered pegylated Fab fragment. A recent phase 2 trial for PsA demonstrated improvement in 409 patients who were randomized to either placebo, certolizumab 200 mg every 2 weeks, or certolizumab 400 mg every 4 weeks.⁴⁸ The ACR20 response rate at 12 weeks was higher in certolizumab-treated patients—58% in those treated every 2 weeks, 51.9% in those treated once a month, and 24.3% in those given placebo ($P < .001$ for both)—and response was observed as early as week 1. The PASI75 response rate at week 24 in patients with psoriasis involving 3% BSA or greater at baseline was 62.2% with 200 mg every 2 weeks and 60.5% with 400 mg every 4 weeks, as opposed to a placebo response rate of 15.1% ($P < .001$ for both).

Evidence is accumulating that cardiovascular disease develops in patients with PsA prematurely and may contribute to the early mortality seen in those with this disease.⁴⁹ Potential contributors to cardiovascular disease include inflammation-induced atherogenesis and metabolic syndrome, which has been recognized with increased frequency in patients with PsA. A recent study by Tam and colleagues⁵⁰ showed that use of TNF inhibitors for PsA was associated with a reduction in carotid intima-media thickness and correlated with a reduction in markers of inflammation but was independent of changes in lipid profiles. No studies, however, have yet demonstrated a decrease in cardiovascular mortality rates or improvement in survival in patients with PsA treated with anti-TNF agents.

In summary, anti-TNF- α medications have shown the greatest efficacy of any treatment to date for the various clinical aspects of PsA. Their efficacy

in treating joint disease activity, inhibiting structural damage, and improving function and QoL are similar, as demonstrated by a recent meta-analysis.⁵¹ These agents tend to be well tolerated, and patients generally acclimate to parenteral administration, especially when they experience significant efficacy. Safety concerns are present, such as risk for infection, but no new concerns have arisen in the PsA population when compared with the more extensively studied RA patient population. However, it should also be noted that almost 40% of the patients treated with anti-TNF agents do not achieve even an ACR20 response, thus additional medications are necessary.

OTHER BIOLOGIC AGENTS

Co-stimulatory blockade agents

Alefacept is a fully human fusion protein that blocks the interaction between lymphocyte function-associated antigen-3 (LFA-3) on antigen-presenting cells and CD2 on T cells or by attracting natural killer lymphocytes to interact with CD2 to yield apoptosis of particular T-cell clones, and it has demonstrated efficacy in a phase 2 trial of PsA.⁵² However, though approved for the treatment of psoriasis, it was withdrawn from the market by the manufacturer effective November 16, 2011. This decision was apparently driven by business needs.

Abatacept (cytotoxic T-lymphocyte antigen [CTLA] 4-Ig) is a recombinant human fusion protein that binds to the CD80/86 receptor on antigen-presenting cells, thus blocking the second signal activation of the CD28 receptor on T cells. It is administered intravenously once a month and was evaluated in a phase 2 trial for PsA. In the standard-dose arm of 10 mg/kg given intravenously monthly ($n = 40$), 48% achieved an ACR20 response as compared with 19% in the placebo arm ($P = .006$), although efficacy was greater in the subgroup not previously exposed to anti-TNF therapy.⁵³ This agent is well tolerated, with the main safety issue being risk for infection, which was comparable to the rate seen with other biologic agents. A phase 3 trial using a subcutaneous preparation of abatacept for PsA is in progress.

Anti-interleukin-12/23 agents

Both IL-12 and IL-23 are overexpressed in psoriasis plaques. IL-23 is a key cytokine that stimulates the proliferation and activation of Th17 lymphocytes, which were recently appreciated as being important inflammatory cells in a variety of inflammatory diseases. Ustekinumab, a human monoclonal antibody that inhibits receptor binding of IL-12 and IL-23, has been shown to be very efficacious in treating psoriasis. Two phase 3 trials have been reported. In PSUMMIT 1, 615 patients with active PsA who had not been treated with anti-TNF agents were randomized to placebo, 45 mg ustekinumab, or 90 mg ustekinumab. ACR20 responses at 24 weeks showed a significant benefit for drug (42.5% for 45 mg, 49% for 90 mg) in comparison to placebo treatment (22.8%). ACR50 and ACR70 responses were also significantly higher in drug-treated patients. Dactylitis and enthesitis improved, as did QoL. A PASI75 response was achieved by almost 60% of the drug-treated patients as compared with 11% of the placebo-treated patients.⁵⁴ Infections were the most common side effects. The PSUMMIT 2 trial included 312 PsA patients with active disease who had failed anti-TNF agents.⁵⁵ This trial demonstrated ACR20 responses in 44% of the drug-treated groups versus 20% in the placebo-treated arm ($P < .001$). Responses were slightly higher in patients who had not previously failed treatment with an anti-TNF agent. The PASI75 responses in these trials are not as impressive as those reported in the trials of patients with psoriasis, probably because of the fact that in psoriasis trials the baseline PASI score was much higher than in the PsA studies.

ABT-874 is another IL-12/23 inhibitor that has shown a significant and enduring skin response with monthly subcutaneous dosing and will probably be studied for treatment of PsA.

OTHER POTENTIAL TREATMENTS

A pilot trial of an anti-IL-15 compound has shown efficacy in treating PsA.⁵⁶ The IL-1 receptor antagonist anakinra has not shown significant efficacy.⁵⁷ Rituximab, an anti-CD20 agent that ablates B lymphocytes and is approved for the treatment of RA and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, did not show a significant response in an open-label trial of 21 patients with PsA.⁵⁸

Another therapeutic approach, not aimed at inflammation but instead aimed primarily at reduction of bone erosions, is to reduce

osteoclastogenesis. Denosumab, an inhibitor of receptor activator of nuclear factor κ B (RANK) ligand, has been shown to not only improve osteoporosis but also reduce the erosion rate in RA.⁵⁹ It is anticipated that this type of approach will show utility for PsA as well, especially given the known proclivity for excess osteoclast production and activation in this disease.

TREATMENT RECOMMENDATIONS

Several treatment recommendations for PsA have been published. GRAPPA published a set of treatment recommendations for the domains of PsA.⁴ These recommendations are based on formal literature reviews of therapies for disease of the peripheral joints, spine, skin, and nails and for enthesitis and dactylitis and on discussions among GRAPPA members (rheumatologists and dermatologists) (Fig. 122.2). A treatment grid was developed (Table 122.1) in which each domain was categorized as mild, moderate, or severe based on measures of disease severity and impact on function and QoL to help the clinician in making treatment decisions. Specific treatments are recommended for each clinical domain according to the level of severity and impact while providing quality of evidence and level of agreement among the GRAPPA members surveyed. It is recommended that the most severe domain be treated accordingly while ensuring that the treatment will also be effective for other affected domains. These guidelines are currently being updated. The European League Against Rheumatism also developed treatment guidelines for the management of PsA based on a literature

review.⁶⁰ Although they recognized that PsA was a heterogeneous disease requiring multidisciplinary treatment, they did not include dermatologists in the group that developed the criteria. They did, however, recommend that dermatologists and rheumatologists collaborate in the care of patients with PsA who have significant skin involvement.

CONCLUSION

PsA is a multiple-domain disease characterized by inflammation of the peripheral joints, skin and nails, spine, entheses, and digits. Mild disease in the joints and skin can be treated with antiinflammatory agents and topical treatments. A number of systemic treatments of PsA, such as inhibitors of TNF- α , have shown significant benefit in treating more severe disease and have demonstrated an ability to control damage as assessed by radiographic progression and to improve QoL and functional status. A number of other agents that inhibit cytokine expression or block cellular interactions have either demonstrated benefit or are being tested for PsA. Observation of the effectiveness of these agents has helped elucidate the pathogenesis of PsA and psoriasis, which in turn may lead to newer effective interventions. Multimodal pharmacologic and nonpharmacologic therapy is optimal, and the rheumatologist should occupy a central role in coordinating these approaches.

A key aspect of treatment is accurate diagnosis and assessment, which facilitates the institution of appropriate therapy in a timely fashion. Because

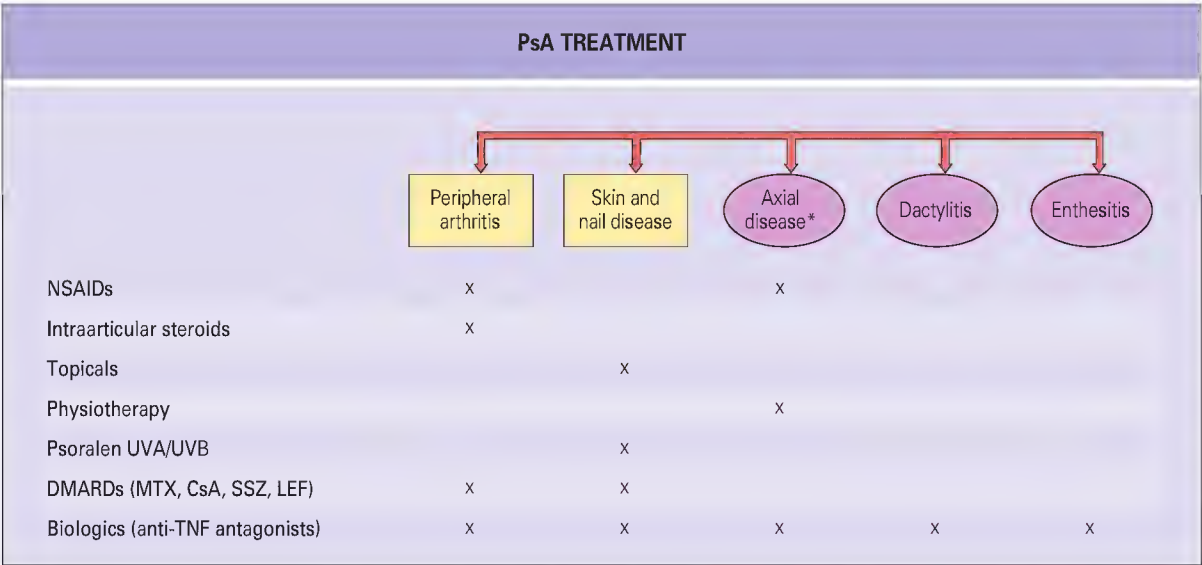


Fig. 122.2 Treatment options for psoriatic arthritis (PsA). Anti-TNF, tumor necrosis factor inhibitor; CsA, cyclosporine; DMARDs, disease-modifying antirheumatic drugs; LEF, leflunomide; MTX, methotrexate; NSAIDs, nonsteroidal antiinflammatory drugs; SSZ, sulfasalazine; UVA/B, ultraviolet A/B. *Based on data from ankylosing spondylitis trials (used as a surrogate for spondylitis in patients with PsA).

TABLE 122.1
Disease severity of psoriatic arthritis clinical domains

	Mild	Moderate	Severe
Peripheral arthritis	<5 joints No damage on radiograph No LOF Minimal impact on QoL Pt. evaluation mild	≥5 joints (S or T) Damage on radiograph IR to mild treatment Moderate LOF Pt. evaluation moderate	≥5 joints (S or T) Severe damage on radiograph IR to mild to moderate treatment Severe LOF Pt. evaluation severe
Skin disease	BSA < 5, PASI < 5, asymptomatic	No response to topical agents, DLQI < 10, PASI < 10	BSA >10, DLQI >10, PASI >10
Spinal disease	Mild pain, no LOF	LOF or BASDAI > 4	Failure of response
Enthesitis	1-2 sites, no LOF	>2 sites or LOF	LOF or >2 sites and failure of response
Dactylitis	Pain absent to mild, normal function	Erosive disease or LOF	Failure of response

BASDAI, Bath Ankylosing Spandylitis Disability Activity Index; BSA, body surface area; DLQI, Dermatology Life Quality Index; IR, inadequate response; LOF, loss of physical function; PASI, Psoriasis Area and Severity Index; QoL, quality of life; S, swollen; T, tender.
Data from Ritchlin CT, Kavanaugh A, Gladman DD, et al. Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 2009;68:1387-94.

in most patients the skin manifestations of psoriasis develop long before arthritis symptoms occur, the dermatologist or primary care physician is in an ideal position to screen for arthritis and make an early diagnosis. Through appropriate treatment and coordinated care with rheumatologists, it appears to be possible, given current therapies, to prevent progressive structural damage in those whose disease is likely to progress. Significant efforts are under way to further develop and validate outcome measures that accurately map the natural history of PsA and demonstrate the impact of increasingly

effective emerging therapies on a patient's function and QoL. International treatment recommendations have been developed to aid individualized therapeutic decision-making.

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123 Enthesopathies

■ DENNIS MCGONAGLE ■ MICHAEL BENJAMIN

- The term *enthesopathy* embraces all pathologic alterations at any enthesis. However, *enthesitis* specifically implies that there is inflammation at an attachment site.
- Anatomic and imaging studies demonstrate that the enthesis itself can be closely integrated with functionally adjacent bone, periosteum, and sometimes synovium. At the latter it forms a synovio-entheseal complex.
- Recent concepts concerning the enthesis provide a unifying biomechanical basis for all spondyloarthritis related disease.
- Although enthesitis at sites like the Achilles tendon and plantar fascia is readily apparent clinically, its recognition is difficult at inflamed synovial joints owing to soft tissue changes in associated inaccessible sites, including much of the spine. However, improvements in magnetic resonance imaging and ultrasonography have transformed our recognition of enthesitis at clinically inaccessible sites.
- The clinical features of enthesopathy vary depending on the location, severity, and underlying disease, although pain and loss of function are common.
- The traditional therapeutic spectrum includes physical modalities, analgesics, nonsteroidal antiinflammatory drugs, local injections (e.g., corticosteroids), and irradiation. There is a lack of evidence for efficacy of traditional disease-modifying antirheumatic drugs such as methotrexate and sulfasalazine in enthesitis.
- Anti-tumor necrosis factor therapy may be efficacious for isolated severe peripheral enthesitis or inflammatory polyenthesitis associated with spondyloarthritis related disease.

INTRODUCTION

I will lay sinews upon you, and cover you with flesh, and form skin over you. (Ezekiel 37:6)

This quotation, which is more than 2500 years old, amply illustrates the importance of anchoring tendons to bones as a prerequisite for recognizable body form and locomotion. The enthesis is the crucial link responsible for bridging the gap¹ between the force-generating units (muscles) and the levers responsible for moving the body (bones). Defined simply, the enthesis is a site of attachment of a tendon, ligament, or joint capsule onto bone or cartilage. Because attachment sites are ubiquitous, virtually the entire skeleton can be affected by pathologic disorders of the enthesis. Historically, entheseal disease was best recognized in large, clinically accessible tendons and ligaments, including the Achilles tendon and plantar fascia, but the advent of magnetic resonance imaging (MRI) has confirmed that enthesitis is present throughout the skeleton in early stages of spondyloarthritis and is common at clinically inaccessible sites such as the vertebral bodies.

Any pathologic alteration of an enthesis, whether traumatic, degenerative, or caused by inflammatory or metabolic diseases, is termed an *enthesopathy* (Box 123.1). If the pathologic process involves the formation of a bony spur, the latter is called an *enthesophyte*. The term *enthesitis* is restricted to inflammatory disease and, in general, refers to seronegative spondyloarthritis.

HISTORY

Although the word *enthesopathy* was first used by Niepel,² it was Ball's 1970 Heberden Oration lecture³ that primarily triggered the interest of rheumatologists. Ball initiated the important view that the enthesis is centrally affected in ankylosing spondylitis, in contrast to rheumatoid arthritis, in which it is largely synovial structures that are inflamed.³ In the following years, the primarily pathoanatomic concept of enthesitis was introduced into the clinical terminology of undefined conditions such as the syndrome of seronegative enthesopathy and arthropathy in children, in addition to a constitutive feature of spondyloarthritis as defined by the preliminary European Spondylarthropathy Study Group classification criteria.^{4,5}

The original observations on enthesitis in ankylosing spondylitis did not establish a possible causal link with synovitis or osteitis. More recently, on the basis of MRI, which shows that enthesitis is common in diseased synovial joints at clinical presentation, it has been suggested that synovitis in spondyloarthritis is secondary to entheseal inflammation—in contrast to the primary synovitis of rheumatoid arthritis.⁶ Focal insertional point inflammation or enthesitis does not explain all the pathophysiologic aspects of seronegative spondyloarthritis including osteitis, but in recent years the enthesitis concept has been developed to provide a unifying concept for disease (see later). Interestingly, although the primacy of enthesitis in seronegative spondyloarthritis has been contentious in the English literature, it has gained widespread acceptance in the French-language literature.⁷ At the present time, the cellular and molecular study of enthesitis remains problematic, owing to the difficulty in obtaining suitable clinical material and the inaccessibility of many entheses compared with synovium.

ANATOMY AND PATHOLOGY

Anatomy

The *enthesis* is defined as the site of attachment of a tendon, ligament, joint capsule, or fascia to bone. There are two major types: fibrous and fibrocartilaginous. The former are characterized by pure dense fibrous connective tissue that links the tendon or ligament to the bone, the latter by a transitional zone of fibrocartilage at the bony interface. In long bones, fibrous entheses are generally located at a considerable distance from a joint and are thus typical of tendons and ligaments attached to diaphyses. The insertions of deltoid and pronator teres muscles are good examples. In contrast, fibrocartilaginous entheses are characteristic of tendons and ligaments attached to epiphyses and apophyses, where the insertional angle of the tendon or ligament relative to the bone changes throughout the range of joint movement. They are best typified by the Achilles tendon and by the tendon of supraspinatus muscle (Fig. 123.1). It is noteworthy that disease in spondyloarthritis is virtually restricted to fibrocartilaginous entheses, and thus they alone are considered in more detail. Four zones of tissue are typically recognized at such attachment sites⁸:

1. **Dense fibrous connective tissue:** Parallel bundles of collagen fibers separated by longitudinal rows of fibroblasts or "tenocytes."
2. **Uncalcified fibrocartilage:** Fibrocartilage cells, which are commonly, although not invariably, arranged in longitudinal rows, replace the fibroblasts. These cells are associated with an extracellular matrix containing type II collagen fibers and aggrecan (Fig. 123.2).
3. **Calcified fibrocartilage:** Less cellular than its uncalcified counterpart, this zone has an extracellular matrix that is calcified. A straight interface called the *tidemark* separates calcified from uncalcified fibrocartilage and is the mechanical boundary between hard and soft tissues.

BOX 123.1 DIFFERENTIAL DIAGNOSIS OF ENTHESOPATHY

- Traumatic or degenerative disease
- Spondyloarthritis (termed *enthesitis*)
- Diffuse idiopathic skeletal hyperostosis (DISH)
- Calcium pyrophosphate dihydrate or hydroxyapatite deposition disease
- Chronic fluoride intoxication
- Chronic retinoid toxicity
- Endocrine disorders (acromegaly)

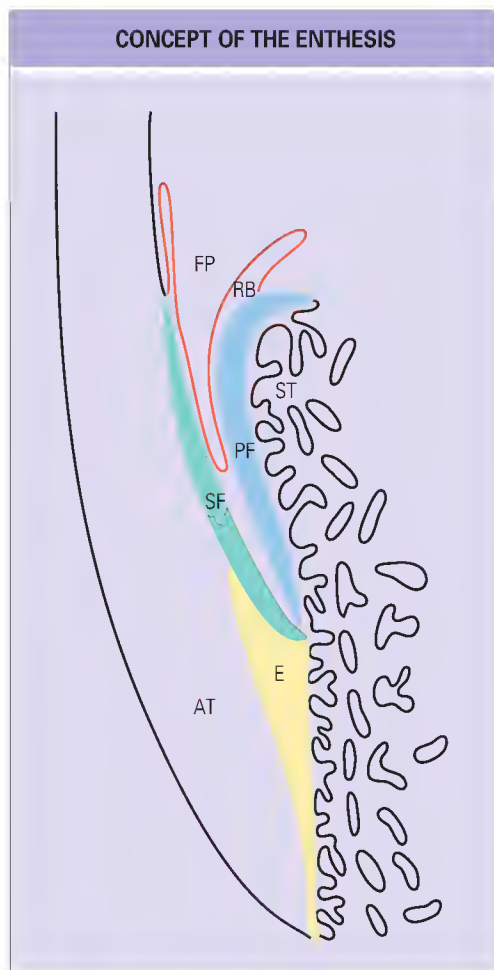


Fig. 123.1 The concept of the enthesis organ, with the Achilles tendon (AT) insertion as an example. Historically, enthesal disease was seen strictly in terms of focal inflammation at the site of tendon, ligament, or capsule attachment to bone. However, the enthesis is more than a focal insertion and has been viewed as an organ (the enthesis organ), an integrated group of tissues including the insertion site itself and the immediately adjacent bone. All these structures are covered or lined by fibrocartilage. The adjacent trabecular bone network is also an integral part of the enthesis. The colored regions represent different fibrocartilages associated with the enthesis: tan, enthesis fibrocartilage (E) at the tendon-bone junction; blue, periosteal fibrocartilage (PF) on the bony surface of the superior tuberosity (ST); and teal, sesamoid fibrocartilage (SF) lining the deep surface of the tendon. A fat pad (FP) that protrudes into the retrocalcaneal bursa (RB) is covered with synovium (red outline).

In contrast, the *tissue boundary* is the junction between calcified fibrocartilage and the underlying bone. Although this interface is equally abrupt, it is more tortuous, with the degree of irregularity varying between sites.

4. **Bone:** A bony cortex at a fibrocartilaginous enthesis barely exists, because even in a large tendon like the Achilles, the subchondral bone plate is generally little thicker than one or two trabeculae. Indeed, the cortex can be focally absent at microscopic sites. It is important to recognize, therefore, that bone at the site of an enthesis is closely integrated with adjacent trabecular (cancellous) bone, which thus

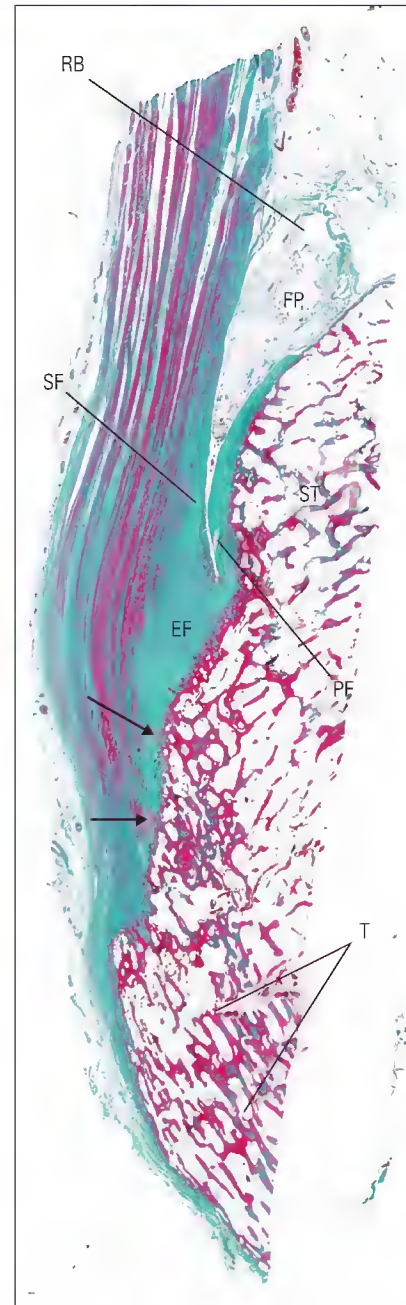


Fig. 123.2 Actual histologic section of the Achilles enthesis organ. Arrows indicate the distal part of the insertion. Many entheses throughout the body have this anatomic configuration. EF, enthesis insertion fibrocartilage. FP, fat pad; PF, periosteal fibrocartilage; RB, retrocalcaneal bursa; SF, sesamoid fibrocartilage; ST, superior tuberosity; T, trabeculae.

contributes to the anchorage of the soft tissue. Indeed, Benjamin and colleagues⁹ have compared the role of bony spicules adjacent to a tendon/ligament attachment site with that of the anchorage functions of the roots of a tree. Recognizing the mechanical integration and direct continuity of cancellous bone adjacent to an enthesis with that of the attachment site itself could help to explain why osteitis and enthesitis are frequently linked. In connection with the basic anchorage role of an enthesis, however, it should also be noted that there are complex interdigitations of bone and calcified fibrocartilage that knit them into each other, which promotes the basic function of tendon/ligament anchorage.¹⁰ There are no Sharpey fibers where fibrocartilage is present at entheses because the subchondral bone plate is too thin. Sharpey fibers are, however, a feature of fibrous entheses.

Fibrocartilage

Fibrocartilage is a dynamic tissue that develops at sites where entheses are subject to shear and compressive forces. It also has the ability to promote bone formation, as shown in histologic analyses during postnatal growth.¹¹ The gradual (rather than abrupt) bending of the soft tissues of entheses

close to joint margins, which is a consequence of matrix stiffening by proteoglycans in enthesis fibrocartilage, dissipates stress concentration at the attachment site. However, it also means that parts of the enthesis and adjacent tissues are compressed during joint traction. The idea is best understood in relation to the Achilles tendon and is the archetypal example of the enthesis organ concept (see Figs. 123.1 and 123.2).^{8,12,13} When the foot is dorsiflexed, the Achilles tendon bends gradually in the region of the fibrocartilage plug as the insertional angle at which the tendon approaches the heel is changed. Consequently, the immediately adjacent part of the tendon is compressed against the superior tuberosity of the calcaneus. Mutual compression of tendon and bone leads to the formation of a sesamoid fibrocartilage in the deep surface of the former and a periosteal fibrocartilage on the surface of the latter. Facilitating the movement of the tendon relative to the bone is a bursa (the retrocalcaneal), and the tip of the Kager fat pad moves in and out of this space with foot movements to minimize pressure changes and promote boundary lubrication.¹⁴ Basic mechanical engineering principles would suggest that a tendon that kinks under load would be more liable to failure. The enthesis itself, the sesamoid and periosteal fibrocartilage, the bursa, and the fat pad collectively comprise the Achilles enthesis organ as originally defined.⁸ Together, they all function in one way or another to reduce stress concentration at the enthesis itself. Because the deep crural fascia in the lower part of the leg effectively serves as a retinaculum to reduce bowstringing and the bending that would otherwise occur at the enthesis, it too can be considered part of the enthesis organ complex.

This concept of an enthesis organ has wide applicability, and an enthesis organ is seen at many other sites in the body.¹³ Fundamentally, the development of an enthesis organ depends on the presence of either a microscopic pulley site immediately adjacent to the enthesis itself or an enthesis that is located in a pit, that is, the adjacent bone is slightly raised in comparison. The rheumatologic significance of the enthesis organ concept is that it helps to explain why patients with enthesopathies can have symptoms that affect the immediately adjacent area rather than just the tendon/ligament/bone junction itself. Comparable biomechanical conditions that lead to fibrocartilage formation at and near entheses exist at other sites, including the regions where tendons or ligaments wrap around bony pulleys (e.g., where the peroneal tendons wrap around the lateral malleolus at the ankle) and some synovial joints (sacroiliac and sternoclavicular joints).

Entheses are often regarded as being well supplied with pain and proprioceptive receptors. However, studies of the rat Achilles tendon enthesis have shown that a healthy enthesis is aneural and that nerve fibers are restricted to neighboring tissues, for example, the epitendon and particularly the tip of the Kager fat pad that protrudes into the retrocalcaneal bursa.¹⁵ Thus, in its lack of nerve fibers, enthesis fibrocartilage parallels the articular cartilage of a synovial joint. The fibrocartilage is also avascular, and the blood supply of the enthesis is derived largely from vessels in the peritenon and adjacent bone marrow.

Related structures

Benjamin and McGonagle⁸ coined the term *functional enthesis* to refer to the sites where tendons and ligaments wrap around bony pulleys. At such locations there is *contact* between hard and soft tissues but no *anchorage* as at entheses themselves. The similar presence of compressive forces at the fibrocartilaginous enthesis insertion and the wraparound tendons leads to a comparable functional demand for fibrocartilage, and this may explain why this region also can be affected in seronegative spondyloarthritis. Essentially, a functional enthesis is exactly comparable to part of an enthesis organ, that is, the region in the latter where the sesamoid and periosteal fibrocartilages are in contact with each other yet are not physically attached.

Finally, it has been described recently that many enthesis organ cartilages, by virtue of their intraarticular locations, rely on adjacent synovium for nourishment and lubrication in a manner identical to articular cartilages in synovial joints. This particular anatomic and functional unit is an example of what has been termed a *synovio-entheseal complex* and is key to understanding why enthesitis and synovitis may be intimately linked (Fig. 123.3).^{16,17}

Histopathologic features

Chronic enthesitis is characterized histopathologically by bony erosions and destruction, with inflammatory infiltrates evident in the bone adjacent to the enthesis.¹⁸ Inflammatory cells, including T lymphocytes, and edema in the bone marrow close to fibrocartilage have been observed.¹⁹ In later disease, capsular ossification, myxoid bone marrow changes, chondroid metaplasia, and the formation of synchondroses have been reported.¹⁸ The limited histologic data for sites of acute enthesitis have shown that inflammatory changes occur, including macrophage infiltration.²⁰ There are also

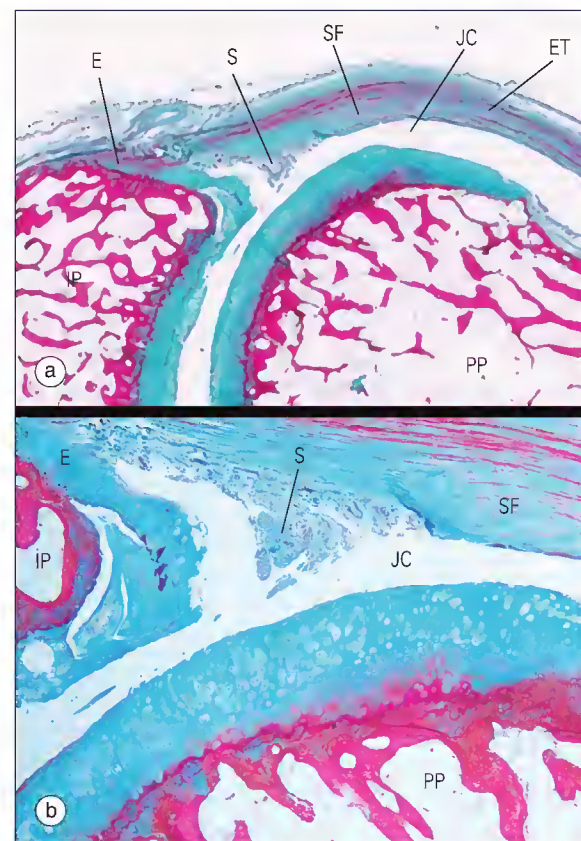


Fig. 123.3 The juxtaposition of an enthesis (E) and a synovial membrane (S) at many locations has led to the introduction of the term *synovio-entheseal complex* to highlight their anatomic proximity. The figure shows how the enthesis of the extensor tendon (ET) in a finger is closely related to a synovium adjacent to the attachment of the tendon to the intermediate phalanx (IP). The synovial fluid could thus be involved in nourishing not only the articular cartilages but also the sesamoid fibrocartilage (SF) that thickens the tendon adjacent to its attachment site. It is readily appreciated that inflammation of the enthesis organ would likely be associated with adjacent synovitis. (a) Low-power view of the whole joint. (b) Higher-magnification view of the juxtaposition of the enthesis, synovium, and sesamoid fibrocartilage. JC, joint cavity; PP, proximal phalanx.

very limited data on the cytokine and growth factor milieu, and much of what are available come from studies of the sacroiliac joint, where transforming growth factor- β and tumor necrosis factor- α (TNF- α) have been reported. In fact, the only direct evidence for TNF at human entheses comes from studies in which TNF blockade leads to regression of enthesitis/osteitis as determined by MRI.²¹

The molecular basis for enthesitis was investigated in a recent study which found that bone morphogenetic protein pathway signaling and its antagonists may play a role in both human enthesitis and animal models of disease.²² Specifically, *noggin*, a bone morphogenetic protein antagonist, may ameliorate experimental disease.

Although it is difficult to obtain suitable tissue from patients with enthesitis, there have been many studies looking at “normal” cadaveric entheses. These have shown that entheses from elderly individuals have a substantial degree of microscopic damage at the attachment site itself and at the adjacent fibrocartilage.²³ These age-related changes are also associated with microscopic inflammatory changes within the enthesis and immediately adjacent synovium. It has been proposed that perturbation in tissue repair or remodeling responses in younger subjects at these sites of high mechanical stress could underlie disease in spondyloarthritis.

ENTHESITIS AND THE PATHOGENESIS OF SPONDYLOARTHRITIS

A universal hallmark of spondyloarthritis

The concept that enthesitis is the universal hallmark in spondyloarthritis, linking its diverse manifestations, is supported by fat-suppressed MRI

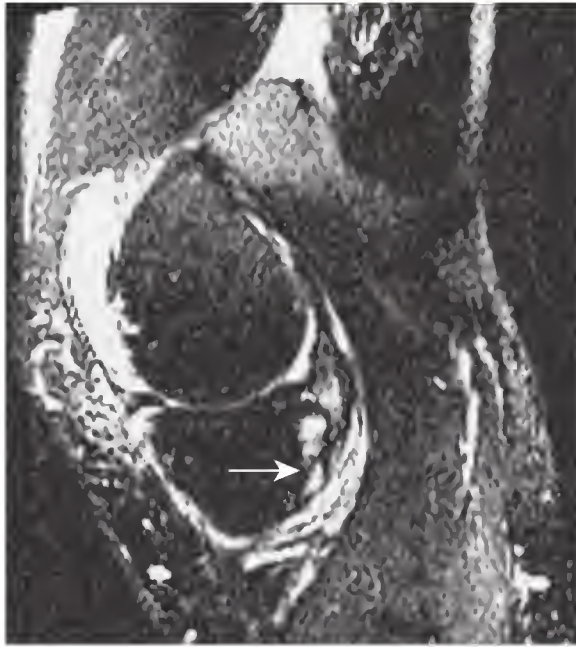


Fig. 123.4 Magnetic resonance image (MRI) of a patient with psoriatic arthritis who clinically had a swollen knee. On MRI, clinically unrecognized enthesitis at the semimembranosus insertion is evident (white arrow). The enthesitis is recognizable by the presence of bone edema. However, not all regions of enthesitis in synovial joints, as elsewhere, have associated bone changes, which makes synovial joint enthesitis difficult to define, even on imaging.

analysis in patients with spondyloarthritis of recent onset. Knee effusions in these patients were associated with adjacent perienthesal high signal compatible with fluid or edema and bone marrow edema maximal at enthesal insertions, in contrast to findings in rheumatoid arthritis, which were predominantly synovium based (Fig. 123.4).²⁴ Enthesitis and capsular inflammation have also been reported to be commonplace in the small joints in psoriatic arthritis but not rheumatoid arthritis.²⁵ Imaging has not shown enthesitis in every inflamed synovial joint, but conventional MRI may have limited diagnostic sensitivity for enthesitis in a joint that is already swollen.

Focal insertional inflammation such as Achilles tendinitis or plantar fasciitis does not explain all of the features of spondyloarthritis, and some investigators have rejected the primacy of enthesitis in spondyloarthritis based on data showing prominent changes in the subchondral bone well away from insertions at the sacroiliac joint.²⁶ Despite the relatively low spatial resolution of conventional MRI and its inability to show all sites of enthesitis, active enthesitis was commonly observed in advanced cases of sacroiliitis and in almost half the cases of early disease.²⁷ However, interpretation of sacroiliac joint abnormalities is based on the traditional concept of enthesitis as representing focal insertional inflammation. The enthesitis organ concept and the related idea of “functional entheses,” as outlined earlier, inextricably link enthesitis and sacroiliitis even when focal insertional inflammation is not demonstrable in the latter.

Enthesitis and osteitis

Enthesitis and osteitis have been viewed as different pathologic processes. However, imaging studies including radiography, MRI, and scintigraphy clearly demonstrate that the underlying bone forms an integral part of the enthesitis²⁸ and is often involved in the disease process in both mechanically induced and inflammatory enthesopathy. The bone cortex is no thicker than the underlying trabecular network, and indeed it may be absent locally at entheses (see Fig. 123.2). The attachment site can be viewed as being a large collection of fibrous strands “inserted” into a trabecular architecture that is analogous to chain mail, that is, deformable, yet resisting tensile and compressive load. Studies of acute peripheral enthesitis have also shown that mechanical and inflammatory disease are associated with MRI-determined bone edema and osteitis in spondyloarthritis-related inflammatory disease and that its severity is related to carriage of the HLA-B27 gene.²⁸

In the light of a better understanding of the insertion proper, it now appears that there is a unifying biomechanical basis for disease localization in spondyloarthritis that can be best understood in relationship to

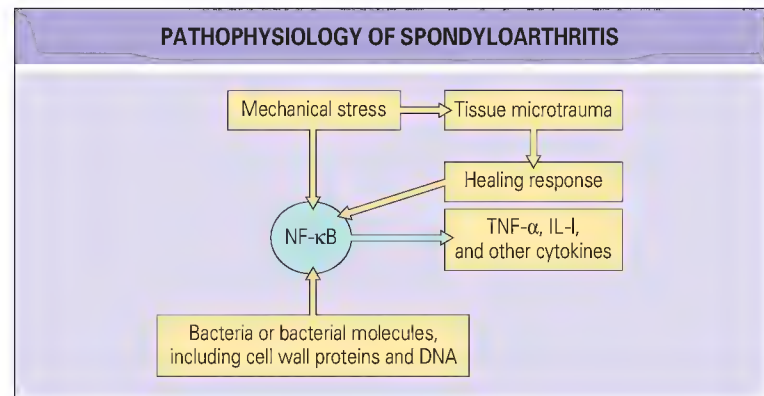


Fig. 123.5 Simplified schematic synthesis of the pathophysiology of spondyloarthritis viewed from the unifying concept of enthesitis. Ultimately, enthesitis is the result of activation of nuclear factor- κ B (NF- κ B) with the induction of proinflammatory cytokines. Diverse factors, including biomechanical stress at insertions and immediately adjacent tissue, with microtrauma and healing response and the deposition of bacterial fragments, convert what would ordinarily be a healing response into a clinically recognizable inflammatory response at insertions and related structures. These factors result in innate immune activation with the presentation of hitherto undefined peptides via HLA-B27, which leads to acquired immune activation and disease expression in ankylosing spondylitis. These factors ultimately result in increased proinflammatory cytokine production. Anti-tumor necrosis factor (TNF) neutralizes these, but as soon as it is stopped, disease usually returns. IL-1, interleukin-1.

enthesitis. Fibrocartilage is a dynamic tissue that occurs at regions of compression and shear and has been found at virtually all the sites of spondyloarthritis, including the joints and aortic wall. It is thus of interest that murine models with humoral and cellular immunity to the major cartilage proteoglycan aggrecan resemble human ankylosing spondylitis¹⁹ and that T-cell reactivity against cartilage has been reported in humans.²⁹ Thus whether fibrocartilage primarily indicates sites prone to microdamage or T-cell direct immune reactivity, or both, in the pathogenesis of enthesitis awaits further study.¹²

An enthesitis-based model

The precise cause and pathophysiology of disease localization to the enthesitis and related structures in spondyloarthritis are incompletely understood, but an enthesitis-based model of disease has been developed. Small particles (0.02 to 1.1 μ m in diameter), such as bacteria, may localize to certain transitional zones, including entheses, where richly and poorly vascularized areas are juxtaposed.³⁰ Bacteria, or their constituent macromolecules, may then contribute to inflammation by mechanisms that are yet to be clearly defined.³¹

Because biomechanical stress occurs at entheses in addition to other locations involved in spondyloarthritis (aorta, lung apex, uvea), it has been suggested that such stress in the presence of microtrauma and subsequent healing, together with the deposition of bacterial products, may convert a physiologic healing response into an inflammatory response.³² Relevant features include the special vascularity of entheses, with subsequent activation of Toll-like receptors by CpG motifs, lipopolysaccharide, or bacterial heat shock protein. These may, either directly or indirectly, induce nuclear factor- κ B activation to a degree that triggers an inflammatory reaction with dendritic cell activation and T-cell costimulation, leading to HLA-B27-related immune responses. This model is presented schematically in Fig. 123.5. When this model is interpreted in light of the explosion of knowledge in relation to innate immune functioning mediated via pattern recognition receptors (including Toll-like receptors), then it is clear that bacterial structural proteins and DNA alone (without viable organisms) could incite inflammatory responses at enthesal sites. Another consequence of this model is that blocking TNF production will not address the underlying pathogenic drive to disease, hence the need for long-term therapy and the relapse observed with cessation of anti-TNF treatment.³³

Although it is difficult to prove the primacy of enthesitis-related inflammation in humans, the primacy of enthesitis in experimental model systems has been demonstrated. It is now clear that in diverse experimental inflammatory spondyloarthritis models, including TNF and interleukin-23 overexpression systems, inflammation commences at insertions.^{34,35}

TABLE 123.1**Reported frequency of clinically recognizable enthesitis in the various forms of spondyloarthritis**

Spondyloarthritis	Frequency of enthesitis (%)
Ankylosing spondylitis	25-28
Reactive arthritis	13-58
Psoriatic arthritis	20
Spondyloarthritis associated with inflammatory bowel disease	7-33
Undifferentiated spondyloarthritis	27

Data from references 36 to 40.

FEATURES

Sites of enthesitis

Peripheral enthesitis is observed in all forms of spondyloarthritis. The frequency of clinically recognizable enthesitis ranges from 13% to 60% (Table 123.1). Such clinically recognizable sites include large tendons and ligaments adjacent to joints and superficial spinal insertions. The entheses of the lower limb are involved more frequently than those of the upper limb, with plantar fasciitis, Achilles enthesitis, or both being especially common. Crucially, many sites of enthesitis, including most of those in the spine and in large joints, are clinically inaccessible, something that contributed historically to the failure to recognize the primacy of enthesitis in spondyloarthritis.

Symptoms and signs

Clinically accessible sites of enthesitis can be asymptomatic, and the enthesitis might be detectable only by ultrasound techniques, but such observations lack histologic validation.⁴¹ However, nagging pain at rest or pain on movement is the main complaint in enthesitis. The degree of pain can vary from mild to disabling. The pain is often pronounced after a period of rest, especially in the morning, and improves gradually with movement. Soft tissue swelling may be visible at superficial sites such as the Achilles tendon insertion. Physical examination of deep-seated entheses such as those on the greater trochanter may reveal tenderness and palpable swelling. The relative contribution of soft tissue inflammation versus bone inflammation to pain and disability at sites of enthesitis remains to be defined.

Clinically, peripheral enthesitis may antedate the occurrence of other spondyloarthritis-related symptoms such as inflammatory back pain or peripheral arthritis, especially in juvenile-onset forms of spondyloarthritis.⁴² However, this observation is unlikely to reflect separate phases of disease and may simply indicate the presence of unrecognized enthesitis at other sites. Clinical scoring methods for accessible superficial sites of enthesitis have been developed, but further work is needed to improve the value of these—both as a diagnostic tool and as an outcome measure.³³

Differential diagnosis

Numerous diseases can lead to the clinical presentation of enthesopathy and have to be considered as potential differential diagnoses of enthesitis related to spondyloarthritis. However, in the vast majority of cases, the diagnosis usually rests between inflammatory disease and degenerative or mechanical disease (see Box 123.1). Particular clinical suspicion is needed in the diagnostic assessment of chest wall enthesitis, because recognition will preclude unnecessary cardiac investigations, for example. A major difficulty with the differential diagnosis of enthesitis is that clinicians probably fail to consider it often enough outside the classically recognized sites such as the foot and elbow.

IMAGING

In general, the diagnosis of peripheral enthesitis is clinically based, and imaging is used mostly in the research setting or for monitoring of therapy. The major need for imaging in enthesitis is probably to facilitate a diagnosis of spondyloarthritis. The value of plain radiographs for the diagnosis of early enthesitis is debatable, because characteristic changes are usually absent in



Fig. 123.6 High-resolution magnetic resonance image for a patient with early psoriatic arthritis who had acute Achilles enthesitis at presentation. There is perienthesal high signal in the soft tissue adjacent to the enthesis and also signal within the enthesis after gadolinium administration, reflecting increased vascularity. At this stage in the disease process, the enthesis fibrocartilage appears to be relatively spared (white arrow).

early disease. With the advent of MRI and ultrasonography, the role of bone scintigraphy will likely diminish even farther.

Magnetic resonance imaging

As stated, enthesitis is difficult to recognize in the axial skeleton. MRI is becoming the method of choice for evaluating spinal polyenthesitis or early inflammatory back pain in spondyloarthritis. Recent work has shown that a baseline MRI of the sacroiliac joint can be fairly reliably used to predict the radiographic development of ankylosing spondylitis at 8 years.⁴³ Also MRI of the spine can be reliably used to differentiate between spondyloarthritis and degenerative disk disease. However, enthesal abnormalities are common in the degenerative disease category.⁴⁴ The role of MRI has taken on great importance especially now that therapies are available which powerfully suppress the inflammatory phase of enthesitis.

Various recent studies have shown that fat-suppression MRI, with or without contrast agent administration, is the most sensitive method for identifying active enthesitis at any site. MRI can show perienthesal inflammation with adjacent bone marrow edema in fat-suppressed T2-weighted sequences (Fig. 123.6). Usually investigations are required for the diagnosis of clinically unrecognized enthesitis in the spine in patients with inflammatory back pain when the presence of enthesitis-associated osteitis may be diagnostic and also useful for monitoring therapy (Fig. 123.7). Although preliminary studies are promising, the value of MRI for the diagnostic and prognostic assessment of synovial joint disease in cases of definite or suspected spondyloarthritis has not been established.²⁴

Conventional radiography

The combination of erosion and bone proliferation is the radiographic hallmark of enthesitis, but this is a comparatively late feature and of limited value for early diagnosis. In early disease during the inflammatory phase, osteopenia or erosions may be evident. Subsequently, when the repair process predominates, soft tissue calcification and bone cortex irregularities at tendon entheses are observed.⁴⁵ This can progress to enthesophytes. The relationship between inflammation, new bone formation, and bone erosion

in spondyloarthritis-associated enthesitis is incompletely understood; our current understanding is depicted in Fig. 123.8.

Ultrasonography

Ultrasound evaluation is readily applicable to demonstrating enthesitis, especially in the peripheral skeleton.⁴⁶ The ultrasound appearance is associated with loss of normal fibrillar echogenicity of the entheses, with hypoechoic thickening and edema with bone erosion or new bone formation at the insertion, or with changes in enthesal vascularity as measured by power Doppler imaging (Fig. 123.9).⁴⁷ Furthermore, ultrasonography may reveal small effusions in the adjacent bursa and guide arthrocentesis. Ultrasonography, including power Doppler techniques, may be especially useful for improved early diagnosis of clinically unrecognized peripheral enthesitis, but, as stated earlier, the difficult issue of histologic validation of ultrasound findings has not been addressed.

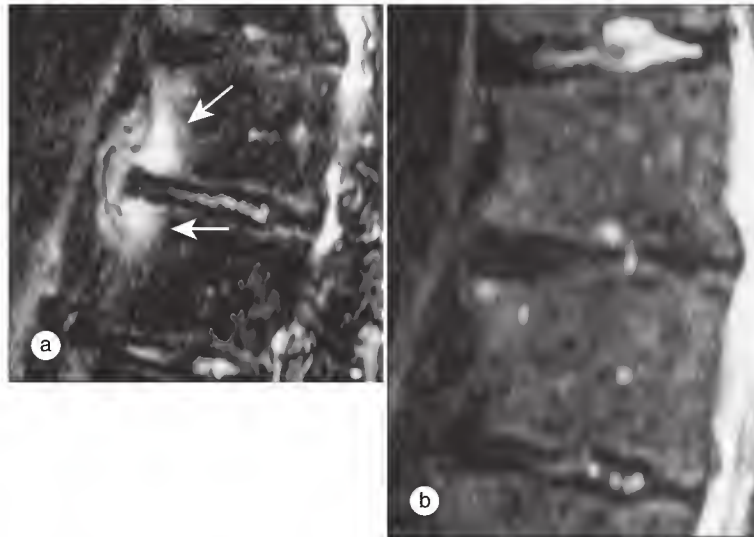


Fig. 123.7 Fat-suppressed magnetic resonance images of a patient with spinal enthesitis before (a) and after (b) treatment with etanercept, a tumor necrosis factor (TNF) blocker. The white arrows illustrate sites of active enthesitis. These images show that spinal involvement in ankylosing spondylitis is largely an enthesitis that should be viewed as a chronic HLA-B27-associated polyenthesitis. It also illustrates how the enthesitis-associated pathologic process is often highly responsive to anti-TNF therapy, with almost complete resolution of these changes after treatment.

MANAGEMENT

Several questions need addressing before initiation of treatment of enthesitis in spondyloarthritis.¹ Is the disease primarily inflammatory (associated with spondyloarthritis), or is it predominantly degenerative (in which inflammation may also be a feature)?² Is it isolated peripheral enthesitis, or is it part of a generalized inflammatory enthesitis such as ankylosing spondylitis? A stepwise approach to treatment of isolated peripheral enthesitis may result in remission. Refractory enthesitis, defined as the persistence of symptoms after a period of 2 years despite adequate treatment, occurs in only a minority of cases with such measures.

First-line therapy

The first-line treatment of isolated peripheral enthesitis consists of nonsteroidal antiinflammatory drugs (NSAIDs), physical therapy, and orthoses. Various NSAIDs have been shown to be effective in the treatment of the spondyloarthritides, including indomethacin, diclofenac, naproxen, piroxicam, and, most recently, meloxicam and the cyclooxygenase-2 inhibitors,

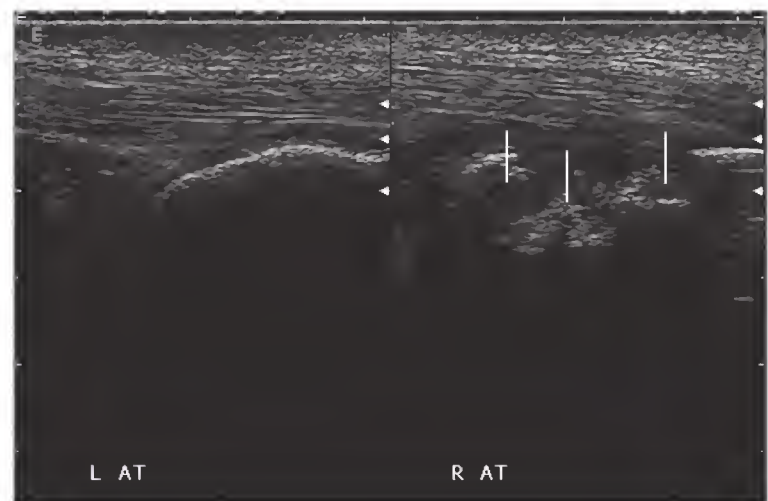


Fig. 123.9 Ultrasound image of an erosive enthesitis at the site of insertion of the right Achilles tendon. Compared with the healthy site, cortical erosions are noted. The white arrowheads indicate the sites of erosion adjacent to the periosteal fibrocartilages. (Courtesy Dr. Richard Wakefield, Department of Rheumatology, University of Leeds, United Kingdom.)

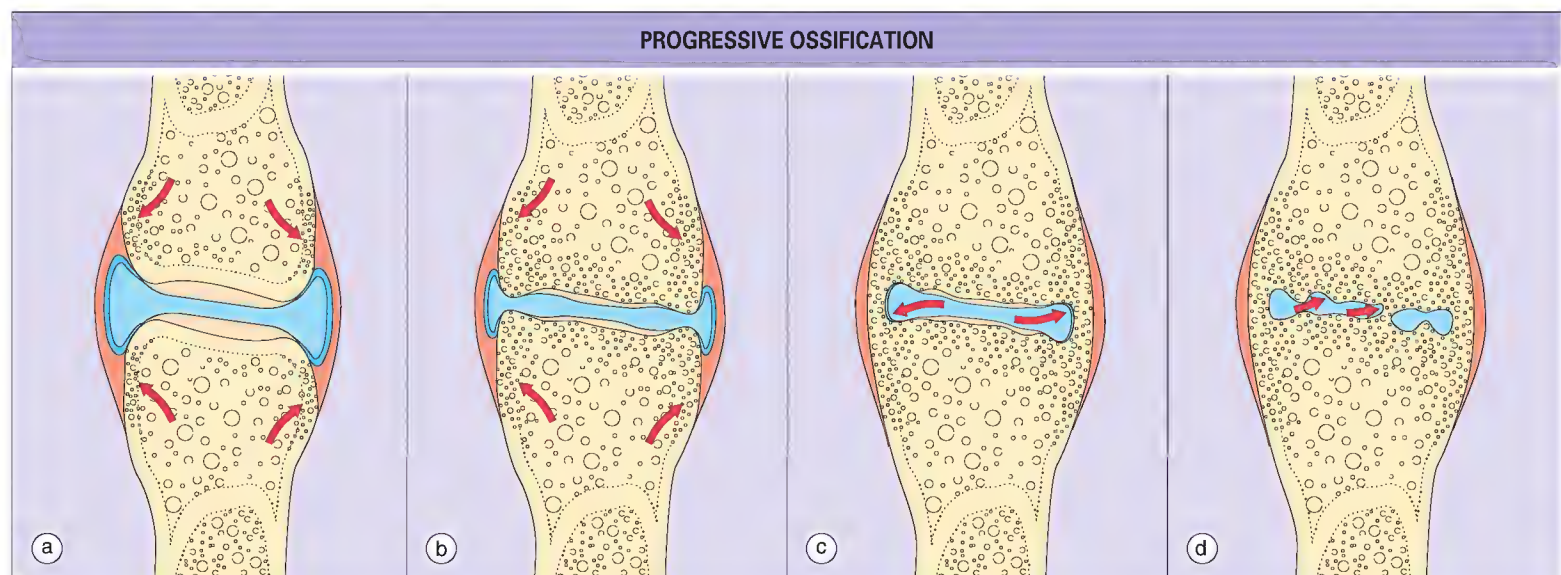


Fig. 123.8 (a) Initially, inflammatory changes are noted at attachments to bone and the adjacent bone marrow as determined by magnetic imaging and scintigraphy. (b) This progresses to bone erosions, at least in the sacroiliac joint in early disease. (c) Capsular ossification leads to peripheral bone ankylosis largely via enthesal calcification. (d) In synovial joints, including the sacroiliac joint and the hip, articular cartilage may be replaced by bony bridges leading to intraarticular ankylosis of bone. The diffuse osteitis that accompanies early enthesitis may result in the joint cartilages' being subject to an immunologic attachment from beneath the growth plate that subsequently culminates in the radiologic appearance in advanced disease.

including celecoxib. Local injections of corticosteroid should be tried in patients with enthesitis at one or a limited number of sites.

Disease-modifying therapy

Conflicting data exist with respect to the use of sulfasalazine or methotrexate. Their efficacy is not impressive, but these agents have not been used early in patients with MRI-determined severe insertional and bone disease. With the advent of anti-TNF drugs, it is likely that the role of surgery for refractory isolated peripheral enthesitis will be very limited. Severe peripheral enthesitis may respond well to anti-TNF agents.⁴⁸

Management of "secondary" enthesitis

For treatment of inflammatory polyenthesitis related to ankylosing spondylitis or psoriatic arthritis, there is no question that the advent of anti-TNF treatment represented a giant therapeutic leap. Treatment with NSAIDs, sulfasalazine, methotrexate, and, more recently, leflunomide in the case of psoriatic arthritis, may be used, especially when synovial joint swelling is evident. Thus far, only the anti-TNF drugs have been associated with regression of both spinal and appendicular skeleton enthesitis (see Fig. 123.6).

The use of bisphosphonates may also have a role in enthesitis-related osteitis, but this needs further evaluation.³³ Surgery does not appear to provide any beneficial effect in enthesitis. However, it may still be useful for the removal of large bone spurs at sites such as the plantar fascia.

A major cause of disability in ankylosing spondylitis is enthesal ossification leading to reduced spinal mobility. There is currently insufficient evidence to show that NSAIDs prevent the ligamentous and capsular calcification that accompanies enthesitis. It was hoped that the anti-TNF agents would retard spinal fusion because they lead to good suppression of enthesitis/osteitis. At the present time there is evidence that a relationship exists between the inflammatory phase of enthesitis and the likelihood of subsequent enthesal new bone formation at the same spinal segment.⁴⁹ The link between inflammation and new bone formation in enthesitis is more complex than hitherto appreciated, because both erosion formation and creation of new bone seem to be anatomically and temporally uncoupled.⁵⁰ The biggest clinical challenge at the moment is to determine whether reversing enthesal inflammation prevents enthesal new bone formation in patients who do not have preexistent spinal joint fusion.

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CONNECTIVE TISSUE DISORDERS

124

Epidemiology and classification of systemic lupus erythematosus

■ JULIA F. SIMARD ■ KAREN H. COSTENBADER

- Systemic lupus erythematosus (SLE) primarily affects women of childbearing age.
- Several non-European groups have an increased prevalence and a more severe course of disease.
- The cause or causes of SLE, a paradigmatic disorder of immune dysfunction, remain unknown, with several environmental factors being important potential triggers for those with underlying genetic influences.
- Epidemiologic evidence has linked environmental factors, including current cigarette smoking, crystalline silica exposure, oral contraceptives, and postmenopausal hormones, with the development of SLE.
- Increased disease severity is associated with poverty, lower education level, and decreased access to medical care, as well as the presence of certain autoantibodies.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease of unclear etiology characterized by autoantibody production and protean organ system manifestations. Autoantibodies in SLE are directed against intracellular targets; antinuclear antibodies (ANAs) are the most characteristic and are present in at least 95% of patients with SLE. Anti-double-stranded DNA (dsDNA), anti-Smith (anti-Sm), anti-Ro, and anti-La antibodies are less common.¹⁻³ This chapter reviews the classification of SLE, gives an overview of its descriptive epidemiology, and considers the role of both host and environmental factors in its etiology.

CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

Criteria for the classification of SLE were developed by the American College of Rheumatology (ACR) in 1971, with subsequent revisions in 1982 and 1997 (Table 124.1).⁴⁻⁸ These criteria aim to be optimally sensitive and specific and require the involvement of at least 4 of 11 different organ systems, but they were not intended to include all possible manifestations. These criteria were developed to define a relatively homogeneous population and allow comparability of research subjects from different settings. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group revised the 1987 ACR criteria to require one of four criteria to be clinical and at least one to be immunologic. These new criteria, as can be seen in Table 124.1, brought back old, previously used criteria such as alopecia and

expanded on others (e.g., neurologic disease extends beyond seizures and psychosis). Their revised system also classifies individuals with lupus nephritis alone if ANA or dsDNA antibodies are present.⁸

Systemic lupus erythematosus heterogeneity and subphenotypes

The classification criteria do not distinguish between phenotypic subgroups of SLE. However, the following non-mutually exclusive clinical phenotypes of SLE have been recognized based on the co-occurrence of various clinical syndromes with specific autoantibodies:

- *Anti-dsDNA/glomerulonephritis*: Anti-dsDNA antibodies are strongly associated with severe SLE and the development and activity of glomerulonephritis.⁹
- *Anti-Ro antibodies/subacute cutaneous LE and Sjögren syndrome*: Anti-Ro antibodies (also called SSA antibodies) are directed against RNA-protein conjugates and are prevalent in many autoimmune diseases, including SLE, particularly with photosensitive rash; Sjögren syndrome/SLE overlap syndrome; subacute cutaneous lupus erythematosus (SCLE); neonatal lupus; and primary biliary cirrhosis. In SLE, anti-Ro antibodies have also been associated with cutaneous vasculitis in SLE.¹⁰ In contrast, anti-La/SSB antibodies are more strongly associated with Sjögren syndrome.¹¹ Although more than half of SCLE patients may fulfill the ACR criteria for SLE, they are probably a distinct phenotype with recognizable annular or psoriasiform photosensitive rashes, less visceral involvement, and the requirement for immunosuppressive therapy.¹²
- *Antiphospholipid antibody syndrome*: Antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, antiprothrombin antibodies, and anti- β_2 -glycoprotein I antibodies, identify SLE patients with a distinct phenotype—high risk for occlusive vasculopathy, livedo reticularis, strokes, and miscarriages—and probably a common etiology and pathogenesis.^{9,13}
- *SLE/mixed connective tissue disease overlap*: This clinically distinct syndrome is characterized by anti-U1 ribonucleoprotein antibodies; puffy hands; arthritis, which can be erosive; Raynaud phenomenon; pulmonary hypertension; and relative protection from renal disease.¹⁴

DESCRIPTIVE EPIDEMIOLOGY

Sex

SLE is predominantly a disease of women, although the excess female preponderance varies with age. Before puberty, SLE is approximately twice as common in girls. During the childbearing years, the female-to-male ratio

■ **TABLE 124.1**
Evolution of criteria classification systems for systemic lupus erythematosus*

Criterion	ACR 1971 ⁵	ACR 1982 ⁶	ACR 1997 ⁷	SLICC 2012 ⁸
Malar rash	Malar rash	Malar rash	Malar rash	Acute cutaneous rash
Discoid rash	Discoid rash	Discoid rash	Discoid rash	Chronic cutaneous rash
Raynaud phenomenon	Raynaud phenomenon			
Alopecia	Alopecia			Nonscarring alopecia
Photosensitivity	Photosensitivity	Photosensitivity	Photosensitivity	
Oral/nasal ulcers	Oral or nasal ulcers	Oral or nasal ulcers	Oral or nasal ulcers	Oral or nasal ulcers
Arthritis	Arthritis without deformity	Nonerosive arthritis in at least 2 peripheral joints	Nonerosive arthritis in at least 2 peripheral joints	Synovitis involving at least 2 joints or tenderness in at least 2 joints with at least 30 min of morning stiffness
Serositis	A. Pleurisy B. Pericarditis	A. Pleurisy B. Pericarditis	A. Pleurisy B. Pericarditis	A. Pleurisy B. Pericarditis
Renal disorder	A. Profuse proteinuria B. Cellular casts	A. Profuse proteinuria B. Cellular casts	A. Profuse proteinuria B. Cellular casts	A. Profuse proteinuria B. Red blood cell casts
Neurologic	A. Psychosis B. Convulsions	A. Psychosis B. Seizures	A. Psychosis B. Seizures	A. Psychosis B. Seizures C. Mononeuritis multiplex D. Myelitis E. Peripheral or cranial neuropathy F. Acute confusional state
Hematologic	A. Hemolytic anemia B. Leukopenia C. Thrombocytopenia	A. Hemolytic anemia B. Leukopenia C. Thrombocytopenia D. Lymphopenia	A. Hemolytic anemia B. Leukopenia C. Thrombocytopenia D. Lymphopenia	A. Hemolytic anemia B. Leukopenia C. Lymphopenia D. Thrombocytopenia
Immunologic	A. LE cells B. False-positive STS	A. LE cells B. False-positive STS C. Anti-DNA D. Anti-Sm	A. False-positive STS B. Anti-DNA C. Anti-Sm D. APS E. Lupus anticoagulant	A. Anti-DNA B. Anti-Sm C. APS C1. Lupus anticoagulant C2. False-positive rapid plasma reagin C3. at least medium anticardiolipin ab C4. anti-β ₂ -glycoprotein I D. Low complement (C3, C4, CH ₅₀) E. Direct Coombs test in absence of hemolytic anemia
Antinuclear antibody	Positive ANA	Positive ANA	Positive ANA	Positive ANA

*A minimum of four criteria is traditionally used to classify systemic lupus erythematosus.
ACR, American College of Rheumatology; ANA, antinuclear antibody; APS, antiphospholipid antibody syndrome; CH₅₀, 50% hemolyzing dose of complement; LE, lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics; STS, serologic test for syphilis.

climbs and reaches a peak ratio of approximately 12:1. After menopause, the disproportionate incidence rates in women decline to approximately twice those in men.^{15,16} Several studies have reported that lupus in men, though rarer, is more severe than that in women.¹⁷⁻²⁰

Age

SLE may develop at any age, although its peak incidence occurs during the childbearing years (15 to 45) in women. In comparisons with adult SLE cohorts, the small populations of children and adolescents appear to have more active SLE, especially lupus nephritis, both at initial evaluation and over time.^{20,21} When compared with adults with SLE, children receive more intensive drug therapy and accrue more damage, often related to steroid toxicity.²⁰ Young age was found to be an important independent predictor of new or worsening proteinuria on routine screening, and onset of SLE during adolescence was associated with more aggressive disease and worse outcomes than was onset later in life.^{21,22} In adult women, however, onset of SLE after menopause appears to result in slightly less severe disease than premenopausal onset does.¹⁶

Ethnicity and geography

Though probably underrecognized and underdiagnosed in developing countries, SLE does occur worldwide. International studies of the incidence and prevalence of SLE are difficult to compare given differences in case

ascertainment and design. Danchenko and colleagues²³ reviewed more than 60 studies on the incidence and prevalence of SLE in the United States, Europe, Asia, and Australia from 1950 to 2006 (Fig. 124.1), and no clear north-south or east-west pattern emerged.²³ The patterns observed in the prevalence studies were similar to those in the incidence reports. Studies of Aboriginal populations in Australia and New Zealand have found a higher prevalence and incidence in these populations than in white Australians.²⁴ SLE in the United States and United Kingdom is most prevalent in those of nonwhite descent, with reports of a higher incidence and more severe disease.²⁵⁻²⁹ In addition to the higher incidence, SLE mortality rates in black females, for example, are three to four times those in white females in the United States (Fig. 124.2).³⁰⁻³² The mean age at onset of SLE is also younger in nonwhite groups,^{26,33} and disease damage accrues more quickly.³⁴

A “prevalence gradient” in those of African origin has been reported when comparing people living in sub-Saharan Africa, where the prevalence of SLE is reportedly low, with those living in Western countries, where the prevalence of SLE is reportedly higher in individuals of African origin.³⁵ The existence of such a gradient could suggest the possibility of genetic admixture or differences in environmental exposure. The lower prevalence in Africa may be due to more severe SLE, inadequate treatment reducing survival, or a lower incidence because of competing causes of death. A study in the United Kingdom revealed a high prevalence of SLE in recent immigrants from West Africa.³⁶ No comprehensive studies of the incidence of SLE have been conducted in Africa, an inherently extremely interesting but challenging population to investigate.

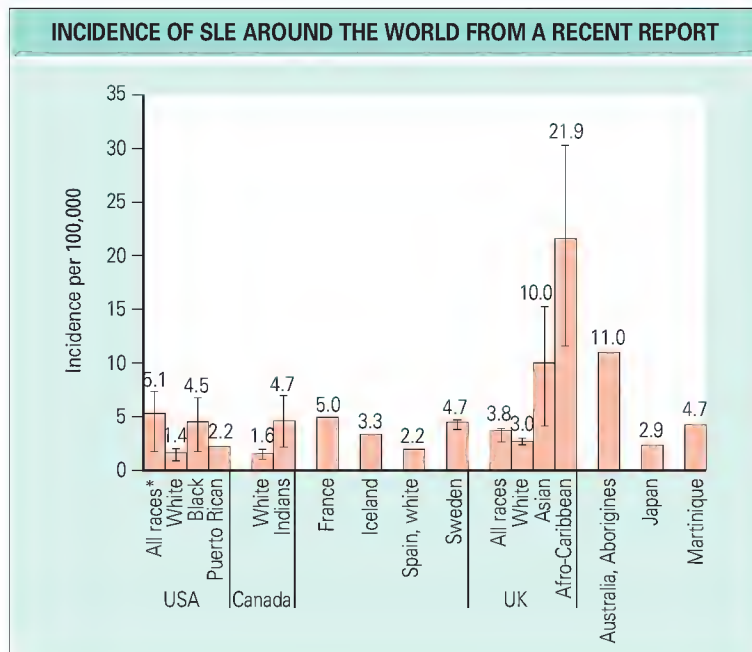


Fig. 124.1 Worldwide incidence of systemic lupus erythematosus (SLE). (From Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus* 2006;15:308-18.)

RISK FACTORS FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Complex interactions between genes and environmental exposures are probably necessary for the development of SLE. Epidemiologic studies have sought to identify potential factors that could be involved in the development of SLE in the genetically susceptible.

Hormonal/reproductive factors

Given the otherwise unexplained female excess, hormonal factors have long been of great interest in studies on the pathogenesis of SLE. Significantly lower androgen (testosterone and dehydroepiandrosterone sulfate) and higher estradiol and prolactin levels were found in women with SLE than in controls in a meta-analysis of clinical studies.³⁷ Mild or moderate hyperprolactinemia has been demonstrated in 20% to 30% of SLE patients and is associated with active disease.³⁸ Case-control studies, however, have been unable to address whether the abnormalities in hormone metabolism observed are a consequence of SLE or its treatment or are related to disease onset.

In nearly 240,000 predominantly white women monitored prospectively for up to 22 years in the Nurses' Health Study, oral contraceptives and postmenopausal hormone therapy were both associated with increased risk for incident SLE.³⁹ Furthermore, the current oral contraceptive dose of ethinyl estradiol was positively associated with SLE in women in a large study using data from the U.K. General Practice Database.⁴⁰ In both studies, risk was particularly elevated in women who recently started contraceptive use, thus suggesting an acute effect in a small subgroup of susceptible women. Data on other reproductive factors in relation to the risk for SLE have been inconsistent apart from early age at menarche, which has been found to be related to risk for SLE in several studies.^{39,41,42}

Cigarette smoking and alcohol consumption

Several,⁴³⁻⁴⁶ but not all,⁴⁷⁻⁵⁰ epidemiologic studies reported a significantly increased risk for SLE in current smokers. Seven case-control studies and two cohort studies examining smoking as a risk factor for SLE were combined in a meta-analysis, which showed an increased risk for SLE associated with current smoking (summary relative risk, 1.5; 95% confidence interval [CI], 1.1 to 2.1) but no elevated risk in past smokers.⁵¹

In a meta-analysis of six case-control studies and one cohort study investigating alcohol consumption and susceptibility to SLE, moderate alcohol intake was not significantly related to risk for SLE (summary odds ratio, 0.8; 95% CI, 0.5 to 1.2).⁵² However, one recent case-control study found that light and moderate consumption was inversely associated with SLE.⁴⁶

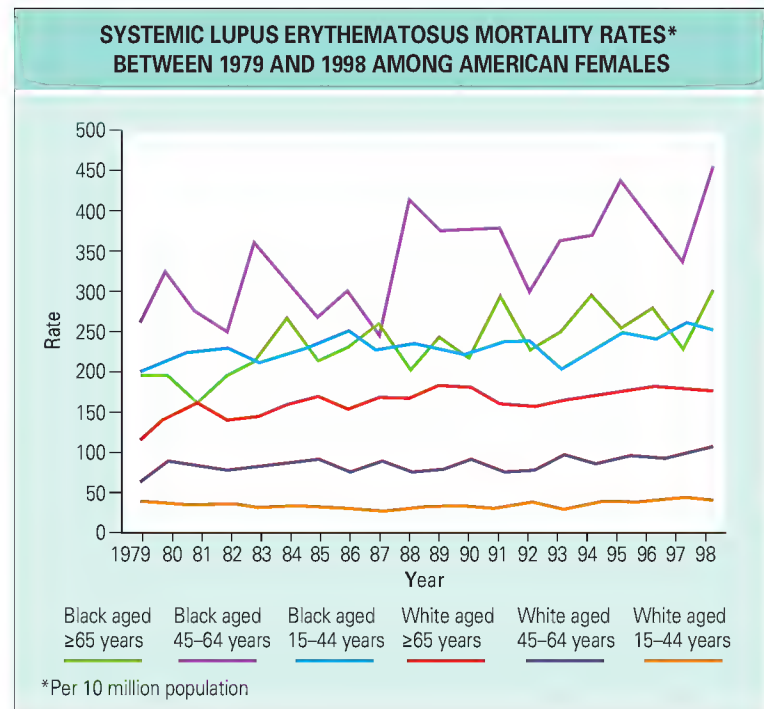


Fig. 124.2 Rates of death from systemic lupus erythematosus stratified by age and race. (From Centers for Disease Control [CDC]. Trends in deaths from systemic lupus erythematosus—United States, 1979-1998. *MMWR Morb Mortal Wkly Rep* 2002;51:371-4.)

Environmental contaminants

Environmental contaminants in common household products and hazardous waste sites and other relatively common exposures may affect sex hormone homeostasis and be associated with autoimmune manifestations.^{53,54} Epidemiologic studies have demonstrated that both recreational and occupational exposure to petroleum distillates, as well as to trichloroethylene and organochlorines, is related to risk for undifferentiated connective tissue disease⁵⁵ and SLE symptoms,^{56,57} but epidemiologic evidence has yet to conclusively connect trichloroethylene and SLE in humans. Two recent studies have reported that pesticide exposure, both agricultural and residential, is associated with increased risk for SLE.^{58,59}

Crystalline silica, a well-known adjuvant that leads to increased production of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor, has been implicated as a trigger of SLE in both murine models and epidemiologic studies. Silica in both agricultural and urban occupational settings has been associated with increased risk for SLE.^{60,61}

Small studies and case reports in the 1990s suggested that silicone breast implants may trigger SLE and related connective tissue diseases, but no association was found in 7442 Swedish women.⁶² Implants may lead to minor reductions in some complement components and a higher prevalence of antibodies to single-stranded DNA.⁶³ Studies suggesting a role of hair dye and other cosmetics, including lipstick, remain unconfirmed.^{49,64,65}

Nutritional factors and ultraviolet light

Lower levels of vitamin D have been observed in subjects with SLE than in healthy controls, but it is unclear whether this is a cause or consequence of the disease. After onset of the disease, low vitamin D levels may be related to disease activity or to the common recommendation that people with SLE avoid sun exposure.⁶⁶ In humans, lower serum and plasma levels of antioxidants have also been reported in SLE cases both before and after diagnosis.^{67,68} No protective effect of either increased vitamin D intake or a variety of antioxidant vitamins from foods or supplements was found in women in a large prospective study.^{69,70}

Exposure to ultraviolet (UV) light may trigger SLE disease flares, including photosensitive rashes, fevers, and other systemic symptoms,⁷¹ but UV light exposure is also the main source of vitamin D production. SLE flares tend to be more common during sunnier months.⁷² In a case-control study in Sweden, a history of more than one serious sunburn before 20 years of age and a sunburn-susceptible skin type were both associated with risk for SLE.⁴⁷ Because photosensitivity secondary to SLE could be present years before diagnosis, this association is difficult to interpret. In a study that used

cumulative months of occupational sunlight exposure as a proxy for past UV exposure, no overall association with risk for SLE was observed.⁷³

Infections and immunizations

Epstein-Barr virus (EBV) seropositivity rates are much higher in adults and children with SLE than in age-matched controls.^{74,75} Many potential mechanisms involving molecular mimicry between EBV and SLE antigens have been advanced.⁷⁶ However, no data have established that EBV infection is linked to future risk for the development of SLE. In fact, in a large Danish cohort study, individuals who were tested for EBV and found to be

serologically negative had a sustained increased risk for SLE that was highest in the 1 to 4 years after testing (standardized incidence rate, 6.6; 95% CI, 3.3 to 13.2). This was probably due to testing for EBV at the initial manifestation of SLE symptoms. No association was found between EBV serologic positivity, infectious mononucleosis, or severe infectious mononucleosis requiring hospitalization and risk for the development of SLE.⁷⁷

A few case reports and case series have suggested links between SLE and pneumococcal, tetanus, *Haemophilus influenzae* type b, hepatitis B, and influenza vaccinations.^{78,79} In the Carolina SLE Study, the largest epidemiologic study to examine such relationships, there appeared to be no association between hepatitis B vaccination and SLE.⁸⁰

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125

Preclinical features of lupus

■ JUDITH A. JAMES

- Autoantibodies and clinical features appear years before the diagnosis of systemic lupus erythematosus (SLE).
- Many patients with SLE have a time before meeting the classification criteria of the American College of Rheumatology, which is characterized by autoantibody production and an isolated clinical symptom.
- Individuals who transition from a preclinical lupus syndrome to eventually meet the SLE classification criteria often have milder clinical features and lupus-associated autoantibodies.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, heterogeneous disease characterized by autoantibody production and potential involvement of nearly every organ system. Consequently, diagnosis can be difficult, which has led to the development and application of classification criteria to aid in the identification of patients with SLE for clinical studies and to assist clinicians in making this diagnosis.¹⁻³ Classification as per the American College of Rheumatology (ACR) requires that a patient meet at least 4 of the 11 defined clinical or serologic parameters.^{1,2} However, new criteria devised by the SLE Inception Cohort Consortium are being proposed and require at least one clinical and one serologic criterion but allow classification based on the presence of 4 of now 17 criteria.³ Invariably, with such a heterogeneous disorder, some individuals will be seen by the health care system with some clinical features but not meeting the classification criteria for SLE. Biologically, by the time that patients receive a formal diagnosis of lupus, the majority have ongoing aggressive inflammatory processes and, oftentimes, irreversible damage (Fig. 125.1). Once these autoimmune cascades are under way, especially after standard immunomodulatory medications have been initiated, dissecting the basic concepts of disease pathogenesis can be quite difficult. Understanding which patients are at risk to transition to organ-threatening lupus is challenging, and this chapter reviews the published literature in this area.

Preclinical lupus is a broad concept that includes individuals with increased genetic risk for the development of SLE but no clinical symptoms or positive results on standard lupus serology tests; such individuals may have multiple autoantibodies and several clinical features consistent with SLE but do not meet the strict SLE classification criteria by the current ACR definition. In addition, some may argue that preclinical lupus should focus on the period before the first clinical feature develops in an individual who will subsequently be classified as having SLE, but after evidence of an immune dysregulation has been obtained so that impending pathogenic autoimmunity is imminent or ongoing. Although both considerations have merit, to be fully inclusive, this chapter will focus on preclinical lupus encompassing the entire period before classification of SLE, with a focus, when possible, on the period between the onset of detectable serologic or cellular evidence of autoimmunity and classification of SLE. Several reviews dealing with this time frame of disease have been published.⁴⁻⁶

Patients in whom a formal diagnosis of SLE is eventually made often have a period when their disease is not clear, and various investigators over the years have given these periods different names. “Latent lupus” is a term that identifies a group of patients with features consistent with SLE but who did not meet the ACR classification criteria.⁷ These individuals had to meet either one or two of the 1971 or 1982 ACR classification criteria plus any number of minor criteria, such as fever, lymphadenopathy, fatigue, low

complement, and others.⁷ Concurrently, “incomplete lupus” defines patients with fewer than four of the ACR classification criteria for SLE.⁸ In addition, “undifferentiated connective tissue disease” (UCTD) is used in a broader sense to define individuals with disease manifestations suggestive but not diagnostic of a specific connective tissue disease (CTD), which includes some individuals who may transition to SLE.⁹ As study of patients with UCTD has progressed, several groups have recognized that the individuals most likely to transition to a defined CTD usually do so early in the course of being diagnosed with UCTD. Therefore, individuals with a diagnosis of UCTD may be deemed as having early UCTD if identified within the first 1 to 3 years of the onset of symptoms. Historically, several other terms have been used in an attempt to put these patients into context, including “incipient lupus,”⁷ “lupuslike” or “probable lupus,”¹⁰ “undiagnosed connective tissue disease” (for patients with a pending evaluation), and “overlap syndromes.”¹¹ This chapter is focused on preclinical lupus and, accordingly, will concentrate on individuals who are subsequently identified as having SLE.

CLINICAL AND SEROLOGIC FEATURES OF INDIVIDUALS WHO TRANSITION TO MEET THE AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR SYSTEMIC LUPUS

Historical data partnered with longitudinal serum collections

Studying preclinical autoimmunity can be quite difficult without the appropriate patient populations and associated biospecimen collections. Through a partnership with U.S. military rheumatologists and the U.S. Department of Defense Serum Repository (DoDSR), we have assembled a cohort of individuals who joined the military when clinically healthy (with normal results on a baseline screening examination, including basic laboratory evaluations such as complete blood counts, complete metabolic profiles, and urinalysis) and at some time in the future met the classification criteria for SLE. In addition to standardized extraction of ACR classification criteria, medication, and other clinical information, serial serum specimens from before and oftentimes at or after the diagnosis of SLE were also available. Using 633 serum samples from 130 patients in whom SLE developed while in the U.S. military, 115 (88%) of the 130 SLE patients were found to have at least one autoantibody present in their available, prediagnosis serum. In some patients this initial autoantibody was present up to 9.4 years (mean, 3.3 years) before SLE was diagnosed. Antinuclear, antiphospholipid, anti-Ro, and anti-La responses were present significantly earlier (mean, 3.2 years) than anti-Sm and anti-nRNP responses (1.2 years; $P = .005$), whereas anti-dsDNA appeared 2.2 years before diagnosis. Anti-ribosomal P and anti-C1q were detectable on average 1.1 and 1.4 years before classification, respectively.^{12,13} Of the patients who had at least two positive samples, one within 6 months of diagnosis and the second more than 6 months before diagnosis, 19 of 26 (73%) had increases in their anti-dsDNA levels (mean, 743 units; SEM, 212 units) within 6 months of diagnosis; levels detected in samples that were taken more than 6 months before diagnosis were lower (mean, 227 units; SEM, 37 units; $P = .018$).¹⁴ Thus, autoantibodies were normally present in SLE patients before being classified as having SLE, occurred at different time points in linked subsets, and had increased levels before diagnosis. Overall, common SLE autoantibodies gradually accrued until the time of diagnosis and then reached a plateau.

Recent technologic advances have produced a multiplexed, bead-based method to test for the presence of autoantibodies directed against the specific protein antigens 60-kDa Ro, 52-kDa Ro, La, Sm/nRNP, nRNP, nRNP

Fig. 125.1 Hypothetic stages of the development of lupus autoimmunity. (Adapted from Harley JB, James JA. Epstein-Barr virus infection induces lupus autoimmunity. *Bull NYU Hosp Jt Dis* 2006;64:45-50. Images depicting SLE clinical features were used with permission of the American College of Rheumatology, © 2012.)

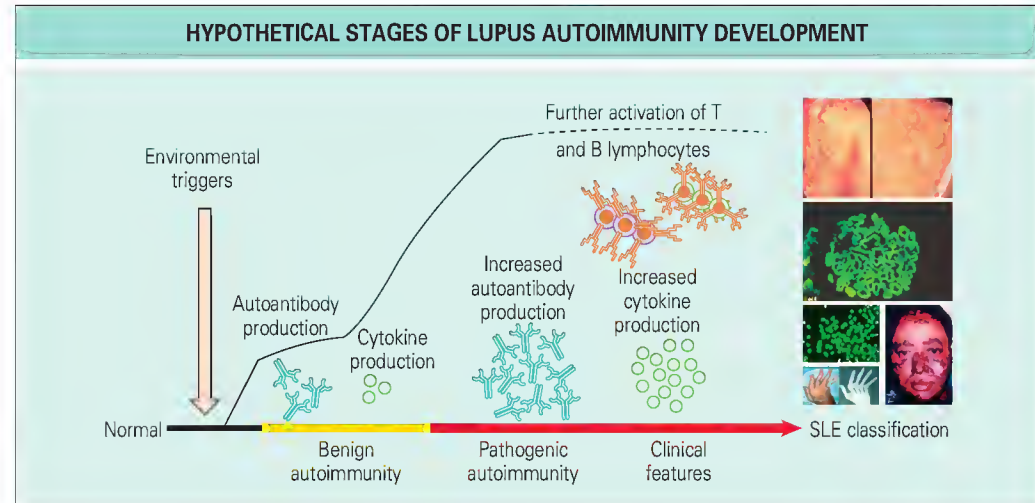
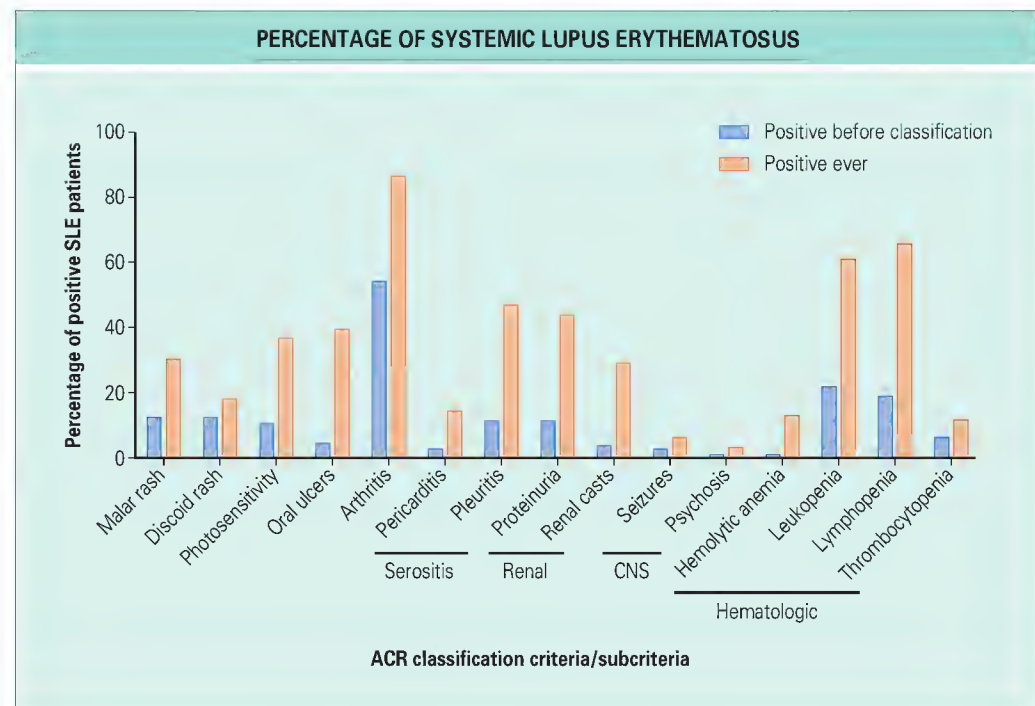


Fig. 125.2 Percentage of patients with SLE positive for each ACR classification criterion before the classification of SLE (blue bar) and cumulatively (pink bar). ACR, American College of Rheumatology; CNS, central nervous system; SLE, systemic lupus erythematosus. (Adapted from Heinen LD, McClain MT, Merrill J, et al. *Clinical criteria for systemic lupus erythematosus precede diagnosis, and associated autoantibodies are present before clinical symptoms*. *Arthritis Rheum* 2007;56:2344-51.)



70K, nRNP A, chromatin, dsDNA, Jo-1, Scl-70, centromere B, and ribosomal P. Of these 114 patients, 33 (29%) initially had a single detectable autoantibody specificity and others had multiple specificities in their first autoantibody-positive sample. Although the target varied in these 33 patients, anti-60-kDa Ro was the most common initial antibody recognized. Antibodies to nRNP A, dsDNA, and La were also commonly found as the single, initial autoantibody.¹³ Some protein targets within linked autoantibody subsets were usually targeted first: nRNP A before or concomitant with nRNP 70K and 60-kDa Ro before or concomitant with 52-kDa Ro. Others occurred with almost equal frequency; anti-Sm and anti-nRNP preceded each other equally but commonly occurred simultaneously or closer together than we could assess from the DoDSR samples. Understanding these early responses may provide the key to identifying early diagnostic markers and developing directed tolerogens for early disease, as well as to discovering potential environmental triggers of this disorder.

Several case reports have documented the onset of antiphospholipid (aPL) syndrome preceding the diagnosis of SLE by years. However, little was known about the actual prevalence and onset of aPL syndrome in patients before the diagnosis of SLE. Sera from the DoDSR were used to evaluate the temporal relationship of aPL antibodies and clinical SLE classification.¹⁵ A total of 24 cases (18.5%) were positive for IgG or IgM aPL antibodies before the diagnosis of SLE. Anticardiolipin antibodies (aCL) appeared from 7.6 years before the diagnosis of SLE to within the same month as the diagnosis of SLE (mean, 3.0 years before SLE classification). In addition, the presence of aCL before clinical classification was associated

with a more severe disease outcome. These patients eventually met an average of 6.1 of the 11 SLE classification criteria as compared with 4.9 criteria for other patients ($P < .001$). The early aCL-positive population also more frequently had renal disease, central nervous system (CNS) disease, thrombocytopenia, and clotting events. In this population, aCL preceded the initial thrombotic events by a mean of 3.1 years.¹⁵

Comparison of the onset of symptoms to the onset of lupus autoimmunity identified 104 patients (80%) who had at least one clinical criterion present before classification.¹³ Discoid rash and seizures had the earliest mean onset times: 1.74 and 1.70 years before diagnosis. Even though the initial clinical findings varied widely between patients, the most common early symptom was arthritis, which occurred in 57 of 104 (55%) individuals with symptoms before the diagnosis of SLE (Fig. 125.2). Males were significantly more likely to have renal involvement as a first manifestation ($\chi^2 = 9.24$; $P = .003$). Since arthritis was the most common initial symptom, patient samples were analyzed for IgG rheumatoid factor (RF) to determine whether RF preceded the onset of arthritis. Of the 130 patients, 17 (13%) were found to have RF, and inflammatory arthritis eventually developed in 16 of the RF-positive patients. RF preceded the development of arthritis in 15 of these 16 cases (z value = 10.2; $P < .0001$), and RF was present on average 2.1 years before the first documented arthritis symptom. ACR-defined renal disease developed in 38 (48%) of the 80 patients who were positive for anti-dsDNA ($P = .05$).¹³ Of these 38 patients, 35 (92%) had anti-dsDNA antibodies before or concurrently with the development of ACR-defined renal disease (z value = 13.3; $P < .0001$). However, in three

TABLE 125.1
Summary table of studies with patients who transitioned to the American College of Rheumatology classification of systemic lupus from a previously identified preclinical state

Year	Reference	Patient population	No. with transition to SLE (%)	Predictors of transition	Follow-up (yr)
1989	Ganczarczyk et al ⁷	Latent lupus (1-2 of ARA 71 or 82), additional minor criteria	7 of 22 (31.8)	No predictors	8 (5-15)
1996	Calvo-Alen et al ²³	Started with 213 with eUCTD (symptoms for less than 1 yr) and had complete 5-yr data on 143	18 of 143 (12.6)	Predictors: discoid lupus, serositis, ANA homogeneous, and anti-Sm by precipitation	5 (1-5)
1997	Mestanza-Peralta et al ²⁸	ITP (splenectomy)	14 of 115 (12.2)	No clear predictors; arthritis, serositis, autoantibodies develop	7.2 (0.08-32.8)
1997	Zimmerman et al ²⁹	ITP (pediatric)	5 of 87 (5.75)	Multiple autoantibodies (dsDNA, aPL, plus others) increased risk for transition	5.5 (1-15)
1998	Danieli et al ²⁴	eUCTD, 84 patients	7 of 33 (21.2)	Fever and anti-DNA antibodies	5 (1-5)
1998	Mosca et al ²⁵	UCTD (1 autoantibody and 1 clinical feature)	12 of 91 (13.2)	Multiple autoantibodies; less sicca, Raynaud phenomenon, and photosensitivity	3 (1-8)
2000	Belfiore et al ³⁰	UCTD	5 of 57 (8.77)	Anti-60 kDa alone associated with transition	5 (1-23)
2001	Cavazzana et al ²⁷	UCTD (retrospective study)	45 of 148 (30.4)	Anti-dsDNA antibodies	5 (1-9)
2004	Ståhl Hallengren et al ⁵¹	ILE (positive ANA and at least 1 ACR clinical criterion)	16 of 28 (57.1)	Malar rash and anticardiolipin antibodies	5.3 (1-10)
2010	Lastrup et al ³²	ILE	7 of 26 (26.9)	Mild disease, absence of renal and CNS involvement	8 (1-8)
2012	Olsen et al ³⁶	ILE	3 of 22 (13.6)	Risk score of female, age <40, and select autoantibody responses	2.4 (0.5-6.5)

ANA, antinuclear antibody; aPL, antiphospholipid; ARA, American Rheumatism Association; CNS, central nervous system; dsDNA, double-stranded DNA; eUCTD, early undifferentiated connective tissue disease; ILE, incomplete lupus; ITP, idiopathic thrombocytopenia purpura; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease.

patients, evidence of an ACR-defined renal disorder appeared before anti-dsDNA was detectable. These data support associations between lupus-specific autoantibodies and specific disease symptoms; however, how the concentration, specificity, and affinity of these autoantibodies change during the preclinical period is not yet known.

The DoDSR has also served as a way to initially examine whether early intervention with antimalarial agents, such as chloroquine or hydroxychloroquine (HCQ), could influence the progression of lupus autoimmunity or clinical onset of disease. Of the 130 patients in the initial cohort, 26 received HCQ before meeting four ACR criteria. Patients treated with HCQ before diagnosis had a longer ($P = .018$) time between the onset of the first clinical symptom and SLE classification than did matched, non-HCQ-treated SLE patients (median times of 1.08 versus 0.29 year, respectively). Patients treated with prednisone before being classified as having SLE also progressed more slowly to meet the classification criteria than did matched non-prednisone-treated SLE patients ($P = .011$). Those who received both HCQ and prednisone ($n = 13$) had a significantly longer time between the initial clinical symptoms and SLE classification than did patients treated with only prednisone ($n = 14$) before diagnosis ($P = .03$). Differences in median times between patients who received nonsteroidal antiinflammatory drugs (NSAIDs) before diagnosis and patients who did not receive NSAIDs were not significant ($P = .19$). Interestingly, patients treated with HCQ also had a lower rate of autoantibody accumulation and a decreased number of autoantibody specificities at and after diagnosis.¹⁶ These findings suggest that early identification of individuals at increased risk for the development of SLE is meaningful since interventions with low-toxicity immunomodulatory agents offer advantages early in the course of autoimmune events.

Retrospective chart review of inception cohorts

Evaluation of preclassification events by retrospective chart review has provided additional insight into the early clinical features of lupus. As one example, a multicenter study of 513 Danish patients with SLE published in 1998 evaluated early clinical manifestations by detailed retrospective chart review. Discoid rash (50 patients [10%], -4.5 years before classification), arthritis (259 patients [50%], -3.0 years), photosensitivity (136 [27%], -1.8 years), malar rash (162 [32%], -1.4 years), and Raynaud phenomenon (78 [15%], -1.7 years) were some of the earliest clinical manifestations found before the classification of SLE.¹⁷

Transition of latent lupus to systemic lupus

In 1989 the Toronto Lupus Group identified a group of 98 individuals who met either one or two of the 1971 or 1982 ACR classification criteria plus any number of minor criteria, such as fever, lymphadenopathy, fatigue, or low complement. Of these individuals, SLE was diagnosed in six within the first year of follow-up, and they were excluded. Also, 70 additional patients had been observed for less than 5 years, which left 22 patients meeting their definition of latent lupus with at least 5 years of follow-up. Of these 22 individuals, 7 (32%) accrued additional criteria leading to the classification of SLE (Table 125.1). No strong associations with baseline clinical or serologic findings were present that could differentiate patients who would transition to SLE during follow-up from those who had persistent latent lupus⁷; however, patients who transitioned appeared to have milder symptoms than did those of their standard SLE cohort (e.g., no renal or CNS involvement).

Transition of patients with undifferentiated connective tissue disease to systemic lupus

One important issue is whether patients with UCTD transition to SLE and, if so, whether those with UCTD at the highest risk of transitioning can be identified by clinical, demographic, or serologic features. Studies of patients with UCTD over the past 2 decades have led to improved recognition of those at the highest risk for the development of defined CTDs, such as SLE, as opposed to the approximately 75% of UCTD patients who will not.^{9,18-23} To this, one may add a 1991 multi-institutional cohort study of 213 U.S.-based early UCTD patients (within 1 year of identification), which has helped detect patients in this group who would transition to SLE. After 5 years of follow-up, 67% had transitioned to a specific CTD (143 individuals), with 18 of these individuals transitioning to SLE (18 of 213, or 8.5% of the original cohort).²² In a univariate analysis, individuals who were more likely to transition to SLE were younger and black, in addition to having symptoms or serologic findings of alopecia, serositis, discoid lesions, anti-dsDNA, anti-Sm, positive antinuclear antibody (ANA) with a homogeneous pattern, Coombs positivity, or a false-positive syphilis test result (which is now recognized to probably represent aPL responses). Regression modeling retained discoid lesions, serositis, anti-Sm (by precipitin), and ANA homogeneous patterns as the best predictors of UCTD patients who would evolve to SLE²² (see Table 125.1).

In a study from a hospital in rural Italy, 84 patients with early UCTD (symptom onset within the past year) were observed for 5 years for transition to another CTD.²⁴ The baseline characteristics of these individuals were typical of UCTD patients and included Raynaud phenomenon (54%), arthralgia (51%), arthritis (23%), fever (23%), and asthenia (16%). A defined CTD developed in 33 of the 84 patients (39%), including SLE in 7 (8.3% of the original cohort). Univariate analysis showed anti-dsDNA, aCL, and fever to correlate with subsequent SLE disease classification; aCL responses, however, were not significant in the multivariate analysis.²⁴ A 5-year follow-up study of 165 Italian UCTD patients with symptoms for less than 2 years showed 10 individuals transitioning to a defined CTD, including 5 with SLE.²⁵

Another study of UCTD patients (at least one clinical feature and autoantibody positive) from Pisa, Italy, were reported with 1 year²⁶ and 5 years²⁷ of follow-up. After 5 years, 83 UCTD patients were available for inclusion, and 18 had transitioned to SLE (22%). The presence of aCL responses and the presence of multiple autoantibody specificities were associated with subsequent SLE classification (see Table 125.1). In another study from Milano, Italy, published in 2001, 148 patients with UCTD were retrospectively evaluated. Of these, a well-defined CTD developed in 36 (average of 4.5 years of follow-up), including 11 with SLE (7.4% of the original cohort). Anti-dsDNA again predicted the evolution to SLE classification.²⁷

A large group of 665 UCTD patients were identified, recruited, and observed in Hungary between 1994 and 1999, with the exclusion of 50 individuals with only Raynaud phenomenon and 31 with only polyarthritis.³³ Of these 665 individuals, a defined CTD developed in 230, including 28 with SLE. Fever, serositis, photosensitivity, ANA homogeneous pattern, and anti-dsDNA were each associated with the subsequent development of SLE. Patients with SLE and a documented UCTD period were more likely to be older and have more serositis, less skin rash, less renal involvement, and less hemolytic anemia than were SLE patients from this same group without a documented UCTD period.³³ In a study from Portugal, 184 patients with UCTD were identified on the basis of positive ANA and at least one clinical feature of CTD. Of these, 74 had a lupus-like disease (based on clinical features and autoantibody profiles); however, longer-term follow-up of these individuals is not readily available. Finally, a study from the Netherlands investigated ANA-positive individuals referred for evaluation in a rheumatology clinic (excluding anti-dsDNA-positive individuals) and monitored them prospectively. Of these 65 individuals with a mean follow-up of 9.3 years, a specific rheumatic disease diagnosis could be established in 38, including 6 who transitioned to SLE after a median of 2.2 years.³⁴

Although the vast majority of patients with UCTD remain in the UCTD category (see Table 125.1), some information about preclinical lupus can be gleaned from the cumulative transition of 93 individuals to an SLE classification in these populations. An ANA homogeneous pattern and individuals positive for anti-dsDNA, anti-Sm, and aCL are at higher risk for transitioning to SLE, as are individuals with multiple autoreactivities or multiple clinical features. Please see reviews¹⁸⁻²⁰ for more detailed information.

Transition of incomplete lupus erythematosus to systemic lupus

Another series of studies observed groups of patients termed as having incomplete lupus erythematosus (ILE) for evaluation and development of predictors to identify those in whom SLE will subsequently develop. Based on the somewhat overlapping definitions, a subset of UCTD patients could also be termed as having ILE; however, these sets of data are delineated in this chapter based on the designation used in the respective manuscript. One of the first papers to discuss ILE and to study these patients was published in 1989.⁸ In this study, 38 patients with ILE (defined as meeting at least one and up to three ACR SLE classification criteria) were monitored for an average of 1.6 years, and only 2 patients transitioned to the SLE classification.⁸ Another study from Puerto Rico used a similar ILE definition and observed 87 patients for a mean of 2.2 years who met at least one ACR clinical criterion for SLE. Of these 87 individuals, 8 transitioned to SLE in the follow-up period. Patients who evolved to SLE were more likely to have photosensitivity, malar rash, oral ulcerations, anti-dsDNA responses, and low levels of C3.³⁵ CNS, renal, and serositis ACR criteria were quite infrequent in the ILE patients who transitioned to SLE in this cohort.

Another large collaborative study enrolled 122 patients in whom ILE had been diagnosed less than 1 year earlier (autoantibody positive with at least one ACR SLE clinical criterion) from 10 centers. On enrollment, 22 of these individuals were classified as having SLE. The remaining 100 ILE patients were evaluated annually for at least 3 years, and 3 of them transitioned to SLE. The most common baseline features in these ILE patients were leukopenia, fatigue, arthritis, and mucocutaneous involvement. The number of individuals who transitioned was insufficient to identify predictors of the

development of SLE. In a Swedish study of 28 ILE patients (fewer than four ACR criteria) with an average follow-up of 5.3 years, 16 individuals transitioned to the SLE classification (57%). Malar rash, aCL responses, and thrombocytopenia were all increased in the subset of individuals who transitioned to SLE.³⁶ An 8-year prospective study of 37 ILE patients (autoantibody positive with at least two but less than four ACR criteria) demonstrated that 7 ILE patients (19%) transitioned to the SLE classification (3.64 per 100 person-years of follow-up).³⁷

Finally, a U.S.-based study monitored 22 ILE patients (fewer than four ACR criteria) for an average of 2.4 years and showed that 3 of the 22 (14%) transitioned to the SLE classification. All patients who transitioned were female and younger and had increases in IgG autoreactivity. Individuals who transitioned were more likely to have autoantibodies against proliferating cell nuclear antigen, β_2 -microglobulin, C1q, and hemocyanin at baseline than were those who remained ILE, and those who transitioned had significant increases in IgG responses against La and liver cytosol type 1. A quantitative risk score based on female gender, baseline ANA higher than 200 units, baseline age younger than 40 years, increase in overall IgG autoreactivity on an autoantigen array, and presence of IgG responses against seven baseline autoantigens was devised and yielded strong differentiation between ILE patients who transitioned to the SLE classification and those who remained ILE ($P = 1.38 \times 10^{-7}$).³⁸ Although nearly all the longitudinal studies of ILE patients found that individuals who transitioned to the SLE classification had relatively mild SLE without major organ involvement, nephritis and serositis developed in one of the patients in the Olsen study,³⁶ and a case report of transition of an ILE patient to severe SLE with major organ vasculitis was reported.³⁸ A summary of highlights from these studies is provided in Table 125.1. In total, an interim summary of the many studies on ILE is that approximately 10% of these patients will transition to SLE, oftentimes with a milder course of disease that lacks nephritis, vasculitis, or major CNS involvement.

New studies are focusing on serologic biomarkers, which are common in patients with incomplete lupus as opposed to patients classified as having SLE and healthy controls. Using a microarray-based platform with 70 autoantigens, elevated levels of at least one IgG autoantibody were detected in 19% of ILE patients versus 26% of SLE patients (both of which were higher than in unaffected family members of lupus patients or healthy controls). In addition, IgG-to-IgM autoantibody ratios showed a stepwise increase from healthy controls to ILE to SLE in this study.³⁹ A newer study from the same group compared 27 SLE patients, 24 ILE patients, 22 unaffected first-degree relatives, and 11 unaffected, unrelated healthy controls. A set of 63 interferon genes were upregulated in 83% of the SLE patients and in 50% of the ILE patients versus no interferon-high individuals in the two control groups. In both the SLE and ILE patients, interferon-high status was associated with a subset of IgG autoantibody responses primarily targeted against DNA- or RNA-binding proteins. Additional longitudinal evaluation of ILE patients, both in the interferon-high and in the interferon-low groups, is necessary to see whether ILE patients with elevated interferon signatures are at higher risk for transition to SLE.⁴⁰

Transition of patients with another systemic autoimmune disease to systemic lupus

A small subset of SLE patients are initially seen with another systemic autoimmune disease and then subsequently transition to SLE meeting the ACR disease classification criteria. A few examples of these disorders include idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenia purpura (TTP), aPL syndrome, discoid lupus, and subacute cutaneous lupus.

Thrombocytopenia is an initial symptom in a small subset of SLE patients (5% to 14%)^{41,42} but has been associated with earlier mortality.⁴³ Therefore, the ability to identify the subset of patients with clinical ITP or TTP who may transition to SLE is clinically important. A number of different studies have evaluated the frequency and associated factors in ITP patients who would transition to SLE. A 1997 study from Mexico of 115 ITP patients requiring splenectomy observed on average for 7.2 years showed that SLE developed in 14 patients (12%).²⁸ Another study from Turkey examined 321 ITP patients, 150 of whom had longitudinal follow-up (average, 2.5 years). Of these 150 individuals, 6 transitioned to SLE.⁴⁴ In pediatric-onset ITP, a 2006 study of 222 children from Israel with 4.2 years' average follow-up found that 3.6% (or 8 of 222) were subsequently classified as having SLE.⁴⁵ Pediatric ITP patients who transitioned to SLE were more likely to have chronic ITP and have higher ANA titers.⁴⁵ Similar findings were demonstrated in a 1997 U.S.-based study of 87 children with ITP in which 9 children transitioned to SLE or a lupuslike disease, all of whom were ANA positive at diagnosis of ITP.²⁹ One pediatric study from Toronto followed the course of 35 children with TTP and found that 9 (26%) met the criteria for

SLE whereas an additional 8 had features consistent with an incomplete lupus phenotype. The best predictor of which TTP patients would transition to SLE was high-grade proteinuria at diagnosis of TTP.⁴⁶

SLE may subsequently develop in a small subset of patients with discoid lupus, and they are usually autoantibody positive at initial evaluation. In a prospective cohort of 150 U.S.-based patients with SLE, 14 originally had discoid lesions and subsequently transitioned to SLE between a few months and 20 years later.⁴¹ Discoid lesions were also found on average years before SLE classification in a Danish cohort (on average 4.5 years before classification¹⁷) and in a U.S. military cohort (on average 3.1 years before classification¹³). Please see Chapter 126 for more information on patients who may transition from one of these other autoimmune rheumatic disorders to the SLE classification.

Transition of patients with only autoantibody production or otherwise dysregulated immune systems to systemic lupus

An earlier preclinical phase of SLE may be when an individual who will subsequently reach the SLE classification has no clinical symptoms but has autoantibodies or other measures of immune dysregulation. Although serologic studies of samples from individuals during this period have demonstrated its existence, longitudinal follow-up of autoantibody-positive, healthy individuals to identify those at highest risk for the development of SLE are not currently available, and this remains an area for future investigation. These studies will be challenging because many healthy individuals may have detectable autoantibodies without clinical symptoms and a systemic autoimmune rheumatic disease will probably not develop in most of them. Please see references 47 to 50 for prevalence and predictors of autoantibody positivity in healthy individuals.

REASONS TO STUDY PRECLINICAL LUPUS AND AREAS FOR FUTURE INVESTIGATION

Several reasons suggest potential benefits in studying preclinical lupus (see Table 125.2 for a partial list). By studying individuals during the preclinical phase, investigators are able to study early disease events without confounding these studies by the influence of immunosuppressive medications, by the sequelae of damage, or by ongoing aggressive inflammation. In addition, by studying patients during these preclinical or early clinical stages, individuals at increased risk for full SLE development or for severe SLE complications may be able to be identified, which could lead to the potential for early intervention before permanent damage occurs. These studies may also result in better understanding of some of the earliest events in lupus

TABLE 125.2
Select reasons for studying preclinical lupus

Reason	Benefit
Understanding disease pathogenesis	Not confounded by disease damage or concurrent medications
Identify at-risk individuals	Allow close monitoring for development of disease and implement early interventions before damage
Prevention studies	Allow development and implementation of prevention studies
Assess disease pathways	Development of disease-specific therapeutic interventions
Identify biomarkers of early disease	Possible development of early screening tests for at-risk individuals; development of improved diagnostics

autoimmunity, which could lead to improved directed diagnostics and identification of biomarkers of early disease activity and potentially provide insight into novel pathways for therapeutic development. In aggregate, multiple studies have demonstrated that selected demographic, clinical, and serologic features can help identify individuals at the highest risk for the subsequent development of SLE.

Early identification will allow closer monitoring and early treatment of major organ involvement. Early intervention would facilitate modulation of the dysregulated immune and inflammatory responses that lead to end-organ damage and the associated increased morbidity and early mortality. Therefore, the field is now poised to be able to use this information to design prospective natural history studies for assessing immune parameters and other serologic responses to identify biomarkers of disease onset and understanding mechanisms of disease to drive directed therapeutic development. Additional cohorts of longitudinal information associated with paired bio-specimens will provide opportunities to ask questions directed at disease pathogenesis and mechanisms of disease, which in turn will provide information on biomarker development, prognostic algorithm development, directed therapeutics, and potential prevention trials.

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126

Clinical features of systemic lupus erythematosus

■ OLGA DVORKINA ■ ELLEN M. GINZLER

- Systemic lupus erythematosus (SLE) is an inflammatory multisystem disease of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis.
- Inflammation in various organs or tissues is due to immunologic aberrations affecting both the innate and adaptive arms of the immune system.
- Serologic abnormalities such as the presence of autoantibodies occur in a predictable course in patients with SLE before the development of clinical features.
- Clinical manifestations may be constitutional or specific, depending on the organ systems involved, including the skin and mucous membranes, joints, kidneys, brain, serous membranes, lungs, heart, and occasionally, the gastrointestinal tract.
- Patients with SLE have various complications caused by the disease or its treatment, in addition to comorbid conditions, such as diabetes mellitus, that may complicate the course of the disease.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory, multisystem autoimmune disease of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis. Its clinical manifestations may be constitutional or specific, depending on the organ systems involved. The skin and mucous membranes, joints, kidneys, brain, serous membranes, lungs, heart, and occasionally, the gastrointestinal tract may be affected. Inflammation in various organs or tissues is due to immunologic aberrations affecting both the innate and adaptive arms of the immune system.

CLINICAL FEATURES

Serologic abnormalities such as autoantibodies develop in a predictable course in patients with SLE before the development of clinical features.¹ The initial feature leading to the diagnosis of SLE, however, can be variable and ranges from general to organ-specific manifestations, with arthritis being the most common.¹

General manifestations

Constitutional complaints such as malaise, fatigue, fever, anorexia, and weight loss are commonly seen in SLE. These may be the initial features or may be due to complications of the disease.

Fatigue occurs frequently and is a disabling symptom for many patients with SLE. Its strongest correlation is with depressive features, and it is frequently independent of serologic or other clinical manifestations of lupus.²

Fever in SLE is a challenging clinical problem. About 42% of patients with SLE have fever as a manifestation of active lupus. Fever may also result from infections, medications, or malignancies. Lupus is a cause of fever of unknown origin in less than 5% of patients. Although involvement of some organ systems, such as skin disease or arthritis, is common in SLE, any system may be involved in variable combinations with other organ systems. Thus, SLE may have such diverse clinical manifestations as rash and arthritis, pleurisy and proteinuria, or Raynaud phenomenon and seizures or fever

of unknown origin. It is only with a high index of suspicion, a careful history and physical examination, and appropriate laboratory confirmation that the diagnosis can be ascertained.

Cutaneous manifestations

Cutaneous lupus can lead to disfigurement in visible areas such as the face, scalp, neck, and hands and produce major psychological stress, occupational disability, and lower health-related quality of life. A new scoring system—the Cutaneous Lupus Erythematosus Disease Area and Severity Index—was therefore developed to differentiate between disease activity and damage. This activity scale measures erythema, scaling, hypertrophy, and mucous membrane disease, whereas the damage scale measures hyperpigmentation, atrophy, and scarring alopecia.³

The skin lesions seen in patients with lupus can be classified into those that are lupus erythematosus (LE) specific and LE nonspecific. Box 126.1 lists the skin lesions per modified Gilliam classification.⁴

LE-specific lesions can be classified into acute, subacute, and chronic.

Acute lesions may be localized or generalized.⁵ The best recognized localized skin manifestation of SLE is the “butterfly” rash or malar erythema (Fig. 126.1), which is usually manifested acutely as an erythematous, elevated lesion that is pruritic or painful and occurs in a malar distribution. This rash spares the nasolabial folds because of their photoprotected area and fluctuates with disease activity. It may last from days to weeks. Its presence facilitates the diagnosis of SLE, and it is commonly accompanied by other inflammatory manifestations.

Subacute cutaneous lupus erythematosus (SCLE) refers to a distinct cutaneous lesion that is widespread, nonscarring, nonindurated, and photosensitive. This lesion is intermediate between the evanescent malar rash of active lupus and chronic scarring discoid lesions. SCLE lesions commonly occur in sun-exposed areas and may be generalized. They originate as erythematous papules or small plaques with a slight scale and may evolve further into the papulosquamous variant and mimic psoriasis or lichen planus, or they may merge to form polycyclic or annular lesions (Fig. 126.2). SCLE may be accompanied by serologic abnormalities, the most common of which is antibody to Ro (SSA), which has been demonstrated in up to 90% of patients. SCLE lesions are also seen in association with anti-Ro antibodies in other autoimmune disorders such as Sjögren syndrome and rheumatoid arthritis.⁵

Discoid lesions are chronic cutaneous lesions that may occur in the absence of any systemic manifestations—as discoid lupus—or may be a manifestation of SLE. These lesions often begin as erythematous papules or plaques with scaling that may become thick and adherent with a hypopigmented central area. As the lesion progresses, follicular plugging occurs along with the development of scarring with central atrophy (Fig. 126.3). Discoid lesions may occur in the malar region or in other sun-exposed areas. Lesions in the scalp lead to extensive and often permanent alopecia. Discoid lupus may be localized or generalized, the latter being more likely to be associated with systemic features and serologic abnormalities.

Firm, deep subcutaneous nodules may develop as a result of lobular panniculitis and are known as lupus profundus.

Mucocutaneous lesions include ulcers of the mouth, nose (Fig. 126.4), or genital area. Nasal septal erosions occasionally lead to nasal septal perforation.

LE-nonspecific lesions are seen frequently in SLE patients and correlate more with lupus activity. Alopecia is a common feature of SLE. Hair loss may be diffuse or patchy. Alopecia may be due to lupus hairs, which are brittle and break off easily, especially in the temporal and parietal areas of the scalp (Fig. 126.5). Alopecia areata occurs less frequently. It may be associated with exacerbations of the disease, in which case hair tends to

BOX 126.1 GILLIAM CLASSIFICATION OF LUPUS ERYTHEMATOSUS (LE)-ASSOCIATED CUTANEOUS LESIONS**LE-specific skin lesions****Acute**

- Localized
- Malar “butterfly” rash
- Generalized erythema

Subacute cutaneous lupus

- Annular/polycyclic
- Papulosquamous (psoriasiform)

Chronic lupus

- “Classic” discoid LE
- Localized discoid
- Generalized discoid
- Hypertrophic (verrucous) discoid LE
- Lupus profundus
- Mucosal LE
- Lupus tumidus
- Chilblains lupus
- Discoid LE/lichen planus overlap

LE-nonspecific lesions**Cutaneous vascular disease**

- Vasculitis
- Leukocytoclastic
- Palpable purpura
- Urticarial vasculitis
- Periarthritis nodosa–like

Vasculopathy

- Degos disease–like
- Atrophy blanche
- Periungual telangiectasia
- Livedo reticularis
- Thrombophlebitis
- Raynaud phenomenon
- Erythromelalgia

Alopecia (nonscarring)

- “Lupus hair”
- Telogen effluvium
- Alopecia areata

Sclerodactyly**Rheumatoid nodules****Calcinosis cutis****LE-nonspecific bullous lesions**

- Epidermolysis bullosa–like bullous LE
- Dermatitis herpetiformis–like bullous LE
- Pemphigus erythematosus
- Bullous pemphigoid
- Porphyria cutanea tarda

Urticaria**Papulonodular mucinosis****Anetoderma/cutis laxa****Acanthosis nigricans (type B insulin resistance)****Erythema multiforme****Leg ulcers****Lichen planus**

Fig. 126.1 Erythematous rash in a malar distribution. Sparing of the nasolabial folds is distinctly seen in this patient.



Fig. 126.2 Subacute cutaneous lupus erythematosus rash: psoriasiform appearance.



Fig. 126.3 Discoid lupus erythematosus with facial involvement. Note the central scarring with hypopigmentation.

regrow when the disease is under control. Alternatively, it may result from the extensive scarring of discoid lesions, in which case it is irreversible. Alopecia may also be drug induced, for example, from corticosteroids or cytotoxic drugs.

Other nonspecific mucocutaneous lesions seen in individuals with SLE include vesiculobullous and urticarial lesions. Urticarial lesions occur in 5% to 10% of patients, are often chronic, and typically represent cutaneous leukocytoclastic vasculitis, which is frequently associated with hypocomplementemia and characterized by persistent wheals (lasting 48 to 72 hours).

Vasculitic lesions may be manifested as palpable purpura, nail fold or digital ulcerations, subcutaneous nodules, livedo reticularis (Fig. 126.6), splinter hemorrhages, and pulp space and palmar/plantar lesions simulating Osler nodes and Janeway lesions. Digital lesions are usually painful secondary to finger pulp inflammation or ischemic changes and can result in



Fig. 126.4 Mucosal ulcers seen on the hard palate and nasal mucosa.



Fig. 126.5 Alopecia affecting the frontal region of the scalp with lupus hairs.



Fig. 126.6 Livedo reticularis seen over the palmar surface of the hand with digital ulcerations and gangrene.

gangrene⁶ (see Fig. 126.6). Secondary Raynaud phenomenon occurs in more than 50% of patients with SLE and, when severe, can lead to ulcerations, with some progressing to gangrene.

Photosensitivity, reported in more than 50% of patients with SLE, is defined as an abnormal cutaneous reaction to ultraviolet radiation (UVR).⁷ Both LE-specific and LE-nonspecific skin disease may be induced or exacerbated by UVR. In addition to the skin reaction, exacerbations of systemic disease may develop. The mechanism for the photosensitivity is unknown, but it has been suggested that lymphocytes from SLE patients are sensitive to 360- to 400-nm light because of a clastogenic factor in these cells. An increase in apoptotic nuclei was found in the upper epidermal layer of UVR-induced skin lesions. The damaged chromatin may then provide a substrate for autoantibody production, with the subsequent development of a local or systemic inflammatory response. Indeed, studies have shown that ultraviolet B light increases the binding of antibody probes for Ro (SSA) and La (SSB) on keratinocytes in a dose-dependent manner.

Musculoskeletal features

Involvement of the joints as either arthralgia, arthritis, or both is one of the earliest and most common initial manifestations of SLE. Active arthritis, often associated with other features of a new lupus manifestation or active exacerbation, may include swollen inflamed joints with effusions or synovitis (or both) on physical examination.⁸ These symptoms often regress or resolve when other manifestations of active lupus respond to treatment. The deforming arthritis in systemic lupus can be categorized as either a mild deforming polyarthritis, an erosive symmetric polyarthritis with rheumatoid arthritis–like deformities, sometimes referred to as “rhumus,” or a nonerosive Jaccoud arthropathy. Jaccoud arthropathy is a generalized capsular and periarticular condition that affects the hands and results in ulnar drift with subluxation of the metacarpophalangeal joints because of joint instability secondary to lax joint capsules, tendons, and ligaments (Fig. 126.7).

Radiographic findings in patients with Jaccoud arthropathy are usually minimal and consist of subluxations and deformities with no evidence of erosions. In rhupus, the findings are more characteristic of rheumatoid arthritis, with erosions seen in the metacarpophalangeal joints. Magnetic resonance imaging (MRI) identifies edema of the capsule and tenosynovitis in patients with Jaccoud arthropathy, whereas in those with rhupus, MRI shows signs of active synovitis and erosions.

Tenosynovitis is seen in 10% to 13% of SLE patients. Autopsy findings show more marked inflammation in the tendon sheaths than in the synovium. The cellular infiltrate in tendon sheaths is mainly lymphocytes and plasma cells with occasional neutrophils and eosinophils. Marked disruption of collagen fibers within the tendon and sometimes fibrosis or nodules within tendon sheaths have been observed.

Painful, tender rheumatoid nodules histopathologically identical to those present in rheumatoid arthritis have been found in 5% to 7% of SLE patients. They may be an early or a late manifestation and are usually transient and slowly regress with response to therapy. These nodules have been found in the absence of rheumatoid factor and can also be detected in the synovium or tendon sheath.

Patients with SLE may have muscle pain or weakness, or both, secondary to inflammatory myositis, drug-related myopathy, or fibromyalgia. The histologic features of myositis in SLE may not be as striking as in idiopathic polymyositis. Ultrastructural pathology in patients with SLE includes inflammation along with muscle atrophy, microtubular inclusions, a mononuclear cell infiltrate, and fiber necrosis. Traditionally, steroid-induced myopathy is well recognized but may present a diagnostic and therapeutic challenge. With the acceptance of hydroxychloroquine and lipid-lowering statins as common standard-of-care medications for patients with SLE, their association with toxic myopathy must be considered in individuals with muscle complaints.^{9,10}

Fibromyalgia has been identified in 22% of patients with SLE and is somewhat more common than in patients with other arthritides. It is more prevalent in the white population and in patients with concomitant anxiety or affective disorder and to a lesser extent in those with poorer self-reported physical functioning.¹¹ Fibromyalgia has been shown to contribute to reduced quality of life in patients with SLE.

Other rare musculoskeletal features have also been reported in patients with SLE, including relapsing polychondritis and progressive cystic bony lesions. This subset of patients has more central nervous system (CNS) disease, synovitis, and other radiologically observed skeletal abnormalities along with higher concentrations of acute-phase reactants.

In addition to the musculoskeletal manifestations related to autoimmune phenomena, patients with SLE exhibit many complications of previous active disease or its treatment. Distinguishing septic arthritis from active



Fig. 126.7 (a) Patient with Jaccoud arthropathy and swan-neck deformities of the hands. (b) The deformities are reduced when the hands are placed on a flat surface. (From Loma Linda University Medical Center.)

inflammatory arthropathy is one of the most critical diagnostic issues in the management of SLE patients. *Salmonella* infections are more common (seen in 59%) than non-*Salmonella* septic arthritis. These pathogens have been isolated from blood and synovial fluid. Renal disease was the most common SLE-related feature found in patients in whom septic arthritis developed. Patients with multiple comorbid conditions in addition to septic arthritis had higher mortality rates.

Acute joint pain in patients with SLE, especially pain localized to a few areas, most commonly the hips, may indicate the development of osteonecrosis. In most large series, osteonecrosis is recognized as an important cause of disability and occurs in about 10% of patients observed over a long period. No general agreement has been reached on the predictive role of any specific manifestation of SLE, such as Raynaud phenomenon or vasculitis, in the subsequent development of osteonecrosis, and there is currently no general consensus on pathogenesis. Patients in whom osteonecrosis developed had higher Systemic Lupus Erythematosus Disease Activity Index scores in the previous year, probably associated with treatment with higher corticosteroid doses. Findings in a nested case-control study suggested that osteonecrosis is related to previous arthritis, corticosteroid use, and treatment with cytotoxic drugs.¹² Diagnosis of osteonecrosis in patients with focal pain can be difficult. Changes in routine radiographs are late findings (Fig. 126.8). Earlier diagnosis can be made with radionuclide bone scans or MRI to demonstrate bone abnormality.

Spontaneous tendon ruptures are noted infrequently. They can occur at any time during the course of the disease and are not necessarily a late complication. The most common site of tendon rupture is the patellar tendon of the knee, but rupture of the Achilles tendon has also been reported, as well as rupture of non-weight-bearing tendons such as the biceps, triceps, supraspinatus, and extensor tendons of the hands.^{13,14} The most common risk factors are preexisting inflammatory arthritis and tenosynovitis.

Even though gouty arthritis is rare in SLE, gout has developed in patients when their lupus became quiescent. Some of these patients were underexcretors of uric acid, although these studies were done only in patients in whom renal disease developed. Gouty arthritis may be due to hyperuricemia secondary to lupus nephritis, usually with renal insufficiency or end-stage renal disease, and can lead to acute gouty arthritis and tophaceous gout (Fig. 126.9).

Renal manifestations

Renal involvement is one of the more serious manifestations of SLE and is associated with increased morbidity and mortality. Survival has increased from a 4- or 5-year survival rate of 50% in the 1950s to an 80% 15-year survival rate recently, although no change has been seen in the incidence of progression to renal failure.¹⁵

The features most commonly seen in patients with lupus nephritis are proteinuria, urinary casts, hematuria, pyuria, a rising serum creatinine value, and hypertension. Renal biopsy is essential in determining the type of kidney



Fig. 126.8 Advanced avascular necrosis of the hip with collapse of the articular surface and secondary osteoarthritis.



Fig. 126.9 This patient was initially seen with Jaccoud arthropathy, and later during the course of systemic lupus with lupus nephritis, tophaceous gout developed.

TABLE 126.1
Activity and chronicity indices for lupus nephritis

	Activity	Chronicity
Glomerular lesions	Proliferation	Sclerotic glomeruli
	Necrosis/karyorrhexis	Fibrous crescents
	Hyaline thrombi	
	Cellular crescents	
	Leukocytic exudation	
Tubulointerstitial lesions	Mononuclear cell infiltration	Tubular atrophy
	Interstitial fibrosis	

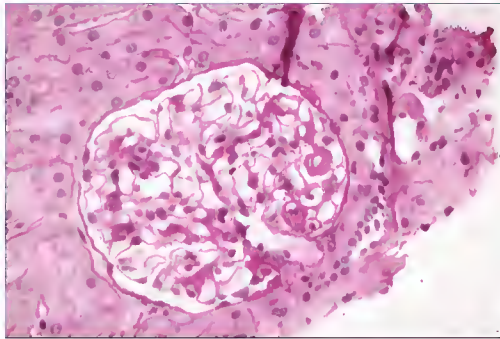


Fig. 126.10 Kidney biopsy specimen showing mesangial lesions (ISN/RPS class II).

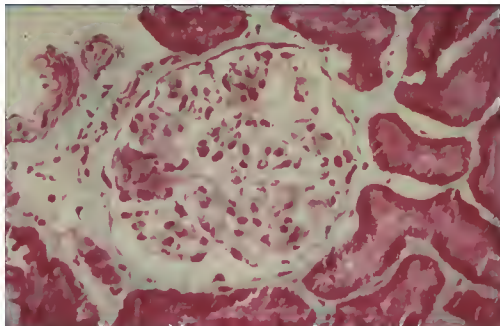


Fig. 126.11 Kidney biopsy specimen showing focal proliferative glomerulonephritis (ISN/RPS class III).

involvement because it influences patient management considerably. Most patients with lupus manifest some abnormality on renal biopsy specimens, either on light microscopy or with special techniques such as immunofluorescence or electron microscopy. Apart from glomerulonephritis, renal involvement in lupus can also be due to interstitial nephritis, tubular disease, thrombotic microangiopathy, vasculitis, arteriolosclerosis, and lupus vasculopathy. Biopsy specimens help differentiate between these varied histopathologies and aid in establishing the prognosis. The main indications for biopsy are new-onset or worsening proteinuria, acute renal failure, and failure to respond to treatment or relapse after treatment. Significant renal involvement may be seen even in patients with low-grade proteinuria defined as 1 g/24 hr, thus supporting the role of renal biopsy even in this subgroup. The morphologic features (Table 126.1) seen on kidney biopsy specimens have both prognostic and therapeutic implications.

The earlier World Health Organization classification was revised in 2003 by the International Society of Nephrology/Renal Pathology Society to allow better description and standardization of the lesions (Table 126.2) seen on biopsy.¹⁶ The classification is based on the changes seen on light microscopy, immunofluorescence staining, and electron microscopy. Mesangial lupus nephritis with accumulation of immune complex deposits within the mesangium (class I) progressing to include mesangial hypercellularity (class II) forms the milder spectrum of the renal lesions. Mesangial lupus nephritis (Fig. 126.10) is the most common lesion seen in the subset of patients with clinically silent lupus nephritis. It responds well to renoprotective therapies even without aggressive immunosuppressive regimens. Depending on the percentage of glomeruli harboring subendothelial deposits, lupus nephritis is further classified as focal (Fig. 126.11) (class III;

TABLE 126.2
International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy along with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy but not by light microscopy
Class III	Focal lupus nephritis* Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis† Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions and as diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. A segmental lesion is defined as a glomerular lesion that involves less than half the glomerular tuft. This class includes cases with diffuse wire loop deposits with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV, in which case both will be diagnosed Class V lupus nephritis with advanced sclerosis
Class VI	Advanced sclerosis lupus nephritis ≥90% of glomeruli globally sclerosed without residual activity

*Indicates the proportion of glomeruli with active and sclerotic lesions.
†Indicates the proportion of glomeruli with fibrinoid necrosis, cellular crescents, or both.
Indicates the grade (mild, moderate, severe) of tubular atrophy, interstitial inflammation, and fibrosis and the severity of arteriolosclerosis or other vascular lesions.
From Weening JJ, D'Agati VD, Schwartz MM, et al, on behalf of the International Society of Nephrology and Renal Pathology Society Working Group on the Classification of Lupus Nephritis. Special feature: the classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15:241-50.

<50% involved) or diffuse (Fig. 126.12) (class IV; ≥50% glomeruli involved). These glomerulonephritides are further described according to the chronicity of the lesions. Membranous lesions (class V) (Fig. 126.13) have mainly subepithelial deposits and may exhibit mesangial involvement. Advanced sclerosis (class VI) is considered the end stage of all the other classes of

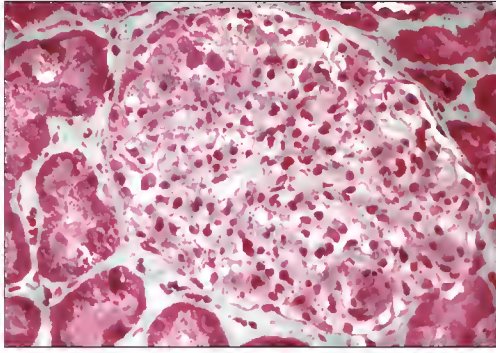


Fig. 126.12 Kidney biopsy specimen showing diffuse proliferative glomerulonephritis (ISN/RPS class IV).

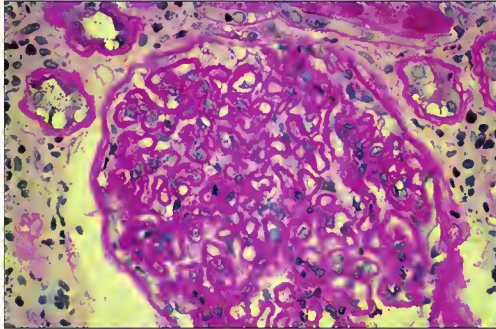


Fig. 126.13 Kidney biopsy specimen showing membranous glomerulonephritis (ISN/RPS class V).

lupus nephritis. Lupus vasculopathy may also be seen and is defined by the presence of hyaline thrombi within the arteriolar lumen or intralobular arteries and tubulointerstitial disease with involvement of the tubular basement membrane and atrophy. Some of the other lesions described in lupus are lupoid nephrosis, focal segmental glomerulosclerosis, IgM nephropathy, and amyloidosis.

Renal flares occur in 27% to 66% of patients with lupus nephritis, depending on the study. They carry risk for further renal deterioration and toxicity from additional immunosuppressive therapy. Class IV patients tend to relapse more frequently with nephritic flares, even when they have previously had a complete response. In class V lupus nephritis, anti-C1q antibodies have the best negative predictive value for predicting flares in the absence of antiphospholipid antibodies.¹⁷

Despite advances in the management of patients with lupus nephritis, 10% of SLE patients progress to renal insufficiency and end-stage renal disease.¹⁸ Aggressive treatment of these patients may increase the risk for infection without adding any benefits if no other systemic manifestations of SLE are present. Moreover, these patients have other comorbid conditions that have to be treated aggressively, such as hypertension and dyslipidemia. Some patients maintained on dialysis continue to have clinical or serologic activity. Patients undergoing hemodialysis or peritoneal dialysis may have problems with venous access thrombosis, especially if they have antiphospholipid antibodies.

Most patients with SLE are suitable candidates for renal transplantation. Disease activity after transplantation is not common, probably because of immunosuppression for prevention of transplant rejection. Patients with SLE and antiphospholipid antibodies are at risk for graft thrombosis and loss even in the perioperative period. This subset of patients must be monitored very closely and may need some adjuvant treatment to counteract the procoagulant effect of the antiphospholipid antibodies.

Type 1 and type 4 distal renal tubular acidosis (RTA) have been reported in patients with SLE. There have been case reports of flaccid paresis as the initial feature secondary to hypokalemia from distal RTA.¹⁹ Tubular basement membrane antibody has been reported to lead to interstitial nephritis in patients with SLE, although it is extremely rare. Renal vein and inferior vena cava thrombosis with nephrotic syndrome can occur. Interstitial nephritis (Fig. 126.14) has also been reported in patients with Sjögren syndrome overlapping with SLE.

Inflammatory aseptic cystitis has been described in patients with SLE, and it is diagnostically challenging to distinguishing it from active lupus glomerulonephritis and infection.^{20,21} Reduced bladder volume and a

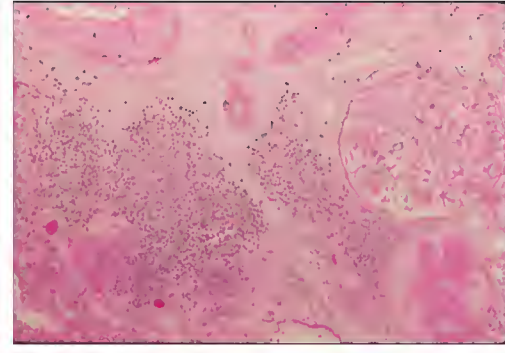


Fig. 126.14 Kidney biopsy specimen showing interstitial nephritis.

BOX 126.2 NEUROPSYCHIATRIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Central nervous system

Acute confusional state
Cognitive dysfunction
Psychosis
Mood disorder
Anxiety disorder
Headache
Cerebrovascular accident
Myelopathy
Movement disorder
Demyelinating syndrome
Seizure disorder
Aseptic meningitis

Peripheral nervous system

Cranial neuropathy
Polyneuropathy
Plexopathy
Mononeuropathy, single/multiplex
Guillain-Barré syndrome
Myasthenia gravis
Autonomic disorder

thickened and irregular bladder wall occur along with symptoms of cystitis. Some patients have ureterohydronephrosis. Immunofluorescence staining of the bladder wall demonstrates immune complex and complement deposition. Both the clinical and radiographic features are generally reversible with corticosteroid therapy.

Neuropsychiatric manifestations

Diagnosis of neuropsychiatric involvement in SLE remains difficult. The American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature has proposed a standardized nomenclature for the neuropsychiatric syndromes of SLE.²² The syndromes include 19 different entities (Box 126.2), about 50% of which are directly attributable to SLE, whereas others are found more in association with it. The most frequent manifestations are headache, psychiatric disorders, and cognitive dysfunction, although the only two included in the ACR criteria for SLE are organic brain syndrome and seizures. These syndromes, which do not always correlate with systemic activity, may occur alone or in combination with other neuropsychiatric manifestations.²³

The neurologic finding can be subdivided according to whether the central or peripheral nervous system is involved.

Intractable headaches unresponsive to narcotic analgesics are the most common feature of central neurologic disease in patients with lupus. The headaches may be migrainous or tension type. Active migraine headaches are associated with higher disease activity scores, worsening of Raynaud phenomenon, and the presence of antiphospholipid antibodies. The mean age at onset of these headaches is higher and the subjective response to analgesics is lower in SLE patients than in healthy controls. Headaches may also be secondary to increased intracranial pressure (pseudotumor cerebri) or cerebral vein thrombosis.²⁴

Seizures in SLE patients may be either focal or generalized. Generalized tonic-clonic seizures occur much more frequently than other types of epilepsy. They are associated with active SLE disease, whereas focal seizures may recur at any time irrespective of disease activity. Fifty percent of seizures are due to concomitant infections, metabolic derangements, or iatrogenic complications. The risk for seizures is increased in patients with higher disease activity at baseline, previous neuropsychiatric disease, and anti-Smith and anticardiolipin antibodies.²⁵ The overall prognosis is very good for these patients in the absence of other infectious or comorbid conditions.

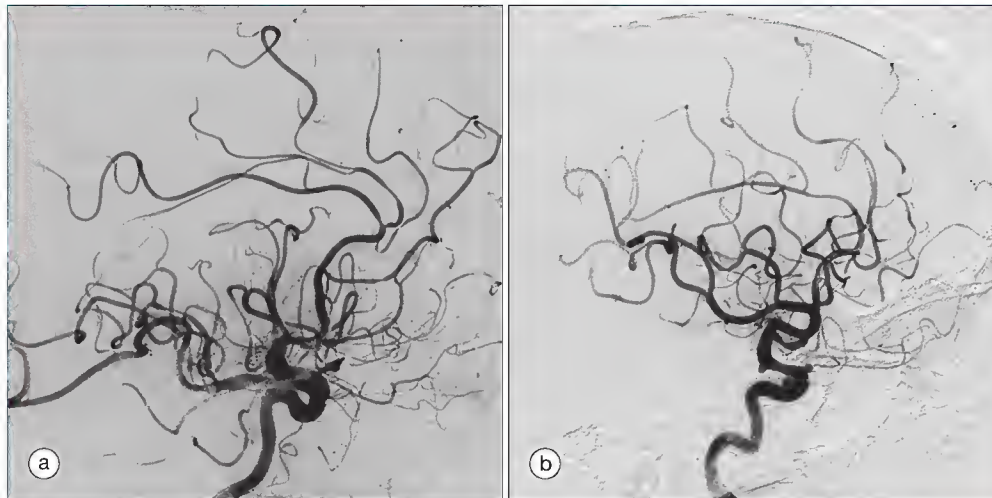


Fig. 126.15 (a and b) Cerebral angiogram demonstrating diffuse multifocal anterior cerebral and middle cerebral arteries compatible with vasculitis.

Chorea occurs in less than 2% of patients with neuropsychiatric SLE. It develops early in the course of SLE and resembles Sydenham chorea. An association of chorea with anticardiolipin antibody has been suggested. It usually resolves spontaneously irrespective of therapy. There have also been reports of ataxia with involvement of the cerebellum and basal ganglia in SLE.²⁶

Cerebrovascular accidents (CVAs) can be caused by an occlusive process or embolic episodes. A major intracranial or extracranial occlusive process may be due to thrombosis, dissection, fibromuscular dysplasia, vasculitis (Fig. 126.15), or atherosclerosis. About 90% of CVAs are ischemic and 10% are hemorrhagic.²⁷ The major period of risk for stroke is within the first 5 years after the diagnosis of SLE. Patients with a history of transient ischemic attacks or cardiac valvular lesions are at high (57% and 87%, respectively) risk for stroke. The risk for recurrent CVA is increased in patients who have previously sustained a CVA (64%). Younger SLE patients are at higher risk for CVA than an age-matched population, and this risk decreases with increasing age of the SLE patients.²⁷ Though rare, there have also been reports of intracranial vasculitis²⁸ at times resulting in CVAs. As in individuals without lupus, patients with hemorrhagic CVAs have a higher mortality rate than do those with ischemic strokes.

Neuropathologic findings (Fig. 126.16) attributable to SLE seen in the brain on autopsy include widely scattered, multifocal infarcts characterized by fibrinoid necrosis of small intracortical arterioles and capillaries, petechial hemorrhage, parenchymal necrosis with variable glial reaction, and vascular endothelial cell proliferation. Changes suggestive of healed vasculitic lesions have also been seen in the brain. The strongest correlation of these infarcts has been with the presence of seizures in neuropsychiatric SLE patients.²⁹

Transverse myelitis, though rare, may be a catastrophic manifestation of SLE.³⁰ It can be the initial feature or may develop at varied times during the course of the disease. The level of involvement of the spinal cord varies from small segments to involvement of the entire spinal cord from the medulla oblongata to the conus medullaris. There is a strong association with optic neuritis, as well as with the presence of antiphospholipid antibodies. Even with prompt diagnosis and aggressive treatment, complete recovery occurs in only 50% of patients, partial recovery in 29%, and worsening or no improvement in 21%. Bladder abnormalities tend to persist even after motor recovery. Demyelinating disorders in SLE are also more often reported in association with antiphospholipid antibody syndrome (Fig. 126.17).

Other rare but reported neurologic syndromes in patients with SLE include aseptic meningitis with associated hypocomplementemia and high titers of anti-double-stranded DNA (anti-dsDNA) antibodies, dementia with leukoencephalopathy, and the syndrome of inappropriate secretion of antidiuretic hormone. One of the conditions that is increasingly being reported in SLE patients is a clinicoradiologic entity: reversible posterior leukoencephalopathy syndrome. It is characterized by a rapid onset of headache, seizures, hypertension, blindness, altered mental status, and specific features on MRI. Diffuse hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the white matter in posterior areas of the cerebral hemispheres are seen but are completely reversible with blood pressure and seizure control. The overall prognosis is very good, with complete neurologic and radiologic recovery occurring within days.³¹

Cranial and peripheral neuropathies have each been reported in about 10% of SLE patients. The most frequently involved cranial nerves are the

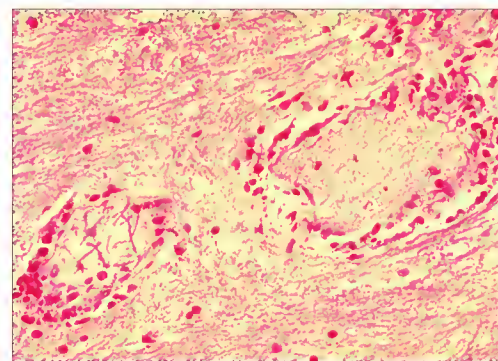


Fig. 126.16 Autopsy findings of fibrin thrombus in a patient with cerebral vasculitis.

sensory and motor nerves of the eye and the trigeminal nerve. Patients may have visual defects, blindness, papilledema, nystagmus or ptosis, tinnitus, hearing loss, vertigo, or facial palsy. Involvement of the postchiasmal visual pathways can also lead to visual hallucinations and cortical blindness. Peripheral neuropathy may include motor, sensory (stocking or glove distribution), or mixed motor and sensory polyneuropathy or mononeuritis multiplex.

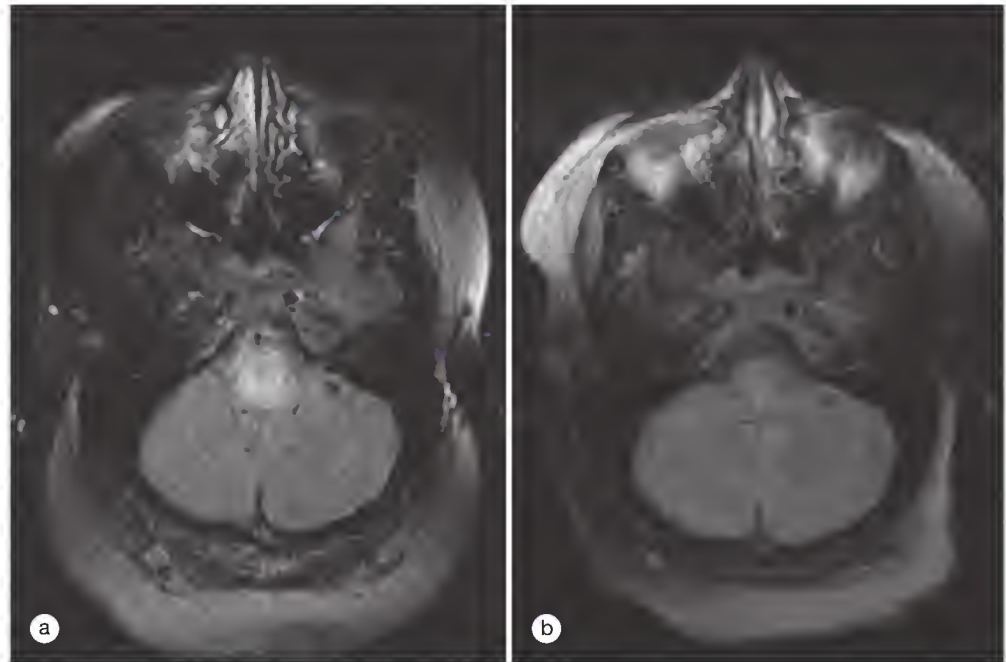
An acute ascending motor paralysis indistinguishable from Guillain-Barré syndrome has been described. Myasthenia gravis has also been reported, especially in women younger than 40 years. Autonomic dysfunction is quite common in SLE and does not correlate with disease activity, duration, or damage and organ involvement.³²

The psychiatric manifestations of SLE present a challenge in terms of both diagnosis and management. Organic brain syndrome is defined as a state of diffuse cerebral dysfunction associated with a disturbance in consciousness, cognition, mood, affect, and behavior in the absence of drugs, infection, or a metabolic cause. Frank psychosis has long been recognized as a manifestation of SLE. In about 60% of SLE patients who exhibit psychosis, it can be the initial feature. It tends to occur early in the course of the disease but has a favorable long-term prognosis after intensive immunosuppressive therapy. It is associated with other clinical and biologic features of SLE. Seventy percent of patients have complete resolution of their symptoms, whereas 30% have chronic mild psychotic symptoms.³³ The use of corticosteroids has been implicated in causing psychosis in some patients; however, its relationship to the lupus process can be confirmed by stopping these agents and demonstrating that the psychosis worsens.

Patients with a psychiatric disorder are more likely to have neurologic abnormalities and subjective cognitive impairment than are patients who do not have psychiatric manifestations. Patients with major psychiatric features (e.g., delirium, dementia, organic hallucinations, delusional syndromes, major depressive episodes) have more severe neurocognitive abnormalities, more ophthalmologic abnormalities, and more calcifications on computed tomography (CT) than do patients with mild depressive symptoms or those without psychiatric manifestations.

The prevalence of cognitive impairment in SLE is likely to be underestimated. Hippocampal atrophy in SLE patients is associated with the total

Fig. 126.17 (a) Magnetic resonance image showing abnormal T2 lengthening suggestive of demyelination involving the central midbrain and medulla in a patient with systemic lupus erythematosus and antiphospholipid antibodies. (b) Resolution of the demyelination in the same patient after treatment.



corticosteroid dose, disease duration, and number of CNS manifestations.³⁴ Hypertension, antiphospholipid antibodies, accumulated damage, and lesions seen on MRI are factors that affect the severity of the cognitive dysfunction. Some of the cognitive disturbances can be explained by their coexisting psychiatric disorder. Cognitive dysfunction has also been noted as abnormalities in the areas of attention, memory, and reasoning in patients without other neuropsychiatric manifestations of SLE.³⁵

Interest in assessing neurocognitive function in SLE has increased because patients frequently complain of minor or even significant cognitive abnormalities during both active neuropsychiatric lupus and inactive disease. The ACR proposed a neuropsychological battery for patients with SLE and established the reliability and validity of this ACR SLE battery.³⁶ In a study of neurocognitive function in SLE, more than 80% of SLE patients who had either active or inactive neuropsychiatric involvement and 42% of patients who had never had neuropsychiatric manifestations demonstrated significant cognitive impairment as compared with 17% of patients with rheumatoid arthritis and 14% of normal controls. Regular prednisone use was associated with decreased cognitive functioning in middle-aged patients with SLE.³⁷ Although this effect of prednisone was independent of measures of SLE-associated disease activity, the authors were not able to exclude the possibility that consistent prednisone use was a surrogate for more severe disease.

The diagnosis of neuropsychiatric lupus is primarily clinical. Exclusion of possible causes such as sepsis, uremia, and severe hypertension is mandatory. Evidence of disease activity in other organs is helpful but not always present. Nonspecific cerebrospinal fluid (CSF) abnormalities such as increased cell count, increased protein, or reduced glucose may be present in about one third of patients.

Antibodies to ribosomal P protein are associated with both depression and psychosis. More specifically, anti-N-methyl-D-aspartate (NMDA) receptor antibodies in CSF, especially against the NR2 receptor, are associated with diffuse neuropsychiatric manifestations of SLE. Anti-DNA antibodies cross-react with high affinity with NMDA receptors and can induce neuronal death by apoptosis in animal models.³⁸ In mouse models, high titers of these antibodies in the maternal circulation could lead to histologic changes in the fetal brain during development. This could explain the development of delayed learning in the offspring of mothers with active SLE.³⁹

Electroencephalographic abnormalities are common in patients with neuropsychiatric lupus but are nonspecific.²³ Computerized quantitative electroencephalography may be more sensitive in detecting the subtle electrophysiologic changes associated with lupus. Radionuclide scans have not uniformly been helpful. However, positron emission tomography showing areas of low attenuation that may represent regions of disturbed cerebral circulation and metabolism appears promising.²³ CT findings such as evidence of cerebral infarction and hemorrhage may reflect specific pathologic processes. Cortical atrophy may be found in patients with SLE but does not necessarily reflect CNS disease. Single-photon emission computed tomography (SPECT) has increasingly been used to identify abnormalities

in patients with neuropsychiatric lupus.⁴⁰ Reduced perfusion in watershed areas of the frontal lobes on SPECT correlates with the severity of cognitive dysfunction. A combination of MRI and SPECT may be especially useful in diagnosing neuropsychiatric lupus because the combination of the two is rarely simultaneously normal in patients with neuropsychiatric manifestations.

Gastrointestinal involvement

Any area of the gastrointestinal tract may be involved by SLE or its complications; such involvement may include esophageal disease, mesenteric vasculitis, inflammatory bowel disease, pancreatitis, liver disease, and peritonitis.⁴¹ About 50% of patients may experience anorexia, nausea, and vomiting without clear evidence of involvement of the gastrointestinal tract.

Esophageal symptoms include dysphagia and odynophagia. Dyspepsia and esophageal dysrhythmias are often associated with the Raynaud phenomenon. An association with antibodies to hnRNP1 protein A1 has been noted and may represent a subset that overlaps with scleroderma. Rarely, esophageal perforation has been found in association with vasculitis.

Acute abdominal pain has been reported frequently in lupus patients. When related to active lupus, involvement of the mesenteric vasculature by vasculitis or thrombosis is the most serious gastrointestinal manifestation. Abdominal angina or lower abdominal pain is typical; it may be insidious and occur intermittently over a period of weeks or months. Arteriography may reveal the presence of vasculitis. Bleeding per rectum may occur, and both small bowel and colonic ulcerations may be seen on colonoscopy. Intestinal perforations from mesenteric vasculitis have been described. The most common finding on a CT scan in SLE patients with an acute abdomen is ischemic bowel disease. Emergency laparoscopy may be required to aid in the diagnosis. Thrombosis of mesenteric vessels may develop when associated with antiphospholipid antibodies. This may lead to intestinal infarction, which has high morbidity and mortality rates.

Lupus enteritis may also be manifested as abdominal pain, most commonly affecting the jejunum and ileum. It is characterized by bowel wall thickening, dilated bowel loops, and abnormal bowel wall enhancement (double-halo or target sign) (Fig. 126.18). It is thought to be caused by vasculitis of the bowel wall. Anti-endothelial cell antibody titers are higher in patients with active lupus enteritis.⁴² Biopsy of the bowel wall may show mucosal inflammation and hemorrhage with lymphocytic infiltration of blood vessel walls.⁴³

Involvement of the large bowel may result in symptoms common to inflammatory bowel disease along with biopsy features of ulcerative colitis. It is difficult to establish whether these findings are related to SLE or due to a comorbid condition.

Cases of protein-losing enteropathy have been reported in SLE patients. It is typically manifested as hypoalbuminemia and anasarca in the absence of nephritis. Biopsy of the wall of the small intestine shows C3 deposits within the capillary wall leading to increased capillary permeability.

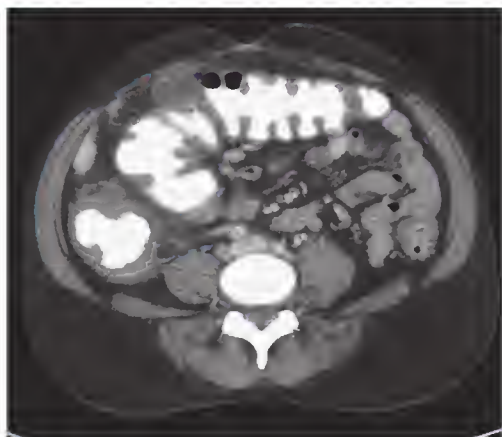


Fig. 126.18 Computed tomography scan of a patient with lupus enteritis demonstrating bowel wall edema involving the entire small and large intestines, or pancolitis.

Diarrhea is present about 50% of the time. Fat malabsorption has also been reported in up to 10% of SLE patients.

Peritoneal inflammation can give rise to acute abdominal syndrome in SLE patients. Ascites may be associated with peritonitis in about 11% of cases. However, at autopsy, evidence of peritoneal inflammation has been found in up to 60% of cases. When ascites is present in conjunction with abdominal pain and active lupus elsewhere, it generally follows the course and response to treatment of the other features of lupus. However, in a small number of patients, ascites may become chronic. In these circumstances it may be painless and associated with only minimal or no other manifestations of active lupus. The peritoneum may also be thickened with adhesions.

Acute pancreatitis occurs in 5% to 10% of patients with lupus, in 22% of whom it is an initial disease manifestation. It has a 27% higher mortality rate than non-SLE-associated pancreatitis does. Although many medications such as corticosteroids and other immunosuppressive drugs have been implicated in pancreatitis, treatment with these agents generally results in resolution of the pancreatitis and improves the prognosis of SLE patients.⁴⁴

Hepatic involvement is common and most often manifested as increased liver enzymes, including aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase. These abnormalities have been associated with active SLE and the concomitant administration of medications. Disease features include chronic active hepatitis, cirrhosis, granulomatous hepatitis, chronic persistent hepatitis, and steatosis. Hepatic involvement in SLE has been reported, usually in association with antiphospholipid antibodies; it is due to thrombosis of the hepatic artery or veins and results in hepatic infarction, Budd-Chiari syndrome, hepatic venoocclusive disease, nodular regenerative hyperplasia, or only transient elevation of hepatic enzymes.

Rarely, patients with SLE may be seen acutely with symptoms of cholecystitis. Inflammation of the gallbladder with thickening of the wall and fluid around it is noted. Such inflammation can be due to vasculitis or serositis.

Reticuloendothelial involvement

Periarterial fibrosis, or “onionskin lesions,” in the spleen has been considered pathognomonic for SLE. It has been proposed that saturation of the reticuloendothelial system contributes to the prolonged circulation of immune complexes and their subsequent deposition in tissue. Indeed, defective Fc receptor function in patients with SLE has been demonstrated and varies with disease activity. Splenic atrophy has been reported in patients with SLE, and the occurrence of splenic lymphoma has also been recognized.

Lymphadenopathy is a common nonspecific feature of SLE. The nodes are usually soft and nontender and vary in size. In some patients, fluctuation of the lymphadenopathy with disease exacerbations may be noted. Pathologically, the lymph nodes demonstrate reactive hyperplasia. Kikuchi-Fujimoto disease is a histiocytic necrotizing lymphadenitis that is thought to be a self-limited form of SLE. It is a benign condition in which patients have regional cervical lymphadenopathy with tenderness accompanied by fever and night sweats. SLE may eventually develop in these patients, and thus they need to be monitored over the long term.⁴⁵

Hematologic abnormalities

Cytopenias, including anemia, leukopenia or lymphopenia, and thrombocytopenia, are frequent manifestations of SLE, although they may or may not be immune mediated.

Fifty percent of patients with SLE have anemia. The most common causes of anemia in SLE patients are anemia of chronic disease and iron deficiency anemia, followed by autoimmune hemolytic anemia as a distant third.⁴⁶ The Coombs test is positive in only 10% of SLE patients with clinically significant hemolysis. The antierythrocyte antibody in SLE is usually “warm-type” IgG antibody. Other causes of hemolytic anemia, such as medications, infections, and microangiopathic hemolytic anemia, must be ruled out.

Several cases of red blood cell aplasia have been reported. Serum IgG autoantibodies have been detected in patients with red cell aplasia and act to inhibit the growth of burst-forming units of erythrocytes in bone marrow. Pernicious anemia has been described in patients with SLE and anti-intrinsic factor antibodies, low cobalamin levels, and megaloblastic anemia.⁴⁷

White blood cell abnormalities are common in SLE. When leukopenia is secondary to active lupus, the bone marrow is usually normal. The white blood cell count rarely decreases to less than 1500/mm³ in active SLE, unless an additional cause is present. In some instances, when the total white blood cell count does reach such low values, associated high spiking fevers require high doses of corticosteroid to suppress active disease. Neutropenia can be due to autoantibodies that inhibit granulocyte colony-forming units in bone marrow. Neutropenia may also be the result of immunosuppressive agents.

Lymphopenia in patients with SLE is multifactorial and frequently associated with antibodies to lymphocytes. Although it is associated with active SLE, it may also be chronically present in patients with no other clinical disease manifestations. Moderate to marked lymphopenia is generally associated with higher disease activity and damage accrual and is a risk factor for serious infections.⁴⁸

Two distinct subsets of patients with thrombocytopenia have been identified in SLE: a subset in which the thrombocytopenia is one feature of severely active multisystem involvement and a second subset in which the thrombocytopenia is an isolated finding. In the former, the thrombocytopenia tends to require aggressive therapy; in the latter, patients usually have a platelet count lower than 50,000/mm³ without serious bleeding. In both groups, patients may have mild petechiae or purpura. Although antiplatelet antibodies are a frequent finding in SLE, they are not always associated with thrombocytopenia. Other autoantibodies to platelet-specific antigens can also mediate thrombocytopenia, such as antibodies to thrombopoietin receptor and to glycoprotein IIb/IIIa.⁴⁹

In some instances of refractory thrombocytopenia with SLE, often without platelet antibodies, antiphospholipid antibody syndrome should be suspected (see Chapter 139). In addition, thrombocytopenia may be a feature of thrombotic thrombocytopenic purpura (TTP) syndrome, which may complicate SLE.⁵⁰ TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia, CNS deficits, renal dysfunction, and fevers. In most patients the onset of TTP occurs after the diagnosis of SLE. A high level of suspicion for TTP is appropriate when a patient with SLE exhibits deterioration in multiple organ systems and microangiopathy because aggressive management with plasmapheresis and immunosuppression is indicated.

In addition to a decrease in the number of circulating platelets, defective aggregation in response to collagen also occurs.⁵¹ Various other abnormalities related to platelet function, including acquired von Willebrand factor deficiency, may occur in SLE. Other causes such as infection or drugs must be ruled out as a cause of thrombocytopenia in patients with lupus.

Myelofibrosis has been reported in SLE and may be reversible with immunosuppressive therapy.⁵² In SLE patients with pancytopenia, abnormalities seen on bone marrow biopsy include global hypocellularity, increased reticulin proliferation, plasmacytosis, dyserythropoiesis, myelofibrosis, and necrosis. Pancytopenia in SLE may result from the effects of drugs, particularly immunosuppressive agents. It may also complicate infections in patients with SLE. In addition, pancytopenia may develop in patients with SLE as a result of hemophagocytic syndrome.

Pulmonary involvement

The features of primary pulmonary involvement in SLE include abnormal pulmonary function, lupus pleuritis, acute or chronic lupus pneumonitis, pulmonary hemorrhage, pulmonary embolism, pulmonary hypertension, and airway and diaphragmatic involvement.^{53,54}

The common abnormality in pulmonary function in SLE patients is a restrictive pattern with decreased tidal volume and forced vital capacity. A



Fig. 126.19 Pleural effusion in a patient with systemic lupus erythematosus.

decrease in the diffusing capacity of carbon monoxide is also noted in most SLE patients, especially in those with a previous history of pneumonitis. Causes of the restrictive pattern seen on pulmonary function tests include pleuritis, respiratory muscle involvement secondary to myositis, and phrenic nerve paralysis.

Pleural manifestations have been reported in 30% to 60% of patients with SLE.⁵³ A clinical history of pleuritic pain is more common than radiographic change. Pleural rubs are found less frequently than either clinical pleurisy or radiographic abnormalities. However, autopsy findings of pleural involvement have been detected in up to 93% of patients with SLE.

Pleural effusions (Fig. 126.19) may occur and are generally small but can occasionally be massive. They are also frequently bilateral. When pleural effusions are significant, other causes of effusion such as infection must be ruled out by thoracentesis before treatment is initiated. The fluid is usually an exudate with a higher glucose concentration, lower lactate dehydrogenase levels, and autoantibodies such as antinuclear and anti-dsDNA antibodies. The visceral pleura may contain nodules with immunoglobulin deposits seen on immunofluorescent staining of a biopsy specimen.

Lupus pneumonitis may initially be seen in either an acute or a chronic form. Acute lupus pneumonitis usually occurs during a generalized multi-system lupus flare and is accompanied by fever, dyspnea, coughing, pleuritic chest pain, and occasionally, hemoptysis. Lupus pneumonitis is associated with the presence of anti-SSA antibodies secondary to possible cross-reactivity between SSA and alveolar cell-surface epitopes.⁵⁵ The histopathologic features are nonspecific and consist of alveolar wall damage or necrosis, alveolar edema or hemorrhage, hyaline membranes, and inflammatory cell infiltrates. Electron microscopy and immunofluorescence studies have shown deposition of IgG, C3, and DNA antigen in alveolar septa. Chest radiography and CT show unilateral or bilateral alveolar infiltrates with ground-glass opacification. Patients with acute lupus pneumonitis have been seen with a miliary pattern of nodules on radiographs mimicking pulmonary tuberculosis. Other causes of pneumonitis should be ruled out and empirical antibiotic therapy started because the differential diagnosis includes infections (both bacterial and fungal), as well as hemorrhage and embolism. These patients often require bronchoalveolar lavage as part of their workup and sometimes open lung biopsy to rule out other causes. Though rare, acute lupus pneumonitis simulating lymphangitic pulmonary malignancy has been reported.

Chronic lupus pneumonitis is manifested as interstitial lung disease (Fig. 126.20) and is characterized by dyspnea on exertion, nonproductive cough, fatigue, and basilar rales. The clinical course is associated with late-onset disease, male gender, and older age.⁵⁶ Histopathologic evaluation of the lung is nonspecific, with findings of architectural destruction, interstitial inflammation, fibrosis, and honeycombing alternating with areas of normal lung

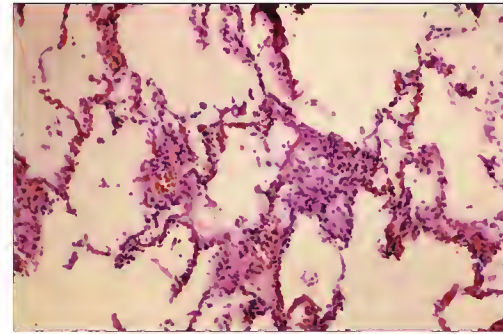


Fig. 126.20 Changes of interstitial lung disease showing inflammation.

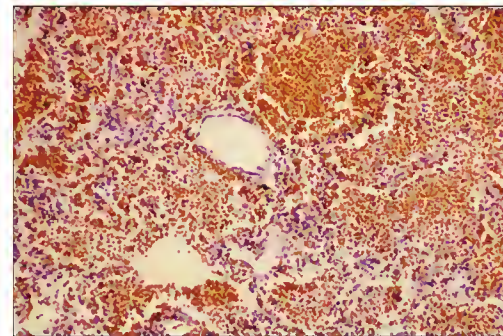


Fig. 126.21 Diffuse alveolar hemorrhage.

tissue. Gallium scans can be used to help differentiate between active inflammation and fibrosis.

Diffuse alveolar hemorrhage is a very serious condition in SLE, with mortality rates ranging from 50% to 90%.⁵⁷ The characteristic finding is an abrupt onset of dyspnea, cough, fever, and infiltrates and a dramatic fall in hemoglobin. Hemoptysis is present in only 50% of patients. The characteristic histopathology includes diffuse intraalveolar hemorrhage with intact erythrocytes and hemosiderin-laden macrophages (Fig. 126.21). Diffuse alveolar hemorrhage is usually due to a vasculitis with pulmonary capillaritis and a distinctive small-vessel vasculitis or microangiitis of the arterioles and small muscular pulmonary arteries. Evidence of diffuse alveolar damage with diffuse alveolar septal thickening, marked hyperplasia of alveolar pneumocytes, and eosinophilic acellular hyaline membranes may also be noted. Bronchoscopy with bronchoalveolar lavage should be performed to diagnose diffuse alveolar hemorrhage and exclude infection.

Pulmonary hypertension can occur in lupus patients as a result of either the disease process or complications such as pulmonary embolism, valvular heart disease, and interstitial lung disease. It is present in 0.5% to 14% of SLE patients. Survival is significantly lower in SLE patients with pulmonary hypertension than in those with idiopathic pulmonary hypertension.⁵⁸ The initial symptoms are nonspecific and include dyspnea on exertion, fatigue, weakness, and a nonproductive cough, and they often develop insidiously. With progressively increasing pulmonary artery systolic pressure, heart failure ensues. Echocardiography is one of the most important noninvasive screening diagnostic tools for detecting pulmonary hypertension. Suspicion for this disorder should prompt right-sided heart catheterization to determine severity and vasoreactivity, which in turn provides prognostic information. Pulmonary function tests show an isolated reduction in the diffusing capacity of carbon monoxide or a restrictive pattern. Vasoreactive patients have a better prognosis and better response to therapeutic agents than do nonvasoreactive patients.

Pulmonary embolism with or without the presence of antiphospholipid antibodies can develop in SLE patients. In patients with SLE in whom catastrophic antiphospholipid antibody syndrome develops, involvement of the lung is noted in 66% and consists of pulmonary embolism, adult respiratory distress syndrome, pulmonary artery thrombosis, *in situ* microthrombi, or even alveolar hemorrhage.

Shrinking lung syndrome occurs a subset of SLE patients with unexplained dyspnea, small lung volumes with restrictive pulmonary function, and an elevated diaphragm. Chest radiographs may reveal an elevated diaphragm but normal lung fields. The pathogenesis is unclear, but it is probably the result of altered respiratory mechanics because of either impaired respiratory muscle or diaphragmatic function or problems in the respiratory

skeletal apparatus. In a postmortem study the diaphragm of a patient with shrinking lung syndrome in late lupus was fibrotic and thinned.⁵⁹

Airway disease has been reported in patients with SLE. Bronchiectasis and bronchial wall thickening have been detected on high-resolution CT scans of the chest in 35% of patients. Rarely, bronchiolitis obliterans and cryptogenic organizing pneumonia have occurred in association with SLE. Acute reversible hypoxemia and adult respiratory distress syndrome have also been reported in critically ill SLE patients.⁶⁰

Cardiac manifestations

Patients with SLE have a myriad of cardiac manifestations. SLE can affect any layer of the heart and cause endocarditis, myocarditis, and pericarditis, which are generally reflected by symptoms and functional disability.⁶¹

Pericardial effusion secondary to pericarditis is the most commonly observed cardiac feature in SLE. On echocardiography, effusions are seen in more than 30% of SLE patients. Clinically, the findings may be classic for pericarditis, with precordial chest pain and a pericardial rub, or it may be painless and silent. Pericarditis can be fibrinous or fibrous with obliteration of the pericardial space by fibrous adhesions. Pericardial fluid is fibrinous and exudative with chronic inflammatory cells, positive antinuclear and anti-DNA antibodies, and reduced complement activity. Occasionally, incipient or overt cardiac tamponade as a result of pericardial effusions may develop and require high doses of corticosteroids and emergency pericardiocentesis.⁶² Pericardial effusions in SLE patients can also be due to other conditions such as renal failure or bacterial and fungal infections. Rarely, constrictive pericarditis can develop in SLE patients.

Clinical myocarditis is seen in about 10% of SLE patients, but autopsy findings reveal changes secondary to myocarditis in 50% of these patients. Myocarditis should be suspected in patients with arrhythmias or conduction defects, unexplained cardiomegaly with or without congestive heart failure, or unexplained tachycardia. Patients with myocarditis usually have associated pericarditis and other features of active SLE, such as mucosal ulcers. Echocardiography demonstrates global or segmental wall motion abnormalities and a reduced left ventricular ejection fraction. Myocarditis has been associated with anti-SSA or anti-Ro antibodies. Endomyocardial biopsy specimens have shown abnormally thickened small-vessel walls, enlarged smooth muscle cells, and lymphocytic and plasmacytic infiltrates. Mitochondrial clumping, disorganization of myocardial fibrils, moderate interstitial edema, and fibrosis are seen on electron microscopy. Myocarditis is associated with higher disease damage accrual and lower survival in these patients than in those without myocarditis, although 80% of patients improve acutely with immunosuppressive agents and intravenous immune globulin.⁶³

Myocardial involvement in systemic lupus may be subtle, with abnormalities detected only with noninvasive testing. Resting electrocardiograms and echocardiograms are abnormal in more than 70% and cardiac radiographs in 55% of SLE patients. Cardiac MRI in SLE patients with active disease demonstrates an increased T2 relaxation time suggestive of increased tissue edema; this is reversible with improvement of overall disease activity.⁶⁴ Exercise thallium scans in SLE patients have shown segmental perfusion abnormalities in 38%, 50% of which are reversible. Resting dipyridamole technetium 99m sestamibi SPECT shows abnormal myocardial perfusion in 64% of patients. In many of these patients with abnormal noninvasive test results, coronary angiograms have been normal, thus suggesting possible small-vessel disease.

Apart from myocardial involvement, patients with SLE have evidence of cardiac autonomic dysfunction. Sympathetic dysfunction occurs more often in older, postmenopausal patients, as well as in those with hypertension and peripheral neuropathy, whereas parasympathetic dysfunction is seen in older, obese, postmenopausal patients and those who have experienced a CVA.⁶⁵ Periodic heart rate variability is less than would be expected physiologically in SLE patients regardless of treatment. Atrioventricular conduction blocks of various grades have been reported and are associated with anti-Ro antibodies and rarely with anti-U1RNP antibodies. The conduction system is replaced by fibrous tissue similar to that seen with congenital complete heart block secondary to anti-Ro antibodies.

Valvular involvement is common in SLE, with vegetations noted on echocardiography in about 60% of patients. During the course of SLE, these valvular abnormalities may develop for the first time, resolve, persist, or worsen. Diffuse valvular thickening is the most commonly seen abnormality and involves either the mitral or aortic valve. This thickening is associated with reduced mobility of the valve. Verrucous vegetations, known as Libman-Sacks endocarditis, are found in 43% of patients. Vegetations can be present within the left atrium as well and simulate intracardiac tumors. On the aortic valve these vegetations are usually seen on the vessel side.

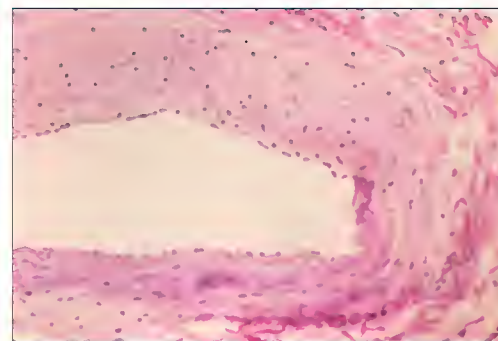


Fig. 126.22 Coronary vasculitis.

Valvulitis can also involve the tricuspid valves and may progress to either hemodynamically significant stenosis or regurgitation requiring valve replacement. Occasionally, multiple valves are involved in the same patient with Libman-Sacks endocarditis. This endocarditis is associated with antiphospholipid antibodies in about 50% of cases.

Coronary vasculitis (Fig. 126.22) is rare in SLE and can occur with or without other features of active disease. Immunopathologic studies have shown immune complex deposits within blood vessel walls. More frequently, coronary artery disease in lupus is a manifestation of generalized atherosclerosis, which is discussed in greater detail later in the section on complications of lupus. Coronary artery occlusion secondary to intraarterial thrombi may also occur in association with a circulating anticoagulant. Myocardial infarction caused by coronary artery aneurysms have been described as well in SLE. Other vascular involvement, including aortitis, has been seen in patients with SLE. The walls of the aorta exhibit immunoglobulin, complement component, and immune complex deposition.⁶⁶ This inflammation may lead to intraaortic thrombosis or aortic dissection.

Other organ systems involved

Endocrine

Because SLE is known to disproportionately affect women more than men, there has always been an interest in knowing the relationship of sex hormones to the disease. Women with SLE have been shown to have lower androgen levels, with the lowest levels seen in patients with the most active disease.⁶⁷ SLE patients also have increased accumulation of hormones with increased estrogenic activity. Apart from hormonal effects, ovarian vasculitis has been reported with diffuse leukocytic perivascular infiltrates and fibrinoid necrosis in ovarian blood vessels.⁶⁸ The changes of vasculitis have also been reported to involve the adjacent fallopian tube. Male lupus patients have a higher frequency of abnormalities in spermatozoa and testicular Sertoli cell function than otherwise normal men do.⁶⁹

Other endocrine abnormalities may develop in SLE patients during the course of the disease. Hyperprolactinemia has been observed in 20% of both male and female SLE patients and has been associated with antiprolactin antibodies. Prolactin levels, however, do not correlate with disease or serologic activity. Hyperprolactinemic patients may be less responsive to therapy than patients with normal prolactin levels. Prolactin levels have correlated with anti-DNA antibody levels in SLE patients.⁷⁰ The syndrome of inappropriate secretion of antidiuretic hormone has been seen in SLE patients. SLE disease duration has been positively correlated with an inappropriate increase in plasma antidiuretic hormone levels.

Adrenal failure has been associated with antiphospholipid antibodies secondary to hemorrhagic infarction of the adrenal glands or arterial thrombosis of adrenal vessels. Thyroid function test results are frequently abnormal in SLE patients, and hypothyroidism may be more prevalent in this population. Clinical thyroid disease has been found in older SLE patients and is associated with the presence of antithyroid antibodies.

Dyslipoproteinemia along with metabolic syndrome is much more prevalent in SLE patients, but whether it is a result of the disease or its treatment still needs to be elucidated.⁷¹ Autoantibodies against insulin receptors leading to hypoglycemia have also been detected.

Eye, ear, nose, throat

SLE can involve any region of the eye, with keratoconjunctivitis sicca and retinal vascular changes being the most commonly seen. Decreased tear film and reduced tear production occur in about 60% of SLE patients with dry eyes. Retinal vascular changes are due to either immune complex-mediated or microvascular thrombosis. These changes tend to correlate with the

severity of disease. The retinal changes seen most commonly in SLE patients are cotton-wool spots and intraretinal hemorrhages. Other ocular abnormalities include peripheral ulcerative keratitis, choroidopathy, uveal effusions, retinal detachment, optic neuritis, and angle-closure glaucoma. Many of the changes may be a result of the treatments used for SLE, such as corticosteroids for glaucoma, cataract, and central serous retinopathy and anti-malarial agents for maculopathy.⁷²

SLE patients have had sudden-onset sensorineural hearing loss, which may be associated with antiphospholipid antibodies.⁷³ Rarely, laryngeal involvement may be seen as cricoarytenoiditis and as bilateral vocal cord paralysis.⁷⁴

COMPLICATIONS AND COMORBID CONDITIONS

Patients with SLE have various complications resulting from the disease or its treatment. They may also have comorbid conditions that may complicate the course of the disease, such as diabetes mellitus. Other than active lupus during the early years of disease, the main causes of death in patients with SLE are infections and cardiovascular events.⁷⁵

Accelerated atherosclerosis

SLE patients have accelerated atherosclerosis that may be manifested as coronary artery disease, cerebral vascular disease, and peripheral vascular disease. Coronary artery disease is an important cause of morbidity in SLE patients. Studies of the incidence rates of coronary events in women with SLE have shown that patients in the 35- to 44-year-old age group were more than 50 times more likely to have a myocardial infarction than were women of similar age in the Framingham Offspring Study.⁷⁶ SLE patients have an increase in both the traditional and nontraditional risk factors for atherosclerosis. Traditional risk factors such as hypertension, diabetes mellitus, metabolic syndrome, and dyslipidemia are more prevalent in SLE patients, but these risk factors are amplified by the presence of certain nontraditional factors, such as renal failure, higher levels of oxidized low-density lipoprotein, and premature ovarian failure.⁷⁷ Longer disease duration, higher cumulative corticosteroid dose, and older age at diagnosis of SLE are found more frequently in patients who had a cardiovascular event, although the higher corticosteroid doses are thought to reflect the severity of disease. Subclinical atherosclerosis can be determined in SLE patients by using methods such as measurement of carotid intima-media thickness (IMT) and electron B tomography.⁷⁸ SLE patients have increased endothelial dysfunction, vascular stiffness, and carotid IMT when compared with control subjects. Peripheral vascular disease affects about 28% of SLE patients and leads to ischemic extremity ulcers, gangrene, femoral artery plaques, and stenosis.

Malignancies

Patients with SLE have an increased incidence of hematologic malignancies, especially non-Hodgkin lymphoma.^{79,80} The incidence of other malignancies (lung cancer and hepatobiliary cancer) is also higher in SLE patients than in controls.⁸¹

Diabetes mellitus

Diabetes mellitus may be type 1, type 2, or steroid induced in SLE patients. It is present as a comorbidity in SLE patients and can affect the same systems as SLE does. Renal, ocular, and neurologic manifestations can be due to either SLE, diabetes, or both, and this can be a barrier to their management.

These patients may need not only aggressive immunosuppressive therapy for their SLE but also tight glycemic control to prevent complications. It is therefore important to be able to differentiate the cause of the manifestations in patients with both diseases.⁸²

Osteoporosis

Osteopenia is present in 50% of SLE patients and osteoporosis in 17%. Vertebral fractures are detected in at least 26%.⁸³ Fractures are associated with older age, postmenopausal status, increased disease damage, and lower bone mineral density at the hip. Bone mineral density is lower in premenopausal women with SLE, even after adjustment for the corticosteroid dose. However, a prednisone dose equivalent to 7.5 mg/day or greater lowers bone mineral density in the lumbar spine. Exercise is protective at the femoral neck in patients taking corticosteroids. Even in men, lean body mass and bone mineral density are reduced with SLE.⁸⁴

Infections

Infections are the most common cause of morbidity, hospitalization, and mortality in SLE patients.⁸⁵ More than half of the infections are viral, and about 40% are bacterial. The common sites of bacterial infection are similar to those in patients without lupus (i.e., urinary tract, respiratory tract, and skin). The most specific viral infection in SLE is herpes zoster infection. Fungal and protozoal infections are also more frequent in SLE patients.

Hepatitis B infections are found more frequently to coexist with SLE in areas of the world where it is endemic. Reactivation of the virus is a risk, and patients therefore need to undergo serial monitoring of their viral load. SLE patients with chronic hepatitis C infection have an increased frequency of cryoglobulinemia and hypocomplementemia and a lower incidence of cutaneous features and anti-DNA antibodies.⁸⁶ SLE patients with positive HTLV-1 serology have higher lymphocyte counts and require a lower maintenance dose of prednisone for treatment.⁸⁷ Certain infections are becoming more prominent with newer biologic therapies. One example is reactivation of John Cunningham (JC) polyomavirus, which has been reported to lead to progressive multifocal encephalopathy in patients taking rituximab.⁸⁸

The clinical findings in SLE patients with flares and infections are often confusing. It is very important to exclude infections because immunosuppressive treatment of the active flares of SLE can exacerbate infections and even be fatal.

Premature gonadal failure

Accelerated ovarian atresia develops in women with SLE as a result of treatment with chemotherapeutic agents. It is seen more frequently in patients who receive agents such as cyclophosphamide at an older age. Premature gonadal failure also occurs in men with SLE.⁸⁹

CONCLUSION

SLE is a disease that predominantly affects women in minority ethnic groups. As discussed, it can affect any organ or system during the course of the disease. The overall survival rate of patients has considerably improved from 50% at 5 years to higher than 90%. Because of the improved survival, we see more patients in a much younger age group with complications and comorbidities of SLE, such as accelerated atherosclerosis and malignancies. Therefore, in addition to developing newer biologic therapeutic agents for managing SLE, we need to consider developing techniques or discovering biomarkers for prevention or early diagnosis of the complications of SLE.

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Genetics of lupus

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- Genetics identifies differences intrinsic to the host that alter the probability of a particular phenotype.
- For lupus, genetics contributes to approximately half the risk for development of the disease, with only about a third of the genetic contribution now identified.
- The known genes implicate pathways that involve particular aspects of the inflammatory response, including pattern recognition receptors and the cascade of signal transduction intermediates, particularly through nuclear factor κ B toward type 1 interferon production. Also, genetic variants in genes influencing immune complex recognition and deposition alter the risk for lupus.
- Much is known but even more remains to be learned about the genetic contributions to lupus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex genetic disorder with no obvious pattern of inheritance conveying risk for SLE in other family members. Indeed, finding a second relative of the first or second degree with lupus occurs in only about 7% of patients with SLE.^{1,2} Still, there is a clear familial tendency, with relatives of SLE patients being at higher risk for disease than other members of the population. Sisters of female lupus patients, for example, are estimated to have an 8- to 29-fold increased risk for the development of SLE.³

These are the usual SLE patients; the exceptional patients who appear to have SLE from a single genetic variant of enormous impact are especially interesting. Although they do not involve genes that ordinarily appear to harbor disease-contributing variants of the more common forms of the disease, they provide much insight into the pathogenesis, as discussed in this chapter.

The genetics of SLE can be considered from many perspectives. There are the traditional allelic, autosomal recessive and dominant, and sex-linked mechanisms. Smaller-magnitude effects from genes that alter risk without a clear understanding of the mechanism constitute the majority of recent genes implicated in the development of SLE.⁴ New mutations, sometimes called *de novo* mutations that first arise in the affected SLE patient and are not found in either parent, probably explain some cases of SLE, including some associated with *TREX1* variants.^{5,6} Lupus is known to be much more common in women than in men, and recent work has suggested that this might be due to the number of X chromosomes, commonly called a gene dose effect (discussed later).^{7,8} To date, no examples of somatic mutations causing lupus in human subjects are available. The technical capacity to evaluate this possibility is now emerging. Indeed, there is no sense of how the many possible environmental factors apparently contributing to SLE might contribute to SLE. Nevertheless, across the phenotype of SLE, many genes operate through a variety of variants and mechanisms, thus providing much complexity to understanding the genetic origins of SLE.

THE BIG PICTURE

Nearly 45 genetic loci containing variants are associated with the development of lupus (probability value, $<5 \times 10^{-8}$) (reviewed in [reference 4](#)) ([Table 127.1](#)), with another 50 or so that also appear close to being established.

Even though many findings suggest that SLE has a strong genetic component, such as the familial aggregation presented earlier^{1,9} and the identical twin concordance rate, which is somewhere between 24% and 50%,¹⁰ the discovery and confirmation of genetic associations have clearly established the importance of genetic variants in the etiology of SLE. Although the probability of the cases and controls having the same allele frequency at any given locus is the major measurement of genetic association, the odds ratio (OR) provides the usual measure of effect size magnitude. Right or wrong, we usually assume that the gene or genes nearest the associated markers are affected by the associated variants. Strikingly, these genes in the neighborhood of the lupus associations are components of specific functions, some overlapping, of the immune response, including immune complex processing, complement activation, receptor activation and immune signal transduction, and interferon activation ([Fig. 127.1](#); also see [Table 127.1](#)). A variant influencing the activity of a gene may operate in one or more cell types at one or more specific stages in development and is engaged in one or more pertinent intracellular relationships, issues that remain largely unexplored. At this point, what is known about expression and cellular function can be used to construct models of cellular responses and interactions that could explain possible mechanisms for how genetic variants alter risk for SLE (see [Fig. 127.1](#)).

GENOMEWIDE ASSOCIATION STUDIES

The major tool for finding disease genes has been the genomewide association study (popularly referred to as a GWAS). Typically in a GWAS, 300,000 to nearly 5 million variable genetic markers are assessed in each case and control. Once thousands of cases and controls are genotyped, the statistical power becomes adequate to detect differences with sufficient confidence (usually set at a probability of chance explaining the finding at 1 in 5×10^8) that the result will usually also be found in a confirmatory study.¹¹ As of this edition, eight GWASs conducted in patients with SLE have reported genetic associations achieving this level of statistical significance.¹²⁻¹⁹

In these GWAS results, most everyone involved is remiss in emphasizing the genes themselves before the particular variations that cause the disease association are known. The associations discovered are with physical pieces of DNA. We assume that the particular association exists because of the function of that piece of DNA, given that chance is the only other known explanatory option. Usually, there are many variants that are possible origins of the disease risk observed because of inexact localization of the origin of the association generated by the disequilibrium that operates throughout the human somatic genome. Identifying the responsible variants and elucidating their mechanism have been the stalling point for progress. Regardless of whether the variants mediate risk through a particular gene, the nearest gene is used as a moniker for the association that happens to be found in their immediate neighborhood.

For each genetic association established by these studies, a small region of genomic DNA associated with SLE is detected by a difference in allele frequency between cases and controls. These markers are not generally the variant that is responsible for the association. Indeed, for the great majority of associations, it is the exception to find a strong candidate variant that has biologic function possibly explaining the association observed, as noted in [Table 127.1](#).

Associated markers typically “tag” a region in the genome that carries with it the causal variant from generation to generation. Consider that there are approximately 37 chromosomal crossovers on the autosomes for each generation.²⁰ These crossover events gradually shuffle genetic variants toward a random distribution across each chromosome, with the process being sufficiently slow that in well-defined ancestral populations, blocks of

TABLE 127.1

Genes associated with lupus ($P < 5 \times 10^{-8}$)*

Gene	Location	Odds ratio	Best <i>P</i> value	Population	SNP with best <i>P</i> value (risk allele)	MAF of best SNP	Causal variant (minor allele)
<i>PTPN22</i>	1p13.2	1.4	3.4×10^{-12}	EU, HA	rs2476601 (A)	0.10	rs2476601 (A) PTPN22 R620W
<i>FCGR2A</i> , <i>FCGR3B</i>	1q23	1.59	$9.1 \times 10^{-7*}$	EU, AA, AS	rs1801274 (T)	0.43	rs1801274 (T) FCGR2A H166R
<i>NCF2</i>	1q25	1.19	4.62×10^{-20}	EU, AS	rs17849502 (G)	0.11	rs17849502 (G) NCF2 H389Q
<i>CRP</i>	1q21	0.49	9.2×10^{-14}	EU, AA	rs3093061 (G)	0.19	
<i>TNFSF4</i>	1q25	1.46	2.5×10^{-32}	EU, AS, HA	rs2205960 (A)	0.35	
<i>IL10</i>	1q31-q32	1.19	4.0×10^{-8}	EU, AA, AS	rs3024505 (A)	0.16	
<i>C1q</i> <i>C1r</i> , <i>C1s</i> <i>C2</i> , <i>C4</i>	1p36 12p13 6p21.3		Convincing family studies*	EU			Multiple, usually gene product deficiencies
<i>RASGRP3</i>	2p24.1	0.7	1.3×10^{-15}	AS	rs13385731 (G)	0.07	
<i>IFIH1</i>	2q24	1.11	1.6×10^{-8}	EU	rs1990760 (T)	0.61	
<i>STAT4/STAT1</i>	2q32.2	1.55	5.17×10^{-42}	EU, AA, AS, HA	rs7582694 (C)	0.42	
<i>PXK</i>	3p14.3	1.25	7.1×10^{-9}	EU	rs6445975 (C)	0.32	
<i>TREX1</i>	3p21.31	44.65	8.5×10^{-11}	EU	rs3135945 (A)	0.01	R11H and others (all uncommon or rare)
<i>TMEM39A</i>	3q13.33	0.72	8.62×10^{-9}	EU, AS	rs1132200 (A)	0.01	
<i>AFF1</i>	4q21	0.81	8.3×10^{-9}	AS	rs340630 (A)	0.44	
<i>BANK1</i>	4q24	1.31	2.62×10^{-13}	EU, AA, AS, HA	rs10516487 (A)	0.13	rs10516487 (A) BANK1 R61H
<i>IL2/IL21</i>	4q26	0.86	2.2×10^{-8}	EU, AA, AS	rs907715 (G)	0.31	
<i>TNIP1</i>	5q32	1.27	3.8×10^{-13}	EU, AA, AS	rs10036748 (G)	0.45	
<i>Mir146a</i>	6q5	1.29	2.74×10^{-8}	AA, AS, EU	rs57095329 (G)	0.21	rs57095329 affects binding of Ets1 to the promoter
HLA and other genes	6p21.3	2.35	1.27×10^{-51}	EU, AS, AA, HA	rs1270942 (G)	0.2	
<i>ATG5</i>	6q21	1.25	5.2×10^{-12}	EU, AS	rs548234 (G)	0.30	
<i>TNFAIP3</i>	6q23	1.72	1.3×10^{-17}	EU, AA, AS	rs2230926 (C)	0.07	TT>A polymorphic dinucleotide; decreased NF- κ B binding
<i>HIP1</i>	7q11	1.43	1.3×10^{-8}	AS	rs6964720 (A)	0.25	
<i>IKZF1</i>	7p13	0.72	2.8×10^{-23}	AS, EU	rs4917014 (C)	0.25	
<i>JAZF1</i>	7p15.2	1.19	1.5×10^{-9}	EU	rs849142 (T)	0.49	
<i>IRF5/TNPO3</i>	7q32	1.54	3.611×10^{-19}	EU, AA, AS, HA	rs12537284 (A)	0.19	Independent variants reduce IRF5 activity
<i>XKR6</i>	8p23.1	0.81	2.5×10^{-11}	EU	rs6985109 (G)	0.49	
<i>BLK</i>	8p23	0.69	2.1×10^{-24}	EU, AA, AS, HA	rs7812879 (A)	0.12	
<i>LYN</i>	8q13	0.77	5.4×10^{-9}	EU, AA, AS	rs7829816 (C)	0.18	
<i>LRRC18</i> , <i>WDFY4</i>	10q11.23	1.24	7.2×10^{-12}	AS	rs1913517 (A)	0.33	rs877819 disrupts YY1 binding and decreases expression of WDFY4
<i>CD44/PDHX</i>	11p13	0.71	4.0×10^{-12}	EU, AS, AA	rs507230 (G)	0.44	
<i>PHRF1/IRF7/</i> <i>KIAA1542</i>	11p15.5	0.78	3×10^{-10}	EU, AA	rs4963128 (T)	0.05	IRF7 Q412R increases IRE transcription
<i>ETS1</i>	11q24.3	1.37	1.8×10^{-25}	AS	rs6590330 (A)	0.41	
<i>SLC15A4</i>	12q24.32	1.26	1.77×10^{-11}	AS	rs1385374 (A)	0.25	
<i>ELF1</i>	13q13	1.26	1.5×10^{-8}	AS	rs7329174 (G)	0.28	
<i>CSK</i>	15q24.1	1.32	1.04×10^{-9}	EU	rs3433034 (A)	0.27	
<i>ITGAM</i>	16p11.2	1.62	1.61×10^{-23}	EU, AS, HA	rs9888739 (T)	0.19	ITGAM R77H compromises leukocyte adhesion
<i>PRKCB</i>	16p11.2	0.81	1.4×10^{-9}	AS	rs16972959 (A)	0.23	
<i>IRF8</i>	16q24.1	1.16	2.08×10^{-10}	EU	rs11644034 (A)	0.17	
<i>TYK2</i>	19p13.2	1.20	3.88×10^{-8}	EU	rs280519 (A)	0.47	
<i>IKZF3</i>	17q21	1.9	4.83×10^{-9}	EU, AA, HA	rs8079075 (G)	0.17	
<i>ZPBP2</i>	17q12	1.92	3.48×10^{-10}	EU, AA	rs1453560 (C)	0.06	
<i>CD40</i>	20q12	0.63	2.0×10^{-8}	EU	rs4810485 (T)	0.24	
<i>UBE2L3/HIC2</i>	22q11.21	0.78	1.48×10^{-16}	EU, AS	rs463426 (G)	0.41	
<i>TLR7</i>	Xp22.3	0.60	6.5×10^{-10}	AS	rs3853839 (G)	0.19	
<i>IRAK1/MECP2</i>	Xq37	1.39	6.65×10^{-11}	EU, AS, HA	rs1734787 (C)	0.17	

*Genetic variants at 45 loci that implicate more than 70 genes as candidates for generating lupus disease risk and participating in the etiology of lupus through association studies, replication in populations of diverse ancestry, and family studies. Variants in *CFHR3/CFHR1*, *NMNAT2*, *ICA1*, *IKKB*, *SCUBE1*, and *CD247* have probabilities approaching genomewide significance ($5 \times 10^{-8} < P < 10^{-7}$) and are the focus of current replication studies. AA, African; AS, Asian; EU, European; HA, Hispanic Amerindian; MAF, minor allele frequency; NF- κ B, nuclear factor κ B; SNP, single nucleotide polymorphism.

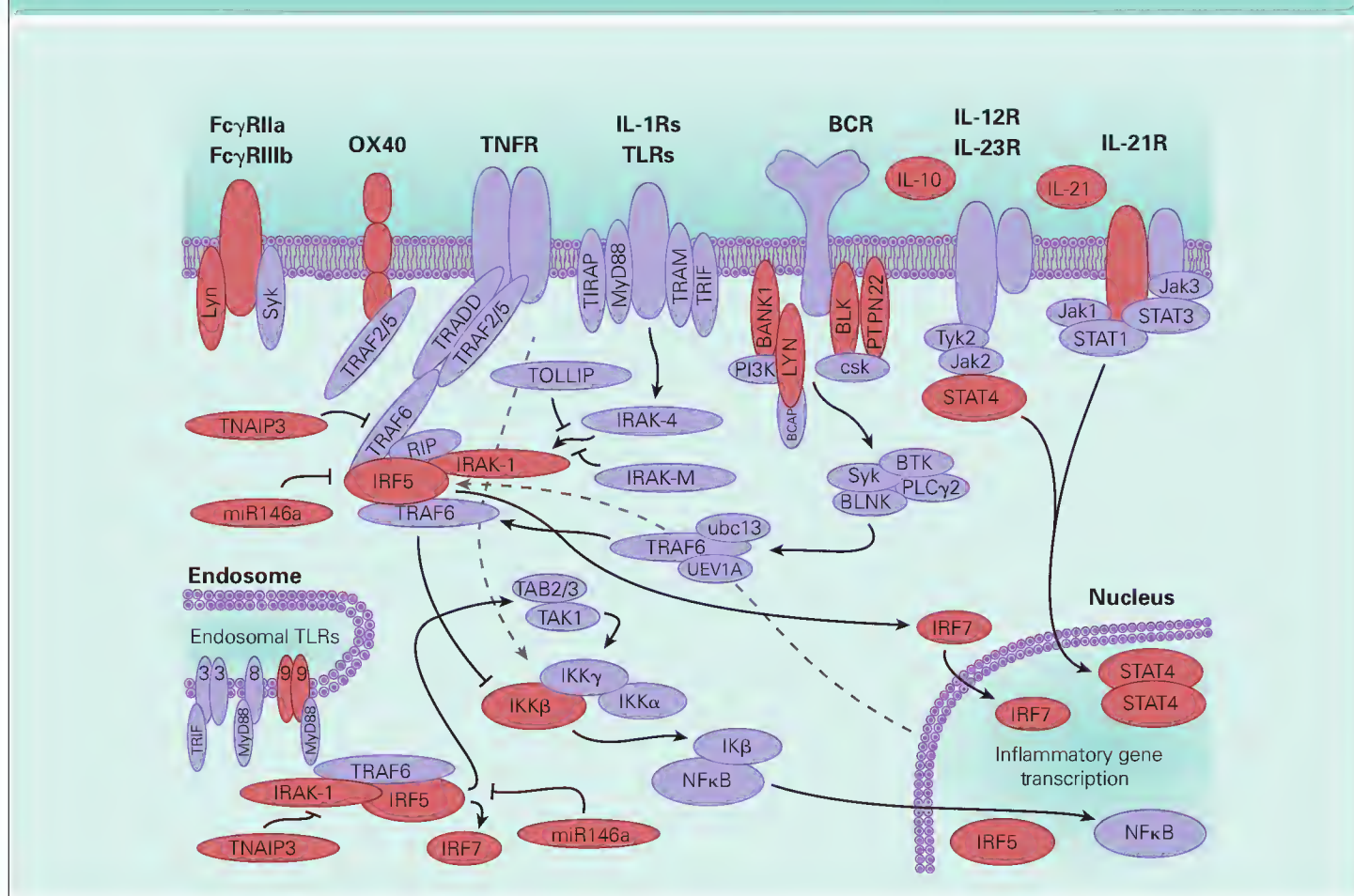
LUPUS RISK GENES REGULATE THE IRF5-STAT4-NF κ B CELL SIGNALING PATHWAYS

Fig. 127.1 Lupus risk genes regulate the IRF5–STAT4–NF κ B cell signaling pathways. Engagement of cell surface receptors, either inhibitory or excitatory, induces signaling events involving numerous lupus-associated genes. Proteins shaded in red are coded by lupus risk-associated genetic loci.

DNA appear to be transmitted intact. The average size of these blocks is directly correlated with ancestral age of the population. For European ancestry, which arose from a population bottleneck approximately 50,000 years ago, the inherited blocks have an average size of about 30,000 bases of DNA. African ancestral populations are evolutionarily much older; the last population bottleneck probably occurred 200,000 years ago, thus providing more time and human generations for crossovers to occur and leading to the smaller average inherited blocks observed of about 11,000 bases.²¹ These properties are used in trans-ancestral studies to localize and help identify the causal polymorphisms responsible for the observed genetic associations for phenotypes that occur in all human ancestries, such as lupus. (A caveat: We do not yet have a genetic explanation for why SLE is more prevalent in non-European ancestries.)

In general, the mechanism of how the genetic associations discovered in GWASs are interrelated would be expected to reveal the underlying genetic architecture and specific genetic relationships that lead to pathogenesis. The prejudice, based on decades of experimental data showing specific biologic interactions at the molecular level, was that the genetic interrelationships will be specific and therefore tend to be epistatic, which means that phenotype expression should require multiple simultaneously present variants at different loci. This is not what the results now teach. Instead, they show additive relationships: one genetic association is usually added to the next as though there were no specific interaction between the genetic associations discovered in GWAS projects. How generally true this tentative conclusion really is must await more complete explanations of the origins of genetic risk, but for now we are left with the surprising finding that genetic risk for the usual form of the SLE phenotype is ordinarily additive across disease risk variants.

ISOLATED CASES

Rare cases of a phenotype often provide genetic differences that lead to major insights into pathophysiology. SLE is no exception in this regard.

Early onset with severe disease may mean that a gene with major impact is operating to produce the phenotype. Lupus or lupuslike disease in both humans and mice appears to occur as a single gene defect in more than 35 genes. Two especially informative examples are discussed.

TREX1

Mutations in the 3' exonuclease TREX1 lead to autoimmunity. This is an informative example of how mutations in a single gene can lead to lupuslike disease. The *TREX1* gene is located at chromosome 3p21.31 and encodes a 314–amino acid protein DNA exonuclease that degrades DNA in the cytosol and nucleus, thereby preventing innate immune activation.²² Nuclear DNA left undegraded by dysfunctional TREX1 constitutes a damage-associated molecular pattern (DAMP) and activates pattern recognition receptors leading to the production of type I interferon, which predisposes to the development of lupus autoimmunity. This autoimmunity can be inhibited or ameliorated in murine models by induced genetic dysfunction of *irf3*, *ifn α* , or *rag2*²² or with inhibitors of reverse transcriptase.²³

Autosomal recessive or compound heterozygous variants of TREX1 are found in many children with Aicardi-Goutières syndrome (AGS), in whom lupus often develops. These patients demonstrate neurologic deterioration along with an SLE-like autoimmunity and elevated levels of interferon- α .²⁴ The known TREX1 variants associated with AGS appear to be a mixture of *de novo* mutations and rare polymorphisms.^{5,25} The *de novo* mutations are most often C-terminal frameshift mutations downstream of the catalytic domains. They alter subcellular localization of the TREX1 protein.

Dysfunctional gene products from the *TREX1* gene are also associated with SLE through an autosomal dominant mechanism in cases of familial chilblain lupus.²⁶ Acral dermatoses and cold sensitivity, especially of the hands, and sometimes evidence of systemic autoimmunity develop in infants with this condition.²⁷ The autosomal dominance is thought to occur through the competitive binding of DNA by the catalytically inactive dominant mutants, which precludes access to DNA by active TREX1.^{28,29}

Rare variants of *TREX1* associated with SLE are found in approximately 0.5% to 1% of the usual SLE patients, with a fraction of these variants probably being *de novo* mutations and the others being rare inherited *TREX1* variants.⁵ The development of autoimmunity attributable to mutations in *TREX1* underscores the importance of homeostatic clearance of danger signals from the cytosol, such as undegraded ssDNA, which prevents cell signaling pathways culminating in the production of cytokines such as type I interferons.

Even though *TREX1* is the most common and most studied of the genes and gene products that cause AGS, we would be remiss to omit mention of other genes in this pathway that appear to operate through the mechanism of disrupting the RNase H2 endonuclease complex (*RNASEH2B*, *RNASEH2C*, and *RNASEH2A*) and the deoxynucleoside triphosphate hydrolase *SAMHD1*, which also cause AGS.

Early complement components

The complement system is made up of small soluble proteins found in plasma that act together as a rapid defense against pathogens in the extracellular space and modulate the inflammatory response. Each of the three complement activation pathways (i.e., lectin, classical, and alternative) involves a proteolytic cascade culminating in C3 convertase.³⁰ Once established on the microbial surface, this convertase targets cells both for lysis and for phagocytosis. Meanwhile, the proteolytic by-products of the complement cascade act as small-molecule mediators of inflammation that recruit and activate inflammatory cells, thereby increasing vascular permeability and the expression of cell adhesion molecules. In addition to its roles in the innate immune system, the complement pathway maintains physiologic homeostasis through the clearance of apoptotic cells and immune complexes.³¹⁻³³ Apoptotic cells bind to early complement components, which enhances their capture by phagocytes and hence limits the inflammatory consequences.^{30,33}

Genetic deficiencies of early complement components result in a high likelihood of the development of SLE (reviewed in reference 34). Subjects with deficiencies of the C1 subcomponents (C1q, C1r/C1s) have a very high risk for the development of lupus (>90%), often with severe morbidity and glomerular nephritis.³⁵ Individuals with a deficiency of C4 also have a risk for the development of lupus (≈50%), whereas C2 deficiency results in an incidence of SLE estimated to be between 10% and 20%.^{36,37} When compared with the average lupus patient (a woman with disease onset in her childbearing years and no known predisposition), lupus in patients with deficiencies of C1q, C1r/C1s, or C4 occur with equivalent incidence in females and males and generally have an onset in childhood.³⁸ Notably, no other autoimmune disease, organ-specific disease, or systemic disease exhibits such an association with complement deficiencies.³⁴ These observations underscore the importance of the complement pathway in the pathogenic mechanisms of SLE and the apparent contradiction that on the one hand, complement is consumed by most lupus patients and is used as a measure of disease activity and, on the other hand, its absence increases disease risk. Attenuation of the inflammatory response by complement components, especially by their action in reducing the impact of immune complexes by many mechanisms, appears to explain why their absence is disease inducing.

EXAMPLES OF LUPUS RISK LOCI IDENTIFIED THROUGH POPULATION SAMPLE STUDIES

HLA

The human leukocyte antigen (HLA) region on the short arm of chromosome 6p21 is known to encode more than 180, mostly immunologically relevant genes, including a set of membrane glycoproteins called the major histocompatibility complex (MHC). MHC molecules either present antigenic peptides from the cytosol or internalize extracellular pathogens to T cells. Genes for the MHC modules are among the most polymorphic in the human genome, with a large number of alleles at many of the various HLA loci. Many, if not most autoimmune diseases demonstrate a strong genetic association with variants in this region. Indeed, the first genetic association with SLE was found to involve the HLA region in 1971.³⁹ We still do not know why the histocompatibility antigens are associated with this disorder. It is widely suspected that the HLA relationship underlies a specific critical antigen in the generation of disease, but the identity of this antigen or other reasons for the association remain unknown.

Strong evidence has shown multiple, independent disease associations with SLE in the HLA region; however, the extensive linkage disequilibrium

in this region (>5 megabases) masks the identity of the genes responsible for the observed associations (see reference 40; reviewed in reference 4). Logistically, it is difficult to identify separate, mechanistically independent variants that affect lupus risk because so many of the HLA variants are inherited together. The strongest associations in the region with lupus are at HLA-DRB1 and the class I HLA-B/HLA-C region. Previously reported associations with *TNFB*, *NCR3*, *MICB*, *NOTCH4*, *AIF1*, *BAT2*, *HLA-DQA1*, and *HLADQB1* may or may not be due to their linkage disequilibrium with HLA-DRB1.^{40,41} The specific explanations for why these powerful associations are found with SLE remain unknown.

TNFAIP3

Tumor necrosis factor- α -inducible protein 3 (*TNFAIP3*) encodes the ubiquitin-modifying enzyme A20, which is a critical regulator of inflammation that dampens nuclear factor κ B (NF- κ B) signals through removal of the K63-linked ubiquitin chains and the addition of K48-linked ubiquitin chains from target molecules such as TRAF6. A20 is activated by CD40 and MyD88-linked toll-like receptor (TLR) signaling. When A20 protein expression is reduced, the risk for development of an autoimmune phenotype in murine B cells is increased.

Variants in *TNFAIP3* have reproducibly been associated with the development of lupus (reviewed in reference 4). A recent trans-ancestral study suggested that the causal variant is located in a region of high evolutionary conservation that is normally bound by NF- κ B.⁴² Functional experiments have revealed that a dinucleotide variant attenuates NF- κ B binding affinity and reduces *TNFAIP3* mRNA and A20 protein expression.⁴² Identification of noncoding functional variants that are likely to drive the increased risk for lupus is promising and was made possible by our enhanced understanding of the role of regulatory elements in the regulation of gene expression. Specifically, expansion of known sequences that are bound by transcription factors is making it possible for groups to develop and test hypotheses to explain the molecular mechanisms driving lupus risk associations, such as that seen at the *TNFAIP3* locus.

ITGAM

ITGAM encodes the α -chain subunit of the heterodimeric immune cell integrin CD11b (also called CR3 and Mac-1). It is involved in a variety of adhesive interactions between monocytes, macrophages, and granulocytes and plays a role in the uptake of complement-coated particles. A nonsynonymous variant in exon 3 of *ITGAM* resulting in an arginine-to-histidine conversion at position 77 (R77H) has been reproducibly associated with SLE (reviewed in reference 4). When assessed in a case-only subphenotypic analysis, this variant has most strongly been associated with lupus patients who exhibit renal disease, discoid skin lesions, or immunologic manifestations.⁴³⁻⁴⁵ The R77H variant reduces the affinity of CD11b for intercellular adhesion molecule 1 (ICAM-1) and ICAM-2 and limits the ability of cells expressing the variant to perform iC3b-dependent phagocytosis.^{46,47} A recent trans-ancestral study of the association of multiple members of the integrin-adhesion molecule pathway found that the combined effects of common variation in *ITGAM* and the *ICAM1-ICAM4-ICAM5* locus resulted in an OR of 4.08, one of the highest disease risk genetic associations found in lupus to date.⁴⁸

Many lupus-associated variants are shared with other autoimmune diseases. The *ITGAM* association, however, appears to be somewhat specific to lupus, with conflicting results in studies on systemic sclerosis.⁴⁹⁻⁵¹ Because the risk allele at *ITGAM* reduces the function and binding capacity of CD11b and because this molecule is a receptor for the inactivated fragment of complement component C3 (iC3b), the relevance to lupus may operate through the complement pathway, analogous to the discussion of complement component deficiencies presented earlier.

IRF5-TNPO3

Genetic variants in the interferon regulatory factor 5 (*IRF5*)-transportin 3 (*TNPO3*) region of chromosome 7 have been associated with SLE in every published lupus study and in every ethnicity study testing this genomic region that has been reported to date (reviewed in reference 4). Indeed, of the nearly 50 genetic associations with SLE now identified (see Table 127.1),⁵² the association with *IRF5-TNPO3* ranks first for replication consistency (16 of 16 studies), high for magnitude ($1.4 < \text{OR} < 2.3$), and very low for cumulative probability of an accidental chance association ($P < 1 \times 10^{-50}$). When evaluating SLE subphenotypes, *IRF5* is most closely associated with anti-Ro and anti-dsDNA autoantibodies, where the OR has been found to be as high as 5.83.⁵³

IRF5-TNPO3 has been associated with seven autoimmune disorders (SLE, rheumatoid arthritis, multiple sclerosis, ulcerative colitis, progressive systemic sclerosis, Sjögren syndrome, and primary biliary cirrhosis^{12,54-61}). Furthermore, the efficacy of interferon therapy for multiple sclerosis is associated with *IRF5-TNPO3* variants,⁶¹ and the *IRF5* variants associated with SLE risk have increased efficacy in the treatment of metastatic melanoma after the infusion of extracorporeally interleukin-2 (IL-2)-expanded autologous T cells.⁶²

IRF5 variants are such attractive candidates for disease risk causation because of the extraordinary importance of *IRF5* to the immune response. *IRF5* is a transcription factor important for immune responsiveness, infection, inflammation, and autoimmunity. Indeed, *IRF5* also induces cell cycle arrest and cell death and is required for B-cell differentiation.^{63,64} Within the *IRF5-TNPO3* region, *IRF5* is typically assumed by most investigators to be the primary suspect gene for altering SLE risk, and *TNPO3* is inappropriately ignored. *TNPO3* acts as a nuclear import receptor for serine/arginine-rich proteins such as the splicing factors *SFRS1* and *SFRS2*.⁶⁵ Moreover, *TNPO3* has been shown to be involved in the nuclear transport of human immunodeficiency virus and some other lentiviruses. Perhaps, disease risk directly involves *TNPO3*, or independent genetic effects lead to biologic changes in the activity of both *IRF5* and *TNPO3*. The presently most popular hypothesis among investigators is that functional variants in *IRF5* that decrease expression or activity are responsible for disease risk association.

STAT4 and STAT1

The *STAT4* and *STAT1* genes are neighbors on chromosome 2 and encode proteins that belong to a family of transcription factors originally isolated by their binding to cytokine-inducible genes.⁶⁶ Both *STAT1* and *STAT4* are expressed in hematopoietic cells (including T cells, B cells, and myeloid cells) and the testis.⁶⁷ Importantly, they are both activated in response to IL-12 and type I interferons.^{68,69}

The IL-12 receptor is a heterodimer that consists of IL-12Rβ2 and IL-12Rβ1, which are coupled to the Janus kinases JAK2 and TYK2. After phosphorylation by JAK2 or TYK2, *STAT4* or *STAT1* dimerizes and is translocated to the nucleus, where dimer binding induces gene transcription. This design makes possible a rapid response to cytokine stimuli such that the expressed latent transcription factor is poised until phosphorylated and then quickly initiates the downstream events. In this manner, the levels of *STAT* proteins can rapidly dictate the magnitude of the transcriptional response.

Many groups have confirmed the association of the *STAT4-STAT1* locus in lupus (reviewed in [reference 4](#)). Currently, the genetic association with lupus is confined to 55.5 kb between exons 3 and 5 of *STAT4*, and the genetic association is often referred to as an association with *STAT4*. It remains possible, however, that variants in the associated region have an impact on the expression of *STAT1* or even a distant gene in a way that alters disease risk. The relatively large size of the region of association and the failure to date to reduce the interval supporting the association is the major impediment to progress in identifying the causal polymorphism. Identifying the causal variant driving this association could elucidate how the dysregulation of *STAT4* or *STAT1* (or some other gene) leads to increased risk for lupus.

CD44

The *CD44* gene spans nearly 100 kb and contains 20 exons that encode a cell surface glycoprotein expressed on most immune cells. Expression of *CD44* is complicated by complex splice variations that result in hundreds of protein isoforms (reviewed in⁴). Immunologically, *CD44* plays critical roles in tumor metastasis, hematopoiesis, apoptosis, lymphocyte activation, and immune cell recirculation and homing.⁷⁰⁻⁷² On the cell surface, *CD44* forms heterodimers that bind to a wide variety of ligands that have been directly linked to autoimmunity, including hyaluronic acid, collagens, and matrix metalloproteinases.^{73,74}

Variants of *CD44* were first implicated in SLE as an extension of linkage.⁷⁵ More recently, a large multi-ancestral fine mapping study produced a genome-wide association with variants in a haplotype directly upstream of *CD44* that appear to influence the expression of *CD44*.⁷⁶ The causal variants for the *CD44* association with SLE disease risk remain unknown.

Sex chromosomes

Women are approximately 10 times more frequently affected by SLE than men are. Despite the many family studies and GWAS projects that have been done, the basis of this sex difference in lupus prevalence is not known. Both

the approximately 14-fold higher prevalence of SLE in men with Klinefelter syndrome (47,XXY) and experiments in mice⁷⁷ suggest that this is a gene dose phenomenon, but which gene or genes are responsible have yet to be defined.^{7,8,78} Strikingly, a recent study found that men with lupus have a significantly higher cumulative genetic risk for SLE than women do and a higher level of gene-sex interaction.⁷⁹ Some genetic variants on the X chromosome demonstrate strong statistical association with the development of lupus after adjusting for the mechanism of inheritance of the sex chromosomes.

The genetic associations found in GWASs on the X chromosome would conceivably be candidates to explain the sex difference in prevalence between male and female SLE, but this expectation has not yet been realized.

TLR7

TLR7 binds RNA in endosomes and activates the interferon response through MyD88. A variant of TLR7 has been found in Asian men and women in multiple studies⁸⁰⁻⁸²; however, the extent to which the association with male SLE is of substantially greater magnitude (OR > 4) than the association with female SLE (OR = 1.34) was unanticipated⁸² because this result is counter to what would be expected if this locus contributed to the female predominance in SLE.

Mechanistically, TLR7 is an important pattern recognition receptor of the innate immune system and initiates a signaling cascade that culminates in the production of type I interferons.⁸³ A twofold increase in TLR7 expression was found to be sufficient to lead to autoantibody production and spontaneous autoimmunity in transgenic mouse models.⁸⁴

IRAK1/MECP2

Epigenetic modifications have been shown to affect disease expression in autoimmunity; for example, abnormal T-cell methylation is strongly associated with the pathogenesis of lupus.^{85,86} In T cells taken from patients exhibiting lupus flares, expression of enzymes that maintain DNA methylation during cell division is reduced, and promoters of methylation-sensitive genes are hypomethylated.⁸⁷ Methyl-CpG-binding protein 2 (MECP2) recruits histone deacetylase enzymes to methylated CpG sequences, which leads to compaction of the chromatin and attenuated gene expression.⁸⁸ Furthermore, genetic variants of *MECP2* have been reproducibly associated with the development of lupus (reviewed in [reference 4](#)). *MECP2* and *IRAK1* are neighbors on chromosome Xq28, and both are reasonable candidates to be SLE risk genes. Data supporting an association with *IRFK1* are just as convincing as the association with *MECP2*. Their variants are in high linkage disequilibrium with each other, thus making identification of the causal variant or the critical gene variation challenging. *IRAK1* deficiency abrogates the development of disease in lupus-prone mice.⁸⁹ Further complicating identification of the molecular mechanisms driving the increased risk for lupus in subjects with the risk allele or alleles, *MECP2* regulates the expression of *IRAK1*.⁹⁰ As in many other lupus risk loci, identifying the causal genetic element or elements at this locus may prove to be difficult. We should not eliminate the possibility that variants at both *IRAK1* and *MECP2* contribute to SLE risk.

SOME OPEN QUESTIONS

Each of the genes known to be involved in SLE (see [Table 127.1](#)) has a story analogous to those just presented, which will no doubt mature and provide a much deeper understanding of SLE pathogenesis. We have discussed only a subset of the known genetic associations, now numbering more than 40 and soon expected to number more than 100 genes convincingly associated with SLE. The complexity of SLE pathogenesis is daunting, as has recently been reinforced by the extraordinary data generated from the ENCODE project.

How many gene variants contribute to SLE? Because only a small proportion of the heritability is explained, much is left to learn. Perhaps there will be hundreds of genes. Perhaps better models and more detail will reveal a greater magnitude for the genes that we already know. Perhaps other approaches not yet explored (sequencing, family studies, somatic mutation) will reveal genes and mechanisms that have not yet been amenable to exploration. No doubt all of these possibilities will contribute to a far more complete understanding of lupus genetics.

THE FUTURE OF SYSTEMIC LUPUS ERYTHEMATOSUS GENETICS

Future editions of this textbook are likely to describe the clinically relevant insights from epigenetics and from the recently achieved ability to sequence the human genome. We would expect to find many new genes causing SLE that operate through *de novo* mutation, somatic mutation, recessive, and compound heterozygous mechanisms. These studies are expected to provide a much more complete description of the genetics of SLE, which will aid in

diagnosis, prognosis, and the development of more specific and possibly more effective therapeutics than are now available.

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An enormous amount of work and resources went into bringing the knowledge of lupus genetics to the point reviewed in this chapter. Unfortunately, because of space restrictions, all of the original sources were unable to be cited individually.

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Immunopathology of systemic lupus erythematosus

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- Systemic lupus erythematosus, the prototypic immune complex disease, is characterized by excessive antibody formation and immune complex deposits in tissue.
- Characteristic lesions include hematoxylin bodies, Libman-Sacks endocarditis, vasculitis, thrombotic microangiopathy, and glomerulonephritis.
- Antibody properties are important in determining the pathogenic potential of immune complexes.
- Complement deficiencies may alter the handling of immune complexes. Genetic variations in receptors for immunoglobulin (Fcγ receptors) influence antibody binding and the pathologic effects of immune complexes.

INTRODUCTION

Systemic lupus erythematosus (SLE), the prototypic immune complex disease, is characterized by excessive autoantibody production, immune complex formation, and immunologically mediated tissue injury. Tissue pathology in all organs reflects a variety of aberrant immunologic mechanisms, but tissue damage in patients with lupus may also reflect nonimmunologic processes. Some aspects of disease, such as early atherosclerosis, may be both initiated and accelerated through immunologic effector mechanisms.

The complexity of the abnormal immunoregulation observed in patients with SLE has made it difficult for clinical investigators to clearly identify the critical elements underlying the immunopathogenesis of SLE. However, several interrelated immunologic elements may be central, beginning with innate immune activation and augmented production of type I interferons. Aberrant adaptive immune responses, related to B-cell and T-cell abnormalities, including defects in B-cell tolerance, autoantigen-specific helper T cells, and intrinsic T-cell functional and biochemical irregularities, result in the production of autoantibodies. Production of at least some of these autoantibodies is driven by increased levels of nucleosomes, perhaps reflecting accelerated apoptosis and defective clearance (waste disposal),¹ and by abnormal cytokine concentrations. The sum of these abnormalities is an array of autoantibodies and circulating immune complexes. Taken together with deficiencies in mononuclear phagocyte function and immune complex clearance, SLE is a critical model for our understanding of immune complex-mediated immunopathogenesis.

Unlike some autoimmune diseases, such as Hashimoto thyroiditis and myasthenia gravis, which are highly organ specific, SLE affects many different organs in a systemic fashion and is not organ specific (Fig. 128.1). In this regard, the autoimmune mechanisms in SLE may be more similar to those found in diseases such as Sjögren syndrome, rheumatoid arthritis, dermatomyositis, and scleroderma, as suggested by Klemperer and coworkers^{1a} in their studies of the “connective tissue” diseases. Certainly, autoantibody formation, immunoglobulin deposition, and primary or secondary infiltration of tissues with mononuclear cells are cardinal features of the disease. Both antigen-specific and antigen-nonspecific immunologic targeting may be important. These processes eventually become apparent through a broad range of pathologic manifestations, including fibrinoid necrosis, hematoxylin bodies, vascular injury, disruption of the dermal-epidermal junction of skin, and glomerulonephritis.

PATHOLOGY

Characteristic lesions

Hematoxylin bodies

Several pathologic findings are characteristic of SLE. Hematoxylin bodies are usually oval or spindle-shaped basophilic structures that may approach the size of an intact cell. Also known as LE bodies, hematoxylin bodies resemble aggregates of chromatin and degenerated cytoplasmic organelles and can be formed *in vitro* from epithelial cell nuclei. Biochemically, they appear to contain both DNA and immunoglobulin,² probably reflecting the interaction of antinuclear antibodies with degenerating nuclear material. Derived from dead cells, hematoxylin bodies are most often described in glomeruli and the endocardium but can occur in almost any organ (Fig. 128.2a). They are identified in only a small number of biopsy specimens but are highly suggestive of SLE. Engulfment of hematoxylin bodies by phagocytes produces the characteristic LE cell, a phagocyte with a large basophilic inclusion (see Fig. 128.2b).

Libman-Sacks endocarditis

At autopsy, the majority of patients who had SLE have nonbacterial, verrucous endocarditis, also known as Libman-Sacks endocarditis. Grossly, these small friable vegetations are often present in large numbers, especially at the forward-flow edges of the valve. The mitral valve is most commonly affected, but verrucae may be seen on other valves, chordae tendineae, and the endocardium. Microscopically, the verrucae consist of proteinaceous deposits and mononuclear cells in the context of platelet thrombi and necrotic cell debris (Fig. 128.3). The occurrence of valvular lesions in association with antiphospholipid antibodies raises interesting speculations about the pathogenesis of verrucous endocarditis, but the valvular abnormalities in primary antiphospholipid syndrome appear to be distinct, with valvular thickening and occasionally nodules but no vegetations.^{3,4} For verrucous endocarditis, it is possible that circulating immune complexes may adhere to the valvular surface, contribute to initial endocardial damage, and serve as a nidus for the deposition of fibrin and platelets.

Cutaneous immunopathology

The pathology of skin lesions illustrates the basic pathophysiologic mechanisms in SLE: immune complex formation with consequent tissue damage, acute vascular and perivascular inflammation, and more chronic mononuclear cell infiltration. Each of these features can be found in the histopathology of cutaneous lupus, although immunoglobulin deposition at the dermal-epidermal junction is the most consistent.

Analysis of lesional skin in SLE may demonstrate liquefactive degeneration of the basal cell layer of the epidermis, fibrinoid necrosis of the dermis, and perivascular and perifollicular infiltrates of inflammatory cells. Chronic lesions exhibit prominent hyperkeratosis and follicular plugging, although these features are less evident in subacute cutaneous lupus and usually absent in acute cutaneous lesions. Disorganization of the basal cell layer of the epidermis is found in chronic cutaneous and subacute cutaneous lesions; it may also be present in acute cutaneous lesions, although it may be more subtle. The mononuclear cell infiltrate, typically with T-cell predominance, in the upper regions of the dermis may disrupt the dermal-epidermal junction in chronic lesions but tends to be more localized to perivascular and periappendageal areas in other lesions.⁵ Edema of the upper dermis with extravasation of erythrocytes can be found in all SLE skin lesions.

In less common forms of lupus skin lesions, the histologic picture is somewhat different. Bullous SLE is characterized by subepidermal bullae without vacuolar degeneration, but with an inflammatory infiltrate (mostly

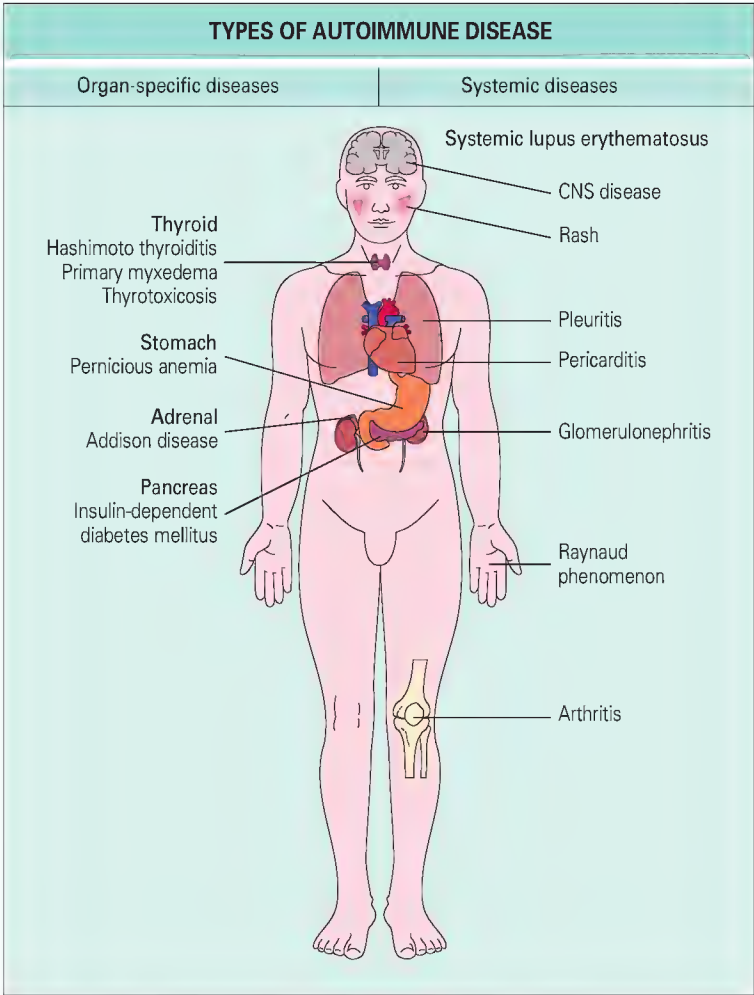


Fig. 128.1 There are two types of autoimmune disease: organ specific and systemic. Although the systemic autoimmune diseases produce symptoms in several organs, each disease may be marked by characteristic patterns of organ involvement. CNS, central nervous system.

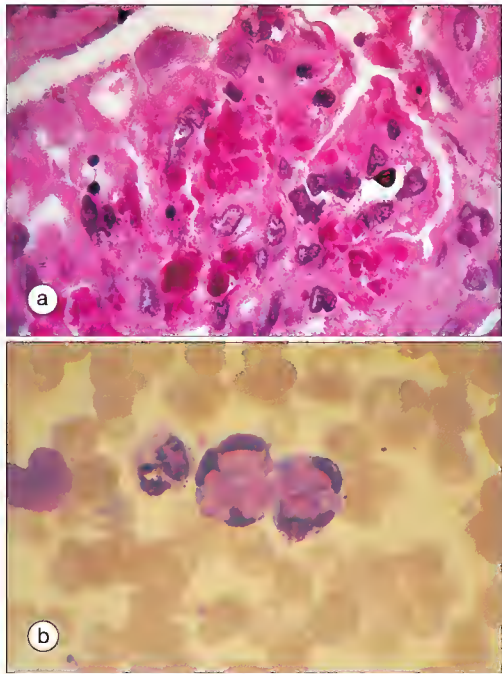


Fig. 128.2 Hematoxylin bodies. (a) A glomerulus containing several lilac hematoxylin bodies, which correspond to exposed nuclei in which the chromatin has undergone swelling and clumpy transformation after complexing with ambient antinuclear antibody (hematoxylin-eosin). (b) LE cells. Two phagocytic cells have ingested large basophilic inclusions. The inclusions, termed *hematoxylin bodies* when seen before ingestion, contain DNA and IgG (Wright stain). (With permission from Professor I.M. Roitt.)

neutrophils) in the dermal papillae.⁶ In lupus profundus or lupus erythematosus panniculitis, deep dermal and subcutaneous involvement with nodules is seen. Lesions in the epidermis may or may not accompany nodule formation.⁷

In almost all cases, deposits of immunoglobulin (IgG, IgA, and IgM) and complement components from the classical and alternative pathways are observed along the dermal-epidermal junction at the site of cutaneous lesions. In the majority of patients with systemic disease, immunofluorescence reveals similar deposits at the dermal-epidermal junction in normal non-sun-exposed skin and at sites of cutaneous lesions. This characteristic immunofluorescence, the lupus band test (Fig. 128.4), may be helpful in diagnosis, although it can also be positive in patients with rheumatoid arthritis, Sjögren syndrome, dermatomyositis, progressive systemic sclerosis, and other clinical conditions.⁷

The dermal-epidermal localization of immunoglobulin and complement may result from accumulation in the subepidermal space of nuclear material derived from apoptotic keratinocytes. At the highly vascular dermal-epidermal junction, these nuclear antigens may have the opportunity to react with circulating autoantibodies, to form antigen-antibody complexes and precipitate as immune aggregates, and to initiate tissue injury. This model suggests a basis for the photosensitivity in SLE whereby ultraviolet irradiation leads to increased apoptosis of keratinocytes, increased nuclear

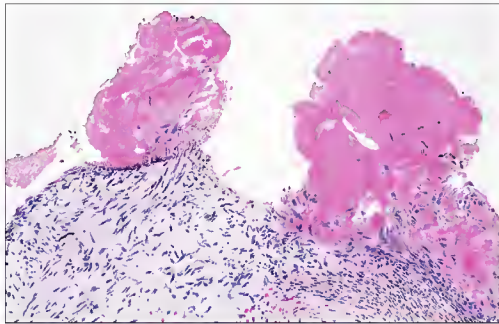


Fig. 128.3 Libman-Sacks endocarditis. Two verrucae on the surface of this valve contain fibrin and necrotic cell debris. Inflammatory cells are localized primarily at the endocardial surface (hematoxylin-eosin).

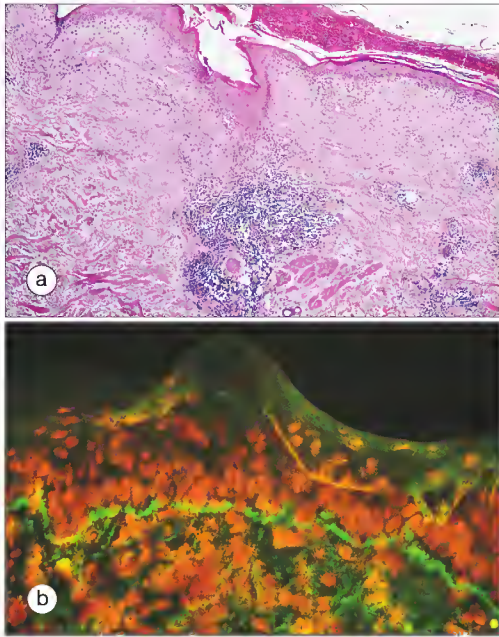


Fig. 128.4 Cutaneous immunopathology and the lupus band test demonstrating immunoglobulin and complement deposition in non-sun-exposed skin. (a) Light microscopy reveals thickening of the dermal-epidermal junction and inflammatory cells associated with a dermal appendage (hematoxylin-eosin). (b) At a higher power, immunofluorescence demonstrates IgM and C3b at the dermal-epidermal junction (bright green horizontal band seen midway through this section). (With permission from Brostoff J, Scadding GK, Male DK, Roitt IM. *Clinical immunology*. London: Gower; 1991.)

debris, and subsequent precipitation of immune complex material at the dermal-epidermal junction. Though attractive, this model does not fully reconcile the presence of immunoglobulin at the dermal-epidermal junction with the absence of accompanying tissue damage and the presence of a lymphocytic infiltrate suggestive of cell-mediated immunity.

Vascular immunopathology

Several types of vascular lesions may occur in SLE. The most common lesion is immune complex deposition in the walls of small arteries and arterioles (Fig. 128.5).⁸ In some instances, the vascular immune deposits occur without an associated inflammatory response and can be demonstrated only by immunofluorescence and electron microscopy. In others, the vascular immune deposits are accompanied by perivascular infiltrates of mononuclear leukocytes. Necrotizing large- or small-vessel vasculitis with fibrinoid necrosis and neutrophil infiltration resembling that seen in polyarteritis nodosa, microscopic polyangiitis, or antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis is relatively uncommon (Fig. 128.6). The necrotizing vasculitis occurring in SLE can be distinguished from that of microscopic polyangiitis or ANCA-associated granulomatous vasculitis by the presence of immune deposits in the vascular wall and the absence of ANCAs. Presumably, these pathologic and serologic distinctions reflect different pathophysiologic mechanisms.

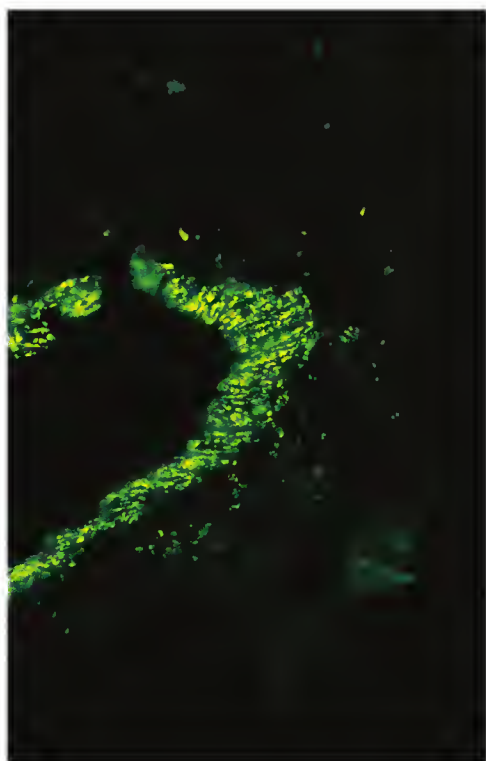


Fig. 128.5 Vascular immune deposits in systemic lupus. Immune complex deposition is demonstrated in the wall of a small intrarenal artery with antibody to human IgG (immunofluorescence, anti-IgG).

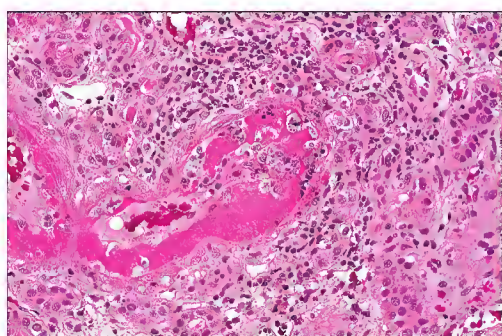


Fig. 128.6 Necrotizing small-vessel vasculitis in systemic lupus. The vasculitis resembles the lesions seen in polyarteritis nodosa/microscopic polyangiitis. Transmural infiltration by lymphocytes and neutrophils can be seen, along with endothelial degeneration and intimal fibrinoid necrosis (hematoxylin-eosin).

The vascular lesions of thrombotic microangiopathy may occur in patients with lupus who have circulating anticardiolipin antibodies, lupus anticoagulant, or both and less commonly in those in whom hemolytic-uremic syndrome develops in association with autoantibody to the von Willebrand factor–cleaving protease.⁹ The lesions of thrombotic microangiopathy in SLE are morphologically indistinguishable from those occurring in hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura. They are characterized by intraluminal fibrin thrombi that may be acute or organizing, but without any accompanying vascular immune deposits (Fig. 128.7).

Immunopathology of lymphoid organs

Lymphadenopathy, either regional or generalized, is a common manifestation of SLE that affects up to 60% of patients.¹⁰ More frequently identified in children and Black individuals, lymphadenopathy may be the initial clinical manifestation of SLE.¹¹ The enlarged cervical, axillary, and inguinal lymph nodes measure up to several centimeters and are typically discrete, soft, and nontender. Histologically, follicular hyperplasia, sometimes forming giant or coalescent follicles, is noted along with enlarged germinal centers and increased numbers of plasma cells and immunoblasts in the interfollicular zones.¹² Hyperplasia and focal necrosis of the paracortical T-cell zones are also observed. Necrotic foci containing hematoxylin bodies are a particularly characteristic, but rare finding. The demonstration of immunoglobulin and complement C3 in the necrotic walls of arterioles and venules suggests immune complex–mediated vasculitis in the pathogenesis of the necrosis. A predominance of paracortical CD11b+CD15+ histiocytes and CD8+ T cells is found adjacent to the necrotic zones.¹³ Lupus-related lymphadenopathy must be distinguished from the tender lymphadenopathy arising from secondary infections or the emergence of a lymphoproliferative disorder after chronic immunosuppression.

Splenomegaly occurs in 10% to 45% of patients, depending on the mode of detection. There is poor correlation between the occurrence of splenomegaly and coexistent cytopenia. The follicular hyperplasia is typically accompanied by periarterial fibrosis of the penicilliary arteries, which produces a distinctive onionskin lesion with multiple tight concentric rings of perivascular collagen. Adjacent calcified fibrous nodules may be observed.¹⁴ Onionskin lesions (Fig. 128.8) have been described in the majority of spleens at autopsy but are not pathognomonic for SLE. Their morphogenesis is unknown, although a role for healed arteritis has been proposed.

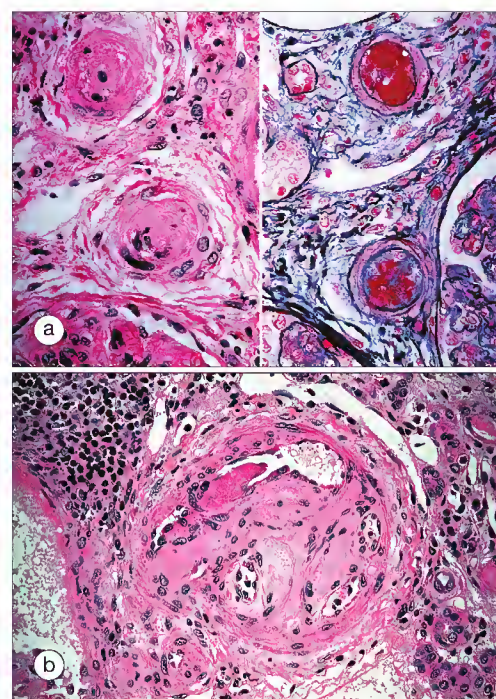


Fig. 128.7 Vascular lesions of thrombotic microangiopathy in systemic lupus. (a) Acute thrombotic lesions with occlusion of the arteriolar lumen by fibrin thrombus that stains eosinophilic (left panel). This intraluminal fibrin produces an orange-staining reaction with the Lendrum stain for fibrin (right panel). The endothelium appears necrotic and desquamated; however, no leukocyte infiltration of the vessel wall is evident. (b) An organized thrombus with recanalization severely narrows a small artery in the kidney from a patient with lupus anticoagulant (hematoxylin-eosin).

Hyposplenism, infarction, and rupture of the spleen have been reported rarely in association with vasculitis of splenic arteries or thromboses related to circulating lupus anticoagulant.

Renal immunopathology

The renal manifestations of SLE, collectively termed *lupus nephritis*, are extremely heterogeneous.¹⁵ All four renal compartments—the glomeruli, tubules, interstitium, and blood vessels—may be affected. The incidence of clinical renal disease underestimates the prevalence of pathologic renal involvement, especially if routine light microscopy is supplemented by the more sensitive techniques of immunofluorescence and electron microscopy. The morphologic features of lupus nephritis are also extremely protean, with the capacity to transform, either spontaneously or in response to treatment.

Lupus nephritis is one of the few renal diseases in which immune deposits can be detected in any or all renal compartments, including the glomeruli, tubules, interstitium, and blood vessels. IgG is found almost universally (>98%) and is usually dominant in intensity. Co-deposits of IgM and IgA are common. Deposits of complement C1 and C3 and properdin can be demonstrated in the majority of cases, consistent with activation of both the classical and alternative complement pathways. When deposits of all three immunoglobulin classes and both C1 and C3 are found, the designation “full house” staining is often applied.

Approach to classification

Investigators have attempted to define and quantify the many morphologic lesions of lupus nephritis in a comprehensive, systematic fashion.¹⁶ Widespread use of the World Health Organization (WHO) classification has improved the uniformity and reproducibility of interpreting biopsy

specimens and has provided the standardized nomenclature essential for clinicopathologic studies addressing outcome and prognosis.¹⁷ In 2004 based on recommendations by the International Society of Nephrology and Renal Pathology Society, the WHO classification underwent minor revision to provide sharper distinctions between the classes (Table 128.1).¹⁸

Even though tubular, interstitial, and vascular lesions are common in lupus nephritis and may contribute significantly to overall disease severity, activity, and chronicity, the WHO classification is based entirely on evaluation of the glomerular alterations. Accurate classification requires careful assessment of the glomerular alterations by light microscopy, followed by integration of the immunofluorescence and electron microscopic findings. The first step is to determine whether glomerular hypercellularity is present in the mesangial, endocapillary, or extracapillary zones. The distribution of the endocapillary hypercellularity is assessed (focal: <50% of the glomeruli affected; diffuse: ≥50%). Attention is given to the presence of infiltrating leukocytes, necrotizing lesions, and glomerular basement membrane thickening. These light microscopic findings are then interpreted in the context of the distribution of the glomerular immune deposits in mesangial, subendothelial, and subepithelial locations as detected by light microscopy, immunofluorescence, and electron microscopy.

The overall distribution of immune deposits detected by immunofluorescence can be refined further at the ultrastructural level. Mesangial electron-dense deposits are typically observed in all classes of lupus nephritis. Mesangial deposits are the defining feature of class I and II and can be considered the common substratum on which the higher classes are built. Both class III and class IV lupus nephritis display subendothelial and mesangial deposits. The distribution of the subendothelial deposits is more focal and segmental in class III and more diffuse and global in class IV, which corresponds to the general distribution of the endocapillary proliferative lesions. Although scattered subepithelial deposits may also be detected in class III and class IV, regular subepithelial deposits are a distinguishing feature of class V.

Class I and class II designate glomerular disease limited to the mesangium (Fig. 128.9). In class I, the glomerular mesangium is normocellular;

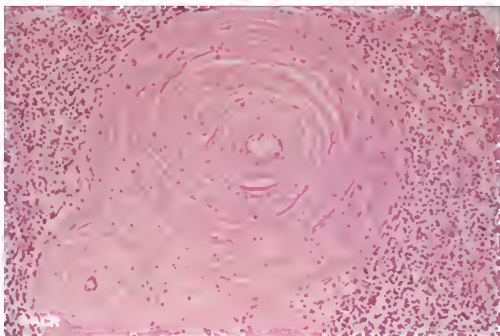


Fig. 128.8 “Onionskin” lesion. Concentric periarterial fibrosis in the malpighian body of the spleen leads to this characteristic structure (hematoxylin-eosin). (Reprinted from the *Clinical Slide Collection on the Rheumatic Diseases*, © 1991, 1995. Used by permission of the American College of Rheumatology.)

TABLE 128.1
World Health Organization classification of lupus nephritis (2004)

Class	Description
I	Minimal mesangial lupus nephritis
II	Mesangial proliferative lupus nephritis
III	Focal lupus nephritis
IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
V	Membranous lupus nephritis
VI	Advanced sclerosing lupus nephritis

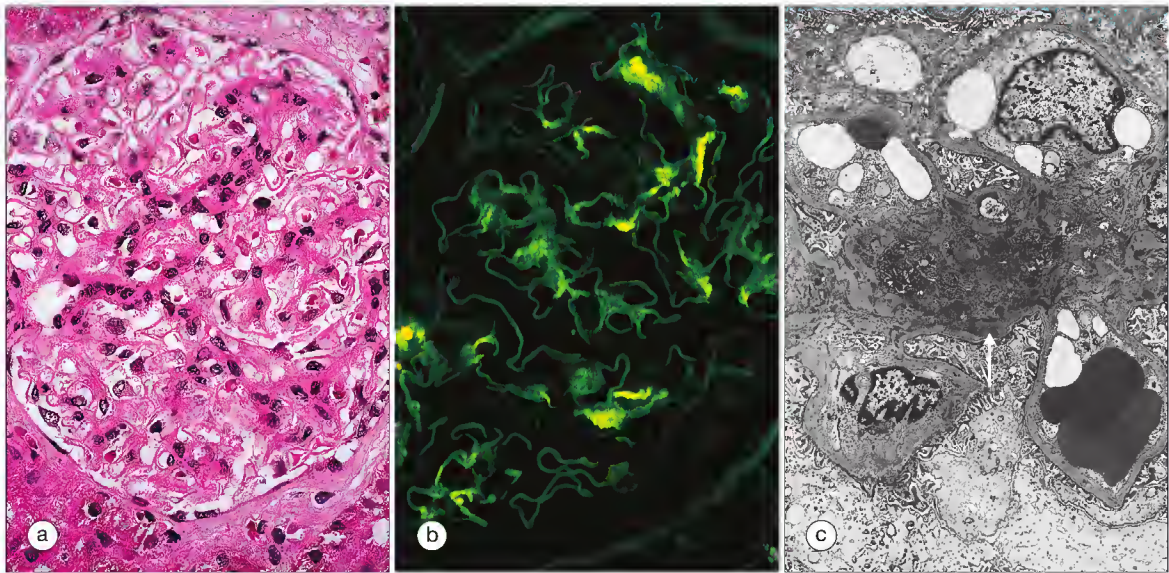


Fig. 128.9 Lupus nephritis class II (mesangial proliferative lupus nephritis). (a) Mild mesangial hypercellularity without compromise of the glomerular capillary lumina (hematoxylin-eosin). (b) Granular deposits of IgG are confined to the mesangial stalk, with sparing of the peripheral glomerular capillary walls (immunofluorescence, anti-IgG). (c) Electron micrograph showing four individual glomerular capillaries oriented around a central mesangial stalk. Electron-dense deposits are present within the central mesangial region (arrow) but do not extend into the peripheral glomerular basement membranes.

however, immune deposits confined to the mesangium can be detected by fluorescence microscopy and electron microscopy. In class II, these purely mesangial immune deposits are accompanied by mesangial proliferation (defined as three or more mesangial cells in mesangial areas away from the vascular pole, as assessed in histologic sections 3 μ m thick).

Most investigators consider class III and class IV lupus nephritis to be qualitatively similar glomerular lesions that differ only in severity and distribution. The glomerular endocapillary lesions are classified according to whether they are focal (affecting <50% of the glomeruli) or diffuse (affecting $\geq$ 50% of the glomeruli) or are segmental (affecting less than half of the glomerular tuft) or global (affecting half or more of the tuft). In assessing the number of glomeruli affected, both active (proliferative) and chronic (sclerosing or scarred) lesions must be taken into account. Class III lupus nephritis consists of a focal, predominantly segmental, endocapillary proliferative glomerulonephritis that affects less than 50% of the glomeruli (Fig. 128.10). Class IV (diffuse) lupus nephritis is distinguished from class III arbitrarily on the basis of involvement of more than 50% of the glomeruli by endocapillary lesions. Typically, the endocapillary proliferation in class IV is relatively diffuse and global (designated IV-G) (Fig. 128.11).¹⁸ However, some cases of class IV lupus nephritis may exhibit a diffuse segmental distribution (designated IV-S).¹⁸ Glomerular endothelial cells, monocytes, lymphocytes, and neutrophils may contribute to the endocapillary hypercellularity (Fig. 128.12a). As in class III, lobules without endocapillary proliferation usually manifest varying degrees of mesangial proliferation (see Fig. 128.10b).

Common light microscopic features of active class III and class IV lupus nephritis include wire loop (subendothelial) deposits, hyaline thrombi, necrosis, hematoxylin bodies, and cellular crescents. Subendothelial immune deposits are the *sine qua non* of active class III and IV lupus nephritis and are typically detectable by immunofluorescence and electron microscopy in

the distribution of the endocapillary proliferation. When large enough to be detected by light microscopy, subendothelial deposits may form “wire loop” thickenings of the glomerular capillary walls (see Fig. 128.12b to d). Some cases of class III or class IV lupus nephritis manifest large intracapillary deposits forming “hyaline thrombi” (see Fig. 128.12b). This term is a misnomer inasmuch as they do not represent true fibrin thrombi but are massive intracapillary immune aggregates. Glomerular necrosis consists of a focus of smudgy fibrinoid degeneration of the glomerular tuft (see Fig. 128.10b). Necrosis may be accompanied by any or all of the following: deposition of intracapillary fibrin, glomerular basement membrane rupture, and apoptosis of infiltrating neutrophils producing pyknotic or karyorrhectic nuclear debris (“nuclear dust”). Although they are the only truly pathognomonic lesions of lupus nephritis, hematoxylin bodies are extremely uncommon and are found in less than 2% of biopsy specimens of lupus nephritis. These smudgy, lilac-staining structures are the tissue equivalent of the LE body and consist of naked nuclei in which the chromatin has been altered by binding to ambient antinuclear antibodies (see Fig. 128.2a). Cellular crescents are a feature of active lupus nephritis that may be encountered frequently in both class III and class IV disease. They are common overlying necrotizing lesions but may also occur in glomeruli with nonnecrotizing endocapillary proliferative lesions.

Active glomerular lesions that persist over time or do not respond to treatment may lead to glomerular scarring (or sclerosis), a feature of chronic and irreversible glomerular injury. In class III, the glomerular scarring is typically focal and segmental, mirroring the distribution of the proliferative and necrotizing lesions. Associated fibrous crescents may form synechiae to the sclerotic segments. Similarly, in chronic class IV lupus nephritis, the glomerular sclerosis is typically more global and diffuse. Of course, glomerular obsolescence is not restricted to class III and class IV but can also supervene on class V. Glomerular sclerosis in lupus nephritis may also occur

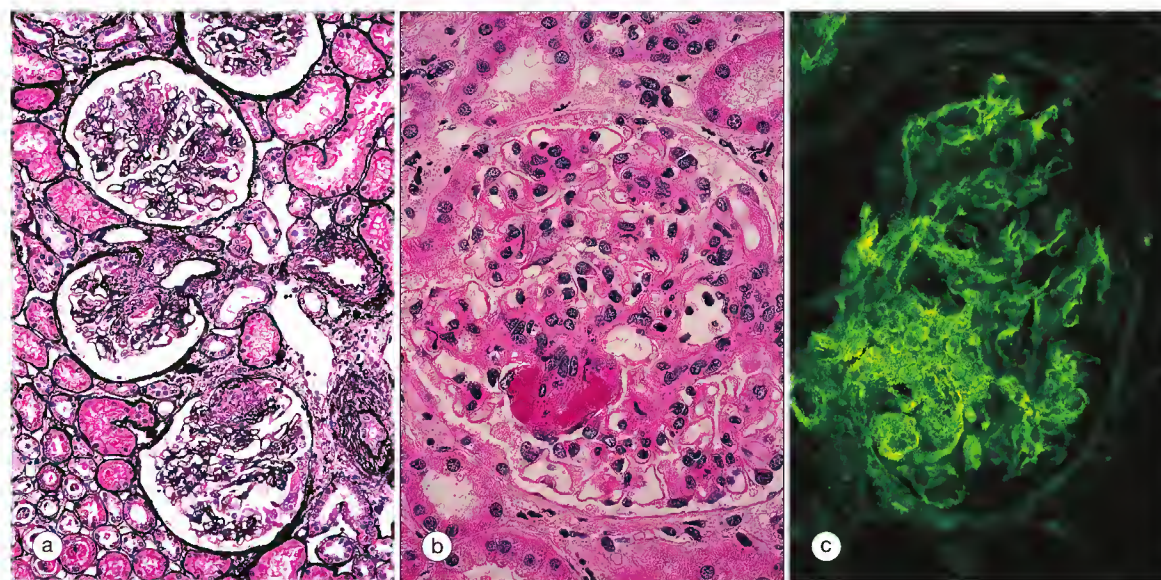


Fig. 128.10 Lupus nephritis class III (focal lupus nephritis). (a) Low-power view showing three glomeruli with segmental endocapillary proliferation causing obliteration of the glomerular capillary lumina in a portion of the glomerular tuft. Adjacent glomerular capillaries are patent. The endocapillary proliferation affected less than 50% of the total glomeruli sampled in this biopsy specimen, consistent with focal lupus nephritis (Jones methenamine silver). (b) Individual glomerulus with segmental occlusion of the glomerular capillaries by endocapillary proliferation with infiltrating leukocytes and fibrinoid necrosis. The remainder of the glomerular tuft displays mesangial hypercellularity (hematoxylin-eosin). (c) Deposits of IgG are identified in the peripheral glomerular capillaries of a segment of the tuft (corresponding to an area of endocapillary proliferation). Mesangial deposits are present in the adjacent glomerular lobules (immunofluorescence, anti-IgG).

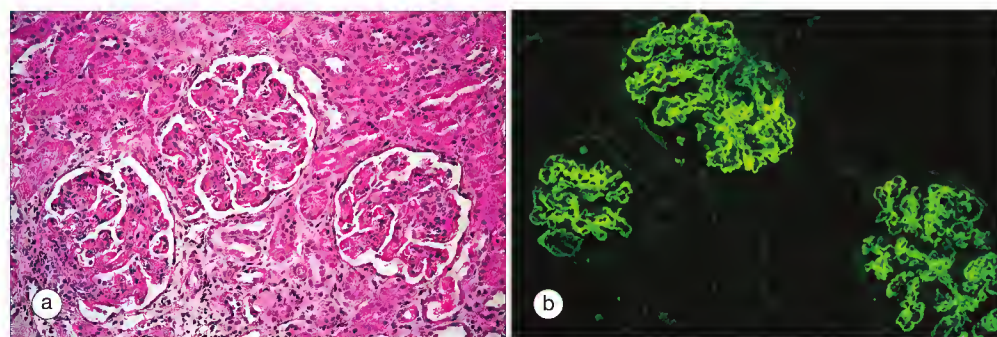
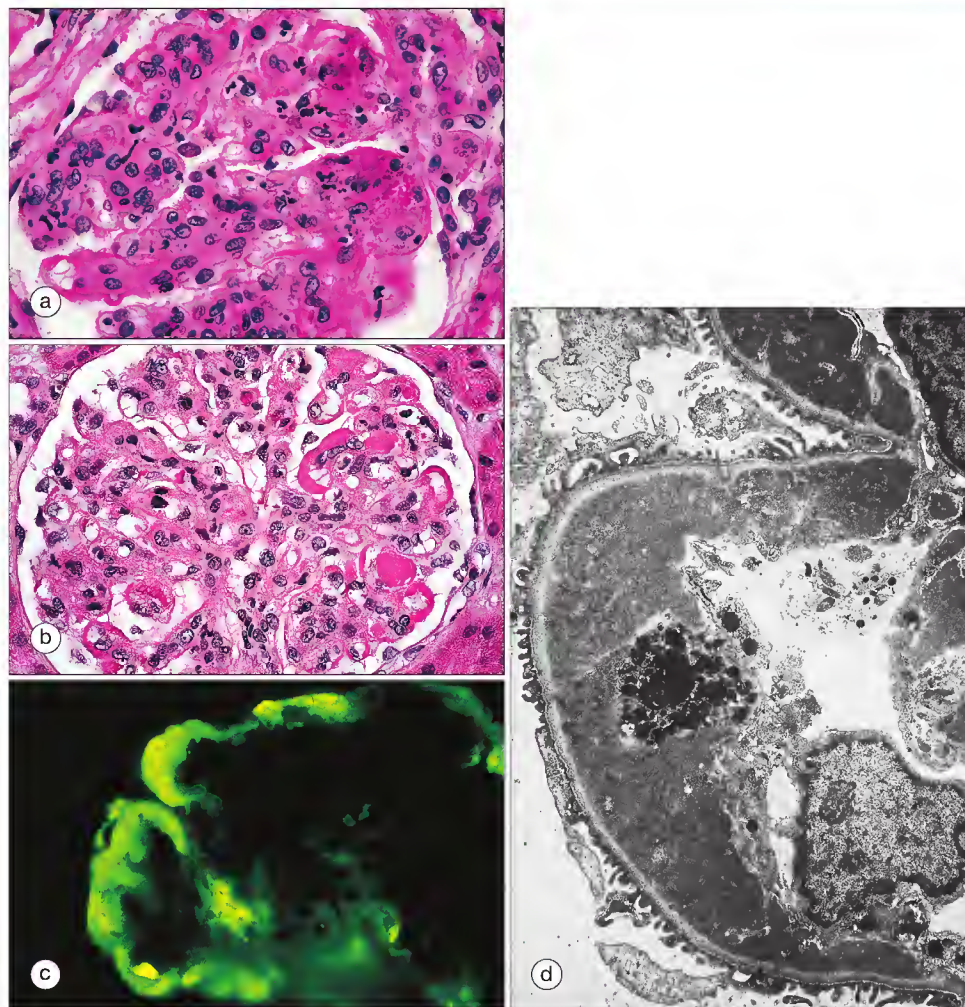


Fig. 128.11 Lupus nephritis class IV (diffuse lupus nephritis). (a) Low-power view showing the diffuse and global distribution of endocapillary proliferation, consistent with class IV-G (hematoxylin-eosin). (b) Diffuse and global deposition of IgG throughout the glomerular mesangium and outlining the peripheral capillary walls (immunofluorescence, anti-IgG).

Fig. 128.12 Lupus nephritis class IV (diffuse lupus nephritis). (a) The glomerular capillary lumina contain many infiltrating leukocytes, including neutrophils. Some of these neutrophils are undergoing apoptosis and forming pyknotic or karyorrhectic nuclear debris (hematoxylin-eosin [H&E]). (b) Several glomerular capillary walls are thickened by eosinophilic deposits that form thick “wire loops.” Some of the immune deposits are so large that they obliterate the glomerular capillary lumina and form “hyaline thrombi” (H&E). (c) By immunofluorescence, the wire loop deposits correspond to large peripheral capillary wall immune deposits located in the subendothelial region. These deposits are comma shaped because they conform to the smooth outer glomerular basement contour (immunofluorescence, anti-IgG). (d) Seen on electron microscopy, the wire loop consists of a large circumferential subendothelial electron-dense deposit that forms along the inner aspect of the glomerular capillary wall between the glomerular endothelium and the glomerular basement membrane.



in the course of aging or as a complication of hypertensive arterionephrosclerosis and does not necessarily imply scarring in the course of immunologically mediated injury.

Membranous lupus nephritis (class V) is characterized by diffuse thickening of the glomerular capillary walls as a result of numerous subepithelial electron-dense deposits often separated by basement membrane spikes (Fig. 128.13). This lesion usually occurs on a background of mesangial hypercellularity and mesangial immune deposits. Because scattered subepithelial deposits may also be encountered in class III and class IV lupus nephritis, the designation membranous lupus nephritis should be reserved for cases in which subepithelial deposits predominate. In a case of class III or IV lupus nephritis, an additional diagnosis of class V is warranted if subepithelial deposits are present in 50% or more of glomerular capillaries or 50% or more of the glomeruli.

The modified WHO classification recognizes a sixth class in which the findings are those of extremely chronic, advanced glomerulonephritis and widespread glomerular scarring.¹⁷ In 2004 this class was defined more specifically as global sclerosis affecting at least 90% of glomeruli without residual activity. Most examples of class VI lupus nephritis undoubtedly represent advanced class IV disease. In some cases the process is so “end stage” that a diagnosis of chronic lupus nephritis is difficult to make on morphologic grounds. Immunofluorescence and electron microscopy may reveal residual small granular electron-dense deposits in the thickened glomerular capillary walls, tubulointerstitial compartment, or vessel walls.

Tubulointerstitial lesions can be encountered in all classes of lupus nephritis, particularly class IV, and correlate closely with the degree of functional renal impairment. Active lesions include interstitial inflammation by lymphocytes, monocytes, and plasma cells, in addition to immune deposits in tubular basement membranes, interstitial collagen, and the walls of interstitial capillaries (Fig. 128.14). The poor correlation between the severity of interstitial inflammation and the presence or amount of tubulointerstitial immune deposits implies a more complex role for cell-mediated immunity.¹⁹ Analysis of T-cell receptor clonotypes has revealed an oligoclonal interstitial T-cell population that persists in repeated biopsy samples, a finding that supports participation in adaptive immunity.²⁰

Prognostic features

Prognosis correlates with the class of lupus nephritis and with measures of activity and chronicity. The prognosis is excellent in class I and II, more guarded in class III and V, and poorest in class IV (particularly in patients with high chronicity and persistent activity that is resistant to treatment). Attempts to quantify the degree of activity and chronicity in lupus nephritis are predicated on the intuitive assumption that active lesions are more amenable to treatment and chronic lesions represent largely irreversible damage. Assessment of disease activity and chronicity provides a helpful, albeit inexact guide to prognosis and treatment. Activity indices, first formulated in the 1960s, have been refined and popularized by Austin's group as the National Institutes of Health (NIH) Activity and Chronicity Index. According to the NIH schema, the activity index is calculated by summing the score for each of six histologic features (glomerular endocapillary proliferation, glomerular leukocyte infiltration, glomerular subendothelial hyaline deposits, glomerular fibrinoid necrosis or karyorrhexis, cellular crescents, and interstitial inflammation), which are graded individually on a scale of 0 to 3+ (0, absent; 1+, <25% of the glomeruli affected; 2+, 25% to 50% of the glomeruli affected; 3+, >50% of the glomeruli affected). The scores for glomerular necrosis and cellular crescents are accorded double weight because of their more ominous importance. Interstitial inflammation is graded as 1+ (mild), 2+ (moderate), or 3+ (severe). The sum of these values gives a total possible activity score of 0 to 24. Similarly, chronicity is graded on a scale of 0 to 12 by summing each of the following four features of chronicity (each scored as 0 to 3+): glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis.

The NIH group initially found an activity index greater than 12 and a chronicity greater than 4 to be predictors of a poor outcome. In subsequent analyses, the combination of cellular crescents and moderate to severe interstitial fibrosis was a sensitive predictor of doubling of the serum creatinine concentration.²¹ The value and reproducibility of these indices have been debated. Schwartz and coworkers noted problems in intraobserver and interobserver reproducibility.²² Although there does not appear to be a precise cutoff for activity and chronicity that predicts outcome, it is generally agreed that greater chronicity portends a worse prognosis. Despite their

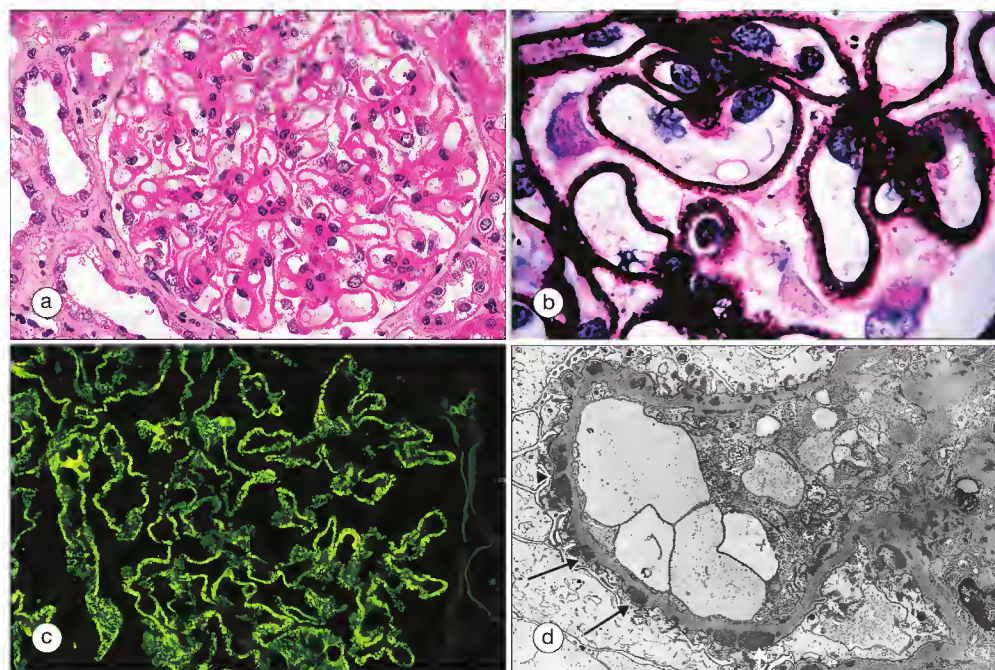


Fig. 128.13 Lupus nephritis class V (membranous lupus nephritis). (a) The glomerular capillary walls are diffusely thickened and have a rigid appearance. Associated mild mesangial hypercellularity is apparent but without evidence of endocapillary proliferation (hematoxylin-eosin). (b) A silver stain delineates the characteristic "spikes" that project at right angles from the glomerular basement membranes, like bristles on a comb (Jones methenamine silver). (c) The immunofluorescence pattern is finely granular and corresponds to deposits along the outer aspect of the glomerular capillary walls (immunofluorescence, anti-IgG). (d) Electron micrograph showing subepithelial electron-dense deposits (arrows) located on the outer aspect of the glomerular capillary wall between the visceral epithelial cells (podocytes) and the glomerular basement membrane. Some of these deposits are separated by intervening projections of glomerular basement membrane material, which results in the appearance of "spikes" (arrowhead). Deposits are also seen in the adjacent mesangial matrix deep to the glomerular capillary lumen.

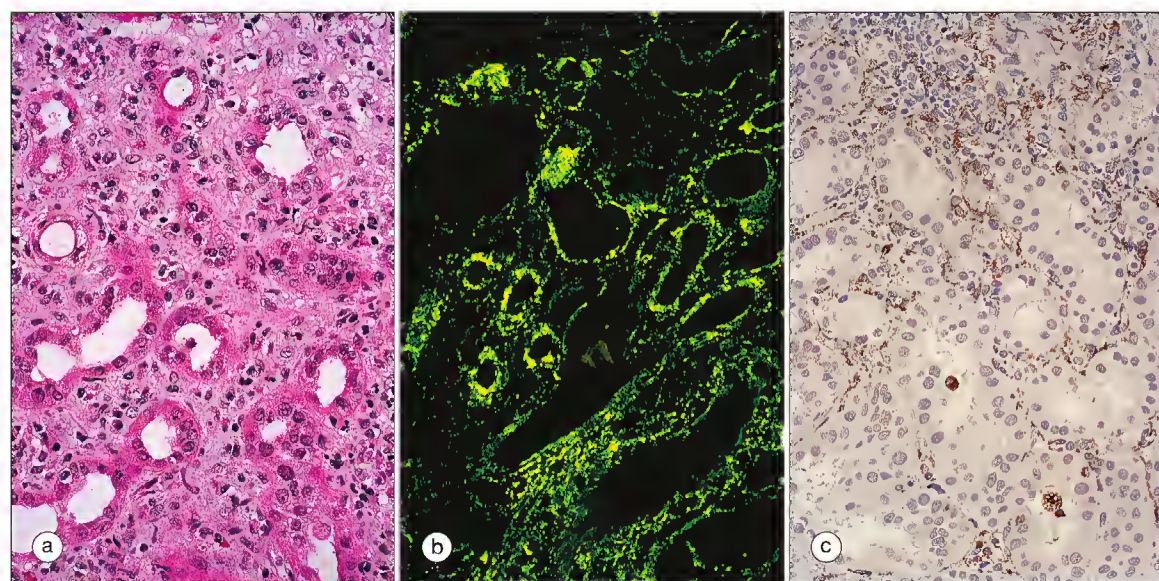


Fig. 128.14 Tubulointerstitial lesions in active lupus nephritis. (a) The renal interstitium is expanded by edema and dense inflammatory infiltrates (hematoxylin-eosin). (b) Example with extensive immune deposits in the interstitial connective tissue and outlining the tubular basement membranes (immunofluorescence, anti-IgG). (c) Immunostaining for CD68 shows many monocytes/macrophages within the renal interstitium between tubules (immunocytochemistry, anti-CD68).

limitations, activity and chronicity indices are of particular value when repeated biopsies are performed in individual patients to monitor disease evolution and response to treatment.

The 2004 classification has provided a framework to test the distinction between classes IV-S and IV-G. Class IV-G disease typically has greater proteinuria, renal insufficiency, and hypocomplementemia, more subendothelial deposits, and less fibrinoid necrosis than class IV-S disease.²³ Some cases of class IV-S disease have a paucity of subendothelial deposits and are associated with ANCA seropositivity, thus suggesting a different pathogenesis.²⁴ Most studies have found that class IV-G disease has a similar renal outcome as class IV-S disease.^{25,26}

Pathogenetic mechanisms

The morphologic subtypes of lupus nephritis are defined according to the distribution of immune deposits within the glomerular tuft. However, we know surprisingly little about the factors that govern the localization of immune deposits within the glomerular filter. It is likely that the diverse morphologic expressions of lupus nephritis reflect differences in the composition and properties of immune complexes, including immune complex load, specificity, size, avidity, affinity, charge, and immunoglobulin isotype (see later). It has been proposed that a mesangial pattern of immune

deposition is favored by a relatively small immune complex load of intermediate-sized, high-avidity complexes that resist elimination by mesangial clearing mechanisms. Larger quantities of intermediate-sized or large immune complexes could overwhelm the mesangium and spill out into the subendothelial zones. Some experimental evidence supports the formation of subepithelial deposits from smaller, low-avidity, cationic immune complexes in relative antigen excess, which may dissociate and reform *in situ*, perhaps favored by electrostatic interactions with the polyanionic constituents of the glomerular capillary wall.

In the past, the paradigm for lupus nephritis has been a classic type III hypersensitivity reaction mechanism of glomerular deposition of circulating autoantibody-containing immune complexes, followed by complement activation and subsequent neutrophil-mediated tissue injury. In recent years, emphasis has shifted away from the exclusive role of renal deposition of preformed circulating immune complexes to recognize the importance of local formation of immune deposits.^{15,27,28} Charge interactions favor the local binding of positively charged nucleosomes to fixed anionic sites in the glomerular capillary wall. Once planted in the glomerular filter, these autoantigens may interact with circulating autoantibody and thereby lead to *in situ* formation of immune complexes. Some anti-DNA antibodies exhibit a range of cross-reactivities to normal glomerular constituents, such as

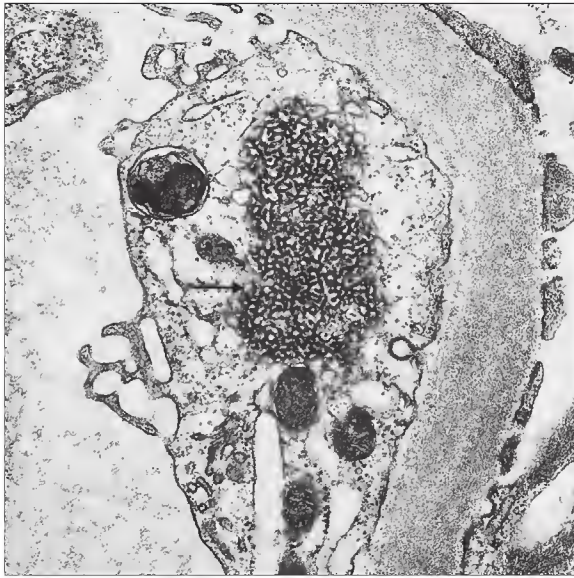


Fig. 128.15 Endothelial tubuloreticular inclusion. On an electron micrograph a large endothelial tubuloreticular inclusion is identified within a glomerular endothelial cell. This intracytoplasmic inclusion consists of interanastomosing tubular structures located within the dilated endoplasmic reticulum of the endothelial cell cytoplasm (arrow).

heparan sulfate proteoglycans, laminin, and type IV collagen, which suggests another potential mechanism of *in situ* immune complex formation.²⁹ Finally, the poor correlation between the quantity of circulating immune complexes and the activity of the glomerulonephritis implies a potential role for local antigen presentation at the level of the glomerulus by activated macrophages or T cells. Fc γ receptor (Fc γ R)-bearing monocytes appear to be essential effector cells in glomerulonephritis, as demonstrated by protection of Fc γ -deficient mice from the development of nephritis but not from the glomerular deposition of immune complexes or complement.³⁰

Neutrophil and monocyte recruitment is particularly marked in active lupus nephritis. A complex network of cytokine activation appears to mediate their influx and promote downstream effects on mesangial proliferation, matrix production, and crescent formation.¹⁵ Inflammatory and fibrogenic cytokines that have been demonstrated to be upregulated in lupus nephritis include monocyte chemoattractant protein type 1 (MCP-1), interleukin-1 (IL-1), IL-2 receptor, IL-6, interferon- γ (IFN- γ), IFN- α , tumor necrosis factor- α (TNF- α), and transforming growth factor- β (TGF- β). The morphologic correlate of increased interferon concentrations is the presence of tubuloreticular inclusions (“interferon footprints”) in the endothelial cell cytoplasm of all classes of lupus nephritis (Fig. 128.15).

A newly recognized entity in SLE is lupus podocytopathy, which is manifested as nephrotic syndrome and diffuse podocyte foot process effacement in the absence of significant immune deposits in the glomerular capillary wall.³¹ The biopsy findings resemble those of minimal change disease or focal segmental glomerulosclerosis and are highly responsive to corticosteroids, thus suggesting possible T-cell-mediated cytokine effects directed at glomerular podocytes.

Central nervous system immunopathology

Involvement of the central nervous system (CNS) in SLE is common and can assume diverse clinical and morphologic manifestations. Neurologic involvement directly attributable to the immunopathologic derangements of SLE must be distinguished from the effects of drugs (e.g., corticosteroids), hypertension, and infections that complicate immunosuppressive therapy. Although the term “lupus cerebritis” is used in common medical parlance to describe the pathologic manifestations of SLE in the brain, most cerebral involvement is actually attributable to vascular lesions.³² In the past, the majority of vascular pathology in the CNS was believed to represent lupus vasculitis, a vascular inflammation caused by deposition of immunoglobulin and complement in vessel walls, as may occur in other organs. It is now recognized that although such necrotizing or inflammatory vasculitis does account for less than 15% of the vascular lesions of CNS lupus, more than 70% of the vascular pathology is attributable to thrombotic lesions of small intracranial vessels, with or without associated endothelial proliferation and perivascular inflammation.³³ Most patients with thrombotic vasculopathy have associated anticardiolipin or antiphospholipid antibodies and lack

immune complex deposition in the vessel walls. There are also rare reports of arterial thromboemboli that have been linked to Libman-Sacks endocarditis.

The parenchymal injury that occurs secondary to lupus vascular lesions (whether inflammatory, thrombotic, or thromboembolic) usually takes the form of microinfarcts or macroinfarcts, sometimes complicated by hemorrhage in subarachnoid, subdural, or intracerebral locations.³⁴ Hemorrhage may also result from bleeding tendencies caused by thrombocytopenia or hypoprothrombinemia in the context of anticardiolipin/antiphospholipid antibody syndrome, immune thrombocytopenic purpura, or thrombotic thrombocytopenic purpura. Depending on the location of the vascular lesions and the distribution and extent of the parenchymal injury, the clinical findings vary widely from localized neurologic deficits (e.g., paresis, cranial nerve palsy, movement disorder, and seizure) to more generalized manifestations (e.g., headache, altered consciousness, psychosis, and impaired cognition). Interestingly, deposition of immune complexes may occur in the choroid plexus, a specialized vascular structure with filtration functions that bears some similarities to the renal glomerulus.

CNS disease of nonvascular origin appears to be less common and less well understood. In most cases no identifiable pathologic lesions are found. A potential role for antineuronal and antigial antibodies has been proposed. Some of these antibodies have specificity for neurofilaments or brain synaptic plasma membrane antigen and can be demonstrated with complement-dependent cytotoxicity assays on cultured human neuronal cell lines. A subset of antilymphocyte antibodies have also been shown to cross-react with neurons. Recent evidence suggests that antibodies to the glutamate receptor may contribute to neurocognitive dysfunction. Anti-DNA antibodies capable of cross-reacting with neuronal excitatory N-methyl-D-aspartate receptors have been detected in the sera and spinal fluid of SLE patients and mediate neuronal apoptosis.³⁵ An association has also been found between anti-ribosomal P protein and the development of lupus psychosis, although the underlying pathophysiology and anatomic correlates remain to be defined.

Cardiac immunopathology

Pathologic changes can occur in the endocardium, myocardium, and pleuropericardial membranes.^{36–39} The occurrence of nonbacterial verrucous endocarditis, characteristic of SLE, also suggests a role for autoantibodies and perhaps immune complexes. Pericarditis is commonly seen in postmortem series, regardless of whether patients had symptomatic evidence of pericarditis. Gross morphologic evaluation reveals a fibrinous exudate, whereas microscopic examination shows perivascular mononuclear cell infiltration with edema and fibrinoid necrosis. A granular pattern of immunofluorescence for IgG is consistent with immune complex deposition.

Clinically significant inflammatory myocardial disease is uncommon, but atherosclerotic coronary artery disease is increasingly being recognized.^{40–42} The role of vasculitis as an initiating event and the roles of continuing vasculitis, corticosteroids, and hypertension as accelerating factors are unclear.^{38,39} Deposition of immune complexes may promote the accumulation of cholesterol in atherosclerotic plaque. Myocardial infarction may also occur as a result of intracoronary thrombotic events without significant atherosclerotic disease.⁴³ Clinical studies support the concept that chronic inflammation drives the development of atherosclerosis in patients with and without SLE. The precise contribution of infiltrating leukocyte subpopulations, autoantibodies, oxidized lipoproteins, and cytokines in the pathology of atherosclerosis in lupus is an area of intense investigation.⁴⁴

Pulmonary immunopathology

Acute lupus pneumonitis occurs in less than 10% of lupus patients. It is characterized by acute alveolar wall injury, including alveolar edema and hemorrhage, hyaline membrane formation, interstitial pneumonitis, and alveolitis.⁴⁵ Vasculitis and hematoxylin bodies are rarely identified. Demonstration of immunoglobulins and complement and ultrastructural identification of electron-dense deposits in the alveolar walls and arterioles support a role for pulmonary immune complex deposition. Acute lupus pneumonitis appears to be more common in patients with anti-Ro antibodies.⁴⁶ Chronic diffuse interstitial lung disease eventually develops in up to 50% of patients with acute lupus pneumonitis. Chronic lupus pneumonitis is distinguished by interstitial fibrosis and chronic interstitial lymphoid infiltrates, septal thickening, and hyperplasia of type II pneumocytes. Pulmonary hypertension has been associated with the development of plexiform microvascular lesions, as well as with medial hypertrophy and intimal fibrosis of branches of the pulmonary artery. A role for anti-endothelial cell antibodies has been proposed.⁴⁷ In addition, deposits of IgG with anti-DNA activity, as well as

IgM and C3, have been demonstrated in the walls of pulmonary blood vessels.⁴⁸ In shrinking lung syndrome, breathlessness without cyanosis is accompanied by reduced chest expansion and atelectasis. Weakness of the respiratory muscles, including the diaphragm and intercostal muscles, may cause a chronic restrictive defect on the basis of fibrosing lupus myopathy.⁴⁹ In many cases, pleuritic inflammation promotes reflex inhibition of diaphragmatic activity.⁵⁰

PROPERTIES OF IMMUNE COMPLEXES

Although not all manifestations of SLE can be attributed to immune complexes, these complexes do appear to play a central role in the pathogenesis and immunopathology of SLE. Thus, critical questions in pathogenesis focus on the nature of the immune complexes and their handling, the nature of the autoantibodies that make up the complexes, and the basis for the increased production of these autoantibodies.

Antibodies and antigens

Of the five classes of human immunoglobulins (IgG, IgM, IgA, IgE, and IgD), IgG is the most common constituent of the immune complexes found in SLE. IgM is more typically associated with lower-affinity antibodies, and IgA often reflects stimulation of mucosal immunity. IgG has four subclasses, each of which has distinct physicochemical and immunologic properties (Table 128.2) that reflect differences both in primary amino acid sequence

and in glycosylation of the subclass-specific heavy chains (Fig. 128.16).⁵¹ The genes encoding immunoglobulin heavy chains are located on the long arm of human chromosome 14.

IgG1 is the most common immunoglobulin in serum, and both IgG1 and IgG3 are produced primarily against protein antigens. IgG2, the second most common immunoglobulin, is typically produced in response to polysaccharide antigens. IgG4 production is associated with prolonged antigenic stimulation. In addition to the nature of the antigen, regulation of IgG subclass production is influenced by the antigen-presenting cells and cytokines released at the time of antigen presentation. There is no doubt that the nature of the IgG subclass in an immune complex influences both the biologic properties of the immune complex *in vivo* (Table 128.3) and the ability to detect the immune complex *in vitro*.

One of the most striking differences among the IgG subclasses is found in the structure of the hinge region (see Fig. 128.16). The lower hinge region participates in binding of the early complement component C1q to IgG and in binding of IgG to its corresponding cell receptors (FcγRs).⁵² Binding of IgG to different FcγRs is sensitive to specific residues within this region in the second constant domain of the heavy chain (C_H2). It is likely that C1q and FcγRs interact with composite sites on IgG, that is, a tertiary structure

TABLE 128.2
Properties of human IgG subclasses

	IgG1	IgG2	IgG3	IgG4
Serum levels (% of total)	60-65	20-25	5-10	3-6
Complement fixation	+++	+	++++	±
Cryoprecipitation	++	+	+++	+
Rheumatoid factor binding	+++	+++	±	+++
Placental transfer	++	±	++	++
Fractional catabolic rate (%)	7-9	7-9	17	7-9
Staphylococcal protein A binding	+	+	—	+
Streptococcal protein G binding	+	+	+	+
Allotypic variants "Gm markers"	Some	Few	Many	None

TABLE 128.3
Important properties of immune complexes

Property	Influenced by
Lattice size	Valence of antibody and antigen Molar ratio of antibody and antigen Absolute concentration of antibody and antigen Association constant of antibody for antigen
Net charge	Charge of antibody and antigen
Complement fixation	Class and subclass of antibody Lattice size Availability of complement components
Complement receptor binding	Quantitative complement fixation Processing of C3b to iC3b and C3dg Availability of complement receptors
Fcγ receptor binding	Lattice size Antibody class and subclass Phenotype of host Fcγ receptors
Glomerular deposition	Lattice size (large/small) Net cationic (positive) charge

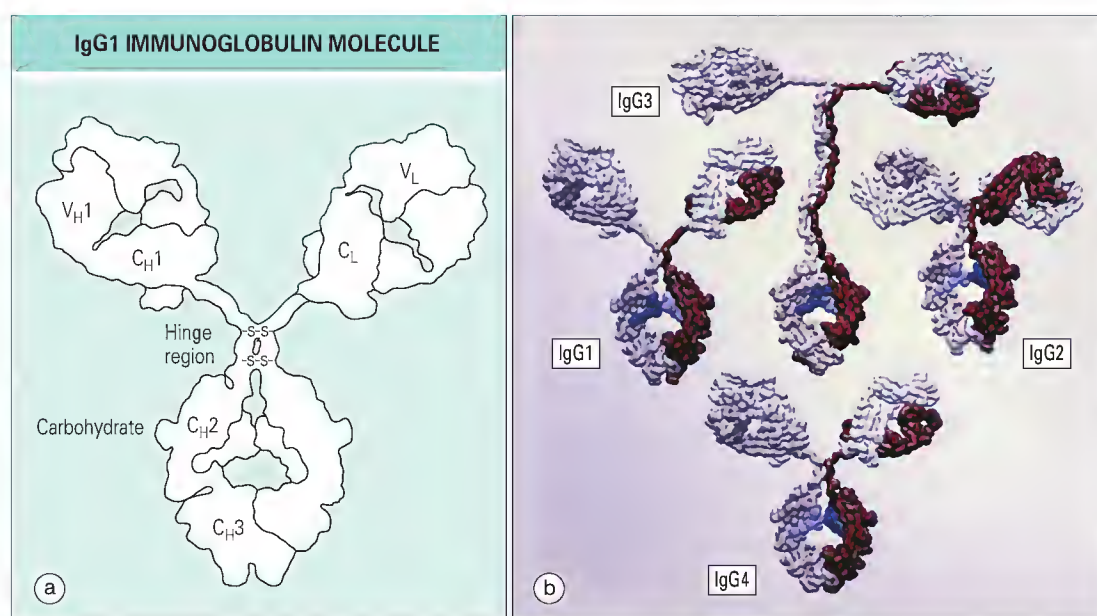


Fig. 128.16 Human immunoglobulin G molecules. (a) Domains, the hinge region, and the carbohydrate moiety are shown in diagram form. (b) Computer-generated space-filling models of the four IgG subclasses. (Reprinted from Shakib F. *The human IgG subclasses*. Oxford: Pergamon Press; 1990, with permission from the author.)

consisting of several different linear regions, conformational determinants, or both. Glycosylation of IgG also influences binding to FcγR; IgG acquires antiinflammatory properties on Fc sialylation with preferential binding to inhibitory FcγR. Variations in the composition of sugar moieties thereby dramatically change antibody-mediated activity.⁵³

Antigens are also critical constituents of immune complexes, not only because they influence the nature of the humoral immune response but also because their own physicochemical properties strongly influence the nature of the complex (see Table 128.3). In addition to size and valence (see the next section), the antigen may also have unique properties that influence its handling. Nucleosomes, which may bind both C-reactive protein and specific antibody as opsonins, may also bind directly to the negatively charged basement membrane of the glomerulus. In SLE, increased apoptosis or impaired clearance of apoptotic blebs (or both) may trigger the release of immunogenic chromatin material. In addition, persistent neutrophil extracellular traps (NETs) released by dying neutrophils during NETosis may serve as a source of modified chromatin⁵⁴ that allows formation of immune complexes with antichromatin antibodies.

Critical properties of immune complexes

The formation and the fate of soluble immune complexes depend on the biophysical and immunologic properties of the antigen and the antibody (see Table 128.3). Such properties include the size, net charge, and valence of the antigen; the class and subclass of the antibody; the affinity of the antibody-antigen interaction; the net charge and concentration of antibody; the molar ratio of available antigen and antibody; and the ability of the immune complex to interact with proteins of the complement system.⁵⁵ Complement fixation is more efficient with larger complexes. Larger complexes also present a broader multivalent array of ligands for complement and FcγRs to bind. Finally, of course, the class and subclass of antibody are important in complement activation and determining which FcγRs can be engaged.

In the clinical setting it is difficult to evaluate these variables, but experimental models have provided ample evidence that they are very important. Large complexes are cleared more rapidly than small ones, complexes between antibody and double-stranded DNA bind to a receptor for a complement fragment (C3b) on erythrocytes (complement receptor type 1 [CR1]) differently than do certain antibody-protein complexes, and complexes with a net positive charge localize to the glomerulus more efficiently than do those with a neutral charge.

Pathogenic mechanisms

Once deposition of an immune complex in tissue has occurred, either through *in situ* formation or by direct immune complex deposition, FcγR-mediated uptake by antigen-presenting cells can lead to amplification of the humoral immune response, and FcγR-mediated activation of mast cells and phagocytes, in addition to activation of complement, leads to an inflammatory response through the generation of soluble mediators, including complement fragments C3a and C5a. These mediators attract and activate polymorphonuclear leukocytes and mononuclear phagocytes; cause the release of additional inflammatory mediators from these cells, mast cells, and basophils; and activate large granular lymphocytes (Fig. 128.17). Binding of immune complexes containing ribonuclear proteins to FcγRs on plasmacytoid dendritic cells can also trigger the secretion of IFN-α and perpetuate the autoimmune responses.⁵⁶ Activation of platelets may cause platelet aggregation and microthrombi, in addition to release of vasoactive compounds that increase vascular permeability. The production of reactive oxygen metabolites, release of hydrolytic enzymes, and secretion of cytokines can cause direct destruction of local tissue and further stimulation of leukocytes. Thus, the continued presence of immune complexes in chronic immune complex-mediated diseases can lead to prolonged tissue damage, which may result in clinically evident vasculitis, pleuropericarditis, cutaneous lesions, and glomerulonephritis.

BIOLOGY OF IMMUNE COMPLEX HANDLING

Normally, antigen-antibody immune complexes are removed quickly and safely by the *mononuclear phagocyte system*, a collective term for the fixed tissue phagocytes found primarily in the liver and spleen. However, when both the antigen and antibody are present for prolonged periods and when defects in the immune complex clearance mechanisms are present, immune complexes may be deposited in host tissues, with subsequent tissue damage. SLE is characterized by defective handling of apoptotic debris leading to the

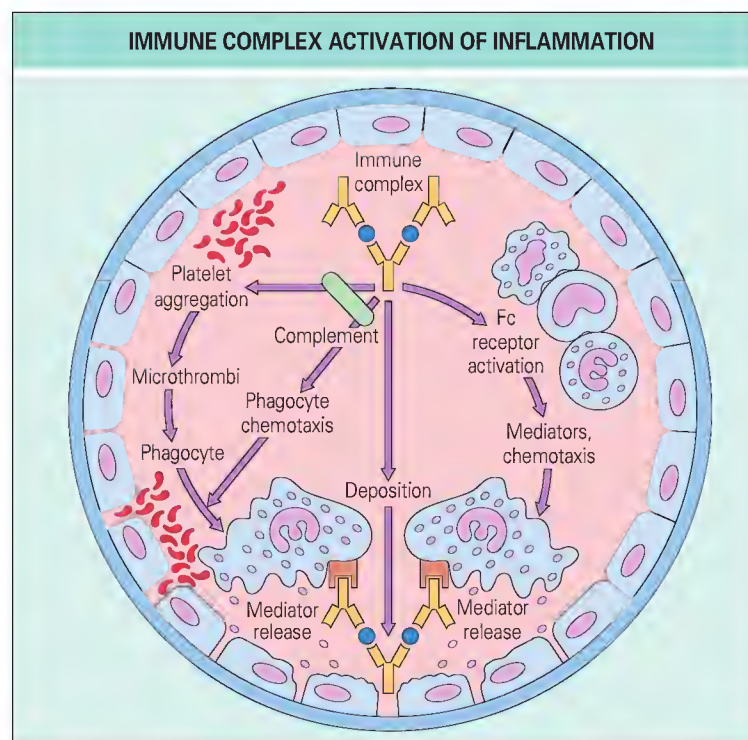


Fig. 128.17 Immune complex activation of inflammation. Immune complexes activate complement, with release of C3a and C5a. In turn, C3a and C5a stimulate neutrophils, mononuclear phagocytes, basophils, and mast cells and induce the release of inflammatory mediators. Immune complexes deposited on the vessel wall cause further deposition of complement and lead to both Fcγ receptor-mediated and complement-mediated stimulation of phagocytic cells.

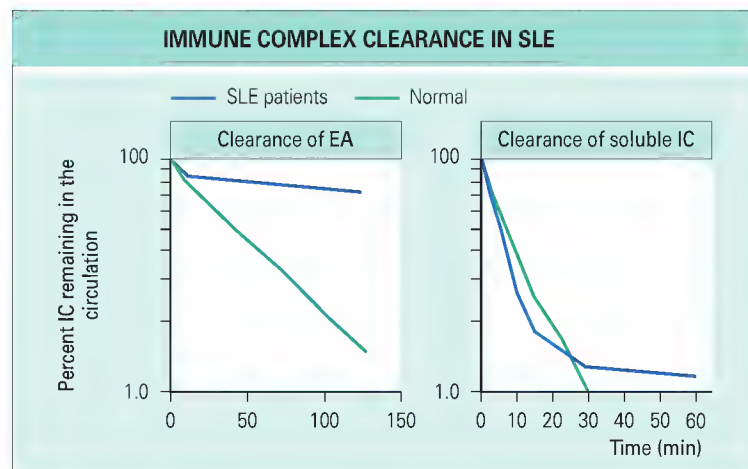


Fig. 128.18 Immune complex clearance in systemic lupus erythematosus. Clearance of antibody-opsonized erythrocytes (EA) is dramatically decreased in patients with active systemic lupus erythematosus (SLE). The EA probe is a sensitive measure of mononuclear phagocyte system Fcγ receptor function. In contrast to the initial clearance of EA, clearance of soluble immune complexes (IC) is more rapid in patients with SLE. Some data indicate that this more rapid disappearance from the circulation does not correspond to an increase in the uptake of immune complexes by the mononuclear phagocyte system but rather reflects greater deposition of immune complexes in the capillary beds as a result of deficiencies in the complement system (see text). However, at later times (15 minutes), clearance of soluble immune complexes is delayed, which may reflect the same Fcγ receptor dysfunction observed with the EA probe.

formation of immune complexes.^{1,57} *In vivo* and *in vitro* abnormalities in both FcγR- and complement-mediated clearance of immune complexes have been described in SLE.⁵⁸⁻⁶⁰ For example, patients with SLE display delayed clearance kinetics of certain IgG-coated erythrocytes, a model immune complex that is used to assess FcγR-mediated clearance (Fig. 128.18). Interestingly, some soluble immune complexes disappear from the circulation of patients with SLE more rapidly than from the circulation of normal

individuals, but this difference may reflect rapid deposition in peripheral tissues as a result of inefficient complement-mediated immune complex solubilization rather than enhanced complement-mediated removal by the mononuclear phagocyte system. Abnormal receptor-mediated clearance contributes to immune complex deposition and is correlated with disease activity (Fig. 128.19), but other factors, such as size and composition, preexisting tissue inflammation, and opportunity for charge-charge

interactions, also influence immune complex handling. The vascular endothelium and the glomerular basement membrane are highly susceptible tissue targets for immune complex damage.

Role of complement in immune complex handling

To prevent disease mediated by immune complex deposition, a number of protective mechanisms have evolved that effectively eliminate immune complexes both from the circulation and from tissues. Central to these protective mechanisms is the complement system, the same system implicated in the pathogenic destruction of tissue.⁵⁷ In addition, C-reactive protein, which can mediate complement fixation, also has an important role, especially in the handling of nuclear debris. Several fundamental points about the complement system deserve emphasis here. Immune complex handling (and clearance) is strongly influenced by three roles of the complement system:

- Complement C1q binds to the immune complexes, and receptors for C1q are important in the uptake of these complexes.
- Complement activation maintains the solubility of immune complexes by preventing the formation of large insoluble immune aggregates and by transforming insoluble complexes into smaller soluble ones.
- Complement activation leads to the opsonization of complexes with complement components or fragments for recognition by complement receptors on phagocytes.

Receptors for both C1q and C3 degradation products (C3b, iC3b, and C3dg) are important in immune complex binding, internalization, and subsequent release of inflammatory mediators.

Receptors for the Fc region of IgG
Structure and function

Immune complexes containing IgG antibodies engage receptors for the Fc region of IgG (FcγRs). In contrast to the complement receptors, which bind fragments of complement components, FcγRs bind IgG ligand in its native form and require clustering or cross-linking of at least two receptors on the same cell to initiate intracellular signaling.⁶¹⁻⁶³ Presumably, this requirement for clustering prevents circulating IgG or complement components from stimulating effector cells in the absence of antigen. Cross-linking of FcγR triggers internalization by FcγR-expressing cells and leads to degranulation by phagocytes and mast cells, immediate release of inflammatory mediators, and synthesis and release of cytokines.^{61,63}

The three families of FcγRs—FcγRI, FcγRII, and FcγRIII (Table 128.4; Fig. 128.20)—are encoded by distinct genes on the long arm of human chromosome 1q21-23. Each family member has distinct ligand-binding properties and is differentially expressed on various cell types (Tables 128.5 and 128.6).^{61,63,64} FcγRI and FcγRIIIa also bind C-reactive protein and serve as its receptors in humans. As members of the immunoglobulin supergene family, all share the common structural motif of two or three immunoglobulin-like disulfide-linked domains in the extracellular portion of the receptor (see Fig. 128.20). Although these receptors share similar but not identical extracellular domains, the transmembrane and cytoplasmic tails are highly divergent. Differences in the promoter regions of FcγR genes lead to differences in their regulation and expression. This extensive diversity is responsible for the variety of functions that these receptors can elicit (see Fig. 128.20 and Table 128.5).^{61,63}

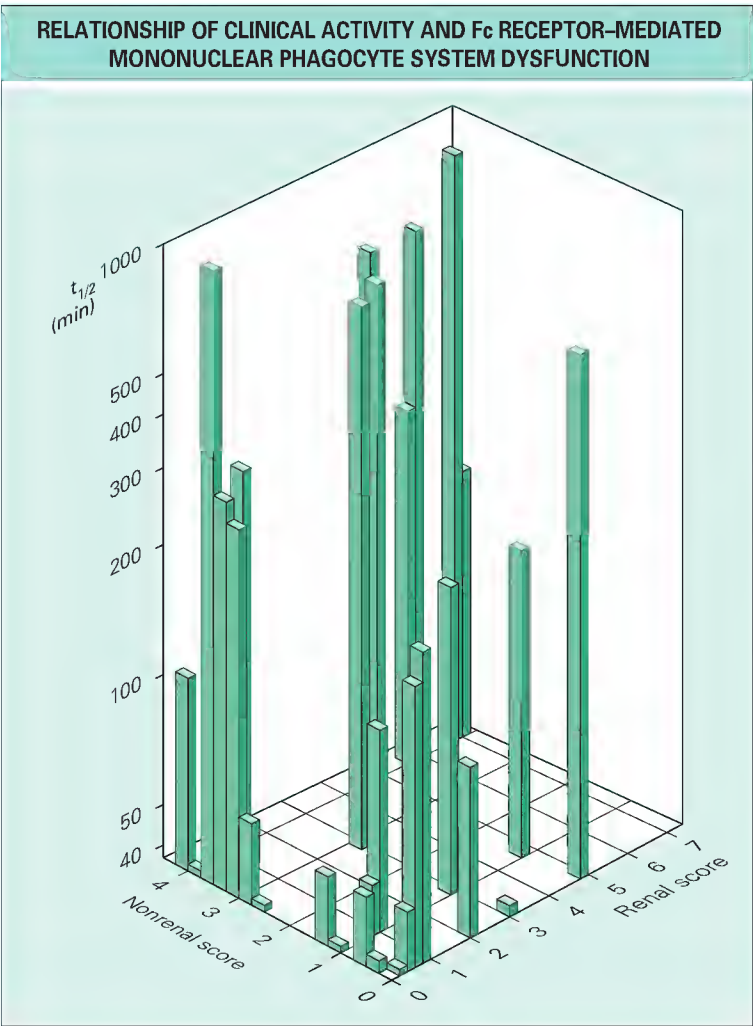


Fig. 128.19 Clinical activity was assessed in terms of both renal and nonrenal manifestations. Longer (taller) clearance half-time values represent greater degrees of dysfunction. Patients with active renal and nonrenal disease showed the greatest degree of Fc receptor-mediated impairment of clearance. (Modified from Kimberly RP, Salmon JE, Edberg JC, et al. The role of Fcγ receptors in mononuclear phagocyte system function. Clin Exp Rheumatol 1989;75:103-8.)

TABLE 128.4
Human Fcγ receptor families

Structural isoforms		FcγRI			FcγRII		FcγRIII	
Distinct genes	A	B	C	A	B	C	A	B
Splice variants	?			a1, a2	b1, b2, b3	c1, c2, c3, c4		
Copy number variation								Low/high
Promoter variants	?			-1082T/G -295T/G	-386G/C -120T/A	-386G/C	?	?
Coding region variants				131H/R	232I/T	(+)	158V/F	NA1/NA2
Membrane anchor	TM γ chain	TM	TM	a1: TM a2: secreted	TM	TM	γ/ζ Complex*	GPI

By convention, distinct genes within an FcγR family are designated with an uppercase letter, whereas the protein products from these genes are designated with the corresponding lowercase letter.
*γ/ζ Complex: although FcγRIIIa is a transmembrane protein, a member of this family of signal-transducing molecules is required for cell-surface expression of FcγRIIIa.
GPI, glycosylphosphatidylinositol membrane anchor; TM, conventional transmembrane protein.

Fig. 128.20 All Fcγ receptors (FcγRs) have extracellular domains composed of two (or three for FcγRIa) disulfide-bonded immunoglobulin superfamily motifs. FcγRIa and FcγRIIIa share the same γ chain. The signaling motif used by FcγRIIb is an immunoreceptor tyrosine inhibitory motif (ITIM), which is similar to the immunoreceptor tyrosine activation motif (ITAM) but has only one tyrosine that forms a docking site for molecules that include an src-homology domain type 2-containing tyrosine phosphatase. The signaling motifs engaged by FcγRIIIb are not completely understood.

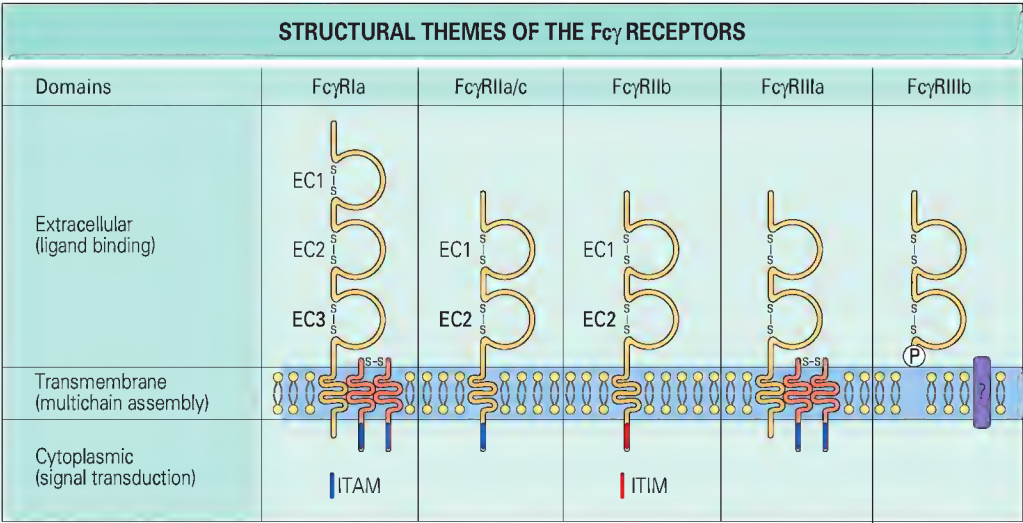


TABLE 128.5
Fcγ receptor cellular distribution

Gene family	Isoform	Cell types
FcγRI	a	Monocytes, Mfs, IFN-γ- or G-CSF-stimulated PMNs, IFN-γ-stimulated eosinophils, DCs
	b/c	mRNA encoding FcγRIb is present in monocytes, Mfs, IFN-γ-stimulated PMNs
FcγRII	a	Platelets, PMNs, monocytes, Mfs, Langerhans cells, DCs, mast cells (B cells, NK cells)
	b	B cells, monocytes, Mfs, DCs, PMNs
	c	mRNA present in monocytes, Mfs, PMNs, platelets, NK cells, and B cells
FcγRIII	a	NK cells, Mfs (including mesangial cells), subpopulation of monocytes, mast cells (subset of T cells)
	b	PMNs, IFN-γ-stimulated eosinophils

FcγRs are expressed in myeloid and lymphoid lineages. Data on protein expression are not complete.
DCs, dendritic cells; G-CSF, granulocyte colony-stimulating factor; IFN, interferon; Mfs, macrophages; NK, natural killer; PMNs, polymorphonuclear leukocytes.

FcγRs capable of triggering cellular activation possess intracellular activation motifs, termed *immunoreceptor tyrosine-based activation motifs* (ITAMs), similar to those of B-cell receptors and T-cell receptors.⁶¹ These activating FcγRs (FcγRI, FcγRIIa, and FcγRIIIa) exert nonoverlapping functions that in concert and on interaction with immune complexes lead to their clearance (binding and internalization), as well as tissue injury at sites of immune complex deposition (generation of reactive oxygen species and release of inflammatory mediators).^{61,64,65} Inhibitory FcγRs (FcγRIIb) have extracellular domains that are homologous to their activating counterparts, but their cytoplasmic domains contain an *immunoreceptor tyrosine-based inhibitory motif* (ITIM). Studies have suggested that inhibitory FcγRs modulate thresholds for activation and can terminate activation signals. They play a central role in afferent and efferent immune responses as negative regulators of both antibody production and immune complex-triggered activation.^{66,67} Both stimulatory and inhibitory FcγRs are often coexpressed on the surface of hematopoietic cells, which provides a mechanism to modulate cell activation initiated by stimulatory FcγRs. Cytokines, C5a anaphylatoxin, and intravenous gamma globulin have been shown to alter the balance in the expression of stimulatory and inhibitory FcγRs and thereby modulate immune complex clearance and inflammatory tissue injury.⁶⁸⁻⁷⁰ The structure-function relationships of each receptor family provide a framework for understanding how FcγRs may contribute to disease susceptibility, pathogenesis, and therapeutic intervention in SLE.

FcγRI (CD64), expressed on monocytes, macrophages, and IFN-γ-stimulated polymorphonuclear leukocytes, is distinguished by its three extracellular immunoglobulin-like domains and its high affinity for IgG (see

TABLE 128.6
Human Fcγ receptors and IgG subclass specificity

Fcγ family	FcγR gene	Glycoprotein (kDa)	Affinity for IgG (K _d)	IgG subclass specificity
FcγRI	FcγRIa	72	10 ⁸ -10 ⁹ M ⁻¹	1, 3, 4 >> 2
	FcγRIb	??	??	Unknown
FcγRII	FcγRIIa-R131	40-50	10 ⁷ M ⁻¹	1, 3 >> 4, 2
	FcγRIIa-H131	40-50	10 ⁷ M ⁻¹	1, 2, 3 >> 4
	FcγRIIb, C	40-50	10 ⁷ M ⁻¹	1, 3 >> 4, 2
FcγRIII	FcγRIIIa-V176	60-70	7 × 10 ⁶ M ⁻¹	1, 3 >> 4, 2
	FcγRIIIa-F176	60-70	3 × 10 ⁶ M ⁻¹	1, 3 >> 4, 2
	FcγRIIIb	50-80	10 ⁷ M ⁻¹	1, 3 >> 4, 2

Table 128.6). It associates noncovalently in the membrane with a homodimer of the γ-accessory chain, a member of the γ/ζ family of signal-transducing molecules, which can also associate with the high-affinity receptor for IgE (FcεRI), the high-affinity receptor for IgA (FcαR), FcγRIIIa (see later), and the T-cell receptor/CD3 complex (although it is distinct from CD3γ). FcγRI, the high-affinity receptor for IgG, is the only FcγR that binds monomeric IgG. FcγRI on monocytes or macrophages may play a part in antigen processing.

Receptors of the FcγRII family (CD32) have low affinity for IgG and interact only with multimeric IgG and IgG-opsonized particles. They are widely expressed and present on most leukocytes and platelets. The FcγRII family has three distinct yet highly homologous genes—*FCGR2A*, *FCGR2B*, and *FCGR2C*—that encode the FcγRIIa, FcγRIIb, and FcγRIIc proteins, respectively, and several alternative splice products, thereby resulting in the expression of six protein isoforms. The three genes are nearly identical in their extracellular domains but highly divergent in their cytoplasmic domains, which determines the effector function mediated by each isoform. Activating and inhibiting receptors differ mainly in the signaling motif in the cytoplasmic domain. FcγRIIa and FcγRIIc contain ITAMs, and they are preferentially expressed in myeloid cells. *FCGR2B* is the only *FCGR* gene encoding an ITIM, the canonic motif for an inhibitory receptor⁷¹ (see Fig 128.20). In addition to different isoforms, at least two allelic forms of FcγRIIa (H131 and R131) and two allelic isoforms of FcγRIIb (I232 and T232) are known. The FcγRIIa alleles differ in two amino acids in the extracellular domain, are expressed codominantly on polymorphonuclear leukocytes, and have differing IgG subclass binding specificities.⁷² The FcγRIIb alleles vary in two amino acids in the transmembrane domain, which leads to differences in signal transduction (Fig. 128.21).⁷³

The low-affinity FcγRIII (CD16) family contains two proteins, each with cell-type-specific expression and each encoded by distinct, yet highly homologous genes (*FCGR3A* and *FCGR3B*).⁶¹ FcγRIIIa is the most abundant FcγR on tissue-specific macrophages in the liver and spleen; thus it is a key receptor for immune complex clearance via binding and internalization. In

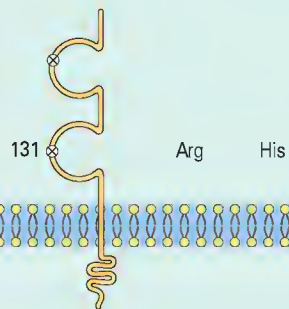
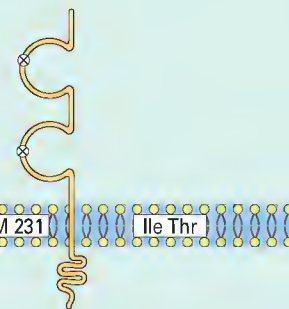
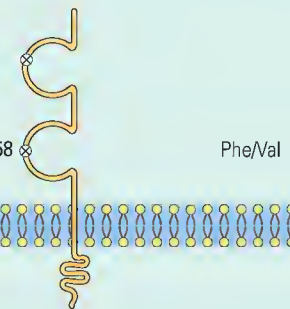
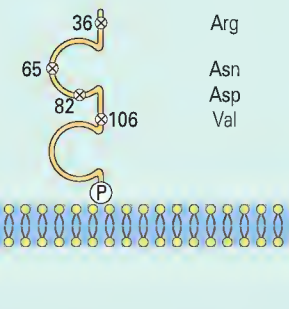
ALLELIC POLYMORPHISMS OF HUMAN Fcγ RECEPTORS										
FcγRIIa			FcγRIIb			FcγRIIIa		FcγRIIIb		
Amino acid position	Amino acid residue		Amino acid position	Amino acid residue		Amino acid position	Amino acid residues	Amino acid position	Amino acid residue	
	R131	H131		I232	T232				NA1	NA2
										
131ArgHis			TM 231IleThr			158Phe/Val		36ArgSer 65AsnSer 82AspAsn 106ValIle (P)		

Fig. 128.21 Allelic polymorphisms in the coding region of the human Fcγ receptors FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb. The R131 and H131 alleles of FcγRIIa have markedly different binding capacities for human IgG2 and murine IgG1 as a consequence of an amino acid substitution in position 131 in the second extracellular domain. The allelic isoforms of FcγRIIb encode an amino acid change in the transmembrane domain (I232 and T232) leading to differences in signaling on coaggregation of FcγRIIb with the B-cell receptor. Polymorphic forms of FcγRIIIa with changes in the sequence at amino acid position 158 result in different binding capacities for all IgG subclasses. The NA1 and NA2 polymorphism of FcγRIIIb, the glycosyl-phosphatidylinositol-linked protein expressed exclusively in neutrophils, reflects four amino acid substitutions resulting in a different number of potential N-linked glycosylation sites (NA1 = 4, NA2 = 6). In contrast to the FcγRIIa and FcγRIIIa polymorphisms, the difference in phagocytic function of the NA1 versus the NA2 alleles does not reflect differences in ligand binding.

addition, it is expressed on dendritic cells, natural killer cells, $\gamma\delta$ T cells, and mesangial cells. FcγRIIIa is a transmembrane protein that most typically associates with a dimer composed of members of the γ/ζ family of signal transduction molecules, which bear ITAMs within their cytoplasmic domains (see Figs. 128.20 and 128.21). These accessory molecules form disulfide-linked dimeric complexes (homodimers or heterodimers) that noncovalently associate with the transmembrane region of FcγRIIIa to enable cell-surface expression and signal transduction. The two allelic forms of FcγRIIIa (F176 and V176) differ in one amino acid at position 176 in the extracellular domain (phenylalanine or valine, respectively),⁷⁴⁻⁷⁶ and they differ in their binding capacity for IgG1 and IgG3 (see Fig. 128.21).

FcγRIIIb provides a dramatic example of structural divergence. It lacks both the transmembrane and cytoplasmic domains and is anchored to the membrane through a glycosyl-phosphatidylinositol moiety. FcγRIIIb is expressed at high levels on neutrophils and is the most abundant FcγR in the circulation. Naturally occurring variations in gene copy number encoding FcγRIIIb have been detected in humans and could constitute a heritable source of susceptibility to autoimmune diseases.^{77,78} Further diversity in FcγRIII structure is provided by an allotypic variation in FcγRIIIb. The two most commonly recognized allelic forms of the glycosyl-phosphatidylinositol-anchored neutrophil isoform of FcγRIIIb, termed NA1 and NA2, differ by several amino acids and N-linked glycosylation sites⁷⁹ (see Fig. 128.21).

Fcγ receptors and systemic lupus erythematosus

The importance of FcγRs in clearance of immune complexes has been shown in a number of different *in vivo* models (see Fig. 128.18); it is likely that both intrinsic (genetic) differences and acquired differences in all three families of FcγRs contribute to net function. For example, experimental blockade of FcγRIIIa by infusion of an anti-FcγRIII monoclonal antibody in both human and nonhuman primates (chimpanzee) inhibits the clearance of IgG anti-D-sensitized erythrocytes, soluble DNA/anti-DNA immune complexes, and to a lesser degree, erythrocyte-bound DNA/anti-DNA immune complexes.⁸⁰ The prolongation of FcγR-mediated clearance of IgG-opsonized erythrocytes by the mononuclear phagocyte system in normal disease-free donors with HLA-DR2 and HLA-DR3 (the same DR alleles associated with SLE) relative to other normal disease-free donors supports a genetic mechanism.⁵⁸

Germline differences in FcγR structure, expression, or function provide the basis for differences in FcγR function between individuals, and these differences may contribute to disease susceptibility and pathogenesis. Review of FcγR deficiencies⁶¹ has revealed the rare association of complete FcγRIIIb deficiency on neutrophils with SLE. More commonly detected are variations in FcγRIIIb gene copy number. The importance of copy number variation is underscored by the strong association between low FcγRIIIb gene copy number and SLE, a mechanism attributed to impaired uptake and

clearance of immune complexes as a result of reduced FcγRIIIb expression on neutrophils.⁷⁸

Currently, several FcγRs have recognized allelic polymorphisms that influence the functional capacity of the receptors⁶¹ (see Fig. 128.21). The FcγRIIa polymorphism (H131, R131) and the FcγRIIIa polymorphism (F158, V158) affect ligand binding—the H131 allele of FcγRIIa is the only FcγR that binds human IgG2 to any appreciable extent. Because IgG2 is a poor activator of complement, FcγRIIa H131 is essential for handling IgG2 immune complexes. A nonsynonymous T/C single nucleotide polymorphism in the *FCR2B* gene that results in a change in an isoleucine to threonine at position 232 in the transmembrane domain of the FcγRIIb protein excludes the receptor from lipid rafts and alters inhibitory function in B cells.^{81,82} Each of these polymorphisms establishes the precedent for genetically determined, functionally important alleles of FcγRs that influence cell triggering and may provide important models for risk factors in disease pathogenesis.

Genetic linkage studies in families in which several members have SLE indicate linkage of the SLE phenotype with a region of human chromosome 1 (1q20-23), the same region that contains the genes that encode all the FcγRs and the associated γ chain (see Chapter 127). Association studies indicate that the low-binding FcγRIIa R131 and FcγRIIIa F176 alleles are enriched in some groups of patients with SLE,^{72,76,83-86} thus suggesting that patients with the potential for less efficient immune complex clearance are at greater risk for immune complex deposition. Indeed, genomewide association studies have confirmed the association of FcγR alleles with SLE.^{72,74,87} Meta-analyses have shown that the FcγRIIa R131 allele is associated with SLE, especially in black individuals, and that the FcγRIIIa F176 allele is associated with SLE in white individuals and in other groups.^{88,89} The association of FcγRIIIa low-binding alleles may be a most important risk factor for lupus nephritis.⁹⁰

The qualitative nature of the immune response is an important principle in all association studies. Differences in the IgG subclass of pathogenic autoantibodies may influence the relative importance of FcγR alleles in disease. For example, in the presence of anti-C1q antibodies, which correlate with severe renal disease and are largely of the IgG2 subclass, *FCGR2A* genes appear to play a crucial role in determining disease severity.^{91,92} IgG2 is the predominant IgG subclass found in the glomeruli of patients with proliferative nephritis, and the frequency of genotypes containing the low-binding IgG2 allele FcγRIIa R131 was significantly greater than expected in patients with class III or class IV nephritis and in patients with intense IgG2 deposition. C-reactive protein, a ligand with particular affinity for the FcγRIIa R131 allele, was consistently present in the renal immune deposits of lupus nephritis specimens.⁹³

Polymorphisms in FcγRIIb that alter signaling (FcγRIIb 2321/T) and variations in the promoter that alter gene expression are associated with

SLE^{73,94,95} (see Fig 128.21). In addition, homozygosity of the hypofunctional allele associated with SLE (the minor allele) is protective against severe malaria.^{96,97} Meta-analysis of association studies of this variant of *FCGR2B* in SLE demonstrated an association of the I87T allele in Asian and perhaps white populations.^{96,98} It is highly likely that additional polymorphic candidate genes are present within this region of chromosome 1.

Acquired differences in receptor expression and function contribute to disease-associated differences in immune complex clearance (see Fig 128.19). The cytokines elaborated during an immune response alter FcγR expression and functional capacity as described later.^{68,99} They differentially regulate the expression of FcγR isoforms with opposite functions, those with ITAMs and ITIMs. This modulation of effector cell function contributes to differences in immune complex handling in SLE.

COMPLEMENT AND Fcγ RECEPTOR FUNCTION: TARGETS FOR TREATMENT

The extensive structural diversity of human FcγRs and the complement system, their importance in immune complex clearance, and evidence of their dysfunction in SLE present the opportunity for novel treatment strategies. Various therapeutic strategies might facilitate handling of immune complexes. Among potential strategies, tissue-specific, cytokine-mediated regulation of FcγR and complement receptor expression might enhance binding and uptake by phagocytes. Administration of complement components might be beneficial in the setting of complete complement component deficiency and lupus-like illness. Blockade of activating FcγRs or co-stimulation of FcγRIIb could alter the threshold of inflammatory effector responses.

Differential regulation of expression of isoforms with opposite functions provides a mechanism for regulation of the signals delivered to effector cells. Cytokines regulate total receptor expression, modulate relative isoform predominance, and thus modulate cellular responses. Specifically, IFN-γ and granulocyte colony-stimulating factor upregulate the expression of different stimulatory FcγRs on monocytes, whereas IL-4 and IL-13 downregulate the expression of all three classes of ITAM-bearing stimulatory FcγRs. In contrast, IL-4 and IL-33 increase and IFN-γ decreases the expression of inhibitory FcγRIIb on monocytes.^{68,99} The complement split product C5a generated at sites of immune complex-triggered inflammation also alters the balance of FcγR by upregulating stimulatory FcγRIIIa expression and downregulating inhibitory FcγRIIb expression on macrophages, thereby lowering the threshold for activation of effector cells and augmenting immune-mediated tissue damage.⁶⁹ Because immune complexes can either enhance or suppress the humoral immune response, depending on the type of FcγR engaged

(stimulatory or inhibitory) and the cell type involved (B cells or antigen-presenting cells), alterations in the balance of FcγR expression can also influence afferent responses.^{53,63} The opportunities for therapeutic intervention are indeed many.

Open studies of intravenous immunoglobulin (IVIG) infusion have been reported for SLE and other rheumatic diseases, but the mechanisms (e.g., blockade of FcγRs, induction of inhibitory FcγRs, binding to antiinflammatory lectin receptors, occupancy of FcγRs, idiotype interactions with autoantibodies, or scavenge complement activation fragments), the indications, and the efficacy of this approach require further study.¹⁰⁰ The antiinflammatory activity of IVIG is attributed, at least in part, to a small fraction of Fc-sialylated IgG molecules that engage the receptor DC-SIGN on a subset of monocytes and cause upregulation of the inhibitory receptor FcγRIIb, thereby protecting against autoantibody-mediated pathology.¹⁰¹

Emigration of neutrophils to inflammatory sites and immune complex-induced acute inflammation can be blocked by decoy FcγR,¹⁰² thus indicating that interventions in the effector stage of immune complex diseases could be accomplished by blocking FcγR or blocking complement activation by enhancing complement regulatory protein function. Early components of complement do not seem to be required for the initiation of inflammatory responses (although they are necessary for clearing apoptotic cells), whereas later components amplify injury, increase the ratio of stimulatory to inhibitory FcγRs expressed,⁷³ and may also act downstream of FcγR activation. By exploiting the intrinsic properties of different FcγRs (e.g., the H131 allele of FcγRIIIa, which binds IgG2, or the V158 allele of FcγRIIIa, which binds IgG with a greater affinity), one could develop a panel of soluble FcγRs with different affinities and subclass preferences that would allow more specific targeting of disease-associated autoantibodies. Changing the glycosylation of IgG is another approach to modulate FcγR-mediated effector formation and interfere with autoantibody-triggered inflammation.^{103,104}

Responses to immune complexes may be modulated by targeted pharmacologic manipulation of protein kinases or phosphatases. Syk inhibitors, which block activating FcγR signaling, are in clinical trials for rheumatoid arthritis and have been shown to suppress skin and kidney disease in lupus-prone mice.¹⁰⁵ Because ITAM signaling is influenced by crosstalk with other signal transduction pathways, such as β₂ integrins and Toll-like receptors (TLRs), these pathways may also be targeted to regulate inflammatory responses.¹⁰⁶ Immune complexes containing nucleosomes engage TLRs and FcγR, and blockade of the cooperative signaling by TLRs on dendritic cells and B cells may alter autoimmune and inflammatory responses.^{107,108}

With our increasing recognition of the role of FcγRs in the pathophysiology of SLE and such a range of receptor-modulating agents, successful therapeutic intervention will be feasible and form the basis of further advances in the treatment of SLE.

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Animal models of lupus

■ DAVID I. DAIKH

- A number of inbred mouse strains carry spontaneous mutations that result in clinical, serologic, and immunologic features in common with systemic lupus erythematosus (SLE).
- These strains have been immensely useful for understanding the pathogenesis and genetics of lupus and for predicting effective treatment approaches to human SLE.
- Induced mouse models with features of lupus are increasingly shedding light on the role of individual genes in the pathogenesis of SLE.

INTRODUCTION

The pathogenesis of systemic lupus erythematosus (SLE) is complex and heterogeneous with respect to specific manifestations of the disease in individual patients. The pathogenesis of most disease manifestations has not been completely elucidated. In some cases, disease manifestations result directly from pathogenic autoantibodies. In others, immune responses induced directly or indirectly by antibody-containing immune complexes result in organ damage and dysfunction. The genetics of SLE is similarly complex. Twins and first-degree relatives of patients with SLE are affected more commonly. However, lupus susceptibility is a polygenic trait, and many disease-associated genetic loci have been identified. Hormonal factors have significant effects on disease expression. Environmental factors such as ultraviolet radiation can also have effects on the severity of disease. In addition, some pharmacologic agents can induce autoimmune disease in certain individuals, and drug-induced lupus shares a number of clinical and immunologic features with SLE.

Animal models have been vitally important in developing our understanding of both the normal immune system and the immunopathogenesis of SLE. In fact, most of our advances in understanding the pathogenesis of SLE, either through studies of basic immunology or through studies of genetic susceptibility, have been the result of discoveries made with the use of animal models. Mouse models have been particularly important in this regard. Broad similarities are found between the murine and human immune systems, and the mouse is the major model system used for basic studies in cellular immunology. In addition, the availability of mouse models with many features of SLE has provided an invaluable opportunity for the study of this disease. Countless studies over a 5-decade period have identified clinical, immunologic, and genetic similarities between many murine lupus strains and SLE in humans. Most recently, for example, complex transcriptional network analysis has identified 20 network “nodes” reflecting diverse functions, including immune cell infiltration, endothelial cell activation, tissue remodeling, and macrophage/dendritic cell activation, that are commonly shared between human lupus nephritis and three murine models of lupus nephritis.¹ Murine lupus models can be classified as spontaneous, induced, and engineered models. Spontaneous models include inbred strains in which features of SLE have arisen naturally and congenic strains that result from deliberate crossing and inbreeding of defined lupus-prone strains to genetically isolate particular phenotypic characteristics and subsequently define the associated genetic loci. Induced models include autoimmune or nonautoimmune mice in which autoimmune disease is induced by exposure to chemicals or other defined substances as a model of environmental or drug-induced lupus. Finally, a rapidly growing number of engineered mouse strains are providing important insight into the role of specific immune pathways in the pathogenesis of SLE. These mouse models

of SLE are also frequently used as preclinical models to establish proof of concept for novel therapeutic approaches and to test the specific efficacy of pharmacologic and biologic agents for the treatment of SLE.

SPONTANEOUS MOUSE MODELS

New Zealand black

The spontaneous development of lupuslike features has been identified in a number of inbred mouse strains (Table 129.1).²⁻¹⁰ The earliest of these strains was the New Zealand black (NZB) mouse, which was developed by Dr. Marianne Bielschowsky at the University of Otago Medical School in New Zealand in the process of generating new inbred mouse strains. She found that early mortality developed in these mice because of widespread hemolysis as a result of autoimmune hemolytic anemia. Development of hemolytic anemia in this strain has been linked most specifically to two genetic loci: Aia3 and Nba2. NZB mice have a life expectancy of 16 to 17 months, as opposed to more than 2 years for normal mice. This strain exhibits many manifestations of B-cell hyperreactivity, including hypergammaglobulinemia, an immunologic characteristic of many SLE patients. Late in life, B-cell lymphomas that are similar to the lymphomas that develop in some people with Sjögren syndrome develop in most NZB mice. Kidney disease secondary to immune complex glomerulonephritis also variably develops in NZB mice, but involvement is mild and it develops only slightly earlier in female mice than in males.

(NZB×NZW)_F₁

Subsequent crosses of the NZB strain with other unrelated strains identified hybrids with additional autoimmune features. The most interesting of these was the cross between NZB and New Zealand white (NZW) mice. NZW mice have a normal to prolonged life span and are generally healthy. However, mating of NZW with NZB mice results in first-generation offspring that have high-titer antinuclear antibodies (ANAs), aggressive kidney disease, and early mortality. This (NZB×NZW)_F₁ hybrid (NZB/W) became the first and best characterized mouse model of SLE, and studies in this strain provided many important early insights into the pathogenesis of autoimmunity.² High-titer double-stranded DNA (dsDNA) antibodies and kidney disease with many features of lupus nephritis, including proliferative glomerulonephritis, develop in NZB/W hybrids. Renal disease is the major cause of the early mortality in this strain¹¹ (Fig. 129.1). Characteristic lupus erythematosus cells (LE cells), a pathologic hallmark of SLE, also develop in NZB/W mice. Circulating autoantibodies and clinical renal disease appear earlier in female B/W mice than in males, and like humans with SLE, the disease is more severe in female mice. Although renal disease is the most obvious clinical manifestation of disease in NZB/W mice, other organs are also involved, including the exocrine salivary glands; sialadenitis and generalized lymphadenopathy mimicking Sjögren syndrome, a frequent secondary complication of SLE, develop in the salivary glands. These mice also appear to have central nervous system (CNS) abnormalities in common with SLE, although developmental abnormalities are also present in the brains of NZB/W hybrids and can confound pathologic studies in this strain. Serologic abnormalities common in SLE are also present in this hybrid, including hypergammaglobulinemia, antilymphocyte antibodies, and hypocomplementemia.² B/W mice produce anti-dsDNA antibodies in high titer. Subsets of IgG, particularly IgG2, are nephritogenic in that they not only induce glomerulonephritis and subsequent proteinuria in lupus-prone mice but can also induce glomerular damage when infused into normal BALB/c mice. Other autoantibodies detectable in NZB/W mice include antinucleosome

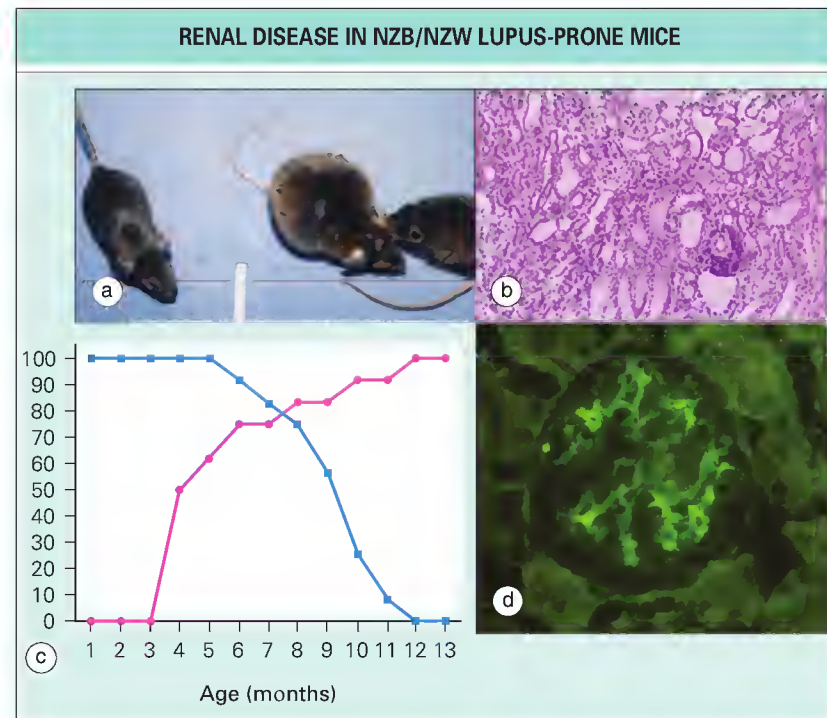


Fig. 129.1 (a) Seven-month-old diseased mouse on the right with fluid retention versus a 3-month-old healthy mouse on the left. (b) Graph showing the percentage of patients in whom proteinuria develops as a result of glomerulonephritis (red) and percent survival (blue). (c) Renal pathology includes inflammation, glomerulonephritis, and tubular dilation. (d) Glomerular immune complex deposition in the mouse kidney.

TABLE 129.1
Spontaneous mouse models of lupus

Mouse strain	Phenotype	References
NZB	Hemolytic anemia, splenomegaly, ANA	2
(NZB×NZW) F_1	ANA, anti-DNA, GN, LAN, SS	2
NZM2410 (NZB, NZW)	ANA, GN, LAN	3, 4
SNF1 ([SWR×NZB] F_1)	ANA, anti-DNA, GN	5, 6
MRL/lpr	LAN, ANA, anti-DNA, GN, vasculitis, SS, cryoglobulinemia	7
MRL/gld	LAN, ANA, anti-DNA, GN, arthritis	8
BXSB/yaa	ANA, anti-DNA, GN, male preponderance	9, 10

ANA, antinuclear antibody; GN, glomerulonephritis; LAN, lymphadenopathy with or without splenomegaly; SS, Sjögren syndrome.

and antihistone antibodies. As noted, the switch to IgG2 is characteristic of the autoantibodies in NZB/W mice as opposed to NZB mice, and many of them are complement-fixing isotopes. Thus, the development of IgG autoantibodies is linked to the hypocomplementemia that develops in this strain. Early expansion of CD5+ (B1) B cells also occurs in NZB and NZB/W mice and correlates with the development of autoantibodies. Elimination of these cells reduces autoantibody levels and substantially prolongs life. These cells are increased in the NZB parental strain as well. A distinguishing feature of CD5+ B cells in both strains is that they frequently exhibit aneuploidy, which appears to be the major factor leading to B-cell lymphomas in both strains. NZB/W mice also have abnormalities in professional antigen-presenting cells (APCs) when compared with nonautoimmune mice. Dendritic cells are increased in diseased mice and have altered expression of co-stimulatory receptors.¹² They also effectively co-stimulate T cells to produce antinucleosome autoantibodies.¹³ These cells produce increased amounts of type I interferons in comparison to controls, which is another immunologic feature shared by this model and SLE in humans.^{14,15} The increasing number of studies relating type I interferons to the pathogenesis of SLE and the observation that interferon- α (IFN- α) worsens disease in NZB/W mice suggest that dendritic cells are a significant factor in the

pathogenesis of autoimmunity in this model. Despite the relationship between B-cell hyperactivity, autoantibody production, and disease, it is clear that lupus is a T cell-dependent disease in these strains. Depletion of CD4+ T cells with monoclonal antibodies prevents the development and progression of disease, and the switch to pathogenic IgG anti-DNA antibodies in B/W mice is T cell dependent.^{11,16} Less clear is the function of regulatory T cells in this model. Foxp3-expressing CD25+ regulatory T cells function in normal mice and humans to maintain peripheral tolerance by suppressing autoreactive T cells and APCs. These cells are present in lower numbers in young prediseased B/W mice than in age-matched BALB/c mice, but their numbers increase significantly with the development of autoimmune disease.¹⁷ These regulatory cells have been variably reported to have normal or decreased suppressor function *in vitro*.^{18,19} However, adoptive transfer of activated CD25+ regulatory T cells retards the progression of active renal disease in NZB/W mice.¹⁷ Thus, although it is not clear whether NZB/W lupus-prone mice have an intrinsic defect in the regulatory T-cell compartment, it appears that they can be induced to suppress autoimmune disease.

The NZB/W model has also been valuable for studies of the mechanisms responsible for the female preponderance of autoimmune disease in humans. Castration of NZB/W mice early in life result in more severe disease that parallels that of female mice, whereas castration of female mice has no effect on the course of disease.²⁰ On the other hand, treatment of female NZB/W mice with androgens limits disease, whereas estrogens accelerate disease. Interestingly, androgens can ameliorate lupus nephritis and prolong survival in NZB/W female mice with advanced disease.²⁰ Thus, the more severe pattern of disease in NZB/W mice can be explained almost entirely by the effect of sex hormones.

As expected from the multiple immunologic abnormalities identified in NZB/W mice, the genetics of autoimmunity in these mice is complex. Genomewide linkage studies in NZB- and NZW-related strains indicate that more than 20 loci influence disease susceptibility or expression (or both). As with human SLE, the major histocompatibility complex (MHC) locus is clearly of importance for disease susceptibility. The major MHC contribution is from the H-2^z locus on chromosome 17 of the NZW parent, but many non-MHC loci are important in the pathogenesis of lupus. One such region identified in NZB mice is the Nba2 locus.²¹ This region contains the interferon-inducible gene *Ifi202*, which is linked to the production of nuclear autoantibodies, including those to native DNA. The effect on autoantibody production appears to be the result of enhanced survival of B cells mediated by *Ifi202*. The implication of a lupus susceptibility gene in NZB autoimmune-prone mice that is regulated by type I interferons is interesting

in light of the increasing evidence in support of a role for interferon-inducible genes in SLE.¹⁵

The value of the NZB/W strain as a model of SLE is also supported by a large number of preclinical studies in NZB/W mice demonstrating the efficacy of immunosuppressive and immunomodulatory agents in ameliorating autoimmune disease. In fact, the efficacy of the major agents currently used to treat SLE was first established in NZB/W mice, including corticosteroids, cyclophosphamide, cyclosporine, and mycophenolate mofetil.²²⁻²⁵ This model is also commonly used to test the efficacy of novel treatment strategies for SLE. Recent examples include antibodies or soluble receptors that block co-stimulatory signals between T cells, APCs, and B cells^{7,8,26-29}; B-cell stimulatory factors^{30,31}; antibodies against immunomodulatory cytokines; and small-molecule inhibitors of immune receptor signaling.³² Other lupus models have also been used to test *in vivo* preclinical efficacy, most commonly in the MRL/lpr³³ and SNF1³⁴ models described later.

New Zealand mixed strains

Progressive inbreeding of NZB/W hybrids to select for severity of kidney disease and coat color produced a group of hybrid strains referred to as New Zealand mixed strains.³ These strains have been used to isolate and characterize specific disease susceptibility loci in the NZB and NZW genomes. The NZM2410 strain, in which high-titer ANAs and aggressive glomerulonephritis develop, has been particularly useful in segregating specific disease characteristics. Backcrossing of specific NZM2410 lines onto the nonautoimmune C57BL/6 background produced hybrid strains that are congenic for different disease susceptibility loci.⁴ The three major loci have been designated Sle1, Sle2, and Sle3/5. Selective crossing of these congenic strains has demonstrated the phenotypic characteristics of each of these genetic loci. Sle1 mediates the loss of tolerance to nuclear autoantigens, including chromatin. Nephritis results when Sle1 is combined with Sle2 or with Sle3/5.³⁵ These data have been interpreted to suggest that the pathogenesis of murine lupus is a multistep process in which the disease is initiated by a gene or genes within the Sle1 locus and then worsened by additional susceptibility genes. Sle2 confers a significant proportion of the B-cell hyperactivity seen in NZB/W mice,³⁶ whereas Sle3 is associated with generalized T-cell activation.³⁷ The Sle3/5 locus appears to contribute to the increased activity of APCs.³⁸ More recently, selective breeding of Sle1 congenic strains has indicated that disease susceptibility is conferred by four subintervals (Sle1a to Sle1d). Detailed mapping of these intervals suggests that polymorphisms in the SLAMF2 gene cluster confer susceptibility at the Sle1b locus and that polymorphisms in the C2 gene confer susceptibility at the Sle1c locus.^{39,40}

SNF1

The SNF1 mouse model (SWR×NZB)_F₁ is another lupus-prone strain derived from the autoimmune NZB strain. Like NZB/W mice, both anti-DNA and antinucleosome antibodies and female-predominant glomerulonephritis develop in SNF1 mice and lead to death by 1 year of age.⁵ The SWR parent is not autoimmune prone and has a normal life span. NZB loci contributing to disease in this hybrid strain include Nba1 and Nba3, whereas probable genetic susceptibility loci contributed from SWR include the T-cell receptor-β (TCR-β), I-A, and Swrl genes.⁴¹ The SNF1 strain has provided much information about the role of nucleosomes as autoantigens and the role of cationic anti-DNA autoantibodies in the pathogenesis of autoimmune kidney disease.⁶ The specificity of the antinucleosome response in SNF1 mice has also been instructive. The autoepitopes for pathogenic T-cell clones derived from SNF1 mice have been mapped in core histones with the use of overlapping synthetic peptides. One of these peptides is homologous to histone H1'₂₂₋₄₂ and stimulates T helper (Th) cells to augment the production of pathogenic autoantibodies. Importantly, a marked expansion of H1'₂₂₋₄₂-reactive Th1 cells occurs early in life in SNF1 mice, and this peptide accelerates glomerulonephritis in SNF1 mice more potently than do other identified nucleosomal epitopes.²⁸

MRL/lpr and MRL/gld

The MRL/lpr mouse has been an informative model of systemic autoimmunity, particularly because it led to the identification and characterization of a single gene that markedly accelerates murine lupus. The parental MRL strain (MRL/mp) was originally established from crossing several standard inbred strains. After multiple generations of MRL/mp, massive lymphadenopathy and splenomegaly were noted to develop in the offspring from one mating. An autosomal recessive mutation was identified and designated *lpr* for lymphoproliferation.⁷ This mutation was localized to chromosome 19. Severe manifestations of autoimmune disease with high-titer autoantibodies

and significantly more aggressive glomerulonephritis were also found to develop in the MRL/lpr mouse. MRL/lpr mice produce antibodies to DNA and ribonuclear proteins, including Sm. The *lpr* defect represents a mutation in the gene that encodes the Fas protein.²⁹ Fas is a type I membrane protein member of the tumor necrosis factor receptor family that is expressed on activated lymphocytes and in the thymus and transduces an apoptotic signal. Definitive demonstration of the role of Fas in MRL/lpr mice was provided by an experiment in which normal Fas protein expressed from a transgene prevented the lymphoproliferative disease. Another autosomal recessive mutation resulting in a very similar phenotype as the *lpr* mutation was identified in the inbred C3H/HeJ strain. This mutation was localized to chromosome 1 and designated *gld* for generalized lymphoproliferative disease. Bone marrow transplant experiments between wild-type MRL mice and *lpr* and *gld* mutant mice established that the *lpr* and *gld* genes represent a receptor-ligand pair of molecules, and thus *gld* represents a mutation in Fas ligand.⁸ The *lpr* mutation in MRL/lpr mice can be viewed as an epigenetic or accelerating factor for systemic autoimmunity. Massive nonmalignant lymphoproliferation and early mortality develop in MRL/lpr mice, as well as several manifestations of autoimmunity, including glomerulonephritis, vasculitis, and arthritis with variable penetrance, in addition to autoantibody production. This lymphocyte expansion and infiltration are predominantly due to accumulation of immature “double-negative” (DN) T cells lacking CD4 and CD8. Accumulation of these DN T cells in the periphery is not due to abnormal proliferation but rather to loss of their usual programmed cell death. MRL/lpr mice also appear to have B-cell abnormalities associated with autoantibody production. Although lymphoproliferation is the distinguishing feature of MRL/lpr mice, this model has a number of clinical manifestations that are similar to those seen in other murine lupus models and humans with SLE, including glomerulonephritis with complement deposition; necrotizing vasculitis of medium-sized arteries, particularly the renal, mesenteric, and coronary arteries; interstitial pneumonitis; and skin disease. MRL/lpr mice also display signs of CNS involvement. The severity of disease, as well as the range of autoantibodies produced, is dependent on the genetic background on which the *lpr* mutation is expressed. These autoimmune manifestations in *lpr/lpr* mice are most prominent on the MRL background. This strain has also been used frequently to examine the efficacy of therapeutic interventions for SLE.^{42,43}

BXSB

The BXSB mouse is another spontaneous model in which anti-DNA antibodies and immune complex glomerulonephritis develop, as in NZB/W and MRL/lpr mice.⁴⁴ However, BXSB mice are unique among murine models of SLE in that male mice are more severely affected than females. In this model, genetic factors on the Y chromosome rather than hormonal influences accelerate disease in male mice. This factor can act independently of genetic background in that in crosses of BXSB with other autoimmune strains, lupuslike disease develops in *F*₁ male mice with an onset and phenotype like that of BXSB males. However, crosses of BXSB mice with nonautoimmune strains does not lead to autoimmune disease in male offspring. Thus, the Y-linked gene acts as a disease-accelerating factor, but autoimmunity-predisposing background genes are also required for the development of autoimmunity. This was dramatically demonstrated in an experiment in which fatal immune complex-mediated glomerulonephritis developed in otherwise normal mice expressing both *Yaa* and the Sle1 locus. The Y-linked gene is called *Yaa* (Y-linked autoimmunity accelerator). The *Yaa* gene in BXSB has recently been shown to be a duplication of the Toll-like receptor 7 (TLR7) gene, which results in overexpression of TLR7.^{9,10} TLR7 is the innate immune receptor for single-stranded RNA, and overexpression of TLR7 appears to preferentially induce B cells to produce autoantibodies, particularly to nuclear antigens, including single-stranded DNA (ssDNA), dsDNA, and chromatin. As in other murine lupus models, BXSB B cells exhibit an activated phenotype and are hyperproliferative such that B-cell expansion occurs in this strain, except that it is more marked in male animals. Yet as is the case in other murine lupus models, disease in BXSB mice is also dependent on T cells, and disease can be suppressed by treatment with anti-CD4 monoclonal antibody or by blockade of T-cell co-stimulation with CTLA4Ig.⁴⁵

INDUCED MODELS

Spontaneous murine lupus models with clinical and immunologic features of SLE have proved valuable for dissecting pathogenic mechanisms and ultimately for clarifying the genetic basis for systemic autoimmunity. However, there are an increasing number of examples in which autoimmune

disease can be induced in nonautoimmune strains. In some cases these models have shed light on potential mechanisms by which environmental exposure can contribute to the development or severity of lupus. For example, cutaneous lupuslike skin lesions can be induced in TCR- α -deficient mice treated with 5-fluorouracil (5-FU) plus ultraviolet B (UVB) light. These skin lesions have several features characteristic of chronic cutaneous lupus erythematosus, including CD4+ cell infiltration and IgG deposition at the dermal-epidermal junction. Lesions in these mice appear more rapidly and are more severe than lesions that develop in C57BL/6 mice treated with the same dose of UVB light and 10 times more 5-FU. CD4+ cells are required for the development of this skin lesion.⁴⁶

Pristane-induced lupus

Kuroda and colleagues⁴⁷ extensively characterized the lupuslike autoimmunity induced by intraperitoneal injection of the hydrocarbon pristane (2,6,10,14-tetramethylpentadecane) in mice. Autoimmune disease in this model is characterized by autoantibody production and renal immune complex deposition with complement activation. Remarkably, such exposure induces the production of autoantibodies in nonautoimmune strains as well as in autoimmune susceptible strains, although the level of induction, severity of disease, and range of autoantibody specificity are influenced by the genetic background. For example, in response to intraperitoneal pristane, autoantibodies to histones, Sm, Su, dsDNA, and collagen develop in BALB/c mice, whereas SJL/J mice predominantly produce antibodies to ribosomal P protein. The development of autoantibodies and clinical renal disease induced by pristane is dependent on TLR4 and TLR9.⁴⁸ Pristane can also produce inflammatory arthritis in some susceptible strains.

Much effort has been devoted to inducing autoimmune disease in murine models through exposure to known autoantigens such as DNA and RNA. These nucleic acids are more immunogenic when coupled to or associated with protein. For example, nucleosome particles are generally more effective than free DNA in inducing anti-DNA antibodies and ANAs in normal or autoimmune strains. However, bacterial-derived DNA that contains the CpG motif is more effective in inducing autoantibodies in mice, and administration of CpG-containing oligonucleotides can produce autoantibody-mediated immune complex glomerulonephritis.⁴⁹ CpG DNA activates B cells directly.⁵⁰ Signals from these foreign antigens are transduced via the TLR9 receptor and may be important adjuvants in stimulating autoreactivity in humans, in addition to serving as autoantigens.⁵¹

A number of induced murine models of organ-specific autoimmune disease have also been developed, such as experimental autoimmune nephritis.⁵² A very interesting model of autoimmune-mediated CNS disease has been developed by using passive transfer of brain-reactive autoantibodies combined with procedures that break the blood-brain barrier in mice. This model has provided new insight into the pathogenesis of brain dysfunction in SLE, including cognitive dysfunction, memory loss, and emotional disturbance.⁵³

ENGINEERED MOUSE MODELS

Genetically engineered mouse models are increasingly providing important clues to the pathogenesis of lupus through identification of the functions of specific components of the immune system in the context of autoimmune susceptibility (Table 129.2).⁵⁴⁻⁶⁵ Molecular cloning and recombinant DNA techniques coupled with transgenic technologies have provided the ability to modulate normal gene expression by increasing or decreasing normal levels of expression of a specific gene or even by inserting an entire functioning gene into a different genetic background to examine its function *in vivo*. For example, overexpression of genes that promote lymphocyte survival, including *Bcl2* and *BAFF*, leads to the development of autoimmunity and lupuslike phenotypes.^{65,66} Alternatively, specific genes can be rendered nonfunctional via targeted deletion or insertion of a DNA segment to “knock out” the gene. This latter approach has been useful in implicating several diverse pathways in the development of SLE. From such experiments it has become clear that loss of function of any of a large number of single genes can lead to immunologic and pathologic changes similar to those observed in lupus. Examples of single gene defects leading to loss of negative regulation of lymphocyte activation include CTLA-4,^{54,55} CD22,⁵⁶ CD31,⁵⁷ Fyn,⁵⁸ Lyn,^{59,67} FcγRIIB,⁶⁰ PTEN,⁶¹ PD-1,⁶² and PKC-δ.⁶³ The value of such *in vivo* studies is illustrated by studies of the *lyn* knockout mouse, which has clarified the role of this gene in the B-cell hyperactivity observed in murine and human lupus, as well as emphasized the complexity of this autoimmune phenotype. Thus, in mice deficient in *lyn*, which negatively regulates B-cell activity, increased plasma cells and autoantibodies develop. However, even

TABLE 129.2

Engineered models of lupus

Targeted gene	Genotype	Phenotype	References
CTLA4	Knockout	ANA, LAN, GN, early lethality	54, 55
CD22	Knockout	ANA	56
CD31	Knockout	ANA, GN	57
Lyn	Knockout	ANA, GN, LAN	58, 59
Fyn	Knockout	ANA, GN	58
FcγRIIB	Knockout	ANA, GN, LAN	60
PTEN	Knockout	ANA, GN, LAN	61
PD-1	Knockout	ANA, GN, LAN	62
PKCδ	Knockout	ANA, GN, LAN	63
C1q	Knockout	ANA, GN	64
BAFF	Transgenic	ANA, GN, LAN	65

ANA, antinuclear antibody; GN, glomerulonephritis; LAN, lymphadenopathy with or without splenomegaly.

though the development of IgG autoantibodies depends on interleukin-6, the accumulation of plasma cells and autoreactive IgM does not.⁶⁴ Another example of how engineered models can illuminate the importance of specific genes in normal and autoimmune responses comes from studies of the function of the lymphocyte-activating protein CD45. CD45 is a protein tyrosine phosphatase that plays a key role in receptor-activated signal transduction in lymphocytes, including integration of signals from cytokines and co-stimulatory molecules, and it is required for normal lymphocyte development. Dimeric CD45 is maintained in an inactive state when a wedge-shaped domain from one homodimer is inserted into the catalytic site of the other homodimer. Polyclonal lymphocyte activation, lymphoproliferation, autoantibody production, and autoimmune glomerulonephritis develop in mice with a targeted single point mutation that inactivates this inhibitory wedge of CD45.⁶⁸ This *in vivo* genetic study in an engineered mouse model is another example of how loss of negative regulation of lymphocyte activation can lead to autoimmune disease, and it demonstrates the importance of precise lymphocyte regulation in maintaining tolerance and preventing a shift in balance to the development of autoimmunity. It also illustrates how a very small genetic change can upset this balance. Genes involved in clearance of the products of cellular apoptosis, including DNA (DNase I and caspase-activated DNase), chromatin (serum amyloid P), and cellular proteins (C1q), have also been studied *in vivo* by targeted deletion. In each case, antinuclear autoantibodies and immune complex glomerulonephritis develop in the knockout mice.⁶⁹⁻⁷¹ Another group of molecules whose importance in lupus has been demonstrated *in vivo* in animal models and subsequently in SLE are the immunomodulatory cytokines, particularly the interferon gene family. For example, lupus nephritis with antinuclear autoantibodies develops in mice transgenic for IFN-γ, and NZB mice deficient in type I interferon receptor exhibit an attenuation of their lupuslike disease.⁷²

An important factor that must be considered when interpreting the results of studies of engineered mouse models of autoimmune disease is the genetic background of the parental strains. In fact, the genetic background can markedly influence the autoimmune lupus phenotype in gene-targeted mice. Thus, there may be variable components of autoimmune susceptibility in some “normal” mouse strains. This possibility has been verified in a study of the 129 mouse strain, which is widely used in the generation of gene-targeted mice.⁷³ This suggests the possibility that background gene influences might account for some of the autoimmune phenotype ascribed to a single gene in knockout mice and highlights the importance of epistatic gene modifiers in shaping the autoimmune phenotype. Epigenetic interactions between female sex, estrogens, and DNA methylation have also been investigated in a novel inducible epigenetic lupus model.^{74,75} MicroRNA is another epigenetic factor that is being recognized as an important factor in immune regulation, as well as in pathologic immune dysregulation. Interestingly, a distinct microRNA expression pattern has recently been identified in common in three different murine models.⁷⁶

Completion of genomewide association studies in human SLE and advances in exome and whole-genome sequencing are currently leading to very rapid progress in the identification of lupus susceptibility genes in

humans. In many cases the identified candidate genes have also been implicated in the pathogenesis of murine lupus.⁷⁷ For example, polymorphisms in the *STAT4* gene confer significant risk, and deficiency of this gene in NZM mouse strains influences disease severity.^{78,79} Similarly, kallikrein genes are associated with lupus nephritis in humans and mouse models.⁸⁰ Despite these rapid advances in the identification of important genes that confer risk for SLE in humans, ongoing mechanistic and genetic studies in mouse

models will continue to be required. The ability to analyze the function of an abnormal gene *in vivo* is critical to unraveling the functional roles of many of these genes, as well as their interactions with each other. These genetic and functional studies in mouse models coupled with *in vivo* evaluation of the effectiveness of new targeted therapies emphasize the vital role of murine models in the ongoing study and development of effective treatments of SLE.

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130

Autoantibodies in systemic lupus erythematosus

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- Some autoantibodies have high diagnostic specificity for systemic lupus erythematosus, particularly anti-Sm, anti-dsDNA, anti-ribosome P, and anti-proliferating cell nuclear antigen autoantibodies.
- The levels of some autoantibodies parallel disease activity.
- Certain autoantibodies are associated with clinical subsets of disease.
- Some autoantibodies may directly or indirectly cause cell or tissue injury.
- Autoantibody production may be induced or maintained by immunostimulatory antigens released from dead cells.
- Autoantibodies are useful tools for cell biologists to explore the function of cellular antigens.

INTRODUCTION

Nearly all patients with systemic lupus erythematosus (SLE) produce autoantibodies. The first evidence of the existence of autoantibodies was Har-Graves' description of the LE cell phenomenon (phagocytosis of intact nuclear material by polymorphonuclear leukocytes) in 1948.¹ Antinuclear antibodies (ANAs) and anti-DNA antibodies were reported in 1957, and autoantibodies to nonhistone autoantigens (anti-Sm antibodies) were first reported in 1966.¹ Over the next 30 years a diverse array of autoantibodies associated with SLE and other systemic autoimmune diseases were identified. This chapter reviews the major autoantibodies associated with SLE, their diagnostic applications and role in disease pathogenesis, and current hypotheses regarding their origins.

ANTINUCLEAR ANTIBODIES

Most autoantibodies produced by patients with SLE recognize nuclear antigens, although antigens located in the cytoplasm or on the cell surface or secreted by the cell may be recognized. The simplest screening assay is the fluorescent ANA assay (Fig. 130.1). With the use of cultured human Hep-2 cells, more than 95% of lupus patients are found to have positive ANA. "ANA-negative lupus" is usually associated with autoantibodies against cytoplasmic autoantigens, such as Ro (SS-A). Although the sensitivity of the fluorescent ANA assay is high, its specificity for SLE is only approximately 20%, with a positive predictive value of 11% to 13%.² Thus, although a negative ANA assay helps exclude lupus, a positive ANA finding is considerably less useful. A positive ANA test may also be seen with other systemic autoimmune diseases, autoimmune thyroid disease, drug-induced lupus, infections, and neoplastic diseases. Some healthy individuals also have a positive result.³ This is highly dependent on the serum dilution and the person's age (frequency increases with age). Although only about 3% of randomly selected healthy individuals are positive at a 1:320 dilution, this value increases to around 30% at a 1:40 serum dilution.¹

Fluorescent ANA assay

Present-day fluorescent ANA tests generally use Hep-2 cells (a human laryngeal carcinoma cell line) as a substrate for testing diluted serum (see Fig. 130.1a). The titer (see Fig. 130.1b) and pattern (see Fig. 130.1c) are reported. Although interpretation is observer dependent, a 1:160 dilution probably yields the optimal balance between sensitivity and specificity. At

this dilution, patients with SLE can be discriminated from healthy controls 95% of the time.

A variety of staining patterns may be seen, most commonly homogeneous, speckled, nucleolar, cytoplasmic, centromere, and proliferating cell nuclear antigen (PCNA) (see Fig. 130.1c). These patterns result from antibodies recognizing different subcellular structures. A homogeneous pattern may be due to anti-DNA or antichromatin autoantibodies, whereas a speckled pattern is frequently associated with autoantibodies against ribonucleoproteins and cytoplasmic staining with autoantibodies to ribosomes, Ro60, or tRNA synthetases. A nucleolar pattern is suggestive of scleroderma, and a centromere pattern is often associated with CREST syndrome (calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia). Variable staining of interphase nuclei is usually due to anti-PCNA.

Alternative techniques for detecting ANAs

Double immunodiffusion

Double immunodiffusion provided early evidence that certain autoantibodies are more specific for the diagnosis of SLE than are ANAs. Autoantibodies detected with high specificity with this technique include anti-Sm, anti-RNP, anti-Ro (SS-A), anti-La (SS-B), anti-topoisomerase I (Scl-70), and anti-Jo-1. Though highly specific, this assay is labor-intensive and has been replaced largely by enzyme-linked immunosorbent assays (ELISAs) and multiplex bead assays, which can be automated and are more quantitative (Fig. 130.2a and b).

Enzyme-linked immunosorbent assay

The ELISA technique detects binding of the patient's immunoglobulin to antigens immobilized on plastic wells (see Fig. 130.2a).

Crude nuclear extracts have been used in ELISA to substitute for the fluorescent ANA test, but the binding of different antigens is variable, and mixtures of purified or recombinant antigens are used more often. The limitation is that autoantibodies reactive with antigens not included in the mix will not be detected. ELISAs are widely used in automated testing for antibodies against single autoantigens and generally perform acceptably in this setting. However, both false-positive and false-negative results occur, so the test results must be interpreted in light of the clinical situation.

Multiplex bead assays

In multiplex bead assays, individual autoantigens (e.g., RNP, Sm, Ro60) are conjugated to different-colored fluorescent microspheres, followed by incubation with serum and fluorescently tagged secondary antibodies (see Fig. 130.2b). These assays reliably detect autoantibodies against multiple analytes in a single test. However, only antibodies against components of the antigen mix used in the assay can be detected. Thus, these assays provide different information than that provided by the fluorescent ANA test. The fluorescent ANA test is the best screening method but provides limited information about autoantibody specificities. In contrast, multiplex bead assays are less sensitive than the fluorescent ANA test for screening but provide useful information on the types of autoantibodies present in a patient's serum.

Western blot assays

Western blotting involves dissociating cellular antigens in detergents, separating them by size via gel electrophoresis, and transferring them to a membrane. A modification of the Western blot strategy has been used to identify, clone, and express genes encoding lupus autoantigens (see Fig. 130.2c).

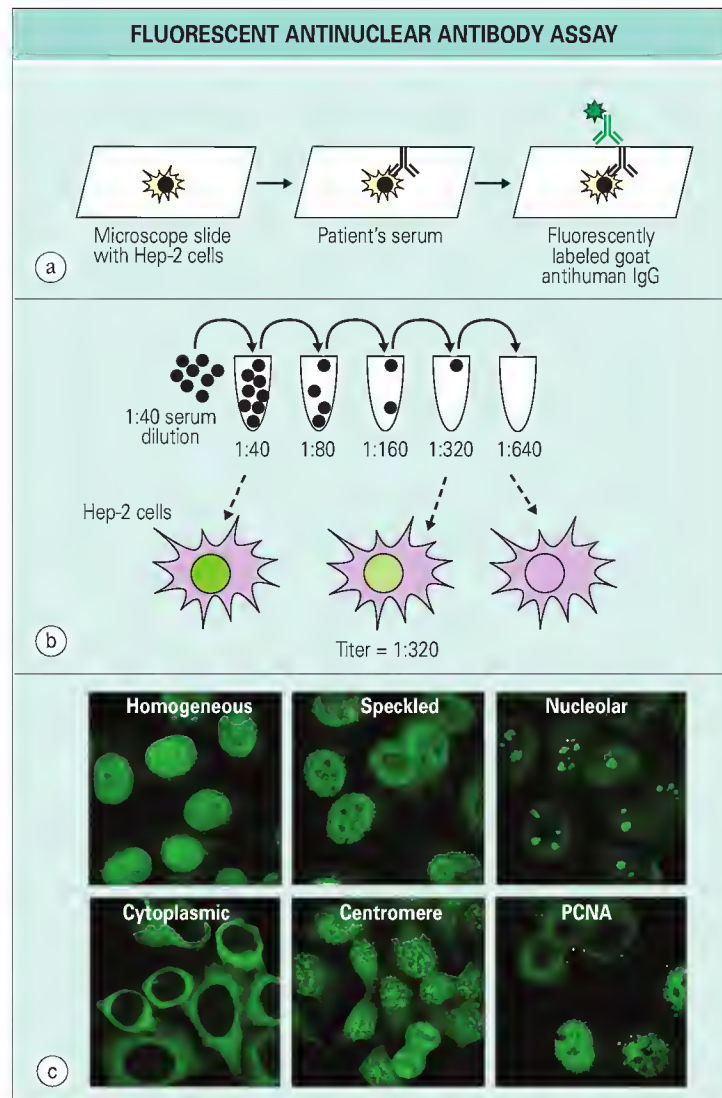


Fig. 130.1 (a) Hep-2 cells are grown on a microscope slide, fixed/permeabilized, and then incubated with a patient's diluted serum. After washing off unbound serum, the cells are incubated with fluorescently labeled goat antihuman IgG antibodies before viewing with an epifluorescence microscope. (b) Antinuclear antibody (ANA) titer. Patient serum is diluted 1:40, and then serial twofold dilutions are used to stain Hep-2 cells. In the example there is a weak fluorescent signal at a 1:320 dilution and no staining at 1:640 (a 1:320 titer). (c) ANA patterns. Illustrated are the staining patterns of anti-DNA antibodies (homogeneous), anti-RNP (speckled nuclear), anti-RNA polymerase I/III (nucleolar), anti-Jo-1 (cytoplasmic), anticentromere, and anti-proliferating cell nuclear antigen (PCNA) (variable intensity).

Immunoprecipitation assays

Immunoprecipitation of radiolabeled cell extracts is an important research tool used to define the components of autoantigens and to detect autoantibodies (Fig. 130.3). Immunoprecipitation assays have shown that many of the major autoantigens contain nucleic acid (DNA or RNA) components plus proteins (Fig. 130.4).

AUTOANTIGENS AND CLINICAL SIGNIFICANCE OF AUTOANTIBODIES

Through the use of immunoprecipitation, Western blotting, and recombinant autoantigen-based assays, autoantibodies specific for SLE, systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), rheumatoid arthritis (RA), or other clinical subsets have been identified and their cognate autoantigens characterized (Table 130.1; see also Fig. 130.3b).

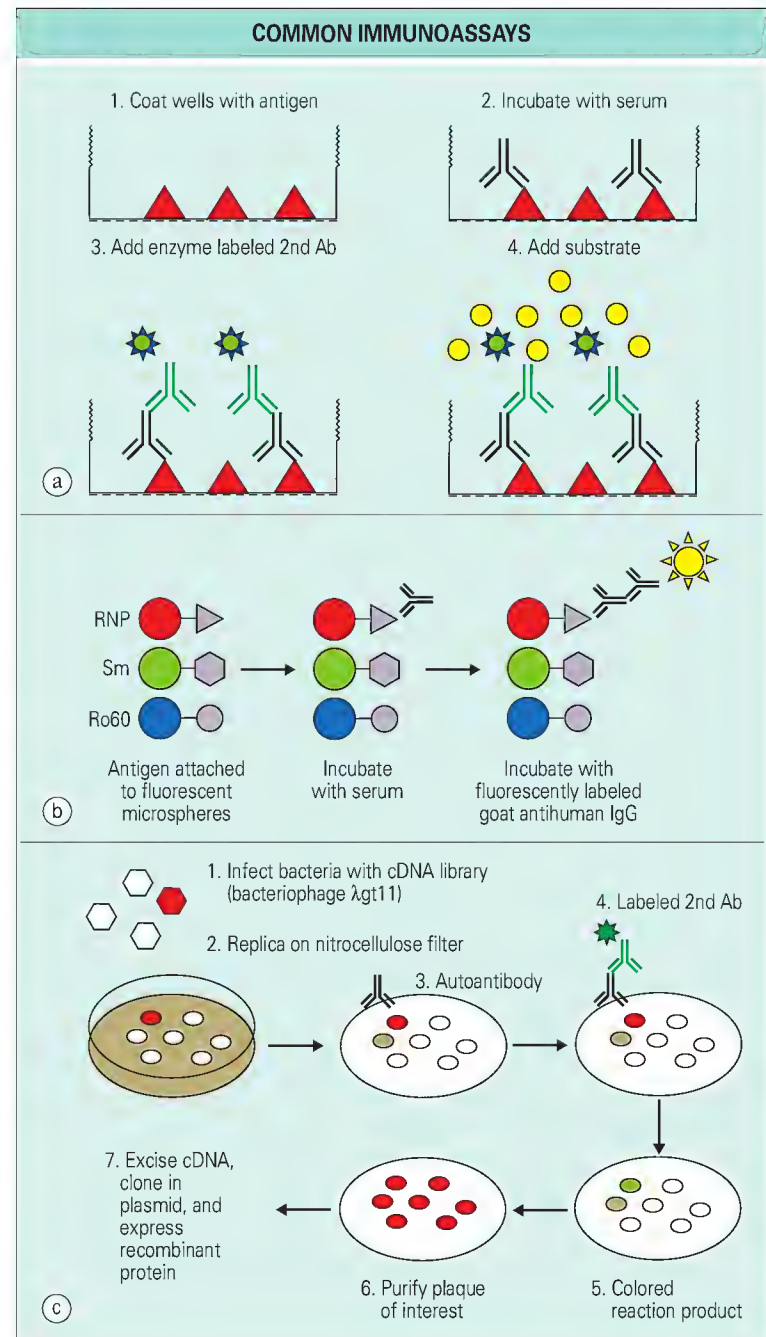


Fig. 130.2 (a) Enzyme-linked immunosorbent assay. The wells of a 96-well microtiter plate are coated with antigen (step 1), followed by the sequential addition of diluted patient serum (step 2), enzyme-labeled goat antihuman IgG secondary antibody (step 3), and substrate (step 4). Colored product is quantified with a spectrophotometer. (b) Multiplex bead assay. Fluorescently tagged microbeads coated with different antigens (in this example, RNP, Sm, and Ro60) are incubated with diluted patient serum followed by goat antihuman IgG antibodies labeled with a different fluorescent dye. Binding of antibodies to each of the differently labeled antigen-bearing beads is determined with a laser detector. In this example, the patient's serum autoantibodies bind only to the anti-RNP beads. (c) Adaptation of the Western blot procedure to clone autoantigen genes. A Petri dish with a lawn of bacteria is infected with a human cDNA library in bacteriophage γ gt11, an expression vector that allows the inserted human genes to be expressed as protein. A replica of the plaques is made by blotting onto a nitrocellulose filter impregnated with an inducer of gene expression, which is then incubated sequentially with diluted patient serum containing an autoantibody of interest and enzyme-labeled secondary antibody. A colored reaction product is deposited over one of the replica plaques to allow that plaque to be purified from the Petri dish. The gene of interest is excised from the bacteriophage, cloned into a plasmid expression vector, and used to generate large amounts of recombinant human protein in *Escherichia coli*.

ANALYSIS OF AUTOANTIGENS AND AUTOANTIBODIES BY IMMUNOPRECIPITATION

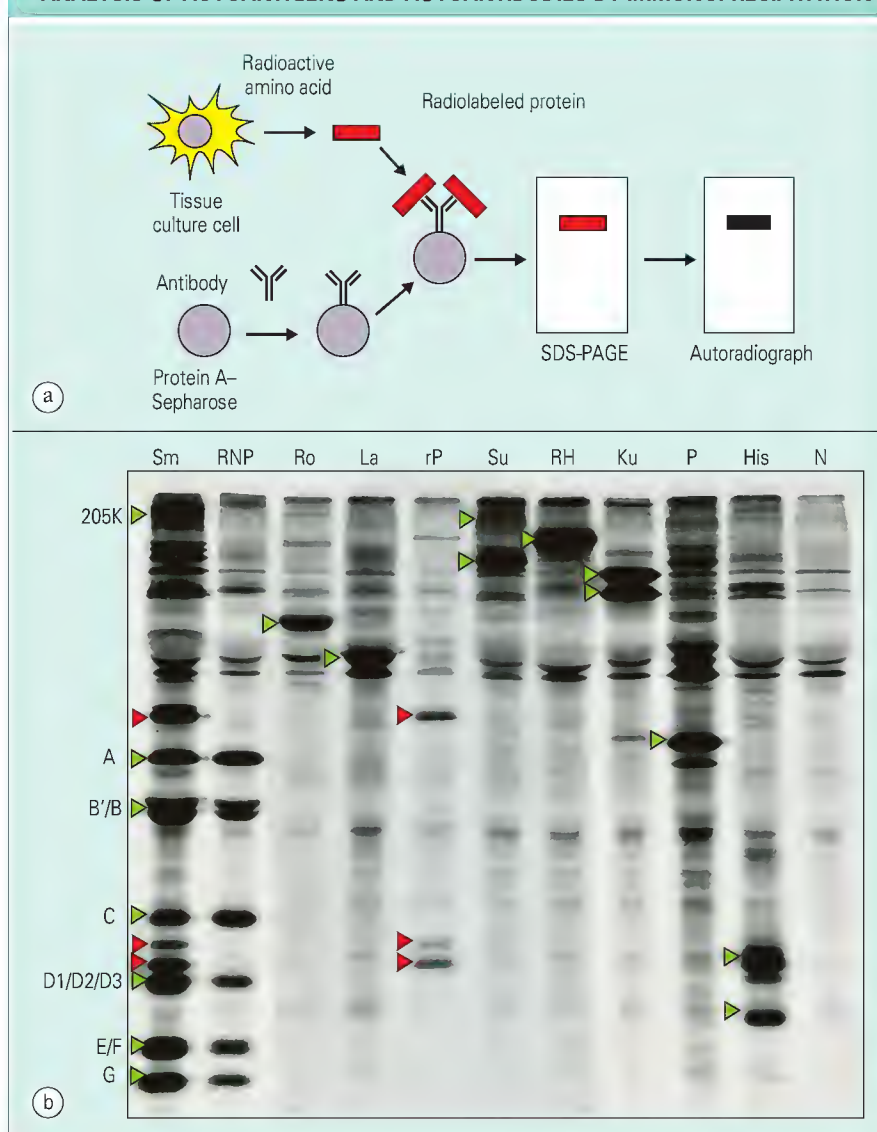


Fig. 130.3 (a) Tissue culture cells are grown in culture medium containing a radioactive amino acid. Cell extract is prepared and incubated with protein A-Sepharose beads preincubated with a patient's serum. Cellular antigens recognized by the serum autoantibodies become attached to the beads, and unbound proteins are washed away. The radioactive proteins are eluted from the beads and analyzed by sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE), followed by exposure to an x-ray film (autoradiography). (b) SDS-PAGE analysis of serum samples. Red arrowheads depict ribosomal P antigens (P0, P1, and P2). These antigens also are immunoprecipitated by the anti-Sm serum in lane 1: anti-Sm immunoprecipitates A-G (green arrowheads) and anti-ribosomal P precipitates P0, P1, and P2. N, normal human serum.

Sm and RNP autoantigens

Anti-Sm and anti-RNP autoantibodies recognize a set of small nuclear ribonucleoproteins (snRNPs) containing uridine-rich small RNA (U1, U2, U4, U5, and U6 RNA) involved in splicing messenger RNA (Table 130.2). All of these contain a group of proteins known as the "Sm core particle" (proteins B', B, D1, D2, D3, E, F, and G), which forms a donut-shaped ring surrounding the RNA strand recognized by the anti-Sm antibodies (see Fig. 130.4a). Along with a single molecule of U1, U2, U4/U6, or U5 RNA, individual snRNPs contain unique proteins: 70K, U1A, and U1C (reactive with anti-RNP antibodies) in the case of U1 snRNPs (see Fig. 130.4a) and 200/205-kDa proteins (U5-205K) in the case of U5 snRNPs. These structures explain the patterns in Figure 130.3b. Anti-RNP antibodies immunoprecipitate the U1 snRNP as an intact particle, and proteins A, B'/B, C, D1/D2/D3, E, F, and G (70K labels poorly) appear in the "RNP" lane (see Fig. 130.3b). Anti-Sm sera also immunoprecipitate proteins A to G, but because all U snRNPs contain the Sm core particle, U5-205K proteins are also present (see Fig. 130.3b, "Sm").

Anti-Sm antibodies are detectable in 10% to 25% of unselected lupus sera, but the prevalence is higher in black than in white patients with SLE (Fig. 130.5). Anti-Sm antibodies are found only in SLE, whereas anti-RNP antibodies are seen in SLE, as well as in other systemic autoimmune disorders.¹ Anti-Sm antibodies are virtually always associated with anti-RNP. In contrast, anti-RNP antibodies are often present without anti-Sm, a pattern characteristic of mixed connective tissue disease. Levels of anti-RNP are generally higher than those of anti-Sm. Usually, autoantibodies are produced against more than one of the protein components of the U1 snRNP, and about 40% of sera contain autoantibodies against the U1 small RNA.⁴

Ro60 (SS-A) and La (SS-B) autoantigens

Anti-Ro (SS-A) antibodies recognize a set of primarily cytoplasmic RNPs consisting of the 60-kDa Ro60 antigen and a single molecule of human Y1, Y3, Y4, or Y5 RNA (see Figs. 130.3b and 130.4b). The 47-kDa La (SS-B) antigen associates transiently with precursors of the small RNAs synthesized by RNA polymerase III, including Y RNA, which protects them from exonucleases.¹ La is a termination factor for RNA polymerase III.

Ro60 also binds misfolded RNA and plays a role in quality control of U2 and 5S ribosomal RNA.⁵ It may confer protection against ultraviolet irradiation by promoting the degradation of damaged (misfolded) RNA. Like the Sm core particle, Ro60 antigen forms a donut-shaped structure through which single-stranded RNA passes. A lupus-like syndrome develops in mice deficient in Ro60, thus raising the possibility that Ro plays an important role in preventing autoimmunity (see later).⁶

Although autoantibodies against the 52-kDa Ro52 protein are strongly associated with anti-Ro60 and anti-La (SS-B), Ro52 is not an integral component of the Y1 to Y5 RNPs. It is an interferon (IFN)-inducible member of the tripartite motif (TRIM) family bearing a RING motif that functions as an E3 ligase and ubiquitinates the transcription factor IFN regulatory factor 8.⁷

Anti-Ro/La autoantibodies are associated with sicca symptoms in Sjögren syndrome, SLE, PM/DM, and SSc. The prevalence of anti-Ro60 in primary Sjögren syndrome is 60% to 80%, whereas in SLE it is 10% to 50%.¹ Significant ethnic differences are seen in the prevalence (see Fig. 130.5). The prevalence of anti-La autoantibodies ranges from 10% to 20% in SLE and Sjögren syndrome (see Fig. 130.5). Anti-La autoantibodies are nearly always associated with anti-Ro60 or anti-Ro52, or both.

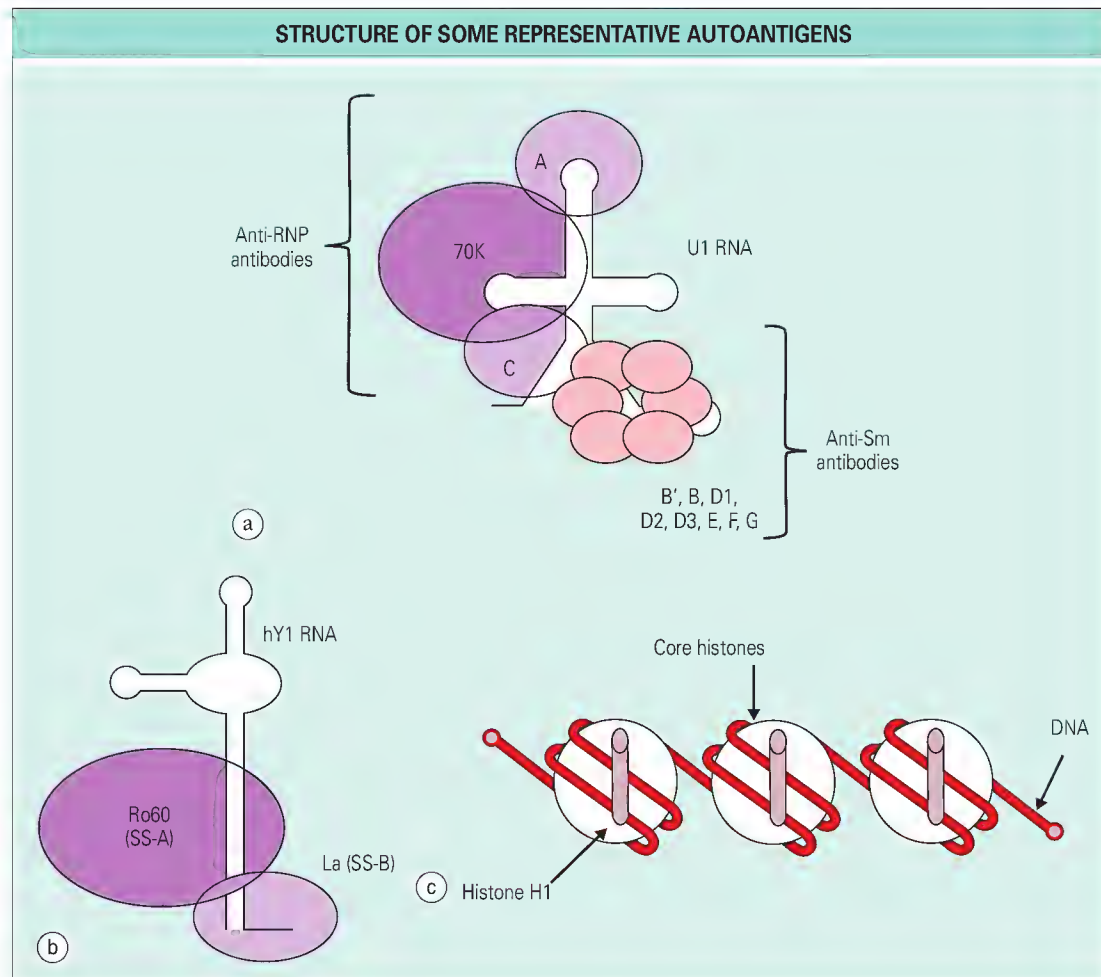


Fig. 130.4 (a) U1 snRNP. The particle contains proteins reactive with anti-Sm antibodies (B', B, D1, D2, D3, E, F, G), as well as anti-RNP antibodies (A, 70K, C), all associated with a single molecule of U1 small RNA. (b) Human Y1 ribonucleoprotein. The Ro60 protein is associated with a single molecule of human Y1 RNA (hY1). La (SS-B) antigen associates transiently with sequences located at the 3' end of the newly synthesized hY1 RNA. (c) Nucleosomes and chromatin. DNA is looped around the core histone (H2A/H2B)₂, H3, and H4 octamers to form nucleosomes with the appearance of beads on a string. Histone H1 is associated with linker DNA sequences. More complex folding and the association of additional nonhistone proteins result in the formation of chromatin fibers.

Anti-Ro60, anti-Ro52, and anti-La autoantibodies are associated with neonatal cardiac conduction abnormalities, including congenital complete heart block.⁸ These autoantibodies pose a risk to the fetus during pregnancy; although the risk for conduction abnormalities is low, screening should be performed in pregnant women with systemic autoimmune diseases, as well as in asymptomatic women with a previous pregnancy complicated by fetal heart block. IgG anti-Ro/La antibodies cross the placenta and damage the conduction system by binding to autoantigens from apoptotic cells, followed by an Fc receptor-mediated inflammatory response consisting of production of tumor necrosis factor- α (TNF- α) and fibrosis.⁸ Anti-Ro60 and anti-La autoantibodies are also associated with subacute cutaneous lupus, a photosensitive skin rash. Subacute cutaneous lupus induced by hydrochlorothiazide, terbinafine, and other drugs is likewise associated with anti-Ro. Transplacental passage of anti-Ro/La antibodies can cause a similar, but transient rash in neonates (neonatal lupus syndrome).⁹

DNA, nucleosomes, and chromatin

Chromatin consists of double-stranded DNA (dsDNA) with its associated histones and nonhistone proteins. The DNA is wound around a core histone octamer consisting of two molecules each of H2A/H2B, H3, and H4.¹ A single octamer with 145 base pairs of DNA wound around it is called a nucleosome (see Fig. 130.4c). Anti-DNA, antinucleosome, and antichromatin autoantibodies exhibit a homogeneous pattern of staining in the fluorescent ANA assay (see Fig. 130.1c).

Autoantibodies against chromatin and nucleosomes are diverse. The LE phenomenon is caused by a subset of these antibodies. The most important target antigen in SLE appears to be the H2A/H2B/DNA complex, although antibodies against this structure are not disease specific. Autoantibodies to chromatin, nucleosomes, and single-stranded DNA (ssDNA) are also found in SSc, drug-induced lupus, and SLE. In procainamide-induced lupus,

anti-H2A/H2B/DNA antibodies may be found a year or more before the onset of symptoms and, at the time of diagnosis, are present in 84% of patients. They disappear after cessation of use of the drug and, unlike anti-dsDNA antibodies, are not associated with nephritis.

Anti-dsDNA antibodies are 95% specific for SLE if appropriate assays are used.¹ At some time during the disease course, approximately 70% of SLE patients have anti-dsDNA antibodies, and at any particular point in time, about half are positive (see Fig. 130.5). The glomerular immune deposits in some patients with lupus nephritis are enriched in anti-dsDNA, thus suggesting that anti-DNA immune complexes are pathogenic.¹ However, not all patients with anti-DNA antibodies develop nephritis. Immune complexes become trapped in the glomerular basement membrane (GBM) during filtration or form *in situ* when nucleosomes are deposited in the GBM and later bound by autoantibodies. Cross-reactivity with endogenous glomerular antigens may be important for nephritogenicity.¹⁰ Mammalian DNA interacts with Toll-like receptor 9 (TLR9), which raises the possibility that immunostimulatory DNA in immune complexes could play a role in renal inflammation (see later). In mice, glomerular inflammation is dependent on IgG binding to stimulatory Fc receptors because Fc γ RI/III-deficient mice have immune deposits but not renal damage.¹¹

Anti-DNA measurements may be useful for monitoring disease activity. Anti-DNA and complement (C3, C4) levels sometimes vary reciprocally over time, although the clinical usefulness of this observation is somewhat controversial.¹² Assays for anti-DNA, such as radioimmunoassay (the Farr assay), *Crithidia luciliae* kinetoplast staining assay, and ELISA, must distinguish between anti-ssDNA and anti-dsDNA antibodies because only the latter are useful for monitoring disease activity. Specificity for dsDNA is ensured by removing ssDNA via S1 nuclease treatment or by using circular dsDNA as in the *Crithidia* assay. The *C. luciliae* kinetoplast is a closed circular DNA molecule packaged in histones that can be used to detect anti-dsDNA antibodies by immunofluorescence. High-affinity anti-dsDNA

TABLE 130.1
Examples of diagnostically important autoantibodies

Disease	Autoantibody	Clinical associations
Systemic lupus erythematosus (SLE)	dsDNA	Highly specific for SLE with renal disease and increased IFN
	Sm	Highly specific for SLE with renal disease and increased IFN
	Ribosomal P0, P1, P2	Highly specific for SLE, increased risk for neuropsychiatric disease
	RNA helicase A	Highly specific for SLE, marker for early lupus
	PCNA	Not specific for SLE; increased risk for thrombosis, fetal loss, and neuropsychiatric disease
Mixed connective tissue disease (MCTD)	Proteins, such as β_2 -glycoprotein I, bound to anionic phospholipids	Not specific for SLE; increased risk for thrombosis, fetal loss, and neuropsychiatric disease
Mixed connective tissue disease (MCTD)	RNP	Highly sensitive for MCTD but not specific
Systemic sclerosis (SSc)	Scl-70 (topoisomerase I)	Highly specific for SSc with a poor prognosis
	Fibrillarin	Highly specific for SSc
	RNA polymerase I/III	Highly specific for SSc with a poor prognosis
	To/Th	Highly specific for SSc
CREST syndrome	Centromere	
Polymyositis	tRNA synthetases: histidyl (Jo-1), threonyl, alanyl, isoleucyl, glycyl, leucyl, aspartyl, and others	Highly specific for myositis with "antisynthetase syndrome" (myositis, interstitial lung disease, inflammatory arthritis, Raynaud phenomenon, mechanic's hands)
	Signal recognition particle (SRP)	Highly specific for myositis with a poor prognosis
Sjögren syndrome (SS)	Ro60 (SS-A)	Sicca syndrome in primary or secondary SS, neonatal lupus/heart block
	Ro52	Sicca syndrome in primary or secondary SS, neonatal lupus/heart block
	La (SS-B)	Sicca syndrome in primary or secondary SS, neonatal lupus/heart block
Rheumatoid arthritis (RA)	Cyclic citrullinated peptide	Highly specific for RA

CREST, calcinosis; Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia; dsDNA, double-stranded DNA; IFN, interferon; PCNA, proliferating cell nuclear antigen.

TABLE 130.2
Nucleic acid components of some major lupus autoantigens

Autoantibody	Autoantigen	Associated nucleic acid	Innate immune receptor
Anti-Sm	U1, U2, U4/U6, and U5 snRNPs	U1, U2, U4/U6, and U5 RNA	TLR7, (TLR3)*
Anti-RNP	U1 snRNP	U1 RNA	TLR7, (TLR3)*
Anti-Ro60 (SS-A)	Ro60 (transiently associated with La)	hY1, hY3, hY4, and hY5 RNA	TLR7
Anti-Su	Argonaute 2	MicroRNA	TLR7
Jo-1 and others	tRNA synthetases	tRNA ^{his} and others	?†
Anti-P0, P1, P2	Ribosomal P proteins	Ribosomal RNA	?
Anti-dsDNA	Nucleosomes	dsDNA	TLR9
Anti-chromatin	Nucleosomes	dsDNA	TLR9
Anti-PCNA	DNA polymerase δ	dsDNA	TLR9
Anti-Ku	DNA-binding subunit of DNA-dependent protein kinase	dsDNA	TLR9

*Ultraviolet radiation-damaged U1 RNA interacts with Toll-like receptor 3 (TLR3).
†Known to be immunostimulatory but the receptor has not been identified.
snRNP, small nuclear ribonucleoprotein.

antibodies detected by the Farr assay may be the most predictive of disease activity.¹² Though controversial, some would institute corticosteroid therapy when Farr assay activity increases.¹³

Ribosomal P0, P1, and P2 autoantigens

Autoantibodies against ribosomal P0, P1, and P2 antigens recognize proteins of 38, 19, and 17 kDa, respectively (see Fig. 130.3b), which are components of the large (60S) ribosomal subunit. They bind primarily to a conserved

epitope on the C-terminal 22 amino acids of all three proteins¹⁴ and form a pentamer with the structure P0-(P1/P2)₂, which is part of the ribosomal guanosine triphosphatase center and mediates ribosomal interactions with elongation factors.

Anti-P0/P1/P2 autoantibodies are highly specific for SLE and have been linked with neuropsychiatric manifestations.¹⁵ The prevalence of anti-P in our cohort is less than 5% (see Fig. 130.5). Although the association of anti-P antibodies with neuropsychiatric lupus is somewhat controversial, a multicenter study did confirm an association between anti-P and neuropsychiatric lupus, but its sensitivity was low.¹⁶ Thus, anti-P antibodies are a good marker for SLE but only weakly predict neuropsychiatric involvement (see Table 130.1). Anti-P autoantibodies can be detected readily by immunoprecipitation (see Fig. 130.3b) but are generally detected by ELISA using a synthetic peptide containing the dominant C-terminal epitope.

PCNA, RNA helicase A, Ku, and Su antigens

PCNA is a 36-kDa auxiliary factor for DNA polymerase δ . Autoantibodies are found in 1% to 5% of SLE sera and are fairly disease specific.¹⁷ They are detected most reliably by immunoprecipitation (see Fig. 130.3b). The antigen is loosely associated with the nucleus in resting (G0) cells. Anti-PCNA antibodies stain the nuclei of proliferating but not resting cells, thereby resulting in variable fluorescence intensity (see Fig. 130.1c). Because of the low prevalence of anti-PCNA (see Fig. 130.5), it is of limited usefulness clinically.

Autoantibodies to RNA helicase A are produced primarily by nonblack SLE patients and are highly disease specific.¹⁴ Unlike anti-Sm, they appear early in disease and then disappear. Their prevalence is 3% to 7.5% in SLE. The antigen is an abundant 140-kDa member of the DExD/H box family (see Fig. 130.3b), which is thought to be a transcriptional coactivator bridging transcription factors and cofactors.

The Ku antigen is a heterodimer consisting of 70- and 80-kDa subunits that bind the termini of dsDNA breaks. It is the DNA-binding subunit of a DNA-dependent protein kinase (DNA-PK).¹⁸ Ku-DNA-PK plays a critical role in the nonhomologous end-joining reaction during immunoglobulin V(D)J recombination and class switch recombination. Deficiency of Ku70, Ku80, or the DNA-PK catalytic subunit causes severe combined immunodeficiency (because of an inability to rearrange immunoglobulin and T-cell receptor gene segments) and defective repair of radiation-induced DNA

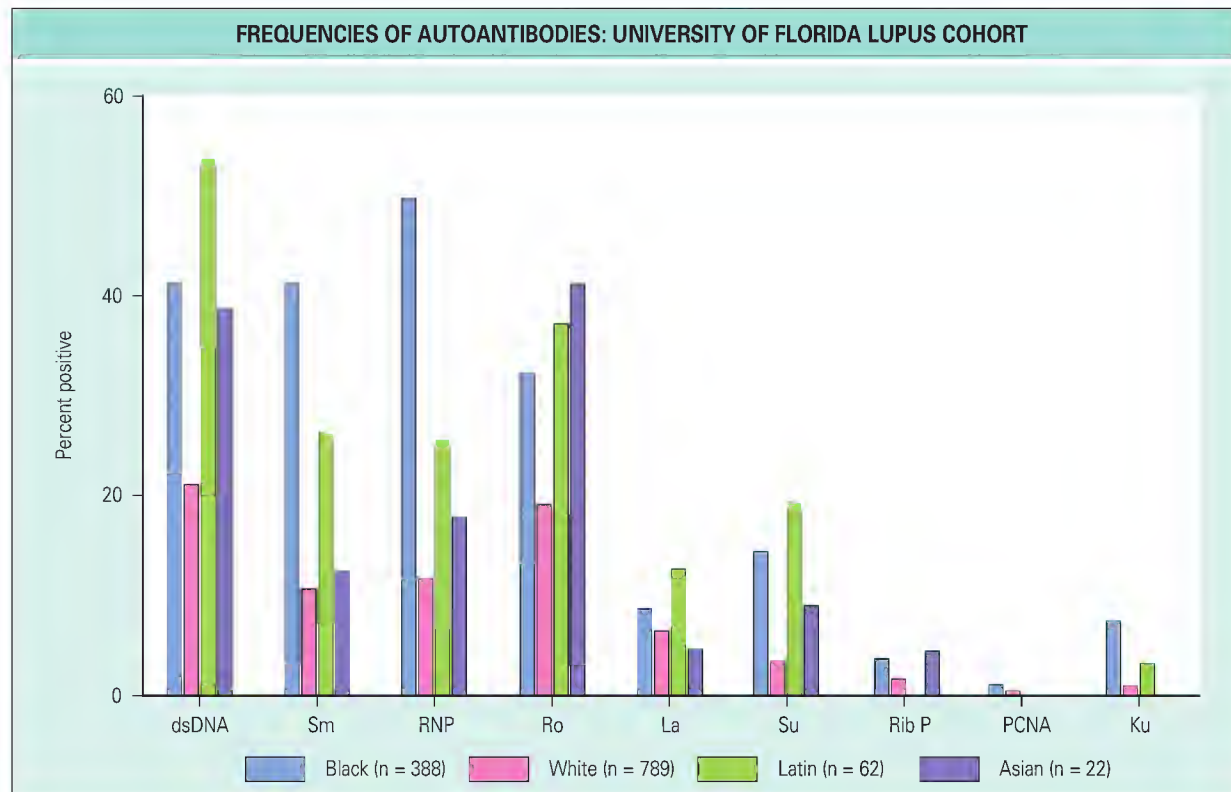


Fig. 130.5 Sera from 1281 patients meeting the American College of Rheumatology criteria for the classification of lupus were tested for lupus-associated autoantibodies either by immunoprecipitation (anti-Sm, anti-RNP, anti-Ro60, anti-La, anti-Su, anti-ribosomal P, anti-PCNA, anti-Ku) or by enzyme-linked immunosorbent assay (anti-dsDNA). The percentage of positive sera is plotted by ethnicity.

damage. Autoantibodies against Ku are found in about 10% of black lupus patients but are rare in whites (see Fig. 130.5). Besides SLE, they can be detected by ELISA or immunoprecipitation in patients with PM/DM, SSc, and PM-SSc overlap syndrome (see Fig. 130.3b).

Anti-Su autoantibodies immunoprecipitate several proteins, including the 100-kDa human Argonaute (Ago) protein hAgo2, a catalytic enzyme in the RNAi pathway.¹⁹ Many of the sera also recognize other components of the pathway, such as hAgo 1, 3, and 4 and Dicer. The prevalence of these antibodies is 10% to 20% in SLE (see Fig. 130.5), but anti-Su antibodies also are seen in SSc, overlap syndromes, and other diseases.

Phospholipid-dependent antigens

The initial evidence for “antiphospholipid” autoantibodies came from the high frequency of false-positive syphilis test results in patients with SLE. The Venereal Disease Research Laboratory or rapid plasma reagin test is positive, but confirmatory testing with the antitreponemal antigen test is negative. The basis for these false-positive reactions is the presence of a phospholipid (cardiolipin) in the antigen mixture. “Anticardiolipin” antibodies do not actually bind the anionic phospholipid but instead recognize serum proteins, most commonly β_2 -glycoprotein I, that bind cardiolipin.²⁰ Autoantibodies against other anionic phospholipid-binding proteins, such as protein S and protein C, are less common. A subset of antiphospholipid antibodies called “lupus anticoagulants” are detected because they prolong *in-vitro* phospholipid-dependent coagulation tests, such as the partial thromboplastin time or the dilute Russell viper venom time. Though termed “anticoagulants,” they are procoagulant and therefore associated with an increased risk for thrombosis and fetal loss.²⁰ Antiphospholipid autoantibodies are found in 20% to 40% of SLE patients, less than half of whom have “antiphospholipid syndrome,” defined as vascular (venous or arterial) thrombosis or pregnancy morbidity with either anticardiolipin antibodies or a lupus anticoagulant. Antiphospholipid autoantibody syndrome is discussed in Chapter 139.

Cell membrane antigens

Patients with SLE can produce autoantibodies against the membrane antigens of erythrocytes, platelets, neurons, endothelial cells, lymphocytes, and neutrophils. Most common are antierythrocyte autoantibodies, which

are demonstrable with the direct antiglobulin (Coombs) test, in which antibodies bound to the patient's erythrocytes are detected by adding antihuman immunoglobulin antibodies to washed erythrocytes and observing for agglutination of the red cells. In some cases, these antibodies cause Fc receptor-mediated destruction of erythrocytes in the reticuloendothelial system of the spleen and liver. Warm autoantibodies (typically IgG), which bind optimally at 35° C to 40° C, are the most characteristic of SLE. They are usually directed against Rh antigens, although in some cases immunoglobulin eluates from lupus erythrocytes contain anticardiolipin antibodies. If removal of IgG-coated erythrocytes by the reticuloendothelial system exceeds the ability of bone marrow to replace them, anemia ensues. Although 10% to 50% of SLE patients are direct Coombs positive, most do not have autoimmune hemolytic anemia.

Antiplatelet autoantibodies cause idiopathic thrombocytopenic purpura (ITP), a disorder of platelet consumption that may exist by itself or in conjunction with SLE. The disease in SLE patients is indistinguishable from “primary” ITP. The main target appears to be the glycoprotein IIb/IIIa (CD41/CD61) complex. Unfortunately, laboratory tests for antiplatelet antibodies are unreliable, complex, and not widely available. Matters are complicated further by the fact that preformed DNA/anti-DNA immune complexes, as well as anticardiolipin antibodies, can bind to platelets.

Autoantibodies against lymphocytes may cause lymphopenia in SLE. A variety of antigenic targets have been identified, including isoforms of CD45. Antineuronal antibodies have been identified in some SLE patients, and anti-DNA antibodies cross-reactive with the *N*-methyl-D-aspartate receptor cross the blood-brain barrier in humans and can cause neurologic disease in mouse models.²¹ However, their association with the neuropsychiatric manifestations of lupus remains somewhat controversial.¹⁶

AUTOANTIBODIES AS THE INITIAL MANIFESTATION OF AUTOIMMUNITY

Autoantibodies can play a direct role in disease pathogenesis, as in the transplacental transfer of anti-Ro/La autoantibodies in neonatal lupus and fetal heart block, autoimmune hemolytic anemia and thrombocytopenia, and antiphospholipid syndrome. It is puzzling, however, why only SLE patients produce certain autoantibodies that recognize intracellular antigens normally sequestered from the immune system. These disease-specific

autoantibodies can be the initial manifestation of disease and may appear months or years before the onset of symptoms. Anti-Ro/La, anti-Sm/RNP, anti-DNA, and antiphospholipid antibodies may appear long before the onset of SLE.²² The development of specific autoantibodies before the onset of disease is not restricted to SLE inasmuch as the same phenomenon is seen in biliary cirrhosis (antimitochondrial), limited (anticentromere) and diffuse (anti-Scl70) scleroderma, PM (anti-tRNA synthetase), and RA (rheumatoid factor and anti-citrullinated peptide antibodies).

MECHANISMS OF AUTOANTIBODY PRODUCTION IN LUPUS

Maintenance of self-tolerance

Mechanisms of self-tolerance are complex and their discussion is beyond the scope of this chapter; only a summary is provided here (see reviews for a complete discussion^{23,24}). Self-tolerance is achieved at multiple levels, both central and peripheral. Lymphocytes that strongly react with ubiquitous self-antigens are generally deleted centrally (before they exit the primary lymphoid organs), whereas autoreactive lymphocytes with lower affinity for self or reactive with antigens not found in the primary lymphoid organs are censored peripherally. Peripheral tolerance is maintained by deletion, anergy, and suppression, as well as by “ignorance,” in which autoreactive lymphocytes exit the primary lymphoid organs, but do not receive a strong enough activation signal. Lymphocyte activation requires two signals, one delivered by the antigen receptor (T-cell antigen receptor or surface immunoglobulin) and a “co-stimulatory” signal. In the absence of a co-stimulatory signal, engagement of the antigen receptor leads to unresponsiveness (anergy). Dendritic cells, the most potent antigen-presenting cells, can either initiate T-cell activation or promote peripheral tolerance, depending on their maturation state: antigen presentation by immature dendritic cells is tolerogenic, whereas presentation by mature dendritic cells is stimulatory. “Ignorance” arises when self-antigens are expressed at levels insufficient to provide a strong signal through the antigen receptor. For instance, self-peptides processed inefficiently by dendritic cells can neither stimulate immunity nor induce tolerance. However, if the same peptides are produced in larger quantity because of abnormal processing, they can activate autoreactive T cells and promote autoantibody production.

Resting B cells do not secrete immunoglobulin until they differentiate into plasma cells. Thus, autoreactive B cells can exist without detectable levels of serum autoantibodies, as shown in transgenic mouse models.²³ To activate autoantibody production, B cells generally need to encounter antigen and receive a second signal from an activated helper T cell. However, T-cell-independent antigens, such as pneumococcal polysaccharide, that carry repetitive epitopes can activate B cells by extensively cross-linking immunoglobulin receptors on their surface. Moreover, though controversial, TLR signaling may drive post-germinal center memory B cells into plasma cell development, thereby potentially maintaining long-term autoantibody production.²⁵

Finally, regulatory T cells (Tregs) are involved in peripheral tolerance. Although several Treg subsets exist, the CD4+CD25+FoxP3+ subset has received considerable attention recently as a regulator of autoimmunity.²⁴ A genetic defect in the transcription factor Foxp3, which controls Treg function, causes IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), in which organ-specific autoimmune diseases such as type 1 diabetes and autoimmune thyroiditis develop. However, for unclear reasons, lupus or other systemic autoimmune diseases do not develop in these individuals.

Chronic interferon overproduction in lupus

IFNs, which are cytokines with antiviral and antiproliferative effects, as well as effects on immune effector cells, are likely to be involved in the pathogenesis of SLE. They are classified as type I and type II.¹ IFN- γ is the sole type II IFN. IFN-I, which includes multiple IFN- α species, IFN- β , and others, is produced by leukocytes and fibroblasts and at high levels by plasmacytoid dendritic cells (pDCs). They all signal via the IFN-I receptor (IFNAR). Binding of IFN-I to IFNAR increases the expression of a group of IFN-stimulated genes (ISGs) regulated by the binding of STAT1 and other transcription factors to a cis-acting consensus sequence termed the *interferon-stimulated response element* (ISRE). This sequence is found in the promoters of all IFN-I-inducible genes. ISGs play a key role in the antiviral response, signal transduction, and apoptosis. Although as many as 100 genes are regulated by IFN-I, the subset involved in antiviral responses is of special interest with regard to SLE because expression of more than 20 of these genes (“IFN

signature”) is increased in peripheral blood mononuclear cells from SLE patients.^{26,27} Elevated IFN-I expression is associated with severe disease, renal involvement, and autoantibodies against dsDNA and RNA-associated antigens such as Sm, nRNP, SSA/Ro, and SSB/La.²⁸

IFN- α treatment of hepatitis C infection and neoplastic diseases can induce ANAs (in up to 22% of patients), anti-dsDNA antibodies, and SLE.^{25,29} Also, individuals with a partial trisomy of chromosome 9 involving the IFN-I gene cluster exhibit chronically elevated IFN-I and develop anti-RNP and anti-Ro60 autoantibodies.³⁰ IFN-I also plays a pathogenic role in murine lupus. Lupus in (NZB $\times$ NZW)F1 mice is accelerated by IFN- α ,³¹ and experimental lupus induced by 2,6,10,14-tetramethylpentadecane (pristane) is associated with the IFN signature and requires IFNAR signaling.³²

The causes of IFN-I dysregulation in SLE are being investigated. Both endosomal and cytoplasmic signaling pathways are responsible for IFN-I production in response to pathogen-associated molecular patterns.³³ TLR7 and TLR8 recognize viral ssRNA, and TLR9 recognizes unmethylated CpG DNA, generally of microbial origin. However, they can also recognize endogenous nucleic acids.^{34,35} TLR7, TLR8, and TLR9 stimulate IFN-I secretion through a signaling pathway that uses the adaptor protein MyD88.³³ In contrast, TLR3 (an endosomal receptor for viral dsRNA) uses a signaling pathway involving the adapter protein TRIF.³³ Foreign nucleic acids in the cytoplasm are also recognized by a variety of innate immune system receptors, including cytoplasmic RNA (e.g., RIG-I) and DNA (e.g., DDX41).³³

The production of anti-Sm/RNP and anti-DNA autoantibodies in pristane-induced lupus requires TLR7, MyD88, and the transcription factors IRF5 and IRF7, but it is independent of other pathways.^{32,36} Lupus in male BXSB mice results from duplication of the TLR7 gene, which enhances TLR7-mediated IFN production.^{36,37} Furthermore, both TLR7 and TLR9 have been implicated in autoantibody production in MRL mice.³⁸ Dysregulated IFN-I production stimulated by endogenous nucleic acids can be involved in the pathogenesis of lupus autoantibodies. Further supporting this model, a subset of patients treated with TNF- α inhibitors develop ANAs, anti-dsDNA antibodies, and even SLE.³⁹ Because TNF- α can downregulate IFN-I production,⁴⁰ these drugs may promote lupus by increasing IFN-I levels.

Endogenous TLR7 and TLR9 ligands

Although TLR9 in late endosomes or lysosomes recognizes the unmethylated CpG motifs common in viral or bacterial DNA, endogenous DNA also contains unmethylated CpG sequences capable of engaging TLR9 but does not cause immunostimulation because it fails to reach late endosomes.⁴¹ However, if endogenous DNA is delivered aberrantly to late endosomes as a result of complex formation with the antimicrobial peptide LL37, it can engage TLR9.⁴² Similarly, the U1 and Y RNA components of Sm/RNP and Ro60 autoantigens, respectively, can reach late endosomes and are endogenous ligands for TLR7.⁴³ Interestingly, the interaction of ultraviolet radiation-damaged U1 RNA with endosomal TLR3 is involved in the pathogenesis of sunburn,⁴⁴ although it is not yet known whether U1 RNA–TLR3 interactions play a role in the pathogenesis of photosensitive lupus rash. Endogenous TLR ligands can gain entry to late endosomes by forming immune complexes or as a result of abnormal processing by antigen-presenting cells.

Nucleic acid-containing immune complexes

Binding of immunoglobulin to nucleic acid-containing autoantigens can inhibit the endosomal degradation of autologous DNA or RNA and promote interactions with TLR7/8 or TLR9. For instance, pDCs express Fc γ RIIa (CD32) and can internalize DNA-containing immune complexes; the DNA is released and engages endosomal TLR9, which results in IFN-I production.³⁴ Likewise, the interaction of snRNPs with immunoglobulin on the surface of anti-Sm/RNP B cells promotes B-cell activation via TLR7 signaling.⁴⁵

Aberrant processing of endogenous TLR ligands

Programmed cell death (apoptosis) generates cellular debris that is cleared by phagocytes. Generally, this process is noninflammatory, whereas necrotic cells are proinflammatory.⁴⁶ Defects in the noninflammatory clearance of cellular debris are associated with autoimmunity. C1q is involved in apoptotic cell clearance, and lupus develops in both patients and mice deficient in C1q. Likewise, autoimmunity develops in mice deficient in serum amyloid P or other molecules that help clear apoptotic cells (Mer, MFG-E8, and CD31). Deficiency of CD14 or mannose-binding lectin, both of which promote the clearance of apoptotic cells, is not associated with autoimmunity,⁴⁶ thus suggesting that defects in the clearance of apoptotic cells do not, by themselves, lead to autoimmunity.

Abnormal intracellular processing of apoptotic cells may promote autoimmunity by allowing endogenous nucleic acids to interact with TLR7/9 within the acidic endosomal compartments. Lysosomes contain RNases and DNases that cleave the nucleic acid components of apoptotic cells. Mice deficient in DNase II, a lysosomal deoxyribonuclease that degrades DNA in apoptotic cells, die *in utero* as a result of IFN- α overproduction.⁴⁷ Conditional knockouts of DNase II develop an inflammatory arthritis resembling RA and low levels of autoantibodies, including anti-DNA.⁴⁸ Mutations of the 3' repair exonuclease *Trex1*, which increase cytoplasmic ssDNA levels and lead to high levels of IFN- α production and a characteristic rash (chilblain lupus), are found at increased frequency in SLE patients.⁴⁹

Defective handling of misfolded RNA is also associated with autoimmunity. A lupus-like syndrome with autoantibodies against nucleosomes and ribosomes plus glomerulonephritis develops in Ro60 knockout mice.⁶ In summary, enhanced delivery of endogenous TLR ligands to late endosomes as a result of immune complex formation, interactions with the antigen receptors of autoreactive (e.g., anti-Sm/RNP) B cells, abnormal processing by phagocytes, or overproduction of the ligands can promote inflammation and autoantibody production.

Characteristics of lupus autoantigens

Although the cell nucleus contains thousands of proteins, few become autoantigens in SLE (see Table 130.1 and Fig. 130.3b). Most of the major autoantigens consist of multiple proteins bound to nucleic acid. The fact that these autoantigens carry immunostimulatory RNA or DNA ("endogenous adjuvants") that can engage endosomal TLRs may help explain why they are autoantigens (see Table 130.2). Autoantigen structure also explains the existence of "linked sets" of interrelated specificities, such as the strong association of anti-Sm, anti-RNP, and anti-U1 RNA autoantibodies. Immune responses to multicomponent autoantigens are analogous to responses to viral particles in which T cells specific for one component of the virion can help B cells producing antibodies against the other components.¹ Thus, the structure of lupus autoantigens may be relevant both to the breaking of tolerance (because of the presence of immunostimulatory nucleic acids) and to the diversity of autoantibodies produced (because T cells responsive to one component can drive B cells specific for other components of the same complex to become plasma cells).

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Pathogenesis of lupus

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- Genetic predisposition is a major determinant of disease in patients with systemic lupus erythematosus (SLE).
- Apoptotic debris is a source of autoantigens in SLE.
- Dendritic cells present autoantigens to T cells and produce proinflammatory cytokines (e.g., interleukin-6, interferon- α).
- B cells produce autoantibodies that mediate tissue injury by numerous mechanisms.
- Abnormal T-cell signaling and gene expression lower the activation threshold of T cells and facilitate the production of proinflammatory cytokines.
- Local regulatory factors play a role in determining organ susceptibility to disease.

A chronic systemic inflammatory response manifested by the presence of a vast array of autoantibodies and gross alterations in T-cell function develops in patients with systemic lupus erythematosus (SLE). The clinical manifestations and organ damage are caused by a self-aimed immune response triggered by unknown factors that is reluctant to end. SLE is considered an autoimmune disease, and immunosuppressive agents represent the mainstay of its treatment.

The pathologic immune response observed in patients with SLE entails the complexity and features of a physiologic protective immune response. Hence, a description of its pathogenesis must take into account myriad elements that act in concert in any given patient to shape an immune system prone to being triggered by factors commonly innocuous, that erroneously directs an organ-damaging response against ubiquitous self-components, and that avoids regulation by the numerous layers of control that normally limit the scale and extent of immune activation.

SUSCEPTIBILITY AND TRIGGERING FACTORS

Strong evidence indicates that SLE has a major genetic component (see Chapter 127). It is characterized by familial aggregation, high concordance rates among twins, and different prevalence and severity between ethnic groups.¹ Several genes that encode proteins involved in the immune response have been associated with SLE. Most risk-associated polymorphisms are found in noncoding DNA regions, and their functional effects remain to be defined. However, rather than representing defect-causing mutations, their presence is predicted to only modulate the function of the associated gene product and perhaps facilitate immune responses to inflammatory stimuli (e.g., by lowering the activation threshold of cells or increasing their inflammatory properties). As a result, most lupus-associated polymorphisms convey a small risk for the development of lupus, and disease probably develops only in individuals who harbor a combination of numerous susceptibility alleles. This concept explains how the accumulation of genes conferring low risk can determine susceptibility and can also account for the observed differences in clinical behavior and severity of disease in patients with lupus. Different combinations of susceptibility alleles will generate different clinical phenotypes.

Female sex and hormones are the second major factor predisposing to the development of SLE. Studies performed in murine models of lupus have shown that estrogens promote autoimmune pathology whereas androgens protect against its development.² Estrogens increase the production of

B-cell-activating factor and synergize the effects of type I interferons (IFNs) on B cells.³ Estradiol and prolactin affect the negative selection process of B cells, and mice treated with these hormones have altered B-cell repertoires and an increased tendency for the development of autoimmune disease.⁴

The current paradigm assumes that the combined presence of several predisposing alleles tilts the balance of the immune system toward a behavior that favors self-reactivity over tolerance; female hormones lean the balance further. Tolerance is probably broken during immune activation in response to environmental factors (e.g., infections; [Table 131.1](#)).⁵⁻⁹ Cellular damage produced by infectious or noninfectious stimuli (e.g., ultraviolet light) increases the exposure of the immune system to self-antigens. However, a breach in tolerance must override strong regulatory mechanisms and probably occurs gradually; it is induced by multiple events, as suggested by the fact that autoantibodies accumulate slowly in patients with SLE years before clinical manifestations.¹⁰ It is important to consider that the immune system changes constantly over the years because of adaptation to the challenges that it encounters. T cells and B cells that become activated increase their numbers, and specific memory cells able to mount better responses on reencounter with the activating agent are created. Hence, the T- and B-cell memory repertoire varies according to the stimuli that have effectively activated the immune system. The immune system of a patient with lupus probably harbors a relatively large number of autoreactive T and B cells that drive a chronic self-aimed immune response. The products of this chronic response (e.g., activated T cells, autoantibodies) can cause target organ damage that results in clinical disease. Thus, in the context of genetic and hormonal susceptibility, encounters with environmental factors (i.e., agents that cause cell damage and activate the immune system) gradually mold a self-aimed chronic response able to instigate organ inflammation. It is important to conceptually separate the development of a chronic autoimmune response from the instigation of target organ pathology. The former is ubiquitous in patients with SLE and necessary for development of the disease. The latter, mainly responsible for clinical manifestations of the disease, is highly variable and regulated by different factors ([Fig. 131.1](#)).

The immune system of patients with SLE has been studied extensively, and defects have been described in most of its components. Each of these defects has been proposed to play a role in pathogenesis of the disease. In this chapter some of these alterations and how they might contribute to form an immune system capable of producing lupus are described.

ANTIGEN-PRESENTING CELLS AND CLEARANCE OF CELL DEBRIS

When monocytes migrate into tissues, they differentiate into two of the most important antigen-presenting cells (APCs), namely, myeloid dendritic cells (DCs) and macrophages. Although the differentiation process varies among tissues, it yields cells capable of acquiring particles and debris and, most importantly, able to detect the presence of danger signals derived from damaged or infected cells. In the absence of pathogen-associated signals, APCs present normal tissue-derived antigens to T cells in a noninflammatory fashion, which contributes to the maintenance of tolerance. In contrast, when APCs detect danger signals (e.g., uric acid released by necrotic cells, microbial products), they undergo a phenotypic transformation that allows them to become powerful T-cell activators.¹¹

Increased T-cell activation by DCs has been proposed as a pathogenic mechanism in lupus. However, because of their inherent plasticity, DCs from patients with SLE have been difficult to characterize. Some reports claim that they express higher levels of co-stimulatory molecules and secrete increased amounts of proinflammatory cytokines (e.g., interleukin-6 [IL-6]); others indicate that when DCs are generated in a nonautoimmune

milieu, their phenotype and function are normal. The immune complexes present in sera from patients with SLE stimulate macrophage and DC activation through immunoglobulin receptors (FcRs).¹² Sera from patients with SLE can induce the differentiation of monocytes into DCs.¹³ Thus, evidence suggests that because of either intrinsic defects, a proinflammatory environment, or both, DCs from patients with SLE have increased T-cell stimulation capacity and altered tolerance-promoting functions (Fig. 131.2).

Plasmacytoid DCs represent a distinct type of APC. When activated during viral infections, they produce IFN- α . Nucleic acid-containing immune complexes can also stimulate them to produce large amounts of type I IFN, which could represent a powerful amplification mechanism since the peripheral blood mononuclear cells of pediatric patients with active lupus have a gene expression profile suggesting that they have been exposed to type I IFN.¹⁴

In normal conditions, the load of autoantigens generated by cell death is cleared by APCs without eliciting inflammation or an immune response.¹⁵ Alterations in this process might be important in the pathogenesis of SLE because a number of commonly targeted autoantigens (e.g., Ro) are exposed to the immune system during apoptosis¹⁶ and apoptosis of peripheral blood mononuclear cells and keratinocytes has been found to be increased in patients with lupus. Increased loads of apoptotic material can overcome the scavenging capacity of the system and induce antinuclear antibodies in otherwise healthy animals.¹⁷ Deficiency of the proteins involved in apoptotic

cell clearance (e.g., C1q) confers a high risk for the development of lupus. Thus, apoptotic cells are probably an important source of antigens in patients with SLE. As occurs with other pathogenic processes, abnormalities in the presentation of antigens derived from apoptotic cells can worsen once the disease is established. Autoantibodies opsonize apoptotic cells in which antigens normally hidden inside the cell nucleus have emerged to the surface in apoptotic blebs. Uptake of opsonized particles induces APC activation and leads to T-cell stimulation, which interferes with the process of tolerance induction normally associated with the presentation of apoptotic cells.¹⁸ In this way, autoantibodies contribute to amplification of the autoimmune pathology and to the breach in tolerance toward the ubiquitous intracellular self-antigens.

In summary, evidence suggests that APCs are involved in the pathogenesis of SLE by virtue of their capacity to uptake and present antigens derived from apoptotic and damaged cells to T cells. Abnormal presentation of self-antigens by intrinsically or ill-differentiated DCs probably plays a role in the initiation and amplification of the autoimmune response in patients with SLE (see Figs. 131.1 and 131.2).

B CELLS AND THE PRODUCTION OF AUTOANTIBODIES

B-cell hyperactivity together with promiscuous autoantibody production is one of the most common immune alterations observed in patients with SLE. Accordingly, the proliferation rate and antibody production are increased in B cells from lupus patients. Autoantibodies in patients with lupus are typically of high affinity and produced by cells that have undergone class switch recombination and somatic hypermutation.¹⁹ These characteristics indicate that T cells were involved in their production and have provided help to autoreactive B cells, mainly by surface-bound CD40L and cytokine production.²⁰

Although the autoantibody response in SLE is broad and directed against numerous specificities, several hallmark antigens are intranuclear complexes composed of nucleic acids and proteins. This might be important from a pathogenic point of view since B cells can be stimulated by DNA and RNA through Toll-like receptors.²¹ Evidence obtained from animal models of lupus suggests that the nucleic acids contained in immune complexes can deliver a second signal to the B cell, complementary to the signal conveyed by the Fc portion of the immunoglobulin.²² Nucleic acid-containing immune complexes might be able to stimulate B cells without the need for

TABLE 131.1
Environmental factors postulated to be lupus triggers

Proposed mechanism	Factors	References
Increased cell apoptosis	Ultraviolet light	5
Alteration of self-antigens (e.g., enzymatic cleavage, phosphorylation)	Ionizing radiation	6, 7
	Exposure to heavy metals	
	Drugs	
Molecular mimicry	Viral infections	8
DNA hypomethylation	Drugs (procainamide, hydralazine)	9
	Ultraviolet light	

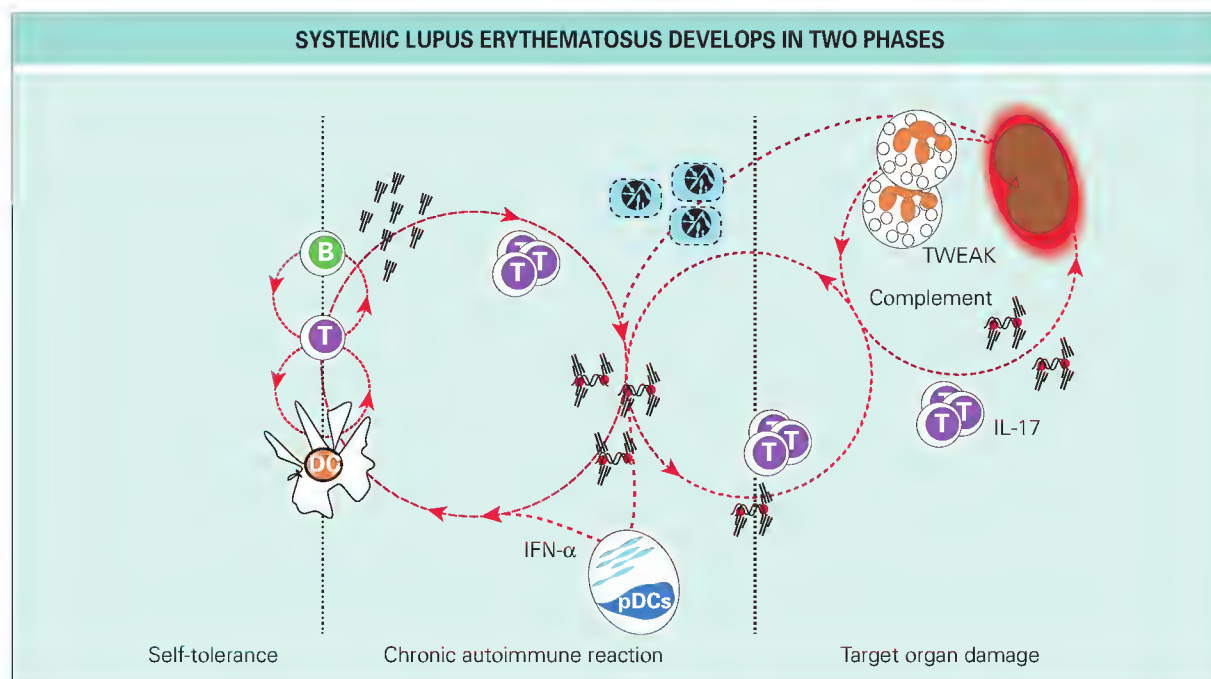


Fig. 131.1 The interplay of genetic, hormonal, and environmental factors initiates an autoimmune response that becomes chronic. Autoantibodies form immune complexes with antigens derived from apoptotic debris. Nucleic acid-containing immune complexes promote the secretion of type I interferon from plasmacytoid dendritic cells (pDCs). These elements further stimulate the immune system and thereby contribute to perpetuation and amplification of the autoimmune response in a cyclic manner. At some point, the products of this immune response (e.g., activated T cells, immune complexes) initiate an inflammatory response in target organs. Local factors may facilitate (e.g., local secretion of proinflammatory cytokines) or hinder (e.g., production of kallikrein) the duration and extent of the local injury. Products derived from damaged tissue may contribute further to amplification of the underlying immune response.

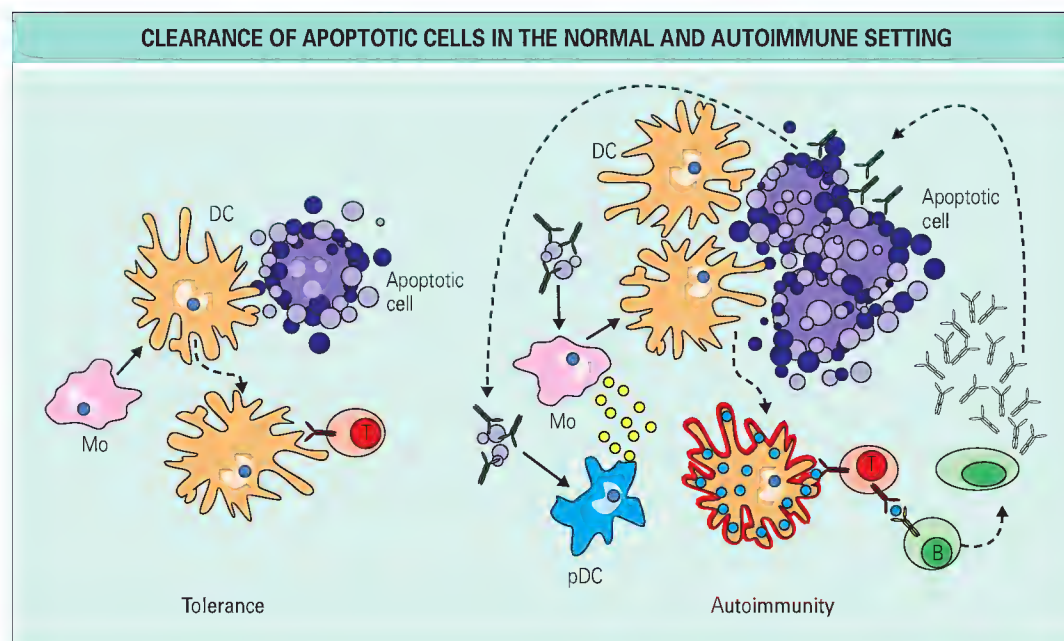


Fig. 131.2 In healthy individuals, apoptotic cell debris is cleared by macrophages and dendritic cells and presented to T cells in a noninflammatory context. This process ensures that autoreactive T cells are inactivated (left). Low-affinity Fc receptors, a low density of complement receptors, and genetic or acquired deficiency of complement factors diminish the capacity of the immune system of patients with lupus to scavenge immune complexes and apoptotic cell debris. These factors, along with an increased load of apoptotic cells, overload the immune system with autoantigens. The increased load in a susceptible individual leads to the development of autoantibodies. These autoantibodies opsonize apoptotic cells, which favors an inflammatory manifestation. Additionally, they form immune complexes that stimulate antigen-presenting cells, thus creating a vicious circle. B, B cell; DC, dendritic cell; Mo, monocyte; pDC, plasmacytoid dendritic cell; T, T cell.

T-cell–derived help, thus providing an alternative pathogenic amplification pathway independent of T-cell help and regulation.

The autoantibodies present in sera from SLE patients have been shown to be pathogenic through different mechanisms. Autoantibodies form immune complexes that can be detected in sera from patients with lupus. When immune complexes are deposited in the renal glomeruli and blood vessels, they induce inflammation by activating complement and engaging the FcRs in neutrophils and other inflammatory cells.²³ A factor that contributes to the immune complex–mediated tissue damage in lupus patients is deficient clearance as a result of genetically determined expression of lower-affinity receptors for IgG and decreased levels of complement receptors on red blood cells.²⁴ Autoantibodies can also induce tissue damage by mechanisms different from immune complex deposition. In murine models, certain autoantibodies obtained from patients can bind to the placenta and ischemic intestine and trigger inflammatory responses through complement and neutrophil activation,^{25,26} which leads to fetal resorption and to ischemia-reperfusion–mediated tissue injury, respectively. Alternatively, autoantibodies can bind to surface receptors and alter cellular function. For instance, some anti-DNA antibodies cross-react with neuronal N-methyl-D-aspartate receptors and cause neuronal apoptosis,²⁷ whereas anti-T lymphocyte antibodies can significantly alter T-cell function and cytokine production by activating intracellular pathways that modify the activation of transcription factors.²⁸ In pregnant patients, specific autoantibodies (e.g., anti-Ro) may cross the placenta and cause cellular damage in the fetus.^{29,30} Finally, penetration of autoantibodies into living cells has been proposed to explain certain cellular changes elicited by their presence.³¹

Each B cell assembles the antibody that it will use as a B-cell receptor and secretes it as immunoglobulin by rearranging its germline DNA in a random fashion. This process allows the creation of a vast array of different specificities but entails the expression of autoreactive antibodies. In fact, a large fraction of immature B cells harbor self-reacting polyspecific antibodies.³² Most self-reactive B cells are eliminated at two checkpoints before reaching the stage of naive immunocompetent cells, the first one at the immature B-cell stage, previous to their egress from bone marrow, and a second one in secondary lymphoid organs, before their maturation into naive immunocompetent B cells. This process, which allows elimination or functional neutralization of autoreactive B cells, is deficient in patients with SLE.³³ Thus, more autoreactive B cells prone to be stimulated by self-antigens are present in patients with SLE. The cause of this defect is mostly unknown but probably related to genetic and hormonal factors.³⁴

B cells are located in secondary lymphoid organs (i.e., spleen, lymph nodes, Peyer patches), where they are exposed to antigens. When a B cell

recognizes an antigen through its surface immunoglobulin, it presents antigen-derived peptides to CD4+ T cells. Local inflammation, cytokines, and pathogen-derived molecules entice antigen presentation by increasing the expression of co-stimulatory molecules on the B-cell surface. If the CD4+ T cell is activated effectively, it delivers a positive signal to the B cell via CD40L and IL-21 that induces the formation of a germinal center. Germinal center B cells proliferate extensively and during the process develop random mutations in the DNA sequences that encode the antigen-binding site of the immunoglobulin. A progeny of B cells with modified immunoglobulin results. A selection process ensues in which only B cells able to recognize with high avidity the antigen that initiated the process survive. In this way the germinal center response increases the avidity of the humoral immune response. How autoreactive B cells produced during the germinal center response are purged and how this process occurs in patients with SLE are matters of intense research. Animal models suggest that the germinal center response is a fundamental element of the autoimmune response in lupus,^{35,36} but specific defects in this process have not been linked to the human disease.

In summary, B cells are central players in the autoimmune response in lupus. They produce high levels of autoreactive antibodies that mediate tissue injury. Furthermore, B cells are able to act as APCs by internalizing soluble antigens, presenting them to T cells, and thereby creating a loop that amplifies and perpetuates the chronic autoimmune response³⁷ (see Fig. 131.1).

T CELLS AND REGULATION OF THE IMMUNE RESPONSE

T cells are central elements of the immune response. They define its characteristics and control its magnitude and length by stimulating or suppressing the function of other cells through direct cellular contact and secretion of cytokines and chemokines. They also act as effector cells that induce apoptosis in cells altered by infection. The behavior and function of T cells are altered in patients with SLE.³⁸ They participate in the chronic autoimmune response of lupus patients by providing help to autoreactive B cells and failing to suppress the pathologic immune response. They infiltrate target organs, where they promote the local inflammatory response by producing cytokines (e.g., IL-17).

Profound molecular defects alter the activation process of T cells from lupus patients. When stimulated through the T-cell receptor (TCR), they exhibit an abnormally rapid and high surge in intracellular calcium levels

accompanied by increased phosphorylation of signaling proteins.³⁹ This is caused by alterations in the composition of proteins associated with the TCR. Normally, TCR signal transduction is initiated by the TCR-associated molecule CD3- ζ . However, in T cells from SLE patients, this molecule is expressed at low levels and in abnormal cellular compartments.^{40,41} Its place is taken by an analogous molecule not normally expressed in T cells (i.e., the γ chain of the FcR). This substitution affects the manner in which SLE T cells respond to antigens. The presence of the FcR γ chain favors an alternative transduction pathway associated with the heightened calcium response. This pathway relies on Syk, a tyrosine kinase that is overexpressed in T cells from lupus patients.⁴²

The molecules involved in T-cell signaling are not distributed randomly throughout the cell membrane. They are localized in cholesterol-rich zones that migrate toward the pole of the cell where antigens are being presented. These zones, known as lipid rafts, allow rapid clustering of the molecules required to transduce the signals initiated in the TCR. This spatial reorganization of signaling molecules to a localized part of the cell membrane facilitates T-cell activation. From the point of view of lipid rafts, T cells from patients with lupus are not normal. Their lipid rafts are preclustered as if the cells were activated. This morphology may indeed reflect a state of activation—by autoantigens or perhaps anti-T-cell antibodies—and results in faster and larger activation kinetics that lead (along with the substitution of CD3- ζ) to the abnormal response on TCR ligation observed in T cells from patients with lupus.⁴³

T-cell activation is a complex process in which several signals, including those initiated by the TCR, are integrated. Importantly, signaling is not uniformly increased in cells from patients with lupus. In fact, decreased activity of other signaling pathways, in particular, the mitogen-activated protein kinase pathway, has been described in lupus T cells. As a result, SLE-derived T cells have lower levels of c-fos, a component of the transcription factor AP-1. Thus, when a lupus T cell is stimulated by an antigen, molecular defects distort the signal and alter the magnitude and quality of the response. Since the expression of certain proteins is excessive and the production of others is deficient, T cells from patients with lupus seem to be overactive in certain functions and fail to respond in others. For instance, expression of CD40L, an extremely important molecule used by T cells to stimulate DC activation and antibody production by B cells, is abnormally increased in T cells from lupus patients, but IL-2 secretion is deficient.

Gene transcription is regulated by a complex multilayered process that includes DNA methylation and posttranslational modification of histones.⁴⁴ DNA methylation acts as a repressor of transcription, and interestingly, two drugs associated with the induction of drug-induced lupus, procainamide and hydralazine, induce DNA demethylation. Moreover, DNA has been shown to be hypomethylated in T cells from patients with lupus, and administration of demethylating drugs causes a lupuslike disease in mice.⁴⁵ Although the mechanisms that lead from DNA demethylation to autoimmunity are not well understood, T cells treated with agents that induce DNA hypomethylation have a decreased activation threshold. Furthermore, the expression of certain genes that are potentially relevant for lupus pathogenesis is augmented when DNA is hypomethylated (e.g., the adhesion molecule LFA-1 and the B-cell-activating molecule CD70). PP2A, one of the major serine/threonine phosphatases, is overexpressed in T cells from lupus patients. This overexpression may result, at least in part, from DNA hypomethylation.⁴⁶ The increased levels of PP2A also affect T-cell IL-2 production. PP2A dephosphorylates the transcription factor CREB, thus further diminishing IL-2 transcriptional activity.⁴⁷

T cells from lupus patients have a distorted pattern of gene expression that alters their function. One of the most obvious is the skewed production of several cytokines (Table 131.2). Since cytokines represent one of the most important means that T cells use to deliver signals, aberrant cytokine production implies faulty immune regulation. The IL-2 secretion defect has been associated with several T-cell abnormalities that not only determine autoimmune pathology but also impair the development of protective immune responses against pathogens. Decreased IL-2 and IFN- γ production has been linked to defects in cytotoxic responses against viruses and other pathogens.⁴⁸ This, along with the use of immunosuppressive drugs, has placed infection-related mortality near the top of the list of causes of mortality in patients with lupus. On the other hand, decreased IL-2 has been postulated to be involved in regulatory T-cell abnormalities. Moreover, activation-induced cell death, a mechanism that allows the contraction of expanded clones of activated lymphocytes at the end of an immune response, also depends on the presence of IL-2. IL-17 is a T-cell-derived potent proinflammatory cytokine. The frequency of T cells able to produce IL-17 is increased in patients with lupus. Moreover, IL-17-producing T cells have been observed in the kidneys of patients with lupus nephritis, thus suggesting a role for this cytokine in the amplification of renal inflammation.⁴⁹

TABLE 131.2
Role of cytokines in the pathogenesis of lupus

Cytokine	Defect	Mechanism
IL-2	Decreased T-cell production	Altered T-cell effector function Altered regulatory T-cell development
IL-6	Increased mononuclear cell production	B-cell stimulation Promotion of IL-17 differentiation (?)
IL-10	Increased mononuclear cell production	B-cell stimulation
IL-12	Decreased mononuclear cell production	Promotion of IL-17 differentiation (?)
IL-17	Increased T-cell production	Promotion of inflammation
IL-21	Increased T-cell production	B-cell stimulation
IL-23	Increased mononuclear cell production	Promotion of IL-17 differentiation
IFN- γ	Defective T-cell production	Altered T-cell effector function

IFN- γ , interferon- γ ; IL-2, interleukin-2.

EFFECTOR T-CELL DIFFERENTIATION FAVORS B-CELL STIMULATION AND SECRETION OF PROINFLAMMATORY CYTOKINES

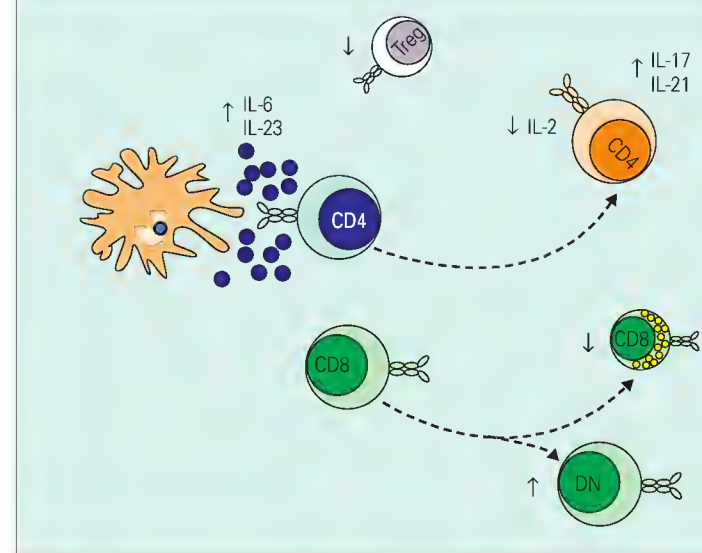


Fig. 131.3 Increased production of interleukin-6 (IL-6) and IL-23 by antigen-presenting cells facilitates the development of a T-cell repertoire rich in interleukin-17 (IL-17)- and IL-21-producing T cells that promote inflammation and B-cell antibody production, respectively. These proinflammatory conditions, along with low secretion of IL-2, probably decrease the differentiation and function of regulatory T cells. Effector differentiation of CD8+ T cells is also impaired. As a result, diminished numbers of cytotoxic cells and augmented double negative (DN) T cells are produced. These alterations directly contribute to disease pathogenesis and at the same time diminish the pathogen-clearing efficiency of the immune system.

T cells acquire the capacity to produce IL-17 when antigen presentation occurs in the presence of transforming growth factor- β and inflammatory cytokines such as IL-6 or IL-21. Such functionally differentiated cells have been called type 17 helper T cells (Th17). IL-12, IL-4, and IFN- γ suppress Th17 differentiation. DCs from patients with lupus secrete higher amounts of IL-6 and lower amounts of IL-12. This combination, along with a paucity of IL-2 and IFN- γ , probably facilitates the priming of naive cells into the Th17 effector phenotype in the altered cytokine milieu characteristic of patients with lupus (Fig. 131.3).

Regulatory T cells limit the length and magnitude of immune responses. Patients with lupus have low numbers of regulatory T cells that exhibit decreased suppressive capacity.⁵⁰ Several factors may account for this. IL-2

is necessary for the development and maintenance of regulatory T cells. Its deficiency, along with the presence of inflammatory cytokines, might hamper regulation; on the other hand, activated T cells are probably resistant to suppression. CTLA-4, a molecule involved in regulatory T-cell function, has been linked to lupus in genetic studies, but no functional consequence of the associated polymorphism has been conclusively demonstrated. Thus, intrinsic defects or the altered cytokine milieu characteristic of patients with lupus might account for the regulatory T-cell defects.

Patients with lupus have increased amounts of double-negative (DN) T cells (i.e., T cells that lack CD4 and CD8) in peripheral blood. Although the reason for this expansion is not understood completely, it is probably driven by excessive T-cell stimulation. DN T cells can stimulate B-cell antibody production by secreting cytokines (e.g., IL-4, IL-10). Importantly, DN T cells produce a variety of proinflammatory cytokines, including IL-17, and are major components of cellular infiltrates in the kidneys of patients with lupus nephritis.⁵¹

The localization of immune cells throughout the body and their entry into tissues are tightly regulated by the expression of receptors on the surface of cells and endothelium. T cells from SLE patients exhibit an increased capacity to bind to receptors expressed by endothelial cells and to migrate in response to chemokines. This ability, conferred by enhanced CD44 expression, probably facilitates their migration into target organs, where they can induce tissue damage and amplify the inflammatory response by secreting cytokines and chemokines.⁵²

In summary, abnormal signal transduction and epigenetic deregulation lead to obvious alterations in T-cell phenotype and function that are manifested as a decreased activation threshold and increased inflammatory capacity. T-cell-dependent regulation of the immune system is thus skewed toward autoreactivity and inflammation, and T-cell effector functions are enhanced (see Fig. 131.3).

LOCAL FACTORS THAT CONTRIBUTE TO LUPUS PATHOGENESIS

The presence of the chronic autoimmune response observed in patients with SLE is a step needed for the development of target organ injury. However, other factors determine the pathogenicity that products of this response exert on target organs. Injection of immune complex-containing serum from patients with SLE caused glomerulonephritis only in mice that expressed IgG receptors (FcγRIIA) in neutrophils and lacked the integrin Mac-1. Glomerulonephritis did not develop in Mac-1-sufficient mice even though the amount of immune complex deposition in the renal glomeruli

was comparable to that observed in susceptible Mac-1-deficient mice.⁵³ An analogous phenomenon occurs in patients with SLE. Although most have immune complex deposition in the renal glomeruli and the dermoepidermal junction, local inflammation develops in only a fraction. Moreover, even though the deposits are chronic, the inflammation can be episodic. This indicates that the mere presence of chronic autoimmune disease is not sufficient to cause clinically relevant lupus.

Some of the molecules associated with lupus may contribute to the disease by increasing organ susceptibility to immune-mediated damage. Overexpression of the phosphatase PP2A in the T cells of an otherwise healthy mouse did not cause autoimmunity, but it did increase the renal damage with induced glomerulonephritis. This effect was explained by increased production of the proinflammatory cytokine IL-17.⁵⁴

The response of the target organ itself is an important determinant of the magnitude of injury instigated by the autoimmune response. Certain polymorphisms in kallikrein genes are associated with ameliorated glomerulonephritis in mice, and single nucleotide polymorphisms in the *KLK1* and *KLK3* genes are associated with nephritis in patients with SLE. This suggests that the amount of kallikrein produced on immune complex deposition regulates the intensity of the immune response and thus the extent of immune-mediated glomerular damage.⁵⁵ Calcium/calmodulin-dependent protein kinase type IV (CaMK4) is a serine/threonine kinase that can be activated by serum-derived factors.²⁸ In mice of the lupus-prone strain MRL/lpr, CaMK4 induces the proliferation of glomerular mesangial cells and promotes their production of IL-6,⁵⁶ thus suggesting that the response of glomerular mesangial cells to immune complex deposition and serum-derived factors can actually contribute to the amplification and perpetuation of renal disease in these mice.

CONCLUDING REMARKS

Lupus is the clinical manifestation of a series of gross alterations in immune function and regulation. These alterations gradually accumulate in individuals who harbor genetic and hormonal susceptibility factors when their immune system interacts with stimuli derived from the environment. The immune system of patients with lupus develops an autoimmune response directed against several widely expressed autoantigens that becomes chronic. Unknown factors trigger target organ damage when the products of the chronic autoimmune response produce inflammation in critical organs. Understanding the mechanisms that underlie both the breach in tolerance and the development of tissue injury will allow the development of better therapies that can alleviate this complex disease.

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132

Drug-induced lupus

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- Drug-induced lupus (DIL) remains an underrecognized clinical entity.
- Most of the reported associations are case reports or case series and have not been examined carefully in epidemiologic studies.
- Some of the newer biologic and anticytokine therapies, including anti-tumor necrosis factor- α agents and interferon- α/β , appear to be associated with an increased incidence of DIL.
- Understanding the mechanisms behind DIL will probably provide important insight into the pathogenesis of autoimmunity.

HISTORICAL ASPECTS

Lupus develops when people with the appropriate predisposing genes are exposed to certain environmental factors, and drug-induced lupus (DIL) represents the clearest example of a defined environmental agent triggering lupus in genetically susceptible individuals. The first definite association between a drug and the onset of lupus was made in 1954 with the observation that a lupus-like illness developed in approximately 7% of hydralazine-treated patients.^{1,2} In the following decade, procainamide and anticonvulsants were added to the list of lupus-inducing drugs. With the advent of modern autoantibody testing, it became clear that many therapeutic agents are capable of inducing antinuclear antibodies (ANAs) in patients. Depending on the agent, clinical features resembling idiopathic lupus will develop in a variable proportion of these patients. More than 100 drugs have now been reported to cause DIL (Box 132.1), including a number of newer biologics.

EPIDEMIOLOGY

The annual incidence of DIL in the United States has been estimated to be 15,000 to 30,000 new cases per year. Approximately 30,000 to 50,000 patients are affected at any given time, which represents 6% to 12% of all lupus cases.³ The frequency of DIL is probably underreported because many cases are mild and self-limited once the offending drug is removed. The epidemiology of DIL reflects the population taking the particular lupus-inducing drug. For example, older men are more likely to take procainamide and hydralazine for cardiovascular disease, and younger women are more likely to take minocycline for acne. As expected, more cases of procainamide- and hydralazine-induced lupus occur in men and more cases of minocycline-induced lupus occur in women. However, DIL is two to four times more likely to develop in women who take hydralazine or procainamide than in their male counterparts. The reasons for this observation are unclear but may involve both hormonal and nonhormonal gender-associated factors. Little is known about racial susceptibility to DIL. Whites have been reported to be affected up to six times more frequently than blacks and to have more severe disease.⁴ However, this may simply represent demographic bias in the populations studied.

GUIDELINES FOR DEFINING DRUG-INDUCED LUPUS

No diagnostic criteria for DIL have been established, and many cases of DIL do not satisfy the American College of Rheumatology criteria for idiopathic

lupus. In addition, most reported associations are either case reports or case series with no epidemiologic or long-term clinical or laboratory studies to confirm a causal effect. Borchers and colleagues⁵ proposed criteria that include sufficient and continuous exposure to a drug, at least one symptom characteristic of lupus, no previous evidence of lupus or other autoimmune disease, and resolution of the disease within weeks or months after cessation of the suspected drug. A positive ANA is not required in this classification system, and the authors acknowledged that a negative ANA result should not rule out DIL when other laboratory test results support the diagnosis. Thus, clinicians should determine whether there is a temporal relationship between onset of the drug therapy and development of the clinical and serologic signs of lupus, as well as resolution of these clinical and laboratory signs after treatment with the drug is discontinued. Disease remission on discontinuation of a drug and recurrence with restarting the drug would confirm causality, and this has been reported for hydralazine,¹ procainamide,⁶ isoniazid,^{7,8} chlorpromazine,⁹ quinidine,¹⁰ and minocycline.¹¹

The diagnosis of DIL can be particularly difficult to make in patients with underlying systemic rheumatic diseases. Drug-induced rheumatic complaints may also be misinterpreted as an exacerbation of the underlying illness. The physician may then intensify the treatment regimen, thereby perpetuating the real problem. This could potentially happen, for example, with minocycline, sulfasalazine, or anti-tumor necrosis factor (TNF) agents in patients with rheumatoid arthritis.

CLINICAL FEATURES

It is not possible to distinguish DIL from idiopathic lupus by clinical features, although patients with DIL generally have a milder illness. Myalgia, fever, and serositis are more common in DIL. Arthralgia, but not frank arthritis or joint effusion, is also more common in DIL. In contrast, renal involvement, central nervous system disease, malar rash, discoid rash, photosensitivity, and oral ulcers occur less frequently in DIL.^{12,13} A positive “lupus band” test and Sweet syndrome have also been described in DIL, but these features are neither sensitive nor specific in differentiating DIL from idiopathic lupus.

In hydralazine-induced lupus, discoid rash and malar rash occur commonly, but leukopenia, neuropsychiatric symptoms, pericarditis, skin vasculitis, and renal involvement are less likely to develop than in idiopathic lupus. In procainamide-induced lupus, arthralgia, myalgia, constitutional symptoms, and serositis are the most common symptoms³ (Table 132.1). Pericarditis and rarely pericardial effusion or tamponade have been reported in DIL associated with procainamide,^{14,15} hydralazine,¹⁶ isoniazid,¹⁷ and sulfasalazine.¹⁸ Severe cases of DIL with hydralazine^{19,20} and procainamide treatment,²¹ as well as with quinidine,²² penicillamine,²³ and interferon (IFN)²⁴ treatment, have also been reported to involve immune complex glomerulonephritis. It is important to remember that the impaired renal function in these patients may also be due to other underlying medical conditions, such as hypertension or diabetes, or be due to medications such as nonsteroidal antiinflammatory drugs (NSAIDs). Minocycline-induced lupus is characterized by small-joint polyarthralgia and arthritis and diffuse myalgia. About half the patients affected have laboratory evidence of liver involvement and 20% have rash. Pleuropulmonary and hematologic involvement is uncommon, and the nervous system and kidneys are usually spared.^{25,26}

Several new clinical associations have been described in recent years. Although it will be impossible to consider every drug, a few are discussed in this chapter.

IFNs have antitumor, antiviral, and immunomodulating properties, and both IFN- α and IFN- β ²⁷⁻³¹ have been linked to the development of ANAs

BOX 132.1 DRUGS IMPLICATED IN DRUG-INDUCED LUPUS

Drugs with good evidence of association	Leuprolide acetate
Adalimumab	Levodopa
Carbamazepine	Levomeprazine
Chlorpromazine	Lithium carbonate
Etanercept	Lovastatin
Ethosuximide	Mephenytoin
Hydralazine	Mesalazine
Infliximab	Methimazole
Isoniazid	Methylsergide
Methyldopa	Methylthiouracil
Minocycline	Metrizamide
Penicillamine	Minoxidil
Phenytoin	Nalidixic acid
Procainamide	Nitrofurantoin
Quinidine	Nomifensine
Sulfasalazine	Omeprazole
	Oral contraceptives
	Olsalazine
Case reports	Oxyphenisatin
Acebutolol	Pantoprazole
Aminoglutethimide	Paraaminosalicylic acid
5-Aminosalicylic acid	Penicillin
Amiodarone	Perazine
Amoprofan	Perphenazine
Anthiomaline	Phenelzine
Atenolol	Phenopyrazone
Atorvastatin	Phenylbutazone
Benoxaprofen	Phenylethylacetylurea
L-Canavanine	Pindolol
Captopril	Practolol
Chlorprothixene	Prazosin
Cimetidine	Primidone
Cinnarizine	Promethazine
Clonidine	Propylthiouracil
Clozapine	Psoralen
COL-3	Pyrithiazine
Danazol	Pyrithioxine
Diclofenac	Quinine
1,2-Dimethyl-3-hydroxypyridine-4-1 (L1)	Rifamycin
Disopyramide	Sulfasalazine
Esomeprazole	Simvastatin
Estrogens	Spironolactone
Etanercept	Streptomycin
Flutamide	Sulindac
Fluvastatin	Sulfadimethoxine
Gold salts	Sulfamethoxypyridazine
Griseofulvin	Terbinafine
Guanoxan	Tetracycline
Hydrazine	Tetrazine
Ibuprofen	Thionamide
Infliximab	Thioridazine
Interferon (α, β)	Timolol eye drops
Interleukin-2	Tolazamide
Labetalol	Tolmetin
Lamotrigine	Trimethadione
Lansoprazole	Zafirlukast

and clinical lupus. In one study of 135 patients undergoing IFN treatment for carcinoid tumors, newly positive ANA developed in 14% of the patients and an autoimmune disorder developed in 19%, including 1 patient with lupus characterized by arthritis, leukopenia, and ANA and anti-double-stranded DNA (dsDNA) antibodies.^{32,33} IFN-α treatment induces ANAs in 18% to 72% of patients receiving it, but DIL develops in only 0.1% to 2.1%. Other have shown the frequency of IFN-induced lupus to be between 0.15% and 0.7%, and anti-dsDNA antibodies will develop in up to 8% of patients receiving long-term IFN therapy.²⁷ Treatment of lupus-prone mice with IFN worsens the disease.³⁴ In addition, lupus patients have elevated IFN levels that correlate with their ANA and anti-DNA antibody titers and disease activity.^{35,36}

Anti-TNF agents are now standard treatment of rheumatoid arthritis, spondyloarthritis, psoriasis, and inflammatory bowel disease. Rash is the

TABLE 132.1 Clinical features of procainamide and hydralazine-induced lupus

Clinical features	Procainamide-induced lupus (%)	Hydralazine-induced lupus (%)
Arthralgia	77	85
Myalgia	44	57
Fever	41	38
Rash	9	27
Adenopathy	8	14
Hepatomegaly	25	24
Splenomegaly	12	14
Pleuropulmonary	75	30
Pericarditis	16	5
Neuropsychiatric	1	4
Renal	<1	13

most common characteristic of lupus induced by anti-TNF agents.³⁷ A 2008 review identified an increased incidence of rash, anti-dsDNA antibodies, low complement levels, leukopenia, and thrombocytopenia in lupus induced by anti-TNF agents versus lupus induced by other drugs.³⁸ Fifty-six patients with DIL were identified, 36 of whom met the criteria for the diagnosis of idiopathic lupus. Of those 36 lupus cases, 21 were secondary to infliximab, 10 to etanercept, and 2 to adalimumab. Notably, the symptoms induced by one anti-TNF agent do not always persist when patients start other anti-TNF agents. Williams and Cohen³⁷ reported lupus secondary to etanercept in a 62-year-old woman with rheumatoid arthritis. It resolved with discontinuation of the medication and did not recur after golimumab was started for the 6-month period reported. In contrast, Subramanian and coauthors³⁹ reported 13 patients with inflammatory bowel disease in whom lupus induced by infliximab developed. Eight patients were switched to either certolizumab or adalimumab. Six patients remained asymptomatic, but DIL again developed in one patient each receiving certolizumab or adalimumab. A 2003 study reported on patients with Crohn disease who were treated with infliximab and monitored prospectively.^{39a} None of the patients had positive ANAs before starting treatment, but more than 56% were positive after 2 years of treatment. Of the patients who were studied further, approximately one third had anti-dsDNA antibodies. Notably, of the 125 patients, DIL developed in only 2 and autoimmune hemolytic anemia in 1. Anti-TNF agents frequently cause ANAs in patients receiving them, but rarely autoimmune diseases. Infliximab causes a positive ANA in 23% to 53% of patients, but DIL in 0.19%; adalimumab causes a positive ANA in 12.5% to 41.4%, but DIL in 0.41%; and etanercept causes a positive ANA in 11% to 48.8%, but DIL only 0.18% (reviewed in reference 40).

Proton pump inhibitors and statins are among the most commonly prescribed medications in the United States, and they are frequently used in rheumatology patients. A recent review of 117 subacute cutaneous lupus erythematosus cases identified 2 caused by lansoprazole, and there are also case reports involving omeprazole, esomeprazole, and pantoprazole.^{41,42} The first case reports of lupus induced by statins appeared in 1991, and there have been less than 20 reports overall.⁴³ In a recent case/noncase study in a French database of adverse drug reactions, 232 cases were classified as DIL.⁴⁴ Of these cases, statins were used in 17 (7.3%). In comparison, in more than 230,000 cases that were not DIL, statins were used in 4.7%. The odds ratio for the development of DIL with statin exposure was 1.67 (95% confidence interval, 1.02 to 1.74), and the odds ratio was greater than 1 with all statins except fluvastatin, for which no cases were recorded in that database.

Complementary and alternative medications

Herbal medications are becoming increasingly popular, and some have been linked to flares of lupus. Alfalfa sprouts were first linked to lupus in 1981, when autoimmune hemolytic anemia developed in a man after their ingestion.⁴⁵ Autoimmune hemolytic anemia, ANAs, anti-dsDNA antibodies, and low complement levels developed in macaques fed alfalfa sprouts. Furthermore, tablets containing L-canavanine, which is a constituent of alfalfa sprouts, reactivated a lupuslike syndrome in macaques in whom lupuslike features originally developed after eating alfalfa sprouts.^{46,47} L-Canavanine was later shown to decrease concanavalin A-induced suppressor T-cell

functions in cells from healthy controls and lupus patients, and this caused increased IgG and anti-dsDNA antibodies from stimulated B cells.⁴⁸

Echinacea has immunostimulatory properties (reviewed in reference 49), and its extracts induce interleukin-1 α (IL-1 α), IL-1 β , IL-6, IL-10, and TNF from human and mouse macrophages *in vitro*.^{50,51} Lupus flares triggered by echinacea have not been reported, but flares of pemphigus vulgaris, an autoimmune disorder of the skin, have been reported after the ingestion of echinacea.⁵² In contrast, though, echinacea extract was safe and effective in controlling autoimmune uveitis.⁵³ The effects of echinacea on autoimmune disorders remain unclear, so it is generally recommended that lupus patients avoid echinacea-containing products.⁵⁴

Melatonin also stimulates the immune system by increasing expression of IFN- γ and IL-2 in human helper T cells and IL-1, IL-6, and IL-12 in human monocytes *in vitro*.⁵⁵ However, melatonin did block or slow the development of lupus in a mouse model of pristane-induced lupus⁵⁶ by decreasing anti-dsDNA antibodies, decreasing proinflammatory cytokines (IL-2, IL-6, IFN- γ , TNF- α , and IL-1 β), and increasing antiinflammatory IL-10. In separate studies, melatonin worsened disease in lupus-prone male Mrl/lpr mice but improved disease characteristics in female mice.^{57,58} Because of these contradictory data, melatonin and the sleep aid Rozerem, a melatonin receptor agonist, should be used with caution in lupus patients.

Extracts from garlic are considered because they increase lymphocyte proliferation and release of histamine from basophils and mast cells.⁵⁹ However, garlic extracts also increase antiinflammatory IL-10 and decrease proinflammatory cytokines (IL-1 α , IL-6, IL-8, IL-12, IFN- γ , TNF- α) from human monocytes treated *in vitro*.⁶⁰ No cases of lupus or lupus flares have been attributed to garlic, but use of garlic is discouraged in lupus patients because of its immunostimulatory properties.

LABORATORY FEATURES

Cytopenia is less common in DIL than in idiopathic lupus, and severe hematologic abnormalities are unusual. A positive Coombs test has been reported in association with procainamide, methyl dopa, and chlorpromazine. Rarely, methyl dopa may induce hemolytic anemia as well.^{61,62}

The ANA in DIL tends to have a homogeneous pattern, although a speckled pattern may also be seen.³ ANAs can persist for years after treatment with a drug is stopped, even after the symptoms resolve. Antihistone antibodies are found in 75% of DIL cases, but they are also found in 75% of idiopathic lupus cases, so it is not a specific test.⁶³ Antihistone antibodies are likewise seen in patients with rheumatoid arthritis, Felty syndrome, and undifferentiated connective tissue disease. Antihistone antibodies may persist even after use of the offending drug has stopped and the symptoms have resolved. The antihistone antibodies in idiopathic lupus are primarily against the H1 and H2B subunits. In contrast, the antihistone antibodies found in most DIL cases are directed against the H2A and H2B subunits. In the case of hydralazine, the antihistone antibodies are directed against the H1 and H3-H4 complex. Patients with procainamide-induced lupus tend to produce IgG antibodies against an (H2A-H2B)-DNA complex, whereas asymptomatic patients receiving procainamide are more likely to have IgM antibodies to H2A-H2B dimers lacking DNA. However, this restricted activity is not specific for DIL because IgG antibodies against the H2A-H2B dimer have been found in the sera of 15% to 20% of antihistone-positive patients with idiopathic lupus. Thus, the diagnostic value of antihistone antibodies is limited.⁶⁴⁻⁶⁷

Antibodies to single-stranded DNA (ssDNA) are similarly not specific for DIL. In contrast, antibodies to dsDNA are found in approximately half of patients with idiopathic lupus, but in less than 5% of those with DIL.^{13,68} Most notably, antibodies to Smith antigen appear to be very specific for idiopathic lupus because they are rarely found in DIL.⁶⁸ Finally, DIL also tends to be characterized by normal complement levels. However, a recent review reported a more frequent occurrence of elevated anti-dsDNA titers and low complement levels in anti-TNF-related DIL than in other types of DIL (i.e., not anti-TNF related).³⁸

Antiphospholipid antibodies, including lupus coagulant and anticardiolipin antibodies, have been reported in association with a number of drugs, but chlorpromazine, procainamide, and quinidine/quinine account for the majority of cases.⁶⁹ Chlorpromazine-induced antibodies are generally IgM and are not commonly associated with thrombosis. In contrast, the lupus anticoagulants induced by procainamide or quinidine/quinine are generally IgG and are associated with a higher incidence of thrombosis. In a small study, anticardiolipin antibodies, lupus anticoagulant, and thromboses developed in melanoma patients treated with IFN- α at or near the end of a 4-week regimen.⁷⁰ The rapid development of thromboses with IFN- α is unique when surveying other reports of drug-induced antiphospholipid antibodies, but the underlying melanomas being treated by IFN- α may also

be contributing. Notably, DIL anticoagulants resolve within weeks to months of stopping treatment with the suspected drug, but anticardiolipin antibodies can persist.⁶⁹

THERAPEUTIC OPTIONS

The symptoms of DIL generally resolve once treatment with the offending drug is stopped, so the most important aspect of treating DIL is recognizing that a drug is responsible for the illness. The development of a positive ANA while receiving a drug is not sufficient reason to discontinue the drug, although careful monitoring for subsequent clinical illness is important. Constitutional and musculoskeletal symptoms are usually controlled adequately with aspirin or other NSAIDs. Low-dose prednisone is occasionally necessary, and higher doses of prednisone may be used for resistant or symptomatic pericardial effusion. The rare cases of biopsy-proven renal disease or vasculitis should be treated with aggressive immunosuppression as for idiopathic lupus. Although most symptoms of DIL resolve within weeks of discontinuing treatment with the offending drug, occasional patients may take up to 1 year to recover completely.³

PATHOGENESIS

Even though methyl dopa and levodopa have similar chemical structures and hydralazine and isoniazid share a hydrazine side chain, the other molecules known to induce lupus have little in common. This suggests that no single chemical structure is responsible for inducing autoimmunity.

Instead, many lines of evidence show that DNA demethylation contributes to the pathogenesis of DIL. DNA methylation refers to the methylation of carbon 5 in cytosines to form deoxymethylcytosine (dmC). DNA methylation patterns are established during development by the “*de novo*” DNA methyltransferases 3a and 3b (Dnmt3a and Dnmt3b) and then are maintained by Dnmt1 each time that a cell divides. As cells enter mitosis, signals transmitted through the ERK and JNK pathways upregulate Dnmt1. When Dnmt1 encounters a dmC in the parent DNA strand, it catalyzes transfer of the methyl group from S-adenosylmethionine to the corresponding dC in the daughter strand, thereby replicating the methylation pattern. This is a crucial step because if DNA methylation is inhibited, either by preventing Dnmt1 upregulation or by interfering with the transmethylase reaction, the methylation patterns will not be replicated in the daughter cell. Consequently, genes that are normally silent can become demethylated and expressed. Furthermore, because the changes are heritable, the errors will be replicated during subsequent cell divisions. Thus, it is at this point that DNA methylation and consequently gene expression become sensitive to the environment.⁷¹

Inhibiting DNA methylation in CD4+ T cells makes them autoreactive by causing overexpression of the adhesion molecule LFA-1 (CD11a/CD18). LFA-1 normally binds ICAM-1 on antigen-presenting cells and surrounds the T-cell receptor–major histocompatibility complex (TCR-MHC). Such binding stabilizes the TCR-MHC interaction and provides additional co-stimulatory signals that result in T-cell activation when the TCR recognizes both the antigenic peptide and the MHC molecule. Treating CD4+ T cells with DNA methylation inhibitors such as 5-azacytidine (5-azaC) increases LFA-1 expression. This enables T cells to respond to lower-affinity interactions between the TCR and “self” class II MHC molecules without the appropriate antigen, thus making the T cells autoreactive. Autoreactivity also develops when T cells are transfected with LFA-1.⁷² These autoreactive T cells recognize and respond to self class II MHC molecules on B cells, with antibody production being overstimulated both through effects on cell-surface co-stimulatory molecules and by secretion of stimulatory cytokines such as IFN- γ .^{73,74} Autoreactive T cells also respond to self class II MHC molecules on macrophages and kill them by inducing apoptosis. This releases apoptotic chromatin from the dying macrophages,⁷⁵ which is highly antigenic. Genetic deletion of any of the molecules involved in clearing apoptotic material or overwhelming of the mechanisms that clear apoptotic materials causes lupuslike autoantibodies to nuclear antigens, including chromatin and DNA.^{76,77} Because macrophages are responsible for clearing apoptotic chromatin, macrophage apoptosis will further augment the autoantibody responses. Thus, T cells made autoreactive by inhibition of DNA methylation contribute to lupuslike autoimmunity by generating antigenic chromatin (macrophage apoptosis) and autoantibodies (B-cell stimulation).

The pathologic significance of demethylated CD4+ T cells was first demonstrated when murine CD4+ T cells treated with 5-azaC were injected into genetically identical mice. The modified cells caused anti-DNA antibodies and immune complex glomerulonephritis.⁷⁸ More recent studies

have used transgenic mouse models to confirm that inducing T-cell DNA demethylation by blocking ERK and JNK signaling *in vivo* causes lupuslike autoimmunity.⁷⁹⁻⁸¹

Procainamide and hydralazine, the two drugs that cause DIL most often, are inhibitors of DNA methylation. Treating CD4+ T cells with procainamide or hydralazine caused overexpression of LFA-1 and made CD4+ T cells autoreactive, just like 5-azaC did. Procainamide inhibits Dnmt1 enzymatic activity,⁸² whereas hydralazine prevents Dnmt1 upregulation during mitosis by inhibiting signaling via the ERK pathway.⁸³ Interestingly, N-acetylprocainamide, the acetylated metabolite of procainamide, does not cause DIL flares in patients with previous procainamide-induced lupus.⁸⁴ It is less potent in causing T-cell LFA-1 overexpression and autoreactivity *in vitro*, and it also has a reduced ability to cause autoimmunity in animal models.⁸⁵

It is not known whether the other drugs listed in Box 132.1 also affect DNA methylation. It is likewise not known whether DNA demethylation in cells other than T lymphocytes also contributes to DIL. Nonetheless, the adoptive transfer and transgenic mouse models demonstrate that T-cell DNA demethylation alone is sufficient to cause lupuslike autoimmunity.

CONCLUSION

Practicing physicians need to be aware of the potential problem of DIL. Prompt recognition and treatment are associated with an excellent outcome in most cases. The number of reported associations is expected to increase as new drugs are developed. Since some of these case reports may represent idiosyncratic reactions or the coincidental development of idiopathic lupus, rigorous epidemiologic, clinical, and laboratory testing should be done to confirm the association. Finally, physicians need to be aware that many patients with chronic diseases ingest over-the-counter alternative medicines that could potentially induce the development of autoimmune diseases, including lupus.

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Assessing disease activity and outcome in systemic lupus erythematosus

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- Disease activity indices strive to capture the heterogeneous, multisystemic disease manifestations of systemic lupus erythematosus (SLE).
- In addition to disease activity, it is important to assess the impact of the disease, its treatment, and associated damage on the health-related quality of life of patients with SLE.
- It is challenging to design randomized controlled trials for SLE and to assess their outcome.
- Evidence-based composite responder indices appear to be best suited for assessing the treatment effects of investigational products.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous, relapsing, remitting disease that affects many dimensions of a patient's life. Disease activity typically affects multiple organ systems without a predictable pattern, even in the same patient. In part because of earlier diagnosis and treatment, the survival rate of patients with SLE has increased to greater than 90% 5 years after diagnosis and to 80% 10 years after diagnosis, with fewer deaths being attributed to SLE since 1970.¹ No uniform therapeutic regimens have been established, and treatment is largely determined by physicians' judgment of patients' clinical outcomes. Rather than focusing on survival, outcomes in randomized controlled trials (RCTs) of SLE are designed to assess therapeutic responses.

In clinical practice, the patient's history, physical examination, and laboratory findings primarily guide assessment of disease activity and efficacy of treatment. The patient's history and physical examination should be comprehensive with a focus on the characteristic organ system involvement of SLE (see Chapter 126). Some laboratory features may also correlate with the signs and symptoms of SLE activity. Anemia, leukopenia, thrombocytopenia, hypocomplementemia (low C3 or C4 values, or both), elevated erythrocyte sedimentation rate, a rise in anti-double-stranded DNA antibody levels, or any combination of these features may be associated with increased SLE disease activity. Proteinuria, hematuria, urinary casts, and a rise in creatinine levels may signify renal involvement in SLE. Clinical and laboratory features should be interpreted together while keeping in mind other connective tissue diseases and nonrheumatic conditions that may be included in the differential diagnosis.

A variety of disease activity indices (DAIs), in addition to measures of damage, patient-reported fatigue, and health-related quality of life (HRQOL), have been designed to aid in the assessment of SLE. Although DAIs are used by some practitioners in clinical practice, they were developed for use in longitudinal observational studies (LOSs) and have subsequently been validated in RCTs. In 1998, an international consensus conference on outcome measures in rheumatology (OMERACT 4) recommended that four core domains be assessed in RCTs of SLE: disease activity, damage (because of SLE, its treatment, or both), HRQOL, and adverse events.^{2,3} The European League Against Rheumatism Task Force on SLE published similar

recommendations in 2009.⁴ A guidance document for the development of new therapeutic agents for patients with SLE issued by the U.S. Food and Drug Administration in 2010 encouraged the measurement of outcomes, including disease activity, damage, SLE flares, concomitant corticosteroid use, patient-reported outcomes, and biomarkers.⁵ Understanding the reasons supporting regular assessment of these domains will facilitate the ability to evaluate therapeutic responses in patients with SLE.

Because individual measures of clinical response in SLE reflect only a portion of what can be considered the "true outcome," it is important to consider disease activity within the context of the many effects of SLE on patient well-being.⁶ Thus, the strengths and limitations of organ system-specific and global DAIs and the generic and disease-specific measures of HRQOL must be understood and are best used together to complement each other.

DISEASE ACTIVITY INDICES

Four SLE DAIs have been used in RCTs: the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and its modifications, including the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA-SLEDAI), SLEDAI 2000 (SLEDAI-2K), and SLEDAI-2K 50%; the British Isles Lupus Assessment Group (BILAG) Index, classic and 2004 modification; the Systemic Lupus Activity Measure (SLAM and SLAM-R modification); and the European Consensus Lupus Activity Measure (ECLAM).⁶ They capture global or organ-specific manifestations (or both) attributed to SLE rather than secondary manifestations, including damage as a result of disease, its treatment, and associated comorbid conditions.

Systemic lupus erythematosus disease activity index

The SLEDAI and its modifications measure disease activity based on 24 questions assessing the clinical manifestations of SLE, including physical findings and laboratory values weighted across organ systems.⁷ Although the maximum score achievable is 105, even with very active disease, scores rarely exceed 20. Preferential weighting is based on the manifestations of vasculitis, central nervous system (CNS) involvement, and active renal disease. Modeled on clinicians' global judgment, the original SLEDAI was not intended to detect gradations of disease activity within an organ system: neither worsening nor partial improvement. Completed rapidly with minimal training, the SLEDAI has been cross-culturally validated with reproducibility and reliability by expert clinicians and trainees.⁶

In contrast to the original SLEDAI, which measures manifestations over the past 10 days, the SELENA-SLEDAI and SLEDAI-2K have been modified for use in RCTs to score manifestations over the past 28 to 30 days.^{8,9} They measure ongoing disease activity with improved clarification and attribution for individual items. The SLEDAI-2K descriptors, definitions, and weighted scores are presented in Table 133.1.¹⁰ Cross-sectional analysis of data collected by the SLEDAI-2K has indicated that the most appropriate cutoff score for active disease is 3 or 4.¹¹ Recently, to increase sensitivity in detecting improvement in disease, the SLEDAI-2K Responder Index-50 (S2K RI-50) was developed and validated in LOSs and found to reliably detect 50% improvement in the 24 descriptors, with partial improvement allowed to be acknowledged (see Table 133.1).^{12,13} A Web-based program is now available for training and use of the S2K RI-50.¹⁴

TABLE 133.1

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)¹⁰ and SLEDAI-2K Responder Index-50¹² improvement definitions

Descriptor		SLEDAI-2K score and definitions	SLEDAI-2K Responder Index-50 improvement definitions (summarized)
Seizure	8	Recent onset; excludes metabolic, infectious, or drug causes	≥50% reduction in the frequency of baseline seizures (days/mo)
Psychosis	8	Altered ability to function in normal activity because of a severe disturbance in the perception of reality. Includes hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, and bizarre, disorganized, or catatonic behavior. Excludes uremia and drug causes	≥50% improvement in psychotic manifestations as judged by a physician
Organic brain syndrome	8	Altered mental function with impaired orientation, memory, or other intellectual function; rapid onset and fluctuating clinical features; inability to sustain attention on the environment; plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Excludes metabolic, infectious, or drug causes	≥50% improvement in organic brain manifestations as judged by a physician
Visual	8	Retinal changes of SLE. Includes cytooid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Excludes hypertension, infection, or drug causes	≥50% improvement in findings on retinal examination as assessed by a physician
Cranial nerve	8	New onset of sensory or motor neuropathy involving the cranial nerves	≥50% recovery of motor or sensory function in the affected nerve or a ≥50% decrease in the severity of pain within 1 mo from the event on the basis of a decrease in lupus disease activity without worsening in either
Lupus headache	8	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia	≥50% decrease in the severity of pain as determined by the patient on a numerical scale of 1-10
Cerebrovascular accident	8	New onset of CVA. Excludes arteriosclerosis	≥50% recovery of motor or sensory function related to a CVA within 1 mo from the event on the basis of a decrease in lupus disease activity as determined by a physician without worsening in either
Vasculitis	8	Ulcerations, gangrene, or tender finger nodules; periungual infarction; splinter hemorrhages; or biopsy or angiographic proof of vasculitis	≥50% improvement in the vasculitis lesions present with no new lesion or worsening in either
Arthritis	4	≥2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion)	≥50% reduction in the number of joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion)
Myositis	4	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyographic changes or a biopsy specimen showing myositis	≥50% increase in muscle power or ≥50% decrease in the level of creatine phosphokinase/aldolase with no worsening in either
Casts	4	Hem-granular or red blood cell casts	≥50% decrease in the total number of casts (heme-granular and red blood cell casts)
Hematuria	4	>5 red blood cells/high-power field. Excludes stone, infection, or other cause	≥50% decrease in the number of red blood cell/high-power field at this visit
Proteinuria	4	>0.5 g/24 hr	≥50% decrease in the range of proteinuria
Pyuria	4	>5 white blood cells/high-power field. Excludes infection	≥50% decrease in the number of white blood cells/high-power field
Rash	2	Inflammatory-type rash	≥50% decrease in the involved body surface area and/or activity of most active lesion with no worsening in either
Alopecia	2	Abnormal, patchy or diffuse loss of hair	≥50% decrease in the total scalp area involved by patchy alopecic lesions or ≥50% reduction in diffuse alopecia with no worsening in either
Mucosal ulcers	2	Oral or nasal ulcerations	≥50% decrease in the number of ulcers at this visit
Pleurisy	2	Pleuritic chest pain with a pleural rub or effusion or pleural thickening	≥50% reduction in pain severity and/or ≥50% reduction in the amount of fluid (on imaging) with no worsening in either
Pericarditis	2	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiographic or echocardiographic confirmation	≥50% reduction in pain severity and/or ≥50% reduction in the amount of fluid (on imaging) with no worsening in either
Low complement	2	Decrease in CH ₅₀ , C3, or C4 below the lower limit of normal for the testing laboratory	≥50% increase in the level of any complement or normalization of 1 of them without a drop in either
Increased DNA binding	2	Increased DNA binding by the Farr assay above the normal range for the testing laboratory	≥50% reduction in the level of anti-DNA antibodies
Fever	1	>38° C. Excludes infectious cause	≥50% reduction in the degree of fever above normal
Thrombocytopenia	1	<100,000 platelets/mm ³ ; excludes drug causes	≥50% increase in the level of platelets, but <100,000 platelets/mm ³
Leukopenia	1	<3000 white blood cells/mm ³ ; excludes drug causes	≥50% increase in the level of white blood cells, but <3000 white blood cells/mm ³

CH₅₀, 50% hemolyzing dose of complement; CVA, cerebrovascular accident; SLE, systemic lupus erythematosus.

British isles lupus assessment group disease activity index

The BILAG was developed to measure disease activity in individual organ systems based on an intent-to-treat principle.¹⁵ The BILAG 2004 is a major revision of the “classic BILAG” and expands the scoring of manifestations within organ systems to nine: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematologic¹⁶; ophthalmic was added, previous abdominal and hepatic manifestations were combined into a single gastrointestinal category, and vasculitis was redistributed into the specific organ system of involvement. Eighty-six items are scored for SLE disease activity occurring within the past 4 weeks versus the previous month. Scores are converted into letter categories representing the need for therapy (Table 133.2). The BILAG and BILAG 2004 are the only DAIs that score features as improved, the same, worse, or new rather than as present or absent. A single numeric summary score has been developed for the classic BILAG and BILAG 2004, similar to the global score generated by the SLEDAI, although it is a discontinuous measure.¹⁶ Table 133.3 presents a comparison of the key components of SLEDAI-2K and BILAG-2004.

As with SLEDAI-based indices, the BILAG and BILAG 2004 have been used as outcome measures, as well as to define eligibility criteria for RCTs.¹⁷ Scoring rules for this detailed and comprehensive instrument are outlined for the user, and effort is made to ensure accuracy of reporting by those less familiar with use of the BILAG. Internet-based training courses, computer-assisted scoring, and independent formal adjudication panels have been used in RCTs to address variability in interpretation and scoring of the BILAG. Importantly, adjudication of BILAG scoring ensures that the physical examination findings and laboratory results accurately reflect reported improvements or worsening in disease manifestations. The BILAG and

BILAG 2004 are not generally used in clinical practice despite computerized programs available for scoring.

Systemic lupus activity measure and European Consensus Lupus Activity Measure

The SLAM is based on signs and symptoms observed over the past 4 weeks, with weighting of more severe clinical manifestations. It uniquely includes patient-reported symptoms of fatigue. In the more recent revised index, SLAM-R, scores range from a minimum of 0 to a maximum of 81.¹⁸ The ECLAM scores nine clinical and three laboratory manifestations of SLE over the past 4 weeks, with scores ranging from 0 to 10; physician global assessment of disease activity (PGA) is the reference “gold standard.”¹⁹

Lupus flare definitions

Multiple definitions are used to define flare in SLE, some adapted from the DAIs summarized earlier. The SELENA-SLEDAI Flare Index (SFI) was developed as the primary endpoint for the SELENA RCTs to define mild/moderate versus severe flares; it incorporates the SELENA-SLEDAI score, corticosteroid use, and PGA score to determine flare severity.^{8,9}

“Mild/moderate” flares are defined as new or worsened clinical features resulting in increases in the SELENA-SLEDAI score of 3 or more points, prednisone use less than 0.5 mg/kg/day, PGA score of 1.0 to 2.5 on a 0 to 3 visual analog scale (VAS), or any combination of these measures. Severe flares are defined as changes in SELENA-SLEDAI scores to higher than 12 or clinical manifestations requiring doubling of the prednisone dose or an increase to 0.5 mg/kg/day or greater.

“Severe” flares have been defined by the BILAG as the development of a new “A” or two simultaneous “B” scores in any organ system and “moderate” flares as a new BILAG B score from previous B, C, D, or E scores.²⁰ No definition for a “mild” flare based on the BILAG index has been validated.

A pragmatic definition of a “major” flare as defined by Fortin and colleagues^{21,22} included new or increased use of immunosuppressive therapy, new or increased use of corticosteroids at 0.5 mg/kg daily or greater, and hospitalization or death because of SLE disease activity. These straightforward criteria typically do not require adjudication in RCTs.

The SFI, BILAG, and Fortin definitions of flare have been used in RCTs, and some trials have used more than one definition. To reach a consensus on a single definition of flare in SLE, an international effort sponsored by the Lupus Foundation of America was initiated in 2006 to develop a clinically meaningful definition of flare for use in RCTs, LOSs, and clinical practice: “A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or increase in treatment.”²³ Specific criteria to distinguish between mild, moderate, and severe flares remain to be established.

Measures of damage

The relapsing, remitting, and chronic nature of SLE results in irreversible damage over time as a result of the disease, its treatment, or both. The Systemic Lupus International Collaborating Clinics (SLICC)/American

TABLE 133.2
Scoring of BILAG and BILAG-2004 for each organ system

Letter categorization	Definition
A	Severe disease requiring increases in prednisone to >20 mg daily and/or the addition of immunosuppressive agents
B	Less active disease requiring low-dose prednisone and/or symptomatic treatment with nonsteroidal antiinflammatory drugs and/or antimalarials
C	Mild disease requiring symptomatic therapy such as simple analgesics or stable disease on current therapy
D	Previous organ system involvement without current disease activity
E	No previous or current disease involvement in that organ system

BILAG, British Isles Lupus Assessment Group.

TABLE 133.3
Comparison of the BILAG 2004 and SLEDAI-2K Disease Activity indices

	BILAG 2004	SLEDAI-2K
Method of development	Physician intention to treat categorized by organ system	Delphi consensus by physician and statistician panel
Number of manifestations	86	24
Time frame considered	Previous 28 days	Previous 10 or 30 days
How scored	Improved, same, worse, new, not present	Present or absent
Score	A-E “intention-to-treat” categories; numerical scoring also available	Numerical scoring: 0-105
Weighting	None	Greatest for CNS and vascular involvement
Laboratory variables considered	Proteinuria, creatinine, glomerular filtration rate, urinary sediment, anemia, leukopenia, neutropenia, thrombocytopenia, active hemolysis, Coombs test positivity	Casts, hematuria, proteinuria, pyuria, low complement, increased DNA binding, thrombocytopenia, leukopenia

BILAG, British Isles Lupus Assessment Group; CNS, central nervous system; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

College of Rheumatology Damage Index (SDI) was developed to capture damage from disease activity, medications, and comorbid conditions that has been present for 6 or more months with the intent of identifying irreversible damage. Twelve organ systems are assessed, with a maximum of 47 points.²⁴ The SDI reflects the impact of disease distinct from disease activity, with early accumulation of damage being associated with a poor prognosis and increased mortality.²⁵ However, typically it has not performed well in RCTs in differentiating active from control therapy and may best be used as an entry criterion to balance randomization.

Other measures of damage include organ-specific definitions of worsening or loss of function, such as the urinary protein-creatinine ratio or glomerular filtration rate based on timed urine samples or the presence of osteopenia or osteoporosis secondary to SLE, its treatment with corticosteroids, or both.⁶

OTHER OUTCOME MEASUREMENTS

Health-related quality of life

HRQOL is defined as the impact of disease on the physical, psychological, mental, and social aspects of health, as influenced by the expectations and life experiences of an individual patient.²⁶ It is important to assess HRQOL in SLE, especially since it has clearly been shown that disease activity, damage, and HRQOL are independent of each other and thus reflect different domains affected by disease.³ Both generic and disease-specific measures have been used in RCTs and LOSs in SLE.

The Medical Outcomes Short Form 36-Item Survey (SF-36) is a generic instrument that is widely used for rheumatic and nonrheumatic diseases; it includes eight domains: physical functioning, role physical, bodily pain, general health perceptions, vitality (which includes fatigue, energy, and pep), social functioning, role emotional, and mental health impact.²⁷ The physical component summary score (PCS) positively weights four “physical” domains—physical functioning, role physical, bodily pain, and general health perceptions, as well as vitality—and negatively weights the remaining three. The mental component summary score (MCS) positively weights the four “mental” domains—vitality, social functioning, role emotional, and mental health impact—and negatively weights the 4 physical domains. The SF-36 has best reflected the impact of SLE on HRQOL in LOSs and frequently has been the only patient-reported outcome in RCTs,^{27,28} or utilized with a measure of fatigue.^{29,30} Minimum clinically important differences

have been defined for improvements in the PCS and MCS (2.5) and individual domain (5.0) scores, as well as for deterioration (−0.8 and −2.5, respectively).^{31,32}

Patients with SLE most commonly complain of fatigue and an inability to engage in activities important to them.^{33,34} The SF-36 queries fatigue in the vitality domain, also including “pep and energy” and two specific measures of fatigue, the Krupp Fatigue Severity Scale (KFSS) and the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F), which have been used and validated in RCTs of SLE and nonrheumatic diseases.³⁵ The KFSS, a nine-item scale, measures the impact of fatigue on specific types of functioning, such as motivation, exercise, and work, family, or social life.³⁶ The FACIT-F includes 13 fatigue-related items that assess the impact of fatigue on usual activities, eating, and social activity over the past 7 days.³⁷

Recognition that generic HRQOL measures may not include all issues important to patients with SLE has led to the development of several disease-specific questionnaires (Table 133.4).^{38–40} All are at different stages of development and validation cross-culturally and geographically for use in multinational RCTs, as well as in daily clinical practice. The Lupus Quality of Life tool (LupusQoL), developed in the United Kingdom, has been translated and cross-culturally validated in 13 languages, for use in the United States, Canada, France, Germany, and Spain, and is to date the only one with published RCT data.⁴¹ This has been accomplished on a smaller scale by a comparison of the generic SF-36 with LupusQoL in a cohort of 41 patients at one site in Canada; it was demonstrated that together, both instruments offer complementary information.^{28,42} The Systemic Lupus Erythematosus Quality of Life tool (SLE-QoL), developed and validated in Singapore, measures the physical and psychological aspects of SLE; 40 items are summed to yield a global score.⁴³ Patients rate specific items based on their frequency and importance over the past month. Unlike the LupusQoL, the SLEQoL places less emphasis on physical functioning and pain.⁴⁴

The Lupus Patient-Reported Outcome tool (LupusPRO) was developed and validated based on feedback from an ethnically heterogeneous SLE population from the United States across both genders.⁴⁰ It includes issues pertinent to men with SLE: physical and mental health, cognition, procreation, body image, and effects of SLE medications, as well as items not considered to reflect HRQOL, such as desires, goals, coping, social support, and satisfaction with care. Rapidly completed in less than 10 minutes, it is designed to identify areas of HRQOL that require further, repeated assessment. To aid in the use of an SLE-specific HRQOL measurement in daily practice on a monthly basis, a shorter questionnaire derived from 10 of the LupusPRO items, the Lupus Impact Tracker, was derived for use in clinical

TABLE 133.4
SLE-specific health-related quality-of-life instruments

Name	Features	Scoring	Where developed
Lupus Quality of Life tool (LupusQoL)	34 items distributed over 8 domains: physical health, pain, planning, intimate relationships, burden to others, emotional health, body image, fatigue	Each domain scored separately with no global score	UK; cross-culturally adapted and validated for use in the US, Canada, and France, with translations available in multiple European, Latin American, and Asian languages
Quality of Life in SLE (L-QoL)	Assesses the overall impact of SLE and its treatment on 25 items based on the needs of the patient	Responses (true or not true) are summed, with higher scores indicating poorer health	UK
Systemic Lupus Erythematosus Quality of Life (SLE-QoL)	40 items covering 6 domains: physical functioning, activities, symptoms, treatment, mood, self-image	Global score; a higher score indicates worse HRQOL	Singapore; cross-culturally adapted for use in Chinese-speaking patients in Singapore (SLEQoL-C)
Lupus Patient-Reported Outcome tool (LupusPRO)	44 items across 10 HRQOL domains: lupus symptoms, lupus medication, physical health, emotional health, pain, vitality, procreation, cognition, body image, general health; also included are 4 “non-HRQOL” domains: desires-goals, coping, social support, satisfaction with care	HRQOL and non-HRQOL scores derived by the mean of the relevant domains and transformed to scores ranging from 0 (worst QOL) to 100 (best QOL). A higher score signifies better health	US
Lupus Impact Tracker	A 10-item subset of the LupusPRO covering fatigue, pain, performance of usual activities, fulfillment of family responsibilities, ability to plan activities, anxiety, depression, concentration, self-image, and medication side effects	Global scores ranges from 0 to 40 and is converted to a lupus impact score that ranges from 0 to 100; a higher score signifies poorer HRQOL	US

HRQOL, health-related quality of life; SLE, systemic lupus erythematosus.

TABLE 133.5
Responder indices used in randomized controlled trials

Responder index	Method of derivation	Criteria to define “response”
Responder index for DHEA trials	FDA-sponsor consensus	No treatment failure Improvement in the SLEDAI or SLAM without deterioration in the other Improvement in patient global assessment or the KFSS without deterioration in the other
Response Index for Lupus Erythematosus (RIFLE)	Delphi process	Complete response based on resolution of abnormal signs in specific organ systems, including renal, neurologic, mucocutaneous, and musculoskeletal Partial response based on decreased features of disease within an organ system but not full resolution
SLE Responder Index (SRI)	Phase 2 data mining	No new or increased use of proscribed medications or early dropout ≥4-point reduction in the SELENA-SLEDAI score No new BILAG A or >1 new B scores No PGA deterioration from baseline >0.3 points
British Isles Lupus Assessment Group–based Composite Lupus Assessment (BICLA) endpoint	Phase 2 data mining	Reduction of all baseline BILAG A and B scores No new BILAG A or 2 new B scores No worsening in baseline SLEDAI or PGA scores No treatment failure

BILAG, British Isles Lupus Assessment Group; DHEA, dihydroepiandrosterone; FDA, Food and Drug Administration; KFSS, Krupp Fatigue Severity Scale; PGA, physician global assessment of disease activity; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLAM, Systemic Lupus Activity Measure; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

practice and shown to accurately reflect the impact of SLE on patients’ lives and well-being.^{45,46}

Global assessments of lupus disease activity

Most RCTs involving SLE query PGA but not patient global assessment of disease activity (PtGA). As in rheumatoid arthritis, the appropriate question is phrased, “In all the ways your disease affects you today, how are you doing?” on a 0 to 100 mm VAS scale. Responses correlate with answers to the transition question in the SF-36, “Compared with a year ago, how is your general health today?”⁶ It should be noted that PGA and PtGA offer information from different perspectives; patients’ perceptions of the impact of their disease may be associated with psychosocial stressors that may not be apparent to the physician, who will focus on assessment of disease activity and damage, including CNS and renal manifestations, which may be less obvious to the patient. Thus, it is not uncommon find that PGA and PtGA do not correlate well in RCTs.^{3,6}

Composite responder indices

Responder indices define patients who have improved with treatment versus those who have not based on multiple components. Composite responder indices require improvements based on different outcome measures that generally do not correlate closely with each other, thereby adding power and decreasing the sample sizes required for RCTs; those used in recent RCTs are listed in Table 133.5.⁶ In addition to the specific components defined within each index, “responses” first require that patients not be “treatment failures,” as defined prospectively in each trial. Definitions of treatment failure typically include withdrawal because of adverse events or the use of prohibited medications.

The Response Index for Lupus Erythematosus was defined according to specific improvements in organ system manifestations as determined by a Delphi consensus process, but it did not differentiate between active and control therapy when included in an RCT.⁶ In recent phase 3 RCTs, composite responder indices were designed based on data mining of phase 2 studies of belimumab and epratuzumab: the SLE Responder Index (SRI) and the BILAG-based Combined Lupus Assessment (BICLA), respectively (see Table 133.5).⁴⁷⁻⁴⁹ These indices demonstrated the importance of developing evidence-based responder indices.^{50,51} Responses on the SRI are based on no “treatment failure” and improvement of 4 or more points in the

SELENA-SLEDAI score, without worsening of the BILAG by one “A” or two simultaneous “B” scores and “no deterioration” in PGA by more than –0.3 points on a 0 to 3 scale. The SRI was subsequently used as the primary endpoint in two successful phase 3 RCTs: BLISS-76 and BLISS-52, one for “validation” and the other for confirmation.

Similarly, in the BICLA, responses are based on no “treatment failure,” loss of all “A” or “B” BILAG scores, and no worsening of the total SLEDAI score and “no deterioration.” It is the predefined primary endpoint in the ongoing phase 3 studies of epratuzumab, EMBODY 1 and 2.^{48,49}

CONCLUSION

It should be noted that no single regimen is accepted as standard-of-care therapy for SLE and that the choice of treatment is dependent on the active disease manifestations in an individual and the treating rheumatologist. Outcome measures in RCTs assessing investigational treatments must account for individual differences, as well as previous and current use of background corticosteroid and immunosuppressive medications. Changing background therapy during the course of a trial may mask any potential benefit from the investigational therapy. To maximize the ability to identify the treatment benefit of an investigational agent added to background therapy it is critical to use responder indices, predefine the use of corticosteroids and immunosuppressive agents, and restrict changes in their doses.⁶

Over the past 3 decades, existing DAIs and definitions of flare have been refined, and damage- and disease-specific HRQOL instruments and evidence-based responder indices have been developed. Nonetheless, the heterogeneous multisystemic nature of SLE poses a unique challenge in assessing outcomes in clinical practice, as well as in RCTs. No one DAI is sufficient to capture responses to therapy, nor is it possible to accurately identify all the aspects of a patient’s life that are affected by SLE at any given time. Disease activity, including recognition of flares and damage as a result of the disease and its treatment, HRQOL, and global assessment of disease activity should be evaluated when measuring outcomes in daily practice, as well as in RCTs—provided that instruments exist that may be pragmatically used in each setting.⁶ Development and further refinement of composite responder indices that include components that can be used in clinical practice will facilitate better understanding of the results from RCTs, as well as translate their utility into day-to-day use.

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Management of nonrenal and non-central nervous system lupus

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- Quality of life and prognosis can be improved without prescribing lupus medication by screening for lupus comorbidities (e.g., accelerated atherogenesis, osteoporosis) and by encouraging lifestyle modifications (e.g., smoking cessation, exercise).
- Lupus medications for non-organ-threatening disease include topical antiinflammatory agents, nonsteroidal antiinflammatory drugs, antimalarials, and low doses of corticosteroids when needed.
- Methotrexate, mycophenolate mofetil, azathioprine, and cyclophosphamide account for 95% of all prescriptions of immunosuppressive drugs for treatment of systemic lupus erythematosus (SLE) and are employed to reduce steroid use and ameliorate organ-threatening disease.
- Only one targeted therapy (belimumab) is approved for treatment of SLE. Several other biologic agents on the market may have niche roles in treating active disease.

INTRODUCTION

The management of lupus erythematosus involves a variety of approaches, including physical measures, education, surgery, and medication. A large number of interventions are available that are relevant and can affect outcome and prognosis.¹ These include lifestyle measures and preventive strategies.

GENERAL MANAGEMENT CONSIDERATIONS

A patient newly diagnosed with lupus or one new to a practice setting is better equipped to deal with the disease if the treating physician has an educational session with the patient and with those closely involved in the patient's care (Box 134.1). This session should include a review of physical and lifestyle measures, distribution of brochures or information relating to access to patient resources, discussion of coping mechanisms, overview of relevant therapeutic approaches, emphasis on the importance of adherence to the treatment regimen, and consideration of all concerns or questions. Fatigue is present in 50% to 90% of patients with systemic lupus erythematosus (SLE) and can be one of its most debilitating symptoms.² Causes include inflammation, medication, fibromyalgia, psychosocial distress, infection, cytokine dysregulation, hormone imbalances, and comorbidities (e.g., anemia, interstitial lung scarring, malnutrition). Fatigue is managed by treating the underlying cause (e.g., with antiinflammatory therapies) and by instructing the patient to pace activities, follow good sleep hygiene practices, engage in aerobic exercise, obtain emotional support, and avoid stimulants unless medically supervised. Aerobic capacity is decreased by 30% to 40% in SLE patients and correlates with obesity, fatigue, bone demineralization, reduced cardiovascular functioning, muscle atrophy, and decreased quality of life. Exercise, particularly isometric as opposed to isotonic strengthening regimens if synovitis is present, improves these factors.³ Smoking can be harmful in lupus via several mechanisms: it can worsen Raynaud syndrome, decrease tissue oxygenation, cause deleterious effects because of the presence of hydrazines in tobacco smoke, and interfere with the effectiveness of hydroxychloroquine.⁴ Modest use of alcohol has no influence on SLE. Lupus patients are sensitive to alterations in barometric pressure and thus experience more stiffness, and seasonality may play a role,

with aggravation of Raynaud syndrome in winter months and increased ultraviolet light exposure during the summer. Individuals with SLE do not take more pain medication than the general population unless comorbidities such as avascular necrosis or fibromyalgia are present. The use of opiates is generally unnecessary and is potentially harmful.

The role of stress and trauma in lupus is controversial, but the following have been observed: (1) Discoid lupus lesions can occur in scars from prior skin trauma. (2) Although results from animal models (e.g., the Lewis rat, which has a hypofunctioning CRH neuron) suggest that a lupuslike disorder can result from abnormal stress responses, there is no evidence that physical or emotional trauma can induce SLE. (3) A majority of patients with lupus associate flares with physical or emotional trauma, but evidence-based studies have not been able to confirm this perception.⁵ Optimizing coping mechanisms with counseling, biofeedback, anxiety reduction measures, and cognitive behavioral therapy improves outcome and prognosis. The rates of adherence⁶ in the United States with regard to keeping appointments, filling prescriptions, and following physician advice relating to lupus (e.g., sun avoidance) ranges from 40% to 90%.

Lupus patients should avoid alfalfa sprouts (which contain high concentrations of L-canavanine) and echinacea (which can act as an immune activator), should eat one or two fish meals a week or take fish oil capsules (eicosapentaenoic acid is antiinflammatory), and should not be deficient in immune regulation-enhancing vitamin D (low levels are associated with more disease activity and can result from sun avoidance). There is no specific lupus diet except for dietary measures to reduce risks from corticosteroid use and protein-sparing diets in patients with advanced renal impairment.⁷ Over 50% of lupus patients use complementary and alternative medicine approaches.⁷ As long as these approaches do no harm and are not a substitute for accepted lupus therapies, there is no need to avoid them.

Preventive strategies that improve outcome

A variety of approaches can improve outcome and prognosis in lupus patients without the use of any antiinflammatory or disease-modifying medications. The best-documented interventions involve sun avoidance and sun protection measures⁸ (Box 134.2). Ultraviolet A (UVA) and UVB light enhance the antigenicity of epidermal DNA, allowing anti-Ro (if present) to be exposed to the cell surface and provoking an inflammatory response via apoptotic blebs. Sun exposure is greatest at midday and at higher altitudes. Sun sensitivity is self-reported in two thirds of individuals with SLE and is confirmed by objective phototesting in one third. Commercially available sunscreens consist of ultraviolet light-absorbing chemical agents in cream, oil, lotion, alcohol, gel, or foam vehicles that can block UVA, UVB, or both. Outpatients should use agents with a sun protection factor (SPF) of at least 15, which blocks 93% of UVB rays; a sunscreen with an SPF of 50 blocks only 5% more. Broad-spectrum protection is present if UVA-2 is also blocked in addition to UVB (UVA-1 might actually help lupus).

Caution should be exercised in administering live attenuated vaccines to those taking immunosuppressive drugs, but household transmission from healthy individuals receiving such vaccines have not been reported. Routine immunizations such as influenza, pneumococcus, and hepatitis B vaccinations are safe, but their potency may be impaired.⁷ The prevalence of reactivity to nonarylamine sulfa antibiotics (which are sun sensitizing) is increased among lupus patients, and their use should be considered on an individual basis. One third of SLE patients have antiphospholipid antibodies, and one third of these patients experience a thromboembolic event. Individuals with high-risk thrombogenic profiles should be evaluated to determine whether they are candidates for thromboprophylactic interventions. Such interventions include treatment with low-dose aspirin, warfarin, heparin, or platelet antagonists. See Chapter 139.

BOX 134.1 GENERAL MANAGEMENT CONSIDERATIONS TO REVIEW WITH LUPUS PATIENTS

1. Education: Explain what lupus is and its causes. Provide educational literature and Web/resource listings.
2. Physical and lifestyle measures: Provide recommendations on diet, exercise, physical measures, immunizations, smoking cessation, and sun protection, and emphasize the importance of adherence to the treatment regimen.
3. Emotional support: Counsel on how to deal with fatigue and on coping and stress-reduction strategies.
4. Adjunctive measures: Provide information on health maintenance (e.g., gynecologic examinations, colonoscopy, annual physical examinations, eye examinations), screening for accelerated atherogenesis, complications of medications, and osteoporosis. Emphasize the need to establish a relationship with a primary care provider who will communicate with the lupus physician.

BOX 134.2 SUN PROTECTION AND SAFE SUN HABITS

- Outdoor activities should be scheduled before 10 AM and after 4 PM.
- Up to 80% of ultraviolet (UV) rays penetrate cloud cover and can be reflected from water, concrete, sand, snow, tile, and reflective glass in buildings. Extra care is important at higher altitudes.
- Clothing is an excellent form of sun protection, especially loose-fitting, lightweight dark clothing, sunglasses, and broad-brimmed hats.
- Protective clothing blocking UV-B light with a sun protection factor of 30 or higher is commercially available online. Sunblocks should be applied 15 to 30 minutes before sun exposure and can be applied liberally. UV-A protection is also desirable. Sunscreens should not be applied to broken skin or rashes.
- UV-B sunblocks with avobenzone and zinc oxide also blocks UV-A1 rays, and titanium dioxide products are the best for very sensitive skin.
- Sunblocks are available as creams, lotions, gels, sprays, lotions, and sticks and in waterproof and heat-resistant forms, as well as in lip and eyelid formulations.

Fractures have been reported in 5% to 21% of individuals with SLE. Inflammation, use of glucocorticoids, vitamin D deficiency, renal dysfunction, ovarian failure, and hypothyroidism are the most common associations with osteoporosis in lupus patients.⁹ Bone densitometry should be performed at 1- to 2-year intervals in patients at higher risk. Preventive strategies include adequate supplementation with vitamin D and calcium and appropriate antiresorptive therapies when indicated.

A clear-cut demarcation of who is responsible for treating which aspect of the care of the lupus patient—primary care physician or lupus specialist—may be lacking. This is unfortunate, because coordination of care between these providers is critical. SLE patients are at increased risk of accelerated atherogenesis.¹⁰ They should be screened and treated for hypertension, hyperlipidemia, glucose intolerance, and atherosclerotic disease. Preventive strategies can clearly influence morbidity, mortality, and quality of life.

Local therapies

Topical corticosteroids are the most effective local treatment for cutaneous manifestations of lupus.⁶ These medications are available as fluorinated or nonfluorinated preparations and are sold in differing potencies in a variety of vehicles such as ointments, gels, creams, and lotions. Fifty years of experience have guided practitioners to the optimal following regimen: (1) non-fluorinated (over-the-counter) creams are weak but safe for long-term use, especially for facial lesions. (2) Fluorinated steroids are quite effective but should never be used on a facial lesion for longer than 2 weeks (otherwise, they will lead to cutaneous atrophy and telangiectasias). (3) Ointments are 80% absorbed, whereas creams are only 20% absorbed (but are better tolerated); most other vehicles fall in between. (4) Intralesional injections or occlusive dressings ameliorate focal areas of inflammation. (5) Ninety percent of all lupus prescriptions are written for one of three preparations: desonide (mild potency), triamcinolone (moderate potency), or clobetasol (high potency). Topical calcineurins are approved by the U.S. Food and Drug Administration (FDA) for eczema and can be applied with or without corticosteroids for cutaneous disease. These include pimecrolimus creams and tacrolimus ointments. Controlled trials have documented their modest efficacy for treatment of lupus rashes, and they are safe for long-term use in adults.¹¹ (Their use is associated with a very small increased risk of lymphoma in children.)

BOX 134.3 ACTIONS OF ANTIMALARIAL AGENTS THAT APPLY TO SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)**Physiologic effects**

Blockade of the effects of Toll-like receptors 3, 7, and 9 through alteration of pH or competitive inhibition that decreases innate immune system activation
Inhibition of phospholipase A₂ and phospholipase C
Stabilization of lysosome membranes
Decreased production of estrogen
Hypoglycemic, antihyperlipidemic, and antithrombotic actions
Ultraviolet light protection
Antiangiogenic effects
Inhibition of B-lymphocyte stimulation (BLyS, BAFF)

Clinical consequences

Hydroxychloroquine has sustained beneficial effects on overall survival, disease-free survival, and damage accrual.
Hydroxychloroquine delays the onset of SLE and reduces the number and severity of clinical flares.
Antimalarials protect against thrombosis, renal damage, and major infections in SLE.

BAFF, B-cell activating factor; BLyS, B-lymphocyte stimulator.

Nonsteroidal antiinflammatory drugs

Over 70% of lupus patients use one of the nonsteroidal antiinflammatory drug (NSAID) preparations on an intermittent or regular basis, mostly for fever, headache, myalgias, arthralgias, arthritis, and/or serositis.¹² NSAIDs can be safely prescribed to most lupus patients provided patients are closely monitored on a regular basis. NSAIDs should be used in pregnancy only occasionally and with great caution. Topical NSAIDs (diclofenac or keto-profen gel, salicylates) are safer and should be considered as a first-line treatment for local or regional inflammation. The majority of lupus patients who take NSAIDs on a frequent basis report that it improves their quality of life and diminishes pain.

Antimalarials

Antimalarials have been used to manage lupus since the 1950s, and over 300 million people have been prescribed these drugs for rheumatic disorders worldwide since that time (see Chapter 55). Ninety-five percent of all prescriptions are for hydroxychloroquine (HCQ). Chloroquine is usually reserved for refractory skin lesions, and quinacrine is given to patients who have a retinal contraindication for use of chloroquines. It is sometimes recommended for patients with profound fatigue or is used in combination with chloroquines.

Lupus-specific mechanisms of action

The mechanisms of action of the antimalarials relevant to lupus are noted on Box 134.3 and include an antagonist effect on the nucleic acid-sensing Toll-like receptors (TLRs), especially TLR3, TLR7, TLR8, and TLR9.¹³ This decreases the activation of the innate immune system via plasmacytic dendritic cells and interferon- α .

Clinical outcomes for lupus in evidence-based studies

A Canadian cooperative trial examining the use of HCQ to treat SLE in 1990 first demonstrated the agent's ability to reduce flares and decrease the risk of organ-threatening dissemination.¹⁴ Data from other cohorts documented the importance of HCQ in managing lupus, including, a sustained effects on overall survival, disease-free survival, and damage accrual.¹⁵ HCQ may even delay the onset of lupus, reduces clinical flares, and is most efficacious if used early in the disorder. Antimalarials improve survival in a time-dependent manner. The drugs are protective against thrombosis and have lipid-lowering properties, especially in patients taking corticosteroids. HCQ has beneficial effects on glycemic status and has a protective effect against renal damage and the development of major infections. There is a suggestion that it diminishes the activity of associated Sjögren syndrome and is safe in pregnancy.

Recommended community use, monitoring, and safety issues

HCQ is associated with an 80% clinical response rate at 3 months when used in doses of 5 mg/kg/day for non-organ-threatening disease.¹³ Increased

TABLE 134.1

Usual regimens of systemic glucocorticoid (GC) therapy in systemic lupus erythematosus (SLE)*

GC regimen	Representative indications	Common adverse effects (AEs)
Pulse GC (PGC)[†]		
≥250 mg PDNeq/day × 1-5 days Typically 0.5-1 g MP/day IV × 1-3 days, administered monthly as indicated; usually given with oral GC (30-60 mg PDNeq/day)	Life- or organ-threatening complications (e.g., RPGN, myelopathy, severe acute confusional state, alveolar hemorrhage, vasculitis, optic neuritis) [‡] HDGC-refractory disease DPGN or severe FPGN [§]	Same as with HDGC (see later), but overall incidence of AEs may be lower, partly because PGC may allow more rapid taper of oral GC doses. Special considerations due to large dose and route of administration: fluid overload, hypertension, neuropsychiatric symptoms. Rarely: cardiac arrhythmias or sudden death, myalgias/arthritis, seizures, intractable hiccups, GC anaphylaxis.
Very-high-dose GC (VHDGC)[†]		
>100 mg PDNeq/day IV/PO (start with divided doses)	Life- or organ-threatening complications (as for PGC) [‡]	Same as but more severe than with HDGC. Psychosis. Risk of severe or fatal infection may be particularly high (avoid use for longer than 1-2 wk).
High-dose GC (HDGC)[†]		
>30 mg and ≤100 mg PDNeq/day IV/PO	DPGN or severe FPGN (for less than 6-8 wk) [§] Thrombocytopenia, hemolytic anemia Acute lupus pneumonitis, "lupus crisis"	AEs are same for both HDGC and MDGC but incidence and severity are lower with the latter. HPA axis suppression, Cushing syndrome, hypertension, hypokalemia, hyperglycemia, hyperlipidemia, atherosclerosis, OP, ON, risk of infection, skeletal growth retardation, glaucoma, cataracts, skin fragility, acne, insomnia, steroid psychosis, mood swings, etc.
Moderate-dose GC (MDGC)[†]		
>7.5 mg and ≤30 mg PDNeq/day IV or PO	Moderate SLE flares (e.g., myositis, severe pleurisy, ophthalmoplegia [except optic neuritis], thrombocytopenia) With PGC or CYC/AZA for severe disease	AEs are same for both HDGC and MDGC but incidence and severity are lower with the latter. HPA axis suppression, Cushing syndrome, hypertension, hypokalemia, hyperglycemia, hyperlipidemia, atherosclerosis, OP, ON, risk of infection, skeletal growth retardation, glaucoma, cataracts, skin fragility, acne, insomnia, steroid psychosis, mood swings, etc.
Low-dose GC (LDGC)[†]		
≤7.5 mg PDNeq/day PO	Arthritis, mild constitutional symptoms (unresponsive to analgesics/NSAIDs/AM). Generalized lymphadenopathy Maintenance therapy	Least toxic daily regimen. Cataracts, GC withdrawal symptoms (upon tapering to or below LDGC). Skeletal growth retardation can occur. Infection rates are still increased but are lower than with higher dosages. Probably minimal OP, ON, HPA axis suppression.
Alternate-day GC (ADGC)		
	Membranous nephritis with nephrotic syndrome (120 mg PDNeq) During tapering of GC dose. Maintenance therapy (e.g., 15 mg PDNeq for glomerulonephritis)	Decreased AEs (e.g., HPA axis suppression, skeletal growth retardation, infection, Cushing syndrome) compared with daily regimens. OP can occur.

*All PDNeq dosages assume a 60-kg patient; adjustments should be made for patients of different weights.

[†]Adopted from the recommendations of the First European Workshop on Glucocorticoid Therapy.²⁰[‡]CYC therapy, usually IV, is often needed as well.[§]In combination with IV CYC.^{||}"Lupus crisis" refers to acute and severe illness with high fever, extreme prostration, and other symptoms of active SLE (e.g., pleurisy, arthritis, vasculitic rash) in patients who requires large dosages of GC for disease control and in whom infection has, of course, been excluded as the cause of the symptoms.

AM, antimetabolites; AZA, azathioprine; CYC, cyclophosphamide; DPGN, diffuse proliferative glomerulonephritis; FPGN, focal proliferative glomerulonephritis; HPA, hypothalamic-pituitary-adrenal; IV, intravenous; MP, methylprednisolone; NSAIDs, nonsteroidal antiinflammatory drugs; OP, osteoporosis; ON, osteonecrosis; PDNeq, prednisone equivalent; PO, orally; RPGN, rapidly progressive glomerulonephritis.

From Albert DA, Hodler NM, Ropes MW. Does corticosteroid therapy affect the survival of patients with systemic lupus erythematosus? *Arthritis Rheum* 1979;22:945-53.

dosing up to 7 mg/kg/day can manage flares but generally should not be prescribed for longer than 3 months. Up to 10% of patients discontinue the drug during the first few months of use due to rash, gastrointestinal effects, or constitutional complaints. Because HCQ can induce corneal edema and retinal pigmentation (the latter occurs in 3% of patients who have used the drug for 10 years or longer), the American Academy of Ophthalmology recommends that baseline screening should be performed during the first few months of therapy and again at 5 years followed by annual examinations.¹⁶ Chloroquine is usually given at a dosage of 500 mg daily for the first 1 to 2 months, after which treatment is transitioned to HCQ or dosing is gradually tapered to 250 mg as 1 to 2 tablets a week. Chloroquine is much stronger and more toxic than HCQ. Quinacrine is available from compounding pharmacies and is started at 25 to 100 mg daily. The potential for gastrointestinal adverse effects, lichen planus-like rashes, and bone marrow suppression warrant vigilance, with blood testing every 1 to 2 months.

Corticosteroids

Several large studies in the 1950s documented life-saving beneficial effects of corticosteroids in treating a variety of complications of lupus. Since that time, although several large surveys have demonstrated efficacy for renal and central nervous system (CNS) lupus, very few studies have specifically evaluated the use of these drugs for other manifestations of the disorder. Their short-term effects are dramatic, but in the long term they play a role in worsening morbidity and mortality from lupus. For organ-threatening disease, corticosteroids are often prescribed in combination with immunosuppressive steroid-sparing regimens.¹⁷

Lupus patients are prescribed corticosteroids for their antiinflammatory and immunosuppressive effects.¹⁸

Clinical use and experience

Seriously ill patients are administered pulse steroids (1 g daily of intravenous methylprednisolone for several days), a regimen that has additional

pharmacologic effects^{17,18} (Table 134.1). Individuals with stable lupus can be prescribed alternate-day dosing as maintenance, which diminishes immunosuppression and infection risk and is less inhibitory of adrenal responsiveness. Intramuscular steroids include triamcinolone, methylprednisolone, dexamethasone, or betamethasone; effects lasts several weeks to months and can ameliorate constitutional and musculoskeletal flares. Some of these preparations can also be used intraarticularly. Dexamethasone has a theoretical advantage in managing CNS disease because it more readily crosses the blood-brain barrier. The most commonly used oral preparation is prednisone, which is given once daily but can also be dosed every 8 to 12 hours in acutely ill patients, in whom it is metabolized more rapidly. Prednisolone is very similar and may be preferred in children with maturing hepatic function. Intravenous hydrocortisone is efficacious in 15 to 20 minutes (as opposed to 2 hours for intravenous methylprednisolone) but the duration of action is only 4 to 6 hours.

In large lupus cohorts, 80% to 90% have received one of these agents during the course of their disease. Larger studies and a meta-analysis of 52 reports published through the 1960s demonstrated that steroids improved survival but actually did not significantly alter outcome in patients with mild to moderate disease.¹⁹ In a randomized, prospective, double-blind, placebo-controlled flare prevention study, short-term corticosteroid therapy prevented severe flares in 154 SLE patients who were evaluated monthly for 18 months.²⁰ In another cohort, low-dose daily prednisone was not associated with a substantially increased risk of irreversible organ damage.²¹

High-dose daily corticosteroids are efficacious for life- or organ-threatening autoimmune hemolytic anemia, immune thrombocytopenia purpura, bone marrow hypoplasia, acute myocarditis, acute lupus pneumonitis, mesenteric vasculitis, autoimmune pancreatitis, optic neuritis, and retinal vasculitis associated with severe, active SLE. Treatment is usually prescribed at a dose of 1 mg/kg/day of prednisone equivalent for 2 to 4 weeks. A dramatic response is often followed by a slow tapering of approximately 10% per week. If the manifestation is refractory to treatment or if tapering to 10 mg/day of prednisone equivalent cannot be achieved, steroid-sparing immunosuppressive regimens of targeted therapies can be added.

A few non-CNS or nonrenal manifestations of lupus warrant consideration of **pulse corticosteroids** as induction therapy followed by high-dose daily corticosteroids, including any of the aforementioned complications as well as thrombotic thrombocytopenic purpura, Stevens-Johnson syndrome-like skin reactions, severe acute cutaneous disease, or alveolar hemorrhage.

Moderate-dose daily corticosteroids (considered to be 0.25 to 0.5 mg/kg/day of prednisone equivalent) may be given for 2 to 4 weeks followed by tapering for treatment of acute pleurisy or pericarditis, flares of thrombocytopenia, active rashes, or lupus myositis, among other manifestations.

Low-dose daily corticosteroids (less than 10 mg of prednisone equivalent daily) are the mainstay for persistent, chronic, active disease, especially with musculoskeletal, constitutional (fatigue, fever, adenopathy), cutaneous, and serous membrane manifestations or combinations of these.

Complications and monitoring

Long-term steroid use is associated with cutaneous atrophy (from topical fluorinated steroids), ecchymosis, capillary fragility, avascular necrosis, hyperglycemia, increased susceptibility to infection, hyperlipidemia, hypertension, pancreatitis, osteoporosis, cataracts, glaucoma, double vision, alterations in mood and behavior, peptic ulcer disease, fluid retention, weight gain, and many other toxicities.²² Long-term steroid use also is associated with accelerated atherogenesis.

Immunosuppressive therapies

Immunosuppressive agents used for the treatment of nonrenal, non-CNS lupus erythematosus are reviewed here. Cyclophosphamide, methotrexate, azathioprine, and mycophenolate mofetil account for 95% of all prescriptions of immunosuppressive drugs used in SLE, and up to 40% of all lupus patients take one of these agents at some point in their disease. These drugs are rarely used as monotherapy but are almost always given in combination with NSAIDs, antimalarials, and corticosteroids.

Alkylating agents: cyclophosphamide, chlorambucil, nitrogen mustard

Alkylating agents have been used to manage lupus since nitrogen mustard was reported to be beneficial for cutaneous disease in 1947.²³ In view of the toxicity of nitrogen mustard and chlorambucil, neither of these agents has any place in the management of lupus. Cyclophosphamide (CYC) is a

BOX 134.4 STEROID-SPARING REGIMENS USEFUL IN TREATING NONRENAL, NON-CENTRAL NERVOUS SYSTEM COMPLICATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Cyclophosphamide

- Alveolitis
- Hematologic complications: hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura
- Optic neuritis
- Generalized systemic vasculitis

Azathioprine

- Inflammatory arthritis
- Severe cutaneous disease
- Autoimmune hemolytic anemia and thrombocytopenia
- Lupoid hepatitis
- Generalized active lupus

Mycophenolate mofetil

- Lupus pemphigoid, lichen planus-associated lupus
- Alveolitis
- Autoimmune hemolytic anemia and thrombocytopenia
- Generalized active lupus

Methotrexate

- Inflammatory arthritis
- Cutaneous lupus
- Generalized active lupus

Leflunomide

- Inflammatory arthritis

Cyclosporine

- Inflammatory arthritis
- Aplastic/hypoplastic anemia, bone marrow failure
- Oral ulcerations, cutaneous lupus

Apheresis

- Hematologic complications: thrombotic thrombocytopenic purpura, hyperviscosity syndrome, cryoglobulinemia
- Alveolar hemorrhage

Belimumab

- Active generalized disease despite treatment with steroids and immunosuppressive drugs

Rituximab

- Hematologic complications: autoimmune hemolytic anemia, thrombocytopenia
- Inflammatory arthritis

Anti-tumor necrosis factor therapies

- Inflammatory arthritis

Abatacept

- Inflammatory arthritis

nitrogen mustard alkylating agent that has been available since the early 1960s. A prodrug, it is converted by mixed-function oxidase enzymes in the liver to active metabolites. Twenty percent of CYC is excreted by the kidney and 80% is processed in the liver. In SLE, CYC works via direct functional effects on lymphocytes, producing a dose-related lymphopenia, T- and B-cell depletion, and alterations of macrophage function and gene transcription resulting in decreased pathogenic autoantibody production.²⁴ CYC is usually given intravenously at low dosages (Eurolypus regimen, or 500 mg every 2 weeks for six cycles), high dosages (National Institutes of Health regimen, 750 mg/m² monthly for 6 months with an option of every 2 to 3 months for 2 to 3 years), or ablative dosages (e.g., 50 mg/kg/day for 4 days for stem cell transplantation induction).^{25,26} It can also be prescribed orally (especially for vasculitis) in dosages ranging from 25 to 100 mg daily. CYC is the most potent immunosuppressive agent used in SLE and can be employed as monotherapy or prescribed in combination with corticosteroids and other immunosuppressive agents.

Almost every study using a lupus protocol containing CYC has limited its enrollment to patients with CNS or renal involvement. Several reports examining the use of CYC for treatment of “severe connective tissue disease crisis” in 90 patients in London (most of whom had lupus) documented a trend toward dramatic improvement.²⁷ Case series have suggested efficacy for patients with acute life- or organ-threatening complications of lupus such as alveolar hemorrhage, autoimmune hemolytic anemia and thrombocytopenia, optic neuritis, thrombotic thrombocytopenic purpura, and mesenteric vasculitis. Ablative regimens are too toxic to be recommended. Rarely, low-dose daily oral CYC has a place in treating selected refractory cases of inflammatory arthritis or vasculitis (Box 134.4).

The use of antiemetics such as ondansetron, adequate hydration, and the addition of 2-mercaptoethane (mesna) allow CYC to be better tolerated and safer when administered to patients with SLE. There is evidence that the monthly administration of leuprolide acetate (3.75 mg subcutaneously) 2 weeks before a dose of CYC decreases the incidence of premature ovarian failure.²⁸ Infection risks correlate directly with white count nadirs of less than 3000 cells/mm³. Long-term use is associated with a greater risk of malignancy, especially bladder cancer and gynecologic dysplasias.

Azathioprine

Azathioprine (AZA) is a purine synthesis inhibitor converted in the body to the active metabolites 6-mercaptopurine and 6-thioinosinic acid. It reduces numbers of circulating B and T lymphocytes, immunoglobulin synthesis, and CD28-mediated costimulation.²⁹ The majority of prescriptions written for AZA in SLE patients are for treatment of nephritis. Its nonrenal indications include inflammatory arthritis, severe cutaneous disease, pneumonitis, hepatitis, protein-losing gastroenteropathy, autoimmune hemolytic anemia, and thrombocytopenia. AZA is not very effective as induction monotherapy, but in combination with corticosteroids, the agent is steroid sparing and decreases flare rates. It is commonly prescribed in combination with other immunosuppressive regimens and targeted therapies.^{30,31}

Dosing is usually initiated at 50 mg daily orally for the first week and built up to 150 mg daily, or about 3 mg/kg/day, over several weeks. Approximately 10% of patients are unable to tolerate the drug due to deficiency of the enzyme thiopurine methyltransferase (TPMT) and experience nausea, bone marrow toxicity, rash, or fever.³² Measurement of TPMT activity before initiation of therapy may identify patients at greatest risk of bone marrow suppression (i.e., those homozygous for the deficiency). If this test is not available, then starting at a low dose and building up slowly with frequent complete blood count monitoring is usually a satisfactory means of safely administering the drug. AZA is associated with an increased risk of skin cancer, human papillomavirus-induced cancers, and, after 10 to 20 years of continuous use, lymphoma.³³ Although it is classified as a pregnancy category D drug, AZA has a well-established safety record as an option for lupus patients who wish to conceive.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid that inhibits inosine-5'-monophosphate dehydrogenase. By preferentially depleting guanosine nucleotides in T and B-lymphocytes, it inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation.³⁴

The use of MMF for treatment of SLE has been studied since 1990, but no controlled trials were conducted until after 2000. Lupus nephritis is the principal indication for MMF and is the reason for treatment in a large majority of patients taking the drug. Dosages range from 500 mg/day in transplant patients to 3 g/day with those with active nephritis, but most patients are prescribed 1500 to 2000 mg/day in divided doses. A small number of studies have evaluated the use of MMF for nonrenal and non-nervous system manifestations. It has a rapid onset of action compared with other immunosuppressives in that effects can be observed in 2 to 4 weeks. The author's group reviewed results in 75 patients given MMF for any indication and demonstrated a more than 50% improvement in composite British Isles Lupus Assessment Group (BILAG) scores in half of the patients. It might be steroid sparing as well.³⁵ Although MMF is prescribed for pemphigoid and lichen planus lesions by dermatologists, it appears to be ineffective for chronic cutaneous lupus. There is limited evidence that it has some efficacy for hematologic or pulmonary involvement in SLE.³⁶ Gastrointestinal adverse effects or intolerance has been reported in 10% to 30% of lupus patients given MMF. The author recommends that MMF be considered after methotrexate or AZA for nonrenal, non-CNS lupus.

Methotrexate

Few evidence-based studies of the use of methotrexate (MTX) in SLE have been conducted, and only two enrolled more than 40 subjects. A double-blind, prospective, randomized, controlled trial involving 41 patients concluded that 15 to 20 mg of MTX weekly for 6 months was significantly effective in controlling cutaneous and articular activity of SLE as measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores and was steroid sparing.³⁷ In a 12-month, double-blind, placebo-controlled trial of MTX involving 86 patients, the agent was steroid sparing (22% reduction in dose), slowed damage scores, and reduced disease activity as measured by the revised Systemic Lupus Activity Measure (SLAM) score.³⁸ MTX is most effective for articular, cutaneous, serosal, and constitutional

manifestations of SLE.³⁹ Dosages of 10 to 25 mg weekly are recommended, but if renal impairment is present, dosing at levels of 10 mg a week or less is advised.

Leflunomide

Leflunomide was found to be significantly more effective than placebo in treating mild to moderate lupus, especially lupus with arthritis, based on SLEDAI scores.⁴⁰ Leflunomide has been used in Asia for treatment of nephritis, but there is no experience with its use for this indication in North America or Europe.

Cyclosporine

In lupus studies cyclosporine has been found to have a definite niche use for specific complications that do not respond to other treatments: cytopenias (especially bone marrow aplasias), oral ulcerations, eczema-like lesions, urticaria, and nephritis.⁴¹ A randomized, controlled trial involving 89 patients with severe SLE demonstrated that cyclosporine was as effective a steroid-sparing agent as AZA.³¹ The author usually prescribes 100 mg twice daily and finds that cyclosporine can clear skin lesions within days.

Niche therapies and specialized approaches

Approximately 10% of patients with nonrenal, non-nervous system SLE may benefit from treatments outside of the usual NSAID, antimalarial, corticosteroid, and routine immunosuppressive regimens at some time in the course of their disease.⁴²

Antileprosy drugs

Dapsone inhibits folic acid and para-aminobenzoic acid, blocks the alternate pathway of complement activation, promotes neutrophil cytotoxicity, and is a mild anti-tumor necrosis factor (anti-TNF) agent. It has been used in selected cases of cutaneous vasculitis, bullous lupus, urticaria, oral ulcerations, lupus panniculitis, and subacute cutaneous lupus.⁴³ Thalidomide and lenalidomide have similar actions, are teratogens, and improve refractory cutaneous disease but may have an unacceptable risk-benefit profile because of associated neuropathy and procoagulant action.⁴⁴

Other immune-modulating and immunosuppressive agents

Tacrolimus is used primarily for treatment of nephritis, and its topical forms improve cutaneous lupus. Rapamycin is an anti-transplant rejection agent that is under study in a phase 2 trial for treatment of SLE. Mizoribine is a purine antagonist similar to AZA used widely in Japan. Fludarabine, cytarabine, and cladribine are antineoplastic agents that are too toxic for use in lupus patients. Antilymphocyte and antithymocyte globulin is used in lupus patients as part of stem cell protocols. Retinoids (e.g., acitretin) can be helpful for subacute cutaneous lupus and refractory skin lesions but are sun sensitizing.⁴⁵ Intravenous immune globulin is used to treat nearly every complication of the disease, and studies suggest that this very expensive intervention is beneficial for thrombocytopenia, immunoglobulin G subclass deficiency, and chronic inflammatory demyelinating polyneuropathy.⁴⁶

Hormonal interventions

Dehydroepiandrosterone (DHEA) has modest effects on disease activity and is available over the counter, but its application for approval in the treatment of SLE was rejected by the FDA.⁴⁷ Little if any benefit is seen for the prolactin-blocking agent bromocriptine.⁴⁸ The impeded androgen danazol is prescribed in rare cases for the treatment of autoimmune hemolytic anemia or thrombocytopenia. A controlled trial of testosterone failed to meet its primary endpoint.⁴⁹

External procedures used to achieve a medical effect

Plasmapheresis (including plasma exchange) is used in SLE for thrombotic thrombocytopenic purpura, cryoglobulinemia, neuromyelitis optica, pulmonary hemorrhage, and hyperviscosity syndrome.^{50,51} It has relative short-term benefits for severe, organ-threatening disease in patients unresponsive to high-dose steroids and immunosuppressives.

Laser therapy is occasionally used for telangiectasias and refractory discoid lesions. Photopheresis is occasionally used for refractory skin manifestations. Cold UVA light in the 340 to 400 nm spectrum has antiinflammatory effects and is prescribed in infrequent cases. Total lymphoid irradiation is effective but is far too toxic for SLE patients, and lymphocytapheresis is generally ineffective.

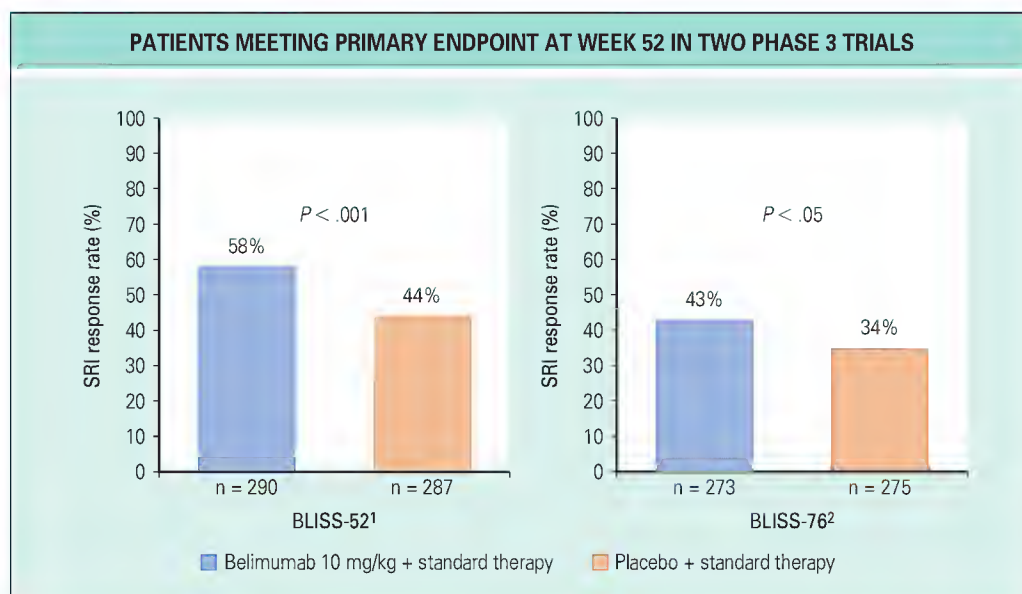


Fig. 134.1 Summary of results of the BLISS-52 and BLISS-76 phase 3 studies of belimumab for treatment of systemic lupus erythematosus. Figure shows percentage of patients demonstrating improvement at week 52 as judged by the Systemic Lupus Erythematosus Responder Index (SRI). (Adapted from Navarra SV, Guzman RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomized, placebo-controlled, phase 3 trial. *Lancet* 2011;377:721-31; Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918-30.)

Targeted therapies

Approved in March 2011, belimumab is the only targeted therapy approved by the FDA for treatment of lupus. It is indicated for autoantibody-positive disease with ongoing activity. A human monoclonal antibody to soluble (not membrane-bound) B-lymphocyte stimulator, belimumab was studied in phase 2 and 3 trials with over 2000 participants.⁵²⁻⁵⁴ It produced significant improvements as measured by an instrument known as the *Systemic Lupus Erythematosus Responder Index*, which included a four-point reduction in SLEDAI score, no real organ domain involvement (one BILAG A score or two BILAG B scores), and no more than a 10% reduction in physician global assessment (Fig. 134.1). Approximately 70% of patients receiving the drug respond in 3 to 6 months after being given monthly doses of 10 mg/kg administered over 1 hour, preceded by three infusions over a month as a loading dose. Belimumab appears to be steroid and immunosuppressive sparing and has an excellent safety profile. The author prescribes it for patients who have active disease despite treatment or are intolerant of corticosteroids and immunosuppressive regimens.

Other targeted therapies on the market but not approved for treatment of SLE include abatacept, rituximab, anti-TNF therapies, and anakinra. Abatacept did not meet its primary endpoint in an industry-sponsored nephritis and nonnephritis trial. The Immune Tolerance Network of the National Institutes of Health is conducting an ongoing study, and its post-hoc analysis of data from the industry-sponsored trial suggested that abatacept is beneficial.^{55,56} The anti-CD20 chimeric monoclonal antibody rituximab failed to meet its primary endpoints in both nephritis and non-nephritis trials.^{57,58} However, both studies mandated that the placebo and rituximab arms of the protocol include the administration of highly effective therapies: high-dose corticosteroids and immunosuppressives. Both groups improved, and the underpowered study and its open-label follow-up were discontinued prematurely. There is evidence from cohort studies and case series that selected patients with lupus arthritis, hemolytic anemia, and thrombocytopenia respond to this agent, and it has demonstrated efficacy when added to traditional steroid and immunosuppressive regimens. The use of anti-TNF therapies or anakinra in SLE is poorly studied, but these agents do not appear to be of any significant benefit.

A variety of innovative targeted therapy approaches are currently under study (Table 134.2).⁵⁹ Stem cell therapies should be considered only in patients with life-threatening complications of SLE for whom all other appropriate interventions have failed.

TREATMENT OF LUPUS ERYTHEMATOSUS WITH MEDICATION

General principles

Lupus runs the gamut from disease requiring no specific antiinflammatory treatment to life- and organ-threatening manifestations for which intensive therapeutic protocols are indicated. If organ involvement is present (e.g., cardiopulmonary, renal, hepatic, or CNS involvement, cytopenias), patients are usually managed with high-dose corticosteroids and immunosuppressive

TABLE 134.2

Targeted therapies in systemic lupus erythematosus

Mechanism of action	Examples of targets
T cells	CTLA4-Ig; modified CD40L mAb; ICOS; expansion of CD4+CD25+ cells, CD8+CD28- cells
B cells	mAbs to CD20, CD22, proteasome/plasma cells; anti-BlyS, TACI-Ig, BAFF-RFc
Complement	Anti-C5a
Cytokines	mAbs to sIL-6R, IL-6, IL-10, IL-17, IL-18, anti-TNFs
Innate immune system	Anti-IFN- α and IFN- γ ; blockade of TLR7 and/or TLR9
Toleragens	Peptides derived from nucleosomes, Sm Ag, Igs, 16/6 idiotype, spliceosome
Inhibition of cell surface receptor activation	Syk-kinase inhibition; sirolimus

BAFF-RFc, B cell activating factor-rasette-forming cells; BlyS, B-lymphocyte stimulator; ICOS, inducible costimulatory; IFN, interferon; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; sIL, soluble interleukin; Sm Ag, Smith antigen; TACI, transmembrane activator and calcium republishing initiator; TLR, Toll-like receptor; TNF, tumor necrosis factor.

Adapted and updated from Wallace DJ. Advances in drug therapy for systemic lupus erythematosus. *BMC Med* 2010;8:77.

agents. Failure to use corticosteroids in this situation often results in significant organ damage. Non-organ-threatening involvement is approached with nonsteroidal drugs, antimalarial agents, and, if necessary, low-dose corticosteroids and immunosuppressive drugs. Lupus is a multisystem disease, and the treatment is usually more inclusive than, for example, just managing a rash, because a patient with a rash may also have fatigue, aching, or fevers.

Constitutional manifestations

The presence of fatigue, fever, weight loss, or malaise resulting from active inflammatory SLE, and no other factors such as infection or anemia, warrants a trial of a moderate-dose (0.5 mg/kg/day) prednisone equivalent for several weeks.

Cutaneous and cutaneous disease

Acute cutaneous lupus erythematosus represents active systemic disease and is nonscarring and transient. It is managed in the short term with moderate-dose corticosteroids.⁶⁰ Chronic cutaneous lupus erythematosus (discoid lupus) necessitates use of the sun protection measures and topical therapies discussed earlier in the chapter.⁶¹ The medications characteristically used for treatment are the antimalarial drugs. HCQ is the agent of choice, followed by quinacrine if chloroquines are contraindicated (e.g., in cases of retinal

disease) or if severe fatigue is present. Chloroquine can be used short term for treatment of severe rashes, after which patients are usually transitioned to treatment with HCQ. Subacute cutaneous lupus erythematosus responds to the aforementioned measures but can be more resistant to antimalarial agents and amenable to the addition of retinoids.⁶² Lupus profundus and bullous lupus respond to MMF or dapsone in addition to antimalarials.

Generalized cutaneous manifestations of lupus include oral ulcerations, malar rashes, alopecia, and urticaria. Specific interventions for these signs include treatment with cyclosporine (especially for urticaria) or triamcinolone in a dental gel for oral ulcerations, along with buttermilk or hydrogen peroxide gargles for oral ulcerations. The author prescribes nonfluorinated steroids, a short course of fluorinated steroids, tacrolimus, or pimecrolimus for the butterfly rash of lupus. Hair loss is common and frustrating and is often the last manifestation to improve after a flare. Intralesional steroid injections, cysteine-based shampoos, and minoxidil-based hair products are among numerous adjunctive therapies.

Cutaneous manifestations of SLE include Raynaud syndrome, chilblain, cutaneous vasculitis, and livedo reticularis.⁶³ The latter generally is not treated. Vasomotor instability in lupus is approached with cold-preventive measures, biofeedback, and cognitive-behavioral therapy. Calcium channel blockers (especially nifedipine), 5-phosphodiesterase blockers (e.g., sildenafil) for mild to moderate activity, and the addition of prostaglandins, bosentan, or antiinflammatory agents for digital vasculitis or gangrene can be beneficial. Sometimes chilblain responds to aspirin in addition to the aforementioned measures.

Musculoskeletal lupus

NSAIDs, antimalarial drugs, and corticosteroids all improve the synovitis and inflammatory arthritis seen in SLE.⁶⁴ The choice of therapy depends on the area of involvement, duration and severity of symptoms, and amount and degree of disease activity outside of the musculoskeletal system. When necessary, MTX, leflunomide, AZA, or anti-TNF regimens (but not MMF) also can be ameliorative. Five percent to 10% of patients with SLE have a mild myositis (creatinine phosphokinase levels of less than 1000), which responds to several weeks of 0.5 mg/kg/day of prednisone equivalent or less.

Cardiopulmonary disease

Serositis (pericarditis, pleurisy) responds immediately to NSAIDs and corticosteroids. Antimalarial agents improve it over weeks to months.⁶⁵ Acute lupus pneumonitis and pulmonary hemorrhage are life-threatening complications and require high-dose corticosteroids with or without CYC or apheresis.⁶⁵ Interstitial lung disease is a chronic process that takes years to evolve and is most often seen in overlap syndromes and associated Sjögren syndrome. It is managed with corticosteroids and immunosuppressives. Assessment for pulmonary hypertension should be part of baseline screening in most patients with lupus. Present in 2% to 5% of lupus patients, this serious complication is managed with vasodilator therapy, anticoagulation, and endothelial cell activation antagonists, but antiinflammatory regimens can lower pressures as well. Pulmonary embolism should be considered in any lupus patient with an acute onset of chest pain and shortness of breath and warrants anticoagulant therapy.

Outside of the pericardium, myocarditis and endocarditis are infrequently observed manifestations of lupus.⁶⁶ Most myocarditis is viral in origin (even in lupus patients), but lupus myocarditis warrants a short trial of high-dose corticosteroids. Myocardial dysfunction and microvascular angina are far more common than previously thought and are treated with β -blockers and nitrates. Coronary arteritis is very rare and responds to short courses of high-dose corticosteroids. Libman-Sacks endocarditis warrants further evaluation to rule out a superimposed bacterial endocarditis or immune complex vegetation, which might embolize. Blood-thinning and antimicrobial measures may be instituted.

Hematologic disorders

Anemias are common in lupus, especially in young women with heavy periods. Replacement regimens improve iron deficiency and vitamin B₁₂ deficiency.⁶⁷ Decreased bone marrow activity is representative of lupus-associated anemia of chronic disease and responds to disease-modifying therapies. Autoimmune hemolytic anemia is a serious complication of SLE and warrants high-dose corticosteroids along with immunosuppressive agents and/or targeted therapies (e.g., rituximab).⁶⁷ Leukopenias represent active inflammation and are also a complication of immunosuppressive regimens. Qualitative platelet dysfunction may occur, for which there is no optimal therapy; idiopathic thrombocytopenic purpura is managed with corticosteroids, immunosuppressive therapies, intravenous immune globulin, rituximab, and/or splenectomy. Thrombotic thrombocytopenic purpura is a life-threatening complication of lupus and the cause of death in 1% to 5% of cases; it is treatable with apheresis, steroids, and rituximab.⁶⁸

Miscellaneous nonrenal, non-nervous system complications

Rare but serious manifestations of SLE include retinal vasculitis, mesenteric vasculitis, and pancreatitis, which are treated with high-dose corticosteroids and immunosuppressive regimens once thromboembolic and drug causes are ruled out.

SUMMARY

Lupus is a pleomorphic disorder. When a patient comes for treatment of recent-onset disease, the first step is to stage the disease and assess what areas are involved. Once this is accomplished, a single physician should ideally oversee management of the disease in concert with a treatment team. Nonmedication interventions such as providing patient education, working with the mind-body connection, screening for comorbidities, and initiating prevention measures (e.g., sun avoidance) have been shown to improve prognosis. Non-organ-threatening disease is additionally managed with NSAIDs, antimalarial drugs, low-dose corticosteroids, and infrequently immunosuppressive or targeted therapy regimens. Severe lupus usually mandates an induction course of high-dose corticosteroids and the addition of immunosuppressives and consideration of targeted therapies. The prognosis of SLE has improved greatly over the last few decades as more treating physicians have adopted a multidisciplinary treatment approach.

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135 Treatment of neuropsychiatric lupus

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- In patients with systemic lupus erythematosus (SLE), nervous system events are diverse, are common, and negatively impact health-related quality of life.
- Approximately one third of neuropsychiatric events in SLE patients are attributable to lupus.
- Diagnostic tests, including neuroimaging and assessment of cognitive function, are used to support the findings on clinical evaluation.
- Therapeutic intervention must be tailored to individual patients' needs and includes symptomatic and supportive therapies in addition to lupus-related immunosuppression and anticoagulation.
- Defined immunopathogenic mechanisms help to inform the selection of specific treatment strategies.

INTRODUCTION

The reported prevalence of neuropsychiatric (NP) disease in systemic lupus erythematosus (SLE) is highly variable (21% to 95%),¹ as is the prognosis following an NP event. This may reflect differences in study methodology, bias in the selection of patients, or a change over time in global disease severity. Many classifications of NP events in SLE lack definitions of individual manifestations as well as standardized methods for investigation and diagnosis. In 1999 the American College of Rheumatology (ACR) produced a standard nomenclature and case definitions for 19 NP syndromes² that are known to occur in SLE patients. These can be segregated into central and peripheral NP syndromes or studied individually (Table 135.1). For each of these NP syndromes potential causes other than SLE were identified, either for exclusion or as an "association." This component of the ACR classification, in combination with other variables, provides a framework for determining the attribution of NP events.

CAUSES OF NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

NP events attributed to SLE (NPSLE) are primary manifestations of the disease, in contrast to complications of the disease (e.g., hypertension) or of its treatment (e.g., infection) (Fig. 135.1). Recent studies suggest that all nervous system events, regardless of cause, have a significant negative impact on health-related quality of life and that up to one third of NP events in SLE patients are attributable to SLE.¹ NP events due to lupus are likely a consequence of *vascular abnormalities*, *autoantibodies*, and *inflammatory mediators*.¹ Evidence from animal and human studies suggests two separate and potentially complimentary autoimmune pathogenic mechanisms for NPSLE (Fig. 135.2): (1) *vascular injury* involving large- and small-caliber vessels mediated by antiphospholipid antibodies, immune complexes, and leukoagglutination; clinical sequelae include focal NP events such as stroke and diffuse NP events such as cognitive dysfunction; (2) *inflammation-mediated injury* with increased permeability of the blood-brain barrier, intrathecal formation of immune complexes, and production of interferon- α and other inflammatory mediators; clinical sequelae include diffuse NP manifestations such as psychosis and acute confusional states.

SELECTED CLINICAL MANIFESTATIONS OF NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

Headache

The association between SLE and headache, including migraine, is controversial, with wide variation in the reported prevalence (24% to 72%) in SLE¹ and a high prevalence in the general population (e.g., up to 40% of individuals report having a severe headache at least once per year³). Some investigations, including a meta-analysis of the multiple studies on the issue, found no increase in the prevalence of headache in SLE.⁴ Only one study⁵ reported an association between headache and other clinical features of active lupus. Other potential causes are infection, including aseptic meningitis, and idiosyncratic reactions to medications such as antibiotics and nonsteroidal anti-inflammatory drugs. Thus, although headache may be a component of generalized active SLE in individual patients, it is likely that most headaches in SLE patients, especially those that occur in isolation, are due to non-SLE causes.

Psychosis, mood disorders, and anxiety

Psychosis occurs in up to 8% of SLE patients¹ and is characterized by delusions (false beliefs despite evidence to the contrary) and/or hallucinations (perceptual experiences, typically auditory, that occur in the absence of external stimuli). This rare but dramatic manifestation of NPSLE must be distinguished from psychotic symptoms due to other causes, including high doses of corticosteroids, nonprescription drug abuse, schizophrenia, and depression. In contrast, depression and anxiety occur in 24% to 57% of SLE patients¹ but have no features that are unique to SLE, which leads to uncertainty about the cause and attribution in individual cases. Associations between the presence of anti-P protein antibodies and psychosis or depression in SLE are supported by some but not all studies.^{6,7}

Cerebrovascular disease

The many forms of cerebrovascular disease occur in 5% to 18% of SLE patients,¹ and the cause is likely multifactorial. Coronary heart disease is 5 to 10 times more frequent in SLE patients than in control populations even after adjustment for traditional cardiovascular risk factors.⁸ Accelerated atherosclerosis also contributes to the increased rate of cerebrovascular events in SLE. The prothrombotic state caused by antiphospholipid antibodies provides a rationale for therapeutic intervention with anticoagulants in selected cases.

Seizures

Generalized and focal seizures occur in 6% to 51%¹ of SLE patients. These may occur with active generalized multisystem lupus or as isolated neurologic events and sometimes in association with antiphospholipid antibodies, which co-occur with microangiopathy, arterial thrombosis, and cerebral infarction.

Demyelination, transverse myelopathy, and chorea

Demyelination, transverse myelopathy, and chorea are rare manifestations of SLE that occur in no more than 1% to 3% of patients.¹ Clinical and neuroimaging evidence of demyelination is frequently indistinguishable from signs of multiple sclerosis and may represent concordance of these two

TABLE 135.1

Neuropsychiatric syndromes in systemic lupus erythematosus as defined using the American College of Rheumatology nomenclature

Central nervous system	Peripheral nervous system
Aseptic meningitis	Guillain-Barré syndrome
Cerebrovascular disease	Autonomic neuropathy
Demyelinating syndrome	Mononeuropathy
Headache	Myasthenia gravis
Movement disorder	Cranial neuropathy
Myelopathy	Plexopathy
Seizure disorder	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

From The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599-608.

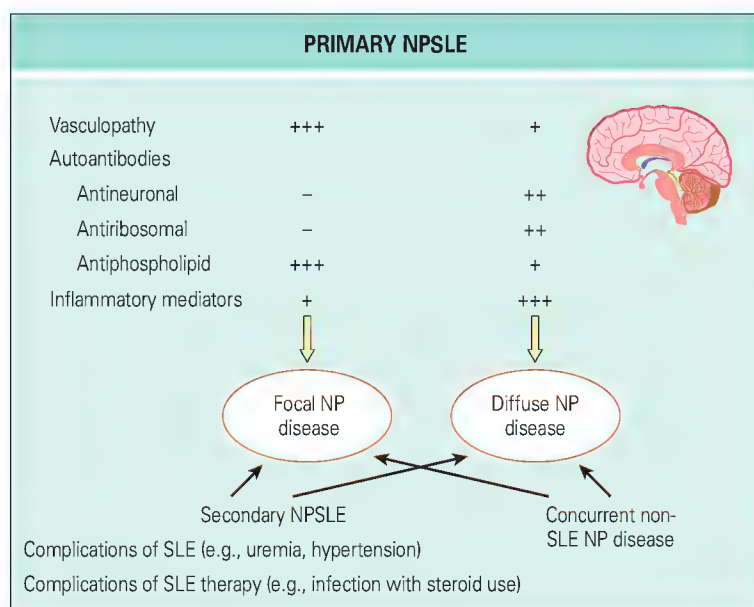


Fig. 135.1 Factors contributing to neuropsychiatric (NP) events in patients with systemic lupus erythematosus (SLE). Focal and diffuse nervous system events may result from direct autoimmune/inflammatory mechanisms related to SLE (primary NPSLE), as a consequence of complications of the disease (e.g., hypertension) or its treatment (e.g., infection) (secondary NPSLE), or as a concurrent non-SLE-related NP event. (Adapted from Hanly JG. *Neuropsychiatric lupus*. *Curr Rheumatol Rep* 2001;3:205-12.)

autoimmune conditions. Transverse myelopathy and chorea⁹ present acutely and are frequently associated with the presence of autoantibodies. Neuro-myelitis optica, also known as *Devic's disease*, is a severe demyelinating disorder that causes longitudinal transverse myelitis of at least three vertebral segments and recurrent optic neuritis. Devic's disease has been reported in patients with SLE and is associated with neuromyelitis optica autoantibodies whose antigenic target is aquaporin-4. Arterial thrombosis due to antiphospholipid antibodies is likely another contributory mechanism in transverse myelopathy. The cause of chorea is less clear, but it may be a consequence of a direct interaction of antiphospholipid antibodies with neuronal structures in the basal ganglia.

Neuropathy and myasthenia gravis

Sensorimotor neuropathy is the most common neuropathy and has been reported in up to 28%¹ of SLE patients, frequently occurring independent of other disease characteristics. These abnormalities are persistent but are

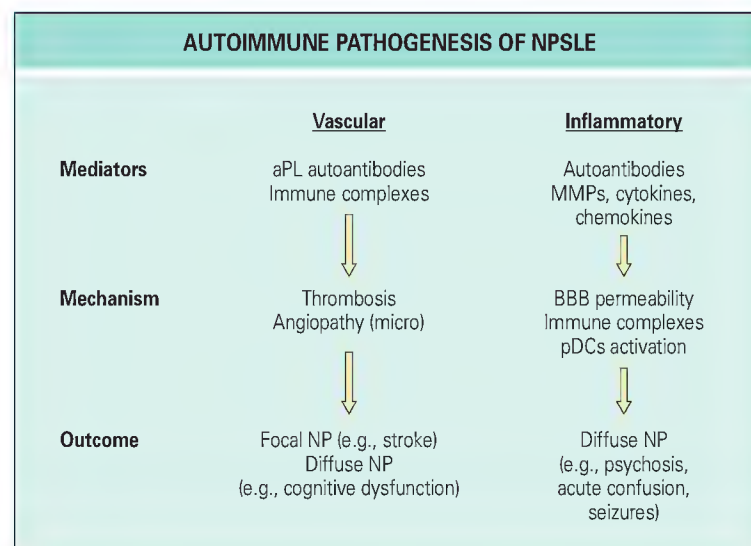


Fig. 135.2 Autoimmune pathogenic mechanisms for neuropsychiatric events attributed to systemic lupus erythematosus (NPSLE). These mechanisms include (1) vascular injury involving both large- and small-caliber vessels mediated by antiphospholipid antibodies (aPL), immune complexes, and leukoagglutination; this results in focal NP events such as stroke and in diffuse NP events such as cognitive dysfunction; (2) injury due to inflammation in which increased permeability of the blood-brain barrier (BBB), formation of immune complexes, and production of interferon- α and other inflammatory mediators leads to diffuse NP manifestations such as psychosis and acute confusional states. MMPs, matrix metalloproteinases; NP, neuropsychiatric; pDCs, plasmacytoid dendritic cells; SLE, systemic lupus erythematosus.

often stable over several years.¹⁰ Other less frequent forms of neuropathy include cranial neuropathy, autonomic neuropathy, plexopathy, mononeuritis multiplex and Guillain-Barré syndrome. Myasthenia gravis has been reported only rarely.

Acute confusional state

The term *acute confusional state* has replaced *organic brain syndrome* and is synonymous with *encephalopathy* and *delirium*. It encompasses a state of impaired consciousness or level of arousal that can progress to coma. Characteristics include fluctuation in arousal or attention, disturbed mood, and impaired cognition. It has been reported in 4% to 7% of SLE patients,¹ and other disorders such as metabolic abnormalities and hypertensive encephalopathy should be considered as potential alternative causes.

Cognitive dysfunction

Cognition includes reception of external stimuli, information processing, learning, storage, and expression. Disturbance in any of these can result in disruption of normal thought and present as cognitive dysfunction. Clinically overt NPSLE events such as stroke are associated with cognitive dysfunction, as is the presence of antiphospholipid antibodies.¹¹ Thus it is not surprising that cognitive dysfunction is more common in patients with past or current clinically overt NPSLE than in those with no such history. Most cross-sectional studies have detected no association between the presence of cognitive impairment and either active systemic disease or the use or dosage of corticosteroids in patients with SLE. No single pattern of SLE-associated cognitive dysfunction has been found, but commonly identified abnormalities include overall cognitive slowing, decreased attention, impaired working memory, and executive dysfunction (e.g., difficulty with multitasking, organization, and planning). Although cognitive impairment may be viewed as a distinct subset of NPSLE it can also serve as a surrogate of overall brain health that may be affected by a variety of factors, including other NP syndromes.

No simple screening test for cognitive dysfunction in SLE patients is currently available because most lack sensitivity in detecting mild but clinically significant dysfunction. Self-report instruments to screen for cognitive difficulties have been validated by some studies^{12,13} but not others.¹⁴ Computerized testing has the potential to facilitate efficient screening of SLE patients by nonexperts,¹⁵ but formal testing remains the only definitive way to diagnose cognitive impairment, and appropriate patients should be

referred for a neuropsychological assessment. The ACR proposed battery of neuropsychological tests for the assessment of cognitive function in SLE² is comprehensive, but its widespread use remains limited because such test batteries are time consuming to administer, require specialized training, and are subject to practice effects with repeated use.

Cognitive dysfunction, as identified by formal neuropsychological assessment, may be subclinical¹⁶ and has been reported in up to 80% of SLE patients,¹ although most studies report a prevalence ranging between 17% and 66%.^{16,17} Longitudinal studies have generally identified stable test performance with persistent or emergent cognitive dysfunction seen in the minority of patients.^{18,19} Several non-SLE causes of cognitive dysfunction may also be present in lupus patients, including sleep deprivation, mood disorders, fatigue, and medication use. Whether these are the sole or contributing causes of cognitive dysfunction in individual patients requires careful consideration.

DIAGNOSIS OF NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

The first step in the management of a patient with SLE who experiences an NP event is to determine whether the event can be convincingly attributed to SLE rather than considered a complication of the disease or its therapy or whether it reflects a coincidental disease process. In the absence of a diagnostic standard for most of the NP manifestations of SLE this determination is made largely by a process of exclusion. Thus the diagnosis is derived from a careful analysis of the clinical, laboratory, and imaging data on a case-by-case basis. Each source of information may be used to a varying extent, depending on the clinical circumstances (Table 135.2). Examination of the cerebrospinal fluid (CSF) should be used primarily to exclude infection. Measurement of CSF autoantibodies, cytokines, and biomarkers of neurologic damage is still a subject of research. Of the circulating autoantibodies, antiphospholipid antibodies are likely to provide the greatest diagnostic yield. The value of measuring anti-P protein antibodies remains uncertain given the conflicting findings to date. The role of anti-NR2 antibodies in NPSLE is currently unknown, but the most convincing evidence of a clinical-serologic association has emerged from a limited number of studies examining CSF autoantibodies in SLE patients. Electroencephalography and nerve conduction studies are used to investigate seizure disorders and peripheral neuropathy, respectively. Neuropsychologic testing should be conducted to address specific concerns about cognitive ability, because the clinical significance of detecting isolated subclinical deficits is not generally clear. Both standard and more advanced structural neuroimaging may help to determine the attribution of an NP event to SLE, and as more information accumulates, functional brain imaging may also prove useful.

Neuroimaging

One of the most significant contributions of neuroimaging in SLE is in determining the cause of central nervous system (CNS) manifestations.²⁰ A second key contribution is in distinguishing acute and possibly reversible

CNS changes from chronic or irreversible ones. Currently, a variety of magnetic resonance–based imaging methods are available, including standard structural magnetic resonance imaging (MRI), magnetization transfer imaging (MTI), diffusion-tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI).

Structural MRI is routinely used to determine the appearance and integrity of white matter and gray matter²¹ and to detect global and regional cerebral atrophy. All have been documented in SLE²² and are associated with a variety of clinical outcomes, including cognitive dysfunction.²⁰ However, a limitation of conventional structural MRI is its poor specificity with respect to the underlying pathologic process. In addition, correlations between structural changes and NP manifestations of SLE are low, which makes structural MRI a poor marker for disease progression or treatment outcomes.²¹

The sensitivity and specificity of conventional imaging may be improved with the addition of more advanced methods such as MTI, DTI, MRS, and fMRI.²⁰ MTI measures magnetization transfer between bound and unbound hydrogen molecules (e.g., between white matter and CSF). The transfer is diminished by either decreased bound molecules (e.g., demyelination) or increased unbound molecules (e.g., edema). Decreased whole-brain magnetization transfer on MTI has been reported in SLE patients even in the absence of other structural MRI changes,²³ and tends to be more pronounced in patients with longstanding NPSLE than in patients with active or acute disease.²⁰ DTI provides information about the integrity of white matter tracts by measuring the degree of anisotropy of water diffusion. This can be used in addition to conventional MRI to detect subclinical and/or diffuse white matter damage.²⁰ MRS measures biochemical compounds, including *N*-acetylaspartate (NAA), choline, and creatine, within predetermined regions of interest. Decreased NAA, believed to reflect neuronal/axonal loss or dysfunction, has been reported in SLE patients, even in the absence of visible damage on structural MRI. Decreased NAA has also been associated with other pathologic CNS conditions, such as vasculitis and antiphospholipid syndrome (APS). Whereas MRS examines biochemical changes in brain tissues, fMRI measures changes in local brain deoxyhemoglobin levels that likely reflect neuronal activity, thereby providing an indirect measure of brain function. Thus fMRI may be informative regarding dysfunction or redistribution of functions as a result of SLE.²⁰ Despite its limitations, however, structural MRI remains the neuroimaging method routinely used in clinical practice, because more advanced methods like MTI, DTI, MRS, and fMRI are troubled by variability in results among scanners and a lack of normative or standardized guidelines for interpretation. In the future, however, multimodal imaging is likely to become the standard of practice in the diagnosis and monitoring of neurologic disorders, including NPSLE.

TREATMENT OF NEUROPSYCHIATRIC EVENTS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Before initiation of treatment for any NP event in individual SLE patients it is important to determine as accurately as possible whether the event can be attributed to SLE or to an alternative cause (Table 135.3). In some patients both SLE and non-SLE factors may be contributing. Thus a first step is to identify and treat conditions such as hypertension, infection, and metabolic abnormalities. Symptomatic therapies such as antiepileptic drugs, anxiolytics, and antidepressants also should be used when appropriate. For example, treatment of even mild anxiety and depression may improve cognitive complaints and/or function. The selection of more specific treatment for NP events for which SLE is felt to be the sole or most significant contributing factor is guided by which immunopathogenic mechanism is predominant and must be tailored to the individual patient's needs despite a paucity of controlled studies to guide treatment decisions.

Inflammation-mediated injury

Immunosuppressive therapy with high-dose corticosteroids, azathioprine, and cyclophosphamide is used to varying degrees. With the exception of one study involving 10 patients²⁴ there are no placebo-controlled studies examining the benefit of either oral or intravenous corticosteroids in NPSLE. Similarly, pulse intravenous cyclophosphamide therapy, akin to that used in the treatment of lupus nephritis, has been reported to be beneficial in NPSLE, although only one controlled study has been performed. An open-label study involving 13 patients with lupus psychosis reported a favorable outcome in all patients treated with oral cyclophosphamide for 6 months followed by maintenance therapy with azathioprine.²⁵ A study by Barile-Fabris and colleagues²⁶ compared intermittent intravenous

TABLE 135.2
Investigations in neuropsychiatric systemic lupus erythematosus

Autoantibodies	Antineuronal (anti-NR2?) Antiribosomal P Anti-NMO/aquaporin Antiphospholipid
Cerebrospinal fluid	Exclusion of infection, assessment of blood-brain barrier Autoantibodies Inflammatory mediators, degradation proteins
Electrophysiologic assessment	
Neuropsychological assessment	
Neuroimaging	Brain structure (CT, MRI, MTI, DWI) Brain function (PET, SPECT, MRA, MRS, fMRI)

CT, computed tomography; DWI, diffusion-weighted (magnetic resonance) imaging; fMRI, functional magnetic resonance imaging; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTI, magnetization transfer imaging; NMO, neuromyelitis optica; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

TABLE 135.3
Management of neuropsychiatric events in patients with systemic lupus erythematosus

Treatment strategy	Examples
■ Establishment of NPSLE diagnosis	Cerebrospinal fluid examination primarily to exclude infection Autoantibody profile (antiphospholipid, antiribosomal P) Neuroimaging to assess brain structure and function Neuropsychological assessment
■ Identification of aggravating factors	Hypertension, infection, metabolic abnormalities
■ Symptomatic therapy	Anticonvulsants, psychotropics, anxiolytics
■ Cognitive rehabilitation	
■ Immunosuppression	Corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil, B-lymphocyte depletion
■ Anticoagulation	Heparin, warfarin

NPSLE, neuropsychiatric events attributed to systemic lupus erythematosus.
 Modified from Hanly JG. Neuropsychiatric lupus. *Curr Rheumatol Rep* 2001;3:205-12.

cyclophosphamide with intravenous methylprednisone administered for up to 2 years to SLE patients with predominantly neurologic disease. They reported a significantly better response rate with cyclophosphamide (95%) than with methylprednisone (54%) ($P < .03$). In virtually all studies, immunosuppressive therapy was used in conjunction with corticosteroids and in addition to symptomatic therapies, such as antipsychotic medications. More targeted immunosuppressive therapies—for example, B lymphocyte depletion with anti-CD20 used alone or in combination with cyclophosphamide²⁷—are promising but require further study.

Vascular injury

Anticoagulation is strongly indicated for focal disease when antiphospholipid antibodies are implicated, and such therapy will usually be lifelong.¹ Because there are no controlled studies to provide guidance on the optimal intensity of anticoagulation required to treat NPSLE caused by thrombosis, one must rely on studies related to prevention of recurrent thrombosis at any anatomic location in patients with APS. Two controlled studies in APS patients found no significant difference between low-intensity warfarin treatment (target international normalized ratio [INR] of 2.0 to 3.0) and high-intensity treatment (target INR of more than 3.0) in the prevention of recurrent thrombosis.^{28,29} However, a minority of patients had arterial thrombosis, and controversy continues on the optimal target INR for the management of such patients.³⁰ Potential adjunctive therapies to consider, especially for patients who experience recurrent thrombosis while receiving warfarin, are antiplatelet agents, antimalarials,³¹ and statins.³²

Treatment of cognitive impairment

The presence, characteristics, and severity of cognitive impairment should first be confirmed by formal neuropsychological assessment. Two approaches, pharmacologic treatment and cognitive rehabilitation, can be considered, although neither has yet been studied systematically in SLE, let alone shown confirmed evidence of efficacy. Only one placebo-controlled study of pharmacologic therapy for SLE-associated cognitive dysfunction has been performed.²⁴ Ten SLE patients who were not currently using corticosteroids were enrolled in a double-blind, controlled trial in which 0.5 mg/kg prednisone was administered daily. Except for complaints related to cognition, these patients presumably had inactive SLE at enrollment. The authors reported improvement in cognition in five of the eight subjects who completed the trial. Although the use of antiplatelet or anticoagulant therapy for the treatment of cognitive dysfunction in SLE patients who have antiphospholipid antibodies but no evidence of thromboembolic phenomena has a theoretical basis, this approach lacks evidence of efficacy and

remains controversial. A single-center, controlled study of treatment with memantine over 12 weeks aimed at “cognitive enhancement” did not demonstrate significant benefit compared with placebo.³³ Variability in the presence and persistence of cognitive deficits in SLE patients as well as the lack of a biologically plausible mechanism for treatment efficacy remain major hurdles in the design of clinical trials examining therapies for SLE-associated cognitive dysfunction.

Cognitive rehabilitation strategies

The cognitive rehabilitation literature provides a taxonomy of theoretical approaches that include the cognitive retraining approach, the holistic approach, and the multicontext approach.³⁴ The cognitive retraining approach is based on the premise that repeated practice and stimulation of an impaired cognitive skill via drill-type exercises of increasing difficulty facilitate “mental muscle building.” Currently, this is the basis of many computerized rehabilitation programs. Some studies have demonstrated improved neuropsychological test performance using this approach,³⁵ although such improvements have not been associated with positive changes in daily functioning.³⁴ Other criticisms include failure to address psychological difficulties that often co-occur with cognitive dysfunction³⁴ and a focus on eliminating cognitive “impairment” rather than minimizing “disability.”

The holistic approach is “a theory-based programme of integrated didactic, experiential, procedural and psychosocial training activities, conducted to restore cognitively compromised adaptation, including decrements in interpersonal and vocational participation, self-awareness and self-determination.”³⁶ Patients are involved in setting their own personalized functional goals, which dictate the content of the program.³⁴ Cognitive strategies are introduced didactically and are then applied in real-life training exercises during and between sessions. In its purest form, this approach involves a lengthy multidisciplinary program (e.g., 5 to 8 hours of treatment per day, 4 to 5 days per week, with 400 to 1200 total contact hours), but modified holistic models that are less intense and more flexible with regard to scheduling are more commonly implemented in practice.³⁶ No studies have been published examining the use of this method in SLE patients, although evidence of effectiveness in studies of other neurologic populations provides some promise of efficacy.

Like the holistic approach, the multicontext approach emphasizes generalizability of training from the therapeutic environment to real-life situations by emphasizing practice and application of cognitive strategies within multiple environments. Concurrently, patients are taught to recognize situations in which a particular strategy may or may not be helpful. Transfer of skills from one situation to the next is facilitated by setting up a predetermined level of success that must be achieved before the skills are applied in a different situation. Unlike the holistic approach, however, this method does not typically include psychosocial interventions. Harrison and colleagues³⁷ have explored the feasibility and effectiveness of using multicontext rehabilitation strategies in SLE patients in an uncontrolled, nonrandomized study. They enrolled 17 women with SLE between the ages of 25 and 60 who reported cognitive difficulties that either interfered with adaptive functioning or caused emotional distress. All completed the MINDFUL program (Mastering the Intellectual Navigation of Daily Functioning and Undoing the Limitations of Lupus), which involved eight weekly 2-hour “psychoeducational group intervention” sessions that focused on cognitive strategy training applied across multiple real-life situations. In addition, the MINDFUL program included a psychosocial support component. The feasibility of this approach in the SLE population was demonstrated by the 100% retention rate. Patients reported better affect and overall quality of life as well as memory self-efficacy, which has been linked to cognitive performance in daily life. Nonetheless, controlled studies are still required to delineate the therapeutic components of such intervention, as well as factors that may interfere with improvement when they are applied to SLE patients with cognitive impairments. In the absence of data on cognitive rehabilitation efficacy some suggestions still seem reasonable. Collaborative, outcome-based goal setting with a focus on disability reduction should be the first step of any rehabilitation program. Combining cognitive retraining with compensatory strategies has the greatest chance of success, especially if there is transfer of skills learned in the clinic to real-life situations. Since most patients have multiple interrelated problems, a multidisciplinary approach to rehabilitation may be best.

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Systemic lupus erythematosus:
treatment—renal involvement

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- Urinalysis is the single most useful test to monitor for renal involvement and relapses after response to treatment.
- Evidence-based recommendations have been developed for the management of lupus nephritis.
- Patients with mild proliferative disease may benefit from glucocorticoids in combination with azathioprine.
- Combinations of mycophenolic acid and moderate to high dosages of glucocorticoids are recommended for induction and maintenance treatment in most patients with moderately severe class III-IV lupus nephritis. Low-dose intravenous cyclophosphamide is an alternative option in white patients.
- In severe proliferative nephritis with acute renal impairment or substantial crescents or necrosis in the biopsy specimen, best available evidence supports the use of combined pulses of intravenous methylprednisolone and high-dose cyclophosphamide as induction treatment. Extended courses of pulse cyclophosphamide or mycophenolic acid may be used for maintenance treatment.
- Patients with pure membranous disease may benefit from glucocorticoids alone or in combination with mycophenolic acid, cyclosporine, or cyclophosphamide.
- One third to one fourth of lupus patients with moderate to severe proliferative lupus nephritis experience relapse after achieving partial or complete response. In cases of severe nephritic flare, early reinstitution of immunosuppressive treatment may preserve renal function.
- In lupus nephritis, tight control of blood pressure and dyslipidemia is of paramount importance.

INTRODUCTION

Effective treatment of lupus nephritis depends on recognition of early phases of renal involvement, before scarring, atrophy, and fibrosis occur. However, many forms of lupus renal disease, including severe forms of glomerulonephritis, are asymptomatic and insidiously progressive. The marked heterogeneity among individual patients in terms of pattern and evolution of disease, as well as response to treatment, presents additional challenges. Yet notwithstanding the capricious nature of the disease and its intrinsic complexities and subtleties, nephritis is one of the most gratifying aspects of lupus to treat because the majority of patients respond well and eventually reach remission. Moreover, novel agents have been added in the therapeutic armamentarium for lupus nephritis, offering options in refractory cases and opportunities for individualization of treatment according to disease characteristics and the patient's needs.

DIAGNOSIS AND ASSESSMENT OF
DISEASE ACTIVITY

Clinical presentation

Nearly half of the patients present with asymptomatic urine abnormalities such as hematuria and proteinuria. Nocturia and/or foamy urine are rarely

reported by patients unless they are specifically asked. Persistent glomerular hematuria is common but rarely found without concomitant proteinuria, which is the dominant feature of lupus nephritis.¹ Nephrotic syndrome accounts for an additional 30% to 40% of cases, whereas rapidly progressive glomerulonephritis is less common and accounts for fewer than 10% of the initial presentations. Hypocomplementemia (especially low levels of C3) and anti-DNA antibodies are frequently encountered. Renal involvement usually appears within the first 2 years of lupus, and its frequency decreases significantly after the first 5 years of disease.

The clinical presentation does not always predict the underlying histologic class of nephritis. This is especially true in patients receiving therapy that may modify findings. Patients with mesangial nephritis tend to have low-grade proteinuria (less than 1 g of protein per 24 hours) with hematuria but typically no cellular casts. Patients with membranous glomerulopathy have proteinuria, often at nephrotic range (more than 3 g of protein per 24 hours), but otherwise blunt urine sediments. Serum C3 levels tends to be normal and anti-DNA antibodies, when present, are usually found in low titers. In contrast, patients with proliferative nephritis may have hypertension, nephritic urine sediment with various degrees of proteinuria (often at a nephrotic range), low C3 levels, and typically high titers of anti-DNA antibodies.

In lupus nephritis, proteinuria reflects the extent of involvement of peripheral glomerular capillary loops, and the disorder tends to increase incrementally from mesangial to proliferative to membranous nephropathy. The latter involves all glomerular capillary loops and is typically accompanied by heavy proteinuria. Concomitant podocytopathy may contribute to enhanced urine protein excretion in some patients.

Urinalysis

Urinalysis is an effective method to detect and monitor disease activity in lupus nephritis. Precautions to be considered to ensure the quality of the urine examination include expeditious examination of a fresh, early morning, nonrefrigerated specimen and flagging of specimens from patients at risk of nephritis to improve the chances for a vigilant examination. Hematuria (usually microscopic, rarely macroscopic) with dysmorphic (fragmented or misshapen) cells (Fig. 136.1) indicates inflammatory glomerular or tubulointerstitial disease. Granular and fatty casts reflect proteinuric disease, whereas erythrocyte, leukocyte, and mixed cellular casts reflect nephritic disease. Broad and waxy casts are found in chronic renal failure. In severe proliferative nephritis, urine sediment may contain the full range of cells and casts ("telescopic urine sediment"). Urine sediment abnormalities in active lupus nephritis are typically accompanied by significant proteinuria (more than 0.5 g of protein per 24 hours), although isolated hematuria and/or pyuria appearing in the context of generalized lupus activity, and not explained otherwise, might be an early sign of kidney involvement and dictates diligent follow-up.²

Renal biopsy

The invasive nature of renal biopsy often provokes anxiety among patients, and some physicians may question its use in patients with newly identified lupus who have typical nephritic or nephrotic syndrome considering the current availability of efficacious noncytotoxic immunosuppressive agents. Still, renal biopsy is essential to document the class and severity of renal abnormalities in lupus since neither can be accurately predicted by laboratory tests. Due to the potentially aggressive nature of lupus nephritis, any sign of renal involvement—in particular, reproducible proteinuria of 0.5 g of protein or more per 24 hours, especially with glomerular hematuria—should be an indication for biopsy.³ Clinically relevant biopsy findings are

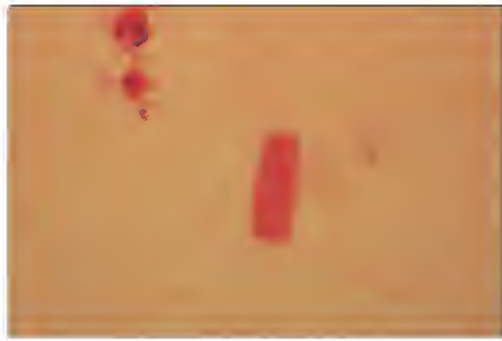


Fig. 136.1 Urinalysis is the single most useful test to monitor for renal involvement and relapses after remission in lupus patients. Dysmorphic red blood cells are seen in the urine of a patient with active glomerulonephritis and active urine sediment. Note the fragmented red blood cells and the abnormal sizes and shapes of the majority of cells. The cellular cast in the middle of the figure contains red blood cells. (Courtesy Dr. James E. Balow.)

BOX 136.1 ACTIVITY AND CHRONICITY INDICES*

Activity index (lesions are scored 0 to 3 with a maximum score of 24 points)

- Hypercellularity: endocapillary proliferation compromising glomerular capillary loops
- Leukocyte exudation: polymorphonuclear leukocytes in glomeruli
- Karyorrhexis/fibrinoid necrosis (weighted $\times 2$): necrotizing changes in glomeruli
- Cellular crescents (weighted $\times 2$): layers of proliferating epithelial cells and monocytes lining Bowman capsule
- Hyaline deposits: eosinophilic and periodic acid–Schiff–positive materials lining (wire loops) or filling (hyaline thrombi) capillary loops
- Interstitial inflammation: infiltration of leukocytes (predominantly mononuclear cells) among tubules

Chronicity index (lesions are scored 0 to 3 with a maximum score of 12 points)

- Glomerular sclerosis: collapse and fibrosis of capillary tufts
- Fibrous crescents: layers of fibrous tissue lining Bowman capsule
- Tubular atrophy: thickening of tubular basement membranes, tubular epithelial degeneration, with separation of residual tubules
- Interstitial fibrosis: deposition of collagenous connective tissue among tubules

*Scored on a scale of 0 to 3 representing either (a) absent, mild, moderate, and severe lesions or (b) the presence of lesions in none, <25%, 25%–50%, and >50% of glomeruli, respectively.

more frequent in the presence of significant proteinuria,⁴ although biopsy can also be considered in cases of persisting isolated glomerular hematuria, isolated leukocyturia (after other causes, such as infection or drugs, are excluded), or unexplained renal insufficiency with normal urinary findings.

Pathologic renal lesions should be classified according to the revised 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system (Table 136.1),⁵ with assessment of active and chronic glomerular, tubulointerstitial, and vascular lesions (Table 136.2 and Box 136.1).⁶ In several studies of lupus nephritis, class IV nephritis has been found to be the most common (approximately 40% of cases), followed by class III and V with approximate frequencies of 25% and 15%, respectively.

Monitoring of lupus nephritis

Renal function

Renal function is commonly assessed by measurements of blood urea nitrogen, serum creatinine (SCr) level, and creatinine clearance. SCr level is relatively insensitive for detection of early changes in glomerular filtration rate (GFR), and its absolute level is influenced by muscle mass and age. In early renal disease, an initial decline in GFR may lead to only a slight increase (0.2 mg/dL or less) in SCr concentration due to increased proximal tubular secretion of creatinine. Consequently, patients with a true GFR of 60 to 80 mL/min may still have an SCr concentration that is approximately 1.0 mg/dL. However, once SCr levels exceed 1.5 to 2.0 mg/dL, changes in SCr level correlate well with changes in the GFR. Assessment of renal

TABLE 136.1

Histologic classification of lupus nephritis according to the International Society of Nephrology/Renal Pathology Society (2003)

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
Class II	Mesangial proliferative lupus nephritis Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
Class III	Focal lupus nephritis Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
Class IV	Diffuse lupus nephritis Active or inactive diffuse, segmental or global endocapillary or extracapillary glomerulonephritis involving $\geq 50\%$ of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into <i>diffuse segmental</i> (IV-S) lupus nephritis when $\geq 50\%$ of the involved glomeruli have segmental lesions and <i>diffuse global</i> (IV-G) when $\geq 50\%$ of the involved glomeruli have global lesions. <i>Segmental</i> is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V nephritis may occur in combination with class III or class IV, in which case both will be diagnosed. Class V nephritis may show advanced sclerotic lesions.
Class VI	Advanced sclerotic lupus nephritis. $\geq 90\%$ of the glomeruli globally sclerosed without residual activity.

TABLE 136.2

Evaluation of renal biopsy specimens in lupus nephritis

Renal biopsy parameters	Evaluation
Assure that sample is adequate	Specimens with <10 glomeruli are suboptimal
Light microscopy stains	<i>Hematoxylin-eosin</i> : best to identify inflammatory cells <i>Trichrome (Masson)</i> : best for interstitial fibrosis, glomerulosclerosis <i>Periodic acid–Schiff (PAS)</i> : identify basement membrane abnormalities
Immunofluorescence studies	Useful for identification of immune deposits
Electron microscopy	Helps to define distribution (subendothelial, epithelial, membranous deposits) of immune complexes
Activity and chronicity indexes	Useful in organizing renal biopsy report as a complement to World Health Organization classification
Important elements to consider	Activity index: crescents, fibrinoid necrosis Chronicity index: interstitial fibrosis, tubular atrophy, glomerular sclerosis

function is most readily achieved by measuring creatinine clearance in 24-hour urine collections; the requisite 24-hour urine collection is cumbersome, and errors in collection may lead to unreliable estimates. Predictive equations to estimate GFR offer a rapid alternative method of evaluating renal function based on SCr concentration and anthropometric data. To this end, the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD)

equations are widely used in clinical practice, although they both lack accuracy when true GFR is 60 mL/min/1.73 m² or more.⁷

Changes in renal function are more important than absolute values of renal function, and reproducible changes in SCr concentration (20% to 30% increase or more) or GFR (10% or more deterioration from baseline) are of concern because they indicate significant ongoing loss of renal function. Persistently increased SCr levels (2.0 mg/dL or higher) at the time of response to immunosuppressive treatment is associated with positive likelihood ratio of 10.8 for subsequent development of end-stage renal disease (ESRD).⁸ Conversely, reduction of SCr concentration (even within the “normal” range of values) at 6 months after induction therapy is associated with increased likelihood of a favorable long-term renal outcome (odds ratio, 14.9).⁹

Proteinuria

Timed urine collection to calculate 24-hr protein excretion is considered the gold standard, and values are obtained at baseline and before major therapeutic decisions. Collections of urine in which creatinine concentrations deviate significantly from population averages for males (20 mg/kg/day) or females (15 mg/kg/day) should raise suspicions about the adequacy of the urine collection. Spot urine protein-creatinine ratio (UPCR) measured in a first-morning-void urine sample is a valid and conveniently repeatable measure for detecting within-patient changes in proteinuria and is currently recommended for monitoring patients with lupus nephritis.^{3,10} In general, the numeric ratio approaches the number of protein grams per 24 hours of proteinuria (normal UPCR is less than 0.2). Reduction in UPCR to less than 1.0 at 6 months after initiation of immunosuppressive treatment has a positive predictive value of 87% for good long-term outcome (defined as SCr level of less than 1.4 mg/dL),⁹ whereas persistence of a UPCR of more than 0.5 despite immunosuppressive treatment is associated with increased risk (positive likelihood ratio, 5.6) for the development of ESRD.⁸

Urinalysis

Findings of the analysis that examines centrifuged urine for red blood cells, white blood cells, and cellular casts can reflect inflammation in the kidney, but there are few data on the reproducibility of these measures. Resolution of active urine sediment is a feature of renal response but has to be sustained for several months to be clinically meaningful. Reappearance of urine cellular casts has more than 80% sensitivity and specificity for flares (defined as increases in SCr concentration and/or proteinuria) and may precede other signs of flare by several weeks.¹¹

Serologic Testing

Increased anti-DNA antibody titers and low complement (C3/C4) concentrations tend to be associated with increased activity and worse renal outcomes in lupus nephritis. Changes in the concentrations of these markers, rather than their absolute levels, tend to be more valuable clinically. Although serum C3 concentration has generally higher sensitivity than serum C4 concentration (72% to 85% vs. 28% to 74%), both tests have modest specificity for active lupus nephritis.¹² The diagnostic accuracy of serum levels of anti-double-stranded DNA (dsDNA) is also modest, with positive and negative likelihood ratios ranging from 1.5 to 4.8 and 0.3 to 0.8, respectively.³ Other tests such as anti-C1q and antinucleosome antibodies have higher sensitivity and specificity rates for active renal disease, but further validation is required. Lupus patients with either rising anti-DNA antibodies or falling complement levels should be closely monitored for signs of active renal disease, at which point preemptive therapy should be instituted.

Biomarker levels

A number of serum and urine biochemical and molecular biomarkers, including urine levels of the chemokine monocyte chemoattractant protein-1 (MCP-1) and neutrophil gelatinase-associated lipocalin (NGAL) and serum levels of tumor necrosis factor–like weak inducer of apoptosis (TWEAK), have been studied in lupus nephritis.¹³ Most of these results, however, are limited by the short duration of the studies, the inclusion of a relatively small number of patients, and the lack of confirmation by independent investigators. Importantly, none of the biomarkers has been validated in the context of prospective studies as a true surrogate of long-term renal outcome.

Assessment of prognosis and risk stratification

Numerous demographic and clinical variables can affect prognosis in lupus nephritis, and individual patients have unique combinations of such risk factors (Box 136.2). Although individual risk factors are heterogeneous and vary in their overall impact, patients with a greater number of risk factors have a worse prognosis, are less likely to respond to therapy, tend to respond

BOX 136.2 FACTORS GENERALLY ACCEPTED TO BE ASSOCIATED WITH ADVERSE PROGNOSIS AND HIGH RISK OF RENAL PROGRESSION IN LUPUS NEPHRITIS

Demographic: Black race; limited access to health care, males, children

Clinical: Hypertension; severe extrarenal disease affecting major organ; failure to achieve or marked delay (>2 years) in achieving renal remission; multiple flares of lupus nephritis; pregnancy

Laboratory: Nephritic urinary sediment; azotemia; anemia; thrombocytopenia; antiphospholipid antibodies; thrombotic microangiopathy; hypocomplementemia (especially falling levels); high anti-DNA titer (especially rising titers); persistent severe nephrotic syndrome

Histologic: Proliferative glomerulonephritis (World Health Organization class III-IV); mixed membranous (class V) and proliferative (class III-IV) glomerulonephritis; cellular crescents; fibrinoid necrosis; very high activity index (>12); moderate to high chronicity index (>3); combinations of active (cellular crescents) and chronic (interstitial fibrosis) histologic features; extensive subendothelial deposits

Modified from Balow JE, Boumpas DT, Austin HA. Systemic lupus erythematosus and the kidney. In: Lahita RG, editor. Systemic lupus erythematosus. San Diego: Academic Press; 1999, p. 657-85.

more slowly, and thus require more aggressive treatment. Patient characteristics associated with poor outcomes include male gender, low socioeconomic status, azotemia, anemia, dyslipidemia, hypertension, antiphospholipid syndrome, failure to respond to initial immunosuppressive therapy, and occurrence of flares with worsening of renal function.¹⁴⁻²¹ Combinations of severe active disease indicators (crescents and fibrinoid necrosis) and marked chronic changes (moderate to severe tubulointerstitial fibrosis and tubular atrophy) on renal biopsy are particularly ominous. The impact of race on the severity of disease, response to treatment, and final outcome is becoming increasingly apparent.

THERAPEUTIC AGENTS AND CONTROLLED TRIALS IN LUPUS NEPHRITIS

Of all lupus manifestations, nephritis has been most extensively studied in randomized controlled trials. Many of these trials have been plagued by generic problems, including a small number of patients, variable disease duration, diverse racial and socioeconomic backgrounds of patients, and relatively short follow-up times. Because proliferative (class III-IV) lupus nephritis has a higher prevalence and worse prognosis, most trials have involved patients with this type of nephritis.

Glucocorticoids and cytotoxic drugs

Glucocorticoids are effective in inducing a rapid control of lupus nephritis and are included in all treatment regimens. Pulses of intravenous (IV) methylprednisolone (MP) have become a popular part of initial treatment, although no formal studies have examined whether (1) they are more efficacious than daily oral glucocorticoids, or (2) there is a significant difference between the main dosages employed (500 to 1000 mg vs. 1 g/m²). Many clinicians think that IV pulses of corticosteroids are more effective in rapidly evolving glomerulonephritis, and when they are used in combination with moderate doses of daily glucocorticoids, the severity of adverse effects such as cushingoid appearance, acne, and hirsutism may be lessened.

Seminal studies at the National Institutes of Health have established IV cyclophosphamide (CYC) pulse therapy in combination with glucocorticoids as the gold standard for the treatment of severe lupus nephritis. In patients with proliferative lupus nephritis and renal impairment or adverse histologic features such as crescents and fibrinoid necrosis in 25% or more of glomeruli, seven pulses of IV CYC (0.5 to 1 g/m²) and IV MP on consecutive months, followed by quarterly pulses of IV CYC/IV MP for another 2 years, were superior and prevented more relapses than a shorter regimen limited to seven doses (Box 136.3).^{22,23} Follow-up to a total of 11 years provided further documentation of the benefit of combined IV CYC/IV MP pulses in the long-term outcome of lupus nephritis.²⁴ A meta-analysis of RCTs in patients with class IV lupus nephritis concluded that IV CYC plus glucocorticoids reduced the risk for doubling of SCr concentration (relative risk [RR], 0.59; 95% confidence interval [CI], 0.40 to 0.88) compared with

BOX 136.3 NIH PROTOCOL FOR ADMINISTRATION AND MONITORING OF PULSE CYCLOPHOSPHAMIDE THERAPY

- Estimate GFR by standard methods.
- Calculate body surface area (BSA) (m^2):

$$BSA = \sqrt{\text{Height (cm)} \times \text{weight (kg)} / 3600}.$$
- Cyclophosphamide (CYC; Cytoxan) dosing and administration:
 - Initial dose 0.75 g/m^2 (0.5 g/m^2 if GFR is less than one third of expected normal value).
 - Administer CYC in 150 mL normal saline intravenously over 30 to 60 minutes (alternative: equivalent dose of pulse CYC may be taken orally in highly motivated and compliant patients).
- Obtain WBC count at days 10 and 14 after each CYC treatment (patient should delay prednisone dose until after blood samples are drawn to avoid transient corticosteroid-induced leukocytosis).
- Adjust subsequent doses of CYC to maximum dosage of 1.0 g/m^2 to keep nadir WBC count above 1500/mL. If WBC nadir falls below 1500/mL, decrease next dose by 25%.
- Repeat IV CYC pulses monthly (every 3 weeks in extremely aggressive disease) for another 6 months (seven pulses), then quarterly for 1 year after remission is achieved (as indicated by inactive urine sediment, proteinuria of $<1 \text{ g/day}$, normalization of complement levels [and ideally anti-DNA titer], and minimal or no extrarenal lupus activity).
- Protect bladder against CYC-induced hemorrhagic cystitis:
 - Diuresis with 5% dextrose and 0.45% saline (2 L at 250 mL/hr); frequent voiding; continuation of high-dose oral fluids for 24 hours. Patients should return to clinic if they cannot sustain inadequate fluid intake.
 - Consider administration of mesna (each dose is 20% of total CYC dose) intravenously or orally at 0, 2, 4, and 6 hours after CYC dosing. Mesna is especially important to use if sustained diuresis may be difficult to achieve or if pulse CYC is administered in outpatient setting.
 - If difficulty is anticipated in sustaining diuresis (e.g., severe nephrotic syndrome) or voiding (e.g., neurogenic bladder), insert a three-way urinary catheter with continuous bladder flushing with standard antibiotic irrigating solution (e.g., 3 L) or normal saline for 24 hours to minimize risk of hemorrhagic cystitis.
- Antiemetics (usually administered orally):
 - Dexamethasone (10-mg single dose) plus
 - Serotonin receptor antagonists: granisetron 1 mg with CYC dose (usually repeat dose in 12 hours); ondansetron 8 mg three times a day for 1 to 2 days
- Monitor fluid balance during hydration. Induce diuresis if patient develops progressive fluid accumulation.
- Complications of pulse CYC:
 - Expected: nausea and vomiting (central effect of CYC), mostly controlled by serotonin receptor antagonists; transient hair thinning (rarely severe at CYC doses $\leq 1 \text{ g/m}^2$).
 - Common: significant infection diathesis only if leukopenia not carefully controlled; modest increase in herpes zoster (very low risk of dissemination); infertility (male and female); amenorrhea proportional to age of patient during treatment and to cumulative dose of CYC. In females at high risk of persistent amenorrhea, consider using leuprolide 3.75 mg subcutaneously 2 weeks before each dose of CYC.

GFR, glomerular filtration rate; IV, intravenous; NIH, National Institutes of Health; WBC, white blood cell.

glucocorticoids alone, although it had no significant impact on overall mortality (RR, 0.98; 95% CI, 0.53 to 1.82).²⁵ Intermittent pulse IV CYC is as effective as daily oral CYC but has fewer adverse effects, and thus the former has become the preferred approach.²⁶

Treatment with CYC is associated with considerable toxicity, particularly gonadal dysfunction, which is both age and dose dependent. In one series, the rates of amenorrhea after a long course (15 pulses or more) of IV CYC was 17% for women younger than 25 years of age, 43% for those 26 to 30 years of age, and 100% for patients older than 31 years. The respective rates of amenorrhea in patients who received short courses (seven pulses or fewer) of IV CYC were 0%, 12%, and 25%.²⁷ Ovarian protection with depot gonadotrophin-releasing hormone agonists such as leuprolide 3.75 mg (administered as a monthly subcutaneous injection 2 weeks before pulse IV CYC) has been shown to reduce the rates of amenorrhea (5% vs. 30% in untreated individuals), although data are scarce.²⁸ Other potential adverse

effects of CYC are infectious complications (especially herpes zoster), myelotoxicity (with a leukocyte nadir occurring 10 to 14 days after the CYC pulse), and bladder irritation or even malignancy. Forceful diuresis, use of antiemetic agents, dose adjustments to maintain a safe white blood cell count of $1500/\text{mm}^3$, or more, and concomitant use of moderate rather than high doses of glucocorticoids (0.5 mg/kg/day) are important to reduce toxicity.

The Euro-Lupus Nephritis Trial compared lower doses of IV CYC with the standard high-dose regimen in European patients with lupus nephritis, for the most part patients with milder forms of disease (average SCr concentration, 1.2 mg/dL ; average UPCr, 3.0). A less intensive regimen of IV CYC (500 mg every 2 weeks for a total of six doses) followed with azathioprine (AZA) as maintenance treatment had comparable efficacy—but less toxicity—than a short course of high-dose IV CYC (eight pulses) also followed by AZA.²⁹ At 10 years' follow-up, rates of death, sustained doubling of SCr level, and ESRD were comparable in the low-dose and high-dose groups (11% vs. 4%, 14% vs. 11%, and 5% vs. 9%, respectively),³⁰ which suggests that low-dose IV CYC may be a reasonable option for white patients with mild to moderate proliferative lupus nephritis.

Pulses of IV CYC (0.5 to 1 g/m^2 for 6 monthly doses), cyclosporine (CsA) (5 mg/kg/day , then adjusted according to changes in SCr level), and glucocorticoids alone were studied in an RCT involving 42 patients with pure class V lupus nephritis (median GFR, $83 \text{ mL/min/1.73 m}^2$; median UPCr, 5.4).³¹ All patients received alternate-day oral prednisone (1 mg/kg every other day for 8 weeks, then tapered). At 1 year, remission rates were 27% with prednisone, 60% with IV CYC, and 83% with CsA. Relapse rates per 100 patient-months were 2.0 with CsA versus 0.2 with IV CYC. IV CYC and CsA may be equally effective in treating membranous lupus nephritis; with CsA, however, maintenance therapy may be required to prevent relapses.

Azathioprine

The efficacy of AZA in an induction-maintenance regimen was evaluated in a study that compared treatment with AZA (2 mg/kg/day) and pulsed IV MP (three sets of 3 pulses of 1000 mg) with combination therapy using IV CYC (750 mg/m^2 , 13 pulses in 2 years) and oral prednisone in 87 patients with class III-IV lupus nephritis, 56% of whom had estimated GFRs of less than 70 mL/min .³² After a median follow-up of 5.7 years, doubling of SCr concentration and renal relapses were more frequent in the AZA/IV MP than group than in the IV CYC group (16% vs. 4%, and 27% vs. 4%, respectively). Per-protocol repeat biopsies showed that, although both regimens reduced the number of active lesions, progression of chronic lesions was more effectively halted by IV CYC.³³ During the 10-year follow-up, renal relapses were significantly more common in the AZA/IV MP group (hazard risk, 4.5 compared with IV CYC) and sustained doubling of SCr concentration was also more frequent with AZA (16% vs. 8%), although statistical significance was not reached.³⁴ Nonwhite race was an independent predictor for deterioration of renal function irrespective of type of therapy. AZA may therefore be used as induction treatment in milder cases of proliferative lupus nephritis, especially in white patients. A single open-label trial has also reported efficacy of AZA in combination with oral prednisone in pure class V lupus nephritis.³⁵ AZA has been considered a safe and effective option for maintenance of response in lupus, including cases of moderately severe proliferative lupus nephritis initially treated with CYC.^{30,36}

AZA interferes with the *de-novo* synthesis of inosinic acid via feedback inhibition of 6-thiosinosinic acid. AZA is converted into its active metabolites, which accumulate in tissues and are thought to be responsible for many serious toxicities of the drug. This process is inactivated by thiopurine methyltransferase (TPMT). Codominant genetic polymorphism is seen, with 85% to 90% of people exhibiting high TPMT activity and 10% to 15% showing intermediate TPMT activity, differences caused by heterozygosity at the TPMT locus. Approximately 1 in 300 individuals inherits absolute TPMT deficiency as an autosomal recessive trait. Intermediate TPMT activity is predictive for development of severe adverse effects of AZA. However, the utility of polymerase chain reaction testing to identify TPMT polymorphisms before administration of AZA needs to be evaluated in terms of cost effectiveness. Leukopenia and hepatotoxicity may occur. AZA is considered safe during pregnancy, has not been linked to malformations of newborns, and is therefore suitable for pregnant lupus patients requiring treatment.

Mycophenolic acid

Mycophenolic acid (MPA), an immunosuppressive agent, has been tested extensively both as a remission-inducing agent and as maintenance therapy in lupus nephritis. MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase, a critical rate-limiting enzyme involved in

the *de-novo* synthesis of purines. The drug functions as a relatively selective antimetabolite, inhibiting T- and B-lymphocyte activation. MPA is administered orally as the morfolinoethyl ester (mycophenolate mofetil, or MMF) or as a salt (enteric-coated mycophenolate sodium, or eMPA). Evidence from transplantation medicine and a single RCT in patients with lupus nephritis³⁷ suggest that the two formulations are likely to be equivalent in inducing improvement of lupus nephritis, with a 720-mg dose of eMPA roughly equivalent to a 1-g dose of MMF. Dose-dependent adverse effects include leukopenia, nausea, diarrhea, and infections. Although the target MMF dosage for induction treatment is 3 g/day, dosages higher than 2 g/day may not always be tolerated, mainly due to gastrointestinal complaints.

Induction therapy

A number of RCTs have compared MPA with CYC as induction treatment in lupus nephritis. Initial trials showed equal or even superior efficacy of MPA, but findings were limited by flaws in the design such as low numbers of patients, underrepresentation of severe forms of lupus nephritis, suboptimal drug dosing, and short follow-up. To overcome these issues, the Aspreva Lupus Management Study (ALMS) included 370 patients with active class III-IV (83%) or class V nephritis, with an average SCr concentration of 1.1 mg/dL and UPCR of 4.1.³⁸ Patients were randomly assigned to receive induction treatment with oral prednisone (60 mg/day, tapered) plus either MPA (target MMF dosage 3 g/day) or IV CYC (monthly pulses of 0.5 to 1 g/m²) for 6 months. Although the trial was designed to demonstrate the superiority of MPA over CYC, at the end of the induction phase, response rates did not differ between the two groups (MPA, 56%; CYC, 53%). Notably, only 16 patients (8.6%) in the MPA group and 15 (8.1%) in the CYC group achieved complete renal response (UPCR of 0.5 or less) after 24 weeks. Post-hoc analysis demonstrated that black and Hispanic patients were more likely to respond to MPA than to CYC (60% vs. 39%, respectively).³⁹

A Cochrane database systematic review and meta-analysis of RCTs compared MPA (MMF) with IV CYC as induction therapy in proliferative lupus nephritis and found no significant differences in mortality (RR, 1.02; 95% CI, 0.52 to 1.98), incidence of ESRD (RR, 0.71; 95% CI, 0.27 to 1.84), complete renal response (RR, 1.39; 95% CI, 0.99 to 1.95), and renal relapse (RR, 0.97; 95% CI, 0.39 to 2.44).^{40,41} MPA-treated patients had significantly lower risks of ovarian failure (RR, 0.15; 95% CI, 0.03 to 0.80) and alopecia (RR, 0.22; 95% CI, 0.06 to 0.86) but not of major infection (RR, 1.11; 95% CI, 0.74 to 1.68). Together, evidence for equivalent efficacy of MPA and CYC, coupled with the ease of administration and the more favorable gonadal toxicity profile of the former, have led to the recommendation to use MPA as initial treatment in most cases of class III-IV lupus nephritis.³ However, the long-term (beyond 5 years) benefit of MPA treatment in terms of hard outcomes remains to be determined.

Severe lupus nephritis

Only high-dose IV CYC demonstrated long-term efficacy in an RCT that included cases of severe lupus nephritis with GFR of 25 to 80 mL/min or with crescents or necrosis in 25% or more of glomeruli.²² Post-hoc analysis of the data for 32 ALMS patients with a baseline GFR of less than 30 mL/min/1.73 m² showed similar rates of renal response at 6 months in MPA- and CYC-treated patients.³⁸ In Asian patients with mixed class IV+V nephritis and noninflammatory necrotizing vasculopathy (average SCr concentration, 1.4 to 1.7 mg/dL), complete renal response at 6 months was achieved by 44% of patients treated with MPA (MMF) compared with 0% of patients treated with IV CYC.⁴² Higher rates of renal response at 12 months were seen with MPA than with IV CYC (54% vs. 26%), although more relapses occurred with MPA than with CYC (44% vs. 11%) in a retrospective cohort study in patients with crescentic nephritis.⁴³ These results vary from those reported in a study of 90 patients with class III-IV lupus nephritis who received induction-maintenance treatment with MPA, which found that patients with a baseline GFR of less than 60 mL/min/1.73 m² had significantly lower rates of complete renal response than patients with a baseline GFR above this value at 6 months (31% vs. 6%), 12 months (56% vs. 21%), and 24 months (49% vs. 8%).⁴⁴ Although there is preliminary evidence to suggest that MPA may be efficacious in severe lupus nephritis, further studies with longer follow-up are required. Combination IV CYC/IV MP pulse therapy is still considered by many experts as the treatment of choice in patients with the severest form of lupus nephritis (rapidly progressive glomerulonephritis/crescentic nephritis).

Membranous lupus nephritis

MPA has demonstrated antiproteinuric effects in class V lupus nephritis, but there is lack of large RCTs to formally test its efficacy. A post-hoc analysis of the data for patients with pure class V lupus nephritis and an average UPCR of 5.0 to 5.8 who participated in two RCTs demonstrated comparable

response rates at 6 months in MPA- and CYC-treated patients.⁴⁵ A small randomized study compared MPA (target MMF dosage 1.5 to 2 g/day) with tacrolimus (titrated to a trough blood level of 6 to 8 mg/L), both in combination with oral prednisone, in Chinese patients with class V lupus nephritis and nephrotic syndrome.⁴⁶ At 24 months, response rates were 71% in the MPA group versus 55% in the tacrolimus group. The two groups had similar longitudinal profiles of serum albumin and creatinine levels. Both agents were well tolerated, and no relapse occurred. Therefore MPA could be used as a first-line immunosuppressive agent in patients with class V lupus nephritis and nephrotic-range UPCR, but additional controlled studies are needed to definitively establish use of MPA in these cases.

Maintenance therapy

In an initial trial in 59 lupus patients with severe renal disease (95% black or Hispanic, 78% with class IV disease, average SCr concentration of 1.6 mg/dL) who received initial treatment with glucocorticoids and monthly IV CYC pulses, both MPA and AZA were superior to quarterly IV CYC pulses for subsequent immunosuppression (relapse-free survival rates during 25 to 30 months of follow-up were 78%, 58%, and 4%, respectively).⁴⁷ Two subsequent RCTs compared MPA and AZA for maintenance treatment in lupus nephritis. The MAINTAIN trial included 105 European patients with proliferative lupus nephritis who received initial treatment with glucocorticoids and low-dose IV CYC (six fortnightly pulses of 500 mg).⁴⁸ Based on baseline randomization, AZA (target dosage 2 mg/kg/day) or MPA (target MMF dosage 2 g/day) was given at week 12 to all patients irrespective of their response to induction treatment. Over a 3-year period, the two groups experienced similar results in terms of renal flares (19% with MPA, 25% with AZA) and doubling of SCr level (6% with MPA, 8% with AZA). Repeat renal biopsies at 2 years failed to detect any significant differences between the two drugs.

These results are different from those reported from the ALMS maintenance study.⁴⁹ This trial included 227 patients (44% nonwhite) who showed a clinical response to either MPA or IV CYC during the induction phase.⁵⁰ These patients underwent a second random assignment to receive either MPA (target MMF dosage 2 g/day) or AZA (target dosage 2 mg/kg/day) and were followed for another 3 years. MPA proved superior to AZA in terms of treatment failure (16% vs. 32%) and renal flares (13% vs. 23%). Rate of treatment failure was 11% for sequential use of MPA after IV CYC compared with 21% for continued treatment with MPA after MPA, and 36% for sequential use of AZA after MPA. Infection rates were similar in the MPA- and AZA-treated groups, but withdrawal due to adverse events was more common with AZA. A meta-analysis of the aforementioned trials (n = 371 participants) found that risk of renal relapse was significantly greater with AZA than with MPA (RR, 1.83; 95% CI, 1.24 to 2.71), although there was no difference in incidence of ESRD, doubling of SCr level, or any adverse event except for leukopenia.^{40,41} We think that both agents can be used for maintenance of remission in lupus nephritis based on availability and potential for pregnancy (AZA preferred).

MPA should be continued if the drug was successful as induction treatment, whereas in the most severe cases, we opt for induction with IV CYC followed by long-term maintenance treatment with MPA.

Calcineurin inhibitors

Calcineurin inhibitors, including CsA and tacrolimus, are inhibitors of T-cell-mediated responses, with tacrolimus being about 10 to 100 times more potent. They were initially used in transplantation medicine but have also shown efficacy in lupus nephritis.

Cyclosporine

CsA has been studied for the treatment of both proliferative and membranous lupus nephritis.

In a randomized study, 40 patients with newly diagnosed class III-IV lupus nephritis and mild renal insufficiency were assigned to sequential therapy with either CYC (eight IV pulses for induction, oral pulses for maintenance) or CsA (4 to 5 mg/kg/day for induction, then tapered).⁵¹ During the induction phase (9 months), nearly three out of four patients in each group showed complete or partial response. At the end of the maintenance phase (18 months), the respective numbers showed a trend in favor of CsA (response rates of 95% vs. 52%), which was attributed to higher antiproteinuric potency. Infectious adverse effects were comparable in the two groups, although CsA was associated with transient increases in blood pressure and reductions in GFR. Another study compared CsA with AZA as a maintenance regimen in an RCT involving 69 patients with class IV lupus nephritis and preserved renal function.³⁶ Patients were initially treated with three daily pulses of 1 g IV MP followed by oral prednisone and CYC for

3 months. After this, they were assigned to receive either CsA (4 mg/kg/day for 1 month and then tapered) or AZA (1.5 to 2 mg/kg/day) for at least 2 years. The rate of flares was comparable in the two groups, and there was no difference in proteinuria and blood pressure levels. This suggests that CsA can be an alternative option for maintenance treatment in lupus nephritis patients with preserved renal function when other agents are not available, are contraindicated, or are not tolerated.

In a trial in patients with membranous nephritis, patients were randomly assigned to receive alternate-day prednisone alone or in combination with either IV CYC (six pulses administered every other month) or CsA (5 mg/kg/day, then adjusted).³¹ After 1 year, the cumulative probability of remission was 27% with prednisone alone, 60% with IV CYC, and 83% with CsA. Relapses of nephrotic syndrome occurred significantly more often after completion of CsA treatment than after IV CYC treatment, which suggests that although CsA is effective as induction therapy in class V nephropathy, maintenance treatment (with CsA or another immunosuppressive agent) may be required to prevent relapses. Common adverse events include mild gastrointestinal complaints, hirsutism, gingival hyperplasia, hypertension in more than 20% of patients, and nephrotoxicity, which is reversible after dose adjustment or drug discontinuation. The drug should be avoided in patients with impaired renal function.

Tacrolimus

Tacrolimus has been used as induction and maintenance therapy in lupus nephritis, particularly in Asian patients.^{49,52} Advantages over CsA include a lower incidence of blood pressure elevation, hyperlipidemia, and adverse cosmetic effects; however, nephrotoxicity still occurs. In a 24-week prospective study involving 60 Chinese patients with active lupus nephritis (87% class III-IV), patients were randomly assigned to receive MPA (MMF 1.5 to 2 g/day), tacrolimus (0.08 to 0.10 mg/kg/day), or IV CYC (monthly pulses of 0.5 to 0.75 g/m²), all in combination with oral prednisone (0.8 to 1.0 mg/kg/day, tapered). After 6 months, renal response occurred in 75% of the patients in the MPA and tacrolimus groups, and 60% of the patients in the CYC group ($P = .445$). More infections occurred in those receiving MPA (40%) and CYC (40%) than in those given tacrolimus (15%), whereas hyperglycemia was more frequent with tacrolimus (25% vs. 10% to 15% with MPA and CYC).

A small RCT compared MPA with tacrolimus in Chinese patients with pure class V lupus nephritis and nephrotic syndrome.⁴⁶ Patients received oral prednisone (0.8 mg/kg/day, tapered) and either MPA (target MMF dosage 1.5 to 2 g/day) or tacrolimus (titrated to a trough blood level of 6 to 8 mg/L). At 24 months, complete and partial response rates were 57% versus 11% ($P = .049$) and 14% versus 44% ($P = .197$) in the MPA and tacrolimus groups, respectively. Both agents were well tolerated, and no relapse occurred during the study period.

Biologic agents

Rituximab

Multiple small, uncontrolled studies have reported efficacy of rituximab (anti-CD20 monoclonal antibody) in lupus nephritis, particularly in patients in whom conventional immunosuppressive regimens, including CYC and MMF, have failed. Pooled data from centers in the United Kingdom and Spain reported complete or partial renal response in 67% of 164 lupus nephritis patients treated with rituximab (375 mg/m²/wk for 4 weeks, or 1000 mg/wk for 2 weeks), used in the majority of cases as second-line treatment for refractory or relapsing disease; 76% of these patients also received concomitant CYC or MMF.⁵³ The presence of nephrotic syndrome or renal failure at the time of rituximab administration was a predictor of poor prognosis and nonresponse. In a systematic review of 300 published cases, response criteria were met by 87% of patients with class III nephritis, 76% with class IV nephritis, and 67% with class V nephritis.⁵⁴

The LUNAR study, a randomized, double-blind, phase 3, multicenter trial comparing rituximab with placebo in 144 racially diverse patients with class III-IV lupus nephritis (average SCr concentration, 1.0 mg/dL; average UPCr, 4.0) failed to meet its primary endpoint, however.⁵⁵ Both groups received high-dose glucocorticoids (IV MP 1 g twice followed by oral prednisolone 0.75 mg/kg/day for 16 days, then tapered) and MPA (MMF 3 g/day). By week 52, the two groups did not differ in rates of complete or partial renal response, although there were numerically more responders in the rituximab group (57% vs. 46%). This trial was criticized for its use of high background immunosuppressive treatment, which might have diluted any effect attributable to rituximab. Until more data become available, we believe that rituximab constitutes a valid therapeutic option for patients whose disease is refractory or relapsing⁵⁶ while they are receiving conventional immunosuppressive agents.

Belimumab

Belimumab (anti-BLyS [B-lymphocyte stimulator]) has not been formally tested in lupus nephritis. Among patients who participated in the two phase 3 RCTs leading to drug approval, 20% had a UPCr of more than 0.5 and 6% had a UPCr of 2.0 or higher at baseline.^{57,58} Post-hoc analysis of the data for this subgroup of patients showed a positive trend in favor of belimumab for reduction of renal flares (1.4% in the 10 mg/kg-dose group vs. 2.8% in the placebo group) and reduction of proteinuria at 52 weeks.⁵⁹ A study of BLyS blockade in lupus nephritis, potentially as an add-on treatment in patients with incomplete response or frequent relapses, is reasonable.

Abatacept

Abatacept (CTLA-4-immunoglobulin) blocks CD28 costimulation on T cells and has been shown to halt progression of nephritis in lupus-prone mice, especially when combined with CYC.⁶⁰ An RCT compared two different doses of abatacept against placebo in 298 patients with class III-IV lupus nephritis. All patients received background immunosuppression with MPA (MMF 2 to 3 g/day) and oral prednisone (30 to 60 mg/day, tapered). After 12 months, abatacept treatment failed to increase the rates of complete response (defined as normalization of GFR, UPCr, and urinary sediment) over placebo, although a greater reduction in proteinuria was observed in patients with nephrotic syndrome at baseline.⁶¹ A post-hoc analysis showed that if less stringent outcome criteria were applied, complete response rates would be higher and significant differences (reaching almost 18%) would be noted in favor of abatacept.⁶² Additional clinical studies of the use of abatacept in lupus nephritis are now in progress.

TREATMENT OPTIONS AND RECOMMENDATIONS

Treatment of lupus nephritis depends on the histologic class and severity of disease, patient preferences, and access to medical care. A working classification of the severity of lupus nephritis, although arbitrary, is essential in

TABLE 136.3
Severity of lupus nephritis*

Proliferative disease	
Mild	Class III without severe histologic features (e.g., crescents, fibrinoid necrosis); low chronicity index (≤ 3); normal glomerular filtration rate; nonnephrotic-range proteinuria
Moderately severe	Mild disease as defined above with partial or no response after the initial induction treatment or delayed remission (>12 mo), or Class III nephritis with adverse histologic features or reproducible increase of $\geq 30\%$ in serum creatinine levels, or Class IV nephritis without adverse histologic features
Severe	Moderately severe as defined above but not responding after 6-12 mo of immunosuppressive treatment, or Class III-IV nephritis with impaired renal function and fibrinoid necrosis or crescents in $>25\%$ of glomeruli, or Mixed membranous and proliferative (class V+III-IV) nephritis, or Class III-IV nephritis with high chronicity alone or in combination with high activity (chronicity index > 4 or chronicity index > 3 and activity index > 10), or Rapidly progressive glomerulonephritis (doubling of serum creatinine within 2-3 mo)
Membranous nephropathy	
Mild	Nonnephrotic-range proteinuria with normal renal function
Moderate	Nephrotic-range proteinuria with normal renal function at presentation
Severe	Nephrotic-range proteinuria with impaired renal function at presentation ($\geq 30\%$ increase in serum creatinine level)

*Concomitant treatment with corticosteroids or other immunosuppressive drugs may modify urinary sediment and/or histologic findings and should be taken into consideration.

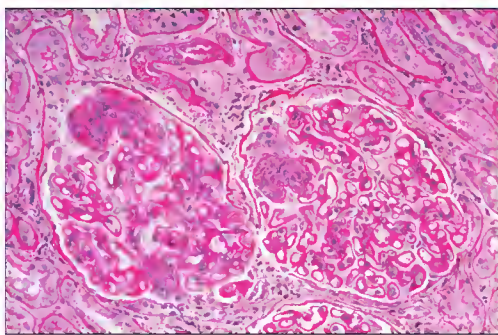


Fig. 136.2 Focal segmental (class III) lupus glomerulonephritis. In this patient with normal serum creatinine and nonnephrotic-range proteinuria, the absence of severe histologic features, the limited involvement (fewer than 50% of the glomeruli are involved), and the lack of significant chronic changes such as tubular atrophy and interstitial fibrosis suggest a mild disease. (Courtesy Dr. James E. Balow.)

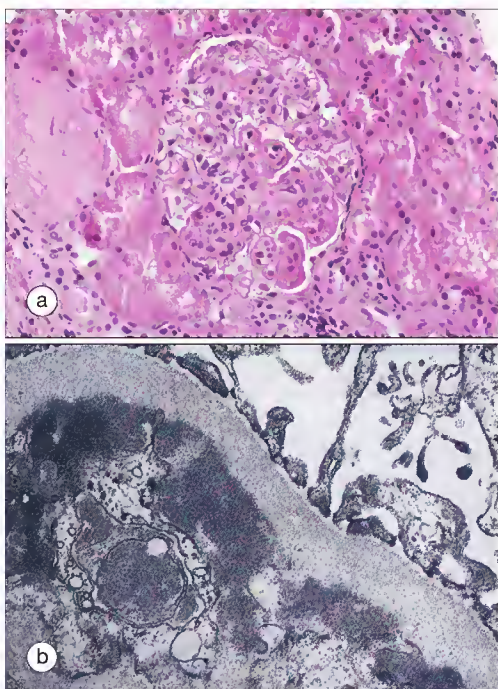


Fig. 136.3 Moderately severe diffuse proliferative (class IV) lupus nephritis. (a) Dramatic decreases in mesangial and endocapillary cellularity produce a lobular appearance of the glomerular tufts and compromise the patency of most capillary loops. (b) Note the presence of darkly staining subendothelial deposits in the electron micrograph, which results in the thickening of the capillary wall. This patient had active urine sediment, normal renal function, and nephrotic-range proteinuria. (Courtesy Dr. James E. Balow.)

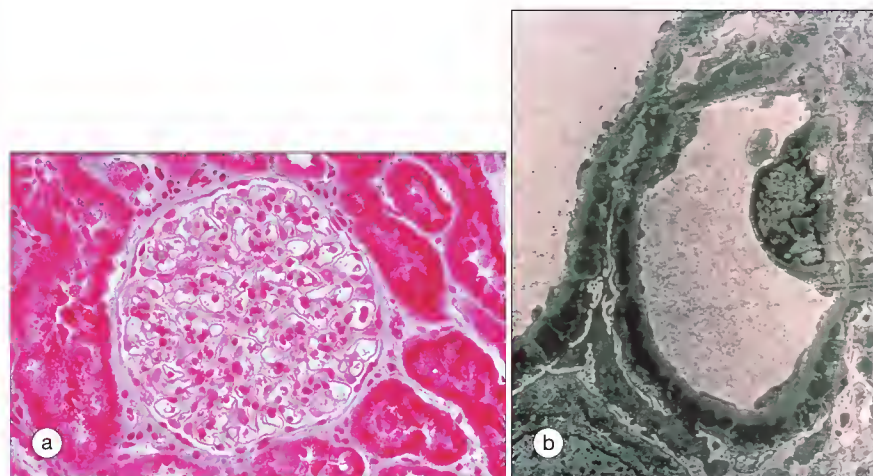


Fig. 136.4 (a) In membranous (class V) lupus nephropathy the capillary walls of the glomerular tuft are prominent and widely patent, resembling "stiff" structures with decreased compliance. (b) Electron microscopy reveals glomerular subepithelial (epimembranous) immune complex deposits that have been incorporated into the glomerular basement. The presence of severe nephrotic-range proteinuria despite normal renal function and the absence of significant chronic interstitial changes suggest a moderately severe disease. (Courtesy Dr. James E. Balow.)

discussing treatment recommendations (Table 136.3 and Figs. 136.2 to 136.5). Patient choices are particularly important, with several studies demonstrating unwillingness of patients to opt for the potent regimens containing cytotoxic agents when confronted with the potential adverse effects. Fertility is an especially emotional issue. Patients at high risk of ESRD should be thoughtfully counseled not to risk compromise of both future health and fertility because of renal failure by rejecting effective therapy for lupus nephritis.

Current strategies for management of lupus nephritis include an initial *induction phase* (lasting 3 to 6 months) aimed at substantially decreasing disease activity (or even attaining remission) and a *maintenance phase* in which the primary goal is to maximize the therapeutic effect and consolidate the response. During this later phase, the balance between the benefits of different regimens in avoiding relapses or smoldering disease activity and issues such as drug adverse effects and quality of life become more pressing. Table 136.4, Box 136.4, and Fig. 136.6 summarize treatment recommendations for all types of lupus nephritis that are based on the American College of Rheumatology¹⁰ and European League Against Rheumatism (EULAR)/European Renal Association–European Dialysis and Transplant Association (ERA-EDTA)³ recommendations for the management of lupus nephritis.

PROLIFERATIVE LUPUS NEPHRITIS

Initial (induction) treatment

Mild disease

A trial of prednisone (0.5 to 1.0 mg/kg/day for up to 4 to 6 weeks) with gradual tapering to alternate-day treatment (0.125 to 0.25 mg/kg) if response occurs, along with monitoring for flares, is our preferred approach for the most mild cases. Addition of alternative immunosuppressive therapy (AZA 1 to 2 mg/kg/day), either from the beginning or during tapering of glucocorticoids, may assist in tapering and decrease cumulative glucocorticoid dose. In selected cases, use of three consecutive pulses of IV MP (500 to 750 mg/pulse) may expedite remission and allow the use of lower dosages of oral prednisone (0.5 mg/kg/day). If the patient does not achieve complete response (clearing of cellular casts and proteinuria, normalization of complement levels, and minimal lupus activity) within 3 months, or if nephritis worsens, we consider initiation of MPA or IV CYC. Delay in cytotoxic therapy beyond 3 to 4 months because of a partial response may have a significant adverse impact on the response to cytotoxic therapy (suboptimal response or increased risk of flare).

Moderate disease

MPA in combination with glucocorticoids is recommended as first-line treatment for most patients with moderately severe lupus nephritis based on evidence of equivalent efficacy, more favorable toxicity profile, and easier administration compared with CYC-based regimens. Administration of three consecutive pulses of IV MP (500 to 750 mg/pulse) may allow the use of lower dosages of oral prednisone (0.5 mg/kg/day); higher dosages (up to 1 mg/kg/day) may still be required to control severe extrarenal activity. MPA exerts dose-dependent immunosuppression, and in RCTs, higher response rates were observed with higher average MPA dosages. Accordingly, the target dosage of MPA during the induction phase should be, if tolerated,

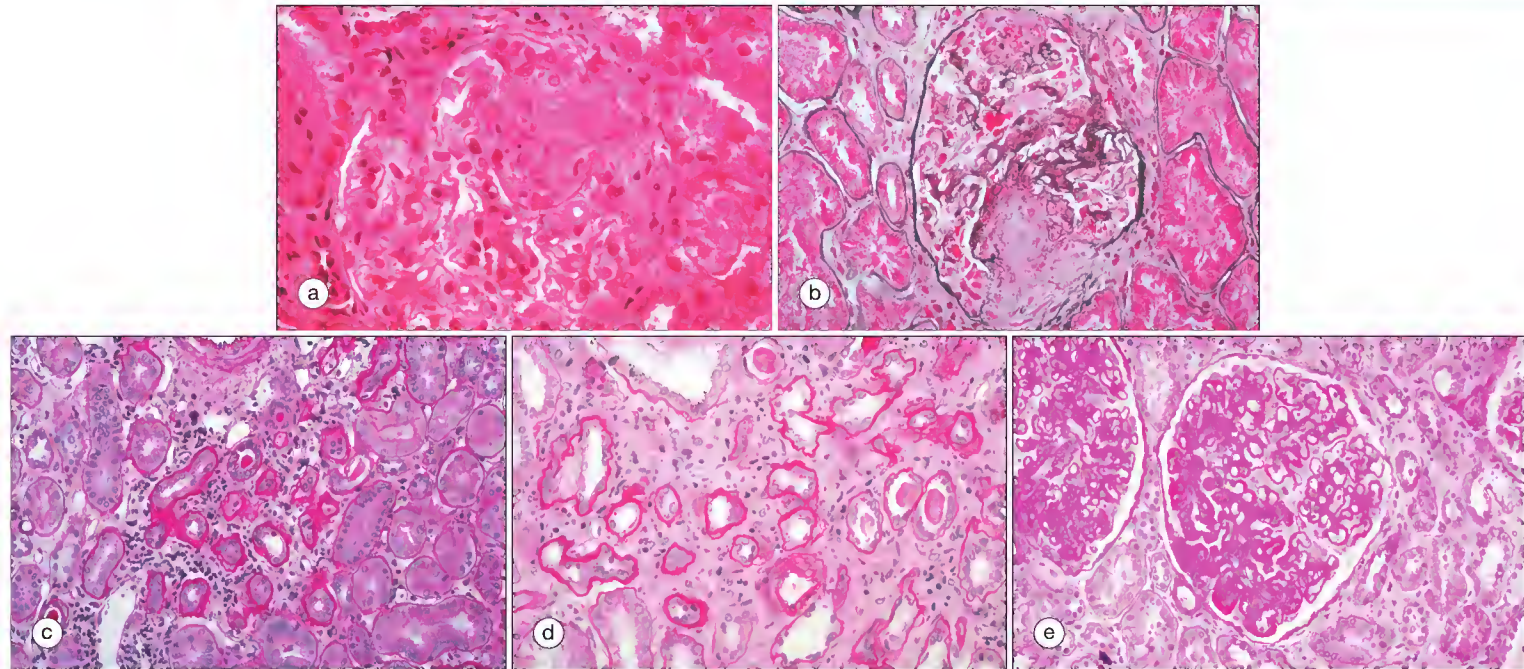


Fig. 136.5 High-risk histologic features suggesting a more severe nephritis. (a) Fibrinoid necrosis with karyorrhexis in a patient with class III glomerulonephritis. (b) Cellular crescents with layers of proliferative endothelial cells and monocytes lining a Bowman capsule along with a predominantly mononuclear interstitial infiltrate. (c) Moderate and (d) severe interstitial fibrosis and tubular atrophy. Note the thickening of the tubular basement membranes and tubular epithelial degeneration with separation of residual tubules due to deposition of collagenous connective tissue among tubules. (e) Mixed membranous and proliferative lupus glomerulonephritis. Note the combination of membranous lesions with the characteristic prominent and widely patent capillary walls, typical of membranous nephropathy, along with mesangial and endocapillary cellularity that compromises the patency of the involved capillary loops, typical of proliferative disease. (Courtesy Dr. James E. Balow.)

TABLE 136.4

Recommended treatment of lupus nephritis*

Histologic type/severity	Type of therapy	
	Induction	Maintenance
Proliferative		
Mild	- High-dose glucocorticoids (0.5-1 mg/kg/day for 4-6 wk with gradual tapering to 0.125 mg/kg every other day within 3-4 mo) alone or in combination with AZA (1-2 mg/kg/day) - If no response within 3-6 mo, treat as moderately severe	- Low-dose glucocorticoids (≤ 0.125 mg/kg on alternative days) alone or with AZA (1-2 mg/kg/day) - Consider further gradual tapering at the end of each year of response
Moderate	- MPA (MMF 3 g/day) with glucocorticoids (0.5 mg/kg/day for 4 wk, then taper) for 6 mo. Consider three initial pulses of IV MP (500-750 mg/pulse), or - Pulse IV CYC (3 g over 3 mo) with glucocorticoids as above - If no response within 6-12 mo, treat as severe	- Low-dose glucocorticoids (≤ 0.125 mg/kg on alternative days) with MPA (MMF 2 g/day) for 18-24 mo after initial response; then consider gradual tapering, or - AZA (2 mg/kg/day)
Severe	- Monthly pulses of IV CYC (0.5-1 g/m²) in combination with pulse IV MP for 6 mo. Background glucocorticoids (0.5 mg/kg/day for 4 wk, then taper), or - MPA (MMF 3 g/day) - If no improvement, consider MPA or rituximab	- Low-dose glucocorticoids (≤ 0.125 mg/kg on alternative days) in combination with quarterly pulses of IV CYC for at least 1 yr beyond response, or - MPA (MMF 2 g/day)
Membranous		
Mild	High-dose glucocorticoids alone or in combination with AZA (2 mg/kg/day)	Low-dose glucocorticoids alone or with AZA (1-2 mg/kg/day)
Moderate/severe	- High-dose glucocorticoids in combination with MPA (MMF 3 g/day), or - Bimonthly pulse IV CYC (0.5-1 g/m², six pulses), or - CsA (3-5 mg/kg/day)	- Low-dose glucocorticoids - AZA (2 mg/kg/day) - CsA (3 mg/kg/day) - MPA (MMF 2 g/day)

*See text for dose and further details.

AZA, azathioprine; CsA, cyclosporine A; CYC, cyclophosphamide; IV, intravenous; MMF, mycophenolate mofetil; MP, methylprednisolone; MPA, mycophenolic acid.

MMF 3 g/day (or eMPA 2160 mg/day) given for 6 consecutive months. Dose reduction should be considered in patients with a GFR of less than 30 mL/min. If gastrointestinal complaints develop, reduction of the daily dose, splitting of the total dose into three or four doses per day, or use of eMPA can be attempted. Although a few studies have reported associations between clinical endpoints and MPA pharmacokinetics (drug trough blood levels at 12 hours, or the area under the curve from 0 to 12 hours),^{63,64} further studies

are needed to determine whether MPA therapeutic drug monitoring can improve efficacy in lupus nephritis. Evidence from the EuroLupus Nephritis Trial²⁹ suggests that the low-dose IV CYC regimen (3 g over 3 months) may be a valid alternative for white patients. When neither MPA nor CYC can be used, patients may be given a trial of AZA (2 mg/kg/day) in combination with IV MP pulses, although this regimen is associated with increased risk of relapse.³² Tacrolimus has been efficacious in Asian patients, but additional

BOX 136.4 JOINT EULAR/ERA-EDTA RECOMMENDATIONS FOR THE TREATMENT OF LUPUS NEPHRITIS**Initial (induction) treatment of lupus nephritis**

- For class IIIA or A/C ($\pm$ V) and class IVA or A/C ($\pm$ V) lupus nephritis: consider
 - MPA (target MMF dose 3 g/day [or eMPA at equivalent dose] for 6 months) (evidence A*), or
 - Low-dose IV CYC (3 g over 3 months) (evidence B), in combination with glucocorticoids
- For severe lupus nephritis with adverse clinical or histologic prognostic factors: consider
 - Similar regimens (MPA (evidence B), low-dose IV CYC (evidence C), but also
 - High-dose IV CYC (0.75 to 1 g/m² for 6 months) (evidence A) or,
 - Oral CYC (2 to 2.5 mg/kg/day for 3 months) (evidence B), in combination with glucocorticoids
- For class V lupus nephritis with nephrotic-range proteinuria: consider
 - MPA (target MMF dose 3 g/day [or eMPA at equivalent dose] for 6 months) (evidence B), in combination with glucocorticoids
 - Alternative options, or for nonresponders: high-dose IV CYC (0.75 to 1 g/m² for 6 months) (evidence A), calcineurin inhibitors (cyclosporine, tacrolimus) (evidence B), or rituximab (evidence C)
- For selected cases of class III-IV or class V lupus nephritis without adverse clinical or histologic prognostic factors, or when MPA and CYC are contraindicated, not tolerated, or unavailable, consider
 - AZA (2 mg/kg/day) (evidence B/C)—associated with higher relapse risk (evidence B)

Subsequent (maintenance) treatment of lupus nephritis

- In patients showing improvement after initial treatment: consider either
 - MPA (initial target MMF dose 2 g/day [or eMPA at equivalent dose]) (evidence A), or
 - AZA (2 mg/kg/day) (evidence A), for at least 3 years, in combination with low-dose prednisone (5 to 7.5 mg/day)
- In patients showing response to initial treatment with MPA:
 - Continue with MPA (evidence C),
 - Switch to AZA if pregnancy is contemplated (evidence C)

Treatment of refractory lupus nephritis

- For patients in whom treatment fails either because of lack of effect or adverse events:
 - Switch from MPA to CYC (evidence C), or
 - Switch from CYC to MPA (evidence C), or
 - Switch to or add rituximab (evidence C)

*Evidence was categorized as follows: A, evidence from RCT(s) or long-term follow-up study of outcomes or post-hoc analysis based on the original randomization allocation without concerns for the validity of the evidence; B, as with A but with concerns about the validity of the evidence, evidence from non-randomized controlled studies without major concerns about the validity of the evidence; C, evidence from non-randomized studies but with concerns about the validity of the evidence, or evidence from case-series, or extrapolation from non-SLE literature, or expert opinion.

AZA, azathioprine; CYC, cyclophosphamide; eMPA, enteric-coated mycophenolate sodium; ERA-EDTA, European Renal Association–European Dialysis and Transplant Association; EULAR, European League Against Rheumatism; IV, intravenous; MPA, mycophenolic acid; MMF, mycophenolate mofetil.

evidence from randomized trials is required. Failure to achieve significant improvement after the initial 6 to 12 months of treatment should precipitate decisions about switching to high-dose pulse IV CYC (see later).

Severe disease

Most investigators agree that, in addition to high dosages of prednisone (0.5 to 1.0 mg/kg/day tapered after 4 weeks), cytotoxic drugs must be administered to patients with severe disease, at least during the induction period. Based on evidence from randomized trials,²² we recommend seven monthly pulses of IV CYC (0.75 to 1 g/m²/pulse) in combination with three initial pulses of IV MP (500 to 1000 mg/pulse) at the start that are continued in patients with more severe disease (crescentic nephritis, rapidly progressive glomerulonephritis) at monthly intervals (one pulse per month) for the first 6 to 12 months. Alternative regimens include (1) oral MPA (target MMF dosage 3 g/day unless there is severe renal impairment) for 6 months,⁴³ or (2) oral CYC (2 to 2.5 mg/kg/day) for 3 months, both in combination with high-dose glucocorticoids.

Subsequent (maintenance) treatment**Mild/moderate disease**

Treatment should include low-dose glucocorticoids (7.5 to 15 mg prednisone on alternate days) in combination with either AZA (2 mg/kg/day) or MPA (target dosage 2 g/day; or eMPA 1440 mg/day), although lower dosages have also been efficacious in patients who did not tolerate higher dosages. A meta-analysis of RCTs demonstrated superiority of MPA over AZA as a response-maintaining regimen in proliferative lupus nephritis; however, both agents yielded extremely low rates of doubling of SCr level, ESRD, and death.⁴¹ Based on the results of ALMS, patients who responded to induction treatment with MPA should continue with MPA, since switching to AZA was associated with more treatment failures.⁵⁰ For patients who were initially treated with IV CYC, and considering the cost difference between the two drugs, we would favor the use of AZA in most cases, especially in white patients.⁶⁵ For pregnant patients and those planning pregnancy, AZA is clearly the drug of choice. Calcineurin inhibitors represent an alternative option.³⁶

The optimal duration of maintenance immunosuppression remains unknown, although recent trials have shown that both AZA and MPA are well tolerated over a period of 3 to 4 years. Gradually tapering the dose of immunosuppressive agent and/or switching from MPA to AZA can be attempted after renal response has been maintained for at least 18 to 24 months, since earlier treatment modifications are associated with increased risk of renal flares.⁶⁶⁻⁶⁸

Severe disease

In patients with severe disease, we recommend maintenance treatment with MPA (target MMF dosage 2 g/day) for at least 3 years, based on the results of ALMS, which showed that the lowest rates of treatment failure were seen in patients who received pulses of high-dose IV CYC followed by immunosuppression with MPA.⁵⁰ IV CYC (0.5 to 1 g/m²), pulsed every 3 months until 12 months beyond renal response, may be used in selected cases, such as in patients who had severe nephritic syndrome and reduced GFR or substantial crescents or necrosis in the kidney biopsy specimen at presentation.^{22,23} Microscopic hematuria and nonnephrotic proteinuria may not clear for several months, even when most other clinical parameters have improved. Treating physicians should realize that complete renal response usually occurs at an average of approximately 1.5 to 2 years after treatment.^{23,32} Therefore abandoning pulse IV CYC therapy because of lack of complete response before at least 2 years of treatment have been completed is not justified unless there is suboptimal response (less than 50% reduction in proteinuria) or worsening of the disease (reproducible reduction in GFR or more than 50% increase in proteinuria at the nephrotic range). In selected patients with severe disease, AZA can be used as a maintenance therapy, provided that near-complete response has been achieved.

MEMBRANOUS LUPUS NEPHROPATHY

Lupus membranous (class V) nephropathy with only background mesangial expansion (pure membranous) has a low risk of progression to ESRD (20% at 10 years). Persistent nephrotic-range proteinuria, impaired renal function, and black race have been implicated as high-risk factors.^{21,69} Persistent nephrotic syndrome increases substantially the risk of arteriosclerotic and thromboembolic complications and adversely affects patient survival. Mixed membranous and proliferative histologic type (class V+VI or class V+III) carries a worse prognosis than even pure proliferative disease, and these patients should be treated the same as those with proliferative disease.

Initial (induction) treatment

A post-hoc analysis of the data for patients with pure class V lupus nephritis and nephrotic syndrome who participated in two short-term RCTs demonstrated comparable antiproteinuric effects in MPA- and IV CYC-treated patients.⁴⁵ MPA (target dose 3 g/day for 6 months) in combination with oral prednisone (starting dose 0.5 mg/kg/day) may therefore be considered as initial treatment for these patients. Evidence from randomized trials also suggests treatment with alternate-day prednisone (0.5 to 1.0 mg/kg) for 2 months tapered to 0.25 mg/kg on alternate days within 3 to 4 months with pulse IV CYC every 2 months (especially in severe disease) or CsA (5 mg/kg/day or less) for 1 year.³¹ Tacrolimus has demonstrated efficacy in Asian patients.⁴⁶ The low-dose IV CYC regimen has not been tested in patients with pure class V lupus nephritis.

Patients with nonnephrotic proteinuria (usually a UPCr of less than 2.0) should be treated initially with titrated doses of renin-angiotensin-aldosterone axis (RAAS) blockers and low-dose glucocorticoids. Careful

RECOMMENDATIONS FOR THE TREATMENT OF PROLIFERATIVE AND MEMBRANOUS LUPUS NEPHRITIS

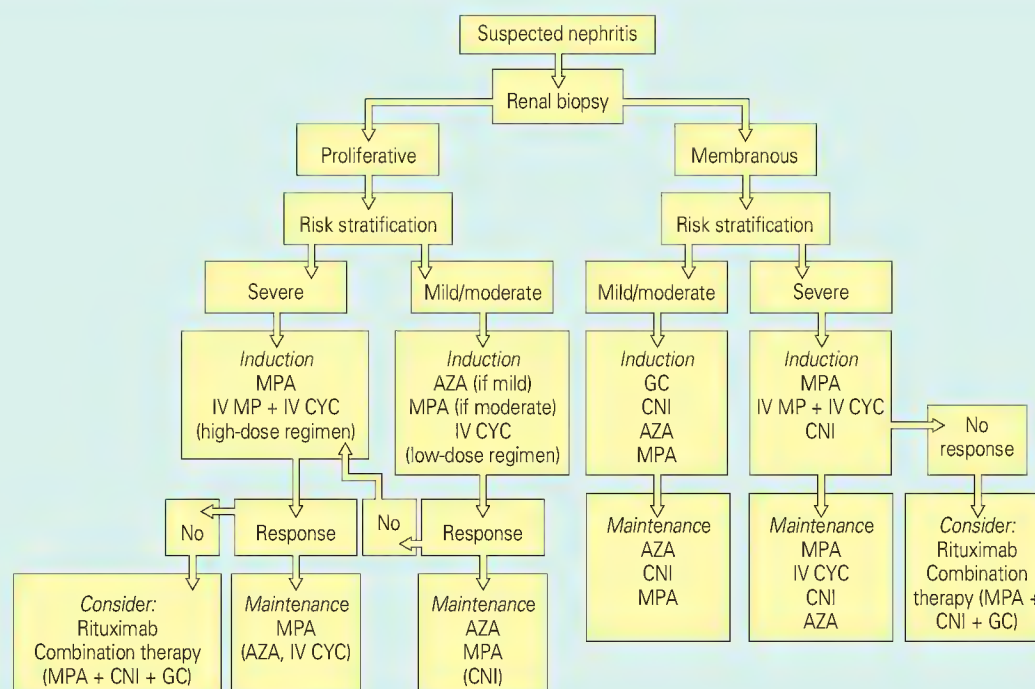


Fig. 136.6 All regimens are administered on a background of glucocorticoids, which includes three consecutive pulses of intravenous methylprednisolone (0.5 to 1 g/pulse), followed by oral prednisone (0.5 mg/kg/day for the first 4 to 6 weeks of induction, and 0.25 mg/kg every other day for maintenance). The National Institutes of Health regimen (seven monthly pulses of intravenous cyclophosphamide 0.5 to 1.0 g/m²) is for high-risk patients (those with impaired renal function, adverse histologic features [crescents, fibrinoid necrosis, chronicity index of more than 3]), and the Euro-Lupus regimen (six fortnightly pulses of intravenous cyclophosphamide 500 mg) is for low- to intermediate-risk white patients. AZA, azathioprine; CNI, calcineurin inhibitors (cyclosporine, tacrolimus); CYC, cyclophosphamide; GC, glucocorticoids; IV, intravenous; MP, methylprednisolone; MPA, mycophenolic acid.

monitoring for progression to nephrotic syndrome or to mixed membranous and proliferative nephropathy is warranted. Addition of an immunosuppressive agent such as AZA, CsA, or MPA may be considered to minimize the cumulative dose of glucocorticoids or in cases of persistent proteinuria (UPCR of more than 1.0).

Subsequent (maintenance) treatment

Maintenance therapy with AZA or lower doses of CsA may help to prevent relapses, although this has not been formally tested. In severe cases, MPA (target MMF dose 2 g/day) may be used for the first 1 to 2 years.

RESPONSE, REMISSION AND RELAPSE

Renal response and refractory nephritis

Defining renal response and relapse has prognostic implications and may assist in therapeutic decisions. The EULAR/ERA-EDTA recommendations defined *partial renal response* as at least 50% reduction in UPCR and normal or near-normal (within 10% if initially abnormal) GFR.³ Partial response should be achieved preferably 6 months and no later than 12 months after initiation of treatment, since this is associated with long-term preservation of renal function.^{8,9,67} The ultimate goal of treatment should be *complete renal response*, defined as a UPCR of less than 0.5 and normal or near-normal (within 10% if initially abnormal) GFR.³ This is based on evidence that in proliferative lupus nephritis, achievement of complete response compared with partial response is associated with lower risk of development of ESRD.^{16,67,70} In some patients a complete response may not be achieved until 1 to 2 years after initiation of immunosuppressive treatment. A sustained complete response lasting at least 3 to 6 months can be considered as a remission but cannot be judged to be a complete remission in the absence of new biopsy findings. Partial response may be an acceptable outcome when all treatment modalities have been exhausted or cannot be used due to the high risk of toxicity.

A significant number of patients have lupus nephritis resistant to standard immunosuppressive treatments. Based on the previous descriptions of outcomes in lupus nephritis, the EULAR/ERA-EDTA recommendations defined *refractory disease* as failure to achieve (1) any reproducible reduction in UPCR during the first 3 to 4 months, or (2) partial renal response after 6 to 12 months, or (3) complete renal response after 1 to 2 years of immunosuppressive treatment.³ There is paucity of data to guide the management of refractory lupus nephritis; in such cases, decisions may be facilitated by repeating renal biopsy. Uncontrolled evidence suggests that for patients who show no response to MPA or CYC, treatment may be switched from MPA to CYC or from CYC to MPA,⁷¹ or rituximab may be given either as add-on treatment or as monotherapy.³⁴ Additional options include calcineurin inhibitors (CsA, tacrolimus),^{72,73} IV immunoglobulin, plasma exchange, or immunoadsorption. Combination treatment with MPA (MMF 2 g/day), tacrolimus (4 mg/day), and glucocorticoids was superior to treatment with IV CYC (six to nine monthly pulses of 1 g/m²) in patients with class V+VI lupus nephritis refractory to previous immunosuppression with CYC or MPA.⁷⁴

Renal relapses

Approximately 30% to 50% of patients with proliferative lupus nephritis experience relapse after showing partial or complete response to therapy.^{8,16,75} The diagnostic workup for patients experiencing nephritis flare is outlined in Table 136.5. Patients may experience nephritic or proteinuric flares, with the former having more adverse impact on renal outcomes.⁷⁶ Nephritic flares consist of a reproducible increase in SCr concentration of 30% or more (or a reduction in GFR by 10% or more) and active urine sediment with an increase in glomerular hematuria by 10 or more red blood cells per high-power field, irrespective of changes in UPCR. Proteinuric flares consist of a reproducible doubling of UPCR to more than 1.0 after complete renal response or a reproducible doubling of UPCR to more than 2.0 after partial response.^{3,76} Patients who show substantial loss of renal function (SCr concentration of more than 2 mg/dL at the time of response), only partial renal response to treatment, and high chronicity and activity indexes on kidney

TABLE 136.5
Diagnostic approach to a patient with nephritis flare

Confirm flare	■ Is there evidence of extrarenal disease activity? ■ Is there evidence of active renal disease (active urine sediment, ↑ SCr, ↑ UPCR, ↑ anti-dsDNA, ↓ C3)?
Exclude other causes of renal dysfunction	■ Dehydration, uncontrolled hypertension, contrast agents, drugs, nonglomerular hematuria
Nephritic or nephritic flare?	■ Nephritic: active urine sediment, ↑ anti-dsDNA, ↓ C3, stable or increased SCr, ± increase in UPCR ■ Nephrotic: increase in UPCR
Mild or severe flare?	■ Mild/moderate: – Stable SCr – Active urine sediment (cellular casts or >10 red blood cells/high-power field) – ↑ UPCR (≤2.0 for mild, >2.0 for moderate) ■ Severe – ↑ SCr ≥30% from baseline – Active urine sediment
Consider renal biopsy if	■ Flare with nephrotic-range proteinuria ■ Nephritic flare if previous biopsy findings showed mesangial or membranous glomerulopathy, to rule out histologic transformation into a more aggressive type ■ Probably no biopsy in a nephritic flare if previous biopsy finding of proliferative glomerulonephritis

dsDNA, double-stranded DNA; SCr, serum creatinine; UPCR, urine protein-creatinine ratio.

biopsy are more likely to progress to ESRD after a nephritic flare.⁸ These observations would seem to argue in support of strategies to minimize the risk of flare in patients with lupus nephritis; however, although preemptive treatment based on a rising anti-dsDNA titer and/or decrease in serum complement levels without additional evidence of clinically active lupus may prevent flares in a few patients, for the most part these flares are mild, and preventing them comes at the expense of overtreating a much larger number of patients.⁷⁷

For severe nephritic flares with reduction in GFR, reinstitution of immunosuppressive treatment with monthly pulses of IV CYC and glucocorticoids is our preferred approach, with MPA considered as an alternative agent. For a proteinuric or a mild nephritic flare, glucocorticoids alone or combined with AZA or MPA can be used. Rituximab has also shown efficacy in the management of proteinuric renal relapses.⁵⁶ Table 136.6 outlines our current approach to the management of renal flares.

COMORBID CONDITIONS

Hypertension

Hypertension is an independent risk factor for progressive renal failure and cardiovascular disease, and it is associated with worse renal outcome in lupus nephritis.^{75,78} Target blood pressure is less than 130/80 mm Hg and less than 125/75 mm Hg in patients with a UPCR of more than 1.0, since this is beneficial in terms of maintaining lower rate of GFR decline. RAAS blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is the initial treatment of choice to control blood pressure in most patients. These drugs exert antiproteinuric effects and may be more effective than other agents in reducing the development of ESRD by mechanisms not necessarily related to the control of blood pressure. Patients receiving RAAS blockers need close monitoring for hyperkalemia and worsening renal function for several weeks after initiation of therapy. Adequate blood pressure control often requires addition of other classes of antihypertensive agents such as diuretics and calcium channel blockers, which exert modest antiproteinuric effect.

Dyslipidemia and cardiovascular morbidity

Patients with lupus nephritis are at increased risk of cardiovascular disease and demonstrate 2.8- to 10-fold increased rates of acute myocardial infarction. In addition to conventional risk factors such as hypertension, diabetes

TABLE 136.6
Treatment recommendation for renal flares

Recommended	Alternative
Nephritic	
Mild/moderate	
High-dose glucocorticoids (if no remission in 8 wk, treat as severe)	Glucocorticoids with AZA or MPA
Severe	
Monthly pulses of IV CYC (± IV MP)	Glucocorticoids with MPA, rituximab
Proteinuric	
Mild/moderate	
Moderate dose of glucocorticoids	AZA or CNI (CsA, tacrolimus)
Nephrotic	
High-dose glucocorticoids	Glucocorticoids with CNI, MPA, or bimonthly pulses of IV CYC Rituximab

AZA, azathioprine; CNI, calcineurin inhibitors; CsA, cyclosporine A; CYC, cyclophosphamide; IV, intravenous; MP, methylprednisolone; MPA, mycophenolic acid.

mellitus, and dyslipidemia, attributed both to increased inflammatory burden and the concomitant use of glucocorticoids, other metabolic abnormalities such as premature menopause, kidney failure, dysfunctional high-density lipoprotein, oxidized low-density lipoprotein particles, and higher plasma homocysteine levels are also more prevalent.⁷⁹ Aggressive management of dyslipidemia (serum low-density lipoprotein cholesterol levels of 100 mg/dL or less and serum triglyceride levels of less than 150 mg/dL) is recommended, particularly if chronic kidney disease has developed. Statins may reduce the risk of venous thromboembolism, but their potential use in primary or secondary prevention of thrombotic events in high-risk SLE patients (those with nephritic syndrome or antiphospholipid antibodies) is uncertain. A single randomized, placebo-controlled trial assessed the effects of fluvastatin (40 to 80 mg/day) in 33 lupus nephritis patients who had received a renal transplant due to ESRD.⁸⁰ At the time of trial initiation all patients had dyslipidemia and were receiving triple immunosuppressive treatment with a calcineurin inhibitor, AZA, and prednisone. Fluvastatin treatment significantly reduced the levels of low-density lipoprotein cholesterol and total cholesterol, and there was a trend toward increased major cardiac events in the placebo arm compared with the fluvastatin arm. The role of daily aspirin for primary prevention in lupus nephritis patients has not been studied formally, but such prophylaxis is worth considering on an individual basis.

Thrombotic diathesis and renal vasculopathy

Nephrotic syndrome is associated with increased synthesis of clotting factors and loss of fibrinolytic proteins, such as protein S and C, in the urine. Together with antiphospholipid antibodies, they contribute to a thrombophilic diathesis in lupus nephritis. Patients with nephrotic syndrome (especially those with membranous nephropathy) should be informed about the potential for thrombosis (usually deep vein thrombosis, pulmonary embolism, or renal vein thrombosis). Renal vein thrombosis, although it may be asymptomatic, usually manifests itself with flank pain, hematuria, and worsening proteinuria.

The role of microvasculopathy in the progression of renal insufficiency in lupus nephritis is perplexing. Extraglomerular and intraglomerular renal vascular lesions; subintimal eosinophilic deposits that stain with periodic acid-Schiff stain; and intimal hyperplasia are common in lupus, even in the absence of hypertension. Immune complex deposition (with or without necrosis) within arterioles and small arteries is seen frequently in immunofluorescence studies. The hypothesis has been put forward that microthrombi in glomerular capillaries may contribute independently to progression of renal disease, but true microthrombi (thrombotic microangiopathy) are rather rare in the absence of antiphospholipid antibodies.⁸¹ Antiphospholipid syndrome-associated nephropathy, characterized by thrombotic microangiopathy and chronic histologic lesions such as fibrous intimal hyperplasia, organizing thrombi with recanalization, focal cortical atrophy, and fibrous occlusions of arteries and arterioles,⁸² occurs in lupus patients with antiphospholipid antibodies. Antiphospholipid

syndrome–associated nephropathy has been found to be associated with hypertension, higher SCr levels, and interstitial fibrosis. In patients with coexistent histologic features of nephritis, hydroxychloroquine and/or antiplatelet-anticoagulant treatment can be considered along with immunosuppressive therapy and RAAS blockade for control of blood pressure and proteinuria, but there are no controlled studies of this therapy. Patients with antiphospholipid syndrome should receive anticoagulant treatment.⁸³ True thrombotic thrombocytopenic purpura (TTP), defined as TTP when lupus is inactive, or a TTP-like syndrome with thrombotic microangiopathic hemolytic anemia in patients with systemic activity, may develop lupus patients in rare cases; because the prognosis is poor, such patients must be recognized and treated early.

LUPUS NEPHRITIS IN PREGNANCY

Glomerular perfusion increases during pregnancy, which causes a reduction in SCr levels. In women with significant prepregnancy proteinuria (UPCR of 1.0 or more) protein excretion may increase significantly between 18 and 36 weeks of gestation followed by a sharp decrease postpartum. Patients with normal or near-normal GFR (SCr concentration of less than 1.4 mg/dL) at the time of conception have no worsening of renal function provided there is inactive urine sediment and UPCR is less than 0.5 to 1.0. These women also have a high probability of successful pregnancy. Women with a variety of glomerular diseases and increased SCr levels at baseline have a 10% risk of developing ESRD, whereas those with an SCr concentration of more than 2 mg/dL have a 35% risk. These patients also have a higher risk of hypertension, worsening of proteinuria, and premature delivery and fetal intrauterine growth retardation.^{84,85}

Pregnant lupus nephritis patients should be followed by a multidisciplinary team. For patients with stable renal disease, treatment includes hydroxychloroquine, low-dose prednisone, AZA, and CsA. Hydroxychloroquine should be administered particularly if immunosuppressive agents need to be stopped. MPA or CYC should not be used in the last 3 months of pregnancy, and biologic agents should not be used for at least 4 months before conception, depending on the agent. RAAS blockers should not be used at the time of conception if possible, due to their potential teratogenic effect during the first trimester, or they should be switched to other antihypertensive agents such as nifedipine or labetalol as soon as pregnancy is confirmed. Aspirin therapy should be considered to reduce the risk of preeclampsia.⁸⁴ For patients who are receiving anticoagulant treatment or for whom such treatment is planned, low-molecular-weight heparin should be prescribed, since warfarin should not be used during pregnancy.

Falling serum complement levels and increased creatinine and uric acid levels during pregnancy should raise the suspicion of lupus nephritis rather than preeclampsia. In these patients the presence of nephritic urine sediment is strong evidence for lupus nephritis. Close surveillance for renal relapse during the postpartum period is essential. Refractory cases can be treated with IV immunoglobulin, immunoadsorption, and possibly plasma exchange, depending on disease severity.^{84,86}

LUPUS NEPHRITIS IN CHILDREN

Compared with adults, children with lupus have more active disease at diagnosis and during follow-up, have a higher incidence of glomerulonephritis (60% to 80%), and receive higher doses of glucocorticoids and immunosuppressive drugs.^{87,88} Response to treatment does not differ significantly between children and adults. Children have a greater capacity to compensate for glomerular damage by compensatory hypertrophy in the less involved glomeruli and thus to preserve renal function, although in the long term hyperfiltration may assist glomerulosclerosis.

As in adults, the management of lupus nephritis in children and adolescents is divided into the induction and maintenance phases, and the treatment of relapses. In mild cases (class II nephritis or class III nephritis with a low activity index) with normal GFR, normal blood pressure, and non-nephrotic proteinuria, oral glucocorticoids (up to 1 mg/kg/day) may suffice. Initial pulses of IV MP (30 mg/kg/day up to 1 g/day for 3 consecutive days) may allow a lower oral prednisone dosage (0.5 mg/kg/day). In patients with class III nephritis and a high activity index (more than 10 to 12) or class IV disease, pulse therapy with IV MP and IV CYC (0.75 to 1.0 g/m²) or MPA can be considered. The clinical and histologic progression of class III-IV nephritis in 16 children who completed at least 3 years of continuous treatment with IV CYC was reported, and significant improvements in disease activity, GFR, and renal activity index were observed.^{89,90} In a study of 13

adolescent patients with class III lupus nephritis who were initially treated with either IV CYC (seven monthly pulses of 0.5 to 1 g/m²) or MPA (MMF 300 to 900 mg/m²), both in combination with oral prednisone (2 mg/kg/day, tapered), followed by maintenance treatment with MPA, renal response rates were comparable with IV CYC and MPA, both at the end of the induction phase (57% vs. 83%, respectively) and after an average follow-up of 2 to 3 years (71% vs. 67%, respectively).⁹¹ A subset analysis of the ALMS data for 24 patients younger than 18 years of age (average age, 14.8 years) showed that IV CYC and MPA were comparable in inducing response at 6 months.⁹² Sixteen patients were subsequently enrolled in the maintenance phase, randomly assigned to receive either MPA or AZA. During follow-up, one patient treated with MPA (13%) experienced treatment failure compared with five patients treated with AZA (63%), although results did not reach statistical significance due to the small number of patients. Important to note, serious infections occurred in 30% of those receiving MPA and 21% of those treated with CYC.⁹²

In a retrospective study, 20 pediatric patients with severe proliferative lupus nephritis (average GFR, 71 mL/min/1.73 m²; nephrotic-range proteinuria in 80%) received 6 months of induction therapy with pulse IV MP (30 mg/kg, followed by oral prednisone 0.5 to 1.0 mg/kg/day) and IV CYC (0.5 g/m²).⁹³ AZA (2 mg/kg/day) was commenced as a remission-maintaining regimen in all patients; in 10 patients, treatment was subsequently switched to oral MPA (MMF 1200 mg/m²/day) due to intolerance or lack of efficacy. When this approach was followed, 70% showed complete response and another 15% experienced partial response. Combinations of MPA and CsA have also been used for the treatment of severe class III-IV lupus nephritis that did not respond adequately to initial induction treatment.⁹⁴ Together, these results suggest that either IV CYC or MPA may be considered for the initial management of pediatric lupus patients with active proliferative nephritis, including severe forms. For maintenance treatment, either AZA or MPA can be used, with MPA exerting more potent immunosuppression. An alternate-day regimen of oral prednisone 10 to 15 mg should be the aim during the maintenance phase.

Renal flares are an important issue that has not been adequately addressed. An alternative to a second course of IV CYC and glucocorticoids, which may be associated with significant long-term toxicity, is initiation of MPA or a combination of IV methotrexate and CYC. Rituximab (600 mg/m², maximum dose of 1 g/m² on days 1 and 15) has been successful in patients with refractory renal and extrarenal disease and can be used as monotherapy or in combination with CYC.⁹⁵

MANAGEMENT OF CHRONIC RENAL INSUFFICIENCY

As in other chronic glomerulopathies, progressive renal injury in lupus nephritis involves predominantly nonimmune mechanisms. Persistent proteinuria, hypertension, and dyslipidemia are implicated in the deterioration of renal function. Maladaptive compensatory mechanisms (glomerular hypertrophy, increased blood flow, intraglomerular hypertension) working in concert with ongoing immunopathogenic processes culminate in progressive decline of GFR. Based on the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (www.kidney.org/professionals/KDOQI/), efforts should aim to minimize exposure to nephrotoxic drugs and contrast agents, avoid dehydration, correct anemia by the use of erythropoietin to keep hemoglobin concentration at 10 to 11 g/dL, use calcium carbonate (650 mg 1 to 3 times a day) to decrease intestinal absorption of phosphates and ameliorate metabolic acidosis, and restrict protein and salt intake (Table 136.7).

END-STAGE RENAL DISEASE AND DIALYSIS

Approximately 10% to 20% of patients with lupus develop ESRD. Progression of lupus nephritis to the point of dialysis does not necessarily indicate ESRD, and 5% to 10% of patients requiring dialysis eventually recover sufficient renal function to interrupt dialysis temporarily or for long periods. Patients with rapid deterioration of renal function are more likely to have a reversible physiologic (e.g., acute tubular necrosis) or pathologic (e.g., crescentic glomerulonephritis) component. In these patients, immunosuppressive therapy may continue during dialysis (pulse IV MP with pulse IV CYC 0.4 to 0.5 g/m² administered 8 to 10 hours before dialysis). We generally consider discontinuing immunosuppressive treatment in patients with an SCr concentration rising steadily to 5 mg/dL or higher, inactive urine sediment, and contracted renal size, or with renal biopsy results showing class VI disease.

TABLE 136.7
Management of chronic kidney disease in patients with lupus nephritis*

Detecting reversible causes of renal deterioration	
■ Hypovolemia	– Vomiting, diarrhea, diuretic use, fever, sepsis
■ Drugs that lower the GFR	– NSAIDs: especially when administered to patients with hypotension
	– ACE inhibitors/ARBs: especially when administered to patients with bilateral renal artery constriction/mononephros
■ Nephrotoxic drugs	– NSAIDs
	– Radiographic contrast material
	– Antibiotics: mainly aminoglycosides
Preventing or slowing the progression of chronic kidney disease (renoprotection, most important in patients with GFR < 60 mL/min/1.73 m ²)	
■ Blood pressure control (<130/80 mm Hg)	– Sodium restriction
	– ACE inhibitors/ARBs
	– Thiazide diuretics (SCr < 1.8 mg/dL), loop diuretics (SCr > 1.8 mg/dL)
	– β-Blockers
■ Reduction of proteinuria (UPCR < 0.5)	– Moderate protein restriction: ≤0.8 g/kg/day
	– ACE inhibitors/ARBs: titrate to maximum tolerated dose, monitor SCr and potassium
■ Lipid-lowering therapy (LDL-C < 100 mg/dL)	– Statins
■ Cessation of smoking	
Treating the complications of chronic kidney disease (usually in patients with GFR of 15–29 mL/min/1.73 m ²)	
■ Anemia (maintain hemoglobin level of 11–12 g/dL)	– Erythropoietin
	– Iron supplementation when transferrin saturation is <25% and ferritin is <300 μg/mL
■ Hyperkalemia	– Potassium restriction, resin
■ Acidosis (maintain HCO ₃ ⁺ ≥ 22 mmol/L)	– Oral sodium bicarbonate
■ Hyperphosphatemia (target serum PO ₄ [–] 2.7–4.6 mg/dL)	– Phosphorus binders (sevelamer, lanthanum)
■ Hyperparathyroidism (target intact PTH 70–110 pg/mL)	– Active vitamin D (calcitriol, doxercalciferol), cinacalcet
■ Further deterioration of kidney disease	– Scheduled placement of arteriovenous access for hemodialysis or peritoneal catheter

*Based on guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (www.kidney.org/professionals/KDOQI/).
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NSAIDs, nonsteroidal antiinflammatory drugs; PTH, parathyroid hormone; SCr, serum creatinine; UPCR, urine protein-creatinine ratio.

Many lupus patients with advancing renal disease experience a decline in lupus clinical and serologic activity. However, up to 50% of patients receiving maintenance hemodialysis continue to experience lupus activity that can be difficult to distinguish from complications of uremia.^{96,97} Lupus activity is more likely to persist during dialysis when renal failure develops relatively rapidly rather than over a more extended period. Another potential issue in patients receiving hemodialysis is the presence of antiphospholipid antibodies or even antiphospholipid syndrome, which is associated with increased risk of vascular access thrombosis.⁹⁸ Peritoneal dialysis is also an option for lupus patients with ESRD and offers greater independence. Retrospective cohort studies have shown comparable long-term outcomes in patients receiving peritoneal dialysis and those receiving hemodialysis, although the former group had higher maximal disease activity on follow-up.⁹⁹ However, patients receiving peritoneal dialysis may be more likely to experience infectious complications (peritonitis and/or exit-site infections), and hypoalbuminemia and use of immunosuppressive agents are major risk factors.¹⁰⁰ Cardiovascular mortality is increased in lupus patients with ESRD,¹⁰¹ and adherence to the general guidelines for the management of cardiovascular risk factors is recommended.

RENAL TRANSPLANTATION

There are no firm rules for the optimal timing of renal transplantation in lupus nephritis patients. Although some patients with living related donors

TABLE 136.8
Novel approaches to the treatment of proliferative lupus nephritis

Approach	Example
A. Nonspecific immunosuppression	
High-dose immunoablative therapy	High-dose cyclophosphamide with HSCT High-dose cyclophosphamide without HSCT
Kinase inhibitors	Jak inhibitors, Syk inhibitors
B. Biologic response modifiers	
Interference with T-cell costimulation	Anti-CD40 ligand antibody CTLA-4-Ig
B-cell depletion	Anti-CD22 antibodies
B-cell activation	Anti-BLyS antibodies or soluble receptors (TAC-Ig)
Cytokine-directed therapy	Anti-IL-21 antibody Anti-IL-6 receptor antibody Anti-IFN-α antibody
Interference with immune complex formation and deposition	Deoxyribonuclease Anti-idiotypic antibodies and competitive peptides
C. Potential targets	
Complement components	Anti-C5 monoclonal antibody Soluble recombinant complement C3 inhibitor
D. New approach	
Immunosuppression and tissue repair	Mesenchymal stem cell transplantation

BLyS, B-lymphocyte stimulator; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; IL, interleukin; IFN-α, interferon-α.

proceed directly to transplantation without prior dialysis, maintenance on dialysis for a period of at least 3 months may allow some patients to recover adequate function for significant periods of time. Transplantation should be performed when clinical (and ideally, serologic) lupus activity has been absent, or at a low level, for at least 3 to 6 months.¹⁰² Comparative studies suggest that patient and graft survival in lupus patients are generally comparable with those in other patient groups.^{103,104} As in patients with other diseases, outcomes were superior in lupus patients who received living-donor organs and underwent preemptive transplantation.^{99,105} Recurrence of lupus nephritis in the renal allograft is a rare event (2% of cases) and not an important cause of graft loss. Patients with moderate to high titers of antiphospholipid antibodies are at increased risk of thrombotic complications and renal allograft loss, and may receive anticoagulation treatment perioperatively.¹⁰⁶ Low complement levels after renal transplantation in association with proteinuria may be considered a risk factor for recurrence of immune deposits, with a negative impact on graft survival.¹⁰²

FUTURE DIRECTIONS

Novel therapies

There are two major approaches to the development of novel treatments for lupus nephritis (Table 136.8). The first is to modify existing immunosuppressive therapies by changing the dose or duration of commonly used drugs, administering these drugs in combination or sequentially to reduce adverse events, or trying more recently developed drugs that have been effective in other diseases. The other major approach is to target specific steps in the pathogenesis of lupus nephritis, such as interfering with T- and B-cell activation by blocking costimulatory molecules, preventing immune complex formation or deposition, and diverting the autoimmune response by inducing antigen-specific tolerance or by interfering with abnormal cytokine networks. High-dose immunoablative chemotherapy with autologous hematopoietic stem cell transplantation has been applied to treat severe SLE manifestations.¹⁰⁷ Until more data are available, stem cell transplantation remains an experimental procedure that needs to be considered in critically ill lupus patients, ideally performed in centers with experience in both lupus and bone marrow transplantation in the context of formal protocols.

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Systemic lupus erythematosus in the pregnant patient and neonatal lupus

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- Disease quiescence in systemic lupus erythematosus (SLE) is an important predictor of pregnancy outcome.
- The presence of antiphospholipid antibodies is associated with an increased risk of maternal thrombosis, recurrent fetal loss, and preeclampsia.
- The presence of anti-Ro/anti-SSA antibodies is associated with neonatal lupus and, in rare cases, fetal congenital heart block.
- Distinguishing lupus nephritis from preeclampsia can be difficult, particularly since the two processes can be superimposed on one another.
- Hydroxychloroquine, low-dose corticosteroids, and azathioprine are considered among the safer medication options in pregnancy.
- Many pregnancies in patients with SLE, if carefully monitored and appropriately treated, result in healthy children.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a rheumatic illness that often affects young women of reproductive age. Pregnancy in the setting of SLE is frequently encountered and can sometimes create management challenges, particularly in women with active disease at the time of conception, a history of organ damage (such as lupus nephritis), and antiphospholipid and/or anti-Ro/anti-La antibodies. Although women with lupus tend to have fewer live births compared with the general population, the vast majority of pregnancies in the setting of SLE are uneventful and result in normal maternal and fetal outcomes. With the advent of effective therapies and an increased understanding of rheumatic diseases, the pregnancy loss rate in SLE has improved dramatically over the years to approximately 17% today.¹

PREPREGNANCY EVALUATION AND COUNSELING

Although the presence of SLE does not have a detrimental impact on fertility, active lupus at the time of conception is a predictor of a negative pregnancy outcome. Disease quiescence at the time of, and 6 months previous to, conception is an important prognostic factor for pregnancy loss and preterm delivery.² The presence of active lupus nephritis is a predictor of increased lupus activity during pregnancy and poor pregnancy outcomes.³ Pregnancy planning should certainly be part of the initial and ongoing evaluation in women of childbearing age, and proper contraception should be used if necessary, particularly in women who are sexually active and taking high-risk medications. The use of emergency contraception should also be discussed with the patient.

Major concerns are the mother's health (including her ability to be a mother to the child), the willingness to risk delivery of a preterm infant, specific risks caused by the presence of antiphospholipid and/or anti-Ro (anti-SSA)/anti-La (anti-SSB) antibodies, and the use of certain medications during pregnancy. There does not appear to be a detrimental impact on a

mother with lupus or on the fetus when *in-vitro* fertilization and other reproductive technologies are used.

Women with SLE who desire to become pregnant should be asked about their pregnancy history, including complications encountered during previous pregnancies, modes of delivery, and fetal outcomes. In women with a history of SLE-related organ damage, such as lupus nephritis and hemolytic anemia, SLE should be quiescent for at least 6 months before conception. Women with severe lung disease (e.g., interstitial lung disease), heart disease (e.g., recent myocardial infarction), or cerebrovascular accident should be advised to avoid pregnancy altogether and perhaps to explore alternatives to childbirth such as surrogacy or adoption.⁴⁻⁶ The reason is the high risk of mortality associated with these complications. Severe pulmonary hypertension, for instance, has a risk of mortality in pregnancy that approaches 30%.

Two serologic markers, antiphospholipid antibodies and anti-Ro/anti-La antibodies, also indicate higher risk of pregnancy complications. The presence of antiphospholipid antibodies is associated with maternal thrombosis, recurrent fetal loss, and an increased risk of preeclampsia.^{7,8} The presence of anti-Ro and anti-La antibodies is associated with fetal heart block and, in some cases, the need for a permanent pacemaker.^{9,10} Box 137.1 is an overview of potential risk factors for pregnancy complications in women with SLE.

MEDICATION USE IN PREGNANCY

Although there are very few clinical trials addressing the safety of medications in pregnancy, clinical experience, anecdotal evidence, and consensus conferences have attempted to address the safety of medications in pregnancy and lactation (Table 137.1; also see Chapter 68).

Hydroxychloroquine not only is generally regarded as safe to use in pregnancy but also is associated with decreased SLE flares when used continuously.¹¹ Unless there is a clear contraindication, treatment with hydroxychloroquine should not be interrupted in the setting of pregnancy.

Nonsteroidal antiinflammatory drugs can be used sporadically in the first and second trimesters of pregnancy, but they are associated with an increased risk of miscarriage and oligohydramnios in the first and second trimesters, respectively. Nonsteroidal antiinflammatory drugs should be avoided altogether in the last trimester of pregnancy due to concerns of premature closure of the ductus arteriosus and worsening of hypertension.

Corticosteroids are sometimes indicated in the setting of a lupus flare. It is important to know which steroids cross the placenta, and therefore affect the fetus, and which ones do not. Dexamethasone and betamethasone cross the placenta and should not be used unless there is an intent to expose the fetus to corticosteroids. Prednisone and prednisolone are deactivated by placental hydroxylases but should be used with caution given the increased risk of maternal diabetes, hypertension, preeclampsia, and premature rupture of membranes. Oral prednisone should not be used prophylactically and, if the drug is necessary, should be given at the lowest possible dose needed to control symptoms.

Antihypertensives may be required in the management of SLE patients. Angiotensin-converting enzyme inhibitors are contraindicated in the setting of pregnancy; methyldopa, nifedipine, and labetalol are generally thought to be safe options.

The impact of therapies affecting B cells, such as rituximab and belimumab, is largely unknown, and these drugs are not recommended in pregnancy. Although many normal pregnancy outcomes have been reported in

patients taking rituximab, there have been reports of preterm birth, infections, hematologic abnormalities, and even death associated with inadvertent rituximab exposure in pregnancy. Avoidance of pregnancy for at least 12 months following rituximab exposure should be strongly considered.¹²

Azathioprine is probably the safest immunosuppressive medication in pregnancy, and although its use has been associated with lower birth weights and prematurity in small human studies, it has been widely used in pregnant SLE patients without any negative sequelae. Safety data from the renal transplant population have been reassuring. Azathioprine is generally regarded to be safe when used at dosages of 2 mg/kg or less.¹³

BOX 137.1 PREDICTORS OF A HIGH-RISK PREGNANCY IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

History of pregnancy complications and a poor obstetric outcome
 Presence of high-titer antiphospholipid antibodies (anticardiolipin antibodies, β_2 -glycoprotein, and/or lupus anticoagulant)
 Presence of anti-Ro and anti-La antibodies
 Current or previous lupus nephritis or ongoing severe renal impairment
 Advanced maternal age (>40 years)
 Multiple pregnancies
 Use of cytotoxic medications at the time of conception, including high-dose prednisone
 Active flare at the time of, or 6 months before, conception

Cyclophosphamide is contraindicated in pregnancy, along with methotrexate, mycophenolate, leflunomide, and warfarin, because of their teratogenicity. If possible, these medications should be discontinued at least 3 months before conception. Case series focusing on both inadvertent and intentional exposure to cyclophosphamide have shown very high rates of fetal loss, although there are some cases in which healthy, live births occurred in women receiving cyclophosphamide.^{14,15} Inadvertent exposure to leflunomide, followed by cholestyramine washout, was not associated with adverse fetal outcomes in one small study.¹⁶

MATERNAL AND FETAL COMPLICATIONS DURING PREGNANCY

Although pregnancy outcomes in SLE patients have improved dramatically over the past several decades, SLE does pose a risk of potentially serious maternal and fetal complications. The majority of SLE pregnancies result in normal fetal outcomes, and the annual mortality rate among pregnant SLE patients is comparable to that in those who are not pregnant. The risk of thrombosis, infection, thrombocytopenia, cesarean section, preterm labor, and preeclampsia is significantly increased in SLE patients compared with healthy women.¹⁷

Distinguishing changes of normal pregnancy from lupus flares

Distinguishing between true flares of SLE and normal complications of pregnancy can be difficult. Skin rashes commonly occur in pregnancy; facial

TABLE 137.1
Potential concerns of commonly used pharmaceuticals and biologic agents in pregnancy and lactation

Agent	Safety in pregnancy	Comments	FDA rating	Safety in lactation
Azathioprine	Probably safe	Risk of immunosuppression in fetus, but renal transplant and lupus pregnancy data suggest safety in pregnancy without adverse effects.	D	Probably safe—enters breast milk at low levels but no reports of adverse pediatric events. Caution advised.
Belimumab	Unknown	No human studies but theoretical risk of fetal immunosuppression. Discontinue before pregnancy.	C	Unknown and not recommended.
Corticosteroids	Probably safe	Some reports of prematurity and cleft palate.	C	Probably safe at low dosages under 20 mg/day but does enter breast milk.
Cyclophosphamide	Unsafe	Teratogenic—do not use except in life-threatening manifestations of SLE.	D	Unsafe—enters breast milk
Cyclosporine	Possibly safe	Renal transplant data suggest fetal growth restriction and prematurity in up to 40% of fetuses, but no increased birth defects.	C	Possibly safe—enters breast milk at low levels so fetal monitoring recommended.
Heparin, unfractionated and low molecular weight	Safe	Does not cross the placenta. Low-molecular-weight heparin preferred.	C	Safe—does not enter breast milk.
Hydroxychloroquine	Safe	Numerous benefits in pregnancy and should be continued.	C	Safe—enters breast milk but approved by American Academy of Pediatrics for breastfeeding.
Intravenous immunoglobulin	Probably safe	Crosses the placenta but has been used without any fetal adverse effects.	C	Probably safe but does enter breast milk so use with caution.
Leflunomide	Unsafe	Teratogenic—discontinue at least 3 mo before pregnancy and use washout method with cholestyramine for at least 3 mo if needed.	X	Unknown if it enters breast milk but considered high risk.
Methotrexate	Unsafe	Teratogenic—discontinue at least 3 mo before pregnancy.	X	Probably unsafe.
Mycophenolate	Unsafe	Teratogenic—consider azathioprine as an alternative.	D	Unknown if it enters breast milk so do not use.
NSAIDs	Probably unsafe	Increased risk of miscarriage, oligohydramnios, and prematurity.	C	Probably safe. Ibuprofen preferred.
Rituximab	Unknown	Very limited data, but preterm births and infectious/hematologic abnormalities reported.	C	Unknown and therefore not recommended.
Sulfasalazine	Probably safe	Crosses placenta so small risk of kernicterus in the newborn, but no reported malformations.	B	Probably safe with few reported adverse pediatric effects.
Warfarin	Unsafe	Teratogenic	X	Probably safe—no increased reports of bleeding.

Data from Ostensen M, Khamashta M, Lackshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006;8:209; Ostensen M, Lockshin M, Doria A, et al. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology* 2008;47(Suppl 3):iii28-31; Hale T. *Medications and mother's milk*. Amarilla, Tex.: Hale Publishing; 2006.

FDA, U.S. Food and Drug Administration; NSAIDs, nonsteroidal antiinflammatory drugs; SLE, systemic lupus erythematosus.

blush, palmar erythema, and mild alopecia should be distinguished from a true lupus-related rash. Arthralgias, myalgias, and backaches are normal symptoms of pregnancy and can usually be managed conservatively with acetaminophen and physical therapy. True synovitis does not occur in normal pregnancy and can be related to a lupus flare. Mild anemia and thrombocytopenia are normal variants of pregnancy, but severe anemia and thrombocytopenia may be an indication of an immune-mediated process, such as immune-mediated thrombocytopenia or hemolytic anemia. The presence of leukopenia and lymphopenia should raise the suspicion of a systemic autoimmune process. A rise in C3 and C4 levels is a normal variation of pregnancy and this can make identifying an SLE flare difficult, so normal complement levels should not automatically be interpreted as an indication of disease quiescence. Double-stranded DNA, however is not affected by pregnancy and can increase when SLE is uncontrolled.

In normal pregnancy, the glomerular filtration rate increases from 100 mL/min to 150 mL/min, with intravascular volume increasing by one third. Patients who have preexisting renal damage and cardiopulmonary compromise may not be able to withstand these changes and may experience preeclampsia or cardiopulmonary failure as a result. It is normal for a mild increase in proteinuria to occur.

Lupus nephritis and preeclampsia

Differentiating between lupus nephritis and preeclampsia can be challenging since both are characterized by proteinuria and hypertension and the two can sometimes be superimposed on each other in the third trimester (Table 137.2). Preeclampsia is defined as new-onset systolic blood pressure of more than 140 mm Hg or diastolic blood pressure of more than 90 mm Hg in the setting of proteinuria (more than 300 mg of protein per 24 hours) after the 20th week of pregnancy. Severe preeclampsia is defined as systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 110 mm Hg with proteinuria of more 5 g protein per day in the presence of pulmonary edema, oliguria, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), intrauterine growth retardation, or oligohydramnios.

Physiologically, some degree of proteinuria, up to 300 mg of protein over 24 hours, is considered a normal variant of pregnancy. If a woman had some proteinuria before pregnancy, even an increase to 1 g can occur in the absence of lupus nephritis. The serum creatinine concentration, however, tends to decrease.

In a study of unselected lupus patients followed prospectively through pregnancy 64% of those patients who had a history of nephritis (regardless of glomerular filtration rates) experienced preeclampsia, compared with 14% of patient without nephritis.¹⁸ Women with SLE are at increased risk of preeclampsia and thus should be considered for daily aspirin therapy. Aspirin treatment decreases the risk not only of preeclampsia but also of preterm delivery, even in high-risk patients without SLE.¹⁹

Antiphospholipid antibodies

Antiphospholipid antibodies, including moderate- to high-titer anticardiolipin antibodies (immunoglobulin G or immunoglobulin M), β_2 -glycoprotein, and/or lupus anticoagulant, are found in up to one third of SLE patients and present management challenges, particularly in the setting of pregnancy. The presence of antiphospholipid antibodies becomes known as

antiphospholipid syndrome when their presence is accompanied by recurrent pregnancy loss and/or thrombosis. Of the three types of antiphospholipid antibodies, the lupus anticoagulant carries the worse prognosis and is a strong indicator of potential complications.²⁰

Antiphospholipid antibodies are associated with placental insufficiency, reduced amniotic fluid, fetal growth retardation, and sometimes fetal death. Although thrombosis and/or severe or early preeclampsia can occur, it is not uncommon for the mother to be completely asymptomatic while trouble is brewing for the developing fetus.

The pathogenesis behind the morbidity and mortality associated with antiphospholipid antibodies is not fully understood, but harm from antiphospholipid antibodies occurs at the level of the placenta, either from placental thrombosis, direct damage to the placenta, or defective placentation. Antiphospholipid antibodies cause complement activation at the placenta; this in turn activates tissue factor, which leads to a burst of inflammation from neutrophils and oxidative stress.²¹ This results in pregnancy loss through damage to the decidual tissues. Other models suggest that fetal loss is caused by the binding of anti- β_2 -glycoprotein antibodies to trophoblast cells, which inhibits their growth.²²

For women who are asymptomatic carriers of antiphospholipid antibodies with no history of pregnancy loss or thrombosis, treatment is generally not needed. Nevertheless, some rheumatologists prefer to prescribe low-dose aspirin for these patients. In women at higher risk, including those with a history of recurrent pregnancy loss or thrombosis, treatment options include low-dose aspirin combined with either unfractionated heparin 5000 to 12,000 units subcutaneously twice daily or enoxaparin 1 mg/kg subcutaneously daily. Generally, a prophylactic heparin dose is favored in women with a history of pregnancy loss, whereas a full dose is given to women with a history of thrombosis. Combination therapy with heparin and aspirin appears to be superior to treatment with aspirin alone in producing live births.²³ For women in whom combination therapy has been ineffective (occurrence of pregnancy loss or thrombosis despite treatment), intravenous immunoglobulin, corticosteroids, and plasmapheresis are treatment options, although the evidence for their effectiveness is questionable. Treatment of high-risk patients is continued for at least 6 to 8 weeks after delivery because of a continuing thrombosis risk in the postpartum period. Women with a history of recurrent thrombosis may need lifelong treatment. Despite the risks associated with the presence of antiphospholipid antibodies, live births have been reported in over 50% to 74% of such patients when treatment was initiated.²³

Neonatal lupus

Antibodies directed toward anti-Ro and anti-La proteins can cross the placenta and create a syndrome known as *neonatal lupus*. The most common manifestation is a photosensitive rash that appears in the infant around 4 to 6 weeks after birth and occurs in up to 20% of infants born to mothers with the anti-Ro antibody. Although this can occur as the classic malar/butterfly rash, more commonly it consists of nonscarring large, circular macules over the face, trunk, and extremities. The rash usually disappears on its own but can be treated with topical corticosteroids.

Hematologic abnormalities including thrombocytopenia and neutropenia, and hepatic abnormalities such as asymptomatic transaminitis can occur in 10% to 15% of cases. These abnormalities often dissipate as the presence of maternal antibodies in the infant diminishes by months 6 to 8

TABLE 137.2 Distinguishing lupus nephritis from preeclampsia

Factor	Lupus nephritis	Preeclampsia (20 wk of gestation and beyond)
Timing	Throughout pregnancy—occurs over weeks to months	Restricted to third trimester—occurs over hours to days
Hypertension	Sometimes present	Always present
Double-stranded DNA	Increased	Normal
Complement levels (C3, C4)	Low/normal	Normal
Serum uric acid level	Unchanged (unless in the presence of renal insufficiency)	Increases
History of preeclampsia	No impact on subsequent pregnancies	Increased risk in subsequent pregnancies
History of lupus nephritis	Increased risk of flare in pregnancy	Increased risk of preeclampsia
Active urine sediment	Yes—cellular and granular casts	No
Renal biopsy	May be indicated	Not indicated
Delivery	Proteinuria and hypertension do not resolve	Rapid resolution of proteinuria and hypertension

of life. For this reason, routine screening of newborns for these abnormalities is not recommended.

The most serious complication of neonatal lupus, however, is congenital heart block, believed to affect approximately 2% of offspring exposed to anti-Ro antibodies.²⁴ This risk increases up to 20% in subsequent pregnancies following the birth of an infant with anti-Ro antibody-associated congenital heart block and may be amplified by the coexistence of hypothyroidism and anti-La antibodies.²⁵⁻²⁷ Passage of anti-Ro antibodies from mother to fetus is not the exclusive cause of congenital heart block; fetal genetic factors and hypoxia may also play a role.

Although the survival rate for infants with neonatal lupus and congenital heart block is 80% at 1 year, the majority of these infants will need the placement of a permanent pacemaker. Recognizing the risk factors predisposing to this condition is imperative because complete heart block can develop rapidly and is relatively irreversible once it occurs. Since congenital heart block usually develops between 18 and 24 weeks' gestation, some experts recommend serial fetal echocardiography during this period. Premature atrial contractions and even moderate pericardial effusions should be taken seriously, because these may foreshadow the development of congenital heart block. If first- or second-degree heart block is detected, treatment with dexamethasone should be initiated immediately. However, the administration of steroids for prophylactic purposes is not advised, even in women with a history of congenital heart block in the fetus, due to the adverse effects that steroids can have on the fetus (intrauterine growth retardation and preterm birth).²⁸ Maternal hydroxychloroquine therapy has been associated with a reduced risk of cardiac neonatal lupus, and this is another reason it should be continued throughout pregnancy.²⁷ Fortunately, if fetal heart block does not occur in the womb, it is unlikely to manifest itself after delivery.

MANAGEMENT

Monitoring

The rheumatologist should participate actively with an obstetrician skilled in the care of high-risk pregnancies in the management of all pregnant

patients with SLE. The rheumatologist's role is to observe for signs or symptoms of active disease, to help diagnose thrombocytopenia and proteinuria should either occur, to advise on maternal medications, and to advise on risks regarding antiphospholipid syndrome and neonatal lupus. Ordinarily the rheumatologist should see a well patient at least once each trimester and an ill patient more frequently during the pregnancy.

Labor and delivery

In women with a history of antiphospholipid antibodies, important considerations at the time of delivery include the discontinuation of low-molecular-weight heparin at least 48 hours before a planned procedure. Many physicians choose to convert at 35 weeks' gestation to unfractionated heparin, which can be continued up to 6 hours before a procedure, particularly in patients at very high risk of thrombosis. The obstetrician should also be alerted to organ system complications that could impact delivery. For instance, in lupus patients with a history of avascular necrosis of the hips, a spontaneous vaginal delivery may cause musculoskeletal damage, so that a planned cesarean section is warranted.

Although there are no restrictions on breastfeeding, certain medications used in lupus are harmful to the neonate and should be used with caution (see Table 137.1). Others, such as hydroxychloroquine, are considered safe in breastfeeding mothers. The lack of maternal breast milk production may also be an issue for mothers receiving high-dose steroids or in pregnancies that result in preterm birth.

Despite the risks associated with pregnancy and perhaps an increased risk of learning disabilities, children born to women with SLE have normal intelligence and development compared with sex- and gestational age-matched controls.²⁹

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138

Sjögren syndrome

■ ALAN N. BAER ■ JOHN C. HALL

- Sjögren syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltration of the salivary, lacrimal, and other exocrine glands, dryness of the eyes and mouth, and circulating autoantibodies.
- It is best defined as the triad of dry eyes, dry mouth, and evidence of an autoimmune process mediating these and other clinical manifestations.
- It is characterized by a predilection for women of perimenopausal and postmenopausal age, a remarkably stable course in the absence of treatment, diverse symptoms, and heightened risk for B-cell non-Hodgkin lymphoma.
- Antibodies to the small ribonucleoprotein particles SSA and SSB are present in a high proportion of patients.
- SS may occur alone (primary) or together with another well-established systemic autoimmune disease (secondary) such as systemic lupus erythematosus, rheumatoid arthritis, or systemic sclerosis.
- The pathogenesis of SS involves mechanisms leading to targeted inflammation of the lacrimal and salivary glands and B-lymphocyte hyperactivity.
- Management is focused on amelioration of the salivary and lacrimal dysfunction and the use of immunomodulatory or immunosuppressive drugs for certain extraglandular manifestations.

HISTORY

In 1933, Henrik Sjögren, a Swedish ophthalmologist, published a comprehensive description of “keratoconjunctivitis sicca,” including its predilection for menopausal women, frequent occurrence in those with deforming arthritis, and its characteristic impairment of both lacrimal and salivary gland secretion.¹ This eye disease had first been recognized as filamentary keratitis in 1882. Sjögren’s histopathologic description of round cell infiltration and acinar loss in the lacrimal and salivary glands has long been equated with that described by Mikulicz in 1892 in a patient with bilateral lacrimal and salivary gland enlargement.² However, Mikulicz syndrome is now known to arise from a variety of distinct pathologic processes, including lymphoma, leukemia, tuberculosis, IgG4-related disease, and sarcoidosis.

The entity Sjögren syndrome (SS) was defined in 1965 as the triad of dry eyes, dry mouth, and rheumatoid arthritis (RA) or other connective tissue disease.³ Classification criteria for SS have evolved with better understanding of the disease and the development of new tests, including anti-SSA and anti-SSB antibodies, minor salivary gland biopsy, salivary scintigraphy, and new ocular surface-staining methodologies and scoring schema. Over the past decade, SS has been defined with greater rigor, thereby ensuring that the patient’s ocular and oral dryness are mediated by immune mechanisms, which are potentially amenable to modulation with newer systemic therapeutic agents.

EPIDEMIOLOGY

SS is a worldwide disease without notable regional differences. The major demographic and phenotypic features are shown in Table 138.1.⁴⁻⁹ The

disease has a female-to-male ratio of 10:1 or higher and is usually diagnosed between the ages of 40 and 60, but it also affects children and the elderly. The annual incidence of SS ranges from 3.9 to 6.0 per 100,000 inhabitants.¹⁰ Current estimates of prevalence range from 0.05% to 0.7%.

GLANDULAR PATHOLOGY

Lymphocytic infiltration of the salivary and lacrimal glands is associated with loss of acini and ducts (Fig. 138.1). The histopathology in the minor labial salivary glands is termed “focal lymphocytic sialadenitis.” The infiltrates surround the intralobular ducts or blood vessels and consist primarily of CD4+ T and B cells. The lymphoid infiltrate is characteristically focal but can become confluent with more severe disease. The lymphocytic predominance is T cells in small infiltrates and B cells in larger ones.¹¹ The proportion of interstitial IgG- and IgM-secreting plasma cells is increased relative to those that are normally present and secrete IgA.¹² Lymphoid follicles with germinal center (GC)-like structures are present in 25% of labial glands in patients with SS.¹³

Lymphoepithelial lesions are a characteristic histologic feature of the major salivary gland involvement in SS (known as “benign lymphoepithelial sialadenitis”), but such lesions are also found infrequently in the lacrimal and minor salivary glands. They are islands of coalescent ductal epithelial cells infiltrated by marginal zone or monocytoid B cells and surrounded by a dense lymphocytic infiltrate.¹⁴ Benign lymphoepithelial sialadenitis is a known precursor of mucosa-associated lymphoid tissue (MALT) extranodal marginal zone lymphoma and is distinguished by lymphoepithelial lesions surrounded by halos of malignant marginal zone B cells (Fig. 138.2). Differentiation of the benign lesion from MALT lymphoma may be difficult because both may contain monoclonal populations of B cells, reactive GCs, and an admixture of lymphocytes and plasma cells.

CLINICAL FEATURES

Glandular involvement

Ocular manifestations

The dry eye symptoms include burning, scratchiness, foreign body sensation, stinging, soreness, photophobia, and lack of tears. The resultant changes in the refractive properties of the cornea may blur vision. The symptoms are often exacerbated by air drafts, low humidity, reading, and viewing a computer monitor and correlate poorly with objective signs of dry eye disease.

Progressive periductal lymphocytic infiltration develops in the orbital and accessory lacrimal glands. In the conjunctiva, squamous metaplasia, loss of goblet cells, and chronic stromal inflammation occur. The cornea is thin, with focal loss of epithelium leading to exposure of the Bowman membrane. Strands of devitalized cells (filamentary keratitis) may form. Alterations in tear volume and composition, including hyperosmolality, have been postulated to contribute to the ocular surface damage.

Many SS patients may have additional causes of dry eye symptoms (Box 138.1), the most common being meibomian gland dysfunction. Ocular complications include bacterial conjunctivitis and corneal abrasion and ulceration.

Oral manifestations

Symptoms of a dry mouth, termed “xerostomia,” are a key feature but have multiple alternative causes (Box 138.2). A true deficiency of saliva, termed

TABLE 138.1
Demographic characteristics and clinical manifestations of patients with Sjögren syndrome in different studies classified by the American-European criteria⁵⁸

Variables	Lin et al ⁴	Alamanos et al ⁵	Ramos-Casals et al ⁶	Malladi et al ⁷	Theander et al ⁸	Baimpa et al ⁹
No. of patients	573	422	286	886	286	536
Year	2010	2006	2010	2012	2006	2009
Country	China	Greece	Spain	Global	Sweden	Greece
Female (%)	91	95	94	95	91	92
Average age at diagnosis (yr)	43	55	55		57	53
Dry mouth (symptom) (%)	85	94	98	93		84
Dry eyes (symptom) (%)	70	100	97	87		89
Parotid gland enlargement (%)	28	26	13		28	30
Salivary hypofunction (%)	92	87	87	71		
Xerophthalmia (%)	95	95	95	91		46
Labial gland biopsies	334			886	271	536
Positive salivary gland biopsy (%)	91	99		81	89	66
Lymphadenopathy (%)	8	7		8		13
Raynaud phenomenon (%)	18	35	17			
Articular (%)	48	39				
Arthritis (%)			20	8		30
Leukopenia (%)	42			19		14
Interstitial lung disease (%)	22	3	6			
Peripheral neuropathy (%)			13			
Autoimmune thyroiditis (%)			28	5		14
Purpura/skin vasculitis (%)		5	10		10	11
ANA (%)	84	94	84		85	68
SSA/B positive (%)			65		58	
Anti-SSA (%)	84	51		76		37
Anti-SSB (%)	41	40		49		19
RF (%)	61	32	54	60	58	37
Hypergammaglobulinemia (%)	61 (IgG >2000 mg/dL)			39 (IgG >1760 mg/dL)	24 (IgG >2150 mg/dL)	26 (IgG >2000 mg/dL)
Low C3 (%)	14		13	16	21	9
Low C4 (%)	17		11	18	22	4
Cryoglobulins (%)		28	10			8
Monoclonal protein (%)			18			4

Blank cells indicate values not provided in published source.

“salivary hypofunction,” does not always accompany xerostomia but is an expected finding. Patients report difficulty chewing and swallowing dry food, speaking at length, and wearing dentures. They may note impaired taste, thickened saliva, intolerance of acidic and spicy foods, a burning sensation in the mouth and tongue, and dry lips. Dental decay and oral infection often ensue.

On examination the tongue blade characteristically sticks to the buccal mucosa. Infralingual salivary pooling is not seen as the patient elevates the tongue. Caries may be evident at atypical sites, particularly at the junction of the dental crown and root, along the gingival margin, and on the cusp tips and incisal edges of teeth. The dorsal surface of the tongue may be hyperlobulated (Fig. 138.3). Oral candidiasis often accompanies more severe dryness and is manifested as lingual papillary atrophy, patchy or diffuse erythema of the mucosa and dorsal surface of the tongue, and angular cheilitis. The lingual erythema and papillary atrophy can improve with antifungal therapy.

Symmetric, nontender swelling of the major salivary glands occurs in approximately 30% of patients with SS, is generally asymptomatic, and has a broad differential diagnosis (Fig. 138.4, Box 138.3). Acutely painful parotid gland swelling usually represents a supervening bacterial parotitis. Slowly progressive enlargement of the glands should raise concern for the presence of glandular lymphoma, particularly when asymmetric.

Extraglandular manifestations

Primary versus secondary disease

The extraglandular manifestations of SS (Box 138.4) may be inherent or reflect the presence of overlapping systemic lupus erythematosus (SLE), RA, systemic sclerosis, or inflammatory myopathy. SS is termed “secondary” when it occurs with another systemic rheumatic disease (for which the classification criteria are met) and “primary” when such a second disease is absent. In the ensuing discussion of extraglandular manifestations, the focus is on primary SS.

Constitutional symptoms

Persistent fatigue, widespread joint and muscle pain, and cognitive symptoms are reported commonly and often do not correlate with antibody markers of the disease. The fatigue is probably multifactorial and may be associated with depression. Cognitive symptoms include subjective memory loss and difficulty concentrating and are often termed “brain fog” by patients.

Cutaneous involvement

Xerosis and associated pruritus are common. Small-vessel vasculopathies are manifested by palpable and nonpalpable purpura and urticarial lesions (Fig. 138.5) and those of larger blood vessels by livedo reticularis and leg

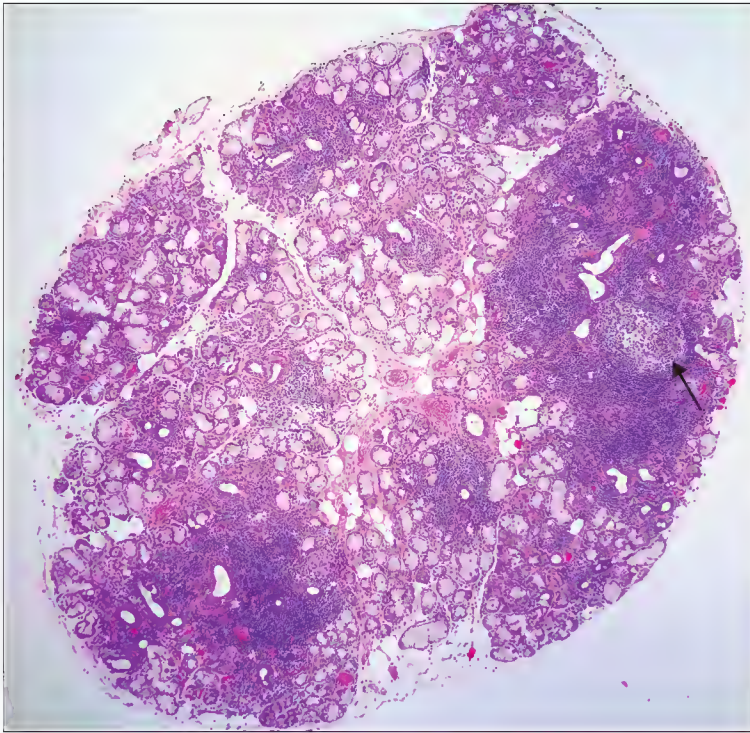


Fig. 138.1 Focal lymphocytic sialadenitis of Sjögren syndrome. This minor salivary gland shows multiple periductal lymphocytic infiltrates. A germinal center-like structure is evident in one such infiltrate (arrow).

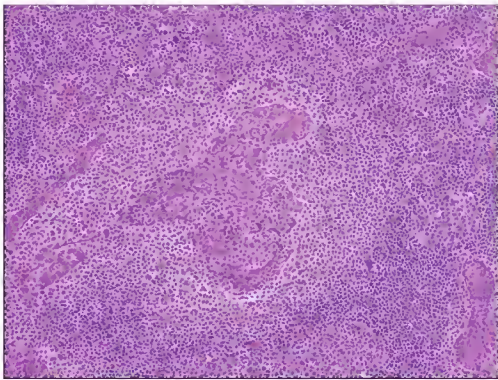


Fig. 138.2 Lymphoepithelial lesion. A myoepithelial island is infiltrated by and surrounded by monocytoïd lymphocytes in this parotid gland specimen from a patient with Sjögren syndrome and mucosa-associated lymphoid tissue lymphoma.

ulcers. Skin lesions of subacute cutaneous lupus erythematosus (SCLE) may develop and on this basis be defined as an SS-SLE overlap syndrome (Fig. 138.6). “Annular erythema of SS” occurs primarily in Asian patients and is characterized by erythematous skin lesions with indurated borders, most often on the upper part of the body. It shares with SCLE a similar morphology and close relationship with anti-SSA and anti-SSB antibodies but lacks a prominent interface dermatitis and HLA-DR3 linkage. Other SS-associated skin lesions include panniculitis, primary nodular cutaneous amyloidosis, and cutaneous B-cell lymphoma.

Musculoskeletal involvement

An intermittent nonerosive symmetric inflammatory polyarthritis occurs in up to 30% of SS patients¹⁵ and particularly affects the fingers, wrists, and ankles. Many SS patients report arthralgia but lack synovitis. More severe forms of arthritis may occur when SS overlaps with another connective tissue disease. Muscle involvement can include a low-grade myositis inclusion body disease or fibromyalgia.

Pulmonary involvement

Pulmonary disease affects 9% to 12% of patients, although pulmonary function tests (PFTs), bronchoalveolar lavage, and computed tomography (CT)



Fig. 138.3 Hyperlobulation of the tongue. Hyperlobulation and fissuring of the tongue are characteristic changes associated with salivary hypofunction in patients with Sjögren syndrome. The papillary atrophy can be a manifestation of oral candidiasis and may be reversed with antifungal therapy.

BOX 138.1 DIFFERENTIAL DIAGNOSIS OF DRY EYE

Primarily evaporative

Lid and ocular surface disease
Meibomian gland dysfunction
Poor lid congruity
Facial nerve paralysis
Low blink rate (e.g., Parkinson disease, video terminal use)
Extrinsic causes that enhance evaporation
Trachoma (vitamin A deficiency)
Use of topical anesthetic drops
Excessive use of preservative-containing drops
Contact lens wear
Allergic conjunctivitis

Primarily aqueous deficient

Sjögren syndrome
Other forms of lacrimal gland disease
Aging
Inflammatory diseases (e.g., acquired immunodeficiency syndrome, sarcoidosis, lymphoma, graft-versus-host disease)
Lacrimal gland duct obstruction from various forms of cicatrizing conjunctivitis
Ocular sensory loss leading to reflex hyposecretion and a diminished blink rate
Corneal surgery
Diabetes mellitus
Neurotrophic keratitis
Chronic contact lens wear
Loss of lacrimal secretory motor function
Drugs (e.g., antihistamines, β -blockers, antispasmodics, diuretics)
Central seventh nerve damage

Adapted from The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf* 2007;5:75-92.

BOX 138.2 DIFFERENTIAL DIAGNOSIS OF XEROSTOMIA

Drug side effect (e.g., single or multiple prescription of drugs with anticholinergic, diuretic, antihypertensive, anxiolytic, or antihistamine effects)
Salivary gland diseases, including Sjögren syndrome
Poorly controlled diabetes mellitus
Dehydration
Mouth breathing, nasal obstruction
Head and neck irradiation (including high doses of radioactive iodine for thyroid cancer)
Psychological factors

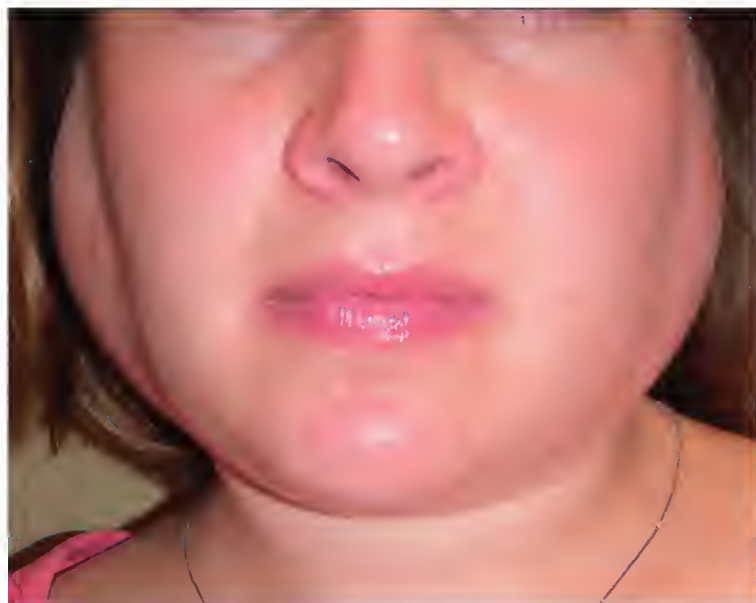


Fig. 138.4 Bilateral parotid gland swelling. Marked swelling of both parotid glands is evident in this young woman with Sjögren syndrome.

BOX 138.3 CAUSES OF BILATERAL SALIVARY GLAND ENLARGEMENT

Infectious

Viral infections (mumps, Epstein-Barr, hepatitis C, human immunodeficiency)

Bacterial

Acute suppurative parotitis

Tuberculosis

Fungal

Autoimmune

Sjögren syndrome

Granulomatous polyangiitis

Inflammatory

IgG4-related disease (including Kuttner tumor)

Allergic parotitis (sialodochitis fibrinosa)

Chronic recurrent parotitis

Kimura disease

Metabolic (causing sialadenosis, which is characterized by painless, bilaterally symmetric parotid enlargement that is soft and nontender on palpation)

Uncontrolled diabetes mellitus

Bulimia

Alcoholism with liver disease

Hyperlipoproteinemia

Neoplastic

Lymphoma

Leukemia

Warthin tumor (papillary cystadenoma lymphomatosum)

Diffuse hyperplastic oncocytic hyperplasia

Granulomatous

Sarcoidosis

Iatrogenic or self-induced

Radioactive iodine

Pneumoparotitis (wind instrument players, glass blowers)

may detect lung abnormalities in up to 75%.¹⁶ SS affects both the upper and lower airways. Salivary deficiency can impair the buffering of refluxed gastric acid and lead to globus, excessive throat clearing, coughing, and hoarseness. Lower airway disease is manifested by dry cough, recurrent bronchitis, and dyspnea. PFTs show mild, small-airway obstruction. Abnormalities on CT include bronchial airway thickening, bronchiectasis, reticular or nodular infiltrates, and air trapping. Transbronchial biopsy specimens demonstrate a subepithelial lymphocytic infiltrate. Chronic inflammation and destruction of submucosal bronchial glands were reported by Sjögren, but the extent to which this occurs in patients with SS is debated. Follicular bronchiolitis is a distinctive pathologic lesion in SS characterized by the formation of hyperplastic lymphoid follicles in the bronchiolar walls and subsequent obstruction of the lumen. A valve phenomenon may result in lung cysts or bullae (Fig. 138.7).



Fig. 138.5 Lesions of palpable purpura are evident on the lower extremity of a patient with Sjögren syndrome.

BOX 138.4 SELECTED SYSTEMIC MANIFESTATIONS OF SJÖGREN SYNDROME

Constitutional

Fatigue

Arthralgia

Musculoskeletal

Polyarthritis

Renal

Tubulointerstitial nephritis

Glomerulonephritis

Neurologic

Peripheral neuropathy

Neuromyelitis optica

White matter disease

Cutaneous

Vasculitis

Subacute cutaneous lupus

Annular erythema

Endocrine

Association with autoimmune thyroiditis

Hepatic

Association with primary biliary cirrhosis and autoimmune hepatitis

Vasculitis

Pulmonary

Airway disease

Bronchiolitis

Bronchiectasis

Interstitial pneumonitis

Lymphoproliferative lesions

Hematologic

Leukopenia

Anemia

Thrombocytopenia

Hypergammaglobulinemia

Cryoglobulinemia

Monoclonal gammopathy

Nonspecific, usual, and lymphocytic forms of interstitial pneumonitis (NSIP, UIP, and LIP, respectively) and cryptogenic organizing pneumonia (COP) may be seen and are usually manifested as dyspnea and cough. NSIP is the most common, whereas UIP and COP occur rarely. LIP is the most characteristic of SS and is marked by lymphoplasmacytic infiltration of the

interstitium, lymphocytes in the alveolar spaces, and lymphoid aggregates along lymphatic routes and around blood vessels. Follicular bronchiolitis often coexists. Affected patients usually have a polyclonal or monoclonal gammopathy. LIP can be a precursor to a bronchus-associated lymphoid tissue (BALT) lymphoma. These rare neoplasms are typically associated with a dry cough, absence of lymphadenopathy, and multiple, often bilateral patchy infiltrates or nodules in a peribronchial distribution.¹⁷

Gastrointestinal and hepatic involvement

An increased prevalence of celiac disease has been observed in some studies.¹⁸ Liver disease occurs in up to 20% of patients with SS, the usual forms being primary biliary cirrhosis and autoimmune hepatitis.

Renal involvement

Clinical renal disease develops in 5% of patients, although a much larger number may have latent involvement. Tubulointerstitial nephritis is most common, tends to occur in younger patients with a shorter duration of disease, and may be manifested as polyuria secondary to hyposthenuria (nephrogenic diabetes insipidus), renal colic, or tubular proteinuria (or any combination of the three). The clinical course is most often indolent, with mild to moderate renal dysfunction.^{19,20} Distal (type I) renal tubular acidosis (RTA) is usually evident and is characterized by an inability of the distal nephron to acidify the urine. Urine pH is higher than 5.5 despite the presence of metabolic acidosis. Patients may have renal potassium wasting and hypercalciuria with potential for the development of hypokalemic paralysis, renal stones, and nephrocalcinosis. Affected patients usually have hypergammaglobulinemia. RTA may be evident only with an ammonium chloride-loading test. Proximal RTA occurs rarely and has features of Fanconi syndrome, including glucosuria, aminoaciduria, phosphaturia, and

uricosuria. Membranoproliferative and mesangioproliferative glomerulonephritides occur rarely as late disease manifestations; are characterized by renal dysfunction, hematuria, or proteinuria (or any combination); and are generally associated with cryoglobulinemia.²⁰

Gynecologic involvement

Vaginal symptoms, including dryness, pruritus, and dyspareunia, are frequent, partly because of the predilection of postmenopausal women for SS. Gynecologic examination does not show an increased prevalence of atrophic changes relative to age-matched controls.²¹ The vagina has no secretory glands. The genital dryness has been postulated to arise from involvement of the Bartholin and minor vestibular glands, but this has not been confirmed.

Neurologic involvement

Both central nervous system (CNS) and peripheral nervous system involvement may occur. Peripheral neuropathy is evident in approximately 20% of SS patients²² and has several forms, the most common being a pure sensory neuropathy.^{23,24} Patients may have more than one type of neuropathy. The symptoms often precede the diagnosis of SS and can occur without overt sicca.^{23,24} Certain forms of peripheral neuropathy can arise as a primary manifestation of the disease, independent of other extraglandular manifestations, whereas others are complications of a systemic vasculopathy.

Pure sensory neuropathy is characterized by loss of small axons with prominent neuropathic pain, loss of pinprick or temperature discrimination, and hyperesthesia. The results of nerve conduction studies are generally normal. The diagnosis is supported by a reduction in the number or abnormal morphology of the intraepidermal nerve fibers on punch skin biopsy specimens. Many affected patients have an asymmetric and non-length-dependent distribution of pain, with involvement of the face, trunk, and limbs. They are often older and have a lower frequency of anti-SSA and anti-SSB antibodies, rheumatoid factor (RF), and hypergammaglobulinemia than do nonaffected patients.^{22,24}

Sensory neuronopathy arises from primary damage to the dorsal root ganglia sensory neurons with subsequent degeneration of short- and long-length axons. Ataxia, loss of deep tendon reflexes, and proximal and distal sensory symptoms, frequently in an asymmetric pattern, are typical. Joint position sense is impaired, with a positive Romberg sign and pseudoathetosis, but muscle strength is preserved. An Adie pupil is often observed. Magnetic resonance imaging (MRI) may show high-intensity T2 signal in the posterior columns of the spinal cord. Biopsy specimens of dorsal root ganglia have shown T-lymphocytic infiltrates around individual neurons.²⁴ Sensory ataxia develops in some patients with painful small-fiber sensory neuropathy, and it has been speculated that these two peripheral neuropathies may share a common pathogenesis.

Sensorimotor neuropathies occur at the same frequency as pure sensory neuropathies and involve large-diameter fibers.²² The usual form is an axonal neuropathy with symmetric sensory deficits in a stocking-glove distribution, impaired vibration sense, mild distal muscle weakness, and diminished or absent tendon reflexes. This form of axonal sensorimotor polyneuropathy is usually associated with systemic disease, including vasculitis, monoclonal proteins, and lymphoma. Demyelinating sensorimotor, cranial, autonomic, and mononeuritis multiplex are rare forms of neuropathy in SS.

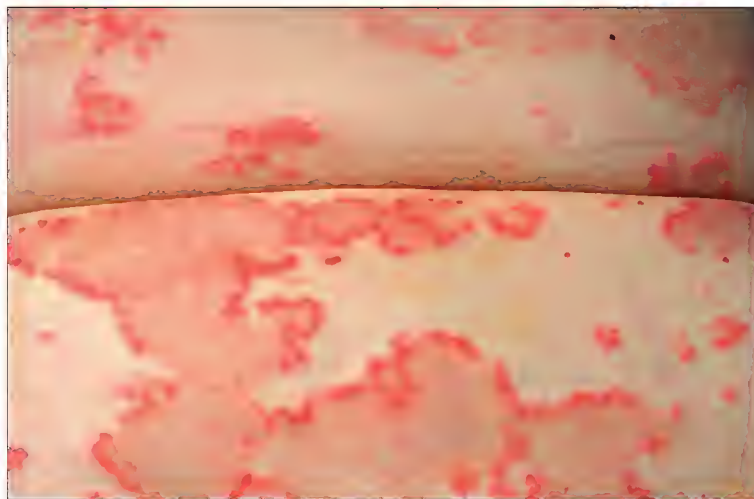


Fig. 138.6 Subacute cutaneous lupus overlap rash. This patient with Sjögren syndrome and anti-SSA antibodies has annular polycyclic lesions consistent with subacute cutaneous lupus.

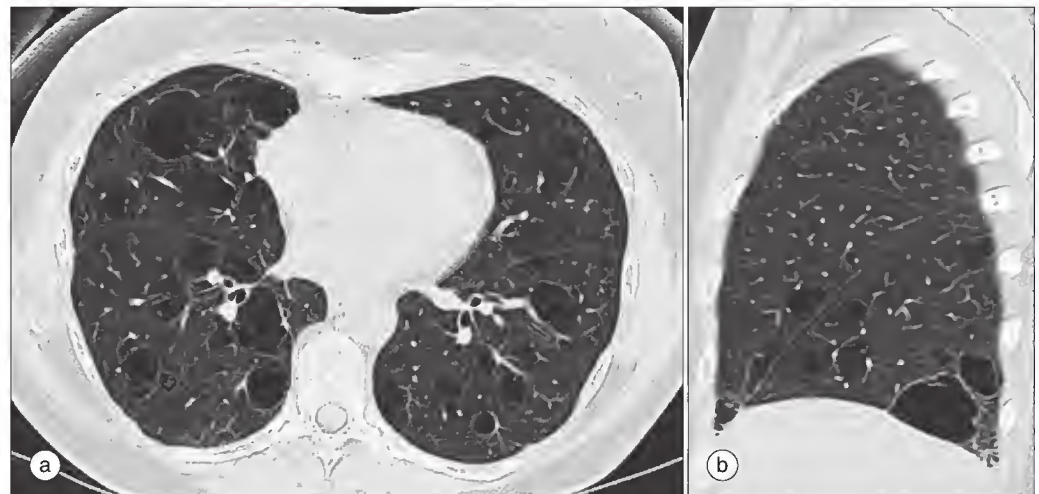


Fig. 138.7 (a and b) Cystic lung lesions. These computed tomography images show multiple thin-walled pulmonary cysts in a woman with Sjögren syndrome.

CNS disease in SS is most commonly a subacute encephalopathy characterized by memory loss, cognitive dysfunction, visual disturbances, dizziness, and impaired concentration and attention.²⁵ MRI may show small punctate white matter T2 hyperintensities in the subcortical and periventricular areas. These white matter lesions occur commonly as a function of age and cerebrovascular risk factors, and their presence in SS patients may thus be difficult to interpret.²⁵ Demyelinating disease resembling multiple sclerosis in SS patients was first reported in 1986,²⁶ but there is doubt about the generalizability of these initial observations. SS has been associated with the neuromyelitis optica spectrum of CNS demyelinating disorders, which is defined by the presence of longitudinally extensive transverse myelitis, optic neuritis, and aquaporin-4 antibodies.

Endocrine involvement

Autoimmune thyroid disease is present in approximately 15% to 30% of patients with SS.^{27,28}

Systemic vasculitis

Vasculitis affects 10% of SS patients and most often involves small blood vessels of the skin, peripheral nerves, and kidneys. Biopsy specimens of purpuric or urticarial skin lesions most often show leukocytoclastic vasculitis. Rare ulcers on the lower part of the legs should prompt a search for serum cryoglobulins. Cutaneous vasculitis is associated with anti-SSA antibodies, RF, cryoglobulins, hypergammaglobulinemia, and frequently signs of systemic involvement, including peripheral neuropathy and glomerulonephritis.

Hematologic abnormalities

Anemia, leukopenia (usually neutropenia), and thrombocytopenia each occur in up to 20% of patients, often in association with each other and serologic disease markers.^{29,30} Hypergammaglobulinemia is found in 20% to 40%, correlates with the presence of anti-SSA and anti-SSB antibodies and RF,^{9,30} and can be pronounced, with globulin levels reaching 4 to 6 g/dL. Monoclonal immunoglobulins, often in small amounts, are present in up to 20% of SS patients.^{9,30} Cryoglobulinemia occurs in 10% to 15% of patients with SS, frequently in association with leukocytoclastic vasculitis and hypocomplementemia. The cryoglobulin is most often mixed, with monoclonal IgMκ RF and polyclonal IgG components being present. Affected patients are at higher risk for B-cell lymphoma and life-threatening vasculitis and should be tested for hepatitis C.³¹

SYSTEMIC AUTOIMMUNITY

Antinuclear antibodies (ANAs) are found in up to 90% of patients,³² the most common being directed against the SSA(Ro)/SSB(La) ribonucleoprotein complex in 60% to 80% of patients. These antibodies to SSA and SSB are not always detectable with a fluorescent ANA test. Antibodies to SSA alone are found with approximately equal frequency as antibodies to both SSA and SSB, whereas antibodies to SSB alone are uncommon in patients with SS.³³ The anti-SSA and anti-SSB antibody profile present at diagnosis generally remains unchanged during the subsequent disease course,³⁴ with the exception of low-titer test results. Anti-SSA and anti-SSB antibodies are associated with a higher prevalence of extraglandular features and more extensive lymphoid infiltrates in the salivary glands.³⁵ RF is found in 40% to 50% of SS patients, usually those with anti-SSA antibodies.

Anticentromere antibodies define a subset of 5% of SS patients with more frequent Raynaud phenomenon and associated autoimmune diseases, especially limited systemic sclerosis and primary biliary cirrhosis.³⁶ Anti-cyclic citrullinated peptide antibodies, present in 5% to 10% of patients, are associated with nonerosive synovitis.³⁷ Antibodies to the cytoskeletal protein α -fodrin are found in 30% to 90% of SS patients, are relatively specific for the diagnosis, but do not have better sensitivity and specificity than anti-SSA and anti-SSB antibodies do.³⁸ Antimitochondrial antibodies are a reliable marker of autoimmune cholangitis in 5% of SS patients,³⁹ but the more prevalent anti-smooth muscle antibodies are a marker of autoimmune hepatitis only when present in high titer.⁴⁰

Antibodies to the muscarinic acetylcholine receptor (M3R) have been postulated to mediate the decrease in salivary and lacrimal gland secretion in SS, but progress has been slow in confirming this.^{32,41}

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

Patients with SS have an increased prevalence of other autoimmune diseases, including celiac disease, thyroiditis, primary biliary cirrhosis, and various systemic rheumatic diseases.¹⁸ SS can be diagnosed in 9% to 14% of patients

with SLE^{42,43} and in 7% to 25% of those with RA.^{44,45} The concept of secondary SS has long implied the presence of serologic, pathologic, and genetic features distinct from those of primary SS, but this is now being challenged. SS patients are often found to have clinical features and serologic markers of more than one rheumatic disease at the time of diagnosis. Thus it is often not possible to classify one disease as secondary to another.⁴⁶ Some differences in the phenotypic expression of SS occurring in the context of other rheumatic diseases have been demonstrated.⁴³

LYMPHOPROLIFERATIVE DISEASE

Patients with SS have a 16- to 19-fold increased risk for the development of non-Hodgkin B-cell lymphoma.^{8,47} The risk is generally higher for primary than for secondary SS and exceeds that of any other autoimmune disease.⁴⁸ The cumulative incidence of non-Hodgkin lymphoma in SS cohorts is 5% to 10% and increases with duration of follow-up. Markers of severe disease are associated with increased risk and include persistent parotid gland enlargement, palpable purpura, cryoglobulinemia, monoclonal proteins, hypocomplementemia, CD4+ lymphocytopenia, and the presence of GC-like structures in baseline labial gland biopsy specimens.⁴⁹

Most SS-associated lymphomas are the marginal zone B-cell subtype, particularly those of MALT origin, and arise in the salivary glands but also occasionally in the stomach, orbital adnexa, nasopharynx, lungs, kidneys, liver, and skin. They are usually low grade and characterized by a small tumor burden.⁵⁰ MALT lymphomas are present at more than one extranodal site in 20% of patients and may disseminate to other sites, including other salivary glands, the lacrimal glands, lung, stomach, and cervical nodes. Infiltration into bone marrow is rare. Diffuse large B-cell lymphoma occurs in SS patients at a frequency roughly equivalent to that of MALT lymphoma^{8,50} and may arise *de novo* or in the setting of a preexisting low-grade MALT lymphoma. It is characterized by older age and advanced anatomic stage at initial evaluation and a median overall survival of less than 2 years.⁵¹

The development of lymphoma is often heralded by persistent enlargement of the salivary or lacrimal glands or a new mass within one of the glands. Affected patients frequently have extraglandular disease.^{8,51} Evaluation of a salivary mass or persistent salivary or lacrimal gland enlargement begins with an initial fine-needle aspiration or core needle biopsy under ultrasound guidance and immunophenotyping by flow cytometry to differentiate benign from potentially malignant lesions. However, the finding of a monoclonal B-cell population does not necessarily indicate the presence of malignant lymphoma. Diagnosis of MALT lymphoma may require additional tissue secured by incisional biopsy or superficial parotidectomy.

NATURAL HISTORY

SS progresses very slowly in the majority of patients in the absence of treatment, without rapid deterioration in salivary or tear gland function or dramatic changes in symptoms or markers of systemic disease activity.^{52,53} Serologic parameters also remain relatively stable, with the exception of an oft-observed decline in IgG levels.^{53,54} Lymphocytic infiltration of the labial salivary glands increases in the majority of patients after intervals of 1 to 12 years, but few studies have been performed.⁵⁵ Mortality in patients with SS is not significantly different from that in the general population.⁵⁴

CLASSIFICATION CRITERIA

The 2012 American College of Rheumatology (ACR) provisional classification criteria for SS were developed primarily for clinical trials, where protocol-driven assessment of ocular surface staining and interpretation of labial gland biopsy findings can be applied rigorously (Box 138.5).^{46,56,57} The most widely accepted classification criteria are those proposed in 2002 by the American-European Consensus Group (AECG) (Box 138.6).⁵⁸ These criteria have not been endorsed by the ACR or European League Against Rheumatism (EULAR) but are widely used in clinical practice, in part because certain component tests, such as the Schirmer test and the whole unstimulated saliva collection, can be performed easily. They have been criticized for their inclusion of patient symptoms, which correlate poorly with objective measures of salivary and lacrimal gland function, yet may constitute 50% of the requisite criteria for diagnosis in an individual patient. The component diagnostic tests for ocular and oral dryness are not diagnostically equivalent. The ACR classification criteria will soon undergo external validation and comparison with the AECG criteria for the purpose of developing a definitive set endorsed by both the ACR and EULAR.

BOX 138.5 AMERICAN COLLEGE OF RHEUMATOLOGY PROVISIONAL CLASSIFICATION CRITERIA FOR SJÖGREN SYNDROME

The classification of SS, which applies to individuals with signs or symptoms that may be suggestive of SS, will be met in patients who have at least two of the following three objective features:

1. Positive serum anti-SSA/Ro and/or anti-SSB/La or positive rheumatoid factor and ANA titer $\geq 1:320$
2. Labial salivary gland biopsy specimen exhibiting focal lymphocytic sialadenitis with a focus score of 1 or more foci per 4 mm²*
3. Keratoconjunctivitis sicca with an ocular staining score of 3 or higher (assuming that the individual is not currently using eye drops daily for glaucoma and has not undergone corneal surgery or cosmetic eyelid surgery in the last 5 years)[†]

A previous diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

History of head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency syndrome
Sarcoidosis
Amyloidosis
Graft-versus-host disease
IgG4-related disease

*Using histopathologic definitions and focus score assessment methods as previously described.⁵⁶

[†]Using the ocular staining score as previously described.⁵⁷

ANA, antinuclear antibody; SS, Sjögren syndrome.

From Shiboski SC, Shiboski CH, Criswell L, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance Cohort. *Arthritis Care Res (Hoboken)* 2012;64:475-87.

DIAGNOSTIC EVALUATION

The diagnosis of SS is most often established with an objective measure of ocular dryness or salivary hypofunction coupled with evidence of underlying autoimmunity.

Ophthalmologic examination

The ophthalmologic examination should include an assessment of tear production (Schirmer test) and ocular surface staining. The latter offers the greatest utility for the diagnosis of dry eye disease and is performed with lissamine green (for the conjunctiva) and fluorescein (for the cornea) (Fig. 138.8). These dyes stain corneal epithelium stroma (thereby revealing defects in the corneal epithelium) and devitalized conjunctival cells. Thresholds of staining that correlate best with other SS phenotypic features have been established.^{57,59} The Schirmer test measures the 5-minute wetting of a standardized strip of filter paper placed in the lower lateral fornix of the eyelid and serves as an indicator of basal (anesthetized) or stimulated (unanesthetized) tear flow. The unanesthetized Schirmer test is supportive of SS when wetting measures 5 mm or less in either eye. This is a stringent cutoff value and thus decreases the sensitivity of the test in patients with mild SS. Schirmer test results decline with age, and therefore the test may not be appropriate for elderly individuals.⁵⁹

Major salivary glands

Salivary flow measurements document gland hypofunction and are measured either with or without stimulation. The whole unstimulated saliva flow rate correlates best with xerostomia and is most relevant to oral health and dental integrity because it reflects the basal flow present throughout the majority of the day, which stems primarily from the submandibular and sublingual glands. Whole unstimulated sialometry requires an analytic balance to weigh the specimen container before and after saliva collection. The patient should not have eaten, chewed gum, or drank water for the preceding 90 minutes. The patient then empties the saliva every minute into a preweighed cup for a period of 5 to 15 minutes.⁶⁰ The volume of saliva is determined by weight, with the specific gravity assumed to be 1 g/mL and less than 0.1 mL/min being considered abnormal. Saliva secretion after an olfactory, gustatory, or masticatory stimulus is larger in volume, involves the parotid glands, and facilitates eating. "Whole" stimulated saliva production can be measured by expectoration or suction of saliva produced after the

BOX 138.6 AMERICAN-EUROPEAN CONSENSUS GROUP CLASSIFICATION CRITERIA FOR SJÖGREN SYNDROME

1. Ocular symptoms: a positive response to at least one of the following questions:
 - Have you had daily, persistent, troublesome dry eyes for more than 3 months?
 - Do you have a recurrent sensation of sand or gravel in your eyes?
 - Do you use tear substitutes more than three times a day?
2. Oral symptoms: a positive response to at least one of the following questions:
 - Have you had dry mouth for more than 3 months?
 - Have you had recurrently or persistently swollen salivary glands as an adult?
 - Do you frequently drink liquids to aid in swallowing dry food?
3. Ocular signs: objective evidence of ocular involvement defined as a positive result on at least one of the following two tests:
 - Schirmer test performed without anesthesia (5 mm in 5 minutes)
 - Rose Bengal score or other ocular dry score (4 or higher according to the van Bijsterveld scoring system)
4. Histopathology: focal lymphocytic sialadenitis as evaluated by an expert histopathologist in minor salivary glands (obtained through normal-appearing mucosa) with a focus score of 1 or higher; the focus score is defined as the number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue
5. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result on at least one of the following diagnostic tests:
 - Unstimulated whole salivary flow (≥ 1.5 mL in 15 minutes)
 - Parotid sialography showing the presence of diffuse sialectases (punctate, cavitary, or destructive pattern) without evidence of obstruction of the major ducts
 - Salivary scintigraphy showing delayed uptake, reduced concentration, or delayed excretion of tracer
6. Autoantibodies: presence in the serum of one or both of the following autoantibodies:
 - Antibodies to Ro (Sjögren syndrome A) antigens
 - Antibodies to La (Sjögren syndrome B) antigens

Revised rules for classification

For primary Sjögren syndrome

In patients without any potentially associated disease, primary Sjögren syndrome may be defined as follows:

- The presence of any four of the six items indicative of primary Sjögren syndrome as long as either histopathology or serology is positive
- The presence of any three of the four objective criteria items (i.e., items 3, 4, 5, and 6)

For secondary Sjögren syndrome

In patients with a potentially associated disease (e.g., another well-defined connective tissue disease), the presence of item 1 or item 2 plus any two from among items 3, 4, and 5 may be considered as being indicative of secondary Sjögren syndrome.

Exclusion criteria

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome
- Preexisting lymphoma
- Sarcoidosis
- Graft-versus-host disease
- Use of anticholinergic drugs (since a time shorter than fourfold the half-life of the drug)

From Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. *Ann Rheum Dis* 2002;61:554-8.

patient chews on paraffin or gum for a period of 5 to 15 minutes or has taken pilocarpine 60 minutes earlier.⁶⁰ Levels lower than 0.7 mL/min define salivary hypofunction.⁶¹

Salivary gland structure is assessed with various imaging modalities (Fig. 138.9). Contrast-enhanced sialography reveals abnormalities indicative of damage to the ductal structures or parenchyma of the parotid gland. Dilatation of the terminal ducts (sialectasia) and loss of intraglandular ductal branching are the most typical findings. This test is difficult to perform, may be painful, and can lead to infection, thus prompting a preference for other modalities. MRI reliably demonstrates the glandular changes associated with SS, including an inhomogeneous pattern of the parenchyma on both T1- and

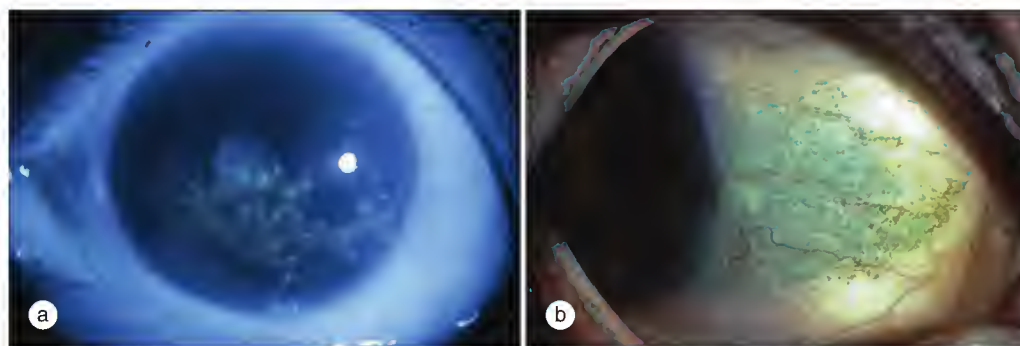


Fig. 138.8 Advanced keratoconjunctivitis sicca in a patient with Sjögren syndrome visualized with fluorescein (a) and lissamine green (b) staining of the ocular surface. Multiple defects in the epithelium of the interpalpebral cornea are evident as fluorescein-staining dots (a). A triangular area of staining of the interpalpebral temporal conjunctiva is evident with lissamine green (b). (From Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol* 2010;149:405-15. With permission from Elsevier.)

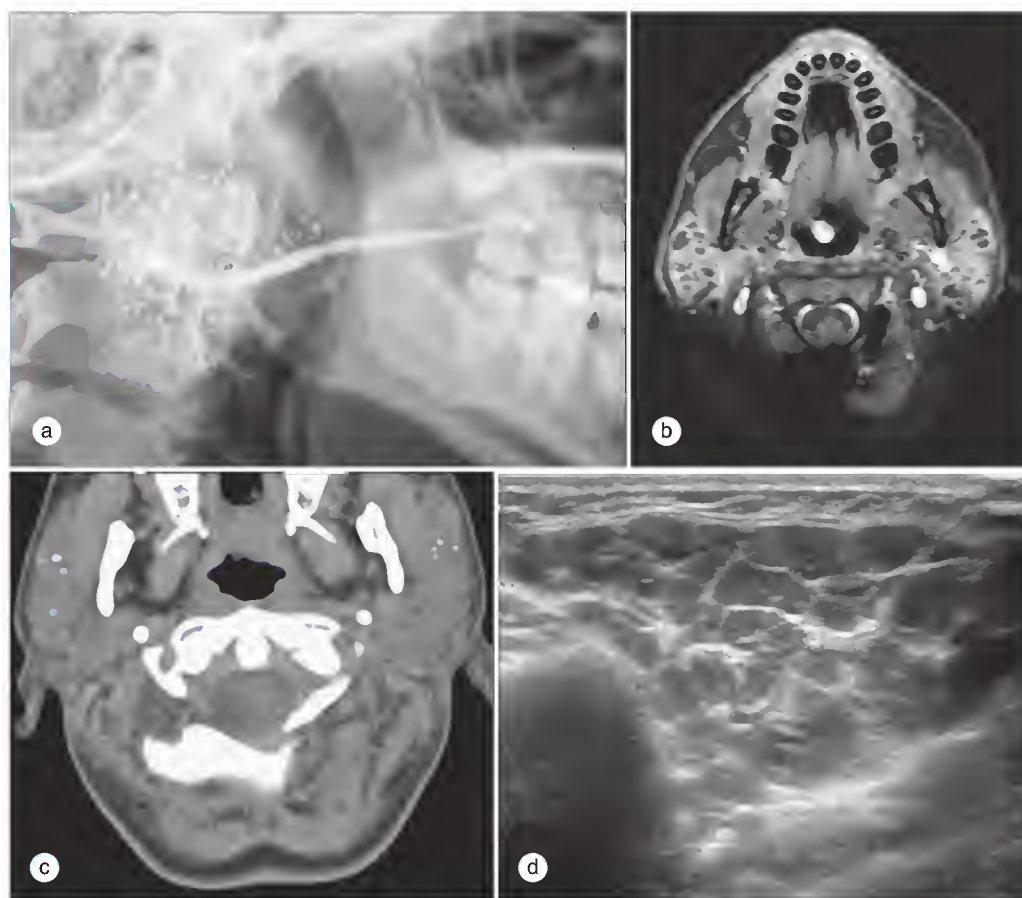


Fig. 138.9 Imaging of the parotid glands in Sjögren syndrome. (a) Contrast-enhanced sialogram in a patient with Sjögren syndrome. The multiple small round opacities present at the termination of the smaller ducts (sialectasia) has led to the appearance of a branchless fruit-laden tree or "mulberry" pattern. (b) Magnetic resonance imaging. On this T1-weighted image, both hypointense cystic structures and hyperintense foci are evident in the parotid gland parenchyma. (c) Computed tomography. In this tomographic section, punctate areas of calcification are apparent in the parotid gland parenchyma. This image is from a study of the same patient as in panel b. (d) Ultrasonography. Note the parenchymal inhomogeneity with numerous rounded hypoechoic areas delineated by hyperechoic linear reflectors.

T2-weighted sequences and multiple hypointense and hyperintense foci of varying size leading to a mottled or salt-and-pepper appearance. Dilation of the ductal system appears hypointense on T1-weighted and hyperintense on T2-weighted images. CT may demonstrate punctate calcification throughout the parotid gland parenchyma; it is used mainly for evaluation of sialolithiasis. Ultrasonography is emerging in importance because it can be performed in the clinical setting and does not involve radiation. It reveals variable degrees of parenchymal inhomogeneity amenable to scoring.

Salivary gland scintigraphy provides a functional analysis of the major salivary glands through measurement of the uptake, concentration, and excretion of technetium pertechnetate with a gamma scintillation camera. It has good sensitivity but fairly low specificity for SS and lacks standardized criteria for abnormal test results, which has led to variation in interpretation between centers.

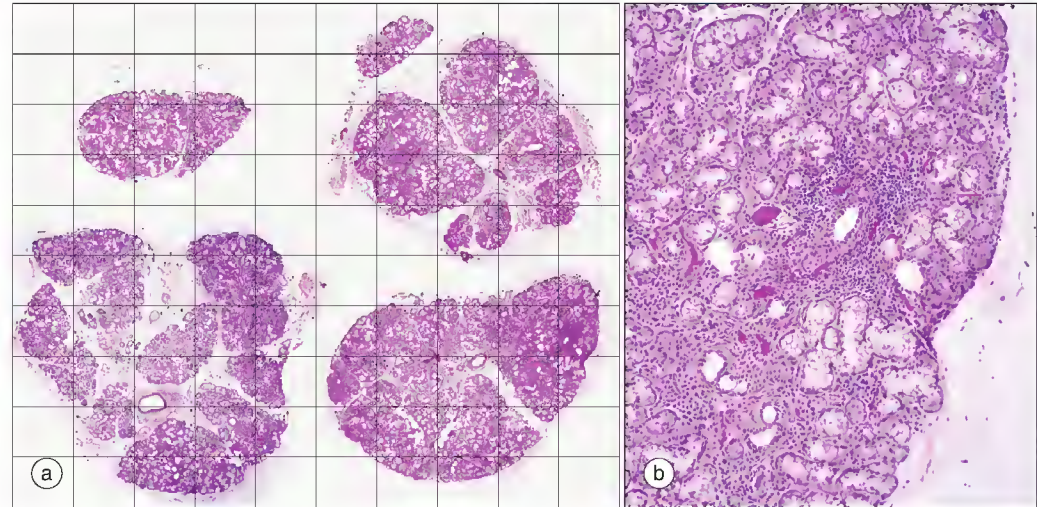
Labial gland biopsy

Labial salivary gland biopsy is essential for definitive evaluation of patients with suspected SS who lack both anti-SSA or anti-SSB antibodies or have weakly positive test results. Additionally, it may provide useful prognostic information on all SS patients⁴⁹ and establish alternative diagnoses,

including amyloidosis, sarcoidosis, IgG4-related disease, and lymphoma. However, it may cause persistent lip numbness in up to 2% of patients.⁶² The preferred biopsy technique is that described by Daniels and colleagues (<http://sicca.ucsf.edu/Oral-Saliva-SOP.pdf>). Approximately six to seven minor salivary glands should be dissected free, fixed in formalin, and embedded whole in paraffin as a group. Interpretation of the biopsy specimen must be performed according to the protocols used for deriving the 2012 ACR classification criteria.⁵⁶

Focal lymphocytic sialadenitis is characteristic of SS and defined by the presence of tightly aggregated clusters or foci of lymphocytes containing 50 or more cells (see Fig. 138.1). Because such lymphocytic foci can also occur in glands that have sustained damage from ductal obstruction, they should be considered a feature of focal lymphocytic sialadenitis only if they are adjacent to normal-appearing mucous acini. The number of lymphocytic foci normalized to 4 mm² of glandular section area is termed the "focus score" and provides a semiquantitative assessment of histologic severity. It is measured in a midspecimen tissue section by counting the number of foci, measuring the total glandular area in the section with a calibrated eyepiece graticule, and then calculating the number of foci per 4 mm² (Fig. 138.10). A score of 1 focus per 4 mm² or higher correlates strongly with the phenotypic features of SS.⁵⁶ It is not considered a pathognomonic

Fig. 138.10 Calculation of the focus score. The surface area of all salivary gland lobules in a tissue section is measured with a calibrated microscope eyepiece graticule (a). The foci in the tissue section adjacent to normal-appearing acini are then counted. One such focus is evident in panel b. The total number of foci in the tissue section is then divided by the total surface area of the glandular tissue to yield the number of foci per square millimeter. This number is then multiplied by 4 to derive the focus score, that is, the number of foci per 4 mm² of glandular tissue in the section.



finding and thus must be interpreted in the context of other phenotypic features.

Sclerosing chronic sialadenitis is a histopathologic pattern subject to misinterpretation as being indicative of SS.⁵⁶ It is characterized by acinar atrophy, duct dilation and hyperplasia, and interstitial fibrosis and occurs as a consequence of aging or ductal obstruction. Chronic inflammation is often present, either focally (but not adjacent to normal-appearing acini) or diffusely.

DIFFERENTIAL DIAGNOSIS

Symptomatic dryness of the eyes or mouth is most commonly caused by drugs with anticholinergic effects. Dry eye disease is often idiopathic.⁵⁷ Salivary gland dysfunction may arise from past irradiation of the head and neck, human immunodeficiency virus infection, graft-versus-host disease, uncontrolled diabetes mellitus, and sarcoidosis. Hepatitis C can be associated with a clinical syndrome indistinguishable from primary SS, although these patients are older and have a higher prevalence of cryoglobulinemia, RF and hypocomplementemia and a lower prevalence of anti-SSA and anti-SSB antibodies.⁶³

PATHOGENESIS

SS is mediated by the interaction of incompletely defined genetic, epigenetic, and environmental factors that induce immune dysregulation, loss of self-tolerance, and the development of overt autoimmune disease. SS is heterogeneous in terms of both clinical expression and severity, which implies the predominance of distinct pathogenic pathways in patient subsets.

Genetic susceptibility

The major histocompatibility complex (MHC) class II genes, mainly HLA-DQ and HLA-DR, are the best documented risk factors, with the DR2 and DR3 haplotypes at the DRB1 locus in white populations being the most replicated.⁶⁴ DR2 and DR3 associations are strongest in SS patients with anti-SSA and anti-SSB antibodies,⁶⁵ thus suggesting that specific MHC alleles influence which protein epitopes are targeted by the immune system.

Genes outside the MHC locus also influence susceptibility to SS. Single nucleotide polymorphisms (SNPs) have been identified in genes involved in the innate and adaptive immune response pathways.⁶⁴ The odds ratios for these associations are modest, which suggests that dysregulation of multiple pathways is necessary to precipitate disease. Polymorphisms in genes of the interferon (IFN) pathways have received particular attention because of overexpression of IFN-inducible genes in SS patients.⁶⁶⁻⁶⁸ SNPs in the transcription factors interferon regulatory factor 5 (IRF5) and signal transducer and activator of transcription 4 (STAT4) have been reproducibly associated with SS.⁶⁹⁻⁷¹ IRF5 is activated by Toll-like receptor (TLR) ligation and drives the production of IFN- α and proinflammatory cytokines.⁷² STAT4 is activated by type I IFN, interleukin-12 (IL-12), and IL-23 and stimulates the production of IFN- γ and IL-17.⁷³ The IRF5 and STAT4 risk alleles have

an additive effect on susceptibility to SS, thus highlighting a potential for IFN- or type 17 helper T cell (Th17)-mediated pathogenesis.⁷¹ SNPs in genes involved in B-cell regulation such as BLK may also contribute to susceptibility to SS.⁷⁴

Environmental factors

The first signs of SS typically occur long before diagnosis, thereby impeding study of its etiology. Autoantibodies can precede the development of SS, as evidenced in part by the study of asymptomatic mothers of children with neonatal lupus who have high-titer anti-SSA or anti-SSB antibodies (or both). These mothers are at an increased risk for SS; however, the fact that SS develops in only a minority indicates that autoantibodies alone are insufficient for induction of disease.⁷⁵

Viruses have been postulated as etiologic agents of SS. In this scenario the host immune response is initially directed against persistently infected cells but becomes misdirected toward host tissues because of chronic antigen exposure, thereby resulting in autoimmunity. Support for this theory stems in part from the nature of the targeted autoantigens. Ro52 is induced by IFNs that are produced at high level during viral infection, and enhanced autoantigen expression in tissues may trigger an autoimmune response.⁷⁶ Complexes of La and RNA encoded by Epstein-Barr virus have been shown to induce TLR activation and type I IFN production.⁷⁷ Similarly, Ro60 can bind RNA, and immune complexes containing this bound Ro60 induce type I IFN production,⁷⁸ thus suggesting a link between autoantibodies and expression of IFN-regulated genes in SS tissues.

The predominance of SS in women during or after menopause, as estrogen levels are declining, points to a potential role for sex hormones in development of the disease. Low serum concentrations of dehydroepiandrosterone and dihydrotestosterone have been demonstrated,⁷⁹ which argues for a protective role of androgens in the development of SS.

Effector pathways

A number of inflammatory pathways have been implicated in the pathogenesis of SS. Interactions between these pathways may be important for sustaining the inflammatory process characteristic of SS and may represent important points of intervention. The putative roles of such pathways in the pathogenesis of SS are highlighted in the following sections (Fig. 138.11).

B cells and B cell-activating factor

B cells dominate the larger lymphoid infiltrates¹¹ and may form organized GC-like structures in the salivary glands of patients with SS. These structures contain segregated T- and B-cell zones, follicular dendritic cell networks, and high endothelial venules characteristic of secondary lymphoid organs.⁸⁰ Their presence suggests that local salivary gland antigens drive the hyperactive B-cell response and formation of high-affinity autoantibodies. Activation-induced cytidine deaminase, an enzyme required for immunoglobulin (Ig) heavy-chain class-switch recombination and affinity maturation, is expressed in ectopic GC-like structures, thus implying that autoantibodies are generated in glandular tissues.⁸¹ Evidence of restricted Ig

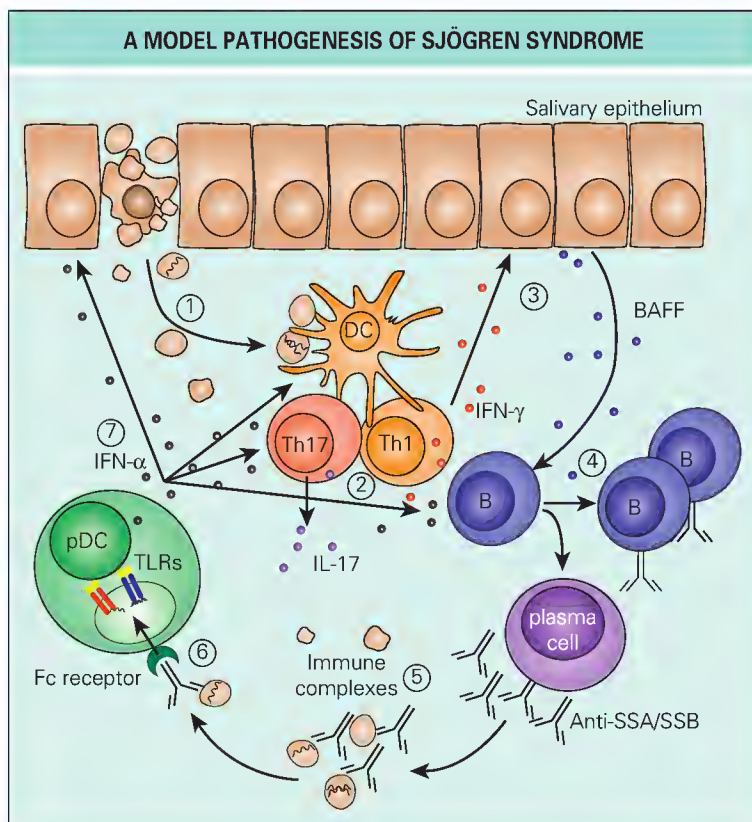


Fig. 138.11 (1) Self-antigens released via exosomes or the apoptotic cell death of salivary epithelial cells undergo endocytosis by dendritic cells (DCs) with subsequent processing and presentation on the cell surface for recognition by T cells. (2) Autoreactive T cells are activated by DCs expressing self-antigens and secrete proinflammatory cytokines, including interleukin-17 (IL-17) and interferon- γ (IFN- γ). (3) IFN- γ enhances antigen presentation by DCs and induces the expression of B cell-activating factor (BAFF) by salivary epithelial cells. (4) BAFF induces the proliferation of autoreactive B cells and supports differentiation into autoantibody-secreting plasma cells. (5) Autoantibodies form immune complexes with autoantigens bound to nucleic acids derived from cellular debris, which (6) can co-ligate Fc receptors and Toll-like receptors (TLRs) on plasmacytoid DCs (pDCs) and induce IFN- α production. (7) IFN- α induces autoantigen expression in epithelial cells and promotes DC activation, T-cell survival, and plasma cell differentiation and autoantibody production. Th17, type 17 helper T cell.

light-chain gene use and somatic hypermutation of Ig heavy-chain genes in infiltrating B cells further supports this notion.^{82,83}

The potent B-cell survival factor B cell-activating factor (BAFF) may drive B-cell hyperactivity.⁸⁴ BAFF levels are increased in SS serum and saliva and correlate with the level of serum autoantibodies.⁸⁵ BAFF is expressed in large amounts by B and T cells infiltrating SS salivary glands,^{86,87} and BAFF levels have been shown to correlate directly with the extent of lymphocytic infiltration and the presence of ectopic GCs. Overexpression of BAFF and subsequent signaling through its receptor on all mature B cells may enhance the proliferation and survival of autoreactive B cells in salivary glands.

Interferons

Type I IFN, which can be produced by all nucleated cells, and type II IFN (IFN- γ), which is produced by activated T and natural killer cells, have evident roles in the pathogenesis of SS. The association of gene polymorphisms in the IFN pathways with susceptibility to SS and the expression of IFNs and IFN-inducible genes (the “IFN signature”) in both peripheral blood mononuclear cells⁶⁶ and labial salivary gland biopsy specimens from patients with SS^{67,68} strongly implicate IFNs in this process. The enrichment of professional type I IFN-producing plasmacytoid dendritic cells (pDCs) in SS tissues⁷⁸ and the evidence that immune complexes containing self-antigens can stimulate type I IFN production by pDCs via TLR ligation⁸⁸ provide a potential mechanistic link between antibody responses and the IFN signature seen in tissues. Furthermore, co-localization of type I and

type II IFN responses in the same regions of salivary glands⁸⁹ suggests reinforcing interactions between the two pathways. For instance, IFN- γ can enhance signaling through TLRs,⁹⁰ thereby potentially enhancing type I IFN responses.

Once produced, IFNs have the capacity to modulate innate and adaptive immune responses.⁹¹ In addition to upregulating MHC and co-stimulatory molecules, IFNs have the ability to promote B-cell differentiation and antibody production, enhance T-cell survival, and induce the maturation of antigen-presenting cells. IFN- γ can also drive the formation of ectopic GCs⁹² and the expression of BAFF.⁹³ If left unchecked, the normal physiologic effects of IFN may drive the immune dysregulation of SS.

T cells

The strong association of SS with specific MHC alleles implies an important role for T cells. The majority of infiltrating T cells are CD4+, and T-cell infiltrates can be oligoclonal,^{11,94} which is suggestive of an antigen-driven immune response. However, it remains unclear whether T cells are directly cytotoxic in salivary glands. IFN- γ , produced by activated T cells, has been shown to induce salivary dysfunction in several *in-vitro* systems.^{95,96} Proinflammatory IL-17-expressing CD4+ T cells, or Th17 cells, have been identified in SS glands,⁹⁷ and IL-17 expression correlated with higher focus scores.⁹⁸

Role of the target tissue

The primary autoantigens targeted in SS are ubiquitous proteins. Therefore, the specific targeting of exocrine glands implies that the tissues are active participants in the disease process, with damage specifically being focused onto themselves. It is likely that the target tissue supplies the antigens that drive the disease process. Whether this is through the release of autoantigens following apoptotic cell death⁹⁹ or the formation of autoantigen-containing exosomes¹⁰⁰ is unclear.

The theory of “autoimmune epitheliitis”¹⁰¹ is based on observations that SS salivary gland epithelial cells express many of the requisite molecules for antigen presentation and immune activation, including MHC class I, MHC class II, and the T-cell co-stimulatory molecules CD80 and CD86, as well as intercellular adhesion molecule 1, vascular cell adhesion molecule, and CD40. Importantly, the characteristics of activation persist in long-term cell culture. It remains unclear whether these characteristics represent intrinsic functional changes in the salivary epithelium or are a consequence of chronic cytokine stimulation and whether these cells present antigens *in vivo*.

Lymphomagenesis

Malignant transformation is probably driven by antigen. Analysis of Ig genes from MALT lymphoma demonstrates restricted heavy- and light-chain gene use, with evidence of class switching and somatic hypermutation¹⁰² that probably occur in ectopic GC-like structures as a result of chronic antigenic stimulation.¹⁰³ BAFF may play a significant role in this process. Upregulation of the antiapoptotic protein Bcl-2 by BAFF has been shown to promote survival of non-Hodgkin lymphoma cells *in vitro*, and *in vivo*, BAFF levels correlate with tumor severity.

MANAGEMENT

Glandular manifestations

Lacrimal and salivary gland dysfunction is managed both topically and systemically.¹⁰⁴ Patients should maintain adequate hydration; avoid hot, dry, and windy environments; and stop smoking cigarettes. Any drugs being used that have anticholinergic side effects should be reconsidered.

For mild dry eye disease, use of preserved artificial tears up to four times per day may suffice. For more severe disease, preservative-free artificial tears should be instilled more than four times per day and a topical gel or ointment applied at bedtime. Suppression of ocular inflammation can be achieved with short courses of topical steroids, prolonged use of topical cyclosporine (0.05%), and nutritional supplementation with flaxseed oil. Punctal plugs or cauterization will preserve existing tears, and systemic secretagogues may augment tear volume. Additional measures include autologous serum tears, scleral prostheses, moisture goggles, and rarely surgery (such as partial tarsorrhaphy). Blepharitis, if present, should be treated with lid hygiene and compresses, as well as systemic tetracyclines.

Vigorous management of salivary hypofunction alleviates the symptoms of dry mouth and prevents dental caries and oral infections. Many patients choose to sip water or sugar-free fluids. Carbonated beverages should not

be used for this purpose because prolonged exposure of the teeth to an acidic oral environment promotes loss of dental mineral. Secretion of saliva can be stimulated by chewing sugar-free gum or sucking on sour sugar-free candy or xylitol-containing lozenges. Saliva replacement and oral lubrication can be achieved with artificial saliva, sprays, and gels. The M3R agonists pilocarpine and cevimeline increase salivary flow rates and improve symptoms of oral and ocular dryness. Side effects of sweating, nausea, and increased urinary frequency may hinder higher-dose or long-term use. These drugs are contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, and iritis.

Brushing teeth at least twice per day, flossing daily, and avoiding cariogenic food help prevent dental caries. The use of prescription-strength fluoride toothpaste combined with professional fluoride treatment at 3- to 6-month intervals is standard of care for those at high risk for the development of caries.¹⁰⁵ Dental checkups every 3 to 6 months allow control and removal of dental plaque, early detection of caries, and topical application of fluorides. Concomitant therapy with calcium and phosphate remineralizing agents may be helpful for severe salivary hypofunction.

Treatment of oral candidiasis requires topical application of antifungal agents if flow of saliva is insufficient to bring systemic antifungal drugs to the oral cavity. Most topical antifungal agents have a high sugar content (e.g., nystatin oral suspension) and thus should be avoided because they may promote dental caries. Options include the use of nystatin vaginal tablets, miconazole buccal tablets, or nystatin troches compounded with artificial sweeteners. Dentures should be cleansed nightly.

Oral immunomodulating or immunosuppressive medications have not been found to improve glandular function in controlled trials. Hydroxychloroquine, methotrexate, D-penicillamine, and mycophenolate have also had disappointing results in open trials. Long-term use of oral corticosteroids has not been shown to alter disease-associated decreases in salivary flow rates.¹⁰⁶ Corticosteroids can be effective in treating parotid gland swelling, but their side effects often preclude long-term use.

Biologic agents have the potential to be clinically efficacious in patients with SS based on their targeting of specific immune pathways and their remarkable success in certain other rheumatic diseases. The tumor necrosis factor (TNF) antagonists infliximab and etanercept did not show benefit in short-duration placebo-controlled trials.^{107,108} Rituximab may augment salivary flow in patients with preserved gland function at baseline.¹⁰⁹ In a double-blind, randomized, placebo-controlled trial, rituximab was successful in depleting peripheral blood B cells and augmenting salivary flow at 5 and 12 weeks after the infusion, but not at 48 weeks, the end of the trial.¹¹⁰ Sequential parotid gland biopsy specimens did show histologic improvement at the 12-week time point, with a reduction in the lymphocytic infiltrate, partial disappearance of GCs, and a decrease in lymphoepithelial lesions.¹¹¹ Rituximab was effective in relieving marked salivary and lacrimal gland swelling in a retrospective review.¹¹²

Vaginal dryness and dyspareunia are treated with vaginal lubricants and moisturizers. Postmenopausal vaginal atrophy responds to vaginal estrogen creams. The external vulvar surface may be treated with lubricating creams and vitamin E oil.

Extraglandular manifestations

Treatment of most extraglandular manifestations involves a hierarchy of treatments starting with those appropriate for milder disease and ending with those for more severe disease.¹⁰⁴ Arthritis is initially treated with hydroxychloroquine with or without nonsteroidal antiinflammatory agents.

More severe disease may require low-dose corticosteroids, methotrexate, leflunomide, TNF antagonists, or rituximab. Fatigue is generally treated in a multidisciplinary fashion, with attention to concomitant depression, fibromyalgia, and sleep disorders. Hydroxychloroquine is often prescribed for this indication, and its use is associated with a reduction in the sedimentation rate and immunoglobulin levels, but the clinical impact of this is uncertain. Rituximab showed possible benefit in reducing fatigue in a randomized clinical trial.¹¹³

Distal RTA is treated with bicarbonate or citrate salts to control the acidosis and prevent the formation of renal stones. In patients with impaired renal function or significant proteinuria, a renal biopsy should be performed. The finding of tubulointerstitial nephritis or glomerulonephritis should prompt treatment with a course of corticosteroids.¹⁹ The role of long-term steroid-sparing immunosuppressive agents has not been defined. Cryoglobulinemic glomerulonephritis requires more intensive therapy, often corticosteroids with cyclophosphamide or rituximab.

Interstitial lung disease in SS does not require treatment if forced vital capacity (i.e., >75%) or diffusion capacity (>65%) is not significantly impaired. Corticosteroids are the first-line treatment and may suffice for lymphoid interstitial pneumonia or organizing pneumonia patterns of involvement. Azathioprine, mycophenolate, and cyclophosphamide can be used as steroid-sparing agents, particularly if the lung disease progresses with corticosteroid monotherapy.¹¹⁴

The nonvasculitic peripheral and cranial neuropathies are managed first with tricyclic antidepressants or antiepileptics (e.g., gabapentin, pregabalin, carbamazepine). For patients who fail to respond, intravenous immunoglobulin (0.4 g/kg/day for 5 days) may be beneficial.¹¹⁵ Vasculitic neuropathies are usually treated with corticosteroids and cyclophosphamide, although rituximab is gaining wider acceptance as an alternative to cyclophosphamide.

Cutaneous vasculitis may not require pharmacologic treatment when manifested as mild intermittent purpura. Support stockings and avoidance of prolonged standing may suffice. More severe flares may require moderate-dose corticosteroids, usually in a tapering dose. Hydroxychloroquine, colchicine, dapsone, methotrexate, azathioprine, and mycophenolate mofetil have potential utility in controlling recurrences and minimizing corticosteroid exposure. Rituximab is being used increasingly for control of cryoglobulinemic vasculitis in SS. Cyclophosphamide is reserved for refractory cases or those with more serious manifestations.

Lymphoma

MALT lymphoma localized to the salivary glands may be observed without treatment if asymptomatic.^{116,117} Patients with large parotid gland swelling or other local symptoms may be treated with low-dose involved-field radiotherapy, rituximab alone, or rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).¹¹⁷ MALT lymphoma associated with severe extraglandular disease (such as cryoglobulinemia) is treated with rituximab alone at 6-month intervals for up to 2 years or rituximab with CHOP.^{116,117} Disseminated MALT lymphoma is treated with chemotherapy, with or without rituximab.¹¹⁶ Similarly, diffuse large B-cell lymphoma is best treated with rituximab and CHOP.¹¹⁶

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Antiphospholipid syndrome: overview of pathogenesis, diagnosis, and management

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- Antiphospholipid syndrome (APS) is a disorder of recurrent vascular thrombosis and/or pregnancy losses associated with persistently elevated levels of antiphospholipid-protein antibodies.
- APS is classified as “primary” when there is no underlying disease and “secondary” in the presence of systemic lupus erythematosus or other autoimmune disorder.
- Long-term anticoagulation is used to prevent recurrent thrombosis.
- Recurrent pregnancy loss may be prevented by treatment with subcutaneous heparin and low-dose aspirin during pregnancy.

ANTIPHOSPHOLIPID SYNDROME: DEFINITION AND HISTORY

Antiphospholipid syndrome (APS) is an autoimmune multisystemic disorder characterized by recurrent arterial and venous thrombosis and/or pregnancy morbidity associated with the presence of persistent antiphospholipid antibodies (aPLs). aPLs are a heterogeneous group of antibodies directed against anionic phospholipids or protein-phospholipid complexes. Laboratory tests to identify aPL includes solid-phase immunoassays (enzyme-linked immunosorbent assay [ELISA]) to detect anticardiolipin (aCL) and anti- β_2 -glycoprotein I (anti- β_2 -GPI) antibodies and functional assays to detect the so-called lupus anticoagulants (LACs) that demonstrate the ability of aPL to prolong phospholipid-dependent clotting reactions.¹ The term *lupus anticoagulant* is a misnomer. The LAC phenomenon results in prolonged plasma clotting times; however, patients with LAC are subject to thrombosis, not to hemorrhage, except in uncommon cases such as in hypoprothrombinemia-LAC syndrome.

Although initially described in patients with systemic lupus erythematosus (SLE), APS was soon recognized also to occur in patients without underlying autoimmune disease. APS was then classified as “secondary” in the presence of SLE and “primary” in the absence of SLE or other autoimmune disorders.

Primary APS is the most common cause of acquired thrombophilia and accounts for 15% to 20% of all episodes of deep vein thrombosis with or without pulmonary embolism, one third of new strokes occurring in patients younger than age 50, and 10% to 15% of women with recurrent fetal loss.² APS also accounts for a significant proportion of thromboembolic disease and recurrent fetal loss in patients with SLE. aPLs are present in 30% to 40% of SLE patients, and 10% to 15% of all SLE patients have clinical manifestations of APS.³ It is now generally accepted that aPLs are the most frequent acquired risk factor for a treatable cause of recurrent pregnancy loss and for pregnancy complications.

In 1999, an international consensus meeting formulated the first classification criteria (known as the *Sapporo criteria*) for patients with APS.⁴ In 2006, these criteria were updated¹ (Box 139.1).

EPIDEMIOLOGY

The presence of aPLs is detected in fewer than 1% of apparently normal individuals and in up to 3% of the elderly population. Patients with syphilis, acquired immunodeficiency syndrome, and other infectious disorders, as well as those with drug-induced aPLs, do not usually have clinical features

of APS. Prospective studies have shown an association between the presence of aPLs and the first episode of venous thrombosis,² the first myocardial infarction,⁵ and the first ischemic stroke.⁶ Antibody profile, isotype, level, and other undefined characteristics of aPLs, as well as underlying disease, may all be determining features in developing the clinical syndrome. It is now recognized that patients with triple aPL positivity, defined as the presence of LAC and high titers of aCL and anti- β_2 -GPI, are at higher risk of thrombosis.^{7,8} Risk stratification for thrombosis in patients with APS is summarized in Table 139.1.

Genetic studies strongly support a genetic basis for disease in families with APS, which suggests an autosomal dominant mode of inheritance. An association with HLA-DR7, DR4, DRw53, DQw7, and C4 null alleles has been reported.⁹

PATHOGENESIS

There is evidence that aPLs can be pathogenic rather than a simple serologic marker for APS. Multiple molecular pathways are implicated in the pathogenesis of APS.

Mechanisms of thrombosis

Despite the persistent presence of aPLs in circulation, thrombotic events occur only occasionally in patients with aPLs, which suggests that the presence of aPLs is necessary but not sufficient for clot formation *in vivo*. The “two-hit hypothesis” has been proposed, which holds that aPLs (first hit) can exert their prothrombotic action only in the presence of another thrombophilic condition (second hit).¹⁰

The aPL interaction with endothelial cells, monocytes, and platelets induces a prothrombotic and proinflammatory phenotype. A growing body of evidence shows that complement activation is a critical early mediator in APS by linking aPLs to thrombosis and fetal injury.¹¹

Additionally, interaction of aPLs with proteins implicated in clotting regulation such as prothrombin, factor X, protein C, protein S, and plasmin may interfere with the inactivation of procoagulant factors and fibrinolysis¹² (Box 139.2).

Mechanisms of pregnancy loss

The pathogenesis of obstetric APS remains uncertain. Intraplental thrombosis was initially suggested to be the main pathogenic mechanism of fetal loss. However, in observational studies of women with obstetric APS not all placentas examined showed placental thrombosis, infarctions, or vasculopathy. *In vitro* studies demonstrated that aPLs may impair trophoblastic invasion and human chorionic gonadotropin production, promoting not only early miscarriages but also fetal loss and uteroplacental insufficiency.¹³ Recent advances have proposed that complement, β_2 -GPI, and annexin V play a central role in fetal loss¹⁴ (Box 139.3).

CLINICAL FEATURES

Overview

APS is the most common cause of acquired thrombophilia. Recurrent thromboses and pregnancy morbidity are the hallmarks of the syndrome. However, thrombocytopenia or hemolytic anemia may occur as the sole manifestation.

BOX 139.1 PRELIMINARY CRITERIA FOR CLASSIFICATION OF ANTIPHOSPHOLIPID SYNDROME**Clinical criteria****Vascular thrombosis**

One or more clinical events of arterial, venous, or small-vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by Doppler ultrasonography, other imaging, or histopathologic analysis, with the exception of superficial venous thrombosis. The histopathologic study does not have to demonstrate significant evidence of inflammation of the blood vessel.

Pregnancy morbidity

- One or more unexplained deaths of morphologically normal fetuses at 10 or more weeks of gestation, with a normal fetal morphology confirmed by ultrasound or direct examination of the fetus.
- One or more premature births of a morphologically normal newborn at 34 weeks of gestation or before due to
 - Severe preeclampsia or eclampsia defined according to current standards, or
 - Recognized placental insufficiency
- Three or more consecutive spontaneous abortions without explanation before 10 weeks of gestation, excluding those associated with hormonal or anatomic alterations in the mother or chromosomal alterations inherited from either parent.

Laboratory criteria

The presence of at least one of the following test results:

- Lupus anticoagulant in the plasma on two or more separate occasions within a period of 12 weeks, detected according to the guidelines of the International Society of Thrombosis and Haemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid-dependent antibodies).
- IgG or IgM anticardiolipin antibodies in plasma or serum in medium-high titers (more than 40 GPL or MPL units, respectively) on two or more separate occasions within a period of 12 weeks, as measured by standardized ELISA.
- IgG or IgM anti- β_2 -glycoprotein I antibodies in the serum or plasma (in titer above the 99th percentile) on two or more separate occasions within a period of 12 weeks, as measured by standardized ELISA according to recommended procedures.

ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin.

BOX 139.2 MECHANISMS OF THROMBOSIS IN ANTIPHOSPHOLIPID SYNDROME

- Interaction between antiphospholipid antibodies and cells (endothelial cells, monocytes, platelets)
- Activation of cell signaling pathways
- Transcription of procoagulant factors (tissue factor) and adhesion molecules
- Complement activation
- Impaired nitric oxide production
- Antiphospholipid antibody inactivation of fibrinolysis

BOX 139.3 MECHANISMS OF PREGNANCY LOSS IN ANTIPHOSPHOLIPID SYNDROME

- Intraplental thrombosis
- Impaired trophoblastic invasion and hormone production
- Activation of the complement system
- Defective placentation due to interference of anti- β_2 -glycoprotein I with trophoblast growth and differentiation
- Displacement of annexin A5 by immunoglobulin G antiphospholipid antibody- β_2 -glycoprotein I complexes

TABLE 139.1
Risk stratification for recurrent thrombosis in patients with antiphospholipid syndrome

	High risk	Low risk
Serologic profile	LAC positivity Triple positivity (LAC + aCL + anti- β_2 -GPI) Isolated persistent positivity for aCL (medium-high titers)	Isolated intermittent positivity for aCL or anti- β_2 -GPI at low titers (<40 GPL or MPL units)
Clinical profile	Presence of systemic lupus erythematosus Coexistent cardiovascular risk factors History of arterial thrombosis Recurrent thrombosis (arterial, venous, or both) despite anticoagulant therapy	Previous single venous thrombosis (particularly in association with transient risk factors)

aCL, anticardiolipin; β_2 -GPI, β_2 -glycoprotein I; LAC, lupus anticoagulant.
Adapted from Les I, Ruiz-Irastorza G, Khamashta M. Intensity and duration of anticoagulation therapy in antiphospholipid syndrome. *Semin Thromb Hemost* 2012;38:339-47.

Any organ can be affected in this disorder, thus the range of clinical features is extremely wide.¹⁵

Some patients who have features of APS alone at presentation later develop features typical of SLE.¹⁶ Conversely, patients with SLE may develop APS some time after the onset of SLE.

Arterial and venous thromboses, which may affect large, medium-sized, or small vessels, are among the main features of APS. In contrast, thromboses associated with congenital thrombophilias (protein C, protein S, factor V Leiden, and factor II 20210A mutations and antithrombin deficiency) are

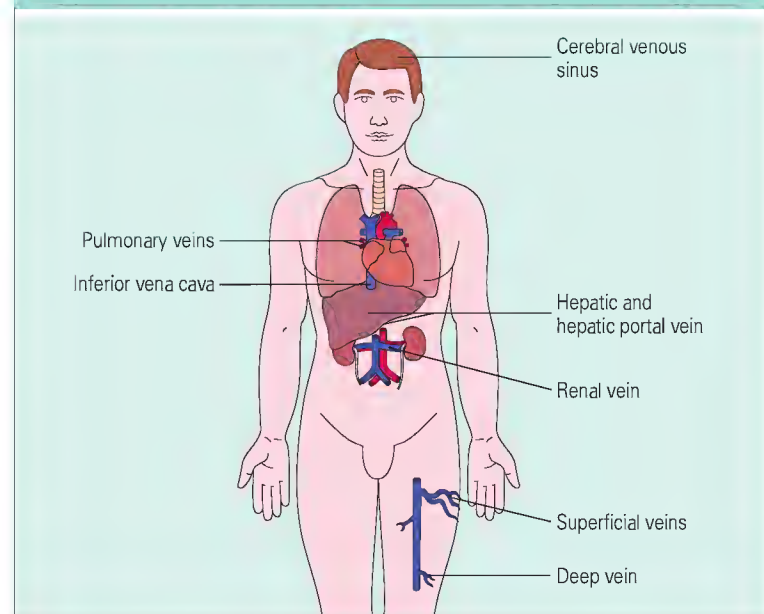
REPORTED SITES OF VENOUS THROMBOSIS IN PATIENTS WITH APS

Fig. 139.1 The deep and superficial veins of the legs are the most frequently reported sites of thrombosis in patients with antiphospholipid syndrome (APS).

almost exclusively venous. Histologic studies of the vascular lesion have shown thrombus without inflammatory infiltrates.¹⁷ In some cases, the vessel wall exhibits marked medial hyperplasia and severe luminal narrowing, the so-called APS vasculopathy.¹⁸

Other features including thrombocytopenia, Coombs-positive hemolytic anemia, abnormalities of cardiac valves, nonthrombotic skin lesions, and a variety of nonthrombotic central nervous system abnormalities are less clearly associated with a specific pathophysiologic mechanism.

Venous thrombosis

In the venous circulation, the deep veins of the lower extremities are the most frequent sites of thrombosis (Fig. 139.1). Reports of pulmonary hypertension caused by either recurrent pulmonary emboli or *in-situ* thrombosis are rare. Other reported sites of venous thrombosis include the pelvic, renal, mesenteric, portal, hepatic, axillary, ocular, and sagittal veins, as well as the inferior vena cava. Venous events usually occur at single sites with a tendency to recur in the same vascular bed as the original thrombotic episode.

Arterial thrombosis

Arterial thromboses are a major feature of APS. Arterial occlusions can affect the vascular tree from the aorta to the small capillaries. Ischemic stroke or transient ischemic attacks (TIAs) are the most common presentation of arterial thrombosis (Fig. 139.2).

Other arterial sites, including retinal, coronary, brachial, mesenteric, and peripheral arteries, are also subject to thrombosis.

Patients with APS who experience arterial thrombosis have been found to be at high risk of recurrence. The prognostic implications of these findings are significant, because ischemic stroke is the most common arterial manifestation of APS and a major cause of morbidity and mortality.¹⁹ There should be a high level of suspicion of APS in young patients who have no risk factors for atherosclerosis.

Pregnancy complications

Pregnancy loss, fetal distress, and premature birth are frequent complications in women with APS. Pregnancy loss can occur at any stage of gestation, particularly during the second and third trimesters (about 50% of cases). This differs from the pattern of pregnancy loss in the normal population, in which pregnancy loss usually occurs during the first trimester and is most often caused by morphologic or chromosomal abnormalities. It is

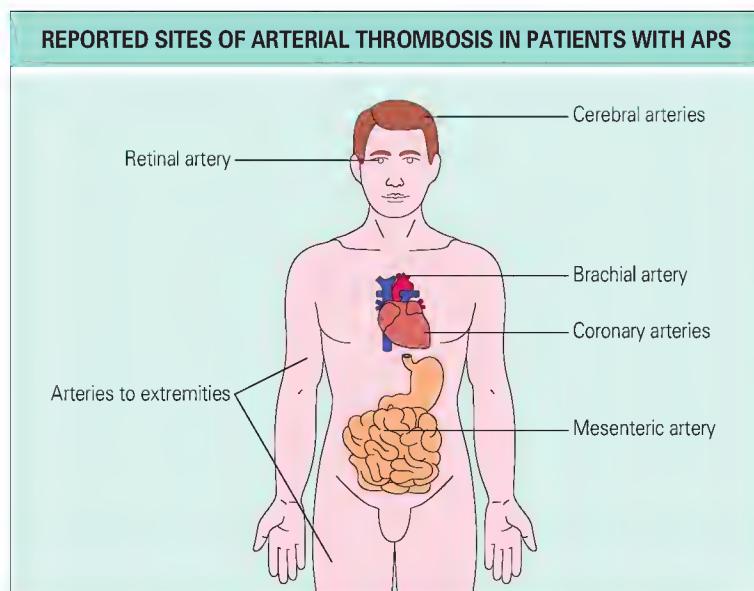


Fig. 139.2 In patients with antiphospholipid syndrome (APS) the intracranial arteries are the most frequently reported sites of thrombosis, which results in stroke and transient ischemic attacks. Myocardial infarction, gangrene of the fingers and toes, and bowel infarction have all been described and are presumed to be secondary to thrombotic occlusion of arteries supplying these sites. In some instances, occlusion of intracranial arteries may be secondary to emboli from heart valve vegetations.

not possible to predict which women who test positive for aPLs will develop complications in pregnancy. However, an adverse previous obstetric outcome, a history of thrombosis, and triple positivity for LAC, aCL, and anti- β_2 -GPI antibodies have been identified as predictors of high risk.^{20,21} Low-titer positivity for immunoglobulin G (IgG) aCL and IgM- or IgA-positive test results seem to be less frequently associated with pregnancy complications.

In APS, thrombotic occlusion of placental vessels and placental infarction are frequently reported. In some instances, however, the extent of placental damage does not appear to be sufficient to account for the degree of fetal distress. The aborted fetus usually appears normal. Although some babies born to mothers with APS may test positive for aCL, complications in neonates because of these antibodies are unusual.

The potential complications of pregnancy in women with APS also include preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), placental insufficiency, intrauterine growth restriction, abruptio placentae, and premature delivery. In addition, pregnant women with APS may experience thrombosis and complications due to treatment. Women with purely obstetric APS are at high risk of thrombotic complications during follow-up.²²

Nervous system abnormalities

Stroke and TIA are the most frequent neurologic complications of APS.²³ Because emboli from heart valve vegetations may be responsible for cerebral ischemia, echocardiography should be performed on patients with APS who experience TIA or stroke.

Cerebral ischemia may be silent, and when multiple events occur (Fig. 139.3) patients may first experience symptoms such as seizure or cognitive dysfunction. Without anticoagulant therapy, strokes may recur and patients occasionally have multiinfarct dementia at presentation. Magnetic resonance imaging (MRI) may show changes that vary from single lesions to multiple hyperintense white matter lesions (Fig. 139.4). Cerebral venous sinus thrombosis has occasionally been reported.

Ocular ischemic events and occlusion of retinal veins can occur.²⁴ Sensorineural hearing loss, presenting as sudden deafness has been associated with aPL.²⁵ Many other neurologic abnormalities not clearly linked to thrombosis include seizures, transverse myelopathy, chorea, Guillain-Barré syndrome, psychosis, and migraine headaches. APS and multiple sclerosis can be difficult to distinguish. A careful history taking, the localization of the lesions on MRI, and the response to anticoagulant therapy may be helpful in the differential diagnosis of these very different diseases.²⁶

Cardiac valve abnormalities

Valvular involvement has a prevalence of more than 80% if highly sensitive techniques such as transesophageal echocardiography are used.²⁷ Left-side valves, especially the mitral valve, are the most frequently involved. Echocardiographic findings include valve thickening, nodules, and vegetations (Fig. 139.5). The valve lesions in APS may be hemodynamically nonsignificant or may lead to valvular regurgitation or stenosis. Mitral regurgitation is reported in some series to occur in up to 25% of patients. Despite this high prevalence, only 4% to 6% of aPL-positive patients with valve disease will require surgical treatment.²⁸ It has been suggested that heart valve disease should be included as a classification criterion for APS.

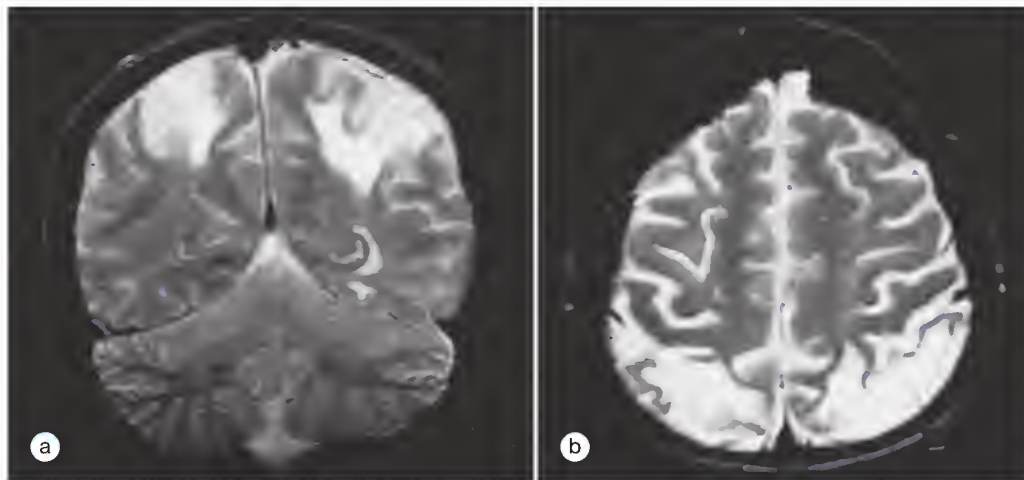


Fig. 139.3 Demonstration by magnetic resonance imaging of biparietal infarctions in a 26-year-old woman with antiphospholipid syndrome. This woman also had a right frontal lobe infarct, which is not shown here. She had no risk factors for thrombosis other than positivity for the lupus anticoagulant and high-positive results on assays for immunoglobulin G anticardiolipin antibodies. Her first pregnancy ended in intrauterine fetal death at 24 weeks' gestation.

Skin manifestations

Skin manifestations associated with APS include livedo reticularis (LR), leg ulcers, cutaneous necrosis, gangrene of the digits or extremities, superficial thrombophlebitis, necrotizing purpura, anetoderma, and nail-fold infarcts.²⁹ None of these manifestations is pathognomonic of APS. LR is the most common skin manifestation of APS. LR can be a marker of a high risk of arterial events.³⁰ LR may occur in patients with a variety of other disorders, including connective tissue diseases, vasculitides, multiple cholesterol emboli syndrome, sepsis, hyperoxaluria, and Sneddon syndrome (in which it is associated with stroke), as well as in normal individuals.

Different types of skin ulcerations may be observed.³¹ Some ulcers tend to occur in the pretibial area and ankle (Fig. 139.6). Large ulcers may resemble pyoderma gangrenosum. The latter should also be distinguished from postphlebotic ulcers, which can occur in patients who have had multiple episodes of deep vein thrombosis in the same leg.

Cutaneous gangrene and nail-fold infarcts are usually consequences of thrombosis of small arteries.



Fig. 139. 4 Demonstration by magnetic resonance imaging of multiple hyperintense lesions in a 34-year-old woman with positivity for lupus anticoagulant, pregnancy losses, history of a transient ischemic attack, depression, and cognitive dysfunction.

Thrombocytopenia and hemolytic anemia

Thrombocytopenia is a well-recognized feature of APS³² occurring in 16% to 46% of patients. Platelet levels fluctuate in the range of 100 to 150×10^3 per mm^3 and are seldom low enough to be associated with hemorrhage (less than 50×10^3 per mm^3).

The pathogenesis of thrombocytopenia in APS is unclear. Hypotheses include binding of aPLs to platelet membrane phospholipids, β_2 -GPI-phospholipid complexes, and coexisting antibodies to platelet membrane glycoproteins.

Patients with aPLs and hemocytopenias who have no history of thrombosis or pregnancy morbidity are not classified as having APS. However, this combination of findings may indeed represent a pre-thrombotic state that precedes the onset of APS ("hematologic APS"), and it has been suggested that thrombocytopenia be incorporated into the clinical criteria for APS.³³

About 10% to 20% of patients with APS have a positive Coombs test result, but hemolytic anemia is relatively uncommon. The simultaneous occurrence of hemolytic anemia and thrombocytopenia, referred to as *Evans syndrome*, is a rare occurrence in series of patients with APS.

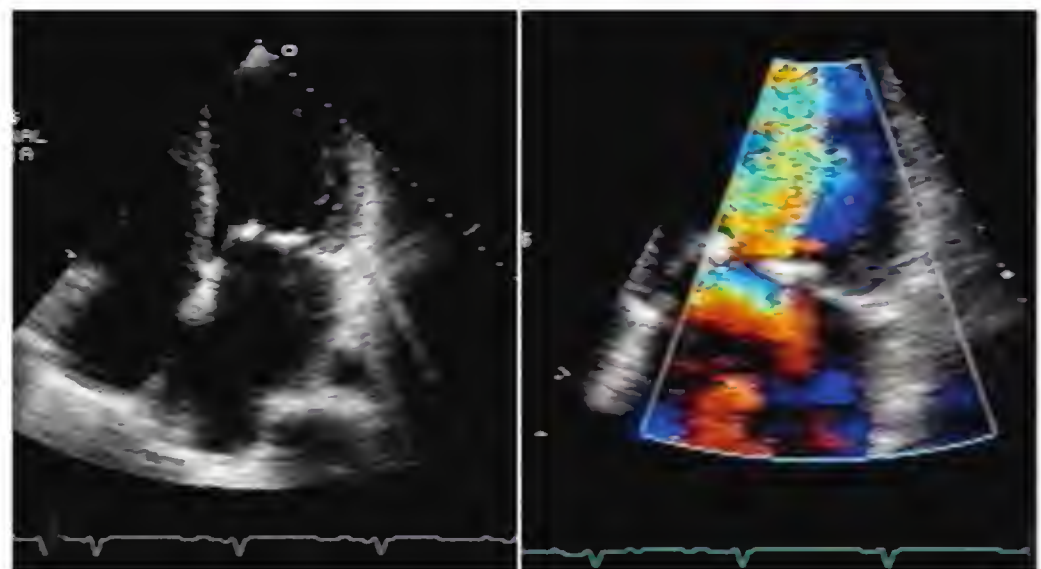
Renal manifestations

Thrombotic microangiopathy is the most characteristic finding in APS nephropathy, although it is not associated exclusively with this syndrome. It is characterized by the triad of hypertension, proteinuria, and renal failure. Fibrous intimal hyperplasia, focal cortical atrophy, and arterial occlusions have also been described.³⁴ Refractory hypertension secondary to renal artery stenosis can be also seen.³⁵



Fig. 139. 6 Large leg ulcers resembling pyoderma gangrenosum in a 55-year-old woman with antiphospholipid syndrome and a history of gangrene requiring amputation of several toes, splinter hemorrhages, mitral valve nodules, and persistent positivity for lupus anticoagulant.

Fig. 139. 5 Two-dimensional transthoracic echocardiogram (left) and color Doppler echocardiogram (right) of a patient with antiphospholipid syndrome. There is nodular thickening of both mitral leaflets. The left atrium is dilated and mitral stenosis is apparent.



Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome (CAPS) is a potentially life-threatening condition characterized by thrombosis at multiple organ sites occurring concurrently or over a short period of time in association with positive results on aPL tests. Even though fewer than 1% of APS patients develop this complication its potentially lethal outcome emphasizes its importance. Ischemia of the kidneys, bowels, lungs, heart, and/or brain is most frequent, and in rare cases adrenal, testicular, splenic, pancreatic, or skin involvement has been seen. Occlusion of small vessels (thrombotic microangiopathy) is characteristic, resulting in symptoms related to dysfunction of the affected organs.³⁶ Depending on the organs involved at presentation patients may have hypertension and renal impairment, acute respiratory distress syndrome, alveolar hemorrhage and capillaritis, confusion and disorientation, abdominal pain and distention secondary to bowel infarction, or multiorgan failure.

Unless the condition is considered in the differential diagnosis, it may be missed, which results in a disastrous outcome for these patients. CAPS must be distinguished from thrombotic thrombocytopenic purpura and disseminated intravascular coagulation.

LABORATORY DIAGNOSIS

Serologic assays used in the diagnosis of antiphospholipid syndrome

Anticardiolipin test

The aCL assay is simple and sensitive and provides helpful information to aid in the diagnosis of APS. This test uses the ELISA technique to detect antibody binding to solid plates coated with either cardiolipin or other phospholipids (Table 139.2). An aCL titer of more than 40 GPL units has been associated with an increased risk of thrombosis. The IgG isotype appears to be more closely associated with clinical manifestations than either the IgM or IgA isotype.³⁷

More specific serologic assays for antiphospholipid syndrome

It has been shown that β_2 -GPI is a relatively specific antigen for autoantibodies present in APS patients.³⁸ Anti- β_2 -GPI positivity has been reported to be associated primarily with thrombosis in patients with APS, but also with pregnancy loss and other manifestations of APS.³⁹

Domain I of β_2 -GPI is an integral component in the pathogenicity of this protein.⁴⁰ The interaction of β_2 -GPI with phospholipids induces major conformational change in this protein that exposes hidden epitopes within domain I. Anti- β_2 -GPI with specificity to domain I (anti-Dm I) increases susceptibility to thrombosis, and high titers are present in patients with triple positivity, which highlights its association with high risk of thrombosis.⁴¹

TABLE 139.2
Current assays used to confirm the diagnosis of antiphospholipid syndrome

Assay	Method
Criteria aPL assays	
Anticardiolipin	ELISA
Anti- β_2 -glycoprotein I	ELISA
Lupus anticoagulant	Clotting/functional assays
Noncriteria aPL assays	
Assays to detect antibodies to other phospholipids (e.g., phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylcholine)	ELISA
Annexin A5 resistance assay	Clotting/mechanistic assay
Assays to detect antibodies to prothrombin or prothrombin/phosphatidylserine	ELISA
Assays to detect antibodies to clotting proteins (e.g., protein C, protein S)	ELISA

aPL, antiphospholipid antibody; ELISA, enzyme-linked immunosorbent assay.

A number of laboratories include in their test panel assays that detect antibodies directed against other negatively charged phospholipids such as phosphatidylserine, phosphatidic acid, phosphatidylinositol, and phosphatidylglycerol. APS patients may also have antibodies directed against zwitterionic phospholipids such as phosphatidylethanolamine or positively charged phospholipids such as phosphatidylcholine (see Table 139.2). Patients with APS have antibodies that bind proteins other than β_2 -GPI, including prothrombin (PT), protein C, protein S, and annexins.^{42,43} A significant percentage of anti-PT antibodies demonstrate LAC activity. Although LAC is a known thrombosis risk factor, currently available data are inconclusive regarding whether anti-PT antibodies are an independent risk factor for thrombosis.⁴⁴ Novel antibodies to vimentin-cardiolipin complexes may have a potential diagnostic role in patients with clinical manifestations of APS but do not conform to the conventional serologic criteria.^{45,46} The value of these tests remains uncertain.

Lupus anticoagulant test

A positive LAC test result indicates the presence of an inhibitor of coagulation that does not react directly with individual coagulation factors but rather inhibits phospholipid-dependent coagulation reactions, an effect that is not associated with bleeding complications. Although aPLs detected in aCL and LAC tests are specific for phospholipids, phospholipid-binding proteins, or a complex of these molecules, the two tests (aCL and LAC) do not necessarily identify the same antibodies. The LAC test is less sensitive but more specific for detection of aPLs. Guidelines and criteria for the detection of LAC have been formulated and revised.⁴⁷

It is now clear that only some autoantibodies, those directed against domain I of β_2 -GPI, are associated with thromboembolic events.⁴⁸ There is no specific ELISA to detect anti-Dm1 antibodies. However, anti-Dm1 antibodies possess LAC activity. Therefore positivity for anti- β_2 -GPI (by ELISA) and the presence of LAC help identify the pathogenic anti- β_2 -GPI antibodies.⁴⁹

MANAGEMENT

Management of thrombosis

Prevention of thrombosis is a major goal of therapy in patients with aPLs, and treatment considers two different clinical groups: (1) patients with APS who have already experienced a thrombotic event; and (2) aPL carriers without previous clotting, that is, purely asymptomatic individuals, patients with SLE, and women with obstetric APS.

Secondary thromboprophylaxis

At present, antithrombotic therapy remains the main therapeutic approach in APS patients with thrombosis. The remaining two key questions are whether patients with APS should receive the same therapy as the general population with similar manifestations and whether arterial and venous events should be treated in different ways.

Two randomized clinical trials have compared high-intensity anticoagulation (target international normalized ratio [INR], 3.0 to 4.0) with standard anticoagulation (target INR, 2.0 to 3.0) for secondary thromboprophylaxis in patients with APS.^{50,51} Neither study found significant differences in efficacy or adverse effects between the two regimens. However, given the overrepresentation of patients with first venous thromboembolism in both trials, the recommendation to administer warfarin therapy to a target INR of 2.0 to 3.0 can be extended only to that subgroup.

Debate persists regarding treatment of patients with arterial thromboses. The Antiphospholipid Antibodies and Stroke Study (APASS) suggested that patients with stroke and aPL positivity who do not fulfill classification criteria for APS should be treated the same as the general population.⁵² However, it is the authors' view that patients with definite APS who have arterial disease and/or recurrent events merit a more aggressive approach, which might include warfarin treatment with a target INR of more than 3.0 or combined anticoagulant-antiaggregant therapy.⁵³

High-intensity oral anticoagulation therapy carries an inevitable risk of serious bleeding complications. Estimating the risk of bleeding in individual patients may help prevent complications.^{54,55} Recent studies in APS patients have found bleeding rates of 0.8% per year (with treatment to a target INR of 2.0 to 3.0). It should be stressed that the mortality rate due to thrombosis is higher than the mortality rate due to bleeding in patients with APS.^{56,57}

For APS patients who show no response to or poor tolerance to warfarin and for those who refuse to take vitamin K antagonists, long-term treatment

with low-molecular-weight heparin (LMWH) may be a safe and effective alternative to warfarin therapy.⁵⁸

It must be emphasized that concomitant vascular risk factors, which increase the likelihood of thrombosis in patients with aPLs, must be addressed.^{59,60} A consensus document on primary and secondary thromboprophylaxis in individuals with aPLs has been published.⁵⁴

Primary thromboprophylaxis

Retrospective studies suggest that patients with lupus and aPLs will develop thrombosis at an annual rate of around 3% to 4%. Also, women with purely obstetric APS may experience subsequent thromboses at a rate of 3% to 7% per year.⁶¹ The actual risk in healthy asymptomatic carriers of aPLs is probably lower. However, asymptomatic aPL carriers who have an aPL profile considered to place them at high risk of a first vascular event (positivity for LAC, aCL, and anti- β_2 -GPI, or so-called triple positivity) have an incidence of first thrombosis as high as 5.3% per year.⁶²

The presence of circulating aPLs should be considered a thrombotic risk factor, with several other variables modulating the final clinical expression. The most important variables are the aPL profile (type, level, and persistence); the coexistence of other thrombotic risk factors such as hypertension, smoking, hypercholesterolemia, or estrogen use; and the presence of an underlying autoimmune disease^{59,63} (see Table 139.1). Actually, the most important prophylactic measure may be the avoidance or reduction of these modifiable cardiovascular risk factors in all individuals with aPL positivity.

SLE by itself is considered a risk factor for thrombosis. For that reason, all patients with SLE and LAC or with aCLs at medium-high titers should be given primary thromboprophylaxis.⁵⁴ Hydroxychloroquine has been shown to protect against thrombosis in lupus patients, including those with aPLs.⁶⁴ Low-dose aspirin may also be effective in this setting.⁶⁵

Thromboprophylaxis in asymptomatic aPL carriers should be individualized based on the antibody profile. For those individuals with a high-risk profile (LAC or aPL triple positivity), especially in the presence of other thrombotic risk factors, low-dose aspirin therapy is suggested.

Thromboprophylaxis with LMWH in high-risk situations, such as surgery, prolonged immobilization, and the puerperium, is recommended.⁵⁴

PREGNANCY MANAGEMENT

With proper management, more than 70% of pregnant women with APS deliver a viable, healthy infant. Preconceptional counseling is essential to estimate the chance of both fetal and maternal problems. Despite the good prognosis achievable with correct management, patients must be aware that there is an increased risk of serious complications, including miscarriage, fetal death, prematurity, preeclampsia, and thrombosis. Pregnancy should be discouraged in all women with pulmonary hypertension due to the high risk of maternal death and should be postponed in the setting of uncontrolled hypertension or whenever a thrombotic event, particularly stroke, has recently taken place.

General pregnancy care in women with antiphospholipid syndrome

All pregnant women with APS should be cared for by high-risk medical-obstetrical clinics.

The objectives of prenatal care in the second and third trimesters are close observation for maternal complications and fetal surveillance testing. The latter should begin at 32 weeks' gestation, or earlier if the clinical situation raises suspicion of placental insufficiency, and should continue at least weekly until delivery. Uterine and umbilical artery Doppler evaluations are widely used to assess the risk of preeclampsia, placental insufficiency, and fetal growth restriction, with normal examination findings having high negative predictive values.⁶⁶

Pharmacologic management of antiphospholipid syndrome during pregnancy

Preconceptional aspirin therapy is desirable due to its possible beneficial effect on early stages of implantation. Early enthusiasm for treating pregnant women with APS using glucocorticoids waned in the early 1990s when two small, randomized trials found a lack of benefit of glucocorticoid therapy. Also, randomized trials have demonstrated that either the addition of intravenous immunoglobulin (IVIG) to heparin or IVIG alone offers no better outcomes.

For therapeutic purposes during pregnancy, women with APS must be categorized into one of three groups: (1) those with recurrent early

(preembryonic or embryonic) miscarriage and no other features of APS, (2) those with one or more prior fetal deaths (more than 10 weeks' gestation) or prior early delivery (less than 34 weeks' gestation) due to severe preeclampsia or placental insufficiency, and (3) those with previous thrombosis irrespective of pregnancy history.

Recurrent early (preembryonic or embryonic) miscarriage

The use of heparin (LMWH or unfractionated heparin) in combination with low-dose aspirin has been investigated by many groups. Recent expert guidelines recommend the combination of aspirin with either unfractionated heparin or LMWH.⁶⁷ However, the authors believe that the option of monotherapy with aspirin cannot be discarded in this subgroup of women, because observational studies have reported 79% to 100% pregnancy success rates with low-dose aspirin alone in this subgroup of women. One study suggests that women with refractory aPL-related pregnancy losses may have improved pregnancy outcomes with low-dose prednisolone taken until 14 weeks' gestation.⁶⁸ These results warrant further investigation.

Fetal death or prior early delivery due to severe preeclampsia or placental insufficiency

The optimal treatment for women who have experienced prior fetal death (more than 10 weeks' gestation) or prior early delivery (less than 34 weeks' gestation) has not been defined by randomized trials. However, because fetal loss is a more severe and specific manifestation of APS, combination therapy with aspirin and heparin is generally recommended.²⁰ When used for obstetric purposes, aspirin is best started preconceptionally. Either unfractionated heparin or LMWH, in combination with aspirin, can be given and is started once pregnancy has been confirmed. LMWH shows better bioavailability, has a longer half-life, and can conveniently be given once daily.

Antiphospholipid syndrome with thrombosis

For pregnant women with APS who have had a prior thrombotic event, low-dose aspirin and therapeutic-dose heparin or LMWH anticoagulation are recommended.²⁰ Heparin does not cross the placenta and is not known to cause any adverse fetal effects. However, long-term use of heparin in pregnancy has been associated with osteoporosis in the mother. LMWH seems safer in this setting. Vitamin K antagonists are teratogenic and should be avoided between 6 and 9 weeks' gestation. Due to the risk of fetal bleeding thereafter, warfarin should be used after 9 weeks' gestation only in exceptional circumstances.

Postpartum period

Antithrombotic coverage of the postpartum period is recommended in all women with aPLs, with or without prior thrombosis.⁶⁷ Those in the former group need long-term anticoagulation, and the authors prefer switching these patients to warfarin after delivery as soon as they are in clinically stable condition. In patients with no previous thrombosis, the recommendation is for continuation of prophylactic-dose heparin or LMWH, with an extension that varies from 1 to 6 weeks after delivery depending on the presence of additional risk factors.⁶⁹ Both heparin and warfarin are compatible with breastfeeding.⁶⁷

MANAGEMENT OF OTHER MANIFESTATIONS OF ANTIPHOSPHOLIPID SYNDROME

Thrombocytopenia usually does not require intervention. In a minority of cases it can be severe, and corticosteroids are the treatment of choice. Anecdotal reports have shown that low-dose aspirin, dapsone, danazol, chloroquine, IVIG, and warfarin have improved steroid-resistant thrombocytopenia. Splenectomy has been safely and successfully performed in some patients with APS with refractory thrombocytopenia.⁷⁰

Headache has been reported to improve remarkably with low-dose aspirin, and in very resistant cases warfarin may be an alternative.

In some cases valvular damage may result in significant hemodynamic compromise, requiring surgery. Both biologic and mechanical valves have been implanted. Regardless of the valve type used, all patients with APS who have valve prostheses require full anticoagulation. Heart valve surgery is a very high-risk procedure in patients with APS.⁷¹ Bleeding and thrombotic complications are the main causes of morbidity and mortality. Therefore

■ **TABLE 139.3**
Alternative therapies for antiphospholipid syndrome (APS)

Treatment	Target effect (<i>in vitro</i> and/or animal studies)	Results of human studies
Hydroxychloroquine	aPL-induced platelet activation Inhibition of aPL-mediated thrombosis in mice Protection of aPL-induced displacement of annexin A5 from phospholipin bilayers	Decreases thrombotic risk in SLE Increases survival in SLE Protective against thrombosis in aPL+ individuals Decreases aPL and/or LAC in SLE patients
Statins	Reversal of aPL-induced endothelial cell activation and TF upregulation Abrogation of enhanced thrombus formation in mice	Decrease proinflammatory and prothrombotic markers in APS Contraindicated in pregnancy
Rituximab	Blocking of B-cell activating factor, which can prevent disease onset in APS mouse model	Effective for aPL-related cytopenias Effective for catastrophic APS Increases response in APS (off-label use) RITAPS study under way
New oral anticoagulants	Dabigatran: inhibition of thrombin Rivarox: inhibition of factor Xa	No data on efficacy and safety in APS patients
Potential immunomodulatory approaches	Anticomplement peptides Inhibition of TF Inhibition of nuclear factor κ B Inhibition of p38 MAPK Peptides mimicking domains of β_2 -GPI or β_2 -GPI receptor blockers Other B-cell inhibitors	Experimental studies No human data

aPL, antiphospholipid antibody; β_2 -GPI, β_2 -glycoprotein I; LAC, lupus anticoagulant; MAPK, mitogen-activated protein kinase; RITAPS, Rituximab in Antiphospholipid Syndrome; SLE, systemic lupus erythematosus; TF, tissue factor.

strict and coordinated perioperative control of the anticoagulant therapy must be accomplished.

It is important to distinguish the renal thrombotic microangiopathy characteristic of APS from other forms of inflammatory renal damage, mainly in SLE patients. The appropriate treatment with oral anticoagulation or corticosteroids depends on the histologic findings. The presence of aPLs seems to be associated with a poorer prognosis for the transplanted kidney in transplant patients with both SLE-related and primary APS. Post-transplant thromboembolic phenomena, the recurrence of thrombotic microangiopathy in the graft despite anticoagulation, and thrombosis of the graft have all been reported.⁷²

ALTERNATIVE THERAPIES FOR REFRACTORY AND DIFFICULT CASES

In patients with recurrent thrombosis, fluctuating INR levels, major bleeding, or a high risk of major bleeding, long-term therapy with LMWH, hydroxychloroquine, or statins has been suggested (Table 139.3).

Hydroxychloroquine

Hydroxychloroquine use has been associated with lower odds of persistent positivity for aPLs and/or LAC in SLE patients.⁷³

At this time, even though there are insufficient data to recommend hydroxychloroquine for primary and secondary prevention, because of its excellent safety profile it might be reasonable to add hydroxychloroquine to anticoagulant therapy in APS patients who develop recurrent thrombosis despite optimum anticoagulation.

Statins

The pleiotropic effects of statins on inflammation, immunomodulation, and vascular function may support their use in combination with warfarin or aspirin in patients with APS.⁷⁴⁻⁷⁶ Statins have profound effects on monocyte,

lymphocyte, and endothelial cell activity, all of which may contribute to thrombosis prevention in APS patients.⁷⁷

Rituximab

Rituximab (RTX) has been shown to be a good treatment for life-threatening CAPS in a small number of patients. Case reports have described the successful use of RTX in patients with aPLs and autoimmune-mediated thrombocytopenia and hemolytic anemia. The rationale for its use in APS is the proposal that B cells are involved in the clinical manifestations of APS.

A systematic review of the off-label use of biological therapies in systemic autoimmune diseases revealed a high therapeutic response with RTX in patients with APS (92%).⁷⁸ The Rituximab in Antiphospholipid Syndrome (RITAPS) study, an open-label, descriptive pilot study, is currently under way to assess the efficacy and safety of RTX in patients with persistent aPL positivity who show resistance to standard anticoagulant therapy.

New oral anticoagulants

Novel oral anticoagulants, including dabigatran etexilate and rivaroxaban, function by directly inhibiting thrombin and factor Xa, respectively. Both agents have been shown to be effective in the management of venous thromboembolism, and they do not require laboratory monitoring. However, at the present time there are no data on their efficacy and safety in patients with APS.

Future treatments

Understanding the molecular mechanisms triggered by aPLs may help researchers design new alternatives to treat the clinical manifestations of APS. It is likely that the current antithrombotic approach in these patients will be replaced by an immunomodulatory approach in the future.⁷⁹ One example is the successful use of eculizumab, a monoclonal antibody that targets C5a, in a patient with relapsing CAPS⁸⁰ and also its use to prevent the recurrence of CAPS in a patient who underwent renal transplantation.⁸¹

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Classification and epidemiology of scleroderma

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- The incidence (number of new cases each year) of systemic sclerosis (SSc) in the United States is 20 cases per million population.
- Prevalence (total number of cases) of SSc in the United States is estimated at more than 276 persons per million population.
- Clinical subtype (limited versus diffuse disease) and the specific autoantibody present are correlated with disease severity.
- Blacks are affected at a younger age and have more diffuse skin manifestations and more severe lung disease.
- The anticentromere antibody is a marker for limited cutaneous SSc and an increased risk of pulmonary arterial hypertension late in the disease course.
- Presence of the anti-RNA polymerase III antibody is a predictor of more severe skin disease and renal crisis.
- Antibody to topoisomerase I is a marker for interstitial lung disease.
- Multiple genetic variants increase SSc susceptibility and influence outcome.
- Survival appears to have improved in the past decades; the major cause of death is lung involvement.

INTRODUCTION

Scleroderma is usually divided into two forms: *localized scleroderma* (morphea, linear scleroderma, and related syndromes), which is confined to skin and subcutaneous tissues, and *systemic sclerosis* (systemic scleroderma), which affects both skin and internal organs (Box 140.1). In turn, systemic sclerosis (SSc) is divided into two major categories: limited cutaneous SSc, which is usually associated with mild to moderate, somewhat delayed organ fibrosis, and diffuse cutaneous SSc, which is characterized by correspondingly earlier and more severe organ damage.¹ This nomenclature has resulted in confusion among both physicians and patients, owing in no small part to the linguistic similarity between the words *localized* and *limited*. This chapter focuses mainly on systemic sclerosis, and the terms *scleroderma* and *systemic sclerosis* are used to refer to the systemic form of the disease unless otherwise specified.

CLASSIFICATION OF SCLERODERMA

The purpose of a disease classification schema is to facilitate accurate diagnosis, to provide reasonable homogeneity of subjects included in clinical research studies, and to predict prognosis reliably. Scleroderma offers a challenge in all these areas.

Box 140.1 provides an overview of the scleroderma classification. It should be emphasized that the 1980 preliminary classification for SSc developed by the American Rheumatism Association (ARA; now the American College of Rheumatology [ACR])² applies only to the systemic form of the disease.

Localized scleroderma

To the rheumatologist the term *scleroderma* refers to SSc, but to the dermatologist *scleroderma* refers to two separate conditions consisting of localized scleroderma and SSc. To further confound the situation, the term *localized*

scleroderma is remarkably similar to *limited scleroderma*, although these conditions are quite distinct. Because of this similarity in nomenclature, patients and physicians are frequently confused.

The use of the word *localized* in regard to scleroderma is meant to designate a fibrosing disease that affects the skin and underlying tissue (subcutaneous layer and occasionally underlying bone) but that does not affect internal organs (i.e., is not systemic).³ With the single exception of a very rare variant (pansclerotic morphea), localized scleroderma does not result in shortened survival.

As noted in Box 140.1, there are several subsets of localized scleroderma, and the schema outlined here is simplified. The most common form of localized scleroderma is plaque morphea and is characterized by patchy and well-circumscribed areas of thickened skin that can occur as a single lesion or as multiple lesions.³

Linear scleroderma (also known as *linear morphea*) refers to a distinct subset of localized disease that is characterized by a line of thickened skin usually involving an extremity. This is more common in children but can occur *de novo* in adults. If onset is in childhood, linear morphea can result in growth retardation of the affected limb and/or flexion contractures of underlying joints.

Scleroderma en coup de sabre (“cut of the saber”) refers not so much to a distinct form of localized disease but to the area of involvement—that is, the frontoparietal skin—and is characterized by a deep furrowing of the scalp and forehead, usually just to one side of midline. There appears to be an association with hemifacial atrophy (Parry-Romberg syndrome), although this may represent a separate entity.⁴

In addition to the features noted there are several other variants of morphea that are discussed in more detail in Chapter 147.

As noted earlier, for the most part, localized scleroderma is a skin and subcutaneous disease that does not affect internal organs and therefore does not shorten survival.³ However, linear disease in childhood can affect limb growth and can therefore have long-term functional sequelae. Scleroderma *en coup de sabre*, particularly when accompanied by hemifacial atrophy, can be a cosmetically devastating condition.

Finally, there is a rare variant of localized scleroderma called *pansclerotic morphea of childhood* (disabling pansclerotic morphea) that is characterized by rapidly progressive fibrosis of skin, subcutaneous tissue, muscles, and occasionally bone that can spread over the entire body, resulting in contractures, muscle atrophy, dermal ulcers, debility, and death.⁵ Although this has been considered a childhood disease, adult-onset cases have been reported.

Table 140.1 lists features that either distinguish localized from systemic disease or are common to both conditions. A positive antinuclear antibody test result and histologic findings of dermal fibrosis can exist in both conditions⁶ and therefore are not helpful in making a clear distinction. However, the presence or absence of Raynaud phenomenon and the pattern of skin involvement are the two most distinguishing characteristics. The presence of one of the three mutually exclusive systemic scleroderma autoantibodies (anticentromere, anti-topoisomerase I, and anti-RNA polymerase III) is very helpful in identifying systemic disease; however, only approximately 60% of patients with SSc have one of these autoantibodies, which makes these tests specific but not particularly sensitive.⁷

Classification schema for systemic sclerosis

The ARA established preliminary classification criteria for SSc in 1980 (Box 140.2).² These criteria were based on a multicenter prospective study of 264 patients with SSc and more than 400 comparison patients with other connective tissue diseases. The usefulness of the criteria is that they distinguish SSc from systemic lupus erythematosus and other autoimmune diseases. However, the criteria perform less well in capturing more mild forms of

BOX 140.1 CLASSIFICATION OF SCLERODERMA

- I. Localized scleroderma
 - A. Morphea
 - B. Linear scleroderma
 - C. Scleroderma en coup de sabre
- II. Systemic sclerosis
 - A. Limited cutaneous systemic sclerosis
 - B. Diffuse cutaneous systemic sclerosis

BOX 140.2 1980 PRELIMINARY CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS

- A. Major criterion
 - Scleroderma (symmetric thickening) proximal to the metacarpophalangeal joints
- B. Minor criteria
 - 1. Sclerodactyly (symmetric skin thickening limited to the fingers)
 - 2. Digital pitting scars or loss of finger pad substance
 - 3. Bibasilar pulmonary fibrosis

Adapted from Appendix I: Criteria for the classification of systemic sclerosis (scleroderma). In: Klippel JH, Stane JH, Crofford LJ, White PH, editors. *Primer on the rheumatic diseases*. New York: Springer; 2008, p. 675.

TABLE 140.1 Comparison of localized scleroderma and systemic sclerosis

Feature	Localized scleroderma/morphea	Systemic sclerosis
Skin findings	Patches or linear distribution of thickened skin	Sclerodactyly ± proximal skin thickening
Raynaud phenomenon	Absent	Present
Digital ischemic changes	Absent	Usually present (digital pitting scars or ulcers, loss of finger pad substance)
Internal organ disease	Absent	Present
Antinuclear antibody	Present in ≥50% of cases	Present in ≥85% of cases
Scleroderma-specific autoantibodies*	Absent	Present in 60% of cases
Biopsy-histologic findings	Dermal fibrosis	Dermal fibrosis

*Scleroderma-specific antibodies include antibodies to centromere, topoisomerase I (Scl-70), and RNA polymerase III.

disease, particularly limited cutaneous SSc, and were established before the widespread availability of tests for the scleroderma-specific autoantibodies. In 1988 LeRoy and coworkers¹ suggested classifying SSc into limited cutaneous and diffuse cutaneous subsets. Limited cutaneous SSc was defined as skin thickening distal to the elbows and knees only, whereas diffuse cutaneous SSc involved thickening on the proximal extremities and/or the trunk in addition to distal thickening. Although distinguishing between limited and diffuse cutaneous SSc appears to be a simple and straightforward system, the situation is complicated by the fact that in some patients, over time, the skin can soften so that an individual who initially had a diffuse pattern early in the disease can have a limited distribution of skin involvement at a later time, typically several years after onset.

To better capture early disease, LeRoy and Medsger⁸ proposed a classification system incorporating nail-fold capillaroscopic changes and autoantibody results (Box 140.3). This system divides SSc into three subsets including limited SSc (without skin thickening), limited cutaneous SSc, and diffuse cutaneous SSc. However, this system has not been universally accepted. Thus there are various case definitions of SSc, which makes cross-study comparisons difficult to interpret.

BOX 140.3 2001 LeROY AND MEDSGER PROPOSED CLASSIFICATION OF EARLY SYSTEMIC SCLEROSIS (SSc)

Limited SSc: Objective documentation of Raynaud phenomenon plus either SSc-type nail-fold capillary pattern
or
SSc-selective autoantibodies (anticentromere, anti-topoisomerase I, antifibrillarin, anti-PM-Scl, antifibrillin, or anti-RNA polymerase I or III)
Alternative definition of limited SSc: Subjective reporting of Raynaud phenomenon plus both
SSc-type nail-fold capillary pattern
and
SSc-selective autoantibodies (as listed above)
Limited cutaneous SSc:
Criteria for limited SSc above plus cutaneous changes distal to the elbows, knees, and clavicles
Diffuse cutaneous SSc:
Criteria for limited SSc above plus cutaneous changes proximal to the elbows, knees, or clavicles.

TABLE 140.2 Clinical features and autoantibodies in systemic sclerosis

Feature	Anticentromere	Antitopoisomerase	Anti-RNA polymerase III
Limited cutaneous	Common	Less common	Less common
Diffuse cutaneous	Very rare	Common	More common
Interstitial lung disease (severe)	Rare	Common	Less common
Scleroderma renal crisis	Rare	Less common	More common
Pulmonary arterial hypertension	Common in long-standing disease	Unclear	Unclear

To date there has not been a simple, clinically feasible, and reliable classification system that can accurately subtype individuals to predict better or worse clinical outcomes. A combined effort of the ACR and European League Against Rheumatism (EULAR) currently is underway to update and integrate the different classification schemes to achieve a more uniform, accurate, and widely accepted case definition.

Classification based on autoantibody profile

Almost all SSc patients (85% to 90%) test positive for an antinuclear antibody on indirect immunofluorescence assay. In addition, most (60% to 70%) test positive for one of the three common scleroderma-specific and mutually exclusive autoantibodies for which tests are commercially available. These include anticentromere, anti-topoisomerase I (also known as Scl-70), and anti-RNA polymerase III antibodies. Antibodies to PM-Scl, fibrillarin, and fibrillin characterize a smaller proportion of SSc patients, and tests for these antibodies are not widely available.⁷ It should be noted that anti-RNA polymerase III is not the same as the anti-RNP antibody (anti-U1-RNP) that is associated with overlap syndromes, particularly mixed connective tissue disease.

In addition to being mutually exclusive, these autoantibodies tend to be present at the time of, or even before, symptom onset and rarely, if ever, switch during the course of disease.

Table 140.2 shows the major clinical associations with the three most common SSc-related autoantibodies. Anticentromere antibodies are the most reliable as indicators of limited cutaneous involvement, prolonged survival compared with diffuse cutaneous disease or subsets with other autoantibodies, and lower risk of significant pulmonary interstitial disease. However, these patients are at increased risk of developing pulmonary arterial hypertension as a later complication of SSc,⁹ so this should not be considered as a “benign” variant.

Autoantibodies to topoisomerase I (Scl-70) are more frequently seen in diffuse cutaneous disease but can be found in the limited subset as well and are relatively good predictors of severe interstitial lung disease.¹⁰

Antibodies to RNA polymerase III are associated more with diffuse rather than limited cutaneous disease and also confer a higher risk of renal crisis.⁷ However, renal crisis has been reported in patients with all antibody subgroups, even in those without antinuclear antibodies. It is prudent, therefore, to be vigilant in following scleroderma patients for this potentially life-threatening complication regardless of autoantibody status.

In summary, there is not yet a classification schema that will reliably predict the development and severity of internal organ disease at an early stage to permit more accurate prognosis, improve the design of clinical trials, allow more focused patient and family education, and dictate appropriate monitoring and treatment.

EPIDEMIOLOGY

Incidence and prevalence

The reported incidence and prevalence of SSc vary widely in studies conducted in different geographic areas and at various times. This variability may be due to differences in case definition and ascertainment methods but could also reflect true temporal and geographic differences. The reported prevalence of SSc in North America varies from 4 cases per million population for the period 1947 to 1952¹¹ to 443 cases per million in 2003.¹² Similarly, the annual incidence rates vary from 2.7 cases per million for the period 1947 to 1968¹¹ to 21 cases per million for the period 1989 to 1991.¹³ Table 140.3 summarizes the results of North American studies that reported incidence and prevalence of SSc over a 62-year period (1947 to 2009). Medsger and Masi¹¹ based their incidence rate calculation on 86 hospitalized patients from 1947 to 1968; the prevalence estimate was derived by multiplying the incidence rate by survival in years. Steen and coworkers¹⁴ determined incidence and prevalence based on 444 hospital-diagnosed cases in Allegheny County, Pennsylvania, over a 20-year period. Maricq and coworkers¹⁵ conducted a cross-sectional population survey in South Carolina, initially screening for the presence of Raynaud phenomenon and then performing a physical examination of responders who had that disorder. The prevalence was calculated based on only two cases that fulfilled the 1980 ARA SSc classification criteria.² Mayes and coworkers¹³ conducted a large-scale study in southeast Michigan from 1989 to 1991 using multiple sources of case ascertainment that included both inpatient and outpatient records and verification of diagnosis by chart review. Patients who fulfilled the 1980 ARA classification criteria² or had sclerodactyly plus two other features of CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) were included. A capture-recapture analysis was used to estimate the total SSc population. The resulting prevalence estimate was 276 cases per million adults (95% confidence interval [CI], 245 to 310). The same study reported an annual incidence rate of 21 new cases per million. Bernatsky and coworkers¹² estimated the prevalence of SSc in Quebec using physician billing and hospitalization databases. SSc cases were ascertained over a 10-year period, and the imperfect sensitivities of the ascertainment methods were accounted for by using a bayesian approach. The reported prevalence of SSc was 443 cases per million (95% CI, 411 to 476) in 2003. As shown in Table 140.3, there is a trend toward higher prevalence estimates in more recent studies, an observation that is related to multiple factors. The 1980 classification criteria

TABLE 140.3
Results of North American studies reporting prevalence and incidence of systemic sclerosis

Study	Period of observation	Prevalence (total cases per million)	Incidence (new cases per million per year)
Medsger and Masi (1971) ¹¹	1947-1952	4	0.6
	1953-1958	7	1.5
	1958-1962	21	4.1
	1963-1968	28	4.5
Steen et al (1997) ¹⁴	1963-1972	—	9.6
	1973-1982	—	18.7
Maricq et al (1989) ¹⁵	1985	286	—
Mayes et al (2003) ¹³	1989-1991	276	21
Bernatsky et al (2009) ¹²	1989-2003	443	—

enabled a uniform case definition across studies and the inclusion of milder cases that may have been missed in previous hospital-based studies. Additionally, the availability of computerized databases and increased awareness of SSc may have led to more complete case ascertainment in more recent reports. Furthermore, an improvement in survival of SSc patients as suggested by several studies^{13,16} would also lead to a higher prevalence as those surviving longer accumulate in the population. Nonetheless, the possibility remains that SSc may, in fact, be increasing in occurrence. However, both the Pennsylvania study¹⁴ and the Michigan study¹³ reported similar incidence rates for the periods 1973 to 1982 and 1989 to 1991 (19 and 21 per million, respectively).

Prevalence estimates and incidence rates vary greatly by geographic area. Table 140.4 summarizes several studies^{12,17-28} reporting the prevalence of SSc in North and South America, Asia, Europe, the United Kingdom, Scandinavia, and Australia. SSc prevalence varies from the highest estimate of 660 per million among the Choctaw Native Americans residing in Oklahoma to the lowest estimate of 38 per million in Japan. Direct comparisons of these figures is difficult due to the fact that some studies used the 1980 ARA classification criteria, others used the less restrictive LeRoy and Medsger criteria⁸ (see Box 140.3), and still others used the physician-reported diagnosis only. Therefore the wide variability of these prevalence estimates across the different geographic areas may reflect methodologic differences in case definition and ascertainment. However, it might also demonstrate true differences in prevalence of susceptibility genes or differential exposure to putative environmental triggers.

As indicated in Table 140.4, the highest prevalence was reported in a Choctaw Native American group in Oklahoma.¹⁷ In addition, the affected Choctaw cases showed a striking homogeneity in disease expression, with 92% of patients showing diffuse skin disease and 83% having antitopoisomerase antibodies. The strongest risk factor for SSc was a uniquely Native American HLA haplotype that was present in 100% of cases compared with only 54% of controls. A subsequent study showed that individuals with SSc were distantly related, which indicates that important susceptibility genes may have been inherited from common founders about 10 generations prior.²⁹

It is of interest that a study in Alberta, Canada, by Barnabe and coworkers¹⁹ also reported a higher prevalence of SSc among the First Nations group compared with the non-First Nations population in the same province, but this comparison did not reach statistical significance. It would be interesting to see if future studies of Native Americans also show an increased susceptibility.

Age at onset

The age at disease onset differs according to gender and ethnic background. The age at diagnosis is lower in female and in black patients.

TABLE 140.4
Results of selected international studies of systemic sclerosis in descending order of prevalence estimates

Study	Region or group	Prevalence (total cases per million)
Arnett et al (1996) ¹⁷	Choctaw Native American (Oklahoma, USA)	660
Kuo et al (2011) ¹⁸	Taiwan	563
Barnabe et al (2012) ¹⁹	First Nations people (Alberta, Canada)	470
Barnabe et al (2012) ¹⁹	Non-First Nations people (Alberta, Canada)	330
Bernatsky et al (2009) ¹²	Quebec, Canada	443
Sardu et al (2012) ²⁰	Sardinia, Italy	350
Lo Monaco et al (2011) ²¹	Northern Italy	341
Rosa et al (2011) ²²	Buenos Aires, Argentina	296
Englert et al (1999) ²³	Australia	233
Le Guern et al (2004) ²⁴	France	158
Alamanos et al (2005) ²⁵	Greece	154
Allcock et al (2004) ²⁶	Northeast England	82
Geirsson et al (1994) ²⁷	Iceland	71
Tamaki et al (1991) ²⁸	Japan	38

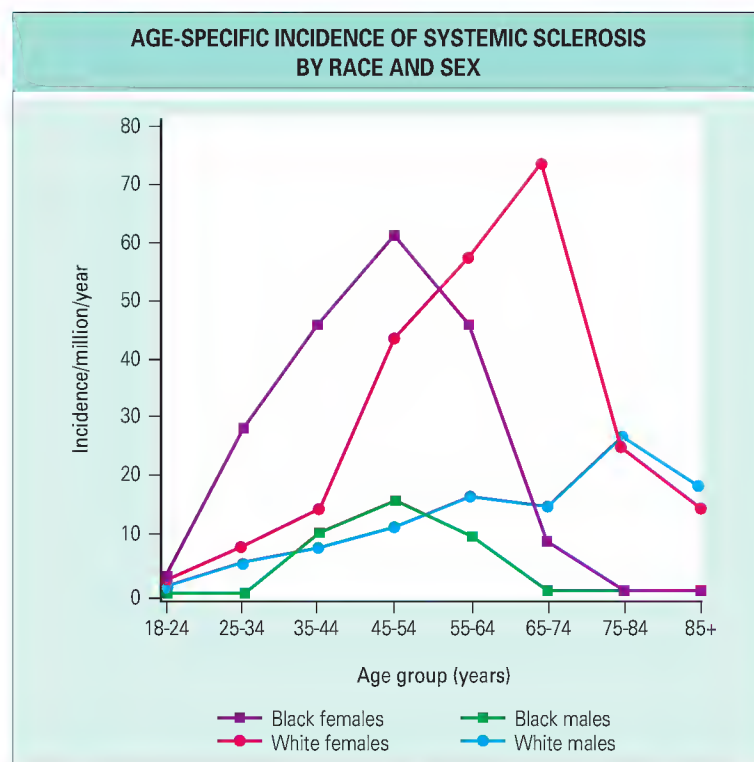


Fig. 140.1 Age-specific incidence of systemic sclerosis by race and sex. (Adapted with permission from Mayes MD, Lacey JV Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large U.S. population. *Arthritis Rheum* 2003;48:2246-55.)

Steen and coworkers¹⁴ reported that the age-specific incidence rate peaked between ages 45 and 54 in African American women and occurred in a slightly older group (age 55 to 65) in European American women. Diagnosis before age 15 was rare. In the 15- to 24-year age group, the incidence was very low, except among African American women, who showed an incidence of 21.2 per million; this was a significantly higher incidence than in European American women of the same age group (incidence ratio, 11.16; $P < .0001$). The incidence rate for African American men also peaked between the ages of 45 and 54, whereas the European American men showed an increase in annual incidence up to the age of 65.

Mayes and coworkers¹³ found very similar results, reporting that African American patients were significantly younger at the time of diagnosis compared with European American patients ($P < .001$). The peak incidence occurred between the ages of 45 and 54 for African American women, whereas the peak incidence among white women occurred in the 65- to 74-year age group. The peak incidence age for African American men was similar to that for African American women. Among European American men, incidence increased gradually until the age of 75 to 84 years. Fig. 140.1 shows the age-specific incidence of SSc by ethnicity and sex in this study. The observed differences in average age at diagnosis might be due to the increased occurrence of diffuse disease in the African American population. Alamanos and coworkers²⁵ also reported differences in age of peak incidence according to gender in a mainly white Greek population. The mean incidence rate was highest in the 45- to 64-year age group for women, whereas the incidence rate peaked in the age group 65 years and older for men.

Racial and ethnic factors

Multiple studies have indicated that individuals of African ancestry have a higher susceptibility to SSc and develop more severe disease. Laing and coworkers³⁰ examined racial differences among 514 female SSc patients, 23% of whom ($n = 117$) were African American. The annual incidence of SSc among African American women was 22.5 per million versus 12.8 per million among European American women ($P < .001$). In addition to having a higher incidence of SSc, African American women were more likely than European American women to develop diffuse disease (49.6% vs. 24.9%; $P < .001$). Pericarditis, pulmonary hypertension, pleural effusion, myositis, and an erythrocyte sedimentation rate of more than 40 mm/hr also were more frequent among African American women, whereas white women were more likely to have digital infarctions. Mayes and coworkers¹³ also reported

a higher prevalence of SSc in African Americans than in European Americans (prevalence ratio, 1.15; 95% CI, 1.02 to 1.30). This finding has been confirmed by Le Guern and coworkers,²⁴ who investigated the prevalence of SSc in a suburb of Paris, France. Among study participants, 26% were of non-European background with mainly northern and sub-Saharan African (16%), Asian, and Caribbean ancestry. The respective prevalence rates of SSc for Europeans and non-Europeans were 140.4 (95% CI, 112 to 170) and 210.8 (95% CI, 128 to 293), respectively, which results in a higher prevalence ratio of 1.5 among non-Europeans. As found in previous studies, non-Europeans were significantly more likely to have diffuse SSc (34% vs. 17%; $P = .04$) and interstitial lung disease (53% vs. 33%; $P = .06$).

Just as there are differences in disease type, there are dissimilarities in autoantibody profile among various ethnic groups. Mayes and coworkers¹³ reported that the anticentromere antibody was present in 27% of European American patients (97 of 359), whereas it was observed in only 9.7% of African American patients (13 of 134; $P < .001$). Reveille and coworkers³¹ reported similar results: anticentromere positivity was more common among European Americans (32% vs. 4%), whereas African American patients were more likely to test positive for anti-RNP antibody (5% vs. 29%) and anti-fibrillarin (4% vs. 17%). Steen and coworkers³² also reported that African American patients were more likely to have anti-topoisomerase I, anti-U1-RNP, and anti-U3-RNP (antifibrillarin) autoantibodies than were white patients and that pulmonary fibrosis was more frequent and more severe in this group with a corresponding decrease in survival. In a study of white Australians and nonwhite Thais with SSc, McNeilage and coworkers³³ reported a higher frequency of antitopoisomerase (76%) and a lower frequency of anticentromere antibody (2%) in the Thais compared with the Australians, of whom 26% had antitopoisomerase antibodies and 51% had anticentromere antibodies.

Gender differences

SSc occurs more frequently in women than in men, with most estimates of female-male ratios ranging from 4:1 to 6:1.³⁴ Reasons for this female preponderance are not clear. Hormonal and pregnancy-related events are obvious possibilities, but few published reports have investigated the association between previous hormone use or previous pregnancy and the subsequent development of SSc. Cockrill and coworkers³⁵ reported that parity conferred an increased risk of SSc among 172 women with SSc compared with their healthy sisters ($n = 256$) in the United States. However, Pisa and coworkers³⁶ reported a reduced risk of SSc among parous women compared with nulliparous women in Italy (odds ratio, 0.3; 95% CI, 0.3 to 0.7) in a study of 46 SSc cases versus 153 controls.

Microchimerism has been proposed as a risk factor for SSc. Iatrogenic microchimerism is a well-known consequence of allogeneic hematopoietic stem cell transplantation. However, natural microchimerism, caused by cell transfer between mother and fetus during pregnancy and resulting in the persistence of small populations of genetically distinct individuals, is a relatively newly recognized concept.³⁷ The persistence of these cells over decades has been proposed as a contributing factor in autoimmune disease pathogenesis.³⁸ However, the presence of these microchimeric cells in normal individuals as well as in SSc patients raises questions about the pathogenic role of this phenomenon.

An alternative explanation for female predominance involves X chromosome abnormalities, specifically the preferential skewing of X chromosome inactivation toward one parental source in the peripheral blood of SSc patients.³⁹ However, the pathogenetic mechanism in terms of increased susceptibility to autoimmunity in general and to SSc in particular has not been established.

Finally, Dieudé and coworkers⁴⁰ reported that a variant of the *IRAK1* (interleukin-1 receptor-associated kinase 1) gene on the X chromosome was found more frequently in SSc women than in controls. This suggests that either this gene variant or one nearby on the X chromosome may contribute to the female preponderance in SSc.

Familial systemic sclerosis and genetic influences

Familial aggregation is more common than expected for this relatively rare disease. Arnett and coworkers⁴¹ reported 11 cases of familial SSc involving first-degree relatives in a U.S. cohort of 703 cases, resulting in a prevalence of 1.6% for familial occurrence. This finding was similar to results of an earlier study by Englert and coworkers⁴² in which 10 familial cases involving first-degree relatives were reported among 710 SSc patients in Australia (prevalence, 1.6%). Assassi and coworkers⁴³ investigated the disease characteristics of 18 multiple-case families identified in a registry of 710 SSc families (prevalence, 2.5%). The observed SSc-related antibody concordance

within each multiple-case family was statistically greater than expected by chance alone ($P = .007$). Similarly, HLA haplotype sharing among the affected sibling pairs was more common than expected ($P = .011$). A family history of SSc, although infrequent, remains the strongest risk factor for SSc yet identified. The familial occurrence of a disease can be the result of shared genetic predisposition and/or exposure to common environmental factors in early life.

In addition to the occurrence of SSc in more than one family member, there is evidence that multiple autoimmune diseases cluster within families of patients with SSc. A study of 121 French families,⁴⁴ a study of 1071 U.S. cases,⁴⁵ and a U.S. population-based study⁴⁶ all came to the conclusion that autoimmune diseases occur more frequently in relatives of SSc cases than would be expected in the general population, although the specific diseases and methods of case ascertainment varied widely among these reports. However, the weight of evidence supports the notion that common genetic factors, shared among many autoimmune diseases, contribute to disease susceptibility.

Genetics of systemic sclerosis

Two large genomewide association studies^{47,48} have confirmed the findings of a previous large study⁴⁹ regarding the association of HLA with SSc susceptibility. In addition, over 30 non-major histocompatibility complex gene variants have been associated with increased susceptibility to SSc.⁵⁰ Most of these SSc susceptibility genes are similar to those identified for systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune disorders and involve pathways in both the innate and the adaptive immune systems. However, with few exceptions, the precise identification of the causal variants and their role in contributing to autoimmunity have not been determined. The particular genetic associations are most striking when the disease is subdivided by autoantibody groups, which suggests that the genetic contribution to SSc pathogenesis differs in these subsets. Geographic differences in the distribution of HLA alleles, as well as non-HLA genetic variants, may contribute to the geographic variation in rates of disease occurrence noted earlier in the chapter.

Environmental considerations

Multiple environmental exposures, particularly exposure to organic solvents and silica dust, have been reported to be associated with the subsequent development of SSc. A meta-analysis of 11 studies (encompassing 1291 cases and 3435 controls) found that the reported risk of SSc was highly variable from study to study and that there appeared to be publication bias, which suggests that studies with positive results were more likely to be published than those with negative findings.⁵¹ Men were at higher risk than women, but the majority of patients did not report exposure to these substances. Thus the role of environmental triggers remains unclear. (For more detailed discussion, see Chapter 147.)

Survival

Improved survival rates for SSc have been reported in recent studies^{13,52} compared with previously published survival data.^{53,54} A survival study¹⁶ of 915 Italian SSc patients showed that patients recruited from 1986 to 1999 had a significantly higher 10-year survival rate than those enrolled from 1955 to 1985 (76.8% vs. 60.6%, respectively; $P < .001$). However, the 10-year survival rates in recent studies also vary, ranging from 55.1%¹³ to 76.8%.¹⁶ The observed improvement in survival might be secondary to earlier diagnosis in recent years (lead-time bias); however, recent improvements in treatment of life-threatening complications of SSc are also likely contributing factors. Steen and Medsger⁵⁵ detailed the changes in organ-specific causes of mortality over 25 years at a single university center. This study showed that diseases of the lung, including both pulmonary fibrosis and pulmonary hypertension, have become the primary cause of SSc-related deaths, replacing SSc renal crisis, which was formerly the leading cause of mortality before the widespread use of angiotensin-converting enzyme inhibitors.

LONG-TERM SURVIVAL OF PATIENTS WITH SYSTEMIC SCLEROSIS



Fig. 140.2 Proportion of surviving patients with systemic sclerosis according to the presence or absence of cardiac, renal, or pulmonary involvement. (Adapted from Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005;118:2-10.)

An international meta-analysis⁵⁶ of individual patient data regarding mortality in SSc has been reported encompassing 1645 incident cases (enrollment within 6 months of physician diagnosis). Data came from seven medical centers in the United States, Europe, and Japan, and standardized definitions for organ involvement were used. All cohorts showed significantly increased standardized mortality ratios in comparisons based on age- and sex-matched country-specific life tables. However, the mortality ratios varied widely, ranging from 1.5 to 7.2, depending on country and the referral base of the involved center. After adjustment for age, sex, and year of enrollment, the presence of anti-topoisomerase I antibodies, as well as the presence of renal, cardiac, and pulmonary involvement, independently increased the risk of death. Renal, cardiac, and pulmonary involvement tended to occur together ($P < .001$). Fig. 140.2 shows the long-term survival of these patients according to the presence or absence of cardiac, renal, or pulmonary involvement. This study confirms the finding of previous studies that the main predictor of mortality is the presence and severity of renal, cardiac, and pulmonary involvement. Laboratory findings such as elevated erythrocyte sedimentation rate, anemia, and proteinuria^{52,57} have also been linked to poor survival.

Not all studies, however, have reported an improvement in survival. For example, Elhai and coworkers⁵⁸ performed a meta-analysis of nine studies which suggested that the standardized mortality ratio for SSc has not changed significantly in the last 40 years.

Two studies^{59,60} investigated SSc mortality rates in the United States using data from the National Center for Health Statistics. In these two studies, the rates of death related to SSc were higher in the African American population than in the European American population. This finding might be related to the higher prevalence and more aggressive disease seen in the African American population and to the disparity in socioeconomic parameters. In another study of SSc patients, a higher inpatient mortality also was seen in African Americans and other nonwhites than in European Americans in South Carolina⁶⁰; this difference remained even after adjustment for other sociodemographic and clinical factors.

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Assessing disease activity and outcome in systemic sclerosis (scleroderma)

■ DINESH KHANNA

- The modified Rodnan skin thickness score assesses 17 body areas and assigns a value of 0 to 3 based on palpation of the skin. Higher scores indicate worse disease and generally correlate with worse internal organ involvement and greater mortality.
- The European Scleroderma Study Group scale is an instrument that includes a 10-point index to measure disease activity (physical or laboratory findings that vary over time and are potentially modifiable by treatment).
- Disease severity, or the effect of disease on organ function, which is either reversible or irreversible, is best assessed with the Systemic Sclerosis Severity Scale.
- The Scleroderma Health Assessment Questionnaire Disability Index is a modified version of the Health Assessment Questionnaire that has been validated in patients with scleroderma and is used to assess functional ability.
- Multiple outcome measures (e.g., modified Rodnan skin score [skin], percent predicted forced vital capacity [lung]) have been found to be feasible, reliable, and valid for clinical trials in scleroderma.
- Effort is undergoing to develop a composite index for clinical trials in patients with scleroderma.

INTRODUCTION

Substantial progress has been made in the development and validation of outcome measures for systemic sclerosis (scleroderma [SSc]).^{1,2} The discussion here is focused on disease activity and disease severity measures in SSc, and an update is provided on outcome measures currently used in clinical trials and clinical care. This chapter does not address outcome measures developed and validated for localized scleroderma or juvenile scleroderma.

MEASUREMENT PROPERTIES OF AN INSTRUMENT: FEASIBILITY, RELIABILITY, AND VALIDITY

An outcome measure should be feasible, reliable, and valid. A feasible measure is accessible, easily interpretable, and associated with low cost. Reliability (precision) is the extent to which a measure yields the same score each time that it is administered if the underlying health condition has not changed. A reliability coefficient of .90 (meaning that 90% of the score is accurate whereas the remaining 10% denotes error) is considered satisfactory for individual comparisons, and .70 or higher is deemed satisfactory for group comparisons.³ Validity is the extent to which the score that a health measure yields accurately reflects the health concept and includes face (sensible), content (comprehensive), construct (measures or correlates with a theorized health construct), and criterion validity (predicts or correlates with the “gold standard”). Sensitivity to change, an aspect of construct validity, assesses whether an instrument score changes in the right direction when the underlying health construct changes; the ability of an instrument to detect clinically important change is crucial to its usefulness as an outcome measure in a clinical trial.

MEASURING DISEASE ACTIVITY AND SEVERITY IN SCLERODERMA

Investigators agree that assessment of disease activity and severity is an important goal in SSc. Based on previous consensus reached in other rheumatic diseases,⁴ activity is defined as the aspect of disease that varies over time and has the potential to be reversible spontaneously or with therapy (e.g., tendon friction rubs, acute-phase reactants, inflammatory polyarthritis). Damage is the cumulative burden of a disease at a given time and is generally irreversible (e.g., calcinosis, end-stage pulmonary fibrosis). Both activity and damage contribute to disease severity; early in SSc, activity predominates, whereas later in the disease, damage is more likely to be the dominant element.⁵

Disease activity in scleroderma

The European Scleroderma Study Group has proposed a composite index to assess SSc-related disease activity in routine clinical care.^{6,7} The index is feasible because it includes measures (clinical examination, patient assessment of activity over the last month, laboratory measures, and percent predicted diffusing capacity of the lung for carbon dioxide [%DLCO]) collected in routine practice. It has face and content validity, and it is scored on a 0 (no activity) to 10 (severe activity) basis, with the greatest weight assigned to deterioration of the relevant organ system as evaluated by the patient with respect to the previous month. The tests required to calculate the index are inexpensive and easily carried out in routine clinical care. The index does have a few limitations: (1) it was developed in patients with established disease and has not yet been studied in those with early SSc, in whom the disease is likely to be active; (2) three patient-reported items relate to changes in skin, vascular, and cardiopulmonary symptoms in the past month, and such changes in activity indices may be challenging because they fail to capture *persistent* activity and might be difficult to determine every month⁸; and (3) the index has not been developed for clinical trials, and its sensitivity of change has not been published.

Assessment of disease severity

A measure of disease severity encompasses both disease activity and damage and should be associated with or predict SSc-associated morbidity and mortality.⁵ The revised Medsger severity index⁸ was developed by international scleroderma experts using consensus methodology, followed by prospective data collection. The authors identified nine organ systems and variables for each organ system that can be used to define severity. The nine organ systems are general, peripheral vascular, skin, joint/tendon, muscles, gastrointestinal tract (GIT), lung, heart, and kidney. Each system is scored from 0 (uninvolved) to 4 (end-stage disease). The individual organ system severity scores have been shown to predict survival in a large observational cohort.⁹ The severity index is not weighted and should therefore not be summed to obtain a “global” severity scale score.

OUTCOME MEASURES IN SCLERODERMA

Although many novel outcome measures are currently in development, this section discusses outcome measures (Table 141.1) that have been shown to be feasible, reliable, and valid in clinical trials and clinical care.

TABLE 141.1
Feasible, reliable, and valid measures used in clinical trials and clinical practice

Instruments	Ready for RCT	Used in clinical practice
Health-related quality of life		
SF-36 version 2*	Yes	No
Health Assessment Questionnaire–Disability Index*	Yes	Yes
SF-6D*	Yes	No
Patient Reported Outcomes Measurement Information System (PROMIS)*	Yes	Yes
UK Functional Scale*	Yes	Yes
Skin		
Modified Rodnan skin score	Yes [†]	Yes
Durometer	Yes [†]	No
Musculoskeletal		
Tendon friction rubs assessed by the investigator	Yes [†]	Yes
Tender joint count	Yes [†]	Yes
Serum creatine phosphokinase value	Yes	Yes
Cochin Hand Function Scale*	Yes	Yes
Hand Mobility in Scleroderma scale	Yes	No
Mouth Handicap in Systemic Sclerosis scale*	Yes	Yes
Cardiac		
Echocardiogram with Doppler imaging	Yes [†]	Yes [§]
Right-sided heart catheterization	Yes	Yes [§]
6-Minute walk test	Yes	Yes
Borg dyspnea index (administered immediately after the 6-minute walk test)	Yes	Yes
Pulmonary		
Pulmonary function test with diffusion capacity	Yes	Yes
High-resolution computed tomography	Yes [†]	Yes [§]
Validated measure of dyspnea*	Yes	No
Breathing VAS from the SSc HAQ*	Yes	Yes
Gastrointestinal		
Gastrointestinal VAS from the SSc HAQ*	Yes	Yes
UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0*	Yes	Yes
Body mass index	Yes	Yes
Renal		
Estimated creatinine clearance	Yes	Yes
Systolic and diastolic blood pressure	Yes	Yes
Serum creatinine	Yes	Yes
Raynaud phenomenon		
Raynaud's Condition Score*	Yes	No
Number of attacks as reported by the patient*	Yes	Yes
Duration of attacks*	Yes	Yes
Raynaud VAS from the SSc HAQ*	Yes	Yes
Patient assessment of the overall Raynaud phenomenon on a VAS*	Yes	Yes
Patient assessment of pain, numbness, and tingling on a VAS*	Yes	Yes
Physician assessment of the overall Raynaud phenomenon on a VAS	Yes [†]	Yes
Digital ulcer		
Active digital tip ulcer count on the volar surface	Yes [†]	Yes
Digital ulcer VAS from the SSc HAQ*	Yes	Yes
Biomarkers		
Acute-phase reactants	Yes	Yes
Serum BNP/NT-Pro BNP	Yes	Yes

*Completed by the patient.

[†]Assessed by the same investigator.

[‡]Standardized central reading mechanism strongly encouraged in multicenter RCTs.

[§]Feasibility may be limited because of cost or lack of availability in clinical care.

^{||}Quality control strongly encouraged in multicenter RCTs.

^{||}For patients with pulmonary arterial hypertension.

HAQ, Health Assessment Questionnaire; NT-Pro BNP, N-terminal brain natriuretic peptide; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short-Form 36-Item Health Survey; SSc, systemic sclerosis; VAS, visual analogue scale.

Modified from Khanna D, Lovell D, Giannini E, et al. Development of a provisional core set of response measures for clinical trials of systemic sclerosis. *Ann Rheum Dis* 2008;67:703-9.

Measuring skin disease in scleroderma

SSc is subclassified into “diffuse cutaneous” or “limited cutaneous” SSc based on the extent of skin involvement.¹⁰

The *modified Rodnan skin score* (MRSS), a measure of skin thickness,^{11,12} has been used as the primary outcome measure in clinical trials of diffuse cutaneous SSc (dcSSc) (see Fig. 142.9). Measurement of skin thickness is used as surrogate measure of disease severity and mortality in patients with dcSSc—an increase in skin thickening is associated with involvement of internal organs and increased mortality.¹² It is generally accepted that the MRSS tends to worsen in early disease and improve in late disease, although the time of peak involvement remains poorly defined. “Early” dcSSc is often defined as the period of rapidly and severely increasing induration (“thickening”) of the skin, which has been thought to peak 1 to 3 years after onset of the disease.¹³ The MRSS was found to be feasible, reliable, valid, and sensitive to change in multicenter clinical trials.¹¹ For example, the MRSS was able to differentiate between treatment with methotrexate and placebo in early diffuse SSc¹⁴ and between cyclophosphamide and placebo in the diffuse SSc subset in the Scleroderma Lung Study.¹⁵ The MRSS also improved in the Autologous Stem Cell Transplant Study. However, recent analysis from three large randomized controlled trials (RCTs) of dcSSc showed that the mean MRSS improved regardless of disease duration at baseline—a general tendency for skin to soften over time was noted, and no difference in this tendency was found in patients with different disease durations at baseline.¹⁶ In another analysis of 629 patients who participated in dcSSc trials, the average MRSS improved in the trials; in patients with disease of less than 18 months’ duration, the MRSS improved in 63% and worsened in 37%. In patients with a disease duration of 18 months or longer, the MRSS improved in 81% and worsened in 19%.¹⁷ This observation differs from the natural history of skin thickening previously reported and has important implications in “prevention of worsening” study designs when using skin softening as an endpoint.¹⁸ Approval agencies continue to consider the MRSS an acceptable primary outcome. If incorporated, the RCT should last at least 52 weeks and the study should also incorporate measures to show improvement in patient-reported outcomes and stabilization of lung and other internal organ involvement (discussed later).

Durometers are hand-held devices used to measure the hardness of material in internationally standardized durometer units. The durometer was included in a multicenter study of early dcSSc and was found to be feasible, reliable, valid, and sensitive to change.¹⁹ High correlation was found between the MRSS and durometer units at baseline (coefficient ≥ 0.69) and during follow-up in the changed (coefficient ≥ 0.70) scores.¹⁹ Use of the durometer may be limited because of its cost.

Other methods have been proposed for measurement of skin disease in SSc, including skin ultrasonography, elastometry, magnetic resonance imaging, and other radiographic techniques,²⁰ but they lack data on sensitivity to change and have not been applied in a multicenter setting.

Measuring musculoskeletal involvement in scleroderma

Musculoskeletal involvement occurs in 40% to 80% of patients and is most problematic in early dcSSc.²¹ Tendon friction rubs (TFRs) are grating, “squeaking” sensations detected on passive or active motion of the affected tendon in patients with SSc. On physical examination, TFRs are most commonly present in the flexor and extensor tendons of the fingers and wrists and the anterior tibial and peroneal tendons. TFRs are associated with a higher likelihood of the development of dcSSc and more severe disease—a higher MRSS, joint contractures, greater physical disability, higher prevalence of cardiac or renal involvement, and decreased survival.^{22,23} TFRs should be measured by the same assessor in an RCT and be incorporated as a secondary outcome measure. In clinical care, the presence of a TFR requires careful monitoring for the development of dcSSc and a more severe disease course.

Hand disability in SSc can be evaluated by using the Cochin Hand Function Scale (CHFS), an 18-item instrument that relates to hand functionality or disability during various tasks in different settings (e.g., in the kitchen, dressing oneself, hygienic tasks, in the office).²⁴ It has three scales—dexterity, rotational movement, and flexibility of the first three fingers. The instrument is feasible and has shown acceptable reliability in patients with SSc.²⁵ The CHFS was found to be sensitive to change in an intervention study that incorporated hand massage of connective tissue and home exercises.²⁶ It is an acceptable secondary outcome measure to assess improvement in hand function.

The Hand Mobility in Scleroderma (HAMIS) is a nine-item performance-based test designed to examine the effects of SSc on hand mobility and

function and is preferably administered by an occupational therapist or research physician.^{27,28} The HAMIS test consists of nine items that assess finger flexion and extension, abduction of the thumb, pincer grip, finger abduction/swelling, dorsal extension and volar flexion of the wrist, and pronation and supination. The HAMIS instrument has shown acceptable reliability and validity. It was found to be sensitive to change in an intervention study that incorporated hand massage of connective tissue and home exercises,²⁶ and it complements the CHFS in studies focused on the hands.

The Mouth Handicap in Systemic Sclerosis scale was developed to assess attributes of mouth involvement in SSc.²⁹ It is a 12-item scale with acceptable reliability and validity. It has three scales that represent handicap associated with a reduction in mouth opening, handicap associated with sicca syndrome, and aesthetic concerns. Its sensitivity to change was shown in an intervention program that included massage of the connective tissue of the face.³⁰

There is great interest in assessing radiographs and ultrasound images in patients with SSc, and erosive disease is seen in 5% to 40% of patients on plain radiographs.³¹ This proportion is higher with new imaging modalities.

Measuring lung disease in scleroderma

Pulmonary disease is now the leading cause of death in patients with SSc.³² Pulmonary disease in SSc falls into two major categories: interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Several recent clinical trials have specifically focused on lung disease in SSc.^{15,33,34}

Pulmonary function tests (PFTs) in patients with SSc-ILD demonstrate a restrictive lung defect with decreased percent predicted forced vital capacity (%FVC) and percent predicted diffusing capacity for carbon monoxide (%DLCO). PFTs are feasible in large RCTs of SSc-ILD.^{15,33,34} %FVC has been used as the main parameter of restrictive lung disease and %DLCO for pulmonary vascular disease. %FVC was able to differentiate between the active group (cyclophosphamide [CYC]) and the placebo group in the Scleroderma Lung Study-1 (SLS). Low %FVC predicts morbidity and mortality associated with SSc-ILD³³ and is sensitive to change in multicenter RCTs.^{15,33} Serial measurements of lung function with PFTs are also prognostic, and a 15% decline in %DLCO at 3-year follow-up corresponds to a significantly increased risk for mortality in patients with idiopathic pulmonary fibrosis,^{35,36} although this has not been assessed for SSc-ILD. %DLCO is sensitive but not specific for SSc-ILD or SSc-PAH and can decline in both diseases. It did not differentiate between the active and placebo groups in two SSc-ILD studies.^{37,38} A disproportionate decline in %DLCO may indicate PAH.

Quality control programs are key for RCTs in SSc-ILD and were recently discussed in detail.^{38,39} Such programs were implemented in the SLS-1 with satisfactory results with respect to achievement of acceptable test quality and are feasible in RCTs.

High-resolution computed tomography (HRCT) of the lungs has been incorporated successfully in recent RCTs.^{15,34} HRCT has two key roles in clinical trials of SSc, as recently discussed³⁸: (1) detection and staging of baseline severity, which can be used effectively for cohort enrichment, and adjusting for baseline severity in key treatment effect analyses (because it is likely that a treatment effect may differ in those with mild and in those with extensive lung disease) and (2) as a surrogate endpoint or more accurate measure of serial change. HRCT can be used to diagnose and quantify the degree of fibrosis, thus supporting its face and content validity. The feasibility of HRCT in multicenter RCTs was demonstrated in two recent studies involving SSc-ILD.^{15,34} The reliability of HRCT was demonstrated in the SLS trial,¹⁵ in which good interreader agreement was found for determination of the absence or presence of pure ground-glass opacity ($\kappa = .76$) and fibrosis ($\kappa = .74$) but fair agreement for honeycombing ($\kappa = .29$). In the SLS a higher degree of the extent of fibrosis seen on baseline HRCT was predictive of the rate of decline in FVC in subjects receiving placebo,³⁹ as well as the response to CYC therapy; patients with the most extensive fibrosis on baseline HRCT responded the greatest to CYC treatment.⁴⁰ A greater extent of pulmonary fibrosis on HRCT correlated well with lower FVC and DLCO values on PFTs. In a recent analysis of 215 patients with SSc monitored for 10 years,⁴¹ an increased extent of overall disease (as defined by the degree and coarseness of reticulation [fibrosis] and the proportion of ground-glass opacity) greater than 20% on HRCT correlated with an increase in mortality (hazard ratio, 2.48; $P < .0005$). Therefore, HRCT can be used for the diagnosis of ILD, cohort enrichment for RCTs, and therapeutic decision-making regarding the use of immunosuppressive agents in clinical care.

The 6-minute walk test—an outcome measure for pulmonary arterial hypertension

The 6-minute walk test (6MWT) measures the distance that a person can walk in 6 minutes and has been used extensively as an outcome measure in

patients with various cardiac and pulmonary diseases. The 6MWT is currently the most widely used primary endpoint for studies investigating PAH, including SSc-related PAH. It has been successfully incorporated into trials of SSc-related PAH and was able to differentiate between active and placebo treatment in a trial of epoprostenol for SSc-related PAH.⁴² Pain and musculoskeletal involvement can influence the 6MWT, and it is not always solely reflective of changes in cardiopulmonary involvement when used in patients with SSc.^{43,44} The 6MWT is not sensitive to change in SSc-ILD. It should not be used as a screening measure but may provide prognostic information in patients with SSc-PAH.

Dyspnea indices

Patient-reported outcome measures are important for assessing the efficacy of a treatment. The *Mahler dyspnea index*⁴⁵ was used in the SLS and assesses the level of dyspnea. Baseline scores depend on ratings in three different categories: functional impairment, magnitude of the task, and magnitude of effort. Baseline scores were able to discriminate between moderate and severe physiologic parameters of breathing (%FVC and %DLCO) and correlated well with the baseline breathing visual analogue scale (VAS; $r = .61$).⁴⁶ The Mahler transitional dyspnea score was able to differentiate between patients receiving CYC and placebo in the SLS at 1 year, thus demonstrating its sensitivity to change.⁴⁷ Another instrument used is the Saint George Respiratory Questionnaire, but it lacks data regarding sensitivity to change.

The *breathing VAS scale* in the *Scleroderma Health Assessment Questionnaire* (S-HAQ) allows patients to assess their degree of difficulty in performing daily activities because of shortness of breath on a continuous 100-mm scale.⁴⁸ The VAS discriminates between moderate and severe reductions in lung function, correlates well with the Mahler dyspnea index ($r = .61$), and was shown to be sensitive to change in an SSc cohort⁴⁸; it did not differentiate between CYC and placebo in the SLS-I.

Other outcome measures for cardiopulmonary disease in patients with SSc have been proposed, including exercise echocardiography and magnetic resonance imaging, but await full validation.

Measuring gastrointestinal tract disease in scleroderma

GIT disease occurs in approximately 90% of patients with SSc. Although radiologic tests are the cornerstone for the diagnosis of specific GIT involvement, their feasibility is questionable in multicenter trials, and radiologic tests may be positive in a significant proportion of patients without symptoms.⁴⁹ Furthermore, many patients with SSc have multiple types of GIT disease with overlapping symptoms, thus making quantification of GIT disease in patients with SSc extremely challenging. A recent Delphi panel⁵⁰ and separate expert consensus⁵¹ recommended the use of patient-reported outcome measures and the body mass index as core set measures. Aside from a simple GIT VAS (part of the S-HAQ⁴⁸) that assesses interference in daily activities, a comprehensive scleroderma gastrointestinal instrument has recently been developed under Food and Drug Administration guidelines. The University of California Scleroderma Clinical Trial Consortium Gastrointestinal Instrument (UCLA SCTC GIT 2.0) is a validated, patient-reported outcome measure to assess GIT symptoms and health-related quality of life (HRQOL) in patients with SSc.⁵²⁻⁵⁴ This 34-item instrument has seven scales—reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning—and a total GIT score. The instrument is feasible and has been shown to have acceptable reliability (test-retest and internal consistency) and validity.⁵³ All scales are scored from 0 (better HRQOL) to 3 (worse HRQOL), except for the diarrhea and constipation scales, which range from 0 to 2 and 0 to 2.5, respectively. Participants who rated their GIT disease as mild had lower scores on all seven scales. Symptom scales were also able to discriminate subjects with corresponding clinical GIT diagnoses. The total GIT score is the average of six of seven scales (excludes constipation) and ranges from 0 (better HRQOL) to 2.83 (worse HRQOL). The instrument is sensitive to change in patient self-rated severity, and minimally important differences have been published.⁵⁵ In addition, the instrument has been recently translated into multiple languages and is available free online at <http://uclascleroderma.researchcore.org/>.

Other outcome measures for GIT disease in patients with SSc have been proposed or are under development, including bioelectric impedance analysis, manometry, gastric transit time, endoscopy, and measures of malabsorption.²⁰ There is lack of data on the sensitivity of these measures to change in SSc.

Measuring vascular disease in scleroderma: Raynaud phenomenon and digital ulcers

The Raynaud phenomenon (RP) occurs in approximately 90% of patients with SSc. Similarly, digital ulcers (DUs) are common in those with SSc and result in digital ischemia and gangrenous lesions, as well as skin breakdown. Several clinical trials have examined the efficacy of various interventions for RP and DUs in patients with SSc.⁵⁶⁻⁵⁸ The Raynaud's Condition Score⁵⁶ (RCS) is now the standard outcome for use in clinical trials of RP and is calculated by summing the daily score over a period of 1 or 2 week.⁵⁶ The RCS assesses the level of difficulty experienced because of RP each day (anchored from "no difficulty" to "extreme difficulty") on a 0- to 100-mm VAS or an 11-point Likert scale. Other measures ready for RCTs include the duration of RP attacks, frequency of RP attacks, and patient and physician global assessment.⁵⁶ However, clinical trials in patients with RP are associated with marked variability in individual outcome measures, and a composite measure is needed.⁵⁹ The S-HAQ VAS for RP (assesses interference in daily activities as a result of RP) is also feasible, reliable, and valid.⁵⁶

Other laboratory measures include the cold stimulus fingertip lactecmy test, laser Doppler flowmetry, and others. These measures are useful for proof-of-concept studies but lack feasibility in large multicenter trials.

Measuring ischemic digital ulcers in scleroderma

Methods considered for measuring DUs include standardized photographs, measurement of the size of ulcers, patient and physician global assessment, simple counts of ulcer frequency, and time for ulcers to heal. A definition of DU has recently been developed with consensus methodology,⁶⁰ and it is defined as loss of surface epithelialization at or distal to the proximal interphalangeal joint and does not include fissures or cracks in the skin or areas of calcium extrusion from calcinosis cutis. In a recent study aimed at assessing the reliability of defining DU, a high level of intrarater reliability ($\kappa = .81$) but poor interrater reliability ($\kappa = .46$) was noted, thus suggesting that the same observer should assess DUs in RCTs.⁶¹ The DU count was found to be feasible, reliable, valid, and sensitive to change in large RCTs involving DUs.^{60,62} The S-HAQ VAS for DU (assesses interference in daily activities because of DUs) was shown to be feasible, reliable, valid, and sensitive to change in a large SSc cohort.⁴⁸

Measuring physical function and health-related quality of life

SSc is associated with detrimental effects on physical functioning and emotional and psychological well-being, and different measures have been used.

The Short Form 36 and Health Assessment Questionnaire–Disability Index

Both the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36) and the Health Assessment Questionnaire–Disability Index (HAQ-DI) have been extensively incorporated into multicenter clinical trials of SSc.^{46,63,64} Both instruments have face and content validity because they measure constructs that are important to patients with SSc, and both measures are easy to administer. Although test-retest reliability for the SF-36 and HAQ-DI has been acceptable in patients with other rheumatologic diseases, no study has formally evaluated reliability in those with SSc. The SF-36 and HAQ-DI were found to be responsive to change in two RCTs.^{63,64} In addition, baseline HAQ-DI scores predict mortality in patients with early dcSSc.^{48,65} The SF-36 and HAQ-DI complement each other, and both should be incorporated in clinical trials as measures of HRQOL.

The *UK Functional Score* (UKFS) is a self-reported, 11-item functional questionnaire. It includes nine items related to upper extremity function and two items related to muscle weakness and lower extremity function.⁶⁶ The UKFS is able to differentiate between limited SSc and dcSSc ($P < .05$) and is highly correlated with the HAQ-DI (coefficient of .90). It was found to change during a longitudinal study, with a correlation of .59 with the HAQ-DI.^{67,68}

Patient-Reported Outcomes Measurement Information System

The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) Roadmap initiative (www.nihpromis.org) is a cooperative research program designed to develop, evaluate, and standardize item banks for measuring patient-reported outcomes across different medical conditions, as well as the U.S. population.⁶⁹ The PROMIS has validated instruments for assessing physical, mental, and social health in adults

and pediatric populations. The instrument can be given as a short form (paper and pencil) or via computer (computerized adaptive tests).^{70,71}

Preference-based measures for health-related quality of life: the Short Form 6D

The Short Form 6D (SF-6D) is a preference-based measure that was derived from the SF-36 by using population-based utilities of health states. Preference-based measures are used in decision and cost-effectiveness analyses. The SF-6D is feasible because it only requires completion of the SF-36. Its test-retest reliability was found to be acceptable. Construct validity was confirmed by showing good correlation with the HAQ-DI and with patient global assessment in a recent clinical trial.⁷² The SF-6D was able to discriminate among the baseline severity of the HAQ-DI and patient global assessment and was sensitive to change.

Other generic and disease-specific measures have been tested in patients with SSc, including the Scleroderma Assessment Questionnaire and measures of anxiety, fatigue, and depression.⁷³ These instruments have not yet been shown to be sensitive to change in SSc.

Biomarkers for scleroderma

Vascular (von Willebrand factor [vWF]), T-cell (soluble IL-2 receptor [sIL-2R]), B-cell (autoantibodies), and fibroblast (type III procollagen N-terminal peptide propeptide [PIIINP]) candidate markers have been proposed as biomarkers for SSc. sIL-2R, vWF, and PIIINP were recently assessed in an open-label trial of infliximab and SSc.⁷⁴ Serum markers were demonstrated to be feasible, and PIIINP and vWF showed change over a 6-month period. Other novel markers include myofibroblast staining, four-gene marker (transforming growth factor- β -regulated and interferon-regulated genes),

and gene expression profiling. Recent data suggests their utility in clinical care and predicting responders to immunosuppressive therapies.^{74a} These biomarkers should be included as exploratory endpoints in ongoing large clinical trials to assess their utility as outcome measures. Other readily available markers are acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein) that are associated with disease activity⁶ and predict mortality,^{48,75} and they were proposed as validated biomarkers by scleroderma experts.⁷⁶ Serum creatine phosphokinase is a widely used marker of muscle activity and damage, and N-terminal brain natriuretic peptide has recently been shown to predict incident cases of PAH.^{77,78} Scleroderma-specific autoantibodies are valuable for predicting skin, vascular, and internal organ involvement. Autoantibodies are useful for cohort enrichment,⁷⁹ but their role as an outcome measure in the context of clinical trials still needs to be demonstrated.

CONCLUSION

In the past decade an increase in the development and validation of several outcome measures in patients with SSc has taken place, and these measures have been implemented in several clinical trials. Effort is under way to develop a composite index for scleroderma.^{50,80}

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Clinical features of systemic sclerosis

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- Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular damage and excessive connective tissue deposition in skin and internal organs.
- Lung disease is the leading cause of mortality, and efforts at early detection of pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) are warranted.
- Cardiac involvement is a poor prognostic indicator. Cardiac magnetic resonance imaging is a useful tool for evaluating myocardial function and perfusion.
- Autoantibodies help characterize disease subsets and risks of visceral involvement, and include anticentromere antibody (limited cutaneous SSc and risk of PAH), antitopoisomerase antibody (diffuse cutaneous SSc and risk of ILD), and anti-RNA polymerase III antibody (diffuse cutaneous SSc and risk of renal crisis).
- There are new classification criteria inclusive of many clinical features of systemic sclerosis that enables classification of patients with definite SSc who previously fell outside of the ACR criteria for the disease.
- Gastrointestinal involvement can affect any or all of the alimentary tract and is a prominent symptom in nearly all patients with SSc.
- Depression, often overlooked, is pervasive in patients with SSc.

HISTORICAL BACKGROUND

The first convincing description of scleroderma was by Carlo Curzio in 1753, and the term *sclerodermie* first appeared in the mid-19th century.¹ In 1862 Maurice Raynaud described tricolor vasospastic changes.² Osler referred to the systemic nature of the disease in the 1894 edition of his textbook of medicine (patients were “apt to succumb to pulmonary complaints or to nephritis”)³; and Klemperer and Boehr proposed in 1942 that scleroderma be considered a “systemic disease of the connective tissue.”⁴ A disorder first described in 1910 and originally termed *Thibierge-Weissenbach syndrome*⁵ was described in 1964 by Winterbauer as CRST syndrome (now known as *CREST syndrome* [calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia]).⁶ LeRoy first elucidated the vascular hypothesis of the pathogenesis of systemic sclerosis (SSc) in 1975.⁷ Later, an autoimmune basis was established. More recently there has been remarkable progress in understanding the molecular mechanisms of fibrosis, microvascular injury, and the autoimmune process in this disease.

EARLY SYMPTOMS

Raynaud phenomenon is typically the earliest symptom in patients with SSc. Other frequent early symptoms are malaise, fatigue, arthralgia, and myalgia. Those patients who progress to develop diffuse skin involvement may initially have puffy fingers (Fig. 142.1) and carpal tunnel syndrome. Skin pigment changes may occur before or after the onset of the skin tightening. Occasionally a patient may describe the onset of gastroesophageal reflux symptoms or dyspnea predating the development of skin changes (e.g., systemic sclerosis sine scleroderma).

VASCULAR SYSTEM

Raynaud phenomenon is present in more than 95% of patients with SSc; its absence actually portends a worse prognosis. Raynaud phenomenon is defined as cold-induced vasospasm of the digits (fingers more than toes), rarely occurring in the ears, nose, or tongue. Although classically described as triphasic color changes of the digits, often a patient will not report all three hues. Initially pallor, a well-demarcated white color change, occurs in response to the vasospasm induced by cold exposure (Fig. 142.2). This may be followed by a dusky discoloration due to ischemia and desaturation of hemoglobin; subsequently, reactive hyperemia occurs and the digits turn red. In addition to the color changes, patients often experience numbness, tingling, and discomfort. A color chart of digital changes has been developed and validated to assist in identifying patients with Raynaud phenomenon, (Fig. 142.3) and, when used in conjunction with a short questionnaire, has 100% sensitivity and specificity for diagnosis of Raynaud phenomenon.⁸

In patients with limited cutaneous SSc (lcSSc), Raynaud phenomenon typically begins many years before the onset of skin or visceral disease. In patients with diffuse cutaneous disease (dcSSc), the onset of Raynaud phenomenon usually occurs simultaneously with or shortly after the onset of skin changes; however, in up to 20% of such patients skin thickening may precede the development of Raynaud phenomenon, and it is this reverse order of disease manifestations that seems to be associated with the development of diffuse skin involvement and also of scleroderma renal disease.⁹

Complications of Raynaud phenomenon include digital pitted scars (Fig. 142.4), fixed ischemic changes with threatened tissue loss, poorly healing digital ulcers, dry gangrene (Fig. 142.5), and autoamputation. Digital pits, one of the current SSc diagnostic criteria, represent areas of ischemic insult to the distal fingertip. Digital ulcers may occur at sites of trauma or may manifest solely as a result of vascular insufficiency. Digital ulcers may occur as necrotic debris with a “heaped up” appearance beneath the fingernail. Any of these digital ischemic manifestations may become secondarily infected. Vascular insult due to Raynaud phenomenon in patients with SSc is made more severe by the superimposed structural abnormality of the vascular disease that occurs due to intimal hyperplasia, medial hypertrophy, and adventitial fibrosis of the vessels (Fig. 142.6). These pathologic changes are not related to vasculitis but rather to a bland vasculopathy.

Digital ulcers may be exacerbated by macrovascular disease, typically ulnar artery vasoocclusive disease.¹⁰ Severe vasoocclusive disease occurs more frequently in patients with an anticentromere antibody.¹¹

SSc patients have characteristic microvascular changes that may be observed using widefield microscopy.^{12,13} Patients with lcSSc typically demonstrate nailfold abnormalities of capillary dilatation, termed the *slow phase*. In contrast, the *active phase*, characteristic of patients with dcSSc, is characterized by capillary dilatation and avascularity, or “drop-out” (Fig. 142.7). Nailfold capillaroscopy can assist in diagnosis and determination of prognosis in patients with new-onset Raynaud phenomenon. Characteristic nailfold capillary changes are under consideration to become part of new classification criteria for SSc in the interest of broadening the SSc inclusion criteria so that patients with earlier findings suggestive of SSc or patients with SSc sine scleroderma will be covered. One such proposal by Maricq and Valter includes the use of nailfold capillaroscopy, anticentromere anti-nuclear antibody assay, and telangiectasia as well as the extent of skin involvement to classify SSc into one of six classes.¹⁴ Additionally, a prognostic model using nailfold capillaroscopy has been evaluated to predict which patients with primary Raynaud phenomenon may be at risk of development of scleroderma spectrum diseases within 5 years. Nailfold capillary changes were been found to have 100% sensitivity in a group of 326 patients with

SSc.¹⁵ This validated model finds that capillary number and the presence of giant capillary loops or microhemorrhages are associated with the likelihood of developing scleroderma spectrum disease.¹⁶ Video capillaroscopy, a new tool permitting evaluation of the same capillaries on subsequent examinations, allows longitudinal follow-up of nailfold capillary changes with access to previous measurements.¹⁷



Fig. 142.1 The hand of a patient with early scleroderma demonstrating the "puffy" phase.

CUTANEOUS FEATURES

Three stages of skin changes may occur in patients with SSc. The initial stage, an inflammatory, edematous stage, is associated with puffiness of the hands and fingers (see Fig. 142.1). Pruritus may accompany this phase. Complications such as paronychia and sores over taut metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints may develop with slow or poor healing. During this initial inflammatory phase, which may last for months, induration and thickening of the skin begin to develop.

Once the inflammatory phase quiets, a longer phase of progressive skin fibrosis may ensue, beginning with acral involvement, distal to the MCP joints, which may progress proximally. In patients who are developing diffuse skin changes there may be involvement of the skin on the face, hands, forearms, arms, chest, abdomen, thighs, legs, and feet. Patients with lcSSc have skin changes limited to the face, neck, and distal extremities. A small subset of patients with dcSSc may demonstrate truncal skin involvement without acral changes. The skin on the chest and abdomen may also be thickened in a bandlike distribution along pressure areas, such as the bra



Fig. 142.2 The hands of a patient with scleroderma who has active Raynaud phenomenon. There is well-demarcated pallor of the fingertips.

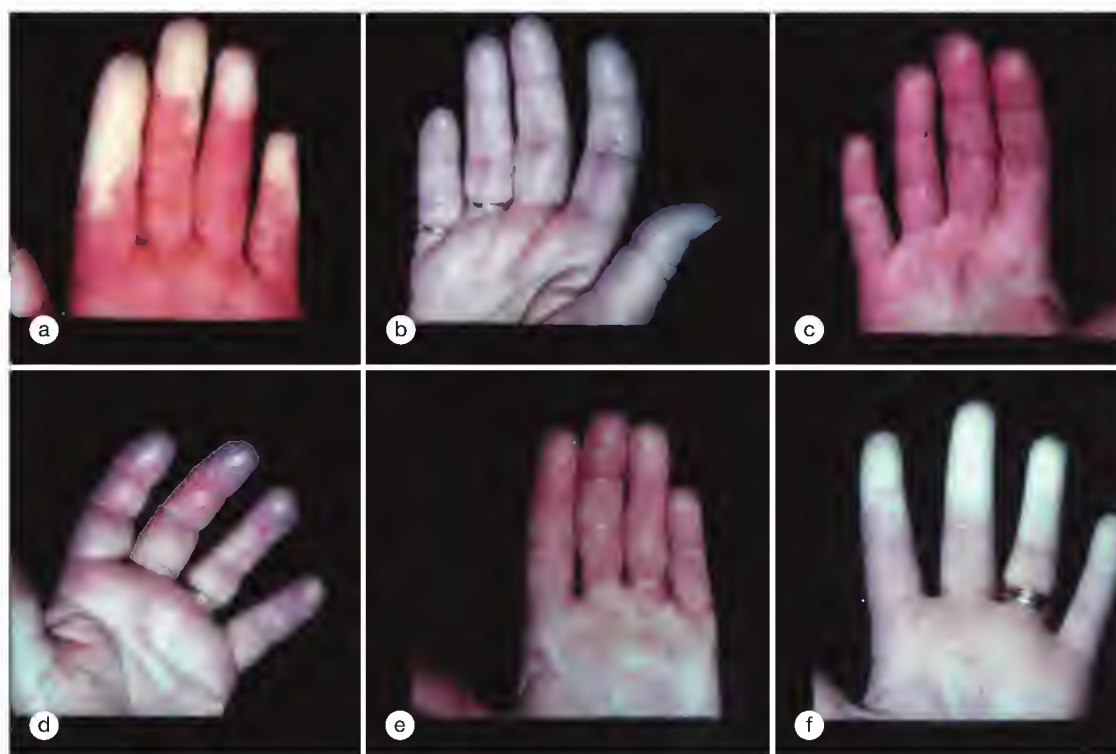


Fig. 142.3 A color chart card demonstrating the possibilities for color changes that a patient may identify as the cold-induced color changes of Raynaud phenomenon. (a, b, and f) Color changes seen in Raynaud phenomenon. (From Maricq HR, Weinrich MC. Diagnosis of Raynaud's phenomenon assisted by color charts. *J Rheumatol* 1988;15:454-59.)

line and belt region. Facial skin thickening does not distinguish between patients with limited and diffuse cutaneous disease, because it is typically involved in both subsets. Characteristic skin changes occur in the perioral region and include tightening and a tethering, causing a reduced oral aperture and “mauskopf” facies (Fig. 142.8). The front teeth may also appear to be prominent because of lip and gum retraction; gum retraction occurs due to both fibrosis and atrophy of the mandible.



Fig. 142.4 Digital pits on the fingertip of a patient with scleroderma.



Fig. 142.5 Digital gangrene on the fingertips of a patient with scleroderma.

Early in the disease course a patient may appear to have limited cutaneous disease, that is, distal skin thickening only; however, over the course of 2 years skin involvement may progress to include the proximal extremities and trunk (diffuse cutaneous disease). Therefore, it may be unreliable to classify a patient as having limited skin disease within the first 2 years from onset of skin changes.

Pigmentation changes occur during both the inflammatory-edematous and progressive fibrosis stages. Depending on the patient's natural skin tones, the skin may become hypopigmented or hyperpigmented. Some patients develop areas of depigmentation, particularly of the scalp, chest, and upper back and over areas of pressure such as the dorsum of the hand or pretibial regions. These areas of vitiligo give the skin a “salt and pepper” appearance owing to perifollicular sparing of pigment loss.

In patients with dcSSc, progressive fibrosis may be followed by a final stage of skin softening, which typically begins 2 years after the onset of skin disease. The skin softening can allow a return to clinically normal skin and occurs most commonly on the trunk and upper arms; joint mobility can also improve. In late-stage SSc the skin may become atrophic and feel thinner, particularly over the fingers, dorsum of the hand, and lower legs. Although it is softer at this stage, it may still be tethered to underlying fibrotic tissue, particularly over the fingers.

The modified Rodnan skin score is a method for grading skin thickness in 17 body areas (Fig. 142.9) and is a validated tool used in clinical trials with small interobserver variability.¹⁸ The score in each area ranges from 0 to 3, with 0 representing normal skin and 3 representing taut or hide-bound skin. A score of 1 indicates mild skin thickening and a score of 2 is consistent with a greater degree of skin tautness.^{19,20} The rate of progression of skin thickening, or the skin thickness progression rate, is of prognostic importance, and there is evidence that patients who come to the first office visit with a history of rapidly changing skin thickness have both an increased mortality and a higher risk of renal crisis.²¹

Other skin manifestations include telangiectasias, digital pits, and calcinosis. Telangiectasias are dilated capillaries most commonly present on the face (Fig. 142.10), hands (Fig. 142.11), mucosal membranes, and chest. Digital pits are small areas of indentation on the distal finger pads caused by ischemic damage related to Raynaud phenomenon. Subcutaneous calcinosis occurs in both limited and diffuse cutaneous disease but is more common in patients with limited disease, particularly those with an anti-centromere antibody. It most commonly occurs over areas of trauma such as the extensor surfaces of the forearms (Fig. 142.12) and of the finger pads.

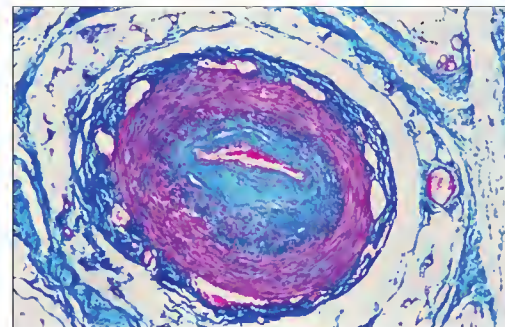


Fig. 142.6 Masson trichrome staining for collagen of a digital artery revealing near occlusion of the vessel lumen due to subintimal fibrosis and periadventitial fibrosis.



Fig. 142.7 Nailfold capillaroscopy using a widefield microscope demonstrating (a) normal nailfold capillaries, (b) “slow” phase capillaries most commonly seen in limited cutaneous systemic sclerosis characterized by capillary dilatation, and (c) “active” phase nailfold capillaries typical of diffuse cutaneous systemic sclerosis with capillary dilatation and avascular areas.



Fig. 142.8 Taut smooth skin over the face and reduced oral aperture of a woman with long-standing scleroderma. Furrowing is present around the mouth, along with some facial telangiectasias.



Fig. 142.10 Facial and lip telangiectasias in a woman with systemic sclerosis sine scleroderma.

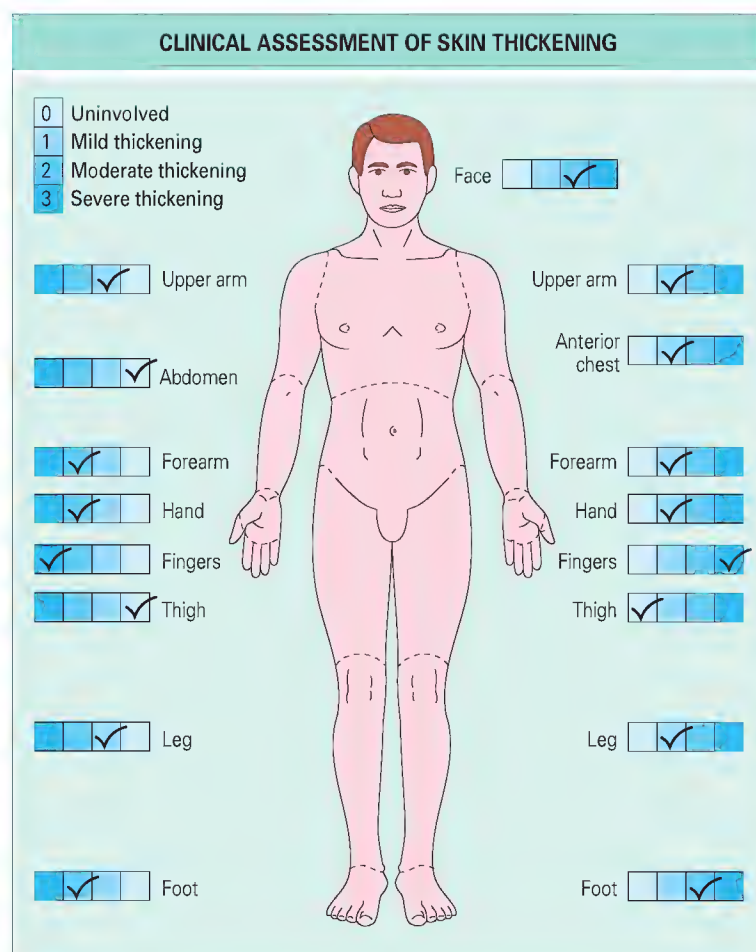


Fig. 142.9 Total skin score. Semiquantitative estimates by clinical palpation of the extent and severity of scleroderma skin changes. In all cases, the initial areas involved are peripheral and are the most severely affected. The mild skin change on the chest and on the upper arms permits classification of this individual's disease as diffuse scleroderma.



Fig. 142.11 Telangiectasias of the fingers.



Fig. 142.12 Subcutaneous calcifications, calcinosis of the left forearm and elbow with cutaneous ulceration. (From Porta F, Matucci-Cerinic M. A limited cutaneous SSc patient with severe calcinosis and acro-osteolysis. In: Silver RM, Denton CP, editors. Case studies in systemic sclerosis. London: Springer-Verlag; 2011, p. 259-66.)

The calcification may remain subcutaneous or may drain from the skin surface, ulcerate, and/or become infected. The subcutaneous deposits are composed of calcium hydroxyapatite.

The American College of Rheumatology (ACR; formerly American Rheumatism Association) classification criteria for SSc were formerly based on the extent of skin involvement, presence of digital pits, and/or radiographic evidence of basilar pulmonary fibrosis.²² It was clear that many patients with disease fell within the spectrum of SSc without meeting the prior ACR classification criteria, thus the ACR and European League Against Rheumatism (EULAR) revised the classification criteria for SSc. Skin thickening proximal to the metacarpophalangeal joints sufficiently classifies a patient with SSc; however, for those patients with lesser involvement of the skin, there are seven other factors that are weighted to help classify a patient as having SSc. These factors include digital pits/digital ulcers, telangiectasias, nailfold capillary abnormalities, Raynaud phenomenon, pulmonary hypertension, interstitial lung disease, and scleroderma autoantibodies. Use of the new classification criteria enhances the sensitivity and specificity to 0.91 and 0.92, respectively, compared with the prior classification criteria sensitivity and specificity of 0.75 and 0.72, respectively, for the validation sample described.^{22a}

SYSTEMIC FEATURES

Gastrointestinal involvement

Gastrointestinal involvement, nearly universal in patients with SSc, often manifests as the first non-Raynaud phenomenon symptom. Gastrointestinal manifestations may be mild or severe and occur in patients with limited or diffuse disease. Even in the absence of symptoms, patients with SSc demonstrate motility abnormalities on functional testing. The entire gastrointestinal tract may be involved from the oropharynx to the anus. Secondary Sjögren syndrome may also contribute to abnormal deglutination and swallowing.

The cause of gastrointestinal manifestations relates to smooth muscle atrophy, to which both microvascular insufficiency and neurogenic factors contribute. Smooth muscle atrophy and fibrosis within the gastrointestinal mucosa play a role in gastrointestinal dysmotility; however, intimal proliferation similar to that seen in other vascular beds also occurs in the gastrointestinal tract.

There may be serious social ramifications for patients with SSc and gastrointestinal involvement, and many patients find it difficult to participate in social events or contributed planning owing to embarrassment and discomfort from gastrointestinal disease. Depression, often present and frequently undiagnosed in SSc, has been shown to correlate significantly with gastrointestinal involvement.²³

Oropharynx

Oropharyngeal involvement includes reduced oral aperture from skin tightening, mandibular atrophy, and a shortened frenulum. Patients with SSc, particularly those with dcSSc, are at increased risk of development of carcinoma of the tongue.²⁴ Xerostomia due to SSc and/or secondary Sjögren syndrome also commonly occurs. Most patients with a complaint of dry mouth do not demonstrate the typical inflammatory infiltrate of Sjögren syndrome on minor salivary gland biopsy but instead have submucosal fibrosis. Mouth-related disability can be formally evaluated using a validated tool, the Mouth Handicap in Systemic Sclerosis scale, which has been shown to relate to global disability assessment using the Health Assessment Questionnaire.^{25,26} Because of the importance and difficulty of adequate oral care, specific recommendations regarding oral care in patients with SSc are available.²⁷

Esophagus

Esophageal dysmotility is present in nearly every patient with SSc owing to involvement of the distal two thirds of the esophagus and sometimes results in symptoms of dysphagia. Reduced lower esophageal sphincter pressure occurs, which causes varying degrees of gastroesophageal reflux and dyspepsia and, in some patients, may result in free reflux of acid and/or gastric contents. Patients experience chronic injury to the esophageal mucosa and increased incidence of Barrett metaplasia.²⁸ Other symptoms include dysphagia secondary to esophageal stricture, early satiety, regurgitation of undigested food, hoarseness, cough, and weight loss. Gastrointestinal bleeding can result from erosive esophagitis, esophageal ulcer, a Mallory-Weiss tear, or mucosal telangiectasia.

Barium esophagography may demonstrate esophageal dysmotility, including loss of primary and secondary peristalsis of the distal esophagus as well as esophageal strictures. Esophageal manometry can be useful to

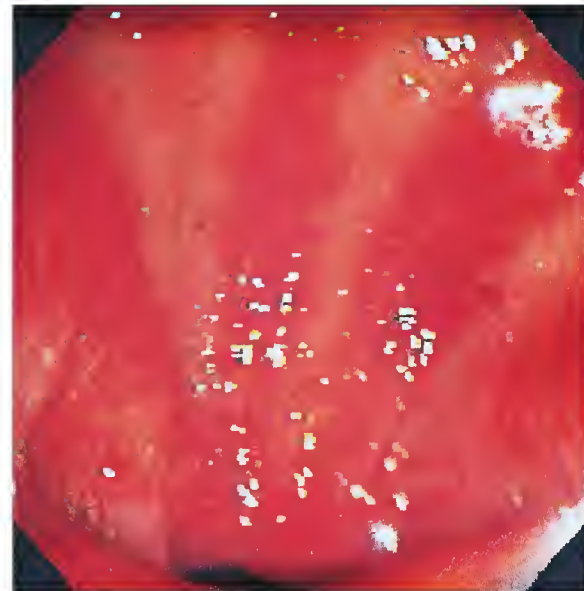


Fig. 142.13 Watermelon stomach. Endoscopic image of the stomach of a patient with scleroderma who experienced recent gastrointestinal bleeding caused by gastric antral vascular ectasia.

document distal esophageal involvement and reduced lower esophageal sphincter pressure in a patient undergoing evaluation for possible SSc. A 24-hour pH probe can also be helpful in monitoring the efficacy of acid-suppressive therapy. Excessive air in the esophagus, reflecting esophageal dysmotility, is a characteristic finding seen on chest radiography or chest computed tomography (CT). Upper endoscopy is performed to assess for sources of bleeding, strictures, metaplasia, or malignancy.

Stomach

Symptoms of gastric involvement include early satiety, bloating, nausea, emesis, anorexia, and weight loss. Delayed gastric emptying can exacerbate symptoms of gastroesophageal reflux and cause bloating. Early satiety and bloating may cause the patient to reduce caloric intake, which leads to weight loss. Gastrointestinal blood loss may result from mucosal telangiectasia, gastritis, or, in more severe cases, gastric antral vascular ectasia. Gastric antral vascular ectasia, described endoscopically as a watermelon stomach (Fig. 142.13), may lead to occult or large amounts of blood loss requiring multiple transfusions and laser therapy.

Small and large intestines

Intestinal dysmotility also causes bloating and cramping. Patients develop diarrhea alternating with constipation due to intestinal bacterial overgrowth. Occult gastrointestinal blood loss may result from mucosal telangiectasias, which may be difficult to detect endoscopically. Pseudoobstruction is a serious sequela of intestinal dysmotility (Fig. 142.14) and manifests as abdominal pain, bloating, and emesis. Although it is a functional ileus, its presentation mimics that of an anatomic obstruction; conservative management is mandated, and surgical intervention should be avoided if at all possible. Large-intestinal mucosal muscular atrophy may result in wide-mouthed diverticula unique to SSc, typically occurring on the antimesenteric surface. Anorectal involvement due to decreased compliance and reduced anal sphincter tone may result in rectal prolapse and/or rectal incontinence.

Hepatic involvement

The liver is rarely primarily involved in SSc; however, an association exists between primary biliary cirrhosis (PBC) and SSc, and a significant proportion of patients with PBC have an anticentromere antibody.²⁹ Antimitochondrial antibodies occur in SSc patients with coexisting PBC. Patients have jaundice and an obstructive biliary picture characterized by elevated alkaline phosphatase and total bilirubin levels. Elevated transaminase levels most often reflect coincident inflammatory muscle disease rather than true hepatic involvement and may indicate a need for muscle evaluation.

Pulmonary involvement

Lung disease is the leading disease-related cause of mortality. Pulmonary disease most typically includes interstitial lung disease (ILD) and/or



Fig. 142.14 Upright abdominal radiograph of a 51-year-old man with systemic sclerosis and pseudoobstruction with pneumatoxis cystoides intestinalis. (From Mitchell M, Bolster MB, LeRoy EC. Scleroderma and related conditions. *Med Clin North Am* 1997;81:129-49.)

pulmonary arterial hypertension (PAH). Other less common lung manifestations include aspiration pneumonia, pleural disease, obstructive airway disease, endobronchial telangiectasia with hemoptysis, malignancy, alveolar hemorrhage, and cryptogenic organizing pneumonia.³⁰

ILD characteristically begins as basilar pulmonary fibrosis and may be seen in patients with either limited or diffuse skin disease, although it tends to be more common and more severe in patients with dcSSc. Approximately 80% of patients have evidence of pulmonary fibrosis at postmortem examination³¹ or on high-resolution CT scans, although clinically evident disease is present in only approximately 40% of patients.³² Patients are at greatest risk of developing ILD within the first 4 years after SSc onset, and black males in their fifth and sixth decades are at the greatest risk of severe lung disease.³³ The presence of anti-topoisomerase I antibody (anti-Scl-70 antibody) is associated with an increased risk of developing diffuse skin involvement and severe pulmonary fibrosis.³⁴ The presence of an anticentromere antibody or anti-RNA polymerase III antibody is associated with a reduced risk of the development of ILD.^{34,35} Patients with ILD usually have exertional dyspnea and dry cough at presentation. Physical examination reveals late inspiratory basilar crackles without signs of congestive heart failure. A chest radiograph may reveal basilar pulmonary fibrosis but may show normal findings.

Pulmonary function testing (PFT) with spirometry, measurement of lung volumes, and tests of gas exchange is the best screening method for ILD. The most sensitive and earliest change is a reduction in diffusion capacity.³⁶ ILD is typically characterized by a reduction in total lung capacity; a reduced forced vital capacity (FVC) is also indicative of restrictive lung disease in the absence of obstructive airways disease (normal ratio of forced expiratory volume in 1 second to FVC). PFT abnormalities may occur before the onset of clinical symptoms, and a noted reduction in lung volumes should prompt further evaluation for ILD. Absence of dyspnea in some cases may relate to an insidious onset of lung symptoms or to the fact that patients with SSc often limit activity levels due to skin or musculoskeletal manifestations. It is important to detect ILD at its earliest stage to initiate treatment before the occurrence of irreversible lung fibrosis. High-resolution computed tomography (HRCT) of the chest reveals ground-glass opacification that is indicative of active inflammation and/or early fibrosis, often referred to as *alveolitis* (Fig. 142.15).³⁷ HRCT findings also include thickening of the interlobular septa, subpleural nodules, honeycomb appearance, and traction bronchiectasis. The CT findings are highly sensitive for ILD in SSc. PFT and HRCT are the standard of care for detecting ILD in patients with SSc. Goh and colleagues³⁸ have developed a useful algorithm to estimate risk

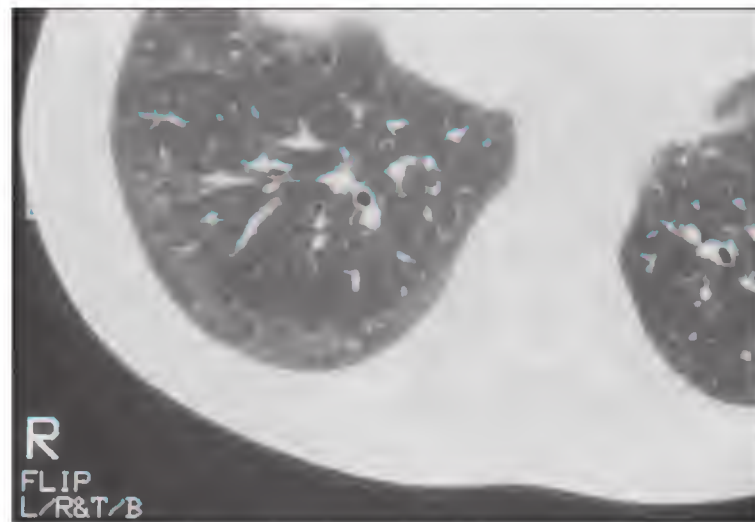


Fig. 142.15 High-resolution computed tomographic scan of the chest of a patient with systemic sclerosis and alveolitis demonstrating ground-glass opacification, a haziness visualized at the lung periphery.

of progression of restrictive lung disease based on spirometry and HRCT findings, and post-hoc analysis of the Scleroderma Lung Study-1 (SLS-1) supports the notion that response to treatment may be predicted from the results of baseline PFT and HRCT findings.³⁹ Bronchoalveolar lavage, historically performed to evaluate for alveolitis, has largely been replaced by HRCT in patients with SSc and lung disease unless evaluation for pulmonary infection is warranted. However, cytokine analysis of bronchoalveolar lavage fluid may provide useful prognostic information.⁴⁰

Pulmonary vascular disease may occur either as a primary vasculopathy or secondary to underlying cardiac disease, hypoxic ILD, or, rarely, chronic thromboembolic disease. Patients with pulmonary hypertension most commonly have dyspnea and/or fatigue at presentation. Atypical chest pain, lower extremity swelling, lightheadedness, and syncope are late symptoms of pulmonary hypertension. Isolated pulmonary artery hypertension (PAH) more commonly occurs in patients with lcSSc, typically presenting many years after the onset of Raynaud phenomenon; however, patients with dcSSc can also manifest isolated PAH occurring relatively early in the disease course.⁴¹ Black patients develop pulmonary hypertension at a younger age than white patients.⁴²

Physical examination findings may include an accentuated P₂ component of the second heart sound (S₂) with or without fixed splitting of S₂. A right-sided S₃ may be present with other signs of right-sided heart failure. Findings of right-sided heart strain on physical examination are not sensitive but, if present, are likely indicative of advanced pulmonary hypertension.

The initial evaluation of the SSc patient with dyspnea should include spirometry with measurement of lung volumes and diffusion capacity. A patient with isolated PAH will demonstrate a reduced carbon monoxide diffusion capacity (DLCO) in the presence of normal lung volumes.⁴³ A declining DLCO may be an early predictor of the development of PAH.⁴⁴ A ratio of FVC to DLCO (FVC% predicted/DLCO% predicted) of more than 1.6 may also be predictive of the presence or development of PAH (mean pulmonary artery pressure of 25 mm Hg or more).⁴⁵ An isolated reduction of DLCO below 40% is predictive of increased mortality,⁴⁶ and the low DLCO may be observed years before the clinical diagnosis of PAH.⁴⁴ An isolated reduction in DLCO may, however, indicate either early ILD, emphysema, or the presence of pulmonary vascular disease; thus two-dimensional Doppler echocardiography and/or HRCT should also be performed.

Echocardiography, although imperfect, is a noninvasive screening tool for detecting pulmonary hypertension (Fig. 142.16).⁴⁷ Pulmonary hypertension can be a difficult disease manifestation to discover, and between 13% and 23% of patients with SSc may have undetected pulmonary hypertension, depending on the threshold value used for its diagnosis (e.g., estimated peak right ventricular systolic pressure [PRVSP] of 30, 35, or 40 mm Hg).^{48,49} Unlike a reduced DLCO, an abnormal PRVSP has not been associated with the future development of pulmonary hypertension, because a PRVSP that is elevated to more than 35 mm Hg has been found, on repeat testing, to be normal in up to 50% of patients 3 years later.⁴⁵ A PRVSP of 40 mm Hg or more by echocardiography has been correlated with reduced exercise tolerance, and a PRVSP of more than 50 mm Hg has been associated with right

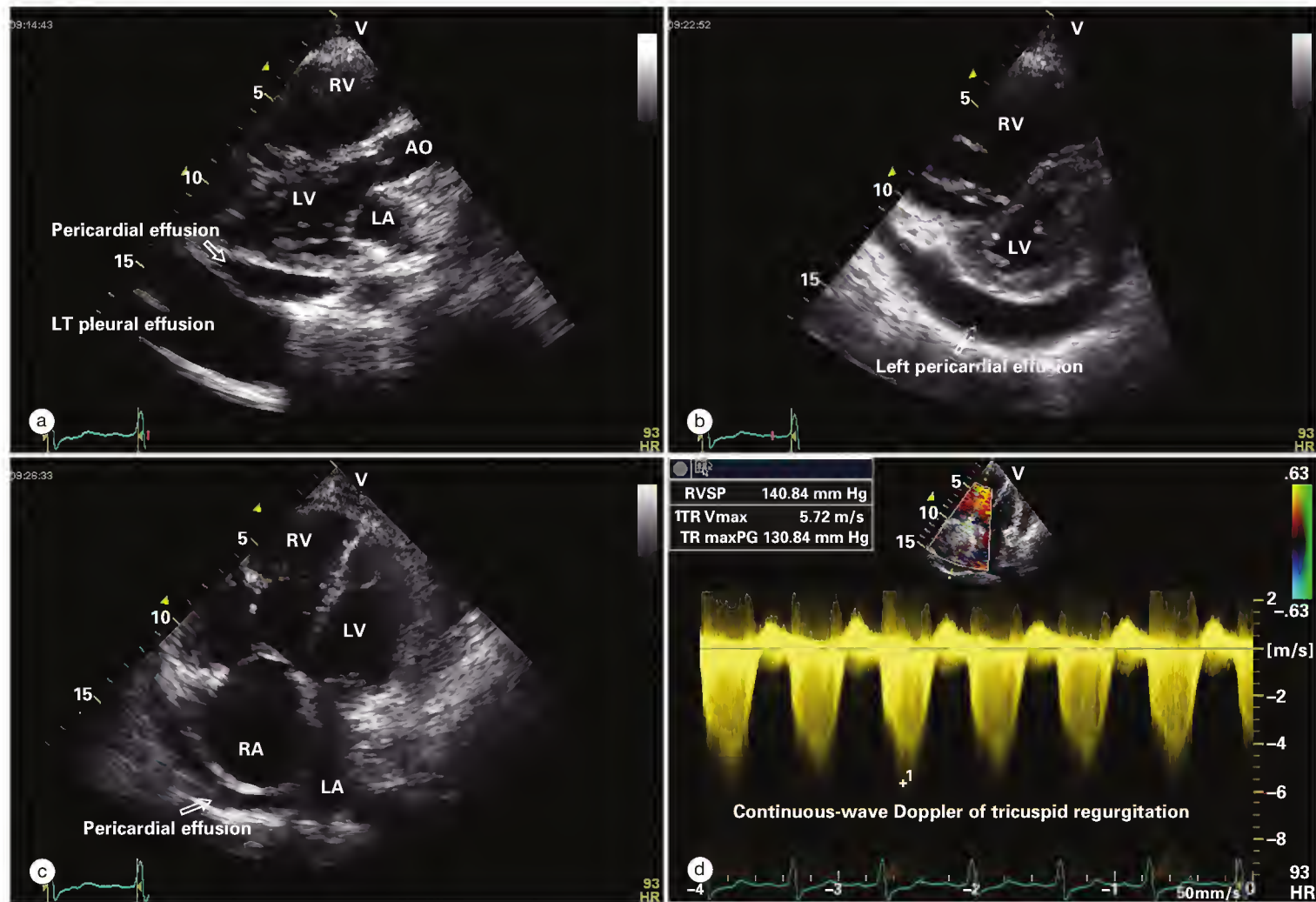


Fig. 142.16 Echocardiographic images for a woman with limited cutaneous systemic sclerosis and pulmonary arterial hypertension. (a) Parasternal long-axis view shows left ventricle, dilated right ventricle, and presence of both a left pleural and pericardial effusion. (b) Parasternal short-axis view demonstrating the D-shaped septum seen with pressure overload of the right ventricle. The right ventricle is dilated and again visible is a moderate-sized pericardial effusion. (c) Apical three-chamber view showing dilated right-sided chambers and a pericardial effusion. (d) Continuous-wave Doppler image of tricuspid valve regurgitation with an estimated peak right ventricular systolic pressure of 141 mm Hg plus right atrial pressure.

ventricular enlargement.⁴⁸ A high index of suspicion for pulmonary hypertension is imperative to permit early detection and, in particular, diagnosis before the development of right-sided heart failure. Functional changes in the right ventricle are indicative of both the chronicity and severity of pulmonary hypertension.

Assessment of serum brain natriuretic peptide (BNP), a marker of all-cause myocardial involvement, can be helpful in the evaluation of a patient with possible right ventricular strain. An elevated BNP level has a sensitivity of 56% and a specificity of 95% for detection of pulmonary hypertension and portends a worse prognosis. Additionally, occurrence of a BNP increase in patients being treated for pulmonary hypertension has been associated with worsened survival.⁵⁰

When clinical or echocardiographic findings raise suspicion of pulmonary hypertension, right-sided heart catheterization should be performed to definitively confirm the presence of PAH, rule out other causes of pulmonary hypertension such as diastolic dysfunction, and guide therapeutic interventions. A mean pulmonary artery pressure of 25 mm Hg or more with a normal pulmonary capillary wedge pressure is consistent with PAH.

The 6-minute walk test is also used to follow patients with PAH and provides information regarding a patient's ability to maintain blood oxygen saturation as well as a functional measure of distance walked to follow efficacy of therapies. However, the 6-minute walk test has limitations in patients with SSc who have pulmonary hypertension, because factors aside from dyspnea, such as muscle weakness or lower extremity discomfort, may limit performance; thus musculoskeletal or vascular features of a patient's disease should be considered.⁵¹

Another tool useful in the evaluation of the patient with PAH is cardiac magnetic resonance imaging (MRI). Cardiac MRI provides three-dimensional projections allowing improved visualization of right ventricular mechanics,

such as ventricular volume and mass, as well as an assessment of the pulmonary circulation. Cardiac MRI detects PAH more accurately than does echocardiography and provides additional information on right ventricular function.⁵²

In patients with known ILD, worsening of symptoms may reflect the presence of secondary pulmonary hypertension, warranting evaluation for pulmonary vascular disease and potentially provision of additional therapies for pulmonary hypertension. Patients with SSc and pulmonary hypertension secondary to underlying ILD have a worse prognosis than patients with ILD without pulmonary hypertension.³² Superimposed pulmonary hypertension may accelerate the patient's need for oxygen supplementation, provide an indication for anticoagulation with warfarin, and/or prompt the need for vasodilator therapy.

The presence of PAH historically has predicted extremely high mortality (Fig. 142.17),⁵³ but new treatment options have improved survival.⁵⁴⁻⁵⁷ The use of potent vasodilators in patients with SSc-PAH has demonstrated a 1-year survival of 78% compared with 45% 1-year survival rates among historical controls. Similarly, a survival advantage has been noted in treated SSc patients with exercise-induced PAH, who show a 3-year survival of 86%. The lowest survival rate has been reported in SSc patients with pulmonary hypertension secondary to underlying ILD, with an estimated 28% surviving at 3 years. Factors associated with a worse prognosis in SSc-PAH include age older than 70 years, higher World Health Organization functional class (class III or IV), and higher mean right atrial pressure or pulmonary vascular resistance. Although the best survival has been observed in patients with exercise-induced PAH or low WHO functional class, this likely represents an earlier stage of disease development in these patients. Early aggressive therapy is warranted because even mortality rates in early disease are not negligible.⁵⁸

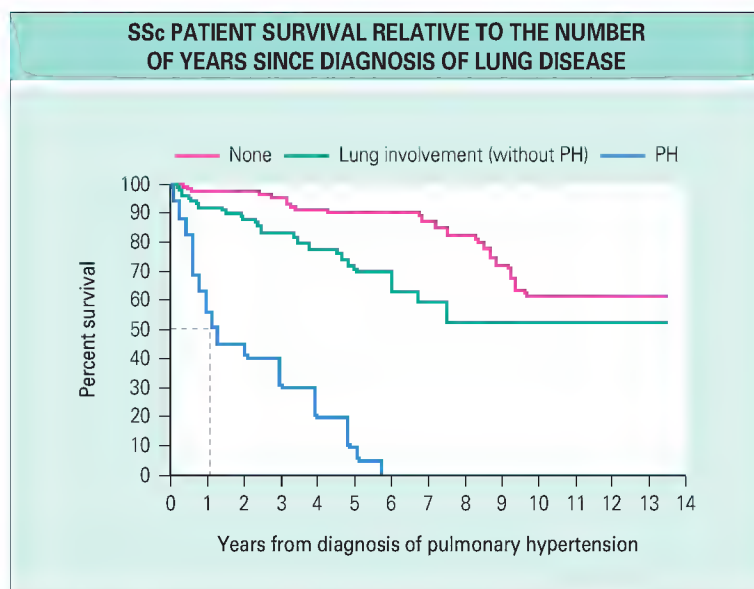


Fig. 142.17 Survival of patients with systemic sclerosis (SSc) with and without lung involvement. The highest survival rate is among SSc patients without lung disease (top line). The middle line shows survival of patients with SSc and interstitial lung disease, and the lowest survival curve is for SSc patients with pulmonary hypertension (pulmonary hypertension).

Cardiac involvement

Cardiac involvement in SSc, although commonly seen at postmortem examination, is clinically variable and may be subtle in presentation.³¹ The clinical presence of cardiac involvement is predictive of a poorer prognosis.⁵⁹ Cardiac manifestations include pericardial disease, dilated cardiomyopathy, autonomic neuropathy,⁶⁰ and arrhythmias. Left or right ventricular diastolic dysfunction has become a more commonly recognized abnormality, and left ventricular dysfunction may be an important component of pulmonary hypertension.^{61,62}

Patients with SSc and cardiac involvement may have symptoms commonly associated with pulmonary involvement, including dyspnea, palpitations, chest pain, or dizziness. It is important to maintain a high index of suspicion for the possibility that cardiac disease may be contributing to these symptoms.

Pericardial disease can manifest as either pericarditis or, more commonly, as a pericardial effusion. Pericardial effusions, typically exudative if secondary to SSc, accumulate slowly so that pericardial tamponade is a rare occurrence. The echocardiographic presence of small to moderate-sized pericardial effusions is not uncommon in SSc, although typically is not of much clinical significance. The gold standard for detecting pericardial disease is two-dimensional echocardiography, but pericardial involvement can also be found on chest CT or cardiac MRI. Pericardial disease can involve a fibrinous pericarditis with adhesions and inflammatory cell infiltrate^{31,63} or uremic pericarditis in patients with scleroderma renal crisis. The presence of a pericardial effusion, a more common manifestation in patients with dcSSc, is a risk factor for the development of scleroderma renal crisis.⁶⁴ Pericardial effusions have been found with increased incidence in patients with SSc-ILD with echocardiographic evidence of pulmonary hypertension (RVSP of more than 35 mm Hg).⁶⁵

Patients with SSc can develop left or right ventricular systolic dysfunction; it is usually a late occurrence in the disease course, typically has an insidious onset, and most commonly is seen in patients with dcSSc. The presence of congestive heart failure has been associated with increased mortality in patients with SSc. Measurement of serum BNP level is also helpful in evaluating and following patients with reduced ventricular function. For patients with significant left ventricular systolic dysfunction, implantation of an automatic defibrillator should be considered using the guidelines for patients with cardiomyopathy of other causes.

Pathologic changes of the myocardium identified in postmortem studies include myositis and fibrosis (Fig. 142.18).⁶³ Additionally, patchy myocardial fibrosis occurs with contraction band necrosis, which increases the risk of conduction abnormalities. Patchy myocardial fibrosis likely occurs as a response to ischemic-reperfusion insult from microvascular involvement. Patients who have an overlap syndrome with inflammatory myositis are more likely to develop myocarditis and present acutely with a dilated

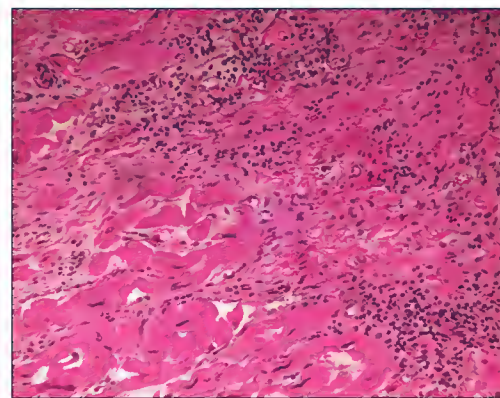


Fig. 142.18 Photomicrograph showing lymphocyte and plasma cell infiltration of the myocardium as well as fibrosis (hematoxylin-eosin, ×10). These changes are largely related to an associated fibrinous pericarditis in this young woman with scleroderma.

cardiomyopathy as a manifestation of underlying muscle disease. Endomyocardial biopsy can demonstrate inflammatory changes with or without fibrosis.

Diastolic dysfunction may occur in patients who have essential hypertension. Additionally, there seems to be a predilection for the development of either right or left ventricular diastolic dysfunction in SSc, and this may reflect myocardial fibrosis and reduced ventricular compliance. Left ventricular diastolic dysfunction appears to occur with greater frequency than systolic dysfunction⁶¹ and is present to a higher extent in patients with pulmonary hypertension.⁴² Diastolic dysfunction may contribute significantly to the presence of pulmonary hypertension (venous rather than arterial) or, on the contrary, right ventricular diastolic dysfunction may result from PAH in this patient population.

Atherosclerotic coronary artery disease appears to occur at an increased rate in patients with SSc, and postmortem studies reveal lesions that involve most commonly the small coronary arteries or arterioles.^{31,66,67} Perfusion defects noted on nuclear medicine testing also occur commonly. Additionally, cardiac “Raynaud phenomenon,” or cold-induced and reversible vasospasm, has been reported.^{68,69} The presence of defects on thallium scanning is predictive of a poorer prognosis and reflects more severe myocardial involvement.

Fibrosis along conduction pathways may cause arrhythmias. Patients may experience transient palpitations or more significant symptoms. Objective testing may be of low yield owing to the fleeting nature of many conduction abnormalities; however, changes may be detected with electrocardiography, Holter monitoring, or longer-duration event monitoring. The conduction defects most commonly found on electrocardiography include a prolonged PR interval, left anterior fascicular hemiblock, and intraventricular conduction delays. The most common finding on rhythm analysis is premature ventricular contractions.⁷⁰ Premature atrial contractions also occur commonly. Additional rhythm disturbances may include multifocal atrial tachycardia or supraventricular tachycardia. Atrioventricular defects or the more lethal rhythms such as ventricular tachycardia are much rarer. Rhythm disturbances occur more commonly in patients with dcSSc, and their presence portends a poorer prognosis.

Echocardiography is a valuable noninvasive method for evaluating cardiac function, providing information about chamber sizes, wall motion abnormalities, and contractility. Pulsed tissue Doppler echocardiography provides additional information about cardiac function in the longitudinal plane, and the subendocardial fibers, mostly longitudinal in orientation, are those affected most by microvascular ischemia. Longitudinal systolic and diastolic abnormalities are often the first signs of cardiac involvement in SSc heart disease.⁷¹

Cardiac MRI has become a useful noninvasive tool in patients with SSc, providing high spatial resolution of the heart with small interobserver and intraobserver variability, and it permits evaluation of ventricular function, mass, and size. It is particularly helpful for assessing the right ventricle. The myocardium may show evidence of changes consistent with fibrosis, with late gadolinium enhancement indicating diffuse fibrosis. Small subendocardial defects may relate to small-vessel ischemic injury.^{70,72} Cardiac MRI permits assessment of perfusion to better evaluate microvascular ischemia and response to therapies.⁷⁰⁻⁷²

Single-photon emission computed tomography (SPECT) evaluates myocardial perfusion and is another method allowing evaluation of function (left ventricular ejection fraction) and wall motion abnormalities. Additionally,

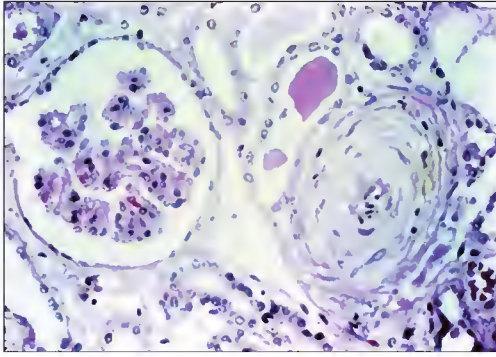


Fig. 142.19 Vascular changes characteristic of systemic sclerosis. This renal arteriole demonstrates endothelial proliferation, medial hypertrophy, and adventitial fibrosis in a patient with scleroderma renal crisis (hematoxylin-eosin).

there is evidence for the usefulness of gated myocardial perfusion SPECT for evaluating early changes in diastolic function in patients with SSc.⁷³

Renal involvement

Scleroderma renal crisis (SRC), one of the cardinal vascular manifestations of SSc, is characterized by neither an inflammatory process nor evidence of glomerulonephritis. SRC is a high-renin state, and the pathologic changes in the blood vessels are similar to those seen in other vessels in patients with SSc (Fig. 142.19). Plasma measures of renin are not, however, predictive of the development of SRC.

Before the advent of angiotensin-converting enzyme (ACE) inhibitors, renal involvement was the leading cause of death in SSc. SRC still occurs; however, with early recognition and aggressive management the outcome is much improved. It is estimated that 10% of patients with SSc will develop SRC, which occurs almost exclusively in patients with dcSSc and develops within the first 3 years of disease.^{74,75} Risk factors for SRC include diffuse skin involvement, tendon friction rubs, anti-RNA polymerase III antibody, new-onset anemia, and pericardial effusion. Nonmalignant hypertension, urine sediment abnormalities, and antibodies to topoisomerase I or centromere are not predictive of SRC. Males, those developing the disorder at an older age, and those with a serum creatinine concentration of more than 3 mg/dL have the poorest outcome.

SRC classically presents with new-onset hypertension. The heralding sign of the increased blood pressure may range from a mild increase in a patient who typically has a low blood pressure to a marked elevation of the blood pressure. Associated signs and symptoms are similar to those seen in malignant hypertension and may include dyspnea, headache, visual disturbances, seizure, pulmonary edema, lower extremity edema, and fundoscopic changes. The presentation of SRC can be identical to that of malignant hypertension, and the proper identification of the patient as having SSc is imperative so that appropriate therapy with ACE inhibitors can be instituted. More than one half of cases of SRC require dialysis; however, many patients can discontinue dialysis within 2 years. It is thus essential that patients continue to receive ACE inhibitors even if renal insufficiency develops, because the disease can correct or be reversed even late into the renal course. Occasionally, SRC presents before the onset of skin changes, which makes the appropriate identification of the patient's disorder and his or her management more challenging.

SRC is characterized by a microangiopathy with anemia and schistocytes on peripheral blood smear, along with thrombocytopenia, renal insufficiency, proteinuria, and active urinary sediment. At presentation SRC may be confused with thrombotic thrombocytopenic purpura, particularly in patients with seizures. Although thrombotic thrombocytopenic purpura may rarely occur in SSc, it is imperative that the diagnosis of SRC be made and ACE inhibition initiated. There is no known role for plasma exchange in the management of SRC.

A variant of SRC termed *normotensive SRC* is characterized by the typical laboratory abnormalities of SRC in the presence of a normal blood pressure and may progress to renal insufficiency and/or the need for dialysis. Normotensive renal crisis occurs most typically in patients who have previously been treated with glucocorticoids, particularly a prednisone dosage (or its equivalent) of more than 15 mg daily.⁷⁶

Renal insufficiency may also occur in patients with an overlap of SSc and systemic lupus erythematosus (SLE) and be caused by an immune-mediated process such as occurs in patients with SLE. Also, cases of antineutrophil

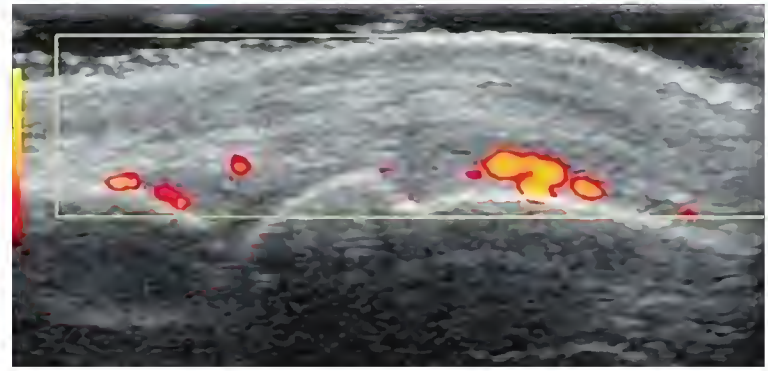


Fig. 142.20 Baseline musculoskeletal sonogram of the second metacarpophalangeal joint. Power Doppler ultrasonography shows positive results with synovial hypertrophy plus effusion. (From Valentini G, Cuomo G, D'Abrascia V, Cappabianca S. A scleroderma patient with swollen and tender joints of both hands. In: Silver RM, Denton CP, editors. *Case studies in systemic sclerosis*. London: Springer-Verlag; 2011, p. 239-50.)

cytoplasmic antibody-associated vasculitis have been reported in SSc and should be considered as an overlap condition with SSc because these patients may have a renal-pulmonary syndrome in addition to SSc.⁷⁷⁻⁷⁹ If an alternative cause to SRC for renal insufficiency is being considered, then renal biopsy may be useful; otherwise, renal biopsy is not necessary to diagnose SRC.

Musculoskeletal involvement

Musculoskeletal symptoms are very common in SSc. The earliest symptoms attributable to scleroderma are arthralgia and myalgia; some patients may develop a true inflammatory arthropathy and/or myopathy. The joints most commonly involved are the PIP, MCP, wrist, and ankle joints. Because of overlying skin thickening it may be difficult to appreciate the presence of joint swelling. Musculoskeletal ultrasonography may be useful in such instances (Fig. 142.20). Progressive skin changes can also cause joint flexion contractures, and these can result in significant debilitation.

Tendon friction rubs are a palpable physical examination sign overlying tendon sheaths, commonly occurring at the finger, wrist, elbow, knee, and/or ankle joints. Tendon sheath discomfort occurs due to inflammation and fibrosis (Figure 142.21). Tendon friction rubs are predictive of dcSSc and are manifest in approximately one third of such patients.

Muscle weakness and generalized fatigue are prominent symptoms. Many patients develop muscle weakness as a result of deconditioning and joint flexion contractures. Proximal muscle weakness may be related to one or more causes; for example, a bland myopathy due to muscle fibrosis or an overlap syndrome of SSc with polymyositis or dermatomyositis with a true inflammatory myopathy. Patients with the latter may test positive for anti-PM-Scl antibody, which is seen more commonly in whites.⁷⁵ The bland myopathy associated with SSc is characterized by a mild increase in creatine kinase level and may or may not show inflammatory changes on electrodiagnostic testing. In some patients, the creatine kinase value is normal but levels of other muscle enzymes (e.g., aldolase) may be elevated. Muscle biopsy generally does not reveal an inflammatory infiltrate. The overlap of SSc with an inflammatory myopathy is, however, characterized by elevated muscle enzyme levels and evidence of inflammatory changes on both electromyography and muscle biopsy.

PSYCHOLOGICAL HEALTH

Patients with SSc often have symptoms of poor psychological health. It has been estimated that nearly 50% of patients have mild depressive symptoms and approximately 17% have moderate to severe depression.⁸⁰ A relationship exists between depression and self-rated disability,⁸⁰ decreased functional status,²³ upper and lower gastrointestinal symptoms,^{23,81} unmarried status,⁸¹ and lower levels of education.^{23,81} Fatigue, chronic pain, and altered personal appearance likely also contribute to depressive symptoms. Each of these symptoms and findings is associated with a poor health-related quality of life. The Center for Epidemiologic Studies Depression Scale is a validated screening tool used to assess for depressive symptoms in patients with SSc.⁸² Clinicians who care for patients with SSc should be highly concerned about the likelihood of depression in their patients, and routine screening is recommended.



Fig. 142.21 Proton-density fat-saturated magnetic resonance image demonstrating fluid surrounding the posterior tibial and peroneal tendons (arrows). (From Khanna D, Khanna PP. A 54-year old woman with pain and stiffness of hands and tendon friction rubs. In: Silver RM, Denton CP, editors. London: Springer-Verlag; 2011, p. 271. Courtesy Dr. T. Pope, Medical University of South Carolina.)

SEXUAL FUNCTION

Sexual dysfunction occurs in both men and women with SSc. Erectile dysfunction occurs in up to 80% of men with SSc and typically begins approximately 3 years after disease onset.⁸³ A reduction in penile blood flow contributes to erectile dysfunction and is due to both endothelial changes in small arteries and corporal fibrosis from excessive collagen deposition.⁸⁴ Altered penile blood flow occurs in the absence of atherosclerotic disease in SSc. Sexual function assessments can be performed by patient interview and enhanced by using a validated questionnaire such as the five-item version of the International Index of Erectile Function.⁸⁵

Sexual dysfunction is less well studied in women with SSc, but patients report symptoms of vaginal dryness, dyspareunia, and vaginal ulcerations, more so after disease onset than before disease onset and also more than patients with other autoimmune diseases.⁸⁶ A significant relationship has been found between sexual dysfunction and gastroesophageal reflux and skin tightness in women with SSc. Decreased libido and decreased number and intensity of orgasms are also reported. Women with SSc experience an early menopause compared with control subjects. It is important for clinicians to consider sexual dysfunction in the health-related quality of life evaluation of patients with SSc.

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SYSTEMIC SCLEROSIS SINE SCLERODERMA

Systemic sclerosis sine scleroderma is a variant of SSc in which the patient has many features of SSc in terms of visceral and/or serologic involvement; however, there is no apparent skin thickening. Such patients nearly always have symptoms of Raynaud phenomenon and test positive for antinuclear antibody (ANA), and they may demonstrate digital pits, telangiectasia, gastroesophageal reflux disease, pulmonary fibrosis, and/or pulmonary hypertension. Results of nailfold capillaroscopy are also typically abnormal, revealing capillary dilatation without avascularity, or the slow phase, typical of patients with lcSSc.

SEROLOGIC FEATURES

Scleroderma is an autoimmune disease characterized by the presence of several autoantibodies. Most patients have a positive ANA test result and, in fact, negativity for ANA is associated with a more severe disease course. It should be noted that many commercial laboratories use immunoassay methods for the detection of ANA, and such assays may yield a relatively high rate of false-negative results on sera of SSc patients. When SSc is suspected it is important to order ANA testing by indirect immunofluorescent assay, preferably using HEp-2 cells as substrate. A truly negative ANA test result in a patient with skin thickening should lead the clinician to consider one of the many causes of pseudoscleroderma, including diffuse fasciitis with eosinophilia, nephrogenic systemic fibrosis, scleromyxedema, sclerodema, and other disorders discussed in Chapters 147 and 170. Alternatively, in the presence of SSc and a negative ANA result a paraneoplastic presentation of SSc should be considered and careful age-appropriate and symptom-related malignancy screening should be performed.

In SSc, the immunofluorescence ANA most commonly has a nucleolar pattern. Positivity for anticentromere antibody is generally seen in patients with lcSSc (20% to 40%). Positivity for anti-Scl-70 antibody is associated with dcSSc and increased risk for the development of ILD. Patients who have an anti-RNA polymerase III antibody have a worse prognosis, show extensive skin thickening with increased frequency of tendon friction rubs, and are more likely to develop SRC, although they have a lower incidence of ILD.^{35,87} The Th/To antibody is associated with lcSSc and pulmonary hypertension, although patients with this autoantibody also may manifest ILD or SRC.⁸⁸ U11/U12-RNP antibody is associated with ILD, often severe; however, tests for this antibody are not yet available for commercial use.⁸⁹

MALIGNANCY

SSc has an increased association with certain malignancies, and as with other autoimmune diseases, it can present as a paraneoplastic syndrome, the latter being associated with a more severe or refractory disease course.⁹⁰ SSc patients, particularly those with underlying pulmonary fibrosis, have an increased risk of lung cancer.^{91,92} As for non-SSc patients who have pulmonary fibrosis, there is an increased risk of development of lung adenocarcinoma. There is some evidence suggesting an increased risk of breast cancer in patients with SSc, but the issue is controversial. Others have found a temporal relationship between the onset of SSc and the diagnosis of breast cancer, although the actual incidence of breast cancer may not be increased.^{92,93} Patients with chronic gastroesophageal reflux are at increased risk of development of Barrett metaplasia, and this then may increase the risk of developing adenocarcinoma of the esophagus.

The treatment of some malignancies requires consideration of irradiation. Historically there have been great concerns about the use of radiation to treat patients with SSc because of the resulting skin fibrosis that can occur after therapy. Newer treatments including implantable radiation pellets do not seem to pose additional risk.

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Etiology and pathogenesis of systemic sclerosis

■ JOHN VARGA ■ ROBERT LAFYATIS

- Systemic sclerosis (SSc) is an acquired chronic connective tissue disease characterized by autoimmunity, vascular damage, and tissue fibrosis.
- The cause of SSc is unknown.
- Multiple genes contribute to risk for SSc, but their effects are modest.
- Vascular injury is an early and primary event that results in obliteration of multiple small vessels and consequent tissue hypoxia.
- Specific autoimmunity and evidence of innate immunity are prominent in target organs and in serum.
- Interstitial and perivascular fibrosis occurs in the skin, lungs, heart, and other internal organs. Fibrosis in these tissues is resistant to therapy and contributes to morbidity and mortality.

INTRODUCTION

The cause of systemic sclerosis (SSc) is unknown, but environmental influences and multiple genetic factors contribute to disease susceptibility and clinical manifestations. The pathogenesis of SSc encompasses interrelated yet distinct vascular, inflammatory, and fibrotic processes. Although inflammation and autoimmunity are prominent in early-stage disease and fibrosis and vascular insufficiency dominate in late-stage disease, considerable patient-to-patient variability exists in the relative contribution of these three pathomechanistic processes to the clinical manifestations of SSc.

Investigation using *in vitro* cell culture, *in vivo* disease modeling with genetically engineered strains of mice, genome-wide gene expression profiling, proteomics and transcriptomics, and the application of “systems biology” approaches is yielding an integrated picture of pathogenesis by annotating the cell types, signaling pathways, molecules, genes, and epigenetic markers that are deregulated in SSc. Injury in genetically predisposed individuals causes endothelial cell perturbation, vascular damage, and concurrent activation of both the innate and adaptive immune systems. Recurrent or sustained injury results in persistent immune responses and progressive obliterative vasculopathy with consequent tissue hypoxia in multiple organs. In some patients, unchecked activation of fibroblasts leads to excessive accumulation of collagen and extracellular matrix (ECM) molecules. Differentiation of bone marrow–derived mesenchymal progenitor cells and resident fibroblasts, pericytes, and vascular cells into biosynthetically active myofibroblasts further exacerbates the fibrogenesis. Over time, vascular insufficiency, tissue fibrosis, and matrix rigidity disrupt the architecture of affected organs and result in their failure. The progressive and intractable nature of these pathogenetic processes accounts for the poor prognosis of patients with SSc.

ETIOLOGY

Multiple genetic factors contribute to disease susceptibility. The etiology of SSc is unknown, although small studies have implicated infections, environmental exposures, occupational factors, and drugs as potential risk factors.

Defining the genetic contribution to systemic sclerosis

The contribution of genetic background to SSc risk is uncertain. One informative study examining the relative risk for SSc in first-degree family members and siblings indicated a 13- and 15-fold increase, respectively. In addition, certain ethnic groups have an increased prevalence of SSc. Despite these familial and ethnic associations, twin studies have not confirmed a strong genetic basis for familial and ethnic aggregation.

A recently completed GWAS analysis confirmed the major histocompatibility complex (MHC), as well as IRF5, and STAT4 gene regions as genetic risk factors for SSc.¹ Additional genetic loci identified in this GWAS included IRF4, CDH7, and CD247. The CD247 locus encodes a T-cell receptor subunit that participates in regulation of the immune response and could have a direct role in the pathogenesis of SSc. It is notable that the HLA region, STAT4, and IRF5 loci encode proteins involved in immune responses, and variants at these loci are also associated with other autoimmune conditions. This lends support for the concept of shared pathogenetic drivers of SSc and other autoimmune diseases and highlights a strong autoimmune component underlying the pathogenesis of SSc.

Gene expression in systemic sclerosis: distinct molecular subsets

Application of comprehensive genome-wide profiling of gene expression has led to the emergence of new paradigms of disease classification. The two major clinical patterns of SSc, limited and diffuse cutaneous disease, can readily be distinguished by using clustering software that looks for patterns of altered gene expression in skin from patients with SSc.¹ This “unsupervised clustering” of an identified “intrinsic classifier” set of genes shows further disease heterogeneity at the molecular level (Fig. e143.1). Best defined is the division of patients with diffuse cutaneous SSc into two subgroups based on the expression of distinct gene clusters that prominently include gene expression “signatures” indicative of proliferation or inflammation. These molecular disease subgroups appear to be stable over time, thus suggesting that they represent underlying disease heterogeneity rather than simply different stages of the same process. Molecular heterogeneity in SSc might underlie the observed differences in clinical manifestations, rates of progression, and responsiveness to therapies. Gene profiling of lesional tissue might also be a sensitive tool for detecting the effects of treatment.

Infectious agents

Although infectious agents have long been suspected as being triggers in SSc, no infection has convincingly been linked to pathogenesis. A “pan-bacteria” polymerase chain reaction–screening approach found no evidence of persistent bacterial infection in the skin in 18 patients with SSc. Some patients with SSc have serum antibodies directed against the UL83 and UL94 protein epitopes of human cytomegalovirus (hCMV). Anti–topoisomerase I antibodies can cross-react with hCMV-derived proteins, thus suggesting molecular mimicry as a mechanism linking hCMV infection and SSc. Because antibodies to UL94 can activate fibroblasts and induce endothelial cell apoptosis *in vitro*, the anti-CMV immune response might have a causative role in vascular damage and fibrosis. In addition, infection with CMV has been implicated in allograft vasculopathy, a common complication of solid organ transplantation characterized by neointima formation and smooth muscle proliferation, similar to the obliterative vasculopathy of SSc, and can stimulate the synthesis of CTGF (CCN2). Human parvovirus B19 infection has also been documented in some cases of SSc.



Genetic contributions

Several associations have been reported when using a target gene approach. Early studies showed relatively weak associations with DRB1*11 and DRB1*0301. However, other studies have suggested that this is actually due to an association with HLA-DQA1*0501, which is in linkage disequilibrium with DRB1*11 and DRB1*0301. A C→T missense single nucleotide polymorphism (SNP) in *PTPN22*, which is associated with a variety of related autoimmune diseases, was seen more frequently in some studies in SSc patients. An SNP in *IRF5*, another gene associated with autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjögren syndrome, has recently been associated with SSc. Replication cohorts have failed to confirm certain SSc associations with candidate genes. A prominent example is an SNP in the promoter region of the gene for connective tissue growth factor (CTGF). In another example, SSc-associated polymorphisms in *SPARC*, identified through microarray studies of fibroblasts from SSc patients, were not confirmed in a subsequent study. Potential explanations for such discrepancies might include ethnic differences in the cohorts studied. The assembly of large DNA banks from patients with SSc and control subjects is now permitting rapid confirmation or rejection of genetic associations. Whole exome sequencing and genome-wide association studies (GWASs) making use of large DNA repositories should clarify important genetic associations in SSc.

BOX 143.1 ENVIRONMENTAL AGENTS AND DRUGS POTENTIALLY IMPLICATED IN TRIGGERING SCLERODERMA-LIKE SYNDROMES

Chemicals	Drugs
Silica	Bleomycin
Heavy metals	Pentazocine
Mercury	Taxol
Organic chemicals	Cocaine
Vinyl chloride	
Benzene	Dietary supplements/appetite suppressants
Toluene	L-Tryptophan (contamination)
Trichloroethylene	Mazindol
	Fenfluramine
	Diethylpropion

Environmental exposure, drugs, and radiation

The occurrence of temporal or geographic clusters suggests shared environmental exposures causing disease. Epidemiologic investigations have generally failed to substantiate putative clusters of SSc. In contrast, well-documented outbreaks of SSc-like illnesses have been reported. As an example, the toxic oil syndrome in Spain was linked to the ingestion of contaminated rapeseed cooking oil. Contaminated lots of L-tryptophan dietary supplements were implicated in the epidemic of eosinophilia-myalgia syndrome (EMS) in 1989, although the precise identity of the contaminant was never fully established. Even though the EMS epidemic largely subsided after withdrawal of dietary L-tryptophan from the market, sporadic cases continue to occur.² Recently, exposure to certain gadolinium-containing radiologic imaging dyes was implicated in causing nephrogenic fibrosing syndrome in patients with chronic kidney disease. Scleroderma-like skin induration, with or without multisystem involvement and evidence of autoimmunity, is prominent in each of these toxicoepidemic syndromes; however, clinical, histopathologic, and laboratory features readily distinguish them from SSc. Men with exposure to silica or working in construction-related occupations have an increased incidence of SSc. Other occupational exposures involve polyvinyl chloride, trichloroethylene, and organic solvents. Anecdotal reports allege an association between SSc and exposure to pesticides, hair dyes, and industrial fumes.

Drugs implicated in SSc-like illnesses include the chemotherapeutic agent bleomycin, as well as pentazocine and cocaine. Use of appetite suppressants has been linked to the development of pulmonary arterial hypertension (PAH). An apparent increase in SSc incidence in women who underwent silicone breast augmentation raised alarm regarding a causal association. Large-scale epidemiologic surveys, however, failed to confirm increased risk for connective tissue diseases associated with breast implants. Radiation treatment of malignant neoplasms has been linked to both *de-novo* SSc and exacerbation of preexisting SSc. Some of the environmental agents and drugs potentially associated with SSc are listed in [Box 143.1](#).

PATHOLOGY

The two pathologic hallmarks of SSc are obliterative microvasculopathy and interstitial/vascular fibrosis in multiple organs.³ Infiltration of target organs by inflammatory cells is often seen in early-stage disease, particularly around blood vessels. In the skin, the infiltrates are composed primarily of CD4+ lymphocytes and monocytes ([Fig. 143.1](#)), whereas CD8+ lymphocytes predominate in the lungs.

Vascular pathology

Vascular injury and endothelial cell activation are the earliest—and possibly primary—pathogenetic events in SSc. Histologic evidence of vascular damage precedes fibrosis and can be detected in clinically affected as well as unaffected skin. Expansion of the intimal layer in small and medium-sized arteries ([Fig. 143.2](#)) is a striking pathologic finding that SSc shares with chronic allograft arteriopathy. Intimal proliferation is due to myointimal cell proliferation and migration and collagen deposition. The basement membranes are thickened and reduplicated. In addition to structural changes, evidence of impaired fibrinolysis and increased levels of circulating von Willebrand factor are prominent. Endothelial injury causes platelet aggregation with ensuing release of platelet-derived growth factor (PDGF), serotonin, and endothelin-1 (ET-1) and endothelial cell apoptosis. Vasculitis

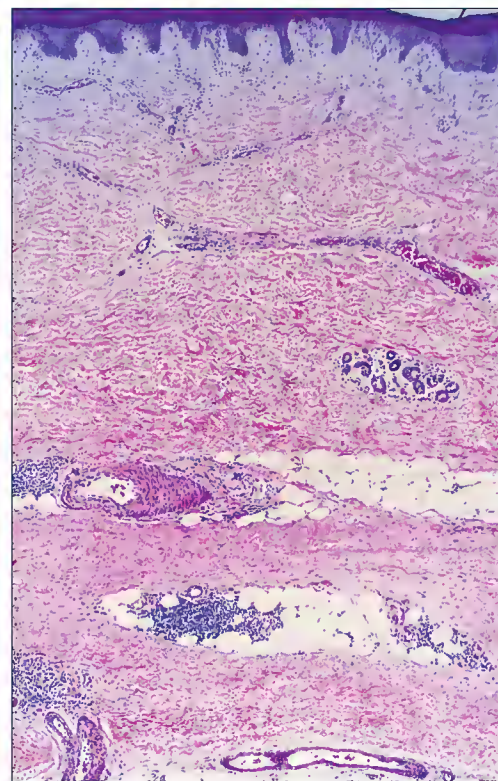


Fig. 143.1 Inflammatory infiltrate in the dermis. This skin biopsy specimen shows a perivascular mononuclear cell inflammatory infiltrate. Note the expansion of the collagenous reticular dermis, encasement of sweat glands, and loss of subcutaneous adipose tissue (hematoxylin-eosin).

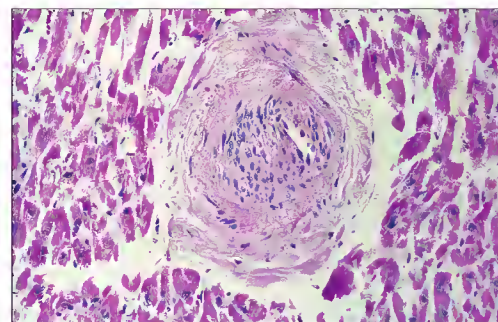


Fig. 143.2 Vascular changes in the myocardium. An intramyocardial artery shows intimal proliferation and marked narrowing of the vascular lumen. Similar findings occur in small arteries in multiple vascular beds. There is also evidence of myocarditis in this specimen, with inflammatory cells located between myocardial cells (hematoxylin-eosin).

or immune complex deposition in vessel walls is uncommon. In advanced SSc, fibrin deposition and perivascular fibrosis cause progressive luminal occlusion. Widespread obliterative vasculopathy of small and medium-sized arteries in multiple vascular beds ultimately results in vascular rarefaction and chronic tissue hypoxia.

Tissue fibrosis

Fibrosis is defined by excessive tissue accumulation of type I collagen and other fibrillar collagens, fibronectin, elastin, cartilage oligomeric protein (COMP), periostin and osteopontin, and proteoglycans such as decorin, fibromodulin, and lumican, as well as matricellular molecules such as SPARC. The process is associated with increased stiffness and loss of compliance of the ECM. Fibrosis disrupts tissue architecture, which results in progressive dysfunction and eventual failure of target organs.

Organ-specific pathologic findings**Skin**

Fibrosis of the skin leads to expansion of the dermis and obliteration of the hair follicles, sebaceous and sweat glands, and other skin appendages.

Collagen fiber accumulation is most prominent in the reticular (deep) dermis and gradually invades the subjacent adipose layer with entrapment of fat cells. Skin biopsy specimens in early stages of SSc may reveal perivascular cellular infiltrates composed of T lymphocytes, monocytes, and less commonly, mast cells⁴ and eosinophils. The number of myofibroblasts, a contractile cell that is intermediate between fibroblasts and smooth muscle cells, is increased in the lesion. With progression of disease, the skin atrophies with thinning of the epidermis, effacement of the rete pegs, and accumulation of compact hyalinized collagen bundles in the dermis (Fig. 143.3). The subcutaneous adipose layer is shrunk or may be completely absent. Evidence of tissue hypoxia because of the paucity of dermal capillaries can be found even in clinically uninvolved “normal” skin.

Lungs

Histologic evidence of lung injury is common in all forms of SSc. The early stages are characterized by patchy infiltration of the alveolar walls by lymphocytes, plasma cells, macrophages, and eosinophils. With disease progression, interstitial fibrosis (Fig. 143.4), often coexisting with vascular damage within the same lesions, predominates. Intimal thickening of the pulmonary arteries, best seen with elastin stain, underlies PAH and at autopsy is

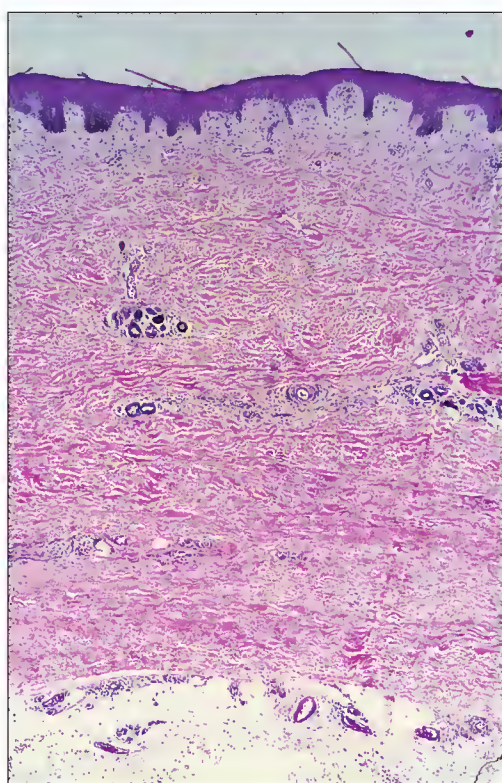


Fig. 143.3 Excess dermal collagen deposition in a patient with established systemic sclerosis. Note the marked thickening and sclerosis of the dermis and scant perivascular inflammatory infiltrates. There is entrapment of cutaneous glands and obliteration of subcutaneous adipose layers (hematoxylin-eosin).

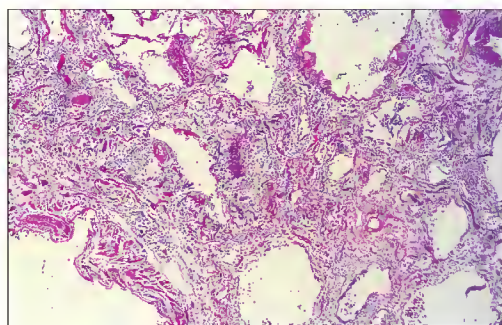


Fig. 143.4 Interstitial lung fibrosis in systemic sclerosis. The alveolar septa is markedly thickened because of the accumulation of connective tissue. An inflammatory cell infiltrate is present. Note the dramatic disruption of normal lung architecture (hematoxylin-eosin).

frequently accompanied by pulmonary emboli and myocardial fibrosis (Fig. 143.5). The most characteristic histologic pattern of SSc lung fibrosis is nonspecific interstitial pneumonitis (NSIP) associated with moderate interstitial inflammation and fairly uniform distribution of fibrosis. Less commonly seen is the usual interstitial pneumonia (UIP) characterized by scattered fibroblastic foci, a pattern is associated with a worse prognosis. Progressive septal thickening impairs gas exchange and contributes to worsening of pulmonary hypertension. Extensive pulmonary fibrosis may predispose to lung carcinoma.

Gastrointestinal tract

Pathologic changes can occur at any level of the gastrointestinal tract from the mouth to the rectum. The esophagus is virtually always affected, with fibrosis in the lamina propria, submucosa, and muscular layers and characteristic vascular lesions. Chronic reflux is often complicated by esophageal inflammation, ulcerations, and stricture formation. Barrett esophagus with metaplasia of the squamous lining of the esophagus into columnar epithelium develops in up to a third of patients.

Kidneys

Acute scleroderma renal crisis is characterized histologically by vascular changes indistinguishable from other forms of malignant hypertension. The most prominent changes occur in the small interlobular and arcuate renal arteries and consist of reduplication of the elastic lamina, marked intimal proliferation, fibrinoid changes, and narrowing and obliteration of the lumen, commonly accompanied by microangiopathic hemolysis and degeneration of tubular cells (Fig. 143.6). A study examining whether renal biopsy findings could predict the outcome of scleroderma renal crisis found that patients with a poor outcome had more extensive vascular thrombosis and glomerular collapse than did those in whom renal function was restored. Scleroderma renal crisis can clinically resemble thrombotic thrombocytopenic purpura (TTP), but in contrast to TTP, the profound reduction in serum levels or activity of von Willebrand factor cleaving protease (ADAMTS-13) does not occur in SSc. The characteristic histologic features of scleroderma renal crisis are illustrated in Figure 143.7.

Heart

Even though only 25% of patients with SSc have clinical evidence of myocardial disease, cardiac abnormalities are found in up to 80% at autopsy. The characteristic myocardial contraction band necrosis is thought to reflect repeated ischemia-reperfusion. Patchy myocardial fibrosis distributed throughout both ventricles is common and often accompanied by cardiac hypertrophy (Fig. e143.2). Significant interstitial and perivascular fibrosis may occur in the absence of clinically evident heart involvement. Skeletal muscle inflammation is frequent in SSc and can be accompanied by acute myocarditis.

Pathologic findings in other organs

Fibrosis of the thyroid glands is common. Broad bands of fibrous tissue are seen, along with atrophy and obliteration of the follicles, in the absence of inflammation. Abnormal thyroid function test results and antithyroperoxidase autoantibodies are frequent. Erectile dysfunction may be an initial manifestation of SSc. Pathologic examination shows extensive proliferative and obliterative changes in the penile blood vessels. Fibrosis of the salivary and lacrimal glands in the absence of inflammation may be associated with Sjögren syndrome. Synovial biopsy specimens show fibrosis and characteristic vascular changes in the small arterioles.

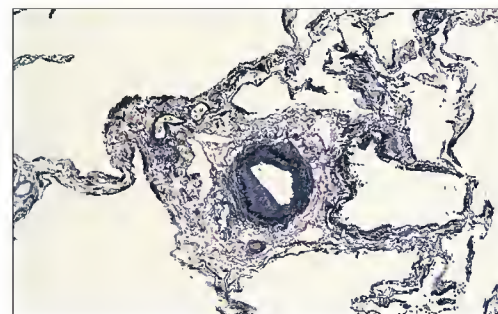


Fig. 143.5 Pulmonary artery lesion. Elastin stain demonstrates intimal thickening (accumulation of matrix on the luminal side of the elastic lamina) in a small pulmonary artery. Note only mild interstitial fibrosis in this specimen from an individual who died of pulmonary hypertension associated with limited cutaneous systemic sclerosis.

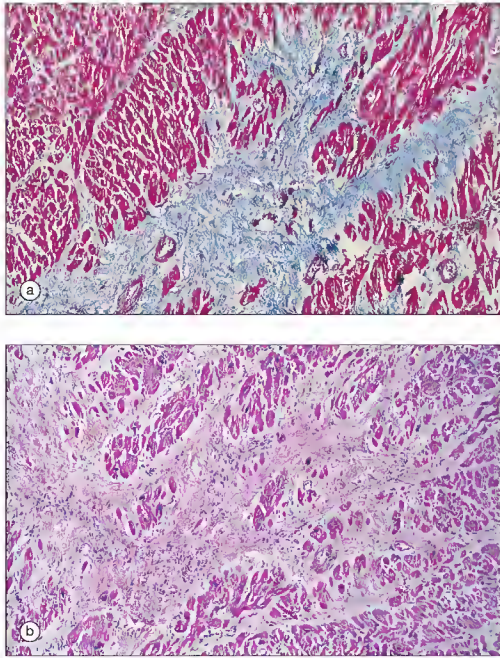


Fig. e143.2 Myocardial fibrosis in systemic sclerosis. (a) Note the dramatic increase in perivascular and perimysial accumulation of collagen (blue with the Masson trichrome stain). (b) Fibrosis involving the conducting system, which can cause heart block.

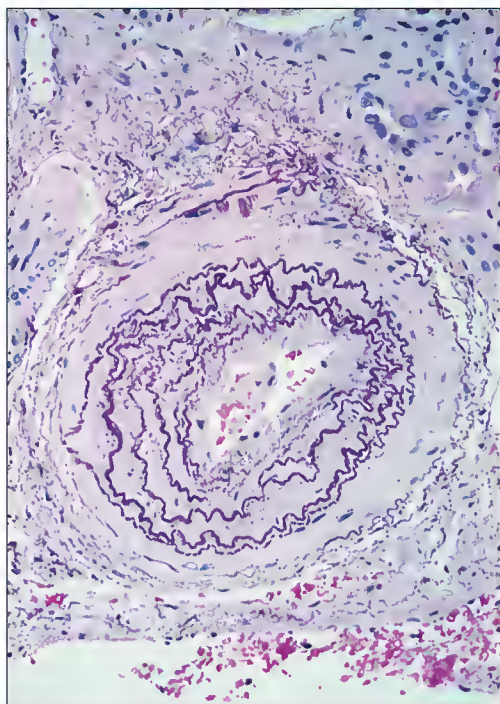


Fig. 143.6 Renal blood vessel in systemic sclerosis. Luminal narrowing is present as a result of intimal proliferation in a renal artery. Note the extensive reduplication of the elastic lamina and concentric layering in the media (onionskin lesion) (elastin stain).

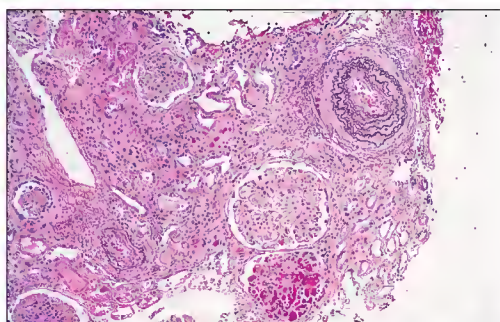


Fig. 143.7 Renal scleroderma. A kidney biopsy specimen shows vascular disease (bottom left and upper right) with luminal narrowing and reduplication of the elastic lamina. One glomerulus (top) shows fibrinoid deposition (darker pink color), indicative of thrombosis.

ANIMAL MODELS

Various experimental manipulations and inbred mouse strains have been studied as models of SSc. None of these putative disease models recapitulates the full extent of the disease attributes listed in Table 143.1, such as the overlapping microvascular/immune/fibrotic pathology, phenotype-specific autoantibodies, temporal and spatial evolution of fibrotic lesions, and progressive multiple-organ damage. Therefore, observations from currently used mouse models of SSc cannot be readily extrapolated to human disease. Contemporary mouse models fall into three categories: (1) spontaneous mutations or genetic manipulations giving rise to mouse strains with heritable scleroderma-like traits, such as skin induration (tight skin mouse [Tsk1], tight skin 2 [Tsk2/+], mice, transforming growth factor- β [TGF- β] receptor transgenic animals); (2) inducible models in which scleroderma is elicited by exposure to chemicals, particularly bleomycin; and (3) transplantation of HLA-mismatched immunocompetent cells resulting in chronic graft-versus-host disease (GVHD) with scleroderma-like skin changes (Table 143.2). Details on the heritable and bleomycin models are presented in the supplementary material.

Immunologic models

Topoisomerase I immunization in mice

Subcutaneous injection of recombinant topoisomerase I in mice results in the time-dependent development of fibrotic changes in the skin and lungs.⁹

TABLE 143.1

Key traits of systemic sclerosis*

Disease attribute	Comment
Disease course	Insidious onset in adults, chronic and generally progressive course; female preponderance
Skin induration	Starts distally in the digits (sclerodactyly), advances centripetally; symmetrical and widespread Early dermal inflammation, followed by fibrosis, most prominent in the reticular dermis Loss of adnexal structures Subcutaneous adipose atrophy Late-stage epidermal thinning, calcinosis cutis
Internal organs	Progressive and irreversible fibrotic damage in the lungs, intestinal tract, heart, and other organs
Vascular involvement	Early vascular endothelial cell activation, microvascular obliterative vasculopathy, subintimal proliferation and perivascular fibrosis, resulting in Raynaud phenomenon, cutaneous telangiectasia, pulmonary arterial hypertension, ischemic digital ulcers
Inflammation/ autoimmunity	Early perivascular infiltration in the skin and lungs by T cells, B cells, monocyte/macrophages; dendritic cells; type 2-skewed immune response; innate immune response; SSc-specific autoantibodies

*An ideal animal model of systemic sclerosis should recapitulate some or all of these features.

Fibrosis develops only when the antigen is administered together with complete Freund adjuvant, which is required to generate a strong IL-6 response; indeed, IL-6–null mice were resistant to fibrosis. Circulating antibodies to topoisomerase I develop in topoisomerase I-immunized mice. This novel mouse model recapitulates a scleroderma-specific antigen driving diffuse fibrosis and autoimmunity.

Type V collagen immunization in rabbits

Immunization of New Zealand white rabbits with type V collagen in Freund adjuvant results in scleroderma-like skin changes. Over a period of 3 months, diffuse cutaneous fibrosis and mild interstitial lung disease develop in the rabbits, as well as changes in the pulmonary microvasculature. Moreover, antinuclear and antitopoisomerase autoantibodies also develop. Although the role of type V collagen in SSc is not well understood, elevated type V collagen expression has been documented in the lesional dermis in patients with SSc and correlates with the extent of skin involvement.

Sclerodermatous chronic graft-versus-host disease

Transplantation of bone marrow or spleen cells from a donor mouse (commonly the B10.D2 strain) into irradiated recipient mice (Balb/c) that differ at minor histocompatibility loci results in sclerodermatous GVHD. Dermal fibrosis develops 14 to 21 days after transplantation. In the early stage, skin infiltration with donor T cells and monocytes/macrophages is prominent. DNA microarray analysis of the skin showed overexpression of both Th1 and Th2 cytokines, TGF- β , and monocyte chemoattractant protein-1 (MCP-1). Induction of inflammation and fibrosis requires donor CD4+ naive T cells and either CD80/86-expressing donor or host antigen-presenting cells.

PATHOGENESIS

Overview of immunity, vascular injury, and fibrosis

The pathogenesis of SSc involves a unique triad of vascular damage, innate and adaptive autoimmunity, and generalized fibrosis. Even though each of these pathomechanistic processes contributes to disease burden, their individual importance varies from one patient to another, with some manifesting primarily vascular complications and others suffering predominantly fibrotic complications. This clinical heterogeneity and diverse outcomes of SSc are likely to be a reflection of the variable contributions of the three pathomechanistic processes in individual patients. Figure 143.8 presents an overview of pathogenesis in which the dynamic interplay between the distinct processes that are responsible for initiating, amplifying, and sustaining tissue damage in SSc is illustrated.

Heritable animal models of scleroderma

Tight skin 1 mouse

The *Tsk1*^{+/+} mouse was described more than 40 years ago as a spontaneously occurring mutant. The skin in these mice is thickened, especially in the intercapsular region, and is firmly bound to the underlying muscle. Histologic examination shows marked fibrosis in the hypodermis but no changes in the dermis. There is no significant difference in dermal collagen content between *Tsk1*^{+/+} mice and age-matched wild-type controls and no evidence of active TGF- β signaling in the skin. In contrast, substantial changes are noted in the expression of genes coding for microfibrillar proteins and Wnt, bone morphogenetic protein (BMP), and CCN3 signaling. *Tsk1*^{+/+} mice have no vasculopathy, and emphysema-like changes develop rather than pulmonary fibrosis. The *Tsk* mutation is an in-frame duplication of exons 17 to 40 of the fibrillin-1 gene that gives rise to an abnormally large molecule.⁵ Other fibrillin-1 gene mutations are associated with the fibrillinopathies, a family of developmental disorders that includes stiff skin syndrome and Marfan syndrome. A Marfan-like skeletal phenotype was described in *Tsk1*^{+/+} mice.⁶ Fibrillin-1 is a connective tissue microfibril that regulates elastic fiber assembly, binds to latent TGF- β binding protein 1 (LTBP-1) and LTBP-4, and controls the bioactivity of TGF- β . Marfan syndrome and a transgenic model of Marfan syndrome in mice are both associated with perturbed TGF- β signaling, which—at least in the mouse—can be reversed by pharmacologic TGF- β antagonism with losartan.⁷

Tight skin 2 mice

Tsk2^{+/+} mice have an autosomal dominant mutation mapped to chromosome 1; however, neither the genetic locus nor the underlying molecular defect is currently known. By 2 weeks of age, *Tsk2*^{+/+} mice have significant skin fibrosis. In contrast to *Tsk1*^{+/+} mice, fibrosis is prominent in the dermis and is accompanied by elastic fiber deposition and loss of subcutaneous adipose tissue. *Tsk2*^{+/+} mice have circulating antinuclear antibody and anticentromere, anti-topoisomerase I, and anti-RNA polymerase II autoantibodies. A modest increase in the perivascular adventitial layer has been detected, but the hallmark obliterative vasculopathy of SSc is absent. In contrast to *Tsk1*^{+/+} mice and human SSc, no pulmonary pathology is seen in *Tsk2*^{+/+} mice. Although early reports described mononuclear cell infiltrates in the dermis, a recent study was unable to reproduce these findings.

Constitutive transforming growth factor- β receptor signaling

A transgenic mouse strain expressing a constitutively active mutant TGF- β type I receptor, T β R1(ca), represents an important advance in modeling SSc.⁸ Crossing a knock-in mouse harboring T β R1(ca) with a transgenic mouse carrying fibroblast-specific inducible Cre recombinase generates T β R1(ca) Cre-ER(T) mice which, on subcutaneous injection of tamoxifen, show constitutive T β R1 activity in fibroblasts but not other cell types. By 5 months of age, diffuse skin fibrosis, loss of subcutaneous fat deposits, and excessive collagen deposition in the walls of small pulmonary arteries develop in the transgenic mice.

Inducible animal models of scleroderma

Bleomycin-induced scleroderma

The most widely used mouse model of scleroderma involves repeated subcutaneous injection of the chemotherapeutic agent bleomycin. Dermal sclerosis accompanied by epidermal hypertrophy and atrophy of subcutaneous adipose tissue develops in these mice. Although skin induration is confined to the injected area, fibrotic changes and increased collagen deposition also occur in the lungs and kidneys. Dermal fibrosis at 3 weeks is associated with myofibroblast accumulation and deposition of collagens, fibronectin, osteopontin and hyaluronic acid (Fig. e143.3). Lesional tissues show evidence of active TGF- β , CTGF, and Wnt signaling and elevated expression of the early

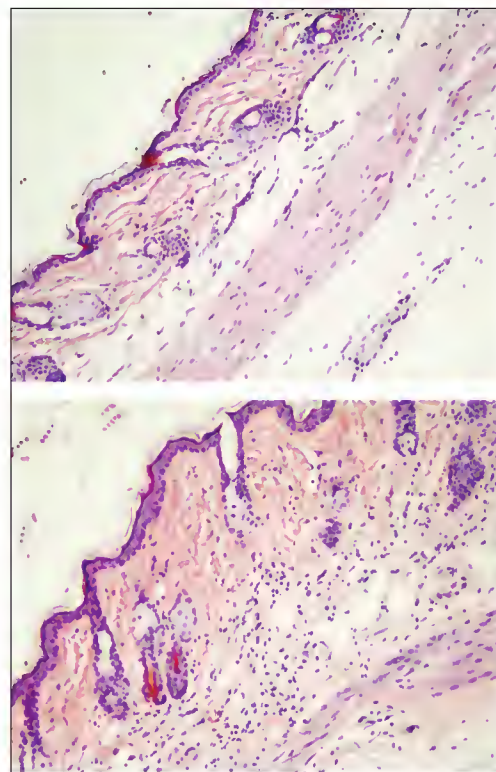


Fig. e143.3 Murine model of scleroderma: bleomycin-induced skin fibrosis. Subcutaneous injections of bleomycin induces dermal fibrosis. Note the hyperproliferative changes in the epidermis, thick and sclerotic dermis with obliteration of dermal adnexal structures, and loss of the subcutaneous adipose layer (upper panel, phosphate-buffered saline; lower panel, bleomycin; hematoxylin-eosin).

response gene *Egr-1*. Reactive oxygen species (ROSs) play a role in triggering inflammation and skin fibrosis, and subcutaneous injection of HOCl, which generates copious amounts of ROSs, mimics the fibrotic response elicited by bleomycin. Bleomycin-induced fibrosis was significantly attenuated in mice with deleted Smad3, β -catenin, or *Egr-1* and in transgenic mice overexpressing the Wnt antagonist Dickkopf-1, thus highlighting the important roles of TGF- β and Wnt signaling in pathogenesis.

Bleomycin-induced tissue fibrosis is mediated via a type 2 immune response, and more severe fibrosis develops in mice with targeted deletion of the type 1 transcription factor T-bet. Although a recent report suggested that CD4⁺ T cells can transfer disease in bleomycin-injected mice, dermal fibrosis can be induced in immunodeficient nude and Rag2^{-/-} mice. These results indicate that T cells are not required for the development of fibrosis by bleomycin.

Intratracheal administration of bleomycin is widely used to model lung fibrosis in rodents. The pulmonary lesions develop rapidly and show a predominantly bronchiolocentric distribution pattern similar to UIP, although the relevance of this model for interstitial lung disease has been questioned. Type 2 helper T-cell (Th2) skewing of the immune response is regulated by the transcription factor GATA3. An exaggerated form of lung fibrosis with increased TGF- β but decreased levels of interferon- γ (IFN- γ) develops in mice transgenic for GATA3 after bleomycin treatment. In mice overexpressing the Th2 cytokine interleukin-13 (IL-13), pulmonary fibrosis mediated via activation of TGF- β *in vivo* develops.

TABLE 143.2
Selected mouse models of scleroderma

Model*	Aspects of the pathogenesis of systemic sclerosis				Key features
	Vasculopathy, vascular activation	Inflammation	Autoimmunity	Fibrosis	
Naturally occurring					
Tsk1	–	–	+	+	Duplication mutation in the fibrillin-1 gene
Tsk2	–	+	+	+	Unknown genetic defect; early cutaneous inflammatory cell infiltrate
Induced					
Bleomycin (subcutaneous)	+	+	+	+	Production of reactive oxygen species, monocytic inflammation, TGF-β activation, topo I-specific autoimmunity. Progressive fibrosis in the skin; the lung and kidneys also affected
Topoisomerase I immunization	–	+	+	+	Freund complete adjuvant required for the phenotype
Angiotensin II	+	+	-	+	Fibrosis develops in skin and multiple organs
Collagen V immunization (rabbit)	+	+	+	+	Rabbits develop antibodies to type V collagen
GVHD (B10.D2 vs. Balb/c)	+	+	–	+	Transfer of spleen cells from B10.D2 mice into irradiated Balb/c mice results in chronic GVHD and fibrosis
GVHD (B10.D2 vs. Rag-2–/–)	+	+	+	+	Transfer of spleen cells into Rag-2-null mice results in systemic fibrosis, inflammation, autoantibodies
Transgenic					
Fibroblast-specific constitutively active TβRI	+	+	–	+	Expression of constitutively active mutant type I TGF-β receptor in fibroblasts causes tissue fibrosis
Wnt10b expression in adipocytes	–	–	–	+	Prominent dermal fibrosis and disappearance of intradermal adipose tissue
*All animal models use mice, except for the type V collagen immunization model, which uses rabbits. GVHD, graft-versus-host disease; TGF-β, transforming growth factor-β; TβRI, TGF-β receptor type I.					

*All animal models use mice, except for the type V collagen immunization model, which uses rabbits. GVHD, graft-versus-host disease; TGF- β , transforming growth factor- β ; T β RI, TGF- β receptor type I.

Fibrosis

Fibrosis is due to deregulated synthesis of and intermolecular interactions among collagens and other ECM macromolecules. Progressive buildup of biochemically and mechanically abnormal connective tissue disrupts tissue architecture and function, which accounts for much of the morbidity and mortality associated with SSc.

In skin fibrosis, a hallmark of SSc, the relative proportions of the main fibrillar collagens (types I and III) are comparable to those in healthy skin. In contrast, the nonfibrillar type VII collagen, which is normally restricted to the basement membrane, is abundant throughout the lesional dermis. Fibronectin is a 220-kDa modular matrix protein with important functions in fibroblast attachment, spreading, and locomotion. An alternately spliced variant of fibronectin that includes the extra domain A (fibronectin-EDA [Fn-EDA]) is required for myofibroblast differentiation and functions as both a structural protein and a signaling molecule. In addition, levels of type V and type VI collagen, hyaluronic acid, COMP (an 86-kDa glycoprotein that regulates collagen fibrillogenesis), lysyl oxidase, and lysyl hydroxylase (PLOD2, an enzyme that catalyzes extracellular collagen cross-linking) are elevated. Recent studies of SSc using DNA microarray technology have revealed strikingly altered patterns of gene expression in the skin (see Fig. e143.1). Many genes that encode collagens and other ECM components (SPARC and COMP) or signaling molecules (TGF- β , CTGF [CCN2], and Wnt) are elevated in comparison to healthy skin. Overexpression of COMP, a protein normally found in cartilage and tendons but not in skin, was also confirmed by immunohistochemistry. Moreover, serum levels of COMP correlate with both the clinical skin score and survival. Because COMP catalyzes collagen fibrillogenesis and enhances cell survival, its upregulation in SSc may be important in the development of fibrosis. The number of genes differentially expressed between normal and SSc biopsy specimens is much greater in skin samples than in explanted dermal fibroblasts, thus indicating time-dependent “extinction” of the activated gene expression in fibroblast cultures. Remarkably, microarray studies have consistently shown that the gene expression profile in SSc fails to distinguish clinically involved and uninvolved skin.

Pathogenesis of fibrosis: cellular and molecular determinants

Fibrosis is characterized by replacement of normal tissue architecture with compact, mechanically stressed, rigid connective tissue. The normal ECM

is composed of the cellular compartment, with both resident cells and circulation-derived infiltrating cells, and acellular connective tissue, which consists of fibrillar and nonfibrillar collagens, fibronectin, SPARC, proteoglycans, elastins, fibrillins, COMP, and adhesion molecules.¹⁰ A major function of the ECM is sequestration of growth factors (e.g., TGF- β) and matricellular proteins (e.g., CCN2/CTGF) in a biologically latent form. The excessive accumulation of connective tissue results from overproduction by activated mesenchymal cells that are responding to soluble molecules, the surrounding ECM, hypoxia, cell-cell interactions, or mechanical cues. Impaired connective tissue turnover and expansion of the biosynthetically activated fibroblast pool further exacerbate the pathologic fibrogenesis.

Cellular determinants of fibrosis

Fibroblasts

Fibroblasts are versatile tissue-resident mesenchymal cells. Fibroblasts derived from different anatomic sites display highly divergent patterns of gene expression that are faithfully retained over time. This “positional memory” is maintained by the distribution of Hox genes called the Hox code.¹¹ In response to extracellular signals, resident fibroblasts or their progenitor cells are induced to migrate and proliferate; produce collagens and other connective tissue molecules; adhere to, contract, and remodel the ECM; secrete growth factors, cytokines, and chemokines; express surface receptors; and differentiate into apoptosis-resistant myofibroblasts. In contrast to the physiologic response to tissue injury in which the fibroblast repair program is tightly controlled and self-limited, pathologic fibrosis is characterized by unopposed fibroblast activation.

Myofibroblasts

The pool of biosynthetically activated effector cells responsible for pathologic matrix accumulation in lesional tissues is expanded through transdifferentiation of differentiated resident cells and influx of circulation-derived mesenchymal progenitor cells.¹² Myofibroblasts are α -smooth muscle actin-positive specialized cells that arise from resident mesenchymal cells in response to TGF- β and Fn-EDA.¹³ Their primary physiologic role is contraction of early granulation tissue during wound healing, where myofibroblasts are detected transiently and then disappear via apoptosis. In contrast, pathologic fibrogenesis is characterized by the persistence of myofibroblasts in lesional tissue, which results in an excessively contracted chronic scar.¹⁴ Myofibroblast contraction itself leads to activation of latent TGF- β , liberation of it from the matrix, and further stimulation of myofibroblast

OVERVIEW OF SYSTEMIC SCLEROSIS PATHOGENESIS: INTEGRATING VASCULAR, IMMUNE, AND FIBROTIC PROCESSES

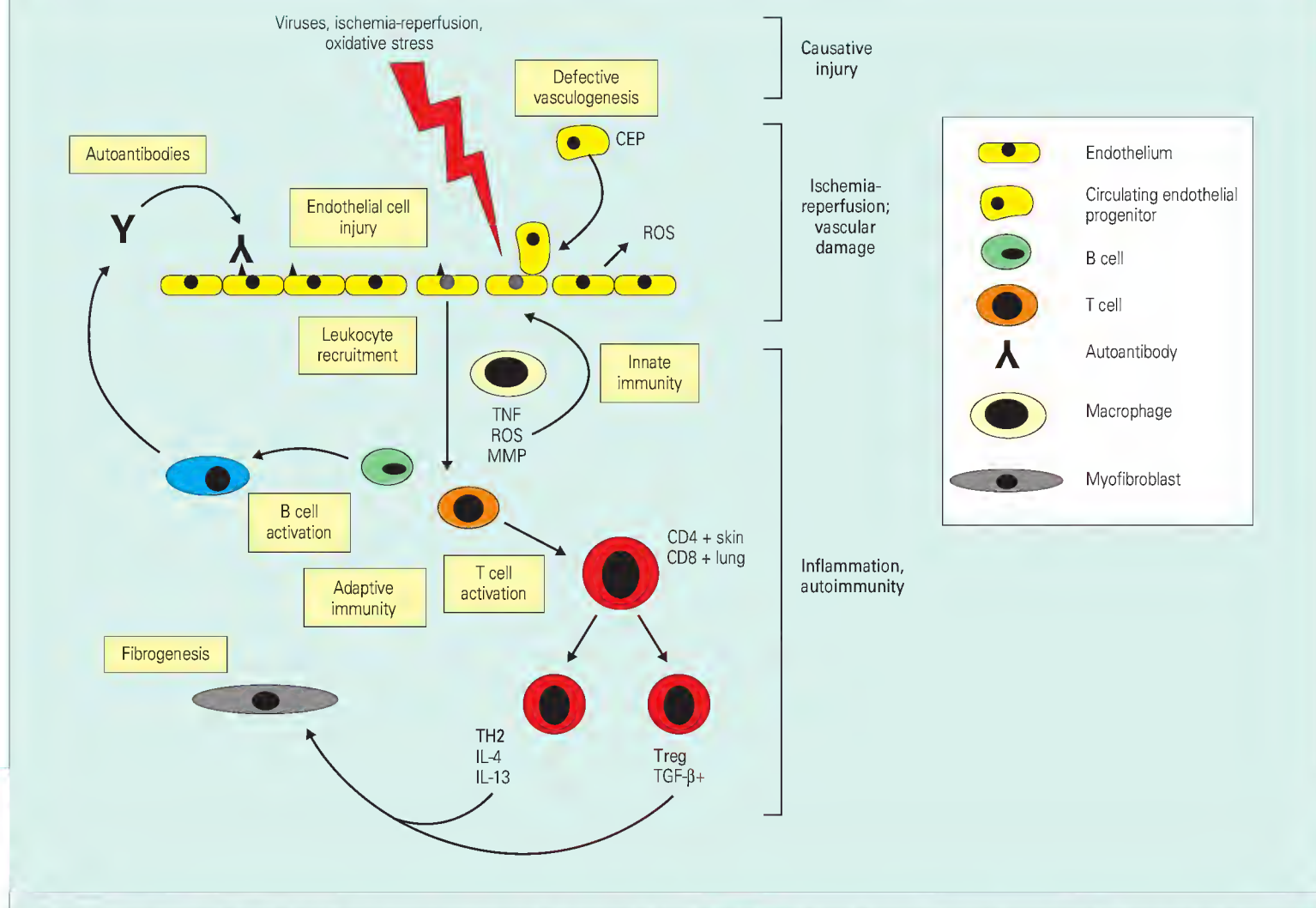


Fig. 143.8 Injury to vascular endothelium initiates a sequence of events, including the release of proinflammatory mediators, growth factors, chemokines, and reactive oxygen species (ROSs), that activate repair processes and lead to widespread tissue injury. Transition from innate immunity (macrophages) to the adaptive immune responses is accompanied by T-cell activation and the development of a type 2 immune response. Type 2 helper T-cell (Th2) cytokines such as interleukin-4 (IL-4), IL-5, and IL-13 exhibit profibrotic activity and orchestrate tissue repair. Regulatory T cells (Tregs) produce transforming growth factor- β (TGF- β). B-cell stimulation leads to the generation of specific autoantibodies that may directly contribute to tissue damage. Failure to replace damaged endothelium from circulating endothelial progenitors enhances leukocyte emigration. Chronic injury leads to persistent fibroblast activation, increased matrix accumulation, and tissue rigidity. CEP, circulating endothelial precursor; MMP, matrix metalloproteinase; TNF, tumor necrosis factor. (Modified from Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. *Trends Immunol* 2005;26:587-95.)

activation in a self-amplifying vicious cycle. In SSc, the extent of myofibroblast accumulation in the dermis correlates with the extent of skin involvement.¹⁵

Pericytes

Pericytes are contractile cells of mesenchymal origin that normally reside in the walls of microvessels, where they form intimate contact with the underlying endothelium. They can be identified by the surface markers CD248 and PDGFR β . Pericytes play an important role in integrity of the microvasculature. Injured pericytes detaching from endothelial cells migrate into the interstitium, where in response to PDGF they differentiate into collagen-producing myofibroblasts. Moreover, detachment of perivascular pericytes from the vessel wall results in loss of pericyte coverage of endothelial cells, which leaves an unstable endothelium prone to rarefaction and thereby links microvascular injury and fibrosis.

Cellular plasticity in systemic sclerosis

During embryonic development and under certain conditions in adults, fully differentiated epithelial cells transform into fibroblasts through the process of epithelial-mesenchymal transition (EMT). During EMT, epithelial

cells lose cell-cell adhesion and apical polarity and acquire mesenchymal features such as motility, invasiveness, heightened resistance to apoptosis, and synthesis of ECM molecules. In cultured cells, EMT can readily be induced by hypoxia, ROSs, Wnts, and TGF- β and is reversed by BMP-7, a member of the TGF- β superfamily. The importance of EMT in the pathogenesis of fibrosis and its role in SSc remain controversial. Recent studies suggest that adipocytic mesenchymal progenitor cells also differentiate into myofibroblasts. In addition, microvascular adventitial pericytes transition to myofibroblasts in response to injury and play a role in SSc and other forms of fibrosis.

Cellular determinants of fibrosis: bone marrow-derived mesenchymal progenitor cells

Bone marrow-derived progenitor cells called fibrocytes have also been implicated in SSc. Fibrocytes are CD34+ progenitor cells normally present in small numbers in peripheral blood that have the unique ability to both synthesize collagen and present antigen. Fibrocytes are identified by expression of CD14+ and the chemokine receptors CCR3, CCR5, and CXCR4. Monocyte-derived circulating multipotent progenitor cells can also differentiate into fibrocytes. This process is modulated by serum amyloid protein

TABLE 143.3
Soluble mediators implicated in fibrosis in systemic sclerosis

Growth factor	Cellular source	Elevated in systemic sclerosis
TGF-β	Inflammatory cells, platelets, fibroblasts, macrophages	+
PDGF	Platelets, macrophages, fibroblasts, endothelial cells	+
CTGF/CCN2	Fibroblasts	+
Insulin-like growth factor-1	Fibroblasts	+
IL-4 and IL-13	Th2 lymphocytes, mast cells	+
IL-6	Macrophages, B cells, T cells, fibroblasts	+
Chemokines (MCP-1, MCP-3)	Neutrophils, epithelial cells, endothelial cells, fibroblasts	+
CXCL4	pDCs	++
Fibroblast growth factor	Fibroblasts	+
Endothelin-1	Endothelial cells	+

CTGF, connective tissue growth factor; IL-4, interleukin-4; MCP, monocyte chemoattractant protein; pDC, plasmacytoid dendritic cell; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; Th2, type 2 helper T cell.

A (SAP), a serum pentraxin closely related to C-reactive protein. Impaired SAP production or deregulated SAP signaling might be implicated in fibrosis and SSc.

Molecular determinants of fibrosis

During physiologic tissue remodeling, synthesis of collagen is tightly regulated. In addition to TGF-β, multiple soluble molecules modulate collagen synthesis through autocrine and paracrine signaling (Table 143.3). Cell-cell contact, integrin-mediated contact with the surrounding ECM, hypoxia, and biomechanical forces also exert profound effects on myofibroblast accumulation and collagen production.¹⁶ The collagen genes harbor conserved regulatory elements that are specifically recognized by positively acting transcription factors such as Sp1, Ets1, Smad3, Egr-1, and CCAAT-binding factor (CBF), whereas Sp3, C/EBP, YB1, c-Krox, and Fli-1 inhibit collagen gene expression. Transcription factors interact in complex signaling networks and recruit coactivators and corepressors, scaffold proteins, and chromatin-modifying enzymes such as p300/CBP, and histone deacetylases (HDACs) that modulate transcription via chromatin modifications.¹⁷

Cell-autonomous regulation of collagen synthesis

Multiple biologic mechanisms exist for suppressing fibrogenic responses and preventing excessive scarring. Smad7, which blocks TGF-β signaling and fibrotic responses, has been shown to be defective in SSc. Other cell-autonomous repressors of fibrosis include transcription factors (Fli-1, p53), the Egr-1 antagonist Nab2, the nuclear orphan receptor peroxisome proliferator-activated receptor-γ (PPAR-γ), phosphatase and tensin homologue deleted on chromosome 10 (PTEN), HDACs, DDR2, and microRNA such as miR-29 (Box 143.2). These intrinsic molecules normally function as natural breaks that restrain collagen synthesis. Impaired expression, regulation, or function of these molecules contributes to fibrosis.

Transforming growth factor-β is a master regulator of connective tissue remodeling

The multifunctional cytokine TGF-β induces a broad array of fibrotic responses (see Box 143.2) and plays a fundamental and dominant role in both physiologic fibrogenesis (wound healing and tissue repair) and pathologic fibrosis.¹⁸ In most cell types, TGF-β is secreted as an inactive precursor complexed to latent TGF-β binding protein (LTBP) and is sequestered within the ECM. On tissue injury, latent TGF-β is converted to its biologically active form. Activation of latent TGF-β is catalyzed by thrombospondins and plasmin or via cell-surface integrins (α_vβ₃, α_vβ₅, α_vβ₆, and α_vβ₈) and is further enhanced by increasing matrix stiffness.

Intracellular TGF-β signaling involves both canonic Smad and Smad-independent signaling cascades. Canonic TGF-β signal transduction involves sequential phosphorylation of the type I TGF-β receptor activin-like kinase 5 (ALK5), a serine-threonine kinase, followed by activation of cytoplasmic

BOX 143.2 FIBROGENIC ACTIVITIES OF TRANSFORMING GROWTH FACTOR-β THAT MAY HAVE A ROLE IN SYSTEMIC SCLEROSIS

- Stimulates the synthesis of extracellular matrix (fibrillar collagens, fibronectin, proteoglycans, elastin, tissue inhibitors of metalloproteinases)
- Inhibits matrix metalloproteinases
- Stimulates fibroblast proliferation, adhesion, chemotaxis
- Stimulates cartilage oligomeric protein and PLOD2 production
- Enhances collagen fibrillogenesis and cross-linking
- Enhances stiffness of the extracellular matrix
- Stimulates connective tissue growth factor and endothelin-1 production
- Stimulates the production of reactive oxygen species
- Stimulates the expression of surface receptors for transforming growth factor-β and platelet-derived growth factor
- Promotes fibroblast-myofibroblast and monocyte-fibrocyte differentiation
- Induces epithelial-mesenchymal and endothelial-mesenchymal transitions
- Inhibits fibroblast apoptosis

Smads (Fig. e143.4a). The activated Smad complex binds to conserved DNA sequences in target gene promoters and recruits transcriptional cofactors such as the histone acetylase p300/CBP. Pharmacologic blockade of ALK5 activity prevents collagen accumulation and myofibroblast differentiation.

Smad-independent transforming growth factor-β signaling

Recent evidence indicates the existence of non-Smad pathways mediating TGF-β responses. As shown in Figure e143.4b, non-Smad signal transduction involves the mitogen-activated protein kinase ERK1/2 and its target Egr-1, other protein kinases (p38 and JNK, focal adhesion kinase [FAK], and TGF-β-activated kinase [TAK1]), lipid kinases such as phosphatidylinositol 3'-kinase and its downstream target (Akt), and the non-receptor tyrosine kinase c-Abl.

The Egr-1 transcription factor belongs to a family of inducible immediate-response genes that also includes Egr-2, Egr-3, Egr-4, and their repressors Nab1 and Nab2. Expression of Egr-1 is induced rapidly and transiently by hypoxia, injury, ROSs, and TGF-β. Egr-1 stimulates collagen gene expression and myofibroblast differentiation and enhances TGF-β synthesis, as well as TGF-β receptor expression. Egr-1 expression is constitutively upregulated in SSc. Mice with targeted deletion of Egr-1 have attenuated fibrotic responses to bleomycin. Nab2 is an inducible corepressor of Egr-1 signaling that inhibits Egr-1-mediated fibrotic responses in a negative feedback loop.

c-Abl is a non-receptor tyrosine kinase that regulates cell proliferation and survival, and its chromosomal translocation (Bcr-Abl) underlies chronic myelogenous leukemia. The c-Abl pathway is constitutively activated in patients with SSc. The tyrosine kinase inhibitor imatinib mesylate (Gleevec) blocks c-Abl-mediated Egr-1 activation and stimulation of collagen gene expression and myofibroblast differentiation *in vitro* and ameliorates bleomycin-induced skin fibrosis in mice.¹⁹

Peroxisome proliferator-activated-γ: the interface between adipogenesis and fibrosis

PPAR-γ is the master regulator of adipogenesis. Recent studies have linked PPAR-γ with inflammation, atherosclerosis, cancer, and fibrosis. Ligands of PPAR-γ abrogate profibrotic TGF-β responses and block the stimulation of Egr-1. The antifibrotic effects are mediated in part through endogenous adipokines such as adiponectin, a member of the complement 1Q-TNF related protein (CTRP) family. Expression of PPAR-γ is upregulated during the resolution phase of wound healing. Treatment of normal mice with rosiglitazone, a potent synthetic PPAR-γ agonist, attenuates bleomycin-induced scleroderma. In contrast, fibroblast-specific deletion of PPAR-γ results in exaggerated skin fibrosis. PPAR-γ mRNA expression and activity are markedly impaired in SSc skin and lung biopsy specimens and in explanted fibroblasts. Because PPAR-γ is a requisite factor for normal adipogenesis, impaired PPAR-γ may account for the prominent loss of hypodermal adipose tissue in SSc.²⁰

Integrin signaling in systemic sclerosis

Fibroblast activity is modulated by the pericellular matrix via cell-surface integrin receptors. Expression of α_vβ₃ and α_vβ₅ integrins is significantly elevated in SSc fibroblasts. These integrins contribute to elevated collagen synthesis and myofibroblast differentiation by activating latent TGF-β and inducing a self-amplifying autocrine feedback loop.

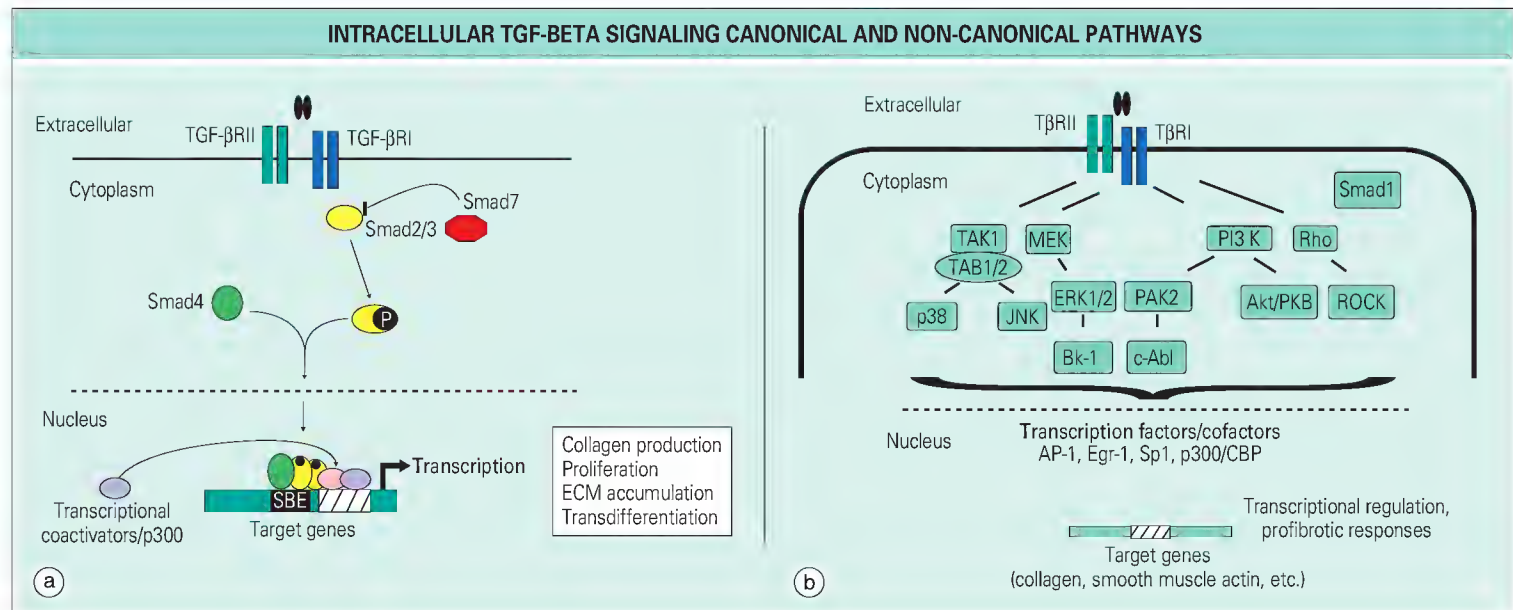


Fig. e143.4 Intracellular transforming growth factor- β (TGF- β) signaling via canonic and noncanonic pathways. TGF- β binds to and activates cell-surface receptors, which results in the phosphorylation of intracellular downstream targets. Activated Smad2 and Smad3 form a complex with Smad4 and transit from the cytoplasm into the nucleus, bind to DNA, and activate (or repress) target gene transcription (a). TGF- β can also activate complex Smad-independent intracellular kinase cascades (b). ECM, extracellular matrix; SBE, Smad binding element.

Biomechanical signaling

Mechanical forces are important modulators of fibroblast morphology, migration, and proliferation; matrix synthesis; and myofibroblast differentiation.¹⁴ As the skin and other tissues become fibrotic, they show increased stiffness and reduced elasticity, which results in mechanical stress. In turn, resident fibroblasts sense biomechanical forces through integrins and changes in cytoskeletal tension mediated by Rho-associated kinase and FAK, which play critical roles in driving persistent fibrogenesis. Activation of these pathways by the stiff matrix perpetuates fibroblast activation and further exacerbates the fibrosis. Moreover, fibroblasts within a stiff matrix can activate latent TGF- β sequestered within the pericellular environment. Remarkably, fibroblasts that are activated as a result of increased substrate stiffness maintain their activated phenotype even when placed in a soft substrate. The phenomenon of “fibroblast mechanical memory,” apparently driven by stable epigenetic modifications, indicates that exposure to biomechanical forces can permanently alter fibroblast function and promote a sustained fibrotic phenotype.²¹ In this manner, a stiff matrix resulting from fibrosis of affected tissue itself drives fibroblast activation, thereby contributing to a self-amplifying loop of sustained fibrogenesis.

Fibrogenic growth factors and chemokines

Multiple growth factors, chemokines and eicosanoids, adenosine, and ROSs that regulate fibroblast biology are abnormally expressed in SSc. These molecules represent potential targets for antifibrotic therapy (see Table 143.3).

Connective tissue growth factor/CCN2

CTGF/CCN2 is a cysteine-rich, 40-kDa matricellular protein with important roles in angiogenesis, wound healing, and development. CTGF/CCN2 expression is generally undetectable in normal tissue but is markedly elevated in SSc, and serum levels correlate with the extent of skin and pulmonary fibrosis in SSc. CTGF/CCN2 expression is induced by TGF- β , IL-4, and vascular endothelial growth factor (VEGF), whereas tumor necrosis factor- α (TNF- α) and iloprost block stimulation. Injection of CTGF/CCN2 by itself induces only a transient fibrotic response in mice but markedly enhances the TGF- β response. Because the biologic responses to CTGF/CCN2 mirror those induced by TGF- β , it has been proposed that the effects of TGF- β are mediated through endogenous CTGF/CCN2; however, CCN2-null fibroblasts show intact TGF- β signaling.

Platelet-derived growth factor

PDGFs are disulfide-linked heterodimeric peptides consisting of an A and a B chain that act mainly on stromal cells such as fibroblasts, smooth muscle cells, and pericytes. The PDGFs play a vital role in wound healing and are increasingly being implicated in fibrosis. Originally isolated from platelets, PDGF isoforms are also secreted by monocytes and macrophages, endothelial cells, and fibroblasts. Since PDGFs play important roles in regulating the differentiation, proliferation, and survival of mesenchymal progenitor cells, dysregulated PDGF signaling plays a role in fibrosis. Signaling via the PDGFR α and PDGFR β receptors, PDGFs act as potent mitogens and chemoattractants and induce collagen, fibronectin, and proteoglycan synthesis; TGF- β secretion; and pericyte differentiation into myofibroblasts. An alternative mechanism for activation of PDGFR signaling by circulating autoantibodies binding to PDGFRs has recently been proposed. Severe multiple-organ fibrosis develops in transgenic mice that overexpress either PDGF isoforms or mutated constitutively active PDGFR α . Expression of PDGF and its receptors is elevated in SSc skin and bronchoalveolar lavage fluid. Although some reports have described the presence of activating autoantibodies to the PDGF receptor in the serum of patients with SSc,²² subsequent reports failed to reproduce these findings.

Wnt/ β -catenin signaling

Microarray studies provide evidence of deregulated Wnt signaling in SSc and in mouse models of scleroderma. The Wnt family of morphogens comprise multiple secreted glycoproteins that regulate development and embryogenesis. Extensive crosstalk between Wnts and the TGF- β and BMP signaling pathways exists; Wnts stimulate TGF- β , and TGF- β can activate β -catenin. The Wnt/ β -catenin pathway can promote fibrogenesis through increased fibroblast proliferation and activation, as well as induction of EMT and other forms of cellular differentiation. Striking scleroderma-like skin induration develops in mice transgenic for Wnt10b.²³

Th2 cytokines in systemic sclerosis

Th2 cytokines stimulate fibroblast proliferation, chemotaxis, collagen synthesis, and production of TGF- β , CTGF/CCN2, and tissue inhibitor of

metalloproteinases (TIMPs). Serum levels of IL-4 and IL-4-producing T lymphocytes are elevated in patients with SSc. Expression of IL-4 is also elevated in lesional skin and cultured fibroblasts. IL-6, produced by T lymphocytes, fibroblasts, and endothelial cells, stimulates collagen and TIMP-1 synthesis and promotes a Th2-polarized immune response. Serum IL-6 levels are elevated in SSc and correlate with skin involvement. IL-13 has been implicated in asthma and fibrotic conditions. It has both indirect (stimulation of TGF- β production) and direct (stimulation of fibroblast proliferation and collagen synthesis) profibrotic effects. Serum levels of IL-13 are elevated in patients with SSc.

Chemokines in systemic sclerosis

Chemokines play important roles in angiogenesis, wound healing, and fibrosis. The CC chemokine MCP-1 stimulates collagen production directly, as well as through endogenous TGF- β . Serum levels of MCP-1, along with those of macrophage inflammatory protein-1 α (MIP-1 α), IL-8, CXCL8, and CCL18, are elevated in SSc and correlate with the severity of skin fibrosis. Mononuclear cells and fibroblasts from SSc patients produce these chemokines spontaneously, and lesional fibroblasts show constitutive upregulation of the MCP-1 receptor CCR2. MCP-1-null mice are resistant to induction of fibrosis. Strong expression of MCP-1 and MCP-3 was noted in lesional skin in SSc, particularly in early disease. Levels of MIP-1 α , CXCL8 and CCL18, RANTES (regulated on activation, T cell expressed and excreted), PARC, and the CXC chemokines IL-8, MIP-2, and fractalkine are also overexpressed in SSc or in animal models of scleroderma. The insulin-like growth factor (IGF) binding protein-1 (IGFBP-1) stimulates collagen synthesis and fibroblast proliferation and induces TGF- β . Patients with SSc have elevated levels of IGF-1 in bronchoalveolar lavage fluid. Expression of IGFBP-3 is markedly elevated in SSc fibroblasts.^{24,25} IGFBP-5 induces scleroderma-like fibrosis in mice.

Endogenous ligands for Toll-like receptors

Toll-like receptors (TLRs) are expressed on both leukocytes and parenchymal cells and serve as critical mediators of innate immunity. Recent evidence has implicated TLR4-mediated innate immune signaling in tissue fibrosis.²⁶ Matrix molecules and their fragments generated *in situ* during tissue damage, such as low-molecular-weight fragments of hyaluronan, biglycan, gp96, and Fn-EDA, are capable of inducing TLR activation. These so-called danger-associated molecular patterns (DAMPs) are aberrantly upregulated in lesional tissue in SSc patients and in mouse models of scleroderma. Stimulation of TLR4 in normal fibroblasts with neoligands such as Fn-EDA induces myofibroblast transdifferentiation, TGF- β secretion, and collagen production. Activation of fibroblast TLRs by DAMPs in SSc might account for the persistence of tissue fibrosis.

Adenosine

Adenosine is a purine nucleoside whose extracellular concentration is rapidly elevated in response to injury or IL-13. Adenosine is a potent stimulus for collagen synthesis via the A2A receptor and MEK1/ERK signal transduction in fibroblasts. Fibrosis is attenuated in mice with targeted deletion of the adenosine receptor.

Paracrine mediators with antifibrotic activity

Soluble mediators can also act as negative regulators of fibrotic responses. IFN- γ , a hallmark Th1 cytokine, inhibits collagen gene expression and abrogates TGF- β stimulation of fibroblast proliferation, matrix contraction, and myofibroblast differentiation. Fibroblasts from patients with SSc are relatively resistant to these inhibitory effects. Hepatocyte growth factor (HGF) is normally secreted by mesenchymal cells and regulates epithelial cell proliferation and function. *In vitro*, HGF inhibits collagen synthesis in normal and SSc fibroblasts. Adiponectin, secreted primarily by adipocytes, has pleiotropic protective effects. Levels of adiponectin are reduced in the serum and lesional tissues of SSc patients and show an inverse correlation with the extent of skin fibrosis. *In vitro*, adiponectin acts as a potent inhibitor of fibroblast activation via induction of adenosine monophosphate kinase. BMP-7, a member of the TGF- β superfamily, is a potent inhibitor of EMT that can prevent and ameliorate fibrosis in various animal models.

Tumor necrosis factor- α

The role of TNF- α in the pathogenesis of SSc is difficult to discern. In cultured fibroblasts, TNF- α acts as a potent inhibitor of collagen gene expression and blocks the fibrotic responses induced by TGF- β . Microarray analysis of sclerodermatous GVHD showed that relative absence of TNF- α in the lesional skin accounted for the development of skin fibrosis rather than epithelial cytotoxicity in this mouse model of scleroderma. Furthermore, mice with targeted deletion of the receptor for TNF- α show

accelerated fibrosis, and transgenic mice overexpressing TNF- α were partially protected from the lung fibrosis induced by bleomycin. In other studies, however, transgenic expression of TNF- α in the lungs was shown to induce pulmonary fibrosis.

The scleroderma fibroblast

Fibroblasts explanted from lesional skin and lung fibroblasts from patients with SSc variably display an abnormal activated phenotype that is partially maintained during their serial passage *in vitro*.²⁷ The “SSc phenotype” is characterized by constitutively increased collagen gene expression and enhanced ECM synthesis, secretion of profibrotic cytokines and chemokines, spontaneous production of ROSs, and increased expression of cell-surface receptors for TGF- β and PDGF. Lesional SSc fibroblasts in culture display a myofibroblast phenotype with activation of FAK.²⁸ It remains unsettled whether the activated SSc fibroblast phenotype represents a stable and heritable abnormality inherent in these cells (possibly because of stable epigenetic histone chromatin modifications) or instead reflects exogenous stimulus-induced activation.

The signal transducers, cofactors, and transcriptional regulatory molecules that are aberrantly regulated in SSc fibroblasts are shown in Box 143.3. Because the characteristic SSc fibroblast phenotype can be induced by TGF- β treatment of explanted normal fibroblasts, it has been suggested that the SSc fibroblast phenotype is due to persistent autocrine TGF- β signaling.²⁹ Moreover, SSc fibroblasts have elevated levels of TGF- β receptors and overexpress thrombospondin and integrins, which can locally activate latent TGF- β at the cell surface. Consistent with the autocrine TGF- β hypothesis, SSc fibroblasts show constitutive TGF- β signaling along with nuclear accumulation of activated Smad3 and constitutive Smad3 interaction with the histone acetyltransferase coactivator p300/CBP. Other studies have demonstrated defective expression or function of endogenous suppressors of TGF- β signaling such as Smad7, PPAR- γ , and caveolin-1, thus suggesting

that failure to shut off activation pathways represents a fundamental intrinsic cell defect in SSc fibroblasts.

Inflammation and immunity

The immune response in systemic sclerosis

As we consider pathogenic mechanisms, we quickly come to conflicting viewpoints and understanding of the role of immunity and autoimmunity in scleroderma. Advocates of the importance of immunity in SSc find support in the nearly universal presence of circulating autoantibodies and of mononuclear cells in affected organs. Skeptics argue that autoantibodies and inflammatory cells are not clearly implicated in directly (or indirectly) causing any pathogenic features of the disease. Despite these reservations, immune dysregulation is apparent at multiple levels in SSc patients and may well be the primary trigger of the disease (Fig. 143.9).

Humoral immunity in pathogenesis

Autoantibodies in SSc might play two different roles: directly mediate tissue injury or alternatively regulate the immune response.

Autoantibodies implicated in tissue damage in systemic sclerosis

Multiple autoantibodies occur in SSc that might directly mediate tissue damage. A list of potentially pathogenic autoantibodies is presented in Table 143.4. Anti-endothelial cell antibodies (AECAs) have been described in SSc that could effectively link autoimmunity and vascular injury. Several investigators have reported cytotoxicity and apoptosis mediated by AECAs. Despite these observations, the importance of AECAs in SSc remains uncertain because different assays are used, their titers are not consistently higher in SSc than in patients with other connective tissue disease, and they appear to lack specificity for endothelial cells. In patients with diffuse cutaneous SSc, AECAs were found to target topoisomerase I, and in patients with limited cutaneous SSc, AECAs were found to target CENP-B, the main target of anticentromere antibodies.

Antibodies to fibroblasts might play a direct role in the pathogenesis of fibrosis. Recent findings include identification of topoisomerase I as a target of antifibroblast antibodies, stimulatory antibodies to the PDGF receptor,³⁰ and upregulation of TGF- β expression by antibodies to fibrillin-1 *in vitro*.^{31,32} However, other studies have failed to confirm these observations.

Nuclear autoantibodies in systemic sclerosis

Another group of SSc-associated autoantibodies react against nuclear components. The list includes antibodies targeting anti-topoisomerase I (also known as Scl-70), centromere proteins (most consistently CENP-B), RNA polymerases I and III, and nucleolar proteins such as U3 and fibrillarin. These antibodies have strong associations with specific disease subsets and organ manifestations, and the stimulus for their production might provide important clues to the pathogenesis of SSc.

BOX 143.3 ENDOGENOUS REGULATORS OF FIBROBLAST ACTIVATION

Transcription factors

Smad3
Sp1
MRTF
Egr-1, Egr-2
Fli-1
PTEN
Nab2
PPAR- γ

Cofactors and epigenetic regulators

p300/CBP acetyltransferase
microRNA (miR29, miR21, Let7)

Others

c-Abl
Bcl-2
FAK
Akt
AMPK

Fig. 143.9 Multiple cell types may be involved in stimulating vascular injury and fibrosis. Ligands for Toll-like receptors (TLRs) stimulate dendritic cells to produce interferon- α (IFN- α) and interleukin-6 (IL-6), which in turn stimulate B cells and monocytes/macrophages. Type 2 helper T cells (Th2 TCs) produce IL-4 and IL-13 and stimulate profibrotic “alternatively activated/M2” monocyte/macrophages. Macrophages produce profibrotic cytokines such as transforming growth factor- β (TGF- β) and platelet-derived growth factor (PDGF). Cytotoxic T cells may injure endothelial cells through granzyme and Fas/FasL. The resulting apoptotic cell debris may be sources for altered antigens that contribute to activation of B cells for production of autoantibodies. Autoantibody/autoantigen/nucleic acid complexes may also be internalized by B cells and dendritic cells activating TLRs.

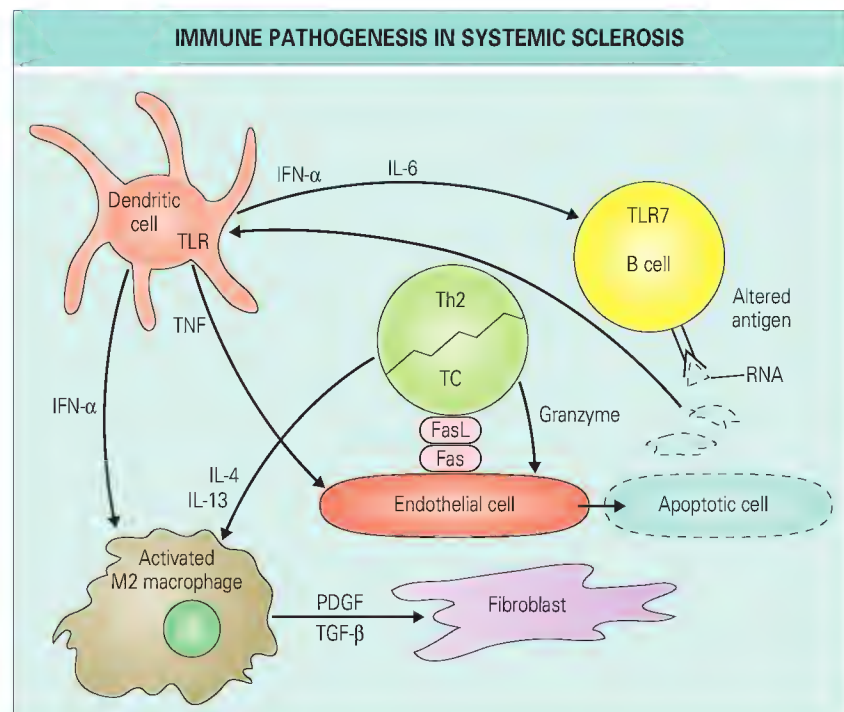


TABLE 143.4
Pathogenetic autoantibodies in systemic sclerosis

Antibody	Target antigen/biologic response
Antiendothelial cell	Endothelial cells
Antifibroblast	Fibroblast cell membrane
Anticollagenase	MMP-1
Anti-PDGF receptor	Cell-surface receptor for PDGF
Anti-topoisomerase I	Induces scleroderma in immunized mice
Anti-angiotensin II receptor 1	Stimulates fibroblast activation
Anti-endothelin 1	Fibroblast activation
Anti-fibrillin-1	Extracellular microfibrils

MMP-1, matrix metalloproteinase-1; PDGF, platelet-derived growth factor.

Neoantigens as autoimmune targets

It has been suggested nuclear autoantigens become targets in SSc because of exposure of “neoepitopes,” that is, antigenic structures not previously seen by the immune system. One intriguing observation is that hypoxia in the presence of certain metals stimulates fragmentation of the autoantigens targeted in SSc.³³ Other insight into the role of SSc-associated autoantibodies comes from mouse strains in which mercury exposure elicits autoantibodies to fibrillar, an antigen targeted by antinucleolar antibodies in some patients with SSc. The protein fragments generated during mercury-induced cell death might be the cause of mercury-induced autoantibodies. ROSs can cause oxidation of autoantigens leading to immune responses to SSc-targeted autoantigens such as topoisomerase I and centromere proteins. These studies suggest a paradigm whereby proteolysis and other modification of autoantigens, caused by somatic mutations, hypoxia, mercury, cell death, or oxidation, trigger the generation of SSc-associated autoantibodies by creating neoepitopes. Whether modified antigens are responsible for the development of SSc-associated autoantibodies in patients with SSc is unknown.

Autoantibodies to nuclear autoantigens in innate responses

Although a direct role in pathogenesis has not been assigned to SSc-associated nuclear autoantibodies, recent data have suggested possible roles in innate immunity. Nucleic acid-containing immune complexes in SLE can stimulate innate immune responses through intracellular nucleic acid receptors that normally respond to microbial DNA or RNA. These include TLR3, TLR7, or TLR9, which bind respectively to double-stranded RNA, single-stranded RNA, and DNA. Several observations suggest innate immune activation in SSc (see later), and direct evidence of TLR responses has been reported primarily in sera containing anti-topoisomerase I. Although topoisomerase I is a DNA-nicking enzyme, it also associates with a variety of proteins that bind RNA. Thus, topoisomerase I in immune complexes in SSc sera might bind DNA or RNA. Internalization of these nucleic acid-containing complexes by dendritic cells appears to stimulate nucleic acid-sensing TLRs as assessed by IFN- α production. Treatment of antitopoisomerase-containing sera from SSc patients with RNase inhibits IFN- α secretion. Thus, TLR7, a single-stranded RNA sensor, is most strongly implicated in stimulation of innate immune responses by antitopoisomerase-containing immune complexes.

Cellular immunity in systemic sclerosis

A major branch point in considering immune pathogenesis is the role of innate versus adaptive immunity. Posed differently, the question is whether the immune process is being driven by responses to specific antigenic stimuli or more general immune stimuli. Although these two arms of the immune system are closely integrated, it is useful to consider evidence for the role of each. At the outset, the defined specificities of autoantibodies found in SSc suggest “adaptive” or antigen-specific immune responses. However, it is important to consider that these specificities might instead be driven by TLR-mediated “innate” immune responses designed to recognize pathogen-associated molecular patterns (PAMPs). Innate immune stimuli might serve to simply amplify antigen recognition caused, for example, by the modified neoantigens discussed earlier.

Innate immunity and dendritic cells in systemic sclerosis

Several recent observations have suggested that the innate immune system is activated in SSc. Increased expression of IFN-responsive genes, known as the IFN “signature” and initially identified in SLE, was found in SSc. Type

I IFNs are secreted upon TLR activation in dendritic cells, which are prominent in SSc lesional skin. The IFN signature is interpreted as evidence of dendritic cell activation. In SSc, TLRs could become activated through the same mechanisms as in SLE, that is, by nucleic acid-containing immune complexes or through the other endogenous ligands discussed earlier. Although type I IFNs have been implicated in the pathogenic aspects of lupus, they have not generally been considered pathogenic factors in SSc because they block the effects of TGF- β on fibrosis. Dendritic cell activation also stimulates TNF and IL-6 production, and these or other undefined mediators might further contribute to pathogenesis in SSc.

Toll-like receptor activation and autoreactive B cells

TLR activation is also a key step in autoreactive B-cell maturation. Notably, TLR7 has been implicated in the formation of antinucleolar antibodies in mice harboring the Y-linked autoimmune accelerator (*Yaa*) gene, which is associated with a duplication of TLR7. These results suggest that autoreactive B cells specific for nucleolar antigens can be activated to secrete autoantibody by taking up nucleolar/RNA-containing cellular debris through surface immunoglobulin receptors. Internalized nucleolar/RNA can bind TLR7 and thereby activate B-cell maturation. Similar mechanisms might lead to autoantibodies to other nucleic acid-binding proteins in SSc, such as anticentromere, antitopoisomerase, and anti-Th/To.

Th2 immune skewing, interleukin-13, and fibrosis

Clinical observations in both SSc and mouse models of fibrosis as discussed earlier implicate Th2 mediators in pulmonary fibrosis. Most importantly, IL-13, a signature Th2 cytokine, stimulates fibrosis in bleomycin-induced murine models of skin and pulmonary fibrosis.³⁴ IL-4 and IL-13 are elevated in the sera of SSc patients, thus suggesting that they play a role in the fibrotic disease in SSc. The results from a recent study showing that circulating T cells from SSc patients are skewed toward a Th2 phenotype and are associated with interstitial lung disease are consistent with these observations. In contrast, patients with SSc and PAH tended to have Th1-skewed T cells for reasons not yet understood.

A genome-wide microarray expression profiling study compared the mouse model of chronic GVHD with SSc skin. The results showed that the IL-13 target MCP-1/CCL2 is overexpressed in both the cGVH mouse model and SSc.³⁵ The fibrotic process was ameliorated in MCP-1/CCL2-null mice.

Monocyte/macrophage activation in fibrosis

Macrophages secrete a variety of profibrotic mediators, including PDGF and TGF- β . Dermal macrophages in SSc patients show activated phenotypes with increased expression of the type I IFN-inducible Siglec-1 and IFN- γ -inducible allograft inflammatory factor-1 (AIF1), a finding implicating IFNs in macrophage activation in SSc. However, since type I and type II IFNs stimulate similar genes, including Siglec-1 and AIF1, either type I or type II IFNs might be responsible for the increased expression of these genes in SSc. Because type I IFNs are typically secreted by activated dendritic cells whereas type II IFNs are typically secreted by natural killer and T cells, determining the type of IFN or IFNs upregulated in SSc might provide some additional hints about the nature of the underlying cellular immune response.

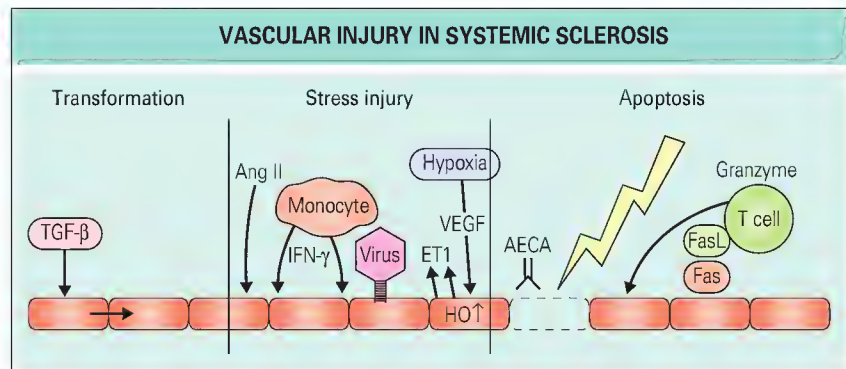
An emerging paradigm defines macrophage activation on the basis of the activating cytokines. “Classically activated” monocytes are activated by the Th1 cytokine IFN- γ , whereas alternatively activated macrophages are activated by the Th2 cytokines IL-4 and IL-13. Alternatively activated macrophages are proposed to be profibrotic, possibly by activating TGF- β . Alternatively activated macrophages have been classified into further subsets, and macrophages activated by type I IFNs also have distinctive features, thus indicating an expanding array of macrophage phenotypes. Monocytes from a subset of SSc patients show increased expression of IFN-regulated genes, whereas SSc patients complicated by PAH express genes associated with alternative macrophage activation, including *MRC1*, a gene highly upregulated by IL-13.

Thus, gene expression data implicate both IFNs and IL-13 in activating monocytes/macrophages in SSc patients, which suggests important roles of these cells in the pathogenesis of SSc.

Adaptive T-cell responses in fibrotic disease

Chronic sclerodermatous GVHD shows that adaptive immune responses can lead to autoimmunity and tissue fibrosis. Oligoclonal expansion of T cells in the skin of patients with SSc supports the importance of antigen-dependent T-cell expansion. Microchimerism secondary to persistent fetal cells has been proposed as a possible source of antigenic stimulus in SSc.^{36,37} Autoantigens, such as topoisomerase I, represent another possible target for oligoclonal T-cell expansion because T cells may be required for

Fig. 143.10 Vascular injury leads to vascular activation, injury, and apoptosis and might result from transient or latent viral infection; soluble mediators such as interferon- γ (IFN- γ), tumor necrosis factor- α , and angiotensin II (Ang II); autoantibodies; reactive oxygen species; and hypoxia. Hypoxia stimulates additional pathogenic factors such as inducible nitric oxide synthase, hypoxia-inducible factor-1, and endothelin-1 (ET-1). Transforming growth factor- β (TGF- β) or other factors might induce endothelial cells to transform into mesenchymal cells. Loss of perivascular pericytes disrupts vascular integrity. AECA, anti-endothelial cell antibody; HO, heme oxygenase; VEGF, vascular endothelial growth factor.



autoantibody production. Topoisomerase-specific T-cell clones have been identified in some antitopoisomerase-positive patients.³⁸

Vascular injury and vasculopathy in systemic sclerosis

Vascular involvement accounts for many of the clinical complications in SSc, and vasculopathy may be the primary event in SSc.³⁹ Vascular obliteration leads to hypoxia, which enhances collagen synthesis and fibroblast activation and is likely to further exacerbate the fibrotic response in SSc. Vasculopathy might result from several mechanisms, including stress-related injury, apoptosis, pericyte detachment, and endothelial-mesenchymal transformation (Fig. 143.10).

Endothelial cell injury

Activated endothelial cells play an important role in recruiting inflammatory cells through adhesion receptors. The adhesion molecules vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) are upregulated in SSc skin, as is MHC class II, thereby providing a means for cognate endothelial interaction with T cells. Soluble markers of activated endothelium such as sVCAM, sICAM, and E-selectin are elevated in the circulation.

Endothelial cell apoptosis

Endothelial cell apoptosis is implicated in the UCD 200/206 chicken model of scleroderma. This model also showed evidence of dermal endothelial cell apoptosis in the dermal vessels of patients with early active SSc. Although electron microscopic findings in SSc are consistent with the notion of endothelial cell death, a recent study has questioned the importance of apoptosis in SSc vasculopathy based on lack of caspase-3 staining.

Cytotoxic factors in endothelial apoptosis

Increased circulating levels and skin expression of granzyme have been reported in SSc. Granzyme is a component of cytotoxic granules containing perforin and granzyme B. Cytotoxic T cells kill target cells through surface expression of Fas ligand (FasL), which engages Fas on target cells and triggers apoptosis. Cytotoxic T cells might mediate vascular injury via granzyme/perforin or Fas/FasL. Several viruses can infect endothelial cells and lead to apoptosis. In particular, hCMV can infect endothelial cells and stimulate neointimal changes in immunodeficient mice. Autoantibodies in SSc patients cross-reacting to a CMV protein can induce endothelial cell apoptosis.

Endothelial cell apoptosis appears to be highly dependent on the vascular bed affected. For example, TGF- β has diametrically opposed actions on pulmonary endothelial cells derived from the pulmonary artery and from the pulmonary microvasculature, which respectively inhibit and promote apoptosis. Isolated vascular involvement of distinct organs (lungs, digits, kidneys) in SSc patients suggests that mediators in different vascular beds have distinct responses to some underlying stimulus. In scleroderma renal crisis, renin and angiotensin II are highly upregulated by an unknown trigger. Angiotensin II, in turn, can stimulate endothelial cell apoptosis,⁴⁰ as well as fibrosis. However, disease in this vascular bed is not typically associated with ischemic digits or PAH, thus indicating that despite similar pathologic processes, different pathogenic mechanisms might be involved at different sites.

Vascular spasm, reactive oxygen species, and hypoxia

Ischemia-reperfusion occurs commonly in SSc associated with the Raynaud phenomenon (Fig. 143.11). Furthermore, there is evidence in SSc that spasm may contribute to disease in other vascular beds. However, most

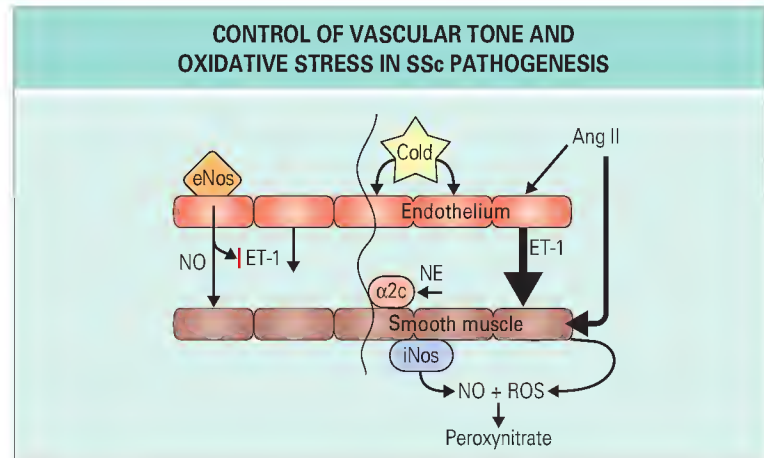


Fig. 143.11 Basal vascular relaxation is maintained by nitric oxide (NO) produced from arginine by endothelial nitric oxide synthase (eNOS). NO relaxes vascular tone through smooth muscle guanylate cyclase and also inhibits endothelin-1 (ET-1). In cold-induced vasospasm, translocation of internal α_{2c} -adrenoreceptors to the cell surface leads to increased sensitivity to circulating adrenocorticoids such as norepinephrine (NE) and causes hypoxia. ET-1, strongly upregulated in systemic sclerosis (SSc), is secreted by endothelial cells and directed toward underlying smooth muscle cells. Angiotensin II (Ang II) is also a potent vasoconstrictor and induces the generation of reactive oxygen species (ROSs). Inflammatory mediators increase inducible nitric oxide synthase (iNOS) in tissues. NO in tissues can react with ROSs and thereby result in peroxynitrate and nitrated proteins.

studies suggest that underlying endothelial cell dysfunction is the primary cause of the increased vascular reactivity. The Raynaud phenomenon represents an exaggerated normal response to cold that is largely mediated by α_{2c} -adrenoreceptors to protect against heat loss. Cold exposure, possibly by enhancing the generation of ROSs, stimulates smooth muscle cell rho kinase, which results in translocation of internal α_{2c} -adrenoreceptors to the cell surface. Upregulation of α_{2c} -adrenoreceptors during stress could explain why patients with SSc show exaggerated cold-induced vasospasm.

Although vascular spasm is not generally considered the primary vascular event in SSc, the resulting ischemia-reperfusion injury might have profound effects on vascular cells. Hypoxia induces the expression of ET-1, VEGF, and PDGF; inhibits endothelial nitric oxide synthase (eNOS); and induces endothelial cell apoptosis. These effects are mediated largely through the transcription factor hypoxia-inducible factor-1 α (HIF-1 α). Hypoxia-induced ET-1 may serve to further exacerbate vasoconstriction. By stimulating the production of inflammatory cytokines, such as TNF- α , IL-1, and IL-6, reperfusion may also contribute to vascular injury. Thus, vasospasm, ischemia, and hypoxia result in the release of soluble mediators that amplify the vasculopathy in SSc.

Endothelium-dependent relaxation and nitric oxide

Nitric oxide (NO) synthase catalyzes the oxidation of L-arginine to equimolar quantities of NO and L-citrulline.⁴¹ Release of NO from the vascular endothelium represents a powerful vasodilator signal to the underlying smooth muscle (see Fig. 143.11). NO plays an important role in the regulation of cardiovascular, nervous, renal, and immune responses. Under physiologic conditions, basal NO generated by eNOS maintains normal vascular

vasodilatory tone. The target of NO in the vascular wall is the soluble guanylate cyclase in smooth muscle cells. Activation of guanylate cyclase leads to the accumulation of cyclic guanosine monophosphate, which triggers smooth muscle relaxation and vasodilatation. In SSc, deficient endothelium-dependent relaxation is suggested by impaired maximal responses to endothelial-dependent vasodilators and normal responses to endothelial-independent dilators. This impairment is associated with an increase in the markers of endothelial cell injury and decreased eNOS in the skin. The consequences of impaired endothelial NO release include defective control of vascular tone. Because NO inhibits platelet aggregation and is a potent chemical barrier protecting endothelial cells from oxidation injury, the impaired NO production associated with endothelial cell dysfunction may contribute to further vascular injury.

Paradoxically, despite the loss of eNOS and endothelial-dependent vasodilatation, several studies have shown increased levels of circulating NO in SSc. This may reflect increased expression of inducible NOS (iNOS) as the vascular damage proceeds. iNOS can be induced by lipopolysaccharide, IFN- γ , IL-1, and other inflammatory signals in a wide range of cell types, including macrophages, and its primary role appears to be regulation of immune functions. However, the effect of increased NO in tissues can potentially be deleterious by reacting with superoxide anion to produce peroxynitrate. Increased levels of nitrated proteins in SSc skin suggest that NO might contribute to tissue injury in SSc.

Endothelin-1

ET-1 and its ET-2 and ET-3 isoforms mediate endothelium-dependent vasoconstriction and are potent mitogens for smooth muscle cells and fibroblasts. ET-1 is a 21-amino acid linear peptide produced from a prepropeptide that is converted to the mature protein by an endothelin-converting enzyme. Thrombin, epinephrine, TNF- α , TGF- β , angiotensin II, and hypoxia can all stimulate the release of ET-1 from endothelial cells. Increased plasma ET-1 levels have been associated with the Raynaud phenomenon and SSc, particularly the diffuse cutaneous subset with associated PAH, pulmonary fibrosis, and scleroderma renal crisis. Increased ET-1 accumulation and ET-1 receptor expression are seen in skin and lung tissue from patients with SSc.⁴² The critical role of ET-1 in SSc vascular disease is illustrated by the efficacy of the endothelin receptor antagonist bosentan in the prevention of ischemic digital ulcers and in improvement of symptoms of PAH.⁴³ ET-1 also enhances fibroblast proliferation and the synthesis of types I and III collagen and decreases the expression of collagenase (matrix metalloproteinase-1).

Intimal hyperplasia

Hyperplasia of the intimal layer of small to medium-sized arteries is a distinguishing pathologic hallmark of SSc. The cells responsible for intimal hyperplasia might arise from endothelial cells, smooth muscle cells, or pericytes (Fig. 143.12). Similar pathologic changes are seen in most forms of PAH, where myofibroblasts are implicated as the cells making up the hyperplastic neointima. One report showed neointimal cells in SSc-associated PAH to be derived from endothelial cells based on factor VIII antigen staining. In the skin, endothelial cell markers, notably VE-cadherin, are absent, whereas smooth muscle actin staining is increased, thus supporting a myofibroblastic phenotype in neointimal lesions. Myofibroblast accumulation on the neointimal lesions might derive from several sources. Markers for pericytes are increased in SSc vasculature, which suggests that pericytes might be responsible for the intimal hyperplasia. Alternatively, neointimal cells might derive from vascular smooth muscle, circulating progenitors, or endothelial cells.

Endothelial-mesenchymal transformation

An alternative explanation for vascular pathology and neointimal formation in SSc is endothelial-mesenchymal transformation, a normal developmental process in which endothelial cells in the developing heart transition into mesenchyme in the atrioventricular and outflow tract but not in the

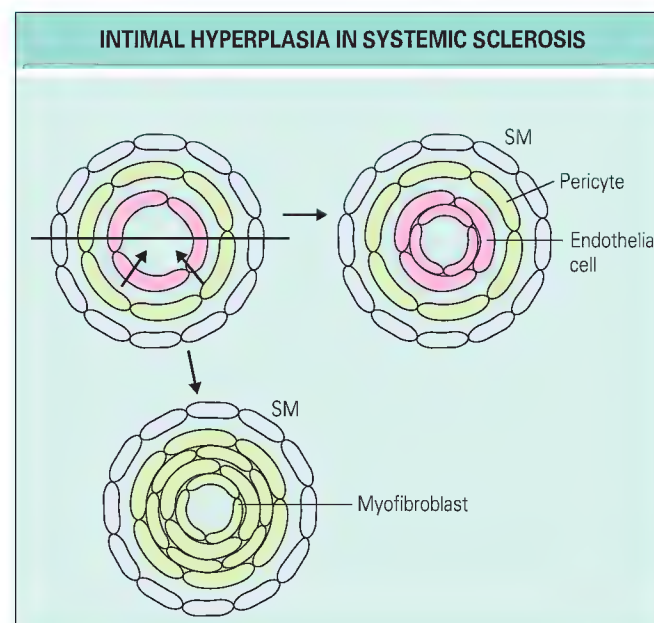


Fig. 143.12 Two cell types have most frequently been implicated in the intimal hyperplasia in systemic sclerosis. Some data support endothelial cells as the primary cell source for neointima, with hyperplasia of this normally single cell layer. Other data more strongly implicate pericytes in hyperplasia of these cells and endothelial cell apoptosis. The resulting lesion is an obliterative vasculopathy. SM, smooth muscle.

ventricular endothelium. Mature endothelial cells can be induced by TGF- β to undergo a similar transition *in vitro*, as demonstrated by the loss of endothelial cell markers such as platelet-endothelial cell adhesion molecule (PECAM) and the acquisition of mesenchymal markers such as α -smooth muscle actin. Endothelial-mesenchymal transformation contributes to cardiac fibrosis in a murine model.

Circulating endothelial cells and vascular progenitor cells

Circulating endothelial cells are mature cells that are shed from blood vessels, are normally present in only very low numbers, but are increased in a variety of vascular diseases, in which they appear to be markers of vascular damage. Circulating endothelial cells are increased in SSc, consistent with the known vascular injury. In contrast, circulating endothelial progenitor cells arise from the bone marrow and contribute to vascular repair. Reports on circulating endothelial progenitor cells in SSc have been conflicting, with both increased and decreased numbers being described. Circulating vascular progenitor cells have promise as potential therapeutic tools for the repair of damaged vessels.

Platelet activation and coagulation

Platelet activation and abnormalities in the coagulation system are often prominent in SSc. Elevated plasma levels of the platelet-specific proteins β -thromboglobulin and platelet factor 4 have been proposed as markers of progression from primary Raynaud phenomenon to SSc. Platelet activation in SSc might occur secondary to endothelial dysfunction and contribute to the occlusive arterial disease by release of PDGF, TGF- β , and serotonin, which also have an impact on fibrosis. The prominent microvascular thrombosis and enhanced intravascular fibrin deposition in SSc suggest defective endothelial control of coagulation and fibrinolysis. Defects in endothelial cell regulation of thrombosis and fibrin deposition may thus contribute to the intimal hyperplasia in SSc.

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Management of systemic sclerosis

■ VIRGINIA D. STEEN

- Effective management of systemic sclerosis (SSc) depends on secure diagnosis and subset classification determined from autoantibody status, the stage of disease, extent of organ-based complications, and the presence of overlap features.
- SSc patients should undergo regular screening for cardiopulmonary complications, even if asymptomatic. Clinical, serologic, and genetic factors may allow individualization of serial investigations in the future.
- Therapies that target the immune system and vasculature have been shown to be effective in placebo-controlled studies.
- Effective treatments for organ-based complications are emerging, especially for scleroderma renal crisis, pulmonary interstitial fibrosis, and pulmonary hypertension.
- Better understanding of the pathogenesis of SSc is likely to lead to the development of targeted approaches to attenuate key mediators of signaling pathways.

INTRODUCTION

The management of systemic sclerosis (SSc) is a major challenge that should be approached with a thorough understanding of current concepts of pathogenesis, the clinical features including classification and natural history, and an appreciation that there is much to be offered to patients. It is necessary to take a systematic approach to diagnosis and evaluation in each case to provide appropriate treatment. Many of the organ-based complications of SSc are treatable, if not curable. In particular, therapeutic advances in management of other medical conditions have been extrapolated to SSc. Angiotensin-converting enzyme (ACE) inhibitors developed for the treatment of hypertension dramatically changed the disease course and survival in scleroderma renal crisis, a previously deadly complication.¹ One-year survival rates of patients with scleroderma renal crisis went from 10% to 70% after this drug became available. Drugs that have less dramatic effects on overall survival but are equally important in terms of morbidity are calcium channel blockers, which were developed for hypertension but help Raynaud phenomenon, and proton pump inhibitors, which were developed to treat common hyperacidity and help the esophagitis resulting from esophageal dysmotility. These drugs have significantly improved the management of two of the most frequent and bothersome symptoms in scleroderma.

Classically, the disease has been divided into limited and diffuse cutaneous scleroderma, but prognosis and management are more importantly affected by the stage of disease, the autoantibody subset, and the type of organ involvement. Staging and subsetting are particularly important in scleroderma because patients have different levels of risk of experiencing the different manifestations of scleroderma during the course of their illness. The disease stage—early disease, chronic stable disease, or late-stage disease—is important when considering what aspects of the disease have the potential to be responded to available therapies. Autoantibody testing has been very helpful in identifying patients who are at risk of specific types of organ involvement.² Thus disease-modifying agents directed at the skin should be used primarily in patients with early disease (symptoms for less than 5 years) who have antitopoisomerase (anti-Scl-70), anti-RNA polymerase III, or an antinuclear antibody (ANA) with a nucleolar pattern. (Tests for the nucleolar-pattern ANAs anti-U3-RNP and anti-Th/To are not commercially available, but these antibodies are identified as an ANA with a nucleolar pattern on immunofluorescent assays). Patients with antitopoisomerase antibodies and nucleolar antibodies are at high risk of severe

pulmonary fibrosis, which needs to be treated aggressively even though these patients may have only limited cutaneous skin disease. Patients with the anticentromere antibody are the only patients with limited scleroderma who are not at risk of severe fibrosis and heart and kidney involvement, but they are at increased risk of isolated pulmonary arterial hypertension. On the other hand, patients with severe diffuse cutaneous disease with antibodies to RNA polymerase III are much less likely to develop severe lung disease but have an extremely high risk of renal crisis (25%).

Severe organ involvement, particularly pulmonary fibrosis, renal crisis, and cardiac involvement, occurs most often during the first 5 years in patients with diffuse scleroderma.³ Therefore if by 5 years such a patient does not have evidence of severe involvement of these organs, the patient has a decreased likelihood of developing these abnormalities during the remainder of the illness. However, any patient can have symptoms related to Raynaud phenomenon, digital ulcers, muscle or joint involvement, calcinosis, or esophageal or other gastrointestinal involvement throughout the entire course of the illness. Pulmonary arterial hypertension most frequently occurs late in the illness, and although it is most common in patients with limited cutaneous disease with anticentromere antibodies, it also occurs in some diffuse scleroderma patients with nucleolar-pattern ANAs.

Despite many advances and increasing numbers of clinical trials addressing scleroderma, unfortunately there still are no treatments that have been shown in a controlled clinical trial to modify mortality. However, over the last 10 years, our experience with clinical trial methodology has given us an appreciation of what has to be done to demonstrate effectiveness. The emergence of a number of attractive potential therapeutic agents that target key pathways in SSc pathogenesis make such treatment a real possibility in the foreseeable future.

PRINCIPLES OF EFFECTIVE MANAGEMENT

Clinical heterogeneity is a hallmark of scleroderma and ranges from prescleroderma or possible scleroderma (the presence of Raynaud phenomenon plus SSc-associated autoantibodies) at one end to rapidly progressive diffuse cutaneous SSc with multiorgan failure at the other. Between these extremes lie limited cutaneous SSc with and without organ involvement, diffuse cutaneous disease with less rapidly progressive skin manifestations but more organ involvement, and extensive diffuse cutaneous disease without organ involvement. Additionally, patients can have overlap syndromes with features of other autoimmune rheumatic disorders, most commonly polymyositis and Sjögren syndrome but also rheumatoid arthritis and systemic lupus erythematosus. These overlap syndromes often present major management challenges because there may be different levels of activity among the various disease components. Clearly not all patients require the same level of investigation or therapeutic intervention. Each patient requires an individual approach to the disease with evaluation and treatment of all appropriate problems.

Optimal management of SSc requires the following (Fig. 144.1):

- Establishing an accurate diagnosis at the earliest opportunity
- Staging disease by onset and rate of symptom progression and determining subset based on autoantibodies and organ system involvement so that appropriate screening, organ diagnosis, and treatment can be achieved in every patient
- Addressing all potential problems through early identification, appropriate therapy, and aggressive intervention for the more serious organ problems
- Educating patients regarding their own risk factors and prognosis and allowing them to participate in treatment with a holistic approach that recognizes the impact of the disease on lifestyle and relationships

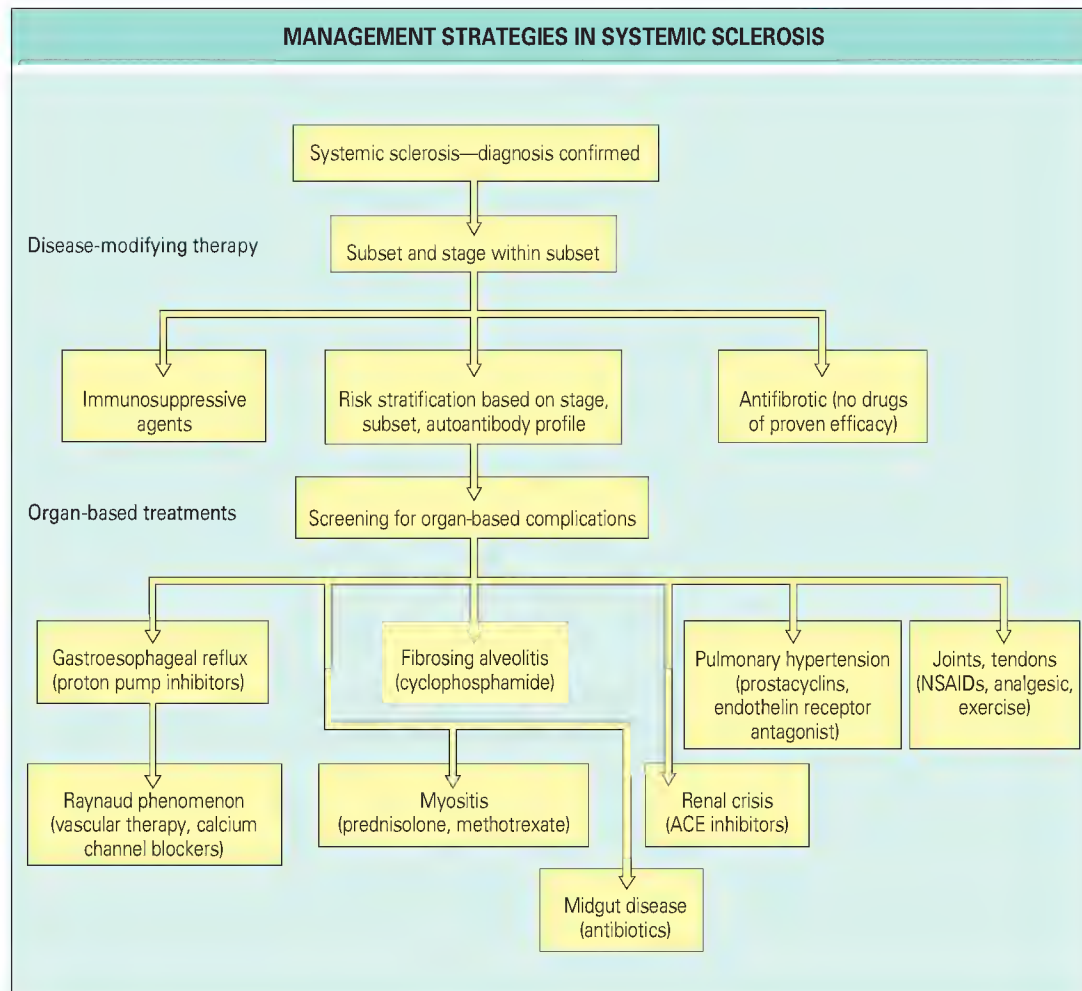


Fig. 144.1 Management in scleroderma requires multiple strategies depending on the specific problems that are present in individual patients. ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal antiinflammatory drugs.

Many manifestations require treatment throughout the course of the disease, based primarily on the symptoms that almost all patients have, such as Raynaud phenomenon; esophageal reflux; arthralgias, arthritis, and tendon involvement; fatigue; and sicca symptoms. These define the background therapy for all SSc patients. Identification of organ involvement requires additional testing, which, along with the stage of the disease, is helpful in determining the degree of disease activity and damage as well as the appropriate treatment. A noninflammatory myopathy or fibrotic arthropathy is treated differently from an inflammatory process. In some situations, identification of abnormalities in organ systems may not lead to any specific therapy but will help focus the timing of further screening or allow early intervention or treatment of associated problems. In general, to treat the whole scleroderma patient, it is important to remember that the whole is the sum of all the different components. Dissecting each potential involvement and making a decision about whether treatment, observation, or future screening is necessary allows the most optimal treatment for all scleroderma patients.

CLINICAL TRIALS IN SYSTEMIC SCLEROSIS

Difficulties in conducting clinical trials in scleroderma are well recognized. The clinical heterogeneity and variable natural history together with a paucity of global assessment measures have made performing clinical trials in SSc challenging.⁴ Other problems include absence of any treatment of proven efficacy to use as a comparative active control arm and understandable reluctance by both patients and their physicians to consider entering a placebo-controlled study involving a potentially life-threatening disorder. In particular, skin sclerosis has been found to be an unreliable measure of disease progression, in part due to its tendency in a cohort to improve over time after the first 12 to 18 months of disease. Thus in most reported placebo-controlled trials there has been improvement in skin score over time in the placebo-treated patients. Alternative approaches include longer-term studies with a time-to-event design and studies using organ-based endpoints

such as markers of lung function or functional capacity that reflect pulmonary disease. The first major study that has shown a statistically significant benefit in scleroderma is the study comparing cyclophosphamide with placebo in pulmonary fibrosis (Scleroderma Lung Study).⁵ Similarly, the recently completed studies examining prostacyclins and endothelin receptor antagonists as treatments for pulmonary arterial hypertension in scleroderma were major studies with positive results even though they were focused primarily on idiopathic pulmonary hypertension.⁶ These studies are among the very first trials in SSc that show both statistically positive results and are clinically meaningful. There is extensive international cooperation in the area of clinical trials,⁷ facilitated by the international Scleroderma Clinical Trials Consortium, which maintains a database of currently recruiting studies (details at <http://www.sctc-online.org>).

DISEASE-MODIFYING THERAPIES FOR SYSTEMIC SCLEROSIS

Few of the agents currently used as disease-modifying treatments for scleroderma-spectrum disorders have undergone rigorous placebo-controlled evaluation, and the results for those which have are mostly disappointing. No agent has been shown to be of unequivocal benefit, and even if such data were available, therapeutic gain must be carefully balanced against toxicity and considered in the context of the natural history of the condition. It may not be justifiable to use treatments with potentially serious adverse effects in patients with some scleroderma subsets such as limited cutaneous SSc, or even stable late-stage diffuse disease. It is likely that organ-based treatment strategies directed toward complications such as renal disease, pulmonary hypertension, or fibrosing alveolitis will have more immediate effect on mortality than the development of generalized disease-modifying strategies. Disease-modifying approaches can be classified according to the underlying pathogenic process that they target, including immunomodulatory and antifibrotic therapies (Table 144.1).

TABLE 144.1

Evidence based review of immunomodulatory and antifibrotic strategies for disease-modifying treatment of systemic sclerosis

Agent	Clinical trial data	Study	Grade*
Immunomodulatory agents			
Cyclophosphamide	Double-blind placebo-controlled trials examining use in SSc-associated pulmonary fibrosis	5, 9	A
Methotrexate	Placebo-controlled trial, 30 patients; significant improvement in skin score	10	A
	Larger North American study; inconclusive results	11	A
Mycophenolate	Favorable outcomes in skin, lung, and survival rate in uncontrolled trials and observational cohorts	12-14	B
Rituximab	Small, open, randomized trial showed favorable skin and lung outcomes, but prospective open study found no effect on skin	16, 17	A
		15	B
Immunoablation	Small short-term study comparing stem cell transplantation with high-dose intravenous cyclophosphamide (Cytosan); very favorable results	21	A
	Ongoing long-term studies USA and Europe	19, 20	C, A
Cyclosporine	Open study, 10 patients; improvement in skin score	23	C
Intravenous immunoglobulin	Improved skin and joint in open study	24	C
Extracorporeal photopheresis	First study suggested benefit but later evaluation equivocal	25	A
Oral induction of tolerance to type I collagen	Favorable pilot data; trial results positive for late-stage disease	26	A
Rapamycin	Small randomized study, no difference compared with methotrexate	27	A
Anti-tumor necrosis factor agents	Open-label study; variable effect on skin, good effect on joints	28	C
Antifibrotic agents			
Interferon- α	No difference with treatment, considered ineffective	29	A
Interferon- γ	Several uncontrolled studies with variable outcomes	30	C
D-Penicillamine	Uncontrolled studies with positive effects but controlled trial without evidence of response	31	B
		32	A
Relaxin	Phase 2 study promising but large phase 3 study negative; considered ineffective	33	A
Minocycline	Small open study with cured patients but larger uncontrolled study showing no effect	69	C
		34	B
Halofuginone	Plant alkaloid that downregulates collagen production in animal models of fibrosis; pilot study in scleroderma with positive results	70	C
Pirfenidone	Encouraging data in lung fibrosis but no formal study in scleroderma	35	A
Tyrosine kinase	Variable effects in several uncontrolled inhibitor trials showing increased toxicity	37, 38	B

*Findings of studies include this type of evidence:

Level A: Randomized Controlled Clinical Trial, cohort study.

Level B: Retrospective Cohort, Exploratory Cohort, Outcomes Research, case-control study; or extrapolations from level A studies.

Level C: Case-series study or extrapolations from level B studies.

Level D: Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles.

Immunomodulatory strategies

Cyclophosphamide

Cyclophosphamide, an immunosuppressive drug of proven efficacy in the management of a number of autoimmune rheumatic diseases, has been reported to be effective for SSc-associated lung fibrosis.⁸ Recently two major clinical trials evaluating cyclophosphamide in scleroderma-associated pulmonary fibrosis have been completed, a North American study evaluating oral cyclophosphamide⁵ and a UK study examining intravenous administration of the drug.⁹ Both showed a significant advantage for cyclophosphamide over placebo, although clinical benefit was modest. One of these studies also examined other aspects of SSc using the Scleroderma Health Assessment Questionnaire and skin score and suggested a more extensive benefit for cyclophosphamide. However, toxicity must be carefully balanced against efficacy. Premature ovarian failure, opportunistic infections, and the possibility of late secondary malignancies are important considerations in planning the route, dosage, and duration of cyclophosphamide administration.

Methotrexate

Methotrexate was studied in a small trial in the Netherlands¹⁰ that included 29 patients and was placebo controlled for 24 weeks followed by a 24-week open-label continuation in those patients who had shown an apparent response. This trial suggested benefit in terms of skin score and lung function test results. A substantially larger study conducted in North America has been reported. Although a minor advantage for active treatment over placebo was observed for skin sclerosis score, this was below the level considered clinically meaningful.¹¹ However, this trial was statistically

underpowered due to recruitment difficulties. Both studies used a 15-mg dose of methotrexate. The drug's usefulness in inflammatory myositis and arthritis can be just as great as in the other connective tissue diseases.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an antiproliferative immunosuppressive agent indicated for prevention of acute renal, cardiac, and hepatic transplant rejection. An open-label prospective study examined the use of 2 to 3 g of MMF daily for treatment of scleroderma, and some improvement in skin thickening was noted in patients with early diffuse scleroderma¹² compared with historical controls. However, in a large retrospective series 109 patients failed to show any improvement in skin score, although investigators did identify a survival improvement.¹³ Double-blind placebo-controlled trials examining the use of MMF to treat scleroderma skin manifestations have been very challenging and difficult to perform, and thus such a trial has not been done. Additional studies have focused on lung function and have shown promising effects with stabilization of lung function.¹⁴ MMF was well tolerated and there is an on-going controlled trial comparing MMF with cyclophosphamide primarily for treatment of interstitial fibrosis, but other disease aspects including skin manifestations will be evaluated.

Rituximab

Rituximab, a monoclonal anti-CD20 antibody that depletes CD20 expressing B lymphocytes, is increasingly being used to treat autoimmune disease. Initially used in immune-mediated cytopenias and lupus, it is now approved for treatment of rheumatoid arthritis and vasculitis. An open-label study involving 13 patients with early scleroderma showed little change in skin scores over a year.¹⁵ A recent small randomized study (eight treated patients

and six control subjects) looked at the use of rituximab in scleroderma patients with interstitial fibrosis.¹⁶ Two cycles (375 mg/m² weekly of intravenous rituximab for 4 weeks) were administered at baseline and at 6 months, and there was significant improvement in skin fibrosis as well as forced vital capacity and diffusing capacity in treated patients compared with untreated patients during the 1-year study. Continued stabilization occurred in these patients with retreatment over a 2-year period.¹⁷ In a prospective study Boselo and colleagues¹⁸ administered rituximab to nine patients with diffuse scleroderma who had shown no response to cyclophosphamide; these patients experienced a 43% improvement in skin score. A prospective controlled trial of rituximab is ongoing but is focused on joint manifestations.

High-dose immunosuppression with autologous peripheral stem cell transplantation

One of the most aggressive approaches to therapy for SSc is the use of immunoablation followed by reconstitution using autologous peripheral stem cell transplantation. The rationale for this therapy is similar to that for its use in other autoimmune diseases. Thus, if SSc is being driven by an autoimmune process, then ablation of autoreactive lymphocyte clones may block pathogenesis. If the immune system is reconstituted in the presence of the neoantigens responsible for autoimmunity then tolerance will be reestablished. However, even if such reestablishment of tolerance does not occur, it is still plausible that the intensive immunosuppression during this treatment will be directly beneficial. A variety of methods of mobilization and conditioning have been used for this treatment. Open-label studies at the Fred Hutchinson Cancer Center and the European Bone Marrow Transplant Registry have consistently shown very dramatic and rapid improvement in skin thickening.¹⁹ Most patients experience more than a 25% improvement in the first 6 months after the procedure. However, the long-term effect on organ systems is still unclear. There are patients who develop new organ abnormalities or a recurrence of aggressive disease after one of these transplants. Patients must be carefully screened at baseline to make sure they can tolerate the transplant-related morbidity, which may be life-threatening, and to determine if they have irreversible organ system disease, so only a small subset of patients would be eligible.²⁰

A recent single-site, small, randomized, controlled study (the ASSIST trial) compared stem cell transplantation with cyclophosphamide therapy. Patients undergoing stem cell transplantation showed significant improvement in skin and lung function over 2 years with no deaths from either severe disease or toxicity of the treatment.²¹ Cyclophosphamide treatment failed in eight of the nine patients receiving it, and seven of these patients crossed over to stem cell transplantation and also showed improvement. However, this study was quite small and included patients with milder disease, and the 2-year duration may have been too short to know whether recurrence of progressive disease will occur. Two large, randomized, controlled trials are currently under way: the Autologous Stem Cell Transplantation International Scleroderma Trial (ASTIS) in Europe and the Scleroderma, Cyclophosphamide or Transplant (SCOT) trial in the United States. Both are comparing stem cell transplantation with monthly pulse cyclophosphamide using similar assessment protocols so that data from these studies may ultimately be combined.

Cyclosporine

Because it suppresses T-cell activation, cyclosporine (cyclosporin A) has attractive properties for treating SSc, especially cases of aggressive diffuse cutaneous SSc in which there is marked immunologic activation. The main problem, however, has been toxicity. For scleroderma there are particular risks, especially from nephrotoxicity. One series found three of eight SSc patients treated with cyclosporin developed renal crisis and they thought that the rate of renal crisis in SSc patients treated using cyclosporine may be twice the expected rate.²² An open-label study of 48 weeks of cyclosporine administration suggested efficacy, although there was significant toxicity, especially at dosages above 3 to 4 mg/kg/day.²³ Tacrolimus, a drug in the same family, also has significant nephrotoxicity, which precludes its routine use in SSc.

Intravenous immunoglobulin

The use of pooled plasma of human polyclonal immunoglobulin G (IVIG) to treat SSc has been reported in several open studies. Usually 2 g/kg of IVIG were given over 2 to 4 days each month for 6 months. These open-label pilot studies have shown encouraging results, although they included patients with disease of variable duration and stage, so interpretation must be guarded.²⁴ Prospective studies are needed to determine its effectiveness in SSc.

Plasmapheresis and photopheresis for diffuse cutaneous scleroderma

Trials of plasmapheresis combined with immunosuppressive therapy were conducted more than 20 years ago, and this regimen was considered to be helpful in cases of diffuse cutaneous SSc; however, this combination has never been thought to be a realistic treatment for scleroderma. Another immunosuppressive strategy is extracorporeal photopheresis following sensitization of host leukocytes by methyl psoralen. In view of the presence of an infiltrate of active immune cells in early SSc, especially the diffuse cutaneous subset, there was a plausible theoretical basis for this mode of treatment. A clinical trial using a sham photopheresis control showed a significant improvement in skin and joints from baseline in treated patients, but this improvement was not statistically different from the results in control patients.²⁵

Tolerance to human type I collagen

In a disease whose pathologic hallmark is increased extracellular matrix deposition it is somewhat surprising that oral type I collagen administration is being proposed. The rationale is based on the observation that oral tolerance to type I collagen can be induced and the hypothesis that there may be an autoimmune reaction to collagen in SSc contributing to local production of cytokines and that induction of regulatory lymphocytes through establishment of oral tolerance may have a beneficial effect by modulating other cell types involved in disease pathogenesis. There are some experimental data supporting this approach, and results of a controlled trial were recently reported showing encouraging trends, particularly in late-stage scleroderma.²⁶ This treatment strategy has the advantage of apparently being safe, and it also may be effective in established disease, which is otherwise difficult to treat.

Other potential immunotherapies

Rapamycin, a macrolide antibiotic with antifungal and antitumor properties, inhibits interleukin 2–dependent T-cell proliferation. A small, randomized, single-blind study failed to find any difference between rapamycin and methotrexate in treatment of SSc, and the rapamycin-treated patients had significant toxicity.²⁷ Tumor necrosis factor- α antagonists have been used in the treatment of scleroderma.²⁸ Infliximab therapy for scleroderma was examined in an open-label study and was associated with some improvement in the Rodnan skin score, but the difference was not thought to be statistically significant. However, its use in scleroderma patients with an inflammatory polyarthritis was successful in controlling the joint symptoms.

Antifibrotic strategies

Interferons

Interferons (α , β , or γ) exert pleiotropic effects on fibroblasts *in vitro*, including downregulation of extracellular matrix gene expression. This led to the hope that the interferons might have antifibrotic activity *in vivo*. There were a number of encouraging pilot studies, and these prompted more extensive evaluation of interferon- γ and interferon- α . A placebo-controlled trial of interferon- α for treatment of early diffuse cutaneous SSc was undertaken in the United Kingdom.²⁹ However, a higher mortality and no benefit for skin manifestations or lung function were found in the active-treatment arm. Phase 2 studies of interferon- γ have suggested a modest benefit for skin sclerosis. There was a controlled trial that showed similar findings, but the patients had disease of very long disease. Overall, it is disappointing that interferons have not fulfilled their early promise; whether they will ultimately have any place in scleroderma treatment remains uncertain. A meta-analysis of recent studies examining the use of interferon- γ in idiopathic lung fibrosis showed improved survival in the treated patients.³⁰ This has prompted reexamination of this important group of biologic therapeutic agents.

D-Penicillamine

D-Penicillamine is a chelating agent that blocks the intramolecular and intermolecular cross-linking of collagen; this makes it a good potential antifibrotic agent, although as an earlier treatment for rheumatoid arthritis it showed some immune-modifying qualities as well. Multiple uncontrolled studies with large numbers of patients showed impressive improvement in the skin score in patients with early rapidly progressive scleroderma as well as a possible decrease in the occurrence of renal crisis and improved survival.³¹ However, there was an excellent double-blind controlled trial that failed to show any difference between high-dose and low-dose D-penicillamine.³² This trial included patients with early diffuse disease, but

they had milder, less aggressive disease than the patients in the earlier uncontrolled trials. Patients in the controlled trial had a mean skin score of 20 (out of a possible 51) at the start of the study, which decreased to 17 after 2 years of treatment. In contrast, patients in the uncontrolled trials had more severe disease at onset, beginning with a skin score of 28, which increased to 33 and then decreased to 17 after 2 years. It is unlikely that any further studies will be done, so it will not be known whether there is a subset of patients who have a more impressive response to this drug.

Recombinant human relaxin

Another agent studied is recombinant human relaxin. This hormone, normally present in significant amounts only in pregnant women, appears to have benefit in SSc. *In vitro* studies suggest that relaxin reduces synthesis of type I collagen by scleroderma fibroblasts, and a dose-escalating placebo-controlled trial has shown benefit based on self-report health assessment questionnaires. Although this treatment approach appeared very promising, a large phase 3 trial in North America yielded negative results, and this agent is no longer under active consideration.³³

Minocycline

Another drug that was initially examined in a very small study is minocycline. This agent has some possible antifibrotic properties in addition to being an antibiotic. The pilot uncontrolled study of 10 patients treated with minocycline was widely reported in the lay press, and results suggested dramatic responses to this drug. A larger open-label clinical trial in patients with diffuse scleroderma failed to show any significant improvement in skin scores after the use of minocycline.³⁴

Pirfenidone

Pirfenidone blocks activation of transforming growth factor- β (TGF- β), suppresses elevation of lung basic fibroblast growth factor, and prevents bleomycin-induced decrease in lung interferon- γ levels. Pirfenidone has demonstrated positive effects in both a pilot study and a phase 2 double-blind trial in idiopathic pulmonary fibrosis. These studies have shown promising results, although the controlled trial had some methodologic problems. Results from several phase 3 trials have recently been reported showing significant delay in deterioration in pulmonary function, and these findings led to approval of the drug for treatment of idiopathic pulmonary fibrosis in Europe and Japan; however, the U.S. Food and Drug Administration (FDA) has required an additional study.³⁵ Pirfenidone has not been tried in scleroderma.

Tyrosine kinase inhibitors

Imatinib mesylate is a small-molecule tyrosine kinase inhibitor that binds to the adenosine triphosphate binding pocket of Abelson kinase (c-abl) and efficiently blocks its tyrosine kinase activity; c-abl is an important downstream signaling molecule of TGF- β . Recent studies suggest that imatinib mesylate strongly inhibits the synthesis of major extracellular matrix proteins by fibroblasts from SSc patients. Treatment with imatinib mesylate efficiently reduced the development of fibrosis in animal models of fibrosis. The potent antifibrotic effects *in vitro* and *in vivo* in animal models, as well as the good clinical experience in other diseases, have led to multiple clinical trials of the use of imatinib mesylate in scleroderma and other fibrotic states. Hinchcliff³⁶ demonstrated impressive effects of imatinib mesylate on scleroderma fibroblasts *in vitro*. The largest of the open-label trials included 30 scleroderma patients and showed an improvement in the modified Rodnan skin score from baseline as well as some improvement in lung function.³⁷ Patients experienced a lot of toxicity, but it was manageable. Another study used a higher dose that produced unacceptable toxicity.³⁸ A small, controlled trial was unable to show significant improvement in modified Rodnan skin scores or skin biopsy findings in patients treated with imatinib mesylate.³⁹ Several other small, open-label studies in scleroderma focusing on skin or lung for which results have been presented in only abstract form have failed to show significant improvement with tyrosine kinase inhibitors. It is unclear whether the toxicity of the tyrosine kinase inhibitors will prevent further studies in subsets of patients.

Other potential antifibrotic agents

TGF- β is thought to be a key factor in the fibrogenesis in SSc. It promotes fibroblast activation and stimulates collagen synthesis.⁴⁰ The powerful profibrotic activity of this growth factor *in vitro* suggests that blockade *in vivo* may have a potent antifibrotic effect. Blocking strategies that have been used in preclinical animal studies include the use of neutralizing antibodies, recombinant soluble receptors, and small-molecule inhibitors of downstream signaling intermediates. Other exciting potential agents include blockers of connective tissue growth factor⁴¹; histone deacetylase 7;

rosiglitazone, which prevents cell differentiation and progression of fibrosis through the transcription factor peroxisome proliferator-activated receptor- γ ; and tocilizumab, a potent inhibitor of interleukin-6, which seems to play a major role in fibrosis in scleroderma and scleroderma animal models.

ORGAN-BASED ASSESSMENT AND TREATMENTS

Progress in managing organ-based complications has been made primarily by drawing an analogy with other medical disorders such as peptic ulcer disease, systemic hypertension, idiopathic pulmonary fibrosis, and pulmonary hypertension. As with many other chronic diseases a multidisciplinary approach to therapy is useful to address patients' physical, emotional, and social requirements as well as their medical problems. Physical therapy and aggressive exercise programs to maintain finger function, prevent joint contractures, and improve strength is extremely important, particularly because the treatment of skin disease is not satisfactory. The natural history of the disease is associated with some improvement in skin thickening, but if there are severe contractures, skin softening will not improve function. Patient education with careful explanation of the disease and its complications is integral to the successful management of the disease. Specialist nurse-educators, telephone help lines, and patient support organizations all have a valuable place in management. Although organ involvement is closely correlated with the stage and subset of the disease, treatments for the specific problems are similar across all subtypes of scleroderma.

Raynaud phenomenon

The most frequent manifestation of scleroderma is episodic peripheral vasospasm (Raynaud phenomenon), present in 95% of cases. Although many studies have confirmed the efficacy of vasodilators in primary Raynaud phenomenon, treatment of scleroderma-associated vasospasm is much more difficult. Calcium channel blockers are a standard treatment, but a recent evidence-based review of the treatment of scleroderma-related Raynaud symptoms found evidence of efficacy for α -blockers, ACE inhibitors, angiotensin II receptor antagonists, antithrombotics and inhibitors of platelet aggregation, biofeedback, hand exercises, relaxation therapy, serotonin reuptake inhibitors, smoking cessation, and warming of the hands and feet (Table 144.2).

There is considerable evidence implicating reactive oxygen species in the pathogenesis of SSc. Indirect support comes from studies showing reduced levels of micronutrient antioxidants in SSc patients and increased susceptibility of serum lipoproteins to oxidation. Further evidence is provided by increased levels of oxidative metabolites of prostaglandins in SSc patients. It has been suggested that oxidative fragmentation of hallmark antigens to reveal cryptic epitopes may provide a mechanistic link between the vascular and immunologic features of SSc. With this background several studies of antioxidant agents have been undertaken. Unfortunately, a recent review of complementary and nutritional therapies including probucol, vitamin E, and ascorbic acid could not confirm any significant effect of these types of treatment in scleroderma and Raynaud phenomenon.

There are a variety of pharmacologic treatments for the management of Raynaud symptoms. Calcium channel blockers remain the first-line agents for Raynaud phenomenon but frequently are not tolerated because of the vasodilatory effects of lowered blood pressure, headache, and peripheral edema.⁴² Angiotensin blockers and 5-hydroxytryptamine antagonists have been shown to be helpful in clinical trials, but a long-term controlled trial using the ACE inhibitor quinapril found it ineffective.⁴³ There are anecdotal reports that antiplatelet agents such as clopidogrel may be helpful in some patients with severe scleroderma-associated vasculopathy, although aspirin has not been shown to be helpful.

The most serious complication of Raynaud phenomenon is critical digital ischemia and ulceration. This is likely due to structural vascular disease as well as vasospasm. Sildenafil, a phosphodiesterase inhibitor (20 mg three times a day), and tadalafil can be particularly helpful in hastening healing of these ulcers.^{44,45} Intermittent infusions of prostacyclin or its analogues have been shown to be effective but they are costly and not available in the United States.⁴⁶ Orally active formulations of prostacyclin or its analogues are an attractive option, but unfortunately two large studies recently published in Europe and North America have failed to conclusively demonstrate efficacy. A pilot study showed the effectiveness of subcutaneous treprostinil, a potent prostacyclin used in pulmonary hypertension, and an oral preparation is now being studied for treatment of digital ulcers in scleroderma.⁴⁷ Bosentan, a dual-specificity endothelin receptor antagonist also used in pulmonary hypertension, has recently been shown in two large studies to prevent the development of new ischemic digital ulcers in scleroderma,

■ **TABLE 144.2**
Vascular therapies for Raynaud phenomenon

Treatment	Examples	Comments	Study	Grade*
Nondrug	Hand warmers, protective clothing	Universally helpful.		
Nutritional	Evening primrose oil	Symptoms improve.		
	Fish oil capsules	Symptoms improve only in primary Raynaud, not scleroderma.		
	Antioxidant vitamins	Theoretical benefit but no controlled trial evidence.	71	C
Pharmacologic for Raynaud phenomenon				
Calcium channel blockers	Nifedipine, amlodipine, diltiazem	Variable and differential response to different agents. Slow titration of dose reduced the severity of adverse effects.	42	A
Angiotensin-converting enzyme inhibitors (quinipril)		No evidence of effectiveness.	43, 72	A
Angiotensin receptor blockers	Losartan	Effective in clinical trial, but limited effectiveness in practice.	68	A
5-HT antagonists	Ketanserin	5-HT receptor antagonist; limited availability.	73	A
Selective serotonin reuptake inhibitor	Fluoxetine	Readily available; clinically less effective, but fewer vasodilatory adverse effects than with calcium channel blockers.	74	A
Treatment for ulcer healing				
Phosphodiesterase inhibitors	Sildenafil, tadalafil	Clinical trials show improvement in Raynaud manifestations and ulcer healing.	44, 45	A
Parenteral vasodilators	Iloprost, prostaglandin E ₁ , treprostinil	Effective in healing ulcers and reducing severity and frequency of Raynaud attacks. Expensive with limited long-term benefit.	46 47	C B
Endothelin receptor antagonists	Bosentan	Clinical trials show decreased new ulcers (approved for ulcers in Europe but not in United States).	48, 49	A
Statins		Single study showing decreased occurrence of ulcers.	50	A
Local management of ulcers		Wound-healing techniques, topical antibiotics, soaking, occlusion, débridement. Systemic antibiotics as necessary. Adequate analgesia (including narcotics if necessary).		
Surgical procedures				
Radical microarteriolytic, digital sympathectomy		Division of adventitia of digital arteries; sometimes termed <i>digital sympathectomy</i> . Useful treatment for individual critically ischemic digits.	51	B
Botulinum toxin A (Botox) "sympathectomy"		Small studies promising but clinical trials needed.	52	C
Débridement, amputation		Autoamputation is best to allow maximum preservation of healthy tissue. Surgery should be conservative and reserved for infection or intractable pain.		

**Findings of studies include this type of evidence:*
Level A: Randomized Controlled Clinical Trial, cohort study.
Level B: Retrospective Cohort, Exploratory Cohort, Outcomes Research, case-control study; or extrapolations from level A studies.
Level C: Case-series study or extrapolations from level B studies.
Level D: Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles.
5-HT, 5-hydroxytryptamine.

although it does not speed ulcer healing.^{48,49} Bosentan (125 mg twice a day) has been approved for the prevention of digital ulcers in Europe but not in the United States. The high cost of this agent may limit clinical use. Statins display pleiotropic effects on endothelial function that may potentially retard vascular injury. A recent study using atorvastatin 40 mg daily showed a decreased frequency of new digital ulcers in scleroderma patients treated with the drug.⁵⁰

Ulcers located over bony prominences, such as the phalangeal joints and elbows, are thought to be caused by repetitive microtrauma and the difficulty in healing to be due to atrophic, avascular tissue overlying the joints. Management of both these ulcers and digital ulcers relies on wound-healing techniques, with soaking, application of topical antibiotic or débriding agents, and occlusion. Systemic antibiotics may be necessary. Adequate analgesia, even use of narcotics, may be necessary because severe pain leads to further vasospasm. Healing often takes a long time and patience is necessary. Surgical treatments that are gaining popularity include radical microarteriolytic (digital sympathectomy) and microvascularization in some patients with involvement of vessels other than digital ones.⁵¹ Endoscopic thoracic sympathectomy is being used in Japan, and botulinum toxin type A⁵² is being used by some hand plastic surgeons instead of digital sympathectomy.

Musculoskeletal complications

Most patients with SSc describe some musculoskeletal symptoms. Arthralgia, stiffness, and carpal tunnel syndrome are common early in the disease. Frank arthritis is uncommon and points toward an overlap syndrome. However, if there is significant synovitis that is not easily controlled, then treatment with hydroxychloroquine, methotrexate, or even anti-tumor necrosis factor may be effective.⁵³ Tendon friction rubs, noninflammatory fibrotic involvement of the tendons, are palpated primarily on the palms, wrists, and lower legs. They are associated with a poor prognosis primarily because they are most often seen in early diffuse scleroderma. They can thus be a clue to the diagnosis of scleroderma and diffuse scleroderma. The consequences of joint and skin involvement are contractures. In diffuse scleroderma these contractures can be very severe in the hands and wrists as well as in the proximal joints. An aggressive hands-on stretching exercise program should be an integral part of treatment for all patients newly diagnosed with diffuse scleroderma. It is very important to try to prevent the development of contractures, because once they are fixed they are extremely difficult to reverse even when the skin improves. Physical and occupational therapists must play an integral role in the management of scleroderma patients. Stretching exercises as opposed to strengthening exercises or

splinting seem to be the most effective and best tolerated and should be the mainstay of a home program as well. Even patients with limited scleroderma who have severe puffiness and tightness of the hands can benefit from a hand exercise program. Antiinflammatory agents and low-dose corticosteroids (5 to 10 mg prednisone/day) can be tried, particularly if there is joint or tendon inflammation. More important, however, is the control of pain. If there is severe pain with motion, the patient will not be able to perform the exercises adequately, and contractures will be worse. Often the pain is severe enough to require even low doses of long-acting narcotics. Most important is to keep patients comfortable to keep them moving.

Muscle involvement can be both a typical inflammatory myositis akin to polymyositis and a blander fibrotic myopathy. Both can be associated with an elevation in the creatine phosphokinase level, but inflammatory findings on electromyography, magnetic resonance imaging, and biopsy should guide the treatment. If the muscle weakness is mild, then methotrexate and/or azathioprine with low-dose prednisone may be enough to treat the inflammatory myositis. If high-dose prednisone is necessary, careful observation of blood pressure is necessary to ensure that renal crisis does not develop. There is no evidence that ACE inhibitors aid in preventing renal crisis, so they should not be used unless the patient develops hypertension. At that time, very close monitoring of the blood pressure and renal function is necessary. Patients with a bland myopathy may respond to low-dose prednisone but more important is muscle strengthening. Patients with mild proximal weakness can develop shoulder contractures, so stretching exercises as well as strengthening exercises should be done.

Skin disease

Skin sclerosis is present in patients with almost all forms of SSc except in some patients with very early disease and those with the rare subtype designated *systemic sclerosis sine scleroderma* in whom vascular and visceral manifestations occur in the absence of skin involvement. Treatment of the disease is rarely dictated by its cutaneous manifestations, however. Visceral involvement is far more important in terms of morbidity and mortality. Nevertheless, skin discomfort, pruritus, burning, and actual pain can be very debilitating in patients with early diffuse scleroderma. Systemic antihistamine therapy can provide some relief for intractable itching; pregabalin seems to be helpful for the prickly, burning pain that may be caused by entrapment of the cutaneous sympathetic nerves by the thickened skin; and narcotic analgesia may be necessary for the painful skin. Use of topical agents has not been associated with clinical softening, but emollients, moisturizers, and topical anesthetics may give some patients temporary relief.

It is not uncommon for patients with severe skin sclerosis to experience stabilization and even softening of the skin with time, especially by 5 years from diagnosis. This improvement in skin thickening, whether it is due to the natural history or the effect of medication, is also associated with improved survival.⁵⁴

Another frequent cutaneous manifestation of scleroderma is the development of cutaneous dilated loops of small blood vessels (telangiectasia). It should be noted that telangiectasia, although it occurs especially in patients with limited cutaneous SSc (sometimes termed *CREST syndrome* [calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia])—also is frequently present in patients with late-stage diffuse cutaneous SSc. Indeed these patients may become more florid in the plateau phase of diffuse cutaneous SSc, even when the skin sclerosis diminishes. These lesions are often distressful to patients cosmetically but also because of concern that they indicate the disease is progressing. Patients should be reassured that they have no relationship to disease activity. Hemorrhage from mucosal telangiectasia is also becoming increasingly recognized as a clinical problem and may require local therapy if it is recurrent. Cosmetic camouflage techniques can be very effective for masking facial telangiectasia, and appropriate advice should be offered to all patients who might benefit. Recently pulsed dye laser therapy has also been used with some success.

In addition to skin thickening, other cutaneous manifestations include calcinotic nodules, especially in limited scleroderma. No medical therapy has been shown to be effective. Local pain, progression of contractures, and functional impairment occur and may contribute to ulcer formation. Surgical removal may be beneficial, although often the calcinosis is too diffuse within the tissue to debulk easily. The pathogenesis of calcinosis is not known and has not been studied very well. A recent study found that the protein expression of osteonectin and matrix carboxyglutamic acid was increased in SSc patients compared with controls and particularly in patients with calcinosis.⁵⁵ These proteins are known to play a role in some types of calcification processes in other diseases, so perhaps further studies will lead to a better understanding of this process. Although warfarin, colchicine,

probenecid, bisphosphonates, diltiazem, minocycline, aluminum hydroxide, salicylate, surgical extirpation, and carbon dioxide laser therapies have been used, no treatment has convincingly prevented or reduced calcinosis.⁵⁶ Tumor necrosis factor- α inhibition was reported to improve calcinosis symptoms in patients with juvenile dermatomyositis, so perhaps it may be helpful in some cases.

Macrovascular disease

In addition to the classic involvement of the renal and pulmonary arteries, macrovascular disease has been reported to be increased in SSc. Involvement of the large arteries in the extremities can lead to ischemia. Increased aortic arterial stiffness, impaired endothelium-dependent vasodilatation, and increased coronary artery calcification have been seen in scleroderma, but in one study investigators could not find increased signs of atherosclerosis or premature myocardial infarctions.⁵⁷ Most survival studies do not show increased coronary artery-related deaths in scleroderma, although cardiopulmonary deaths are very common. One study found that acute myocardial infarctions occurred in only 1% of 1000 hospitalizations of scleroderma patients and was thus quite unusual.⁵⁸

Gastrointestinal complications

Involvement of the gastrointestinal tract is extremely common in scleroderma (Table 144.3). Abnormalities have been demonstrated throughout its length, although esophageal involvement is the most frequently, occurring in up to 80% of patients. Simple measures such as elevating the head of the bed and not eating for several hours before bed are important and useful adjuncts to more sophisticated treatments. Clinical benefit is obtained from acid-suppressive therapies and proton pump inhibitors are dramatically effective, so that use of these as first-line treatment often is justified. High doses may be needed to control severe esophagitis. Additional benefit can be obtained from adding a motility drug such as metoclopramide, although it has many adverse effects. Unfortunately, cisapride and a related motility drug, domperidone, which have fewer adverse effects, are unavailable in the United States. Erythromycin also has some promotility effects, which are most effective in the stomach.

Small intestinal hypomotility with pseudo-obstruction and bacterial overgrowth has been shown to occur frequently in SSc. Bloating, nausea, vomiting, diarrhea, abdominal distention, and malabsorption may occur and may be devastating, because there is no treatment that can reverse this process. Promotility agents including metoclopramide, domperidone, and erythromycin can be helpful, but as noted earlier they often have adverse effects, and the associated cardiac toxicity has led the FDA to withdraw approval for several agents. Broad-spectrum antibiotics, including metronidazole, ciprofloxacin, tetracycline, and amoxicillin in varying dosages, are helpful in treating bacterial overgrowth and can be dramatically effective in some cases. Sometimes intermittent courses of a single agent are effective, but refractory cases may require rotation of antibiotics. There is no one approach that can be used for all patients. Different regimens of antibiotics must be tried. Although a hydrogen breath test may confirm bacterial overgrowth, an empiric trial of antibiotics should be initiated in symptomatic patients even without this test. In severe cases with malnutrition, octreotide (subcutaneous octreotide 0.1 mg twice daily or intramuscular octreotide long-acting release 20 mg/mo) has been used effectively.⁵⁹ Consumption of frequent small meals, use of high-protein supplements, and in refractory cases total parenteral nutrition may be necessary. Gastric or jejunal feeding tubes should not be used, even in patients with severe esophageal problems, because of the poor motility throughout the intestinal track in scleroderma. Gastroparesis is present in up to 50% of scleroderma patients and contributes to the esophageal and small bowel symptoms in these patients.

Gastric antral venous ectasia has a characteristic appearance on endoscopy that has led to the name *watermelon stomach*. It manifests as iron-deficiency anemia due to recurrent or chronic gastrointestinal bleeding, which is often silent and entirely asymptomatic until severe anemia develops. A recent study found this complication not only in patients with long-standing limited scleroderma but also in patients with early severe diffuse scleroderma associated with the anti-RNA polymerase III antibody.⁶⁰ It is an important diagnosis because the condition is potentially life-threatening and also because it is amenable to treatment using laser photocoagulation. Such intervention is warranted because chronic hemorrhage from these and other telangiectatic lesions is a significant cause of iron deficiency in SSc.

Anal involvement is also common but is underdiagnosed. Incontinence, often described as diarrhea by patients, is the most common complaint. It is important to inquire specifically about anorectal dysfunction so that

TABLE 144.3
Gastrointestinal tract disorders in systemic sclerosis

Site	Disorder	Symptom	Investigation	Treatment
Mouth	Tight skin Dental caries Sicca syndrome	Cosmetic Toothache Dry mouth	None Dental radiograph Salivary gland biopsy	Facial exercises Dental treatment Artificial saliva
Esophagus	Dysmotility/esophageal spasm Reflux esophagitis Stricture	Dysphagia Heartburn Dysphagia	Barium swallow Esophageal scintigraphy Manometry, endoscopy	Proton pump inhibitors Minimize NSAID and calcium channel blocker use Elevate head of bed, avoid late meals
Stomach	Gastric paresis NSAID-related ulcer Gastric antral vascular ectasia or watermelon stomach	Anorexia Nausea, early satiety Severe anemia, silent blood loss	Scintigraphy Endoscopy, barium meal Endoscopy	Proton pump inhibitors Metoclopramide, domperidone Laser coagulation
Small bowel	Hypomotility Stasis Bacterial overgrowth NSAID enteropathy Pseudo-obstruction Pneumatosis intestinalis	Weight loss Postprandial bloating Malabsorption Steatorrhea Abdominal pain Distention Diarrhea with blood, benign pneumoperitoneum	Barium follow-through ¹⁴ C glycocholate or hydrogen Breath test Jejunal aspiration Fecal microscopy Plain abdominal radiography Plain abdominal radiography	Rotational antibiotics, metronidazole, ciprofloxacin, rifaximin Domperidone, metoclopramide Octreotide (low dose) Oral nutritional supplements Parenteral nutritional support Conservative management
Large bowel	Hypomotility Colonic pseudodiverticula Pseudo-obstruction	Alternating constipation and diarrhea Rare perforation Abdominal pain, distention	Barium enema/CT of abdomen Barium enema/CT of abdomen Plain abdominal radiography	Dietary manipulation, stool expanders for constipation, loperamide for diarrhea (Resection as a last resort) Conservative management
Anus	Sphincter involvement	Fecal incontinence	Rectal manometry	Kegel exercises, protective measures, sacral nerve stimulation

CT, computed tomography; NSAID, nonsteroidal antiinflammatory drug.

patients can be offered clear advice to help them cope with this distressing manifestation.

Barrett metaplasia of the lower esophageal mucosa is quite common in SSc patients, although the optimal frequency of surveillance and treatment of minor abnormalities is unclear. Reports suggest that metaplasia can improve and that malignant transformation is less frequent than in patients without SSc.

Cardiac disease

Cardiac involvement in scleroderma is common, as demonstrated by a variety of noninvasive tests and autopsy studies, but its contribution to patient outcomes is unclear. Severe cardiomyopathies are unusual but can be associated with renal crisis and systemic myositis. Other cardiac features including pericardial effusions, arrhythmias, and diastolic dysfunction are quite common.

Treatment of cardiac manifestations currently parallels the management of similar clinical events occurring outside the context of SSc. Thus antiarrhythmic agents are used to treat hemodynamically significant dysrhythmias and pacemaker insertion is considered when there is evidence of significant conduction abnormalities. Conduction defects are the most frequent electrophysiologic disturbances in SSc, and these may be associated with reentrant tachyarrhythmias. Some cases have been reported in which reentrant monomorphic ventricular tachycardia in SSc patients responded to local ablative therapy. At this point, optimal treatment of this type of diastolic dysfunction has not been clarified even in nonscleroderma patients.

Levels of markers of myocardial damage such as troponin T and N-terminal pro-brain natriuretic peptide, which are common markers for both left- and right-sided heart failure, are often elevated in SSc and may be helpful in monitoring response to treatment for cardiac disease. There is no evidence that any immunosuppressive or vasodilator has had any specific effect in scleroderma heart disease.

Renal scleroderma

The most important renal complication in SSc is scleroderma renal crisis (Fig. 144.2). Several studies have documented that corticosteroid use (more than 15 mg prednisone per day or equivalent) may predispose to the development of scleroderma renal crisis.⁶¹ Patients at increased risk, particularly

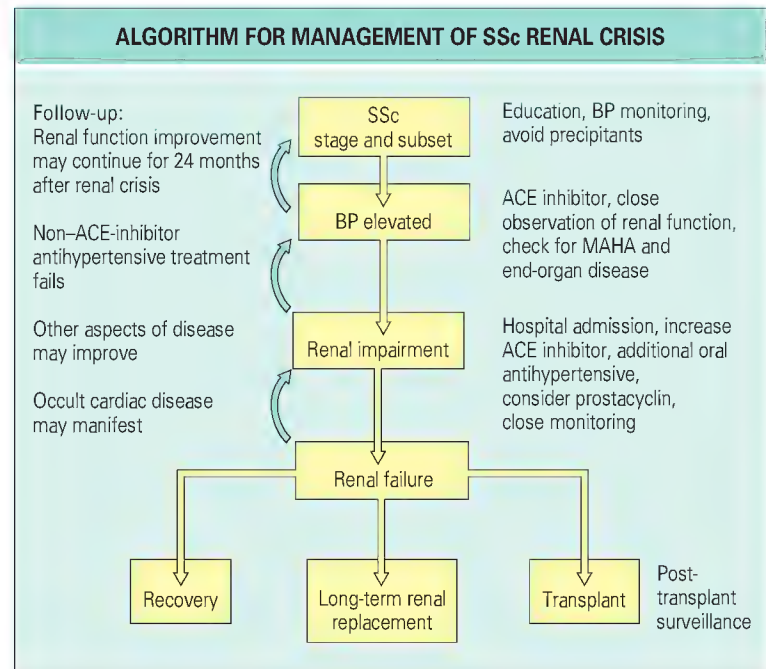


Fig. 144.2 Management of scleroderma renal crisis requires careful evaluation, prompt diagnosis, and aggressive treatment with ACE-inhibitors. ACE, angiotensin-converting enzyme; BP, blood pressure; MAHA, microangiopathy hemolytic anemia; SSc, systemic sclerosis.

those with early diffuse cutaneous disease, should be educated to monitor their blood pressure regularly. New-onset hypertension, often with marked elevation of pressure, and retinopathy and other signs of end-organ damage, including blood and protein in the urine, are indications of a life-threatening illness. Widespread early use of ACE inhibitors has clearly improved survival rate,⁶² but the overall prognosis of scleroderma renal crisis still is not adequate. Thirty percent of patients still progress to renal replacement

therapy. It is nevertheless a significant mark of progress that renal crisis is no longer the most frequent cause of scleroderma-associated death.⁶³

Hypertension should be treated with ACE inhibitors. The use of shorter-acting captopril allows more flexibility in adjusting the dosage, but any ACE inhibitor is effective. Although angiotensin receptor blockers and renin inhibitors should be effective in treating scleroderma renal crisis, there is little information as to their effectiveness compared with ACE inhibitors. Renal function often continues to deteriorate even after blood pressure is adequately controlled, but the ACE inhibitor must be continued. If maximum ACE inhibition has not controlled blood pressure, the use of calcium channel blockers, hydralazine, or clonidine may be necessary.⁶⁴ There is controversy over whether prophylactic use of ACE inhibitors prevents renal crisis. However, two recent studies examining the British and French experience with renal crisis in large scleroderma populations have shown a worse outcome in patients who, for whatever reason, used ACE inhibitors before renal crisis occurred.^{65,66} Additionally, a prospective observational study confirmed that prior treatment with ACE inhibitors before the onset of renal crisis was associated with increased morbidity and mortality.⁶⁷ The reason for a worse outcome may be that the low dosage of ACE inhibitors does not prevent the development of renal crisis and instead blunts the effects of the acute hyperreninemia, thus masking the onset of renal crisis and causing a more chronic, less reversible process. Thus, if an ACE inhibitor is being used, a high-risk patient still needs to be followed very closely.

An audit of the United Network for Organ Sharing database in North America confirmed the feasibility and acceptable long-term outcome of renal transplantation in patients with SSc.⁶⁸ Considerable recovery in renal function often occurs after an acute crisis, and improvement can continue for up to 2 years, which frequently allows dialysis to be discontinued. Therefore decisions regarding renal transplantation should not be made before this time.

SUMMARY

Although SSc is an uncommon disease, it is an important one because it has the highest mortality of any of the rheumatic disorders. Also, much can be learned from it, because it is a paradigm for other more common medical conditions in which immunologically triggered fibrosis occurs, such as liver cirrhosis and idiopathic pulmonary fibrosis. All patients with scleroderma-spectrum disorders should be assessed by physicians familiar with these conditions. In this way the diagnosis is confirmed, patients can be educated about the disease, and follow-up and treatment can be tailored according to stage, subset, and activity. Further advances in management will require interventional studies to confirm the efficacy of current treatments and test novel agents. Management of life-threatening complications should be proactive, with screening of patients at risk and commencement of therapy at the earliest opportunity. Importantly, there have been real advances in the management of the major and most deadly complications. ACE inhibitors appear to have substantially improved survival of renal scleroderma crisis. There is evidence that cyclophosphamide is effective in scleroderma-associated pulmonary disease, and there are now many therapeutic agents approved for use in pulmonary hypertension, which makes even this previous deadly complication treatable. Improved management of Raynaud phenomenon with calcium channel blockers, treatment of reflux with proton pump inhibitors, and aggressive physical therapy have all improved the morbidity of scleroderma.

Survival studies strongly suggest that outcomes for scleroderma patients have improved significantly over the past 25 years, and scleroderma should now be considered treatable, if not curable. More therapeutic agents are being studied in scleroderma than ever before, which brings more hope that they will lead to even better management and effective treatment for all aspects of this difficult disease.

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Pulmonary management of systemic sclerosis

■ CHRISTOPHER P. DENTON ■ VOON H. ONG

- Significant progress has been made over the past decade in the assessment and management of pulmonary complications of systemic sclerosis, particularly interstitial lung disease and pulmonary arterial hypertension (PAH).
- High-resolution computed tomography and lung function tests are critical in detection and treatment of interstitial lung disease and also in prediction of outcome with treatment.
- Patients are most at risk of rapid decline in lung fibrosis in early-stage scleroderma, and treatment with cyclophosphamide may lead to stabilization of disease.
- With a goal-directed approach and current PAH-specific therapies, survival has improved, although the extent to which contributory processes such as coexisting lung disease may operate justifies careful consideration, and use of a screening algorithm for those at risk may improve early detection and treatment.

INTRODUCTION

Pulmonary complications of systemic sclerosis (SSc) are the single largest cause of disease-related mortality in a condition that has the highest death rate of any of the autoimmune rheumatic diseases. There has been significant progress in the area of management—in particular, in the assessment and treatment of both interstitial lung fibrosis and pulmonary arterial hypertension (PAH), the two most important pulmonary manifestations of SSc.

SPECTRUM OF PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS

There are many ways in which SSc can affect the lungs, although the two most important complications are PAH and interstitial fibrosis, shown histologically in [Fig. 145.1](#). This includes involvement of the chest wall skin and underlying connective tissue that may directly restrict respiratory excursion, muscle involvement with inflammation, and fibrosis that impairs ventilation of the lungs. Pleural disease can occur with pleural effusions, although this is less common than in other inflammatory rheumatic diseases and may be a clinical indication of an overlap syndrome.

Interstitial fibrosis is common in SSc but of variable severity and in some cases may not be clinically significant. Identification of more severe cases and prediction of the likelihood of future progression are cornerstones of the management of SSc-associated pulmonary fibrosis. Most often, lung fibrosis has a pattern of nonspecific interstitial pneumonia (NSIP) on histologic examination and high-resolution computed tomography (HRCT), although other forms may occur, especially usual interstitial pneumonia (UIP) and organizing pneumonia, that can later progress to NSIP.

Pulmonary vascular disease represents another frequent and important manifestation. Postcapillary PAH is the most common form of the disease, and this is a complication that has benefited from major therapeutic advances over the past decade. However, other forms of pulmonary hypertension occur, including cases due to lung fibrosis and hypoxia (group 3) and cases associated with cardiac involvement, notably diastolic dysfunction (group 2). Another important form of PAH is classified in the 1' group, pulmonary venoocclusive disease (PVOD).

Recent studies also reported cases of aspiration pneumonia and lung malignancy in patients with SSc and interstitial lung fibrosis. Cardiac complications including cardiac failure and pulmonary edema are also important.

Dyspnea in systemic sclerosis

All patients with scleroderma should be regularly evaluated to identify the presence of symptoms that could reflect significant pulmonary disease. Breathlessness is very frequent in SSc and may have multiple causes ([Fig. 145.2](#)). Careful questioning and assessment for associated factors including chest wall myopathy, deconditioning, and cardiac disease are critical to differentiate the underlying mechanisms. Formal assessment of dyspnea remains challenging, and several scoring systems have been developed to aid in assessment of dyspnea.¹

PULMONARY FIBROSIS

Interstitial lung disease (ILD) is one of the most prevalent and important complications of SSc. Although moderate to severe lung fibrosis is identified in around 25% of SSc cases, overall there are important differences between subsets of the disease. Thus approximately one third of patients with diffuse cutaneous scleroderma (dcSSc) compared with around one sixth of patients with limited cutaneous scleroderma (lcSSc) are affected by significant fibrosis.² Moreover, the frequency of milder disease is high, so that more than half of SSc patients overall have some evidence of interstitial fibrosis. The rate is even higher within some serologically defined subgroups, such as patients who test positive for anti-topoisomerase I autoantibody.³

The main differential diagnosis is between the various forms of diffuse ILD and other important pulmonary complications of SSc, such as PAH. The two complications may occur concurrently, although in the majority of cases there is a clear predominance of one process. Nevertheless, the coexistence of pulmonary vascular disease may have an important impact on outcome.

Investigations

Plain radiography

Although the current preliminary classification criteria for SSc call for chest radiography as a means to determine the presence of lung fibrosis, this is recognized to be an insensitive tool to detect mild ILD.⁴ In general, plain radiography is useful as a screening tool for other pulmonary complications and may provide important additional information but cannot be relied on as a method for defining or excluding significant lung fibrosis. Subtle volume loss may occur in early-stage disease, but this may be apparent only on HRCT scans, and even with established pulmonary disease, the chest radiographic findings may be essentially normal.

High-resolution computed tomography

The cornerstone of detection of lung fibrosis in SSc is HRCT.⁵ HRCT is important because it provides a very sensitive tool for detection of disease and permits the pattern and extent of disease to be assessed. Although there is no consensus on whether to perform HRCT as a screening test in all cases of SSc, in practice most clinicians target only symptomatic patients or those with declining pulmonary function test (PFT) results. Initial assessment should include prone images so that minor interstitial changes of dependency can be excluded, although this may be less of an issue with modern multichannel scanners that require only a short examination time. Resolution of scanners is improving, and radiation exposure is being reduced. Nevertheless, the value of serial CT assessment over and above longitudinal

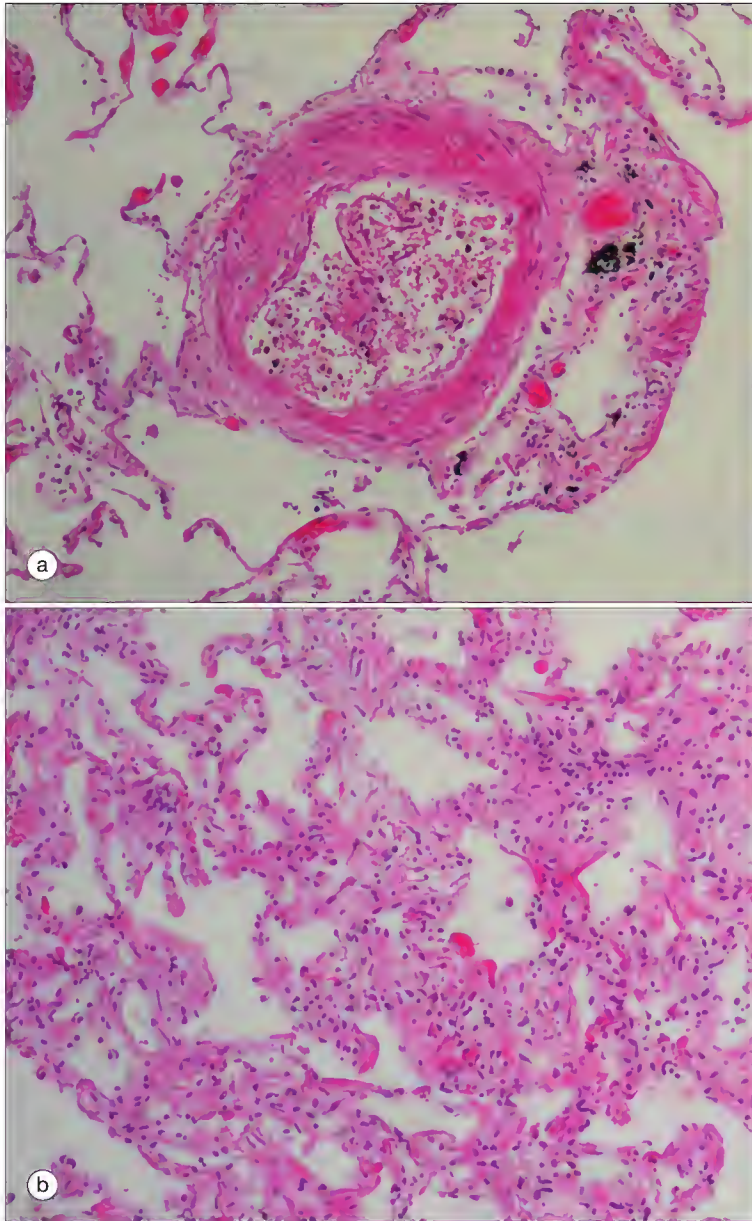


Fig. 145.1 Histopathologic features of systemic sclerosis (SSc)-associated lung disease. (a) Pulmonary arterial hypertension (PAH). Autopsy specimen from a patient with limited cutaneous SSc with advanced isolated PAH showing thickened pulmonary arterial wall and endoluminal proliferative lesions (plexiform lesion), in this case treated with combination targeted therapy including prostanoid, phosphodiesterase-5 inhibitor, and endothelin receptor antagonist. (b) Lung fibrosis in SSc. Nonspecific interstitial pneumonia pattern with preservation of architecture, homogeneous pattern of fibrosis, and absence of fibroblastic foci. This patient was considered to have stable lung fibrosis over several years of follow-up but died of gastrointestinal disease.

measurement of lung function together with baseline HRCT is not established. Examples of HRCT appearance are shown in Fig. 145.3 contrasting mild and extensive disease.

The pattern as well as extent of ILD may be determined by HRCT. This permits identification of an NSIP or UIP pattern of disease, and studies have shown that in scleroderma the HRCT definition correlates well with histologic pattern.⁶ Experienced assessors may identify features that are suggestive of inflammatory activity within lung tissue (alveolitis), but this is very challenging because fine interstitial fibrosis may give rise to an almost identical appearance. The presence of associated volume loss, traction bronchiectasis, and other features may be used in interpreting HRCT findings. In some cases there is clear evidence of reticular change that can reflect only established disease, but in others more diffuse ground-glass attenuation is present, and this more often represents fine fibrosis rather than true inflammation (Fig. 145.4). The development of a simple staging system has been an important and useful step forward in clinical management.⁷ In this algorithm a rapid assessment by HRCT is integrated with basic PFT variables to

determine whether there is mild or extensive disease and stratify the likelihood of progression. More formal scoring of the extent of disease has been used in validating studies, including a threshold analysis. These studies point to a higher risk of progression when more than 20% to 25% of lung volume is affected by fibrosis. However, scoring systems are observer dependent and applicable only to clinical research studies at present. There have been other attempts to use image analysis to determine extent of disease, but such systems have limitations and at present are not considered superior to an experienced observer-based scoring system.

Modern scanning and poststudy reconstruction can be invaluable in defining the precise extent of fibrosis, and such methods may ultimately be important in assessing disease progress and treatment response. Reconstructed images in typical cases of mild and extensive SSc-associated lung fibrosis are provided in Figs. 145.5 and 145.6, respectively.

Pulmonary function testing

Other tests that are valuable include PFTs, which form the mainstay of longitudinal assessment. For use in routine clinical practice the single most important assessment is the forced vital capacity (FVC), expressed as a percentage of the predicted value for age, weight, and gender.⁸ This has been determined to be the most robust assessment in stratifying cases of SSc-associated pulmonary fibrosis for treatment and also in assessing patients at follow-up. It has been validated as an outcome measure in several studies of ILD.

The diffusion capacity of the lung for carbon dioxide (DLCO) is a sensitive marker but also reflects the pulmonary vasculopathy that may coexist with ILD. Measures of total lung capacity are less dependent on exertional effort than FVC but are more demanding to ascertain and appear to add little value in assessment.⁹

Lung biopsy

A lung biopsy can be undertaken using a variety of different methods. These include the use of video-assisted thoracoscopic sampling, which probably is the most widely used method. Other approaches include open lung biopsy, which may be appropriate if larger samples are needed but is much more invasive. Transbronchial biopsy has specific utility in some situations, such as when malignancy or certain infective processes are suspected, but is of very limited value for the assessment of interstitial fibrosis owing to the limited sampling that is possible. It should be noted that the histologic pattern of biopsy specimens in SSc-related pulmonary fibrosis has not been demonstrated to be associated with outcome, unlike in idiopathic lung fibrosis, and this makes biopsy of less importance in uncomplicated typical cases.¹⁰ It remains an important diagnostic tool for cases that are atypical either clinically or on HRCT because there may be major management implications if there is diagnostic uncertainty. There is an excellent correlation between NSIP and UIP designations by HRCT and lung biopsy.⁵ Together these factors mean that biopsy is much less important than in the past, and it is not regarded as a routine test for management of SSc-associated lung disease. An exception is when malignancy is suspected or when there is the possibility of an alternative diffuse lung process, especially if high-dose corticosteroid treatment is considered. Use of high-dose corticosteroids in SSc can be harmful owing to increased risk of renal crisis in SSc, especially in the diffuse subset.

Serologic assessment

For baseline risk stratification and longitudinal assessment of interstitial lung fibrosis in SSc it would be enormously helpful to have reliable serum markers that reflect the extent or activity of fibrosis. In SSc there are a number of potential biomarkers, which can be separated into those that may reflect pathologic processes at multiple sites but have been shown to associate with lung fibrosis and those that have the potential to be more specific for pulmonary disease. Examples of general markers are markers of fibrosis such as CCN2¹¹ and chemokines such as CCL2.^{12,13} As well as being markers of disease, these may also be mediators of pathogenesis and future targets of therapy.¹⁴ In contrast, other more specific markers arise from lung tissue. Glycoproteins secreted by type II pneumocytes such as Krebs von den Lungen-6 (KL-6) and surfactant protein D have been shown to be present at increased levels in the sera of SSc patients with lung fibrosis when the alveolar epithelium is damaged, and by analogy, similar findings have been reported in cases of idiopathic pulmonary fibrosis.¹⁵ It is possible that the levels reflect the degree of damage or repair occurring in diseased lung tissue. It has been suggested that serum levels of these biomarkers correlate with the extent of fibrosis on HRCT and that higher baseline serum KL-6 levels are associated with decline in FVC. Therefore measurement of KL-6 may help to diagnose and monitor progression of lung fibrosis, and this is an important area for future clinical research.

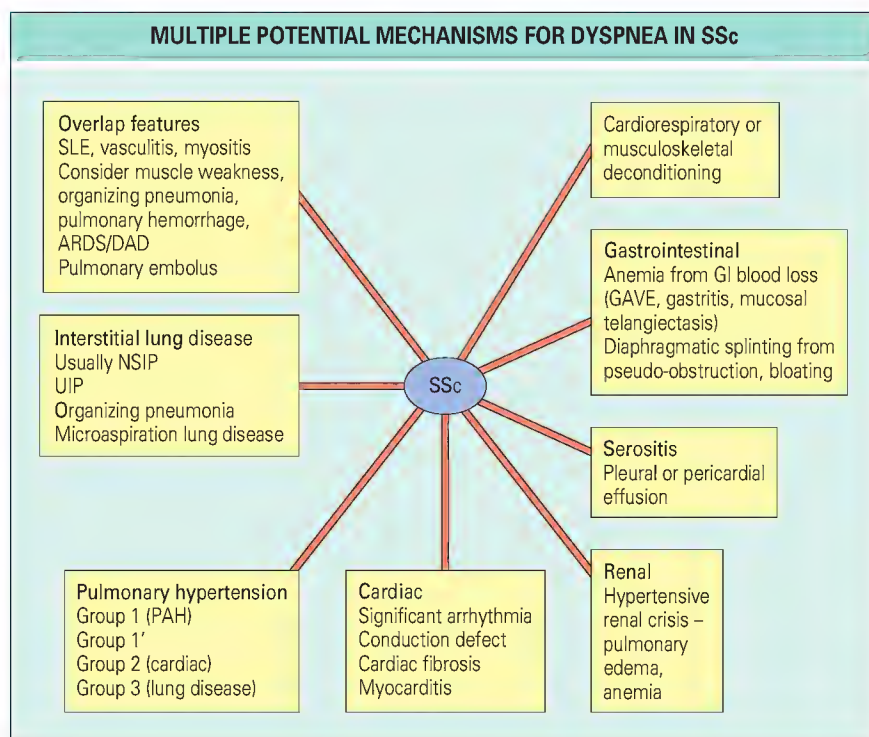


Fig. 145.2 Schematic representation of the multiple interacting mechanisms that may underlie the common symptom of dyspnea in systemic sclerosis (SSc). Musculoskeletal deconditioning is probably the most common basis for this symptom and may respond to cardiorespiratory and physical rehabilitation programs. However, major lung or heart disease must be excluded or investigated before simpler strategies are employed. ARDS, acute respiratory distress syndrome; DAD, diffuse alveolar damage; GAVE, gastric antral vascular ectasia; GI, gastrointestinal; NSIP, nonspecific interstitial pneumonia; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

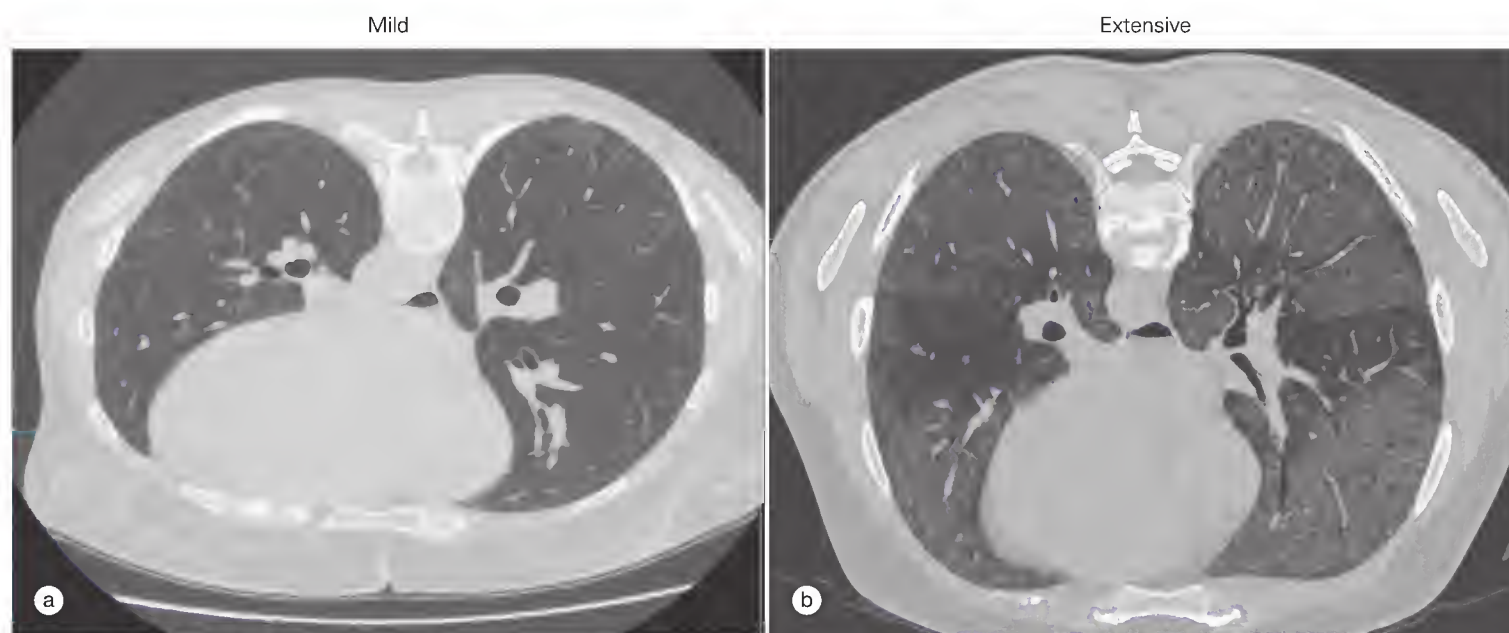


Fig. 145.3 Determining the extent of lung fibrosis in systemic sclerosis (SSc)—a critical role for high-resolution computed tomography (HRCT). (a) Minimal lung fibrosis in early SSc. Initial staging HRCT should be performed with the patient prone so that minor effects of blood distribution or fluid are excluded as explanations for minor basal lung disease. This scan shows trivial disease that would not be associated with chest radiographic findings in the lung fields. (b) Extensive lung fibrosis. This scan shows typical features of extensive lung fibrosis in SSc that will require active treatment because there is a high risk of future decline. In these scans more than 75% of the lung field is involved.

Diethylenetriamine pentaacetic acid lung scanning

Rather than explore the level of soluble glycoproteins derived from pulmonary epithelial cells such as KL-6, a more direct way of exploring epithelial injury in SSc-associated pulmonary fibrosis is measurement of the clearance rate of an inhaled nebulized suspension of diethylenetriamine pentaacetic acid (DTPA). The DTPA is deposited within the alveolar tissue of the lung, and the rate of clearance into the blood and away from the lungs reflects the degree of epithelial layer permeability. A growing body of data point toward DTPA clearance rate as a marker of the likelihood of progression of pulmonary fibrosis in SSc. The test is of limited value in individuals who smoke owing to the known effects of tobacco smoke, which lead to accelerated clearance. A calculated half-life can be used to determine the presence of accelerated clearance, and current studies suggest that a half-life of less than 45 minutes is abnormal. Published data indicate that DTPA lung

studies have additional value over HRCT and that results are linked to disease severity and predictive of disease progression.¹⁶

Bronchoalveolar lavage

In most cases of pulmonary fibrosis in patients with SSc bronchoalveolar lavage (BAL) adds little diagnostic or prognostic information beyond what can be derived from PFTs and HRCT. This is contrary to earlier opinion, which suggested that BAL fluid pleocytosis correlated with alveolar inflammation, considered to be a driving mechanism in pulmonary fibrosis in these patients. Recent studies have shown that BAL neutrophilia or eosinophilia is not predictive of response to immunosuppressive treatment (e.g., cyclophosphamide). In addition, as with HRCT, it has been shown that BAL changes are not specific. In fact, there may be inflammatory changes in all contexts in SSc-associated lung fibrosis.¹⁷

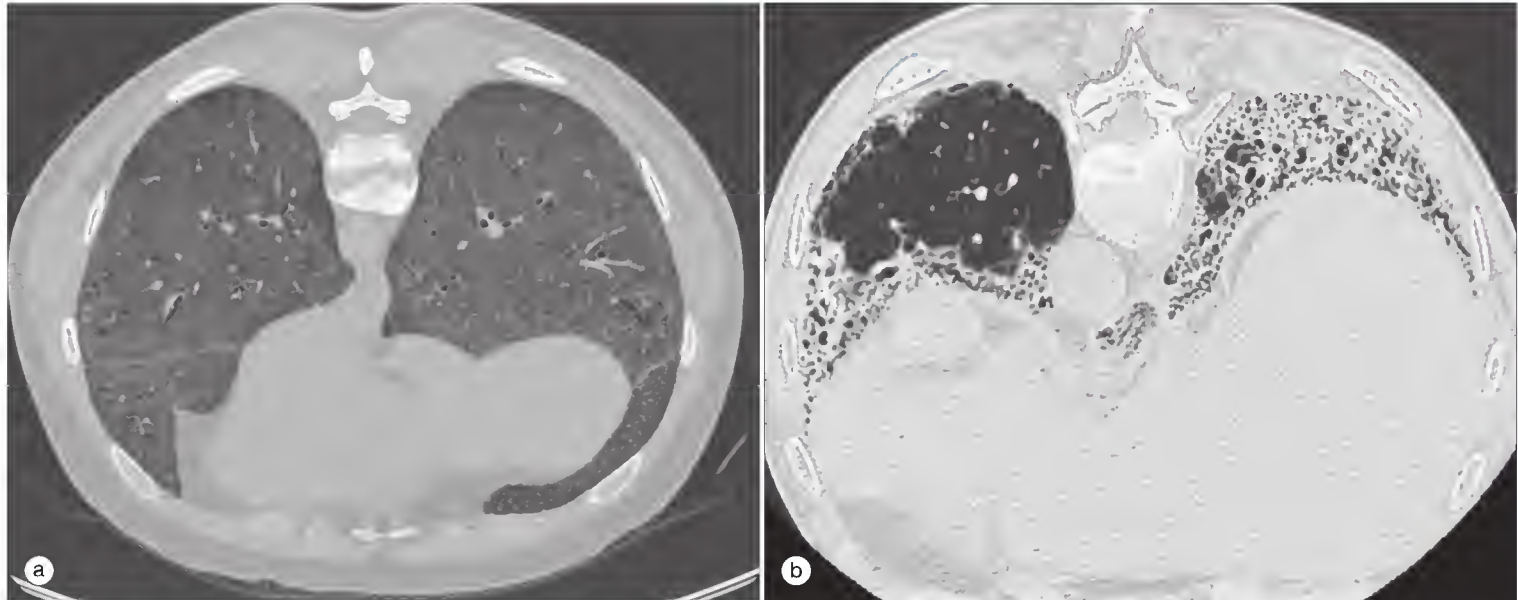


Fig. 145.4 Pattern of interstitial change in systemic sclerosis (SSc)—associated lung disease—utility of high-resolution computed tomography (HRCT). (a) Ground-glass appearance. Amorphous shadowing is present throughout the lung parenchyma in this representative slice of HRCT in a patient with early diffuse SSc. It can be difficult to differentiate inflammation from fine fibrosis, and so this appearance cannot be regarded as synonymous with alveolitis. In later established disease there may be traction bronchiectasis and other features that allow fibrosis to be determined with confidence. Extent of involvement appears to be more important than pattern of abnormality in predicting likelihood of progression. Pattern of change does not predict responsiveness to immunosuppression. (b) Reticular honeycomb appearance. Established fibrosis is associated with a typical coarse reticular pattern of abnormality. Biopsy studies confirmed that there may be inflammatory foci within this tissue, and so some reversibility is possible. As with other appearances in SSc, lung fibrosis extent is more important than pattern of abnormality in predicting outcome.



Fig. 145.5 High-resolution computed tomography can confirm the extent of fibrosis in systemic sclerosis. (a and b) Coronal reconstructions showing basal disease with mild extent and predominantly basolateral distribution. (c) Representative cross-sectional image.

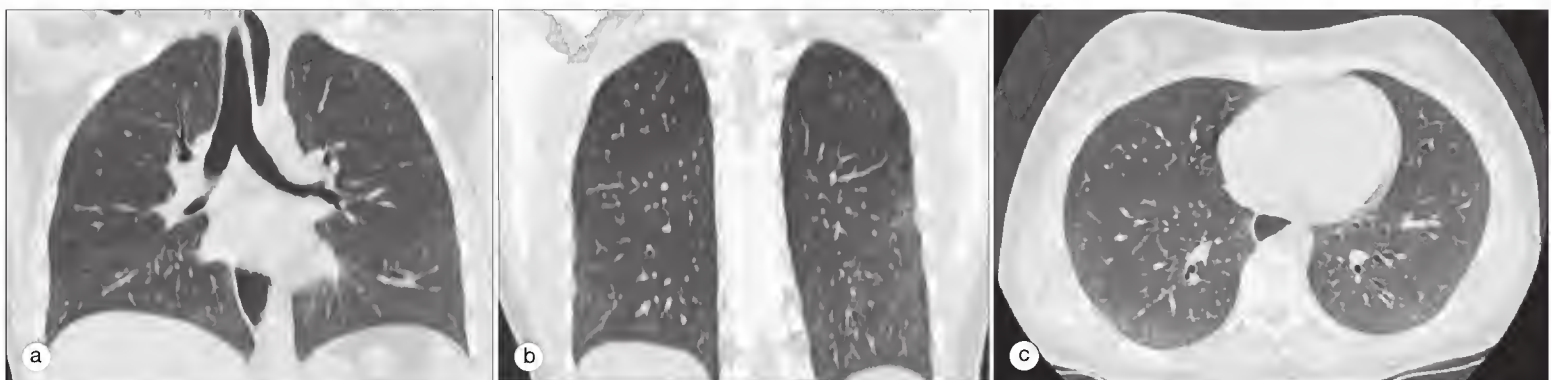


Fig. 145.6 Extensive lung disease in systemic sclerosis. (a and b) Coronal reconstructions showing extensive ground-glass opacification exceeding 25%. (c) Representative cross-sectional image showing subpleural reticulation in the lung bases with dilatation of the esophagus.

BOX 145.1 CLINICAL ASSOCIATIONS WITH SIGNIFICANT LUNG FIBROSIS IN SYSTEMIC SCLEROSIS

- Diffuse pattern of skin involvement
- Autoantibody profile
 - Anti-scleroderma-70 (anti-topoisomerase I autoantibody)
 - Anti-Th/To
 - Anti-PM-Scl
 - Anti-U11/U12
- Less than 3 years' disease duration
- Severe gastroesophageal reflux
- Rapid clearance of diethylenetriamine pentaacetic acid
- High Krebs von den Lungen 6 level

In certain cases, however, BAL is still extremely useful. It can be used to determine the likely presence of infection such as tuberculosis by direct staining or culture as well as by polymerase chain reaction analysis. It may point toward an alternative pathologic process to SSc, such as lymphocytosis in sarcoid. In addition, it has great utility as a research tool.

Screening

All patients with SSc should undergo regular screening for ILD. Recent studies suggest that with annual PFTs and HRCT performed at baseline or if there is suspicion of lung fibrosis during follow-up there is now a much better and more complete ascertainment of moderate to severe lung fibrosis in SSc. Thus there has been a significant improvement in the past decade at the authors' own center. Approximately 34% of patients with diffuse cutaneous SSc (dcSSc) and 16% with limited cutaneous SSc (lcSSc) developed lung fibrosis by 5 years, and there is a steady rise to 45% and 21% for each disease subset, respectively, at 10 years. Because in the authors' cohort the frequency of lcSSc is approximately twice that of dcSSc, the absolute numbers of patients affected with clinically significant lung fibrosis are approximately equal for each major subset despite the apparent relative frequency of this complication among patients with dcSSc. Currently, annual PFTs are recommended as screening tests for lung disease in SSc.

Clinical high-risk associations

Although it is now clear that lung fibrosis is very common in SSc and probably affects up to half of patients with a confirmed diagnosis of SSc, the number with major, potentially clinically significant ILD is much smaller, probably about 25% of cases overall. There are important clinical and investigational features that point toward an increased risk of lung fibrosis, and some of these characteristics are present at diagnosis. This offers the real possibility of risk stratification. Thus patients who have anti-topoisomerase I antinuclear autoantibodies (also known as *anti-scleroderma-70* or *anti-Scl-70* antibodies) have been shown in many independent studies in a variety of geographically and ethnically diverse patient populations to have a significantly increased frequency of lung fibrosis. In some studies,¹⁸ this approaches 66% of cases. There is also an association with other reactivities that are less common, such as those against Th/To,¹⁹ PM-Scl,²⁰ and U11/U12. Conversely, anticentromere reactivity or anti-RNA polymerase-specific antibodies have been found to be somewhat protective from lung fibrosis in prevalence studies, although they are associated with other complications of SSc that may lead to breathlessness, namely, PAH and scleroderma renal crisis. These are important simple clinical indicators. It has been demonstrated that overall diffuse skin involvement is more likely to be associated with lung fibrosis, but the extent of skin disease (as assessed by the modified Rodnan skin score) does not appear to predict extent or severity of lung fibrosis. Another association is early-stage disease. Data from the authors' cohort indicate that over half of those with significant lung fibrosis developed it within the first 3 years of disease onset. Lung fibrosis is also linked with a decline in FVC within the first 4 to 6 years of disease. Thus there is an important population of dcSSc patients who have significant lung fibrosis at diagnosis, and indeed it may on occasion be the presenting feature of the disease. The key features associated with lung fibrosis that are useful clinical pointers are summarized in Box 145.1.

Differential diagnosis

Diagnosis of SSc-associated pulmonary fibrosis is made using a composite of the tests outlined earlier, but HRCT is the most sensitive test for detecting

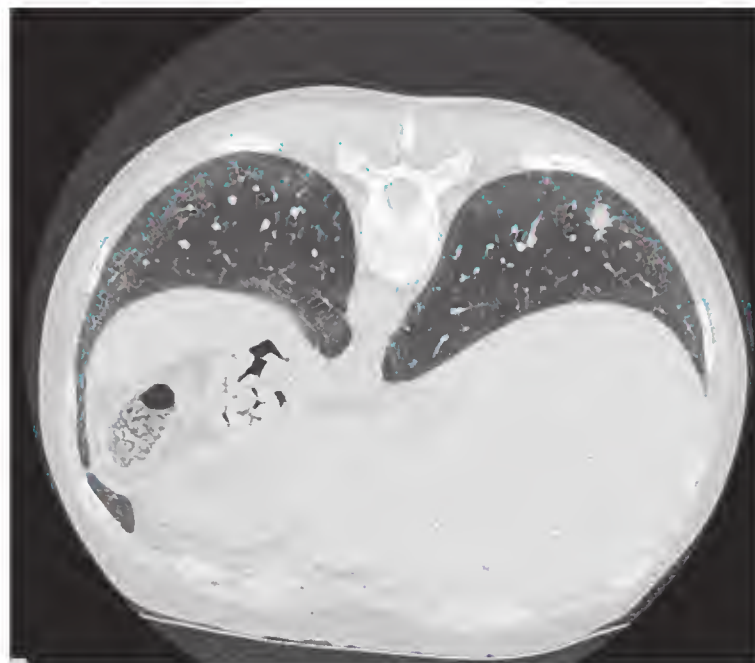


Fig. 145.7 Lung cancer may occur in association with interstitial lung disease in systemic sclerosis. Supine high-resolution computed tomographic scan demonstrates the typical changes of nonspecific interstitial pneumonia with widespread fine subpleural reticulation with some traction bronchiectasis. A spiculated irregular nodule is detected in the right lower base. In this patient, positron emission tomography confirmed increased uptake over the lesion. Due to the proximity of the lesion to the chest wall and ribs, computed tomography-guided biopsy and a bronchoscopic approach were not deemed to be feasible. The patient underwent open lung biopsy, and the histologic analysis confirmed adenocarcinoma.

and determining the pattern and extent of lung fibrosis. This is supplemented by measurement of FVC. Other tests may be performed as necessary. The key to effective management is assessment and staging of lung fibrosis and exclusion or confirmation and delineation of other manifestations of SSc that may lead to dyspnea. It is important that in patients with known lung fibrosis who experience unexplained worsening of breathlessness, the possibility of lung cancer should be considered (Fig. 145.7). Although lung cancer is one of the most common malignancies reported in SSc, the absolute risk is probably low, and its association with severity of lung fibrosis and smoking remains unproven. Another important differential diagnosis is recurrent aspiration related to reflux disease (Fig. 145.8). Severe reflux may be linked to lung fibrosis, but further studies are needed to evaluate a possible causal relationship between the two diseases.²¹

Staging

A simple staging system has been developed recently that integrates lung function test results with HRCT appearance.⁷ This system, the UK-RSA staging method, was developed using a cohort of well-characterized SSc patients who had been followed over time and links lung function together with rapid evaluation of CT appearance. It depends on the strength of HRCT in assessing the extremes of disease—mild or extensive—together with an assessment of volume loss in intermediate cases that cannot easily be categorized by a rapid HRCT review. The FVC as a percentage of predicted value performs well in this context and was found to be more reliable for the purposes of staging than the DLCO. This may partly reflect the impact of coexistent pulmonary vascular disease on gas transfer measurement. An FVC above 70% predicted is associated with a better outcome in terms of progression-free survival. These data are integrated into the simple algorithm shown in Fig. 145.9. This works to the strength of both assessment tools. HRCT is very robust at lower and high levels of disease, and FVC is helpful in between. This method has been shown to perform well and is supported by outcome data. It is strongly recommended that it be used by rheumatologists in assessing and treating SSc-associated pulmonary fibrosis. It has not been applied formally to other forms of lung fibrosis, but similar strategies could be developed, validated, and used.⁷



Fig. 145.8 Severe esophageal dysmotility may predispose to recurrent aspiration in systemic sclerosis. This patient with upper midgut dysmotility had a persistent nocturnal cough. The erect chest radiograph shows right lower zone consolidation consistent with aspiration pneumonia. Optimization of antireflux treatment and prokinetics may help to prevent microaspiration, which may otherwise initiate or exacerbate lung fibrosis.

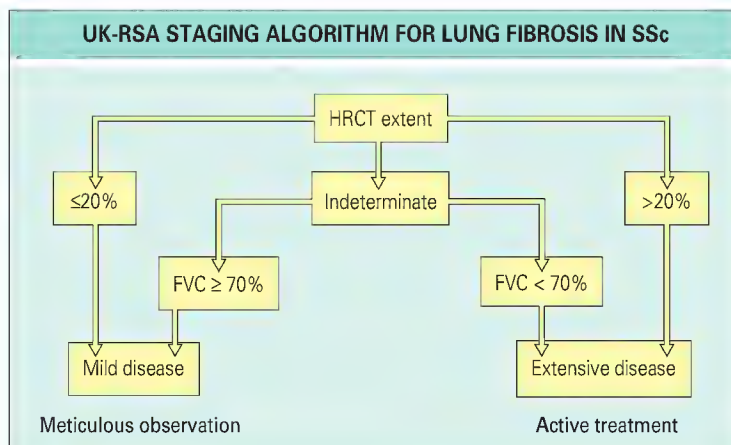


Fig. 145.9 This simple staging system for lung fibrosis in systemic sclerosis (SSc) is derived from analysis of data for a cohort of well-characterized SSc cases and links results of lung function tests and high-resolution computed tomography (HRCT) that are routinely used in disease assessment. Cases can be separated into mild or extensive, and patients with the former may be observed without treatment because they have a lower risk of future progression. Documented worsening should prompt initiation of therapy, currently with immunosuppressive drugs as outlined in the text. FVC, forced vital capacity. (From Goh NS, Desai SR, Veeraraghavan S, et al. *Interstitial lung disease in systemic sclerosis: a simple staging system*. *Am J Respir Crit Care Med* 2008;177:1248-54.)

Treatment

Although lung fibrosis is a major cause of SSc-related death, the treatment of lung fibrosis in SSc remains very inadequate. A fundamental management challenge is the fact that not all cases of SSc-associated pulmonary fibrosis will progress or even be clinically significant. This is a particular issue when HRCT is widely used for diagnosis, because there is a high frequency of detection of subclinical and trivial disease. The decision to treat therefore rests on whether the patient is clinically affected by the disease, whether it is progressive, and what other mitigating factors exist. The staging algorithm outlined earlier is invaluable in differentiating cases for which meticulous observation is appropriate from those that should be actively treated.

Active treatment currently centers on immunosuppressant therapy. In many centers, the mainstay of therapy for SSc-associated ILD has long been corticosteroids and/or cyclophosphamide, given orally or as an intermittent intravenous bolus. Some recently completed randomized controlled trials demonstrated a modest benefit for cyclophosphamide over placebo.²²⁻²⁴ In the published studies the target oral dose was 2 mg/kg/day²² and the intravenous dose was 600 mg/m²/monthly for 6 months,²⁴ and these remain the currently recommended doses for clinical use. One of these studies also included maintenance treatment with azathioprine and low-dose prednisolone.²⁴ Observational studies and case series have also supported the use of other agents, such as mycophenolate mofetil^{25,26} or rituximab,^{27,28} and both are being formally evaluated in clinical trials. Optimum duration and frequency of these agents remain controversial, but total duration of treatment with mycophenolate mofetil should probably be at least 2 to 3 years based on the observation of a decline in lung function when oral cyclophosphamide treatment was discontinued after 12 months in the first Scleroderma Lung Study.²² The evidence suggests that the treatment effect of cyclophosphamide seems to be mainly prevention of further disease progression rather than any reversal of existing fibrotic disease, and therefore stabilization of disease should be considered as therapeutic success. Several novel agents have recently been reported to show promise in the treatment of idiopathic pulmonary fibrosis, although none has been formally assessed in SSc-related ILD. Preliminary evidence suggested that the angiokinase inhibitor BIBF, which inhibits downstream response to platelet-derived growth factor, basic fibroblast growth factor, and vascular endothelial growth factor, may prevent decline in FVC, and this is currently being evaluated in ongoing clinical trials.²⁹ Another exciting potential therapy is pirfenidone, a pyridone compound with antifibrotic, antiinflammatory, and antioxidant properties that has been approved for treatment of idiopathic pulmonary fibrosis in Europe and Japan; pirfenidone treatment has led to improvement in FVC and progression-free survival defined as time to at least a 10% decline in percentage of predicted FVC, at least a 15% decline in percentage of predicted DLCO, or death.³⁰ Although there are clear differences in prognosis and histologic findings in different forms of diffuse lung disease, it is likely that the management of lung fibrosis in SSc will be informed by the results from idiopathic pulmonary fibrosis studies.³¹ For selected SSc patients with advanced pulmonary involvement, lung transplantation may be an option. Single-lung transplant is now considered to be the most successful transplantation approach for ILD.³²

Overall approach to management

Management of lung fibrosis is a key aspect of successful care for scleroderma, and it is increasingly recognized that a multidisciplinary approach involving rheumatologists, respiratory physicians, and thoracic radiologists with an interest in SSc is essential. This approach allows early identification and accurate staging of the lung disease and assessment of the likely future course. This is important because, although lung fibrosis represents one of the most important internal organ manifestations of SSc and there are now prospective clinical trial data suggesting that treatment interventions are potentially beneficial, it is also a complication that may in many patients be mild or slowly progressive. Given this fact, it is clear that potentially toxic therapy can be justified only in patients who have severe disease or who are at risk of progression, and treatments that stabilize disease but do not improve outcome need to be used with great circumspection. The first important aspect of management is the detection of lung fibrosis. All SSc patients should undergo regular pulmonary function testing, followed by HRCT if test results show restrictive abnormalities. Other tests that are routinely available include DTPA lung scanning and measurement of serum levels of KL-6, a glycoprotein produced by pneumocytes. Results of these tests, together with simple clinical features such as diffuse skin disease and laboratory abnormalities such as the presence of anti-topoisomerase I antibodies, allow patients at greatest risk of lung fibrosis to be identified. The staging system described earlier permits classification of cases as mild or extensive. Extensive disease is most likely to progress. There is considerable ongoing discussion about the utility of serial investigations and different lung function variables in assessing decline. Exercise capacity as assessed by the 6-minute walk test has been shown to be unreliable in terms of correlation with lung function or other clinical variables.

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure at right-sided heart catheterization (RHC) of more than 25 mm Hg. PH represents one of the most important areas of recent therapeutic advance in

BOX 145.2 UPDATED CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION**1. Pulmonary arterial hypertension (PAH)**

- 1.1 Idiopathic
- 1.2 Heritable
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
 - 1.4.1 Connective tissue diseases
 - 1.4.2 Human immunodeficiency virus infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
 - 1.4.6 Chronic hemolytic anemia
- 1.5 Persistent pulmonary hypertension of the newborn

1'. Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis**2. Pulmonary hypertension due to left-sided heart disease**

- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension**5. Pulmonary hypertension with unclear and/or multifactorial mechanisms**

From Fourth World Congress of Pulmonary Hypertension, Dana Point, California, 2008.

SSc. As new therapies emerged and clinical trials were undertaken, better classification and more homogeneous patient groups undoubtedly facilitated the demonstration of treatment benefit—initially the superiority of treatment strategies over placebo and later the usefulness of more complex and sophisticated strategies with combination treatments. It also allowed the flourishing of cohort studies that confirmed the impact of better management and treatment options and led to a tremendous increase in awareness of and interest in PH and especially in the subgroup of postcapillary PAH, which is most relevant to cases of SSc. The first proposed clinical classification of PH appeared in 1973, and the current version developed at Dana Point, California, in 2008 underpinned much of the clinical trial and research strategies (Box 145.2).³³ Its key point is that cases of SSc-associated PH may be classified potentially into one of four groups. The Fifth World Symposium on Pulmonary Hypertension held in Nice in 2013 saw an emerging interest in the concept of borderline PH as a marker for high risk of progression to PH in SSc. Features of the different defined groups (see Box 145.2) may coexist and evolve in the same patient over time. The most important is group 1, PAH. The related conditions that are associated forms of PAH and the cases that are idiopathic are also included in this group. The closely related group of 1', which includes PVOD and pulmonary capillary hemangiosis, may occur in SSc, although the precise frequency is unclear and it may occur in association with more classic precapillary PAH, which is the most prevalent and important form of PH in SSc. PVOD is uncommon in SSc, and excluding PVOD clinically is often difficult. PVOD should be considered in the context of an elevated mean pulmonary artery pressure with low pulmonary capillary wedge pressure and acute clinical worsening with frank pulmonary edema after initiation of PAH-specific therapy. Significant left-sided heart disease leading to postcapillary PH (group 2) may coexist in SSc with low cardiac output or an increased pulmonary capillary wedge pressure above 15 mm Hg on RHC. Diastolic dysfunction is common in SSc patients, and other factors including systemic hypertension and renal impairment may affect cardiac diastolic function. PH can also occur due to lung fibrosis, leading to hypoxia (group 3). This is likely to occur in a minority of SSc patients with extensive lung fibrosis. It is more likely that many patients with PAH who have some lung fibrosis have a predominant vasculopathy more similar to isolated PAH in SSc. Coexistent lung fibrosis may well impact outcome and treatment response. Finally, PH secondary to chronic thromboembolic disease (group 4) may occur, although it is

BOX 145.3 HEMODYNAMIC DEFINITIONS OF PULMONARY HYPERTENSION**Pulmonary hypertension (PH): mean PAP 25 mm Hg****Precapillary PH: PWP > 15 mm Hg**

1. Pulmonary arterial hypertension
3. PH due to lung diseases; CO normal or reduced
4. Chronic thromboembolic PH
5. PH with unclear and/or multifactorial mechanisms

Postcapillary PH

2. PH due to left-sided heart disease, **PWP > 15 mm Hg**; CO normal or reduced

PAP, pulmonary arterial pressure; PWP, pulmonary wedge pressure.

From Fourth World Congress of Pulmonary Hypertension, Dana Point, California, 2008.

uncommon in SSc and typically is associated with secondary antiphospholipid syndrome. For these reasons, it is critical that PAH be confirmed by RHC because group 1 PH is probably the most amenable to PAH-specific therapies.

One of the key developments over the last decade is the number of national and international PH registries including REVEAL (Registry to Evaluate Early and Long Term PAH Disease Management)³⁴ and the Mayo registry. These registries aim to advance our understanding of the epidemiology, demographics, clinical course, and disease management of PH. Equally, these registries provide the platform for a rich source of data that will be available to inform the management of PAH in years to come.

Pulmonary arterial hypertension

PAH is defined as a mean pulmonary arterial pressure of more than 25 mm Hg together with a normal (or not elevated) pulmonary capillary wedge pressure (less than 15 mm Hg). It is generally associated with a pulmonary vascular resistance of more than 3 Wood units or more than 240 arbitrary resistance units (ARU). It is essentially an occlusive vasculopathy of the pulmonary arterial tree that leads to increased resistance to pulmonary blood flow with elevated pulmonary pressures. Ultimately this causes strain on the right side of the heart, and this is the main cause of death. It is the most common form of PH in SSc, affecting 82% of SSc patients with postcapillary PH in a recent UK national survey.³⁵ Whether SSc patients with PAH are less able than PAH patients who are otherwise healthy to cope with the increased right-sided heart workload is not yet clear, but this could be one of the potential explanations for why patients with SSc-associated PAH appear to have a worse survival and clinical outcome than patients with idiopathic PAH of the same severity. The observation of pathologic changes over the pulmonary preseptal venules has also fueled speculation that the worse prognosis in SSc-associated PAH may be due to an overlap with PVOD.

The current classification scheme developed at the Dana Point conference³³ simplified the definition of PH and removed formal statements about pulmonary vascular resistance and also exercise-induced PH. The latter change was based largely on the absence of secure robust data about the actual threshold for PH on exercise, because pressures are very dependent on age and fitness. The definitions are summarized in Box 145.3.

Assessment of pulmonary hypertension

When PH is suspected it must be confirmed and the cause ascertained. In many cases of SSc this sequence of events is triggered by clinical suspicion based on symptoms such as worsening dyspnea without other explanation, fatigue, chest pain, and exertional syncope. Clinically, physical findings of a loud pulmonary component of S2 with right-sided heart failure are indicative of late manifestations of PAH. There are, however, few signs of early PAH. Classically, patients with long-standing Raynaud disease, lcSSc, florid telangiectasia with anticentromere antibodies, or positivity for isolated nucleolar-pattern antinuclear antibodies (including anti-U3-RNP or anti-Th/To) are the patients at risk of developing PAH. Investigations may reveal an abnormal result on a lung function test, especially when carbon monoxide transfer factor is diminished in the presence of preserved or relatively preserved lung volumes (assessed by FVC or total lung capacity). An electrocardiogram typically demonstrates signs of right atrial dilatation with right ventricular hypertrophy in those with advanced PAH. Another important investigation is Doppler echocardiography. This may show elevation of the estimated right ventricular systolic pressure (RVSP) or pulmonary artery pressure (adding an estimate of right atrial pressure to the RVSP). The RVSP

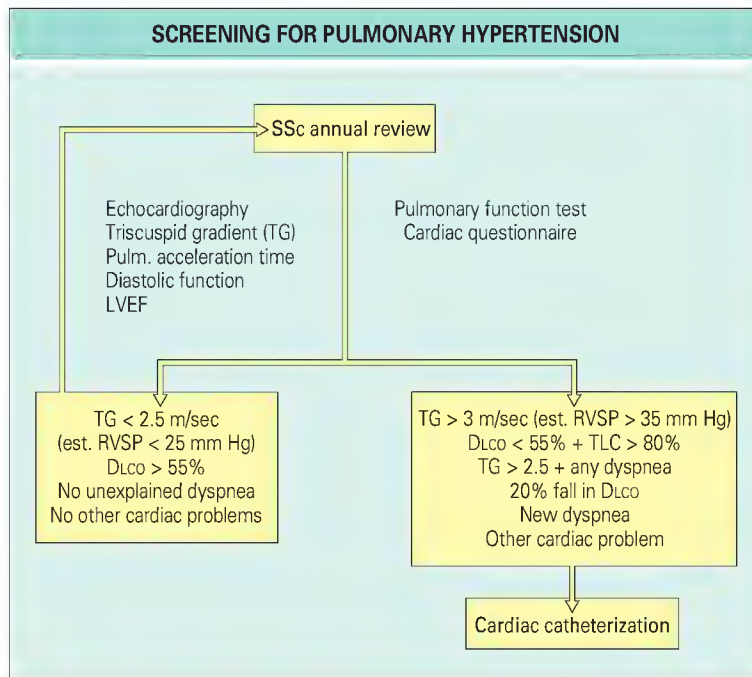


Fig. 145.10 Annual screening for the development of pulmonary hypertension is vital in managing systemic sclerosis (SSc). Currently, a combination of symptomatic assessment, Doppler echocardiography, and pulmonary function testing is employed with the need for right-sided heart catheterization depending on the results of these investigations. DLco, diffusion capacity for carbon monoxide; est., estimated; LVEF, left ventricular ejection fraction; Pulm., pulmonary; RVSP, right ventricular systolic pressure; TLC, total lung capacity.

can be estimated from the maximum velocity of the regurgitant jet of the tricuspid valve into the right atrium during ventricular systole. However, this value is just an estimate and may not be computable in some individuals. Thus the Doppler echocardiographic estimation of pressure must be interpreted in a clinical context and with appropriate thresholds for further investigation that will avoid missing cases of PAH. There are other important features of PAH that can be determined by echocardiography, including right atrial or ventricular enlargement and contractility, the tricuspid annular plane systolic excursion, the Tei index, and the presence of pericardial effusion.³⁶ Some estimate of left ventricular function can also be made, and diastolic dysfunction may be apparent. In addition, there are important aspects of the clinical assessment that point toward PH or PAH.

Screening

Annual consideration of the possible presence of PAH should be part of standard care for all SSc patients. The overall frequency of this complication warrants annual screening. Thus at a clinic visit each year the possibility that an SSc patient has PAH must be formally considered. This should involve standardized assessment for relevant symptoms, including breathlessness and exercise capacity, carried out by an experienced physician. Lung function tests should be performed, bearing in mind that this is an important aspect of screening both for PH and for interstitial pulmonary disease and other complications.³⁷ Echocardiography with Doppler estimation of right-sided heart pressure should also be performed. The current screening algorithm used at the authors' center is shown in Fig. 145.10, and similar approaches have been developed, tested, and validated at most centers. Because of the frequency of PAH in SSc and in overlap syndromes with features of SSc (i.e., mixed connective tissue disease) formal screening is generally considered to be mandatory. Recent studies suggest that the frequency of PAH at 5 years from onset of SSc is approximately 8% of cases, and it is well recognized that PAH may present later in the disease, so that up to 12% of SSc patients may ultimately be affected.² There is growing evidence that survival and long-term outcome, together with responsiveness to therapy, is associated with the severity of PAH at diagnosis, and treatments should logically be implemented as early as possible after onset. Thus there is strong support for an effective framework of screening. Risk features for PAH in SSc are summarized in Box 145.4. Sometimes right atrial enlargement or widened pulmonary artery may be diagnosed based on the HRCT appearance, and this is an important consideration and justification for

BOX 145.4 CLINICAL ASSOCIATIONS WITH PULMONARY ARTERIAL HYPERTENSION

- Limited distribution of skin involvement (although also occurs in diffuse cutaneous systemic sclerosis and overlap systemic sclerosis)
- Anticentromere antibodies
- Antifibrillarin antibodies
- Prominent telangiectasia
- Disease duration longer than 3 years



Fig. 145.11 Typical high-resolution computed tomographic (HRCT) appearance of advanced isolated pulmonary arterial hypertension (PAH). Although HRCT generally is performed to determine the presence and extent of interstitial lung disease, there are important abnormalities in this coronal reconstruction that point toward the presence of pulmonary hypertension, especially proximal dilation of the pulmonary vessels and a pulmonary artery main trunk diameter that is greater than that of the ascending aorta. In this case there is little fibrosis and so the diagnosis is likely to be PAH.

systematic investigation in SSc cases. Typical findings in isolated PAH are shown in Fig. 145.11. Currently attempts are being made to better integrate the noninvasive tools that can be used to assess PAH through development of composite scores that might improve detection and diagnosis. One particular goal is to increase the number of appropriate referrals for invasive study by RHC. Scores have been published to integrate tests but require validation and improvement.^{38,39} The preliminary report from the DETECT study, which is conducting a systematic assessment of nearly 500 patients with high-risk SSc to identify developing PAH, provides an evidence-based screening algorithm that incorporates a combination of clinical features, presence of anticentromere antibodies, abnormal electrocardiographic findings, and echocardiographic parameters.⁴⁰

Diagnosis

As outlined earlier, RHC with estimation of mean pulmonary artery pressure together with measurement of the pulmonary capillary wedge pressure or left ventricular end-diastolic pressure is the only way of definitively diagnosing PH and confirming that it is precapillary in origin. Thus noninvasive tests are useful in selecting patients for RHC but cannot make the diagnosis. This is important, because Doppler echocardiographic estimations of pulmonary artery pressure are often wrong. This test is widely used for screening and taking initial steps toward the diagnosis, but in the important range of 30 to 50 mm Hg estimated pressure the rate of false-positive or false-negative test results is around 30%. The negative predictive value of a low RVSP of less than 20 mm Hg and the positive predictive value of an RVSP of more than 60 mm Hg is much better, and this explains the clear statistical correlation between invasive and noninvasive assessment. This should not be taken as indicating that the two investigations are equivalent, and it has been shown in many studies that the error rate is around 30% for Doppler echocardiographic confirmation or exclusion of PH for estimated RVSP in the important range of 30 to 50 mm Hg. When precapillary PH is detected,

exclusion of thromboembolic disease requires nuclear imaging or CT pulmonary angiography to exclude pulmonary embolism. Prospective studies are underway to assess thresholds for noninvasive diagnosis based on echocardiographic and echocardiographic parameters, and the potential value of serum markers such as NT-proBNP) are also being evaluated.⁴¹ Measurement of this marker may potentially help in interpreting borderline echocardiographic findings or assessing the significance of dyspnea but conceptually can be of use only once PH is well established because levels depend on the presence of right ventricular strain. Confounding factors in interpretation include concurrent left ventricular dysfunction and the association of elevated levels of this peptide with extracardiac disease in SSc.

Staging of pulmonary arterial hypertension

Diagnostic RHC provides valuable information about the hemodynamic significance of PAH through examination of variables such as pulmonary vascular resistance, mean pulmonary artery pressure, cardiac index, and right atrial pressure. There is a clear association between more severe disease and poor outcome. In the authors' own cohort, patients who are in the lower half of the population based on pulmonary vascular resistance or who can attain this level of pulmonary vascular resistance within 3 months of starting specific therapy for PAH have significantly better survival. This provides further evidence for the importance of timely diagnosis and initiation of therapy for this treatable complication of SSc.

Assessment of exercise capacity and exercise desaturation by the 6-minute walk test has become a standard method of evaluation of PAH. The distance on this test was the primary endpoint for many of the pivotal trials that have underpinned the licensing of new PAH therapies. The 6-minute walk test, when performed correctly, may provide a relatively inexpensive tool to assess progress in achieving therapy goals with accurate and reproducible results, but there are risks in extrapolating from the findings in idiopathic PAH. In SSc there are many potential confounders that may influence exercise capacity, including musculoskeletal complications, skin disease, pain, and other factors, such as lung fibrosis or cardiac disease. Musculoskeletal deconditioning is especially important, and there is some evidence that this is a dominant feature that influences the result on the 6-minute walk test and that may respond to rehabilitative exercise programs.

There have been recent attempts to integrate clinical and laboratory data in cases of PAH to help better predict outcome. An example is the risk score developed from data collected in the large North American REVEAL registry for PH, although such a score requires prospective independent validation in other patient groups.⁴²

Functional class assessment is a standardized way of assessing exercise capacity. The PH classification is based on the New York Heart Association functional classes for heart failure. The World Health Organization functional classes for PH include syncope as a PH-specific symptom of advanced disease. Assessment of functional class is relatively subjective and the four-point scale is limited, especially because most cases are diagnosed as functional class III despite screening. Additional categories are sometimes used to reflect the features generally considered to indicate good treatment response.³⁵

Biomarkers

The use of biomarkers to direct treatment represents a realistic therapeutic advance in PAH disease management. Serum levels of NT-proBNP correlate well with severity of PAH and may be helpful in screening for PAH.⁴⁰ Similarly, uric acid levels are independently associated with increased mortality in PAH. An increasing number of surrogate markers are under investigation to assess patients and monitor treatment response. Because most biomarkers reflect different pathophysiologic processes in PAH, it is likely that a panel of markers is needed to provide a comprehensive and accurate assessment of the clinical status and hemodynamic endpoints. Biomarkers related to endothelial dysfunction (e.g., von Willebrand factor, dimethylarginines) and inflammation (growth differentiation factor 15, pentraxin 3, osteopontin) may help in understanding the disease but none is used routinely for risk assessment at baseline in patients with PAH. Recently, differences have been described between lcSSc patients with and without PAH in gene expression in peripheral blood mononuclear cells (including the gene for MRC1, a marker of macrophage alternative activation); this increases the prospects of using gene expression signature to evaluate risk of PAH.

Treatment

There have been tremendous advances over the past two decades in the management of PAH. One of the major developments in the authors'

treatment paradigm is a move away from an approach of escalation of therapies in the event of clinical deterioration to one of goal-oriented strategy. The achievements in therapeutics and the evolution in treatment approaches for PAH have led to an improvement in survival in the current era. Recent data from the authors' cohort of over 500 patients with PAH at Royal Free London demonstrated improvement in survival over the last decade (1-year survival rate of 86% in the current cohort compared with 75% a decade ago). Similarly, data from the French registry showed survival rates for PAH patients of 83%, 67%, and 58% at 1, 2, and 3 years, respectively.

The first study that conclusively showed treatment benefit for specific therapy used intravenous prostacyclin (epoprostenol).⁴³ This randomized prospective clinical trial demonstrated significant improvement in exercise capacity and pulmonary hemodynamics in patients receiving epoprostenol compared with those given placebo. Further evaluation of data for this cohort of patients suggests that survival in the long term may be better than in contemporary cases treated with conventional therapy. However, the short serum half-life of epoprostenol (approximately 6 minutes) indicates that the treatment needs to be administered as a continuous infusion via an indwelling central venous catheter. This is associated with considerable inconvenience, risk of infection in up to 15% of patients at 1 year, and risk of sudden cardiovascular compromise when the pump delivery system fails. As well as being given intravenously, prostacyclin may be administered subcutaneously and by inhalation.

The next major advance in management was the use of oral agents for the treatment of SSc-associated PAH. This occurred through the incorporation of patients with PAH who had SSc and other connective tissue disorders into the pivotal clinical trials, which led to licensing of treatments. The first oral therapy developed was the endothelin receptor antagonist bosentan.⁴⁴ Later, other related drugs as well as phosphodiesterase inhibitors were tested. Thus there are now a substantial number of licensed therapies for PAH associated with SSc.

A number of guidelines regarding the treatment of PAH have been published recently, and these should be followed because they are based on evidence and expert consensus and are endorsed by respected and informed specialist societies.⁴⁵⁻⁴⁹ The current recommendations are summarized in Fig. 145.12. The recommendations are essentially similar for the European Respiratory Society/European Society of Cardiology, the American Thoracic Society/American College of Cardiology, and the Dana Point Fourth World Symposium on Pulmonary Hypertension. There is an important goal in these recommendations, which is to try to ensure that therapy is standardized across centers and regions to reflect current best practice while also taking into account the differences in licensed therapies that are available. The authors of all sets of recommendation are experts, and there is an attempt to integrate the best available evidence for treatment benefit with current practice at most centers. It is an important aspect of management that specialist centers be involved in assessment and treatment planning so that therapies are given appropriately. Emphasis is placed on the importance of a multidisciplinary approach to therapy, and the severity of PAH also is taken into account in treatment planning.

Thus, once the diagnosis is confirmed by RHC, patients receive background therapy with anticoagulants, with management of fluid overload or heart failure in advanced cases. Oxygen therapy with the aim of maintaining saturations above 90% may provide symptomatic relief, particularly in patients with significant lung fibrosis. For PAH in association with SSc some centers recommend a formal vasodilator study at catheterization, although the result is very rarely positive and most centers have abandoned this practice. There is no significant difference between iloprost and inhaled nitrous oxide in this test. Only patients who show significant improvement in mean pulmonary arterial pressure and cardiac output are deemed to be valid responders to the vasodilator test, and so the test result needs to be assessed carefully.

For patients in functional class I who have no symptoms, usually only supportive therapy is given. There are now licensed therapies for patients in functional classes II and III, and these should be initiated at diagnosis. One of the oral agents is begun as an initial therapy. An overview of currently licensed PAH-specific therapies is given in Table 145.1. Although some recommendations favor eicosatrienoic acid as initial therapy in patients with connective tissue disorders, there is no strong evidence for its superiority, and it is entirely reasonable to start with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist. The key focus should be on evaluating response to therapy because it is important to modify treatment if there is not adequate response. The authors' practice is routinely to perform a repeat RHC if the diagnostic study suggests that the patient has advanced PAH and is in a poor prognostic group based on hemodynamics, with pulmonary vascular resistance above 650 ARU or mean pulmonary arterial pressure above 40 mm Hg. If the values of these variables have not moved

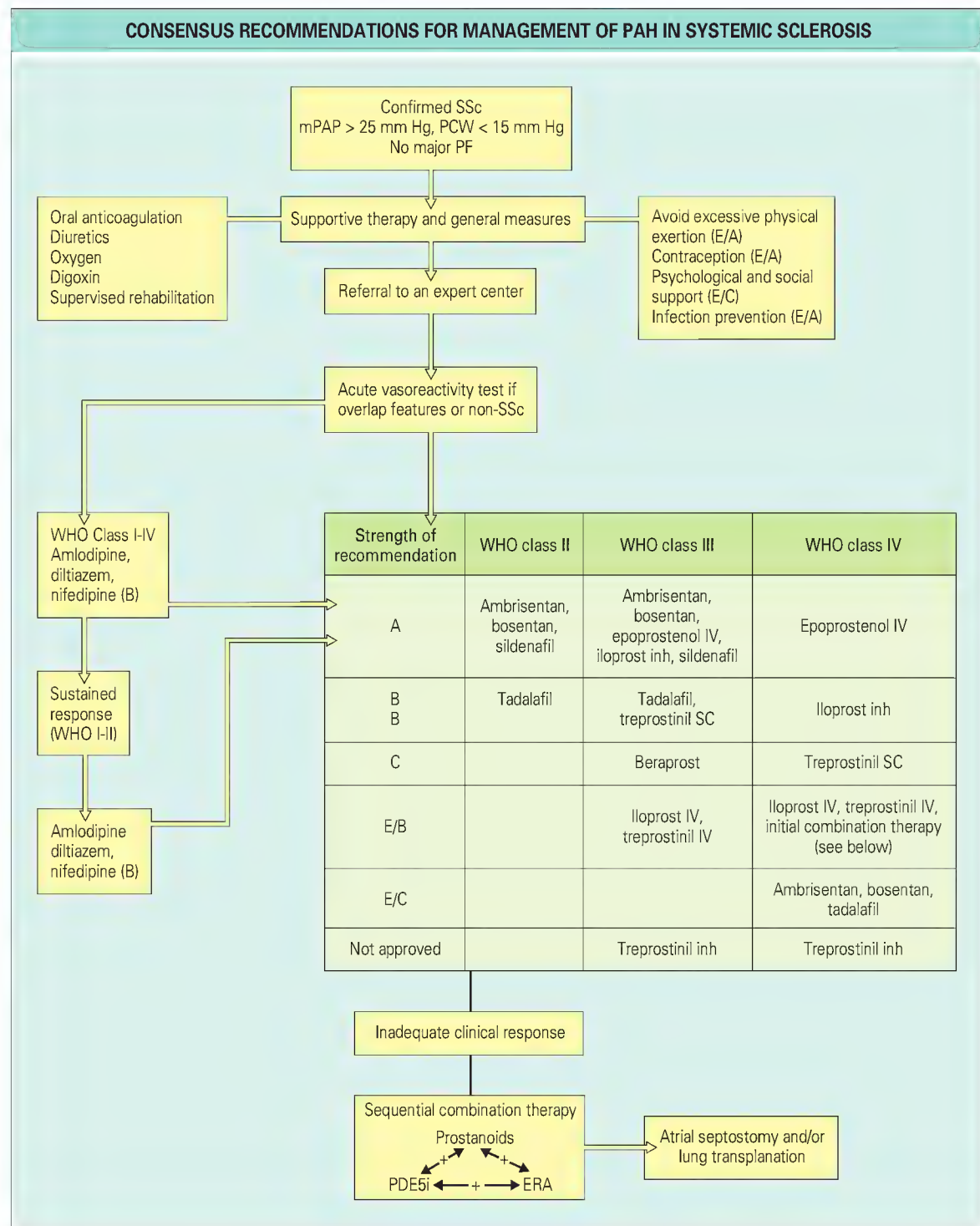


Fig. 145.12 There have been a number of recent publications of evidence-based treatment recommendations for cases of pulmonary arterial hypertension (PAH). These generally are generic for all causes, including other types of PAH not associated with systemic sclerosis (SSc). This algorithm is directed toward SSc-related PAH as outlined in this chapter. ERA, endothelin receptor antagonist; inh, inhaled; IV, intravenously; mPAP, mean pulmonary artery pressure; PCW, pulmonary capillary wedge pressure; PDE5i, phosphodiesterase-5 inhibitor; PF, pulmonary fibrosis; SC, subcutaneously; WHO, World Health Organization. (Modified from Dana Point 2008, ESC/ERS 2009, UK PAH Centres 2008, ACP 2009.)

the patient to a better subgroup at this second study, then combination oral treatment with eicosatrienoic acid and a phosphodiesterase-5 inhibitor is initiated. Less severe cases are followed noninvasively over the first 3 to 6 months with evaluation for substantial improvement in NT-proBNP level if previously elevated, gain in 6-minute walk test distance, and improvement in functional class. Further deterioration prompts addition of a prostanoid, usually subcutaneous or inhaled treprostinil or iloprost. However, in the future oral prostacyclin analogues may be shown to be effective and may be used in a triple-combination oral therapy. There is a growing trend toward the use of combination therapy, especially in patients in the severe stage of the disease. The use of specific therapies in combination make sense in terms of likely synergy through different mechanisms of action, and this approach is often being used. Some limited trial data are already available that confirm

the additional benefit of using specific combinations of PAH drugs, and more evidence is emerging to support this strategy in some cases. At present no trials of combination therapy specifically for patients with SSc-associated PAH have been undertaken, although this subgroup is often included in studies of precapillary PAH. It is hoped that the use of combination treatments specifically in SSc-associated PAH will increase and will be properly evaluated, and that the benefits of a goal-directed step-up approach and an upfront combination strategy will be compared.

Finally, if major progression to functional class IV occurs, then patients are considered for intravenous prostacyclin analogue therapy. Licensed agents include epoprostenol and treprostinil.

Recommendations for cases that are functional class IV at diagnosis generally include intravenous epoprostenol. This is certainly the optimum

■ TABLE 145.1

Licensed therapies available for treatment of pulmonary arterial hypertension

Class of drug	Drug	Route of administration and dosage	Main adverse effects	Comments
Endothelin receptor antagonist	Bosentan	Oral: 62.5 mg twice daily for 1 mo, then 125 mg twice daily	LFT abnormalities in up to 10% and so monthly monitoring required. Potentially teratogenic. Fluid retention and anemia. Reduces oral anticoagulant efficacy.	Nonselective ET _A and ET _B blockade.
	Ambrisentan	Oral: 5 or 10 mg daily	Low risk of LFT abnormalities. Fluid retention common. Anemia. No interaction with oral anticoagulants.	Partially selective ERA with specificity for ET _A .
Phosphodiesterase-5 inhibitors	Sildenafil	Oral: 20 mg 3 times daily	Headache, visual disturbance, epistaxis. Generally well tolerated.	Different formulation licensed for erectile dysfunction.
	Tadalafil	Oral: 40 mg once daily	Headache, visual disturbance, epistaxis. Generally well tolerated.	Longer duration of action than sildenafil.
Prostacyclin analogues	Epoprostenol	Continuous IV infusion: started at 2 ng/kg/min, then titrated upward	Headaches, muscle cramps, diarrhea. Severe worsening if infusion interrupted. Sepsis and other risks from intravenous administration.	Only drug specifically tested in systemic sclerosis-associated PAH in placebo-controlled trial. Reserved for advanced disease.
	Treprostinil	SC or IV infusion: started at 1.25 ng/kg/min, then titrated upward Nebulized inhaled: 18-54 µg 4 times daily	Headaches, muscle cramps, diarrhea. Worsening if infusion interrupted but less immediate than with epoprostenol. Sepsis and other risks from IV administration. Severe local site pain from SC infusion.	Available for IV use and being evaluated for administration by inhaled and oral routes in PAH in clinical trials.
	Iloprost	Nebulized inhaled: 2.5-5.0 µg 6 to 9 times daily	Headaches, muscle cramps, diarrhea.	IV formulation not licensed for PAH.
	Beraprost	Oral: 60 µg daily	Headaches, muscle cramps, diarrhea.	Licensed in Japan.

ET_A, endothelin receptor type A; ET_B, endothelin receptor type B; ERA, endothelin receptor antagonist; IV, intravenous; LFT, liver function test; PAH, pulmonary arterial hypertension; SC, subcutaneous.

current therapy for idiopathic PAH, but fewer data are available for SSc-associated PAH and some centers advocate combination oral therapy for SSc-associated PAH that is diagnosed at this functional level.

Surgical options of heart-lung transplantation or double-lung transplantation are often a particular challenge for SSc patients owing to comorbidity. The presence of gastroesophageal reflux raises the possible risk of post-transplantation obliterative bronchiolitis. Impaired renal function, which is often present albeit not clinically significant, is another barrier, as is osteoporosis, especially in patients who have received long-term corticosteroid therapy. There is always a comprehensive pretransplantation evaluation that addresses these issues. Atrial septostomy can be of benefit in severe cases and is an option in those individuals who have very advanced disease but cannot be considered for transplantation. Benefit is generally short-lived but can be substantial in terms of improved dyspnea and greater exercise capacity. Short-term administration of inotropes has potential in very advanced PAH once other treatment options have been exhausted, although there are particular challenges related to the sensitivity of SSc patients to agents that may provoke peripheral vasospasm.

There are some areas in which SSc-associated PAH needs to be given specific consideration. For instance, it is very unusual for vasodilators to be beneficial in this group of patients, and so long-term treatment with calcium channel blockers is rarely, if ever, appropriate. Although some patients show a short-term decrease in mean pulmonary artery pressure and may have improved cardiac output, in reality long-term responses are very unusual. For this reason, guidelines from the United Kingdom recommend that it not be considered mandatory for the patient to show a vasodilator response test at the time of diagnostic RHC. This may not apply in non-SSc-associated PAH, and so these patients should have a formal vasodilator challenge at diagnosis. Another area of specific consideration is the relatively weak data for the benefit of long-term anticoagulation in SSc-associated PAH. Thus its use is generally a balanced decision made in individual cases. Anticoagulation carries specific hazards in SSc relating to gastrointestinal blood loss due to gastroesophagitis, gastric antral vascular ectasia, and gastrointestinal telangiectasia. In general, when oral anticoagulation is used an international normalized ratio of 2.0 to 2.5 is the recommended target. It should be remembered that a short-term course of antibiotics is often needed for skin or gastrointestinal infection, and this poses an additional challenge. The specific interaction of eicosatrienoic acids and an oral anticoagulant must also be considered in relevant patients.

The selection of first-line agents as a specific targeted therapy for PAH varies among centers. For historic reasons, there is a longer experience with

eicosatrienoic acids than with phosphodiesterase-5 inhibitors in SSc-associated PAH, but this does not necessarily mean that they should always be used as first-line therapy. At present there is no clear evidence that eicosatrienoic acids have different efficacy in SSc-associated PAH, and so the various licensed agents can be considered equivalent.⁵⁰ It is logical to try an alternative eicosatrienoic acid in patients who show liver function test abnormalities when receiving one of these drugs. Once long-term data show that phosphodiesterase-5 inhibitors are equally effective at reducing mortality in SSc-associated PAH, then these could be used as first-line agents. In reality, many patients progress to combination therapy. The recent guidelines are explicit in recommending intravenous epoprostenol in cases of PAH that are diagnosed at the functional class IV level. This is due to the clear benefit in survival in idiopathic PAH. The case for its use in SSc-associated PAH is less clear, although most centers would view this as an appropriate therapy. In the United Kingdom, however, it is often considered appropriate to treat SSc-associated PAH with combination oral therapy at diagnosis and reassess early before moving to intravenous therapy. This is the subject of ongoing analysis.

Disease progression does occur in a majority of these patients and overall the long-term prognosis, although improved, remains poor. Thus there is a major need to develop new treatments, either improvements in currently available PAH-specific therapies or agents targeting novel pathogenic pathways. The number of new potential therapeutics is increasing, and many are currently undergoing clinical trials (riociguat, cicletanine, selexipag, macitentan, and imatinib). Macitentan, a nonselective ET_{A/B} endothelin receptor antagonist, was recently tested in the SERAPHIN phase 3 clinical trial in patients with PAH, including SSc patients.⁵¹ Using a morbidity and mortality composite endpoint (including death, atrial septostomy, lung transplantation, initiation of prostanoid therapy, and other indicators of worsening of PAH), this study found a dose-dependent risk reduction of 30% to 45% in response to macitentan. Other phosphodiesterase-5 inhibitors, including vardenafil, show great promise in improving symptoms, functional status, and hemodynamics and appeared to be well tolerated. Selexipag is an orally available selective prostacyclin IP receptor agonist that exerts greater vasodilatory effect than iloprost and is currently being evaluated in the GRIPHON phase 3 trial with a primary endpoint of time to first clinical event. A clinical trial of the use of oral treprostinil as an add-on therapy to an endothelin receptor antagonist and/or phosphodiesterase-5 inhibitor did not meet its endpoint of improvement in 6-minute walk distance, but results from two additional studies are pending.⁵²

In many cases the outcome of PAH appears to be worse in patients with SSc-associated disease than in patients with equally severe idiopathic PAH. There are a number of potential explanations for this finding, but it does suggest that this group of PAH cases presents a particular treatment challenge.

Another important consideration in the management of SSc-associated PAH is that there are other mechanisms for PH specifically relating to group 2 and group 3 disease that may contribute to outcome. They overlap with those of the 1' group, and there is the possibility that SSc comorbidity, including gut, heart, and renal disease, may impact outcome.

CONCURRENT INTERSTITIAL AND VASCULAR DISEASE

One of the major clinical challenges in assessment and treatment of pulmonary disease in SSc is the potential for multiple complications that may interact and lead to confusion in diagnosis and assessment. This is most apparent in considering interstitial lung fibrosis and PAH. Both complications are sufficiently frequent in SSc that they are likely to occur together by chance in a significant number of individuals. In practice it is usually possible to identify one of these processes as the predominant problem, and this can then be the main focus of management. However, there are challenges in applying data from observational cohort studies or clinical trials,

because most often an attempt is made to use a homogeneous cohort for study, and so cases in which there is the possibility of missed lung fibrosis and PAH are often excluded. Therefore outcome and treatment response data may not be applicable to patients with mixed or coexistent dual pathologic conditions. One example is that in current cohort studies, patients with PAH who have lung fibrosis appear to show blunted response to therapy even though the predominant pathologic condition is PAH rather than PH. Moreover, analysis of the outcome of lung fibrosis based on extent of disease or classification into mild or extensive subgroup is based on data sets from which clinically apparent PH was excluded.

CONCLUSION

In conclusion, although pulmonary complications of SSc have become a justifiable focus of investigation and treatment, it is important to remember that these complications occur in the context of a multisystem disease. Other important manifestations may also be present. For example, cardiac involvement, scleroderma renal crisis, pleural effusion, and chest wall disease arising from fibrosis or skeletal myopathy all may be relevant. In addition, nonlethal complications of SSc are often of greater importance to individual patients than the risk of developing a life-threatening lung manifestation, and so a comprehensive, multidisciplinary long-term care plan must provide the context for management of organ-based disease.

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Raynaud phenomenon

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- Raynaud phenomenon is an episodic reversible peripheral ischemia usually provoked by cold or emotion.
- Classically, constriction of the digital vessels leads to pallor of the digits reflecting poor or absent blood flow, followed by cyanosis secondary to deoxygenation of static venous blood.
- The recovery phase features reactive hyperemia secondary to a chemical vasodilation with resulting erythema.

HISTORY

Raynaud phenomenon is named after Maurice Raynaud, a French physician who described this condition in his medical thesis *De l'Asphyxie Locale et de la Gangrène Symétrique des Extrémités* published on February 25, 1862.

EPIDEMIOLOGY

In Europe, *Raynaud phenomenon* is the blanket term used to describe any form of cold-related vasospasm, which can be further subdivided into *Raynaud syndrome* when there is an associated disorder and *Raynaud disease* when there is not. However, in the United States the terminology most used is *primary* and *secondary Raynaud phenomenon*. Thus care must be taken when making literature comparisons.

Raynaud phenomenon affects 20% to 30% of young women with an overall prevalence in the population of approximately 10% and a female-male ratio of 9:1.¹ By far the largest group is those with primary Raynaud disease, which typically occurs in young women in their teens and 20s and has a familial predisposition. In contrast, more than 50% of the patients referred to a hospital have an associated underlying systemic disease. Raynaud syndrome may predate systemic illness by up to two decades. Epidemiologic studies have shown familial clustering of Raynaud disease, migraine, and irritable bowel syndrome, which may share a common cause in vasospasm followed by a reactive vasodilatation.

ETIOLOGY

There is a wide spectrum of disease associated with Raynaud syndrome, including connective tissue disorders (CTDs) and, less commonly, drug-induced and atherosclerotic disorders. Significant numbers of predominantly male sufferers have Raynaud phenomenon associated with occupational exposure to vibration.

Most cases of severe Raynaud phenomenon are associated with CTD. Raynaud phenomenon occurs in 98% of patients with systemic sclerosis (SSc) and may be their most pressing clinical problem; it occurs in 85% of patients with mixed CTD, between 10% and 45% of those with systemic lupus erythematosus, 33% of those with Sjögren syndrome, and 20% of those with polymyositis/dermatomyositis. In individuals with rheumatoid arthritis the overall prevalence is similar to that in the general population (10%); however, symptoms tend to be more severe.

Various drugs can precipitate or exacerbate Raynaud phenomenon. Of these, nonselective β -blockers and antimigraine preparations are the most frequent culprits. The newer generation of vasodilating β -blockers, however, does not cause this problem.

Hand-arm vibration syndrome (HAVS) is the most common form of occupational Raynaud phenomenon, with a prevalence of up to 50% in

workers using vibrating machines on a frequent basis. In the older age group, obstructive vascular disease is the most common cause. Sixty percent of cases of Raynaud phenomenon occurring in individuals older than age 60 are atherosclerotic in origin. Other conditions associated with Raynaud phenomenon are listed in [Box 146.1](#).

PATHOPHYSIOLOGY

Raynaud phenomenon predominantly affects the digits, although it may involve the nose, tongue, earlobes, and nipples, as well as other organs. A decrease in lung, esophageal, and myocardial perfusion has been reported after cold challenge, which suggests that vasospasm may be systemic in distribution. Furthermore, the links with migraine, irritable bowel syndrome, and cardiac syndrome X all suggest a common etiology. There are three pathophysiologic mechanisms that may mediate or aggravate these symptoms: (1) neurogenic mechanisms, (2) blood and blood vessel wall interactions, and (3) abnormalities of the inflammatory and immune responses.

Neurogenic mechanisms

The endothelium possesses at least five different adrenoceptor subtypes (α_2A/D , α_2C , β_1 , β_2 , and β_3), which either directly or through the release of nitric oxide (NO) actively participate in the regulation of vascular tone. Vasoconstriction evoked by postsynaptic α_2 -adrenoceptors is strongly implicated in the response to cold in patients with Raynaud phenomenon. Raynaud disease is far more common in women than in men. The constrictor effect of estrogen could also be due to a tonic effect of the hormone on sympathetic nerve traffic, a direct effect on adrenergic signaling, and/or amplification of an adrenergic response by vasoconstrictor prostanoids.

The central sympathetic system has some role in the pathogenesis, because local vibration of one hand induces vasoconstriction in the other, which is abolished by proximal nerve blockade. Moreover, stress-induced vasoconstriction has been extensively reported by those with Raynaud phenomenon, which suggests a central nervous system component. Impairment of central neural habituation of the pattern of cardiovascular response evoked by acute emotional stress has been demonstrated in patients with primary Raynaud phenomenon.² So it can be inferred that, throughout the working day, repeated vasoconstriction must occur in the fingers as part of the response to various stressors. This can facilitate the development of vasospasm in individuals who are susceptible to Raynaud disease. The selective serotonin reuptake inhibitor (SSRI) fluoxetine has been shown to reduce the frequency and severity of vasospastic episodes in patients with Raynaud disease and to increase the rate of rewarming after a cold challenge. Because the inhibition of reuptake by an SSRI would be expected to increase the plasma concentration of serotonin, which has vasoconstrictive properties, it is most likely that this agent achieves its beneficial effects by acting within the central nervous system. In addition, a deficit of nerves containing calcitonin gene-related peptide (a potent vasodilatory neuropeptide) has been shown in primary Raynaud disease, but it is not clear whether this is a primary abnormality or secondary to repeated vasospasm.

Raynaud may occur with carpal tunnel syndrome, but this may merely reflect the link between two diseases that frequently coexist in the population, particularly in those with HAVS.

Blood and blood vessel wall interactions

Although CTD is associated with some structural damage of the digital arteries and microvasculature, in primary Raynaud disease only subtle microvascular abnormalities occur, which are not visible using capillary

BOX 146.1 CONDITIONS ASSOCIATED WITH RAYNAUD PHENOMENON**Immune mediated**

- Systemic sclerosis (90%)
- Mixed connective tissue disease (85%)
- Sjögren syndrome (33%)
- Systemic lupus erythematosus (10%-45%)
- Polymyositis/dermatomyositis (20%)
- Rheumatoid arthritis (10%-15%)
- Cryoglobulinemia and cryofibrinogenemia (10%)
- Arteritis (e.g., giant cell arteritis, Takayasu arteritis)
- Antiphospholipid syndrome
- Primary biliary cirrhosis

Occupation related

- Cold injury (e.g., in frozen-food packers)
- Polyvinyl chloride exposure
- Vibration exposure
- Ammunition work (outside job)

Obstructive vascular disease

- Atherosclerosis
- Microemboli
- Thromboangiitis obliterans (50%)
- Thoracic outlet syndrome (e.g., cervical rib)
- Walking-crutch pressure
- Diabetic microangiopathy

Metabolic disorders

- Hypothyroidism
- Carcinoid syndrome

Drug induced

- Antimigraine compounds
- β -blockers (particularly nonselective)
- Cytotoxic drugs
- Cyclosporine
- Bromocriptine
- Sulfasalazine
- Minocycline
- Interferon- α
- Interferon- β
- Cocaine abuse

Infections

- Chronic viral liver diseases (hepatitis B and C)
- Cytomegalovirus infection
- Parvovirus B19 infection

Miscellaneous

- Complex regional pain syndrome type I
- Fibromyalgia syndrome
- Postviral fatigue syndrome (myalgic encephalitis)
- Toxin exposure
- Polycythemia
- Paraproteinemia
- Arteriovenous fistula
- Anorexia nervosa
- Neoplasm

Percent values are percentage of patients with the given disease who have Raynaud phenomenon.

microscopy.³ The endothelium is a functioning organ that releases substances important in maintaining blood flow. These include vasodilators such as prostacyclin (prostaglandin I_2 [PGI_2]) and NO, vasoconstrictors such as endothelin-1, and a variety of mediators of coagulation and inflammation. When the endothelium is impaired there is an imbalance of these substances, resulting in a vasoconstrictor, proinflammatory, and procoagulant endothelium that may lead to vascular damage. Abnormal endothelial responses to both endothelium-dependent and endothelium-independent vasodilatation have been found in patients with primary Raynaud phenomenon; however, in patients with Raynaud syndrome secondary to SSc, this abnormality is limited to the endothelium-dependent vasodilatation. It seems, therefore, that although secondary Raynaud phenomenon is associ-

ated with endothelial damage, in primary Raynaud phenomenon the mechanism of vasospasm may be related to smooth muscle contraction.

A reduction of NO, a potent vasodilator produced by the endothelium, may be involved in the pathogenesis of Raynaud phenomenon, and this can be clinically relevant because blood flow is improved when NO is administered therapeutically. Moreover, plasma levels of the endogenous NO synthase inhibitor asymmetric dimethylarginine have been found to be significantly higher in secondary than in primary Raynaud phenomenon, which further suggests involvement of the NO pathway in its pathogenesis.

It has also been shown that cooling-induced vasospasm is mediated by protein tyrosine kinase in Raynaud phenomenon secondary to SSc, with attenuation of spasm by its inhibitors providing an exciting new therapeutic target.⁴

Levels of other substances produced by the endothelium have also been reported to be abnormal in secondary Raynaud phenomenon. These include elevated levels of endothelin-1, angiotensin II (in diffuse SSc but not in limited SSc), the prothrombotic factor VIII/von Willebrand factor, as well as activators of the coagulation pathway and markers of impaired fibrinolysis. This may suggest that the endothelium plays an important role in the pathogenesis of secondary Raynaud phenomenon by promoting vasoconstriction and thrombosis.

In primary Raynaud phenomenon, however, the evidence for endothelial impairment is less clear, with some studies reporting raised levels of von Willebrand factor in affected individuals but others failing to demonstrate any differences from healthy control subjects. Only endothelin-1 and tyrosine kinase have been postulated as being important in primary Raynaud phenomenon because levels have been found to increase more in affected individuals than in control subjects after a cold challenge.

Blood cellular elements may have a pathologic role in Raynaud phenomenon. The platelets exhibit increased aggregation, releasing the vasoconstrictor and platelet aggregant thromboxane A_2 and other platelet-release products such as transforming growth factor- β and platelet-derived growth factor. The red blood cells appear to be stiff and rigid and thus can occlude the microcirculation. The white blood cells, which, when activated, release prothrombotic free radicals, become very stiff and aggregate, and this leads to a further reduction in blood flow. Some of these changes are likely to be a consequence of the vasospasm of Raynaud phenomenon rather than a cause, but they may augment the symptoms, and their attenuation is a potentially important feature in the drug management of this disorder.

Abnormalities of the inflammatory and immune responses

Disordered immune and inflammatory processes occur in the majority of severe cases of Raynaud phenomenon via their association with the CTDs but also occur in HAVS, which has no clear immune or inflammatory basis. Tumor necrosis factor, lymphotoxin, and phagocyte/macrophage- and T cell-derived proteins, along with immune complex deposition in the vessel wall, are likely to be activated in vascular damage seen in Raynaud syndrome.

Thus there are three clear pathways for promoting the decreased blood flow seen in Raynaud phenomenon. It has still to be resolved which are cause and which are consequence, but it seems that a combination of the factors is involved in the development of Raynaud phenomenon.

CLINICAL FEATURES

Detailed history taking and physical examination are essential for making the diagnosis, finding any associated underlying causes, assessing the likelihood of progression to CTD, and deciding on the most appropriate management. A detailed occupational history allows a diagnosis of HAVS. Drug history is equally important, and it should be noted that even the cardioselective β -blockers can produce a degree of peripheral vasoconstriction in susceptible individuals.

As documented earlier, Raynaud phenomenon is classically manifested by blanching of the affected part (pallor) (Fig. 146.1), followed by cyanosis and then rubor; however, this typical triphasic color change is not necessarily present in all patients, with some experiencing biphasic or monophasic color change. Generally, it is accepted that blanching must be present to allow a diagnosis of Raynaud phenomenon. Symptoms include numbness, cold, and pain secondary to ischemia, which can be severe enough to result in digital ulceration, gangrene, and loss of digits. During the reactive hyperemic stage, patients experience an unpleasant burning sensation or tingling. The most severely affected patients may experience year-round restrictions in daily activity.



Fig. 146.1 Raynaud phenomenon in a patient with systemic sclerosis. The asymmetric involvement and the presence of telangiectasia point to a secondary cause. Digital pitting and scarring is one of the main criteria for the diagnosis of systemic sclerosis.

BOX 146.2 FEATURES SUGGESTIVE OF PROGRESSION OF RAYNAUD PHENOMENON

Clinical

- Older age at onset (>35 years)
- Recurrence of chilblains as adult
- Vasospasm all year round
- Asymmetric attacks (see Fig. 146.1)
- Sclerodactyly or any other sign of connective tissue disease
- Digital ulceration
- Finger pulp pitting scars

Laboratory

- Increased levels of inflammatory markers
- Detection of autoantibodies
- Increased level of von Willebrand factor antigen

Nail-fold microscopy

- Abnormal vessels

The predictors for increased attack rate, severity, and pain are low average daily temperature, stress, older age, female gender, and an underlying cause, particularly CTD. The presence of certain clinical features may suggest a greater likelihood of disease progression to overt CTD (Box 146.2). For instance, sclerodactyly and pitting scars over the finger pulp are associated with later development of CTD (Fig. 146.2).

Patients who experience Raynaud phenomenon for the first time in their third and fourth decades are at high risk of developing CTDs. In very young children, an underlying CTD should also be considered, especially if the symptoms include blanching and are severe. Cyanosis alone is a common benign finding in young children. In SSc, if Raynaud phenomenon precedes the CTD by years, the limited form of the disease is more likely; conversely, the rapid appearance of the symptoms of SSc tends to predict diffuse SSc. Systemic evaluation should concentrate on the presence of migraine (or a family history of migraine), vasospastic angina, and a family history of the disorder (usually markers of primary Raynaud phenomenon). Elderly patients who experience Raynaud phenomenon for the first time usually have underlying atherosclerosis. A full physical examination should be performed to look for any obstructive vascular disease and for signs of associated autoimmune conditions. Simple blood pressure measurements in both arms can help to detect significant occlusive vascular disease above the brachial artery. Signs and symptoms of carpal tunnel syndrome should be actively sought, because sometimes releasing the median nerve can improve



Fig. 146.2 Digital pitting and scarring and sclerodactyly are commonly associated with systemic sclerosis. These lesions fulfill two of the three main criteria for systemic sclerosis; the third criterion is pulmonary interstitial fibrosis.

the symptoms of Raynaud phenomenon. Livedo reticularis could point to cold agglutinin disease, antiphospholipid syndrome, or underlying CTD. Patients with abnormal findings on nail-fold microscopy are much more likely to develop a CTD.

INVESTIGATIONS

Investigations in patients with Raynaud phenomenon have two functions: (1) to confirm the diagnosis and (2) to look for underlying secondary causes or associated conditions.

Diagnosis of Raynaud phenomenon

In the majority of cases the diagnosis of Raynaud phenomenon can be made from the clinical history. However, objective measures of blood flow may be needed in rare situations such as when the patient is unable to give a clear history, when occlusive vascular disease is present and the contribution of vasospasm to the clinical problem needs to be determined, and when documentation is required for medicolegal reasons in HAVS.

Many different techniques can be used to measure blood flow to the digits. In clinical practice, measurement of digital systolic blood pressure before and after local cooling of the hands in cool water at a temperature of approximately 15°C is widely used because of its simplicity. A decrease in pressure of more than 20 to 25 mm Hg is usually significant. This technique can give false-negative results unless precautions are observed. First, the patient must be warm before the recordings are made with the starting digital pressure as near brachial pressure as can be achieved. Second, in premenopausal women, assessment should be avoided in midcycle, because poor blood flow can occur at the time of ovulation. Third, all vasoactive medications should be stopped 24 hours before the test and the test should be avoided when the patient is in the reactive hyperemic phase. Ideally, patients should not have had a vasospastic attack on the day of the test. Therefore, although cold challenge is a good clinical diagnostic test, its false-negative rate precludes its use in compensation cases such as those involving HAVS, and in these cases thermal esthesiometry and vibrotactile thresholds are used instead.

Thermography and laser Doppler flowmetry are other methods used to help in the diagnosis. However, these methods have disadvantages and are usually unnecessary, and they are used mainly in the research setting.

Investigations for secondary causes

More than 50% of patients with Raynaud phenomenon who are referred to a hospital have an associated underlying disease; therefore it is essential to look carefully for any underlying cause. More importantly, early intervention could alleviate the problem, as in patients with vibration exposure or those who take vasoconstrictor drugs. An obvious associated disorder may be easily detected, but difficulty arises in diagnosing early CTDs due to the lag period between development of Raynaud phenomenon and the other features of the CTD.

Blood biochemistry testing, including thyroid function tests and a full blood cell count, should be performed. A normochromic, normocytic or microcytic anemia of chronic disease can be found in patients with CTDs. The inflammatory markers such as erythrocyte sedimentation rate, plasma

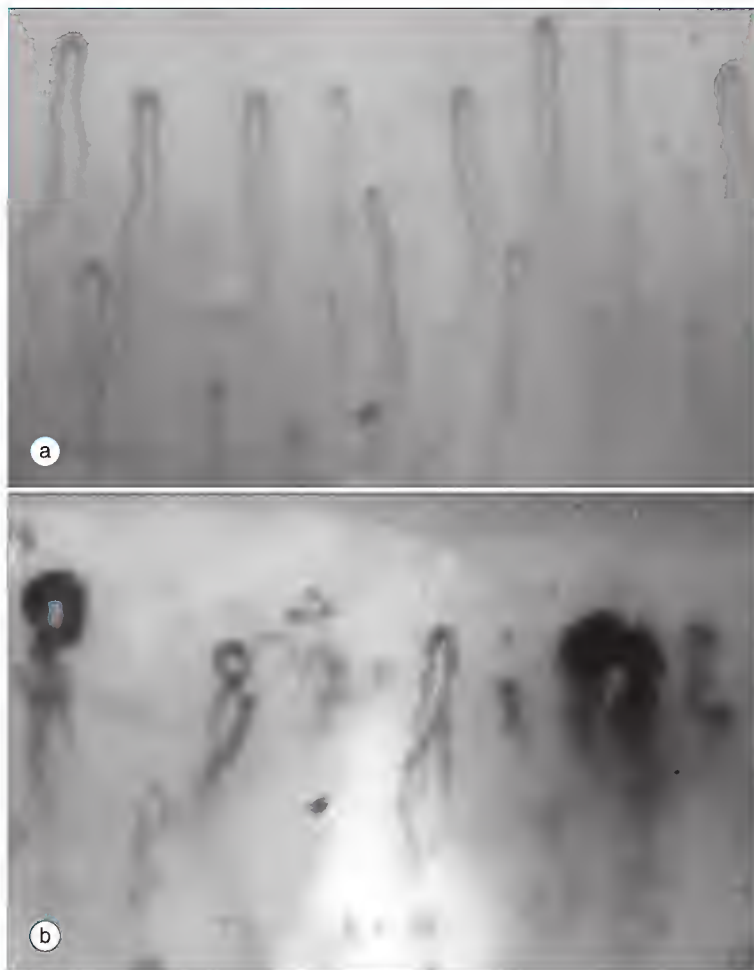


Fig. 146.3 Nail-fold microscopy. (a) Normal capillaries. (b) Tortuous and enlarged capillaries in systemic sclerosis.

viscosity, and C-reactive protein level are usually normal in primary Raynaud phenomenon, but they may be increased in secondary disease. Measurement of creatinine concentration, determination of estimated glomerular filtration rate, and urinalysis help in detecting early renal disease in CTD, diabetes, or atherosclerosis. Thoracic outlet chest radiography can reveal whether a bony cervical rib is present and show if there is any basal lung fibrosis, which may be seen early in CTDs. However, because the rib may be fibrous, if there is a high clinical suspicion of a cervical rib despite a negative finding on chest radiograph, then it is usual to progress to thoracic outlet magnetic resonance angiography.

Immunologic tests may help to detect any immunopathologic origin for secondary Raynaud phenomenon, and these tests and their specific disorders are covered elsewhere. Detection of cold-precipitated proteins can help in the diagnosis of cryoglobulinemia and cryofibrinogenemia. Increased levels of von Willebrand factor antigen tends to occur in patients with secondary Raynaud phenomenon. Focus is placed on the role of investigative techniques that may help to distinguish between primary and secondary Raynaud phenomenon—in particular, Raynaud phenomenon related to SSc, in which pathognomonic changes of tortuosity and dropout are seen. Nail-fold microscopy is useful to examine morphologic and functional changes of the microcirculation and may help to point to Raynaud phenomenon secondary to CTD, especially when associated with positive serum antibody test results (Fig. 146.3). Nail-fold videocapillaroscopy has emerged as an extremely useful and important tool in identifying CTDs. This technique involves direct visualization of the nail-fold capillary vessels with a digital camera attached to a computer. In combination with negative results on immunologic testing, normal nail-fold videocapillaroscopy findings are very suggestive of primary Raynaud phenomenon.

MANAGEMENT

Not all patients experiencing digital vasospasm require drug treatment, but potential prescribers should be aware that the severity of the pain produced

TABLE 146.1
Drugs commonly used in Raynaud phenomenon

Drug	Dosage
Oral	
Nifedipine retard (or other calcium channel blocker)	10-20 mg bid or tid
Naftidrofuryl oxalate	100-200 mg tid
Inositol nicotinate	1 g tid or inositol nicotinate forte 1.5 g bid
Thymoxamine	40-80 mg qid (stop after 2 wk if no response)
Intravenous	
Iloprost	Start infusion (peripheral line) at 1 µg/hr; increase by 1 µg every 30 min until maximum tolerable dose reached (maximum dosage should not be >3 µg/hr). Infusions are given over 6 hr each day for 3-7 days on each occasion.
Prostaglandin E ₁	60 µg in 250-mL physiologic infusion over 3 hr daily for 5-6 days. This can be repeated every 6 wk to cover cold weather in severe cases, especially if associated with critical ischemia or digital ulceration, and should be given via a central line.

by vasospastic attacks and the degree of interruption that patients may experience in their normal daily routine may be profound.

General measures

Education and patient avoidance of triggers are key. Lifestyle measures such as wearing gloves when handling frozen food should be adopted. It is essential that patients stop smoking and, where applicable, avoid vibration exposure. Initial treatment in mild disease is conservative, and drug treatment is avoided. A specialist rheumatology nurse and occupational therapist can provide useful advice, as can patient self-help groups. It is important to advise patients about protecting themselves from the cold. Making simple suggestions such as keeping the trunk warm and providing occupational therapy aids such as key holders to use when the fingers are numb can help. Electrically heated gloves and socks and chemical hand warmers are the perfect solution for some patients.

In the case of HAVS, early diagnosis and early discontinuation of vibration exposure may resolve the problem. Cessation of any vasoconstrictor drugs the patient is taking is essential. Although the contraceptive pill has been linked anecdotally to the development of Raynaud phenomenon, this has never been conclusively demonstrated. It is the authors' policy not to discontinue the contraceptive pill or hormone replacement therapy unless it is clearly related to the patient's Raynaud phenomenon. In the management of digital ulceration in patients with severe Raynaud phenomenon, it is essential to treat any infection aggressively and quickly. In SSc inflammation may be restricted and thus may be missed unless specifically sought.

Drug treatment

Patients whose symptoms are severe enough to cause interference with either their social or work lifestyle should be considered for drug treatment (Table 146.1).

Calcium channel blockers

Dihydropyridine calcium channel blockers, in particular nifedipine, in a long-acting preparation (e.g., nifedipine retard) have now become the gold standard. The short-acting preparations produce violent vasodilatory adverse effects and their action lasts only a few hours. Nifedipine's mechanism of action is predominantly vasodilation, but it also has antiplatelet and possibly other antithrombotic effects. The dosage ranges from 10 to 20 mg two or three times daily; the drug should be introduced very gradually: 10 mg at night for 2 weeks, then in the morning for 2 weeks, then twice a day, and so on. Nifedipine has been found to be useful in decreasing the frequency and severity of vasospastic attacks and improves the objective measures of blood flow after cold exposure. Its use, however, can be limited by the vasodilatory adverse effects to which patients with Raynaud phenomenon appear very susceptible, particularly those patients with primary disease. These effects usually disappear with continued treatment, and therefore,

unless they are intolerable, the patient should persevere for at least 2 weeks before stopping the drug. If adverse effects necessitate discontinuation, other calcium channel blockers such as amlodipine or lercanidipine can be tried.

Two meta-analyses have been published looking at the efficacy of calcium channel blockers in primary Raynaud phenomenon and Raynaud phenomenon secondary to SSc. These showed a 33% and 35% reduction in severity of the attacks in primary and secondary disease, respectively, as well as a moderate reduction in the frequency of attacks.^{5,6}

Other vasodilators

The use of other vasodilators in Raynaud phenomenon remains controversial, because most studies have been small or uncontrolled. Inositol nicotinate (a nicotinic acid derivative) and naftidrofuryl oxalate (a mild peripheral vasodilator with a serotonin receptor antagonist effect) have produced some encouraging results in mild to moderate disease, as has thymoxamine. Another role of these medications is as adjuncts to calcium channel blockers when adverse effects prevent the achievement of a high dosage of the latter. These drugs may take up to 3 months to produce their effects, which suggests that their action in Raynaud phenomenon may be through other mechanisms. Moreover, their vasodilatory adverse effects can also be a problem.

In a meta-analysis, prazosin, an α -blocker, was found to have modest effect in the treatment of Raynaud disease secondary to SSc.⁷ Thus prazosin could be considered for those with concomitant hypertension or as an extra option in those who cannot tolerate calcium channel blockers.

Losartan, an angiotensin II receptor antagonist, has been shown in a randomized controlled trial to be modestly effective in treating Raynaud phenomenon associated with CTD.⁸ There is no similar study assessing response in primary Raynaud phenomenon, however.

Newer oral vasodilating therapies have been investigated with some promise. Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, and vardenafil) have all shown promising results.⁹ A recent meta-analysis concluded that phosphodiesterase-5 inhibitors appear to have significant but moderate efficacy in secondary Raynaud phenomenon,⁹ but a large randomized controlled trial is also needed. The limitations of these studies are their relatively short duration and their use of predominately secondary Raynaud phenomenon patient cohorts. Thus the role these drugs will play in therapeutic regimens is not yet established.

Prostaglandins

Both prostacyclin (PGI₂) and alprostadil (PGE₁) have potent vasodilatory and antiplatelet properties. Treatment with PGI₂ and PGE₁, however, requires intravenous administration through a central line, and both are unstable agents. Thus more stable analogues such as iloprost have been evaluated.

Iloprost

A number of double-blind placebo-controlled studies as well as a meta-analysis¹⁰ of iloprost infusion given intravenously have shown benefit. In addition to its vasodilatory and antiplatelet effects, iloprost has been shown to downregulate lymphocyte adhesion to the endothelium. Compared with nifedipine, it was found to have the same effect in reducing the frequency of vasospastic attacks but was more effective in healing digital ulcers and appeared to produce fewer adverse effects. Iloprost should generally be considered as a second-line treatment of vasospasm but is the first choice for those who have critical ischemia or severe digital ulceration.

Oral and transdermal prostaglandins

Studies of orally active prostacyclin analogues have yielded conflicting results. Treatment with cicaprost proved disappointing, whereas the evidence supporting the use of oral iloprost in Raynaud phenomenon is less clear. Neither high nor low doses were better than placebo in decreasing attacks in Raynaud disease secondary to SSc. Patient opinion, however, tended to favor high doses of iloprost compared with placebo.

Reports of the oral use of limaprost, an alprostadil analogue, in small numbers of patients have been encouraging, but these findings have not been replicated in larger trials. Prostaglandin delivery through the skin has also been studied, but no transdermally applied prostaglandin has achieved license status as yet.

Alprostadil

A study comparing PGE₁ (alprostadil) with iloprost has shown similar benefits for the two drugs in the management of Raynaud phenomenon secondary to CTDs.¹¹ Alprostadil could be considered in patients who experience significant adverse effects from iloprost and cannot tolerate the drug. PGE₁α cyclodextrin has been reported to improve Raynaud phenomenon symptoms, severity of attacks, and healing of digital lesions in SSc patients.

Other medical therapies

Endothelin-1 receptor antagonists also have been investigated. Bosentan has been evaluated for treatment of digital ulceration secondary to SSc, and some benefit has been seen.¹² Evidence supporting its use in Raynaud phenomenon alone is lacking. Furthermore, in addition to the vasodilatory adverse effects common with other drugs, the possibility of liver toxicity has to be considered, and the results of a current major trial are awaited.

The following agents or procedures have been found effective in small studies and need validation: (1) fluoxetine, an SSRI (another serotonin antagonist, ketanserin, was found not to be beneficial for Raynaud disease secondary to SSc¹³); (2) ginkgo biloba (a second larger study did not report efficacy¹⁰); (3) transdermal glyceryl trinitrate patches (may be of some help, but their use may be limited by the frequent occurrence of headaches); (4) digital botulinum toxin injections (may be effective in severe Raynaud phenomenon and cases of digital ulcer¹⁴); (5) high-dose statins (especially in elderly patients with Raynaud disease who have atherosclerosis¹⁵).

Surgery

Operations to remove part of the terminal phalanx and occasionally amputations are necessary in cases of severe ischemia, but with the advent of iloprost this is becoming infrequent. Raynaud phenomenon secondary to an atherosclerotic occlusion or stenosis may benefit from endovascular intervention. In Raynaud phenomenon secondary to carpal tunnel syndrome, surgical decompression has been shown to improve the symptoms significantly, but whether this is through decreased paresthesia or true improvement of blood flow is unknown.

Conventional upper limb sympathectomy via open surgery is invasive and associated with a high relapse rate and poor response patients with Raynaud syndrome. However, a few studies suggest that thoracoscopic sympathectomy may be successful, particularly in cases of resistant digital ulcers, despite some untoward effects. The longer-term results, however, have yet to be evaluated, and this operation is now performed infrequently. Chemical thoracic sympathectomy (by injection of 5% phenol into the second or third thoracic sympathetic ganglion) may be a safe, minimally invasive procedure, and a good success rate in Raynaud syndrome was reported in one series,¹⁶ but no further work has been published and so this treatment also requires further evaluation.

Localized digital sympathectomy enjoyed some support initially because earlier results were encouraging; however, again further work is required in this area because the relapse rates are high and the associated local tissue trauma can be a problem. Periarterial sympathectomy of the radial and ulnar arteries may have a role in treatment of refractory Raynaud phenomenon, but only small case series have been reported. Convincing published evidence is still absent for upper limb sympathectomy; however, it should be remembered that sympathectomy still has an important role in the treatment of Raynaud phenomenon affecting the feet.

CONCLUSION

Raynaud phenomenon is a common condition, and until recently its management was difficult. Careful clinical history taking, physical examination, and selected investigations allow correct diagnosis and its categorization as primary or secondary. This should be done using all available information and the most up-to-date investigations. Not only does this allow early and appropriate detection of serious medical conditions, but it also provides appropriate reassurance for patients who have primary Raynaud phenomenon. When Raynaud phenomenon occurs as a primary disease, it is usually mild, with symmetric involvement and no laboratory test abnormalities, and may need no drug treatment. Features suggesting secondary Raynaud syndrome include painful attacks, ischemic digital ulcers, asymmetric attacks, a positive autoantibody test result, abnormal nail-fold capillaries, and increased levels of inflammatory markers. Therapeutic management of patients requires individualization of drug therapy depending on the clinical presentation. Patient opinion should always be considered, and appropriate education is the cornerstone of therapy. The prospect of new therapeutic agents and extended licenses for current therapies does suggest a degree of optimism for the future treatment of Raynaud phenomenon.

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Localized scleroderma and scleroderma-like syndromes

■ ROBERT W. SIMMS

- Skin induration, the hallmark of systemic sclerosis, can also occur in localized forms of scleroderma, as well as in conditions unrelated to scleroderma or systemic sclerosis. These scleroderma-like syndromes can be classified as “scleroderma variants.”
- The scleroderma variant conditions are unrelated to scleroderma but can be confused with it. This heterogeneous group includes diffuse morphea, eosinophilic fasciitis, scleromyxedema, scleredema, eosinophilia myalgia syndrome, and nephrogenic systemic fibrosis.
- In contrast to systemic sclerosis, the scleroderma variant conditions are rarely associated with sclerodactyly or Raynaud phenomenon, and serum autoantibodies do not occur. However, internal organ involvement may be present and might be associated with plasma cell dyscrasia and eosinophilia.
- The scleroderma variants require accurate diagnosis and different approaches to treatment. Accurate diagnosis may require a full-thickness skin biopsy specimen and careful histopathologic examination with the use of special stains.

A variety of disorders are characterized by sclerosis and induration of the skin, including systemic sclerosis (systemic scleroderma), localized scleroderma (including the subtypes morphea and linear scleroderma), and conditions that mimic systemic sclerosis (Box 147.1). These so-called scleroderma variants might pose significant diagnostic challenges for clinicians and may include localized forms of skin sclerosis, scleredema, scleromyxedema, eosinophilic fasciitis, nephrogenic systemic fibrosis, and chronic graft-versus-host disease (GVHD). A number of drugs (L-tryptophan, bleomycin, and most recently taxane) and environmental exposures (toxic oil syndrome) also produce mimics of scleroderma. Additionally, diabetes and other metabolic conditions may produce skin induration that may be confused with scleroderma. Typically, the scleroderma mimics are not associated with Raynaud phenomenon, nail fold capillary abnormalities such as capillary dropout, capillary dilation or vascular ischemia, calcinosis, or autoantibody formation, which are hallmarks of scleroderma. Other key features that can be used to distinguish between systemic sclerosis and the scleroderma variants are listed in Table 147.1. Careful assessment of the distribution and quality of dermal involvement, history of Raynaud phenomenon, appropriate antibody testing, and full-thickness skin biopsy will generally distinguish these conditions.

LOCALIZED FORMS OF SCLERODERMA

Localized scleroderma is characterized by sclerosis that is confined to the skin and occurs in two principal types that are distinguished by the morphology of the dermal lesions: *linear scleroderma* and *morphea*. *Linear scleroderma* is characterized by the presence of longitudinal bands of skin sclerosis, whereas *morphea* occurs as circumscribed oval plaques. A special form of linear scleroderma involving the head and face, *scleroderma en coup de sabre*, may produce severe facial and skull deformity, as well neurologic abnormalities.¹ Several different subtypes of morphea have been described, including the most common *plaque morphea*, *deep morphea*, *diffuse morphea*, and *pansclerotic morphea*. Additional rare conditions considered within the morphea spectrum include *keloidal or nodular morphea* (sclerotic papules or plaques that resemble keloidal scars), *atrophyoderma of Pasini and Pierini* (depressed hyperpigmented plaques with a sharp border and lacking inflammation and

induration), and *lichen sclerosus et atrophicus* (atrophic white or shiny plaques that may show follicular plugging).² Linear scleroderma tends to be more common in children, whereas morphea is more prevalent in adults.² The estimated annual incidence is 2.7 per 100,000 with a prevalence of 50 per 100,000; the age at onset is about 46 years, and the female-to-male ratio is 2.6.³ Misdiagnosis and delay in treatment appear to be common, especially in children with localized scleroderma.⁴

Morphea

The most common type of morphea lesion is *plaque morphea*, which accounts for approximately 50% of all cases of morphea.³ These lesions typically consist of slowly enlarging single or multiple circumscribed plaques on the trunk or extremities. Initially, they may be erythematous or have a violaceous border but generally become progressively more hyperpigmented over time (Fig. 147.1). Involved skin becomes shiny and lacks sweat glands and hair follicles. Histologically, the early lesions may show a dense inflammatory infiltrate composed of lymphocytes, macrophages, plasma cells, eosinophils, and mast cells. Later stages are characterized by little inflammation and by deposition of collagen extending from the reticular dermis to more superficial structures—indistinguishable from biopsy findings in patients with systemic sclerosis.²

Deep morphea or morphea profunda

Comprising several clinical entities in which inflammation and sclerosis occur in the deep dermis, panniculus, fascia, and even superficial muscle,⁵ deep morphea (or morphea profunda) includes *disabling pansclerotic morphea of children*.⁶ This rare condition is the most aggressive and severe form of morphea because of its propensity to involve deep subcutaneous tissue, fascia, muscle, and bone.⁶⁻¹⁰ It is frequently associated with significant disability and deformity despite intervention.⁶ Chronic ulcers complicating pansclerotic morphea may evolve into squamous cell carcinoma.¹¹

Generalized or diffuse morphea

Characterized by widespread skin involvement with multiple indurated plaques, hyperpigmentation, and frequent muscle atrophy, generalized or diffuse morphea accounts for approximately 15% of all cases of morphea³ (Fig. 147.2). Diagnostic criteria differ among investigators; Takehara and Sato¹² suggested two or more of the following criteria: (1) four or more lesions larger than 3 cm in diameter, irrespective of whether they are of the morphea or linear type, and (2) involvement of two or more of seven areas of the body, the seven areas being the head and neck, the right upper extremity, the left upper extremity, the anterior part of the trunk, the posterior part of the trunk, the right lower extremity, and the left lower extremity.

The presence of a variety of autoantibodies, including antinuclear antibodies and antibodies to histone, nucleosome, U3-RNP, fibrillin, topoisomerase II, and cardiolipin, suggests that morphea is an autoimmune disorder.¹² Additionally, the cytokine profile of morphea lesions involves type 2 helper T-cell activation and overexpression of profibrotic cytokines such as transforming growth factor- β and connective tissue–derived growth factor, similar to the profile seen with systemic sclerosis.^{2,13-15}

Treatment of morphea has included topical tacrolimus, methotrexate, cyclosporine, imatinib, mycophenolate mofetil, ultraviolet A and retinoic acid, and bosentan.¹⁶⁻²⁷ Assessment of efficacy is difficult given the rarity of the condition and slow progression in most cases, and consensus has not been reached regarding standardized assessment. Methotrexate is the most widely used agent for progressive disease; anecdotal reports indicate that it may result in regression of localized lesions.²⁷ The choice of therapy should be based on factors such as activity of the disease, depth of involvement, area of involvement, and rate of progression. Systemic treatment is thought

BOX 147.1 CONDITIONS ASSOCIATED WITH CHRONIC SKIN INDURATION

- 1. Systemic sclerosis
- 2. Localized scleroderma
- 3. Scleroderma variants
 - Scleredema
 - Scleredema adultorum of Buschke
 - Scleredema diabeticorum
 - Scleredema neonatorum
 - Scleromyxedema
 - Nephrogenic fibrosing dermopathy
 - Eosinophilic syndromes
 - Eosinophilic fasciitis (diffuse fasciitis with eosinophilia, Schulman disease)
 - Eosinophilia-myalgia syndrome
 - Toxic oil syndrome
 - Chronic graft-versus-host disease
 - Pseudoscleroderma (local injection of vitamin K, bleomycin, pentazocine)
 - Metabolic diseases
 - Porphyria cutanea tarda
 - Phenylketonuria
 - Werner syndrome
 - Acromegaly
 - Pachydermoperiostitis
 - POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monodonal gammopathy, skin changes)
 - Stiff skin syndrome
 - Reflex sympathetic dystrophy
 - Hemiplegia

to be indicated with subcutaneous involvement, rapid progression, and involvement of functionally or cosmetically sensitive areas.²⁸

Linear scleroderma

Linear scleroderma is considered in some classification schemes as a form of morphea (linear morphea) but is best viewed as a separate entity given its clinical and morphologic characteristics.²⁹ Linear scleroderma occurs most commonly in children and adolescents, in whom it accounts for most cases of localized scleroderma, and much less commonly in adults.^{3,30} The typical lesion develops insidiously as a linear band of sclerotic hypopigmented or hyperpigmented skin beginning on the extremities. It may extend through to the underlying dermis, subcutaneous tissue, muscle, and bone and produce significant deformity. When linear scleroderma involves the face or scalp, it is termed *en coup de sabre* and is related to Parry-Romberg syndrome, a condition associated with hemifacial atrophy of tissue below the forehead with little involvement of the skin. Both *en coup de sabre* and Parry-Romberg syndrome may be associated with central nervous system, ocular, and dental abnormalities. A retrospective study of both conditions in 54 patients seen over a 20-year period from 1984 to 2004 at the Mayo Clinic found that both conditions frequently coexist and are often bilateral, thus attesting to the close relationship between *en coup de sabre* and Parry-Romberg syndrome.³¹ Seizures were found to occur in 13% of patients with both syndromes.³¹ Treatment of linear scleroderma most often involves the use of methotrexate or antimalarial agents, but cyclosporine and tissue allografts have also been used.^{16,23,32} A recent report indicated successful application of adipose-derived regenerative cell-enriched fat grafting for treatment of the *en coup de sabre* deformity.³³ A systematic review suggested that phototherapy, methotrexate/systemic corticosteroids, calcipotriene, and

TABLE 147.1
Distinguishing features of scleroderma and scleroderma-like conditions

Condition	Skin changes and distribution	Extradermal involvement	Dermatopathology	Other
Localized scleroderma	Amorphous plaques (morphea) or lines involving the face (linear) and extremities and sparing the fingers	None	Dermal sclerosis, mononuclear inflammation	Linear especially common in children, autoantibodies common
Scleredema	Trunk, back, neck	Rare	Swollen collagen bundles, mucin accumulation	
Scleromyxedema	Induration, sclerodactyly Limited mouth opening	Rare	Excessive dermal mucin deposition	Serum paraprotein (especially IgG λ)
Nephrogenic systemic fibrosis	Extremities, fingers; symmetric	Frequent, mild (muscle, fascia, lungs)	Fibroblast proliferation, mucin deposition, dermal spindle cell proliferation	After gadolinium exposure in end-stage renal disease
Eosinophilic fasciitis	Extremities, trunk; spares fingers	Rare; low-grade myositis	Dermal and hypodermal sclerosis, normal epidermis, muscle inflammation occasionally	Peripheral blood eosinophilia frequent



Fig. 147.1 Plaque morphea in the popliteal area.



Fig. 147.2 Generalized morphea.

topical tacrolimus were most efficacious in treating morphea and appeared to work optimally with inflammatory lesions.²⁸ Ultrasound may be useful for the initial evaluation of lesions in localized scleroderma, especially in distinguishing active from inactive skin lesions.^{34,35}

CONDITIONS THAT MIMIC SCLERODERMA

Scleromyxedema

Scleromyxedema is a rare condition characterized by deposition of mucin in the skin and other organs and is typically associated with the production of a monoclonal IgG protein.³⁶⁻⁴¹ The first documented cases were described at the turn of the 19th century by Dubreuilh and Reitmann as generalized lichen myxedematosus.^{42,43} Another term formerly used was generalized lichenoid papular eruption. The condition was renamed scleromyxedema by Gottron in 1954.⁴⁴ In Gottron's description, the characteristic features consisted of generalized waxy papules with induration and thickening. Other synonyms of scleromyxedema include scleromyxedema of Arndt-Gottron, papular mucinosis, and lichen myxedematosus. Rongioletti and Rebora³⁷ suggested that scleromyxedema should be used to refer to the generalized form of lichen myxedematosus whereas the more localized form of the disease should be termed papular mucinosis.

Although the pathophysiology of scleromyxedema is unknown, fibroblasts appear to have a central role. Serum from patients with scleromyxedema stimulates the *in vitro* proliferation of normal dermal fibroblasts.⁴⁵ Fibroblasts from patients with scleromyxedema appear to synthesize high quantities of hyaluronic acid and subsequently greater amounts of mucin. Furthermore, the heparin sulfate proteoglycan obtained from scleromyxedema papules has been shown to promote fibroblast growth factor activity *in vitro*.

Approximately 83% of patients with this condition have an IgG paraprotein, although there does not appear to be any quantitative relationship between paraprotein levels and clinical manifestations.⁴⁶ In one study of autologous stem cell transplantation in five patients, only two showed eradication of their monoclonal protein, and no association with clinical improvement was noted.⁴⁷

The histology of scleromyxedema is characterized by a triad of mucin deposition, fibroblast proliferation, and fibrosis.⁴⁸ This occurs primarily in the mid and upper reticular dermis (Fig. 147.3). Elastin fibers tend to be decreased in quantity and the epidermis may be thin. Hair follicles may be atrophic. A slight perivascular and superficial lymphocytic and plasmacytic infiltrate may also be present.

The clinical features of scleromyxedema are characterized by widespread symmetric eruption of small waxy papules, which are often linearly and

closely spaced.⁴⁶ They are typically 2 to 3 mm and dome shaped or flat topped and may include the face, neck, distal end of the forearms, and hands, with the palms, scalp, and mucous membranes generally being spared (Fig. 147.4). The lesions are not usually pruritic; however, the Koebner phenomenon may occasionally occur. Leonine facies may also be seen (see Fig. 147.4). The skin stiffness may decrease range of motion in the joints of the hands and larger extremities. Systemic manifestations may result from mucin deposition around vessels in many organs, including the heart and lungs.³⁸ Dysphagia is the most common extracutaneous manifestation and is associated with esophageal dysmotility. Myopathy occurs in approximately 20% of patients.⁴¹ Initial treatment typically includes systemic corticosteroids and melphalan, sometimes in combination with plasmapheresis. Second-line treatments have included isotretinoin and intralesional corticosteroids. Third-line therapies include cyclophosphamide, cyclosporine, thalidomide, autologous stem cell transplantation, intravenous immunoglobulin, and radiation therapy.⁴⁸⁻⁵² A recent report of a patient with severe scleromyxedema failing to respond to initial therapy with prednisone and intravenous immunoglobulin described a partially favorable outcome with high-dose melphalan and autologous stem cell transplantation and, after relapse, a complete response to bortezomib plus dexamethasone.⁵³

The outcome of scleromyxedema is variable. A chronic progressive course is the rule, but spontaneous improvement may occur. Occasionally, severe extracutaneous involvement may result in increased mortality.³⁸

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis is a recently described progressive systemic fibrosing disorder that occurs in patients with end-stage renal disease who have undergone magnetic resonance imaging with gadolinium enhancement (see Chapter 170).⁴⁹

Scleredema

Scleredema, or scleredema adultorum of Buschke, is a condition that mimics scleroderma and is characterized by firm, nonpitting edema that typically begins on the neck and spreads to the face, scalp, shoulders, and trunk.⁵⁵ The hands and feet are characteristically spared ("inverse" in comparison to systemic sclerosis). The condition appears to occur in several variants that may be associated with or follow an infection or be associated with diabetes, but some cases have neither association. The condition was first described by Buschke in 1902,⁵⁶ who reported it in a 46-year-old carriage varnisher in whom skin hardening developed on the neck and spread to involve all parts of his body except the hands and thighs. This patient's symptoms arose following an episode of influenza. Graff⁵⁷ subsequently described three variants of scleredema. Type I was considered the classic type identified by Buschke and occurs following an infection or febrile illness, with resolution taking place in months to years. Type II had no preceding febrile illness and no apparent underlying cause and tended to follow a slow, progressive course with an increased risk for the development of paraproteinemia, including multiple myeloma. Type III was termed diabetic scleredema given its association with diabetes.

Skin biopsy specimens from patients with scleredema typically show that the epidermis is not involved.⁵⁵ The dermis tends to be thickened, up to four times normal, with swollen collagen fibers separated by wide spaces in which acid mucopolysaccharides are found.⁵⁸ Although patients with

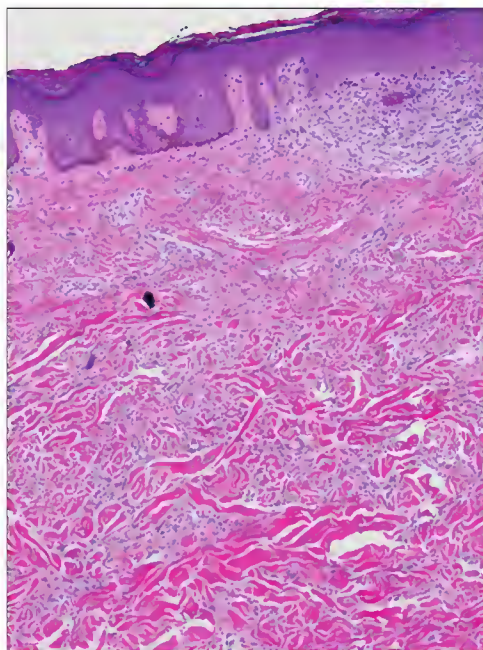


Fig. 147.3 Histologic features of scleromyxedema showing marked fibroblast infiltration, increased and disorganized collagen deposition, and extensive dermal mucin deposits.



Fig. 147.4 Typical waxy papular deposits in scleromyxedema. (Courtesy Dr. Alan Tyndall.)

scleredema have predominantly dermal involvement, some series have indicated extracutaneous involvement, with mucopolysaccharide staining even within the myocardium in one case.⁵⁹ Tongue involvement causing difficulty swallowing and dysphagia has also been described, as has ocular, bone marrow, and salivary infiltration.⁴⁸ Magnetic resonance imaging may show diffuse thickening of the dermis and subcutaneous tissue with hyperintense signals.⁶⁰

Therapy for scleredema has included trials of thyroid hormone, immunosuppressants, antibiotics, corticosteroids, and physiotherapy, but none has proved to be consistently effective.⁴⁶ Several reports have suggested marked improvement following electron beam therapy.⁶¹ A recent report described complete remission of multiple myeloma-associated scleredema after bortezomib-based treatment.⁶² A case of poststreptococcal scleredema was reported to successfully respond to intravenous immunoglobulin.⁶³

Eosinophilic fasciitis

Eosinophilic fasciitis (EF) was first described by Shulman in 1974, who reported two patients with scleroderma-like skin changes and induration of subcutaneous tissue of the extremities associated with peripheral eosinophilia.⁶⁴

Deep dermal biopsy specimens showed evidence of diffuse fasciitis, and the condition was later termed EF.^{65,66} Other terms for this syndrome include Shulman disease and diffuse fasciitis with eosinophilia. Similar conditions resulting from the ingestion of toxic contaminants in two epidemics have also been reported, one termed toxic oil syndrome in Spain and the other eosinophilia-myalgia syndrome in the United States.⁶⁷⁻⁷⁰ The conditions were also characterized by eosinophilia, variable skin fibrosis, and pathologic evidence of fasciitis. In some cases these conditions resulted in severe multisystem involvement and a high mortality rate, which is uncommon with EF.

The histopathologic features of EF include dermal and hypodermal sclerosis associated with fibrotic thickening of the subcutaneous adipose lobular septa, superficial fascia, and perimysium.⁷¹ The epidermis is typically normal. Mild inflammation may be present in the muscle layer. An antecedent history of vigorous exercise or trauma may occur in as many as 50% of patients. Toxic exposure other than aniline-denatured rapeseed oil and L-tryptophan (in the other conditions mentioned) has not been found, although several cases have been associated with positive serologic findings for *Borrelia burgdorferi*; spirochetal organisms have been identified in some patients with EF.^{72,73}

The clinical manifestations of EF often evolve in three stages, the first being pitting and edema; the second being “peau d’orange” and induration, with the arms and legs most commonly affected; and the third consisting of development of the “groove sign,” a dimpled appearance of the medial aspect of the upper part of the arm with elevation where the collapsed branchial vein leaves an indentation (Fig. 147.5).^{74,75} Involvement of the feet and hands is uncommon. Low-grade myositis may be present, although the serum creatinine kinase level is usually normal.⁷⁶ Periarticular involvement may result in flexion contractures and significant functional disability, as well as in peripheral nerve compression, especially carpal tunnel syndrome. True sclerodactyly and nail fold capillary abnormalities do not occur.

Laboratory features include peripheral eosinophilia, which may be present in up to 80% of cases. Laboratory findings include polyclonal hypergammaglobulinemia and increased acute-phase reactant levels such as the erythrocyte sedimentation rate and C-reactive protein.

EF has been associated with malignancy, especially hematologic malignancies, including leukemia and aplastic anemia.⁷⁷⁻⁸²

Published series suggest that corticosteroids appear to be the first line of treatment of EF. Other therapies have included antihistamines, D-penicillamine, antimalarials, and cytotoxic agents. Endo and colleagues⁸³ recently reviewed a large number of EF cases and found that clinical variables associated with a poorer outcome (defined as refractory disease or residual skin fibrosis despite prolonged treatment) included young age, presence of morphea-like skin lesions, and trunk involvement. An important component of treatment is physical therapy to minimize the sequelae of flexion contractions and their subsequent disability. Lebeaux and



Fig. 147.5 The “groove sign” of eosinophilic fasciitis.

colleagues⁸⁴ reviewed treatment outcomes in 34 patients with biopsy-proven EF. Pulse methylprednisolone at initiation of treatment (500 to 1000 mg daily for 3 consecutive days) was associated with better outcomes and a lower need for immunosuppressive drugs.

Chronic graft-versus-host disease

GVHD is the most common serious complication of allogeneic hematopoietic stem cell transplantation. It comes in two forms: acute and chronic. Acute GVHD induces a variety of clinical conditions, including dermal, gastrointestinal, and pulmonary complications, and occurs in approximately 30% to 50% of sibling donor recipients and a higher fraction of unrelated donor recipients.⁸⁵ The pathogenesis of GVHD is multifactorial, but the currently accepted paradigm suggests that donor T cells recognize alloantigenic host peptides and are activated, expand, and migrate to lymphoid organs, where further peripheral expansion occurs. This triggers the cytokine and cytolytic injury manifested as GVHD.

Chronic GVHD (cGVHD) occurs with a high likelihood after acute GVHD. cGVHD is a distinct syndrome but shares overlapping features with acute GVHD, such as an erythematous skin eruption, nausea, vomiting, diarrhea, and cholestatic liver disease. Distinctive or differentiating features of cGVHD include sicca syndrome, obstructive bronchiolitis, and lichenoid or sclerotic skin changes, which bear the closest similarity to scleroderma.⁸⁶ Skin manifestations may also include telangiectases, ulcers, and joint contractures, but the Raynaud phenomenon is not seen. Treatment of cGVHD requires extended-duration immunosuppressive therapy, infection prophylaxis, nutritional management, and physical therapy. Corticosteroids remain the mainstay of therapy, but often they are not fully effective, and long-term use leads to multiple complications. Other agents, including calcineurin inhibitors, sirolimus, mycophenolate mofetil, thalidomide, pentostatin, and extracorporeal photopheresis, have all produced responses in phase 2 trials, but no agent has been shown to be superior to corticosteroids in randomized trials.⁸⁷ Because tumor necrosis factor- α (TNF- α) has been implicated in the pathophysiology of GVHD, TNF inhibition with infliximab has been used with some efficacy in steroid-refractory GVHD involving the gastrointestinal tract in small studies.⁸⁸ Tyrosine kinase inhibitors such as imatinib may have potential efficacy in steroid-refractory cGVHD.⁸⁹ Because T cells are thought to play a central role as effectors of cGVHD, there has been considerable interest in strategies to prevent cGVHD by using *ex vivo* T cell-depleted allogeneic bone marrow transplantation, which appears to be associated with lower rates of cGVHD. Similarly, *in vivo* T-cell depletion with alemtuzumab or antithymocyte globulin has been reported to produce low rates of cGVHD.⁸⁷

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Clinical features, classification, and epidemiology of inflammatory muscle disease

■ CHESTER V. ODDIS ■ DANA P. ASCHERMAN

- Chronic inflammation of striated muscle (myositis) is associated with characteristic cutaneous features (rash of dermatomyositis) and a variety of systemic complications.
- The cellular and humoral immunologic features of inflammatory muscle disease include serum autoantibodies in association with clinical syndromes, with myositis being a major manifestation.
- Painless symmetric proximal muscle weakness with or without rash typically is present.
- Serum muscle enzymes are increased, most notably creatine kinase.
- Electromyographic findings are normal, and muscle biopsy demonstrates inflammatory infiltrates.
- Other organ systems can also be involved, including the lung, heart, gastrointestinal tract, and joints.
- Dermatomyositis is associated with malignancy in the middle-aged and elderly population.

EPIDEMIOLOGY

Classification criteria

Many classification systems have been proposed for polymyositis-dermatomyositis (PM-DM, referred to collectively as myositis or the idiopathic inflammatory myopathies [IIMs] in the remainder of this chapter).^{1,2} The Bohan and Peter criteria have been used most frequently (Box 148.1), with a sensitivity of 70% for definite myositis and a specificity of 93% in discriminating patients with myositis from those with systemic lupus erythematosus (SLE) or systemic sclerosis (SSc).³ Increasing reports of amyopathic dermatomyositis (ADM—rash of DM without muscle weakness), coupled with the detection of several autoantibodies and imaging techniques, have spearheaded an international effort to update the classification criteria for myositis.

Association with other disorders

PM-DM occurs in overlap with SSc more frequently than with any other connective tissue disease and is often associated with one of several serum autoantibodies such as anti-U1-RNP, anti-PM-Scl, or anti-U3-RNP.⁴ In one study, IIM overlapped with another connective tissue disease in the majority of patients (60%) when clinical and serologic features contributed to the classification.⁵ Myositis has also been described in association with other conditions.⁶

Incidence and prevalence by age, race, and sex

The overall incidence of IIM ranges from 2 to 10 new cases per million persons at risk per year, but there is a trend toward increasing incidence over time, probably because of increased physician awareness. A report on the prevalence of inclusion body myositis (IBM) in Western Australia recorded the highest reported figure to date: 14.9 per million, which increased to 51.3 cases per million in those older than 50 years.⁷

Although inflammatory myopathy can occur at any age, the observed pattern of occurrence includes peaks in both childhood and adulthood, with a paucity of patients having an onset in the adolescent or young adult years. As expected, the mean age at the onset of myositis is increased when associated with malignancy. The overall female-to-male incidence ratio is 2.5:1, lower (nearly 1:1) in childhood disease and with malignancy, but very high (10:1) when in overlap with another coexisting connective tissue disease. IIM has a 3:1 to 4:1 black-to-white ratio of incidence and a younger adult-onset peak in blacks.

Environmental factors

The prevalence of IIM in Europe increases significantly (sevenfold) from the north (Iceland) to the south (Greece), which could have either an environmental or a genetic explanation.⁸ Spatial clustering has been reported,⁹ and investigators have noted that expression of anti-Mi-2 autoantibodies in women is associated with the intensity of ultraviolet (UV) radiation,¹⁰ thus suggesting that UV radiation may modulate the clinical and immunologic expression of autoimmune disease in patients with myositis.

Onset of disease is more frequent in the winter and spring months, especially in childhood cases, and uncontrolled observations have noted a history of antecedent respiratory or gastrointestinal complaints, treated with antibiotics, preceding the onset of juvenile dermatomyositis (JDM).¹¹ An infectious trigger is supported by finding serum antibodies to Coxsackie B viruses more frequently in JDM than in juvenile controls with rheumatoid arthritis. Seasonal birth patterns appear to be more common in juvenile myositis than in adult IIM, perhaps suggesting a greater influence of perinatal exposure in childhood myositis.¹² Disease relapses were noted most frequently during the summer months, possibly precipitated by infection or sun exposure.¹³ DM and PM have occurred in patients infected with human immunodeficiency virus, and myositis occurs more frequently in those with chronic graft-versus-host disease (GVHD), thus suggesting that skeletal muscle may be a target in some patients with GVHD.^{14,15}

Genetic factors

The occurrence of IIM in monozygotic twins and first-degree relatives of affected individuals supports a genetic predisposition in some families. Other autoimmune diseases occur four times more frequently in first-degree relatives of patients with IIM (21.9%) than in first-degree relatives of control probands (4.9%),¹⁶ and the same principle applies to JDM.¹⁷

Recent large U.K.- and U.S.-based efforts to study white IIM patients have uncovered significant associations of genotype with clinical and serologic profiles in myositis.¹⁸⁻²⁰ These findings emphasize the importance of HLA haplotypes and peptide-binding motifs in discriminating between IIM subsets. Alleles of the 8.1 ancestral haplotype (HLA-DRB1*03-DQA1*05-DQB1*02), for example, are important risk factors for the development of myositis in antisynthetase antibody-positive patients, as well as in those producing anti-La, anti-PM/Scl, and anti-Ro autoantibodies.²⁰ Although anti-Jo-1 and anti-PM-Scl antibody-positive patients share the 8.1 ancestral haplotype, analysis of the HLA-DPB1 region has shown that DPB1*0101 is associated with anti-Jo-1 positivity but not with the formation of anti-PM-Scl antibodies.²¹

JDM has been associated with HLA-DQA1*0501, and the closely linked DRB1*0301 allele is also a risk factor for IIM in white individuals. Genes regulating cytokines and their receptors, including PTPN22, interleukin-1, and tumor necrosis factor- α , also appear to play a role in the development and course of both childhood and adult-onset myositis.^{22,23}

BOX 148.1 BOHAN AND PETER CRITERIA FOR THE DIAGNOSIS OF POLYMYOSITIS AND DERMATOMYOSITIS

Individual criteria
1. Symmetric proximal muscle weakness
2. Muscle biopsy evidence of myositis
3. Increase in serum skeletal muscle enzymes
4. Characteristic electromyographic pattern
5. Typical rash of dermatomyositis
Diagnostic criteria
Polymyositis:
Definite: all of 1 to 4
Probable: any 3 of 1 to 4
Possible: any 2 of 1 to 4
Dermatomyositis:
Definite: 5 plus any 3 of 1 to 4
Probable: 5 plus any 2 of 1 to 4
Possible: 5 plus any 1 of 1 to 4

Modified from Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292:344-7, 403-7.

TABLE 148.1 Types and frequencies of initial clinical syndromes in patients with polymyositis-dermatomyositis

Syndrome	Estimated frequency (%)
Dermatomyositis rash alone; extremity edema	<1
Painless proximal weakness (over 3-6 mo)	55
Acute or subacute proximal pain and weakness (over weeks to 2 mo)	30
Insidious proximal and distal weakness (over 1-10 yr)	10
Proximal myalgia alone	5

CLINICAL FEATURES

The initial features of myositis vary considerably from patient to patient (Table 148.1); most common is insidious, progressive, and painless symmetric proximal muscle weakness arising over the course of 3 to 6 months. Some patients, especially children with DM, have a more acute onset of disease, with fever, muscle pain, and weakness developing over the course of several weeks. In contrast, a subset of patients exhibit slowly evolving weakness over the course of 1 to 10 years that involves atrophy of the quadriceps muscles or forearms (or both), weakness of the pelvic girdle and distal extremity muscles, and pathologic features of IBM noted on muscle biopsy specimens.

Pharyngeal muscle weakness may contribute to hoarseness, dysphagia, nasal regurgitation of liquids, or aspiration pneumonia. Ventilatory muscle weakness may contribute to dyspnea, although interstitial lung disease (ILD) is a more common cause of pulmonary dysfunction.

Distinctive cutaneous manifestations (see later) may occur before muscle weakness is detected. In patients with a DM rash as the sole or predominant manifestation for more than 2 years, the terms amyopathic or clinically amyopathic DM or hypomyopathic DM are used. These patients remain at risk for ILD, malignancy, or even delayed-onset full-blown DM.²⁴

The initial clinical manifestations often “cluster” together and hence result in distinct syndromes. For example, patients with anti-aminoacyl-tRNA synthetase autoantibodies such as anti-Jo-1 antibody have a constellation of findings in addition to myositis, including fever, Raynaud phenomenon, mechanic’s hands, polyarthritis, and ILD. When myositis overlaps with SSc, Raynaud phenomenon, puffy fingers, sclerodactyly, and distal esophageal (smooth muscle) hypomotility may be prominent clinical features. Myositis overlapping with SLE may include photosensitivity, malar rash, alopecia, polyarthralgia, pleurisy, and leukopenia.

Constitutional

Fatigue is a prominent complaint in patients with IIM, and fever is observed in JDM and adults with antisynthetase syndrome. Weight loss may occur as

TABLE 148.2

Key to muscle grading

Function of the muscle	Grade*		
No contraction felt in the muscle	0	0	0
Tendon becomes prominent or feeble contraction felt in the muscle, but no visible movement of the part	Trace	1	T
Movement in the horizontal plane			
Moves through partial range of motion	Poor–	2–	1
Moves through complete range of motion	Poor	2	2
Antigravity position			
Moves through partial range of motion	Poor+	2+	3
Gradual release from the test position	Fair–	3–	4
Holds the test position (no added pressure)	Fair	3	5
Holds the test position against slight pressure	Fair+	3+	6
Holds the test position against slight to moderate pressure	Good–	4–	7
Holds the test position against moderate pressure	Good	4	8
Holds the test position against moderate to strong pressure	Good+	4+	9
Holds the test position against strong pressure	Normal	5	10

*Three different scoring systems for grading muscle weakness are noted. Adapted from Kendall FP, McCreary EK. *Muscle testing and function*. 4th ed. Baltimore: Williams & Wilkins; 1993.

in any systemic inflammatory disorder, but if persistent and severe, associated malignancy should be considered. Additional factors contributing to weight loss include poor caloric intake associated with pharyngeal dysfunction or esophageal dysmotility. Obstructive sleep apnea is common in patients with IIM and perhaps contributes to their persistent fatigue.²⁵

Skeletal muscle

The onset of muscle weakness is typically insidious, bilateral, symmetric, and painless, with involvement of proximal more than distal muscles. An exception is IBM, in which asymmetric distal weakness and atrophy are as prominent as the proximal muscle findings. In PM-DM, the lower extremity (pelvic girdle) is often affected initially and results in difficulty climbing stairs or arising from a chair or toilet seat. Involvement of the hip flexors correlates with impaired walking speed in juvenile patients with myositis, and impaired strength in specific lower extremity muscle groups predicts gait limitations in children.²⁶

Upper extremity (shoulder girdle) symptoms often follow, with patients experiencing difficulty raising their arms overhead or combing their hair. Neck flexor weakness is manifested by an inability to raise the head from a pillow. Muscle pain may occur and is more common in DM, particularly with exercise. Proximal dysphagia with nasal regurgitation of liquids and pulmonary aspiration reflects the involvement of pharyngeal striated muscle and is a poor prognostic sign seen with severe disease. Pharyngeal weakness also results in hoarseness or dysphonia, which gives the voice a nasal quality. Ocular or facial muscle weakness is very uncommon in PM-DM, and their presence should therefore prompt consideration of another diagnosis.

Physical examination confirms weakness of individual muscles or groups of muscles (Table 148.2). Although the severity of weakness should be assessed serially and recorded with one of the scales in Table 148.2, functional measures should also be considered. In juvenile myositis, the Childhood Myositis Assessment Scale is both reliable and valid for assessing physical function, muscle strength, and endurance.²⁷ Other, more quantitative means of measuring muscle strength are time-consuming and include the use of expensive equipment, but simpler methods using hand-held dynamometers have been validated in other neuromuscular diseases.

Muscle atrophy and joint contractures are sequelae of the damage caused by disease; they are therefore late findings in chronic PM-DM, in contrast to IBM, in which muscle atrophy is more common at initial evaluation.

Skin

DM has a characteristic rash that may precede, develop simultaneously with, or follow the muscle symptoms. Gottron papules and a heliotrope rash

are considered pathognomonic cutaneous features of DM. Gottron papules (Fig. 148.1) are scaly, erythematous, or violaceous papules and plaques located over bony prominences, particularly the metacarpophalangeal and proximal and distal interphalangeal joints of the hands. The Gottron sign (Fig. 148.2) is a macular erythema that occurs in the same distribution and over other extensor areas such as the elbows, knees, and ankles. Later in the course of disease, the affected skin lesions may become shiny, atrophic, and hypopigmented with telangiectases. Seen in less than 50% of patients with DM, heliotrope rash is purplish in color, may be edematous or scaling in nature, and is located in the periorbital area, especially over the upper eyelids (Fig. 148.3). Cutaneous photosensitivity with facial erythema (Fig. 148.4) or a “V” sign over the anterior aspect of the chest (Fig. 148.5) may also be seen in DM. Pruritus is common and underrecognized,²⁸ and its presence differentiates DM from SLE, in which pruritus is uncommon.

The “shawl” sign refers to a rash located over the nape of the neck, upper part of the back, and across both shoulders (Fig. 148.6). Located on the lateral surface of the thighs and hips, the “holster” sign is a feature of DM (Fig. 148.7). Cuticular hypertrophy and hemorrhage with periungual erythema, telangiectases, infarcts, and capillary dilation are seen in both DM and myositis in overlap with other connective tissue diseases (Fig. 148.8). Cracking or fissuring of the lateral and palmar digital skin pads is termed “mechanic’s hands” (Fig. 148.9) and most frequently occurs in patients with PM who have anti-tRNA synthetase or anti-PM-Scl autoantibodies.²⁹ Patients with autoantibodies targeting melanoma differentiation–associated gene 5 (MDA5), also termed clinically amyopathic DM-140 (CADM-140), have

recently been shown to have cutaneous ulcerations, palmar papules, or both as features of severe vasculopathy.³⁰

Other cutaneous findings seen in patients with IIM are listed in Box 148.2.³¹

Calcinosis

Soft tissue calcification, which can be disabling, occurs most commonly in chronic, childhood-onset DM.³² Calcinosis is typically seen in the setting of chronic, active disease or with a delay in initial treatment. Autoantibodies to a newly described 140-kDa antigen have been found in JDM with a clinical phenotype that includes calcinosis.³³ The pathogenesis of calcinosis is multifactorial but may be related to the cytokines found in calcinotic fluid in JDM.³⁴ Because of the disorganized nature of the calcifications in JDM and their different structure and composition from bone, it has been suggested that they do not form from an osteogenic pathway.³⁵

Calcinosis may be intracutaneous, subcutaneous, fascial, or intramuscular in location, with a predilection for sites of repeated microtrauma (elbows, knees, flexor surfaces of the fingers, and buttocks). Complications include the formation of an exoskeleton and cutaneous ulceration with secondary infection and joint contractures. Medical therapy has been disappointing.

Joints

Polyarthralgia and polyarthritis, if they occur, appear early in the course of disease. The distribution is rheumatoid-like, and the symptoms are relatively mild. Joint findings are more common with overlap and antisynthetase syndromes, in which case they can be chronic and deforming³⁶ with instability of the interphalangeal thumb joint (“floppy thumb” sign), erosions,³⁷ and periarticular calcifications³⁸ (Fig. 148.10).



Fig. 148.1 Gottron papules. This erythematous, scaling rash over the knuckles and dorsum of the hand is a common early sign of dermatomyositis. It can be distinguished from the rash of systemic lupus erythematosus, which usually affects the phalanges and spares the knuckles.



Fig. 148.2 Gottron sign. Scaling and macular erythema are evident over the extensor surface of the elbow in a patient with dermatomyositis.



Fig. 148.3 (a) Heliotrope rash of dermatomyositis demonstrating both erythema and diffuse periorbital edema. (b) As opposed to the periorbital edema in (a), this patient has more erythema and scaling with less swelling.



Fig. 148.4 Facial rash of dermatomyositis. Note the malarlike rash of dermatomyositis, which also involves the nasolabial area (an area often spared in systemic lupus erythematosus). Patchy involvement of the forehead and chin is also present.



Fig. 148.5 V-neck rash in a patient with dermatomyositis demonstrating its photosensitive nature over the anterior aspect of the chest.



Fig. 148.6 "Shawl" sign in a patient with dermatomyositis featuring an erythematous rash across the upper part of the back and extending onto the neck in the distribution of where a shawl is worn.



Fig. 148.7 "Holster" sign in a patient with dermatomyositis consisting of erythema on the lateral aspect of the thigh adjacent to hand of the same patient with Gottron erythema.



Fig. 148.8 Cuticular overgrowth with periungual erythema and capillary dilatation in a patient with dermatomyositis.



Fig. 148.9 "Mechanic's hands." Note the erythema, hyperkeratotic changes and cracking of the skin on the lateral aspects of the fingers in this patient with anti-Jo-1 autoantibody.

Lung

The lung is the most common internal organ affected in PM-DM. Dyspnea in patients with myositis has many potential causes (Box 148.3), including parenchymal and nonparenchymal problems such as ventilatory (diaphragmatic and intercostal) muscle weakness or cardiac dysfunction (see the next section). However, ventilatory muscle weakness leading to respiratory failure or significant dyspnea is uncommon and occurs in less than 5% of patients.⁴⁰

The frequency of “intrinsic” pulmonary involvement has been reviewed in many studies.⁴¹ In 70 patients with ILD and either PM or DM,⁴² more than 80% who underwent lung biopsy were found to have nonspecific interstitial pneumonia (NSIP), which was generally responsive to therapy with good survival. A retrospective study from France reported that a quarter of consecutive patients with IIM had ILD, 25% of whom subsequently deteriorated.⁴³ A retrospective analysis of 151 patients with PM and DM from China showed that ILD developed in a fifth.⁴⁴ Older age at onset, the presence of anti-Jo-1 autoantibodies, and joint symptoms were associated with ILD. In this cohort, poor survival with ILD correlated with male

gender, a Hamman-Rich–like manifestation, and a clinical diagnosis of acute interstitial pneumonitis. A prospective study from Sweden identified 11 of 17 (65%) new PM and DM patients over a 2.5-year period with lung disease, 18% of whom had subclinical ILD.⁴⁵ In an enriched population of 90 anti-Jo-1 antibody–positive patients, 77 (86%) met the criteria for ILD.⁴⁶ In contrast to adult PM-DM, pulmonary disease in JDM is rare.^{47,48}

In general, the presence of “ground-glass” opacities on high-resolution computed tomography (HRCT) implies a treatment-responsive condition, whereas “honeycombing” and traction bronchiectasis correspond to fibrosis that is less amenable to immunosuppressive therapy.⁴⁹

Pulmonary function testing (PFT) reveals restrictive physiology with reduced lung volumes (e.g., total lung capacity and forced vital capacity) and a parallel decrease in the diffusion capacity for carbon monoxide. Although HRCT and PFT provide useful information, histopathologic classification may be the most critical determinant of the course of disease. NSIP and the organizing pneumonias (see Box 148.3) represent a more favorable histopathology, whereas usual interstitial pneumonia and diffuse alveolar damage (DAD) portend a more ominous course.⁴⁰ DM-associated ILD may be more commonly associated with DAD, thus indicating that pulmonary histologic differences and HRCT findings may further distinguish PM from DM.^{50,51} In addition, the concomitant finding of anti-Ro/SSA in patients with antisynthetase autoantibodies may be associated with more severe and progressive ILD.^{52,53}

Beyond these issues, parenchymal lung involvement may be associated with other less commonly considered complications. “Secondary” pulmonary arterial hypertension can also develop in patients with progressive ILD as a result of hypoxemia-induced pulmonary vasoconstriction, although “primary” pulmonary hypertension secondary to underlying pulmonary vasculopathy/vasculitis should be considered as well. Diffuse alveolar hemorrhage with pulmonary capillaritis is uncommon but can be lethal. Pneumomediastinum, on the other hand, is being reported increasingly and may be associated with rapidly progressive ILD in the setting of ADM.³⁹

BOX 148.2 CUTANEOUS FEATURES OF THE IDIOPATHIC INFLAMMATORY MYOPATHIES

Pathognomonic signs in dermatomyositis

Gottron papules (60% to 80% of patients)
Heliotrope rash (50% or less)

Less specific signs in dermatomyositis

Gottron sign
Photosensitivity
“V” sign
Pruritic scalp involvement
“Shawl” sign
“Holster” sign
Nail-fold capillary changes with cuticular overgrowth

Other skin findings in polymyositis or dermatomyositis³¹

Calcinosis
“Mechanic’s hands”
Skin ulcers with tender palmar papules³⁰
Panniculitis
“Linear extensor erythema”
Pityriasis rubra pilaris (palmar plantar hyperkeratoses)
Facial seborrhea
Papular mucinosis (scleromyxedema)
Acquired ichthyosis
Vesiculobullous disorders
Urticarial (lymphocytic) vasculitis
Acquired lipodystrophy and acanthosis nigricans
Vitiligo
Multifocal lipotrophy
Poikiloderma

BOX 148.3 CAUSES OF DYSPNEA IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY

Nonpulmonary etiology

Respiratory muscle weakness
Cardiac involvement

Pulmonary etiology

Interstitial lung disease
■ Nonspecific interstitial pneumonitis (NSIP)
■ Usual interstitial pneumonitis (UIP)
■ Diffuse alveolar damage (DAD)
■ Organizing pneumonias (cryptogenic organizing pneumonia [COP])
Pulmonary hypertension
Alveolar hemorrhage
Pneumomediastinum³⁹
Infection (with or without aspiration)
Drug induced (e.g., methotrexate)

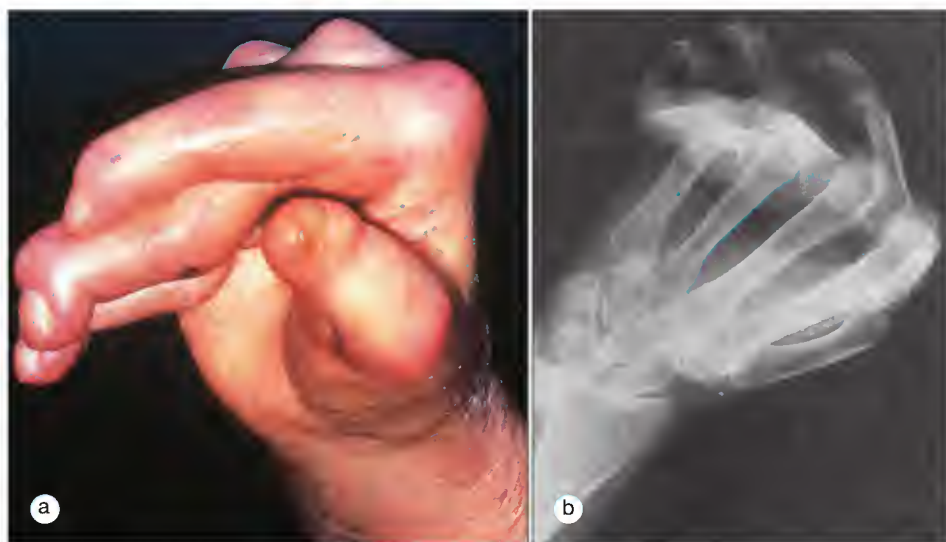


Fig. 148.10 Deforming arthropathy of polymyositis. (a) Rheumatoid-like deformities of the hand in a patient with anti-Jo-1 autoantibody. (b) Radiograph of this patient's hand showing numerous subluxations but minimal bony erosive changes.

Heart

Subclinical heart involvement is common in PM-DM.⁵⁴ The most frequent finding is a rhythm disturbance, and complete atrioventricular block has been reported.⁵⁵ More ominous complications such as congestive heart failure (caused by myocarditis or myocardial fibrosis), pericardial tamponade, and restrictive cardiomyopathy are very unusual.^{56,57} Affected patients complain of palpitations or tachycardia, and other features of congestive heart failure are noted on physical examination. Myocardial infarction may rarely result from coronary vasospasm, accelerated atherosclerosis associated with prolonged glucocorticoid use, or coronary arteritis.

Gastrointestinal tract

The pharyngeal musculature is striated and a potential target for myositis. The voice may become nasal in quality (dysphonia), and oropharyngeal swallowing dysfunction (upper dysphagia) with difficulty in the initiation of deglutition or nasal regurgitation of liquids may result. If severe, aspiration of oral contents leads to chemical pneumonitis with secondary bacterial infection.

Esophageal dysmotility is seen in both overlap disorders and pure PM and DM. Patients note a retrosternal “sticking” sensation on swallowing bread or meat and heartburn with esophageal body and gastroesophageal sphincter involvement, respectively. Postprandial symptoms of pain, bloating, distention (pseudoobstruction), or watery diarrhea with weight loss (malabsorption syndrome) indicate small bowel involvement. “Total gut failure” secondary to an atonic bowel and pneumatosis cystoides intestinalis have also been reported.⁵⁸

Gastrointestinal mucosal ulceration and hemorrhage as a result of vasculitis can occur in JDM. Active and quiescent forms of myositis are increasingly being reported in conjunction with other autoimmune gastrointestinal disorders, including inflammatory bowel disease, primary biliary cirrhosis, sclerosing cholangitis, and celiac disease, in adults as well as children.⁵⁹⁻⁶²

Peripheral vascular system

Raynaud phenomenon is observed in all IIM subsets except for malignancy-associated myositis. Systemic vasculitis is common in JDM but uncommon in adults. The inflammatory vascular lesions of DM include tender dermal and subcutaneous nodules, periungual infarcts, and digital ulcerations.

Kidney

Renal disease is considered unusual in myositis. Generalized edema and rhabdomyolysis with renal failure can be seen in IIM (particularly DM) but do not necessarily indicate primary renal disease.^{63,64} The presence of primary renal disease should prompt a search for an associated connective tissue disease or other associated condition.

DIFFERENTIAL DIAGNOSIS

Noninflammatory myopathies

The differential diagnosis of adult PM-DM is broad and includes numerous conditions capable of affecting skeletal muscle (Table 148.3). The history, physical examination, and differences in laboratory test results serve as the primary method of distinguishing these conditions. Although muscle biopsy may not be diagnostic in some patients with inflammatory myopathy, it is an essential part of the evaluation and should include immunocytochemical and enzyme staining, as well as electron microscopy in selected cases.

Primary neurologic diseases mimicking myopathy include the spinal muscular atrophies, a group of autosomal recessive disorders leading to slowly progressive degeneration of spinal anterior horn cells, and amyotrophic lateral sclerosis, a disease that results in more rapid degeneration of both lower and upper motor neurons (causing bulbar or pseudobulbar palsy). Myasthenia gravis is a disorder of the neuromuscular junction in which weakness often affects the extraocular and bulbar muscles and

TABLE 148.3
Differential diagnosis of muscle weakness

General type	Subtypes/examples
Denervating conditions	Spinal muscular atrophy,* amyotrophic lateral sclerosis*
Neuromuscular junction disorders	Eaton-Lambert syndrome,* myasthenia gravis*
Genetic muscular dystrophies	Duchenne facioscapulohumeral, limb-girdle,* Becker, Emery-Dreifuss types,* distal, ocular
Myotonic diseases	Dystrophia myotonica,* myotonia congenita
Congenital myopathies	Nemaline, mitochondrial, centronuclear, central core
Glycogen storage diseases	Adult-onset acid maltase deficiency,* McArdle disease
Lipid storage myopathies	Carnitine deficiency,* carnitine palmitoyltransferase deficiency*
Periodic paralyses	
Myositis ossificans*	Generalized and local
Endocrine myopathies*	Hypothyroidism, hyperthyroidism, acromegaly, Cushing disease, Addison disease, hyperparathyroidism, hypoparathyroidism, vitamin D deficiency myopathy, hypokalemia, hypocalcemia
Metabolic myopathies*	Uremia, hepatic failure
Toxic myopathies*	Acute and chronic alcoholism; drugs, including penicillamine,* clofibrate,* chloroquine, emetine
Nutritional myopathies	Vitamin E deficiency,* malabsorption*
Carcinomatous neuromyopathy*	Carcinomatous cachexia
Acute rhabdomyolysis*	
Proximal neuropathies	Guillain-Barré syndrome,* acute intermittent porphyria,* diabetic lower limb chronic plexopathies,* chronic autoimmune polyneuropathy
Microembolization by atheroma or carcinoma	
Polymyalgia rheumatica*	
Other collagen vascular diseases	Rheumatoid arthritis, scleroderma, systemic lupus erythematosus, polyarteritis nodosa
Infections	Acute viral, including influenza, mononucleosis, coxsackievirus, and rubella and rubella vaccination; <i>Rickettsia</i> ; acute bacterial, including typhoid
Parasites	<i>Toxoplasma</i> , <i>Trichinella</i> , <i>Schistosoma</i> , <i>Cysticercus</i> , <i>Sarcosporidia</i>
Septic myositis	<i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Clostridium perfringens</i> (<i>welchii</i>), and leprosy

*Conditions most commonly confused with muscle weakness.

becomes worse with prolonged or repetitive use. A similar pattern of activity-increased weakness is found in Eaton-Lambert syndrome. These conditions are distinguishable from IIM on the basis of characteristic electromyographic (EMG) patterns and the absence of increased serum muscle enzymes.

The congenital myopathies, including various forms of muscular dystrophy and nemaline myopathy, are hereditary conditions with an onset of symptoms primarily in infancy or childhood but occasionally in adulthood. Some congenital myopathies such as dysferlinopathies are difficult to differentiate from inflammatory myopathy; however, despite manifesting inflammation on muscle biopsy specimens in a pattern similar to PM (without accompanying major histocompatibility complex [MHC] class I upregulation), they are distinguished by a slowly progressive downhill course that is generally unaffected by glucocorticoid or immunosuppressive treatment.⁶⁵ Confounding this issue, some recently described limb-girdle muscular dystrophies not only demonstrate inflammation but also display steroid responsiveness, thus making them difficult to distinguish from PM.^{66,67} In such cases, gene expression profiles from muscle biopsy specimens may provide important differentiating information.⁶⁸ A comprehensive review of the diagnostic uncertainty associated with the inflammatory myopathies and consideration of other myopathic syndromes has been published.⁶⁹

Metabolic and mitochondrial myopathies that can be confused with IIM occur because of genetic defects that result in abnormal energy metabolism.⁷⁰⁻⁷² In particular, acid maltase deficiency (Pompe disease) can mimic PM. Increasingly recognized forms of weakness that develop in seriously ill patients include both “critical illness polyneuropathy” and “acute myopathy of intensive care.” Other causes of noninflammatory proximal myopathy include vitamin D deficiency, calciphylaxis, adrenal insufficiency, hypophosphatemia, hypothyroidism, hyperthyroidism, carcinomatous neuropathy, and exposure to certain toxic substances.

Other inflammatory myopathies

Viral (e.g., human immunodeficiency, influenza), bacterial (e.g., staphylococcal), and parasitic (e.g., trichinosis, toxoplasmosis) infections can mimic IIM. Giant cell myositis is rare but can be encountered in sarcoidosis. Cutaneous sarcoidosis may resemble DM, whereas sarcoid myositis can mimic PM.⁷³

Focal or more generalized (PM or perimyositis) eosinophilic myositis syndromes should be distinguished from eosinophilic fasciitis and eosinophilia-myalgia syndrome, which rarely cause myofiber necrosis, muscle weakness, or increased creatine kinase (CK).

Statin-induced, immune-mediated necrotizing myopathy (IMNM) is a newly described entity characterized by markedly elevated CK levels and variable degrees of proximal muscle weakness that persist or progress even after discontinuation of the offending agent.^{74,75} Although this subclass of inflammatory myopathy involves myofiber necrosis, regeneration, and macrophagic (rather than lymphocytic) infiltration, the association with anti-hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase (HMGCR) antibodies and response to immunomodulatory therapy distinguish IMNM from various dystrophies that share overlapping histopathologic features.^{74,76} Because some forms of paraneoplastic myopathy also yield predominant myofiber necrosis,⁷⁷ assessment for a history of statin exposure and detection of anti-HMGCR antibodies are critical determinants guiding the diagnostic evaluation, as well as therapeutic intervention.

Malignancy and myositis

Several reports strongly support an increased risk for cancer in patients with PM-DM,⁷⁸⁻⁸⁴ with the strongest association occurring in those with DM. Standardized incidence ratios are 3.0 to 12.6 in patients with DM.⁸⁰⁻⁸² In a pooled analysis of published national data from Sweden, Denmark, and Finland, 618 patients with DM were identified, 198 of whom had cancer.⁸¹ The strongest associations were with ovarian, lung, pancreatic, stomach, and colorectal cancer, as well as with non-Hodgkin lymphoma. A lower, but statistically significant increase in cancer rates was seen with PM.

The overall risk for cancer is greatest in the first 3 years after the diagnosis of myositis,⁸⁵ but an increased risk for malignancy persists through all years of follow-up, thus emphasizing the importance of continued surveillance.^{78,81} Although older individuals with DM are at greater risk, the likelihood of malignancy is increased even in DM patients younger than 45 years.⁸¹

Clinical and histologic features that may predict the presence of a malignancy in a patient with DM include an elevated erythrocyte sedimentation rate, epidermal necrosis, cutaneous leukocytoclastic vasculitis, and

ADM.^{84,86-89} The presence of either pulmonary fibrosis, a clinically confirmed connective tissue disease, or myositis-associated or myositis-specific serum autoantibodies decreases the likelihood of cancer,^{80,90,91} but malignancy in the setting of antisynthetase syndrome and ILD has been reported.⁹²

Given the distribution of tumors just noted, an age- and gender-appropriate evaluation for malignancy should include chest, abdominal, and pelvic computed tomography scans, along with fecal occult blood testing, mammography and pelvic examination in women, and prostate examination in men. Because the increased risk for malignant disease persists long after the development of DM, careful patient follow-up should extend for a number of years.⁸¹ To predict the occurrence of malignancy, one group of investigators developed an artificial neural network method using detailed information from 62 patients with IIM; although a combination of eight variables yielded a global predictive value close to 93% with a sensitivity of 98% and specificity of 91%, this model has not yet been validated.⁹¹

INVESTIGATIONS

General concepts

Standardized guidelines based on expert consensus to assess patients for their inclusion into therapeutic trials for IIM have been published.⁹³ The International Myositis Assessment and Clinical Studies (IMACS) group and the Pediatric Rheumatology International Trials Organization (PRINTO) have been at the forefront of these efforts, which have led to remarkably similar outcome measures⁹⁴:

- Core set measures for assessment of disease activity in myositis trials (Table 148.4)⁹⁵
- Consensus on the minimum percent change in core set measures required to classify a patient as improved in a clinical trial⁹⁶
- Development of an international consensus on preliminary definitions of improvement in adult and juvenile myositis clinical trials^{94,97}
- A consensus document on the conduct of therapeutic trials for adult and juvenile myositis⁹³
- Inclusion of assessment recommendations for nonmuscular involvement, including constitutional features and cutaneous, articular, gastrointestinal, cardiac, and pulmonary manifestations⁹⁸

As a result of the IMACS and PRINTO workshops, considerable progress has been made in standardizing methods of assessing disease activity and damage in adult and pediatric myositis.^{94,99-101} Many other tools using newer diagnostic techniques such as changes in protein and gene expression

■ TABLE 148.4

Proposed preliminary core set measures for assessment of disease activity in adult and juvenile myositis clinical trials

Domain	Core set measures
Global activity	Physician global disease activity assessment by Likert or VAS; parent/patient global disease activity assessment by Likert or VAS
Muscle strength	MMT on a 0- to 10- point or expanded 0- to 5-point scale to include the proximal, distal, and axial muscles (adults and children >4 yr of age); validated method for age <4 yr (to be developed)
Physical function	Validated patient/parent questionnaire on activities of daily living (HAQ/CHAQ); validated observational tool of function, strength, and endurance (CMAS)
Laboratory assessment	At least two serum muscle enzyme activities from the following: CK, aldolase, LDH, ALT, and AST
Extramuscular disease	A validated approach that is comprehensive and assesses cutaneous, gastrointestinal, articular, cardiac, and pulmonary activity; the Myositis Disease Activity Assessment Tool is being validated

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CMAS, Childhood Myositis Assessment Scale; CHAQ, Childhood Health Assessment Questionnaire; HAQ, Health Assessment Questionnaire; LDH, lactate dehydrogenase; MMT, manual muscle testing; VAS, visual analogue scale.

From Miller FW, Rider LG, Chung YL, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2001;40:1262-73.

patterns in affected tissue will complement these outcome measures by providing molecular information that is pertinent to disease mechanisms in myositis.¹⁰²

Serum muscle enzymes

Enzymes that leak from injured skeletal muscle into serum are valuable aids in detecting ongoing muscle injury.¹⁰³

Serum CK is the most reliable enzyme test for use in routine patient care and predicts clinical events. During a flare of disease, serum CK levels will usually increase weeks before overt muscle weakness develops. Conversely, with treatment-induced remission, this enzyme decreases to normal levels before objective improvement in strength. There are exceptions, with some patients with active biopsy-proven myositis (DM > PM and children > adults) having normal CK levels and others having circulating inhibitors of CK activity. Moreover, there is considerable racial variation in CK concentrations such that reference values from white populations do not apply to black persons, in whom the upper limit of normal CK is higher. Serum myoglobin, which is cleared by the kidney, can be a useful marker of muscle damage and is elevated at least as frequently as serum CK.¹⁰⁴ Myoglobinemia is detected by nonenzymatic assays, but the test is cumbersome and not uniformly available. Urinary levels of muscle damage markers such as creatine, choline-containing metabolites, betaine, and citrate have been reported to correlate strongly with global disease damage in juvenile myositis.¹⁰⁵

Electromyography

Typical EMG findings include irritability of myofibrils at rest and on needle insertion (with fibrillation potentials, complex repetitive discharges, and positive sharp waves), as well as short-duration, low-amplitude, complex (polyphasic) potentials on contraction. More than 90% of patients with active myositis will have abnormal EMG findings, thus underscoring the fact that normal EMG findings tends to rule out myopathy or active disease in patients with myositis. EMG examination is helpful in selecting a muscle for biopsy but should be performed on only one side before biopsy of a contralateral muscle to avoid confusion resulting from inflammation artifact caused by injury from the needle itself.

Later in the course of disease, EMG examination may be helpful in detecting low-grade myositis in the setting of chronic damage from fibrosis or fatty infiltration. Glucocorticoid-induced myopathy causes some EMG changes, but the presence of fibrillation potentials suggests active inflammation.

Muscle biopsy

Although open biopsy represents the current “gold” standard for confirmation of the diagnosis of inflammatory myopathy, percutaneous needle muscle biopsy is a convenient and relatively inexpensive method with a high diagnostic yield in PM-DM^{106,107} and allows sampling of several muscles.

Degeneration and regeneration of myofibrils occur in 90% of cases. Chronic inflammatory cells in the perivascular and interstitial areas surrounding myofibrils are present in 80% of cases, but lymphocytic invasion of nonnecrotic MHC class I-expressing fibers is seen in PM (Fig. 148.11),

as well as in IBM. Besides lymphocytes, other cells may also be present, including histiocytes, plasma cells, eosinophils, and polymorphonuclear leukocytes. In chronic myositis, macrophages are seen phagocytosing necrotic fibers and muscle is replaced by fibrous connective tissue or fat. IMNM is also characterized by macrophagic myofiber necrosis, along with variable levels of sarcolemmal MHC class I expression and a relative paucity of lymphocytic infiltration.^{74,76}

There are important immunopathologic differences, however, between DM, PM, and IBM. In DM, B cells and the late component of complement (C5b-C9, membrane attack complex) predominate in the perivascular and perimysial area along with CD4+ T cells, macrophages, and dendritic cells. Perifascicular myofibril atrophy (Fig. 148.12), endothelial cell hyperplasia of blood vessels, deposition of immune complexes in the vasculature, and occasionally, frank vasculitis are noted. In contrast, PM and IBM feature cytotoxic T-cell invasion of myofibrils (Fig. 148.13) with relative sparing of the vasculature. CD4+ T cells, macrophages, and dendritic cells may also be found, primarily in perimysial areas, but unlike DM, B cells are rarely observed.

Magnetic resonance imaging

Application of magnetic resonance imaging (MRI) techniques adds an important diagnostic dimension to the assessment of myositis.¹⁰⁸ Large areas of muscle such as both thighs can be visualized, thereby facilitating selection of the most abnormal site for biopsy and increasing the diagnostic yield.¹⁰⁹ T1-weighted images provide excellent anatomic detail with clear delineation of various muscle groups. Normal tissue is homogeneously dark with a low signal, whereas fat (subcutaneous area and marrow) appears bright with correspondingly high signal intensity. Muscle is darker on T2-weighted images, whereas inflammation is bright on both T1 and T2 images. Adding fat suppression to the T2 technique in the form of short tau inversion recovery (STIR) sequences improves the detection of muscle inflammation by enhancing the bright signal of inflammation and decreasing the fat signal (dark) (Fig. 148.14).

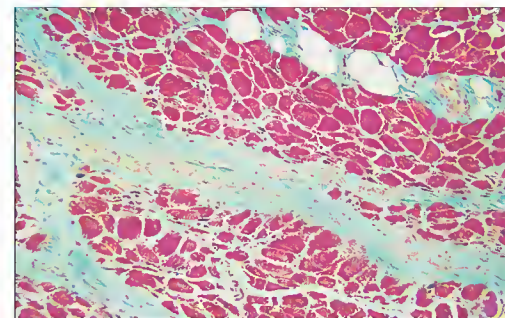


Fig. 148.12 Transverse fresh frozen section of muscle from a patient with chronic dermatomyositis. Note the atrophic, small fibers in the periphery of the fascicles (perifascicular atrophy) and the increase in fibrous tissue separating bundles of myofibers (trichrome stain, low power).

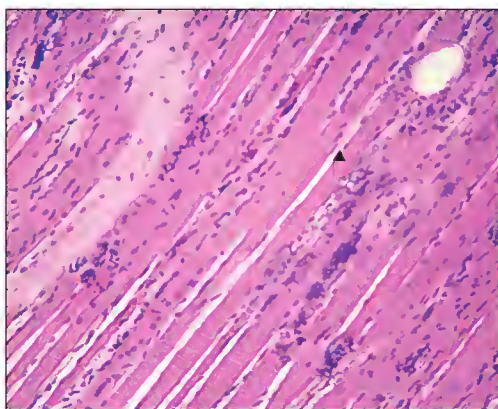


Fig. 148.11 Longitudinal section of fresh frozen muscle from a patient with polymyositis. Several areas of interstitial involvement along with myofiber destruction are seen. The arrowhead indicates an area of degeneration and necrosis of myofibers in association with interstitial lymphocytic and histiocytic cellular infiltration (hematoxylin-eosin, medium power).

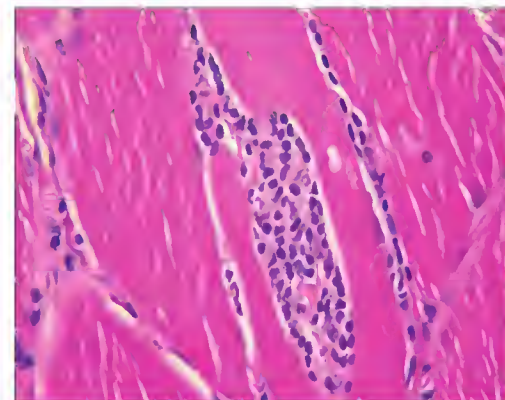


Fig. 148.13 Note the lymphocytic invasion of this intact, nonnecrotic myofiber in the muscle of a patient with polymyositis (hematoxylin-eosin, high power).

Based on these concepts, indications for MRI may include the following:

- Documentation of myositis or disease flare in a patient with normal CK, EMG, or biopsy findings
- Confirmation of ADM, in which case MRI should demonstrate no evidence of inflammation
- Distinguishing chronic active from chronic inactive myositis
- Directing the site of biopsy¹⁰⁹
- Clarifying the diagnosis in atypical cases of inflammatory myopathy and identifying noninflammatory mimics of myositis^{110,111}



Fig. 148.14 Fat-suppressed magnetic resonance image. Note the inflammation (white) in the muscles of the thigh in this longitudinal fat-suppressed image of a child with active dermatomyositis.

An area of recent interest is magnetic resonance spectroscopy, which can demonstrate the bioenergetics of normal and abnormal muscle.¹⁰⁸ Diffusion-weighted MRI can further quantify muscle inflammation and can potentially provide longitudinal monitoring of patients with myositis.¹¹²

Skin

The characteristic cutaneous histopathologic findings of DM include vacuolar alteration of the epidermal basal layer, necrotic keratinocytes indicative of apoptosis, vascular dilation, and a perivascular lymphocytic infiltrate.³¹ This “interface” pattern is similar to that seen with SLE and closely resembles the abnormal findings of a chronic graft-versus-host reaction.³¹ The histopathology of Gottron papules is similar to that observed in other skin lesions of DM. In the absence of other cutaneous features of DM, biopsy of Gottron lesions can be diagnostically useful.¹¹³ Vasculitis or vasculopathy is found in small cutaneous vessels. In turn, microvascular injury appears to be mediated by the terminal components of complement (C5b-C9) in the form of the membrane attack complex. Skin biopsy should therefore be performed in patients in whom the skin findings predominate and are not classic.

Nail-fold capillary microscopy is informative in many connective tissue diseases and is particularly beneficial in JDM, where it predicts severity, as well as the clinical course.^{114,115} A prospective study of nail-fold capillary microscopy in 53 consecutive adults with myositis noted 43% with relevant changes that correlated with disease activity and severity, particularly in DM.¹¹⁶

Serum autoantibodies

Serum autoantibodies are commonly found in PM-DM and are useful in defining clinically homogeneous subsets of patients. Antinuclear or anticytoplasmic antibodies are detected in more than 90% of patients with myositis.¹¹⁷ Although some antibodies are termed myositis-specific autoantibodies (MSAs), the specificity of MSAs is coming under closer scrutiny.¹¹⁸⁻¹²⁰ Autoantibodies typically associated with other connective tissue diseases may also be found in patients with myositis and are termed myositis-associated autoantibodies. Of note, a negative antinuclear antibody test does not exclude the presence of MSAs because antigen targets of the latter antibodies are cytoplasmic in location with subtle immunofluorescence staining patterns. Both MSAs and myositis-associated autoantibodies, along with their clinical associations, are outlined in Table 148.5.

Although a few patients have more than one serum autoantibody, multiple MSAs are rarely detected in the same patient.^{123,124} Anti-Jo-1, directed against histidyl-tRNA synthetase, is one of a group of anti-aminoacyl-tRNA

TABLE 148.5 Myositis-specific and myositis-associated autoantibodies in adult polymyositis and dermatomyositis and juvenile dermatomyositis

Autoantibody	Autoantigen	Clinical Features
Jo-1	Histidyl-tRNA synthetase	Fever, Raynaud phenomenon, mechanic’s hands, myositis, polyarthritis, ILD
SRP	Signal recognition particle (cytoplasmic protein translocation)	Severe necrotizing myopathy; predominantly PM
Mi-2	Helicase	DM (adult > children); “shawl” sign and other DM rashes
PM-Scl	Nucleolar macromolecular complex	Overlap features of myositis and SSc (or either disease alone); mechanic’s hands
U1RNP	Small nuclear ribonucleoprotein	Overlap syndromes (MCTD)
SUMO-1 (small ubiquitin-like modifier 1)	Small ubiquitin-like modifier enzyme (posttranslational modification)	Adult DM, ILD
p155/140	Transcriptional intermediary factor 1-γ (TIF1-γ)	Cancer-associated myositis in adults; >20% frequency in JDM cohorts; severe cutaneous disease in adult DM and JDM
Anti-p140 (also anti-MJ)	NXP-2 (SUMO target; possible role in SUMO-mediated transcriptional repression)	20-25% frequency in JDM cohorts; calcinosis; severe disease (atrophy/contractures)
cADM-140 (MDA-5)	RNA helicase	ADM, ILD; palmar papules and cutaneous ulcerations
PMS1	PMS1 (DNA mismatch repair enzyme)	Myositis (specifics not known)
Ku ¹²¹	70- and 80-kDa nuclear/nucleolar protein complex (DNA break repair and recombination)	UCTD and overlap syndromes (Raynaud phenomenon, ILD, myositis, arthritis)
200/100 kDa ^{76,122}	HMG CoA reductase	Necrotizing myopathy

ADM, omyopathic dermatomyositis; DM, dermatomyositis; HMG CoA, hydroxymethylglutaryl-coenzyme A; ILD, interstitial lung disease; JDM, juvenile DM; MCTD, mixed connective tissue disease; PM, polymyositis; UCTD, undifferentiated connective tissue disease.

TABLE 148.6
Anti-aminoacyl-tRNA synthetase antibodies and their associated antigens in polymyositis-dermatomyositis

Autoantibody	Autoantigen (tRNA synthetase)	Prevalence in idiopathic inflammatory myopathy (%)
Jo-1	Histidyl	20-30
PL-7	Threonyl	<5
PL-12	Alanyl	<5
OJ	Isoleucyl	<5
EJ	Glycyl	<5
KS	Asparaginyl	<1
Tyr	Tyrosyl	<1
Zo	Phenylalanyl	<1

synthetases (Table 148.6) and is the most common MSA—but still occurs in only 20% to 25% of individuals with myositis.

The clinical associations of the various antisynthetase antibodies are similar, but not all patients with an antisynthetase antibody will manifest every feature of the syndrome because myositis will never develop in some.^{86,125} For example, anti-PL-12 antibody-positive patients are more likely to have ILD without myositis, and the more recently described anti-synthetases such as anti-KS and anti-OJ are associated with less frequent myositis.^{126,127} Thus, the non-Jo-1 synthetases are more commonly associated with an incomplete antisynthetase syndrome or features of undifferentiated connective tissue disease. Anti-WS binds the L-shaped tertiary structure of tRNA and is therefore different from the other antisynthetases, but patients with this antibody also have recurrent fever, polyarthritis, and Raynaud phenomenon without myositis,¹²⁸ similar to patients with anti-tRNA synthetases.

Antibodies to signal recognition particle (anti-SRP) represent a separate subgroup of MSAs targeting a ribonucleoprotein involved in translocation. Initially thought to identify patients with pure PM and severe, refractory disease, this antibody has been reported in DM,¹¹⁸ as well as in patients with less severe muscle weakness and extramuscular manifestations such as ILD and arthritis.¹¹⁹ Nevertheless, anti-SRP is often associated with marked elevation of serum CK, severe muscle weakness, atrophy, and overall features reminiscent of limb-girdle muscular dystrophy. Novel autoantibodies against the 7SL RNA component of SRP have also been found, primarily in Japanese patients, two of whom had DM.¹²⁹

Among individuals with immune-mediated necrotizing myopathy who lack anti-SRP autoantibodies are those who possess antibodies targeting a 200/100-kDa complex identified as HMGCR.^{76,122} Clinical characteristics distinguishing statin users from statin nonusers with anti-HMGCR antibodies include older age, increased prevalence of white individuals, and a more favorable response to immunosuppressive therapy.^{122,130} The development of extramuscular complications is extremely rare in both subgroups of anti-HMGCR-positive IMNM.

Mi-2 is a multiunit protein complex that participates in regulation of transcription at the chromosome level. Anti-Mi-2 is an antinuclear antibody that can now be assessed by recombinant enzyme-linked immunosorbent assay (ELISA).¹¹⁸ Though thought to be exclusively associated with the rash of DM and a good response to immunosuppression, anti-Mi-2 has also been observed in patients with PM.¹³¹ Anti-Mi-2 is likewise seen in JDM and in malignancy, in which case the rash can be severe.

An antibody to the DNA mismatch repair enzyme PMS1 was found in 7.5% of a series of 153 sera from patients with myositis and has been proposed as a new MSA,¹³² but no unique or distinguishing clinical features have been identified.

Anti-PM-Scl is an antinucleolar antibody that identifies a subset of patients with myositis who often have features of SSc. This autoantibody may develop in patients with PM-DM or SSC or an overlap of both disorders. By using the PM-Scl-75 subunit in addition to the PM-Scl-100 epitope in ELISAs, an increased number of patients test positive for anti-PM-Scl autoantibodies.^{133,134}

Though not a true MSA, anti-U1-RNP antibodies generating a high-titer speckled pattern on routine antinuclear antibody testing can be associated with myositis, often in patients with so-called mixed connective tissue disease. Individuals with this antibody specificity may have various clinical manifestations of Raynaud disease, SLE, PM, DM, or SSc.

Antibodies to Ro/SSA are seen in at least 10% of patients with PM-DM and are particularly prevalent in individuals who also have antibodies to anti-aminoacyl-tRNA synthetases. The coexistence of anti-Ro/SSA and anti-Jo-1 antibodies may be associated with more severe ILD and a worse prognosis than the presence of anti-Jo-1 alone.^{52,53}

In recent years, new autoantibody specificities have been discovered in adult and juvenile IIM, but follow-up studies on larger cohorts of patients are necessary to validate these preliminary reports. Autoantibodies against a DM-specific autoantigen target—small ubiquitin-like modifier 1 (SUMO-1)-activating enzyme—were found in 8.4% of patients in a U.K. cohort, all of whom had DM.¹³⁵ A recently detected autoantibody against phenylalanyl-tRNA synthetase, anti-Zo, represents the eighth antisynthetase specificity linked with antisynthetase syndrome.¹³⁶

Found in adults with DM, autoantibodies directed against a 155-kDa protein or the 155/140-kDa doublet^{137,138} corresponding to TIF1-γ and related isoforms have proved to be highly specific, moderately sensitive, and highly predictive for malignancy-associated myositis.^{89,139} Antibodies against this same p155/140 target have also been detected in 23% of a JDM cohort and typically correlate with worse skin disease and ulceration than occurs in anti-p155/140-negative JDM cases.¹⁴⁰ Autoantibodies to a distinct 140-kDa protein in JDM were found to be associated with calcinosis in one study,³³ and autoantibodies to the same target autoantigen (termed 142-kDa anti-MJ) were associated with severe JDM in an Argentine cohort of patients.¹⁴¹ Finally, Sato and colleagues described a novel autoantibody termed anti-CADM-140 in adult Japanese patients with ADM and ILD.¹⁴² This antigenic target is distinct from the aforementioned anti-140-kDa, and the antigen has been identified as an RNA helicase encoded by *MDA5*.¹⁴²

OVERVIEW OF THE NATURAL HISTORY AND DISEASE PROGNOSIS

In some patients with DM (but rarely PM), a monophasic illness of brief duration may be followed by remission that does not require continued treatment. The majority of patients, however, have several exacerbations and remissions or persistent disease activity that necessitates chronic use of glucocorticoids or immunosuppressive drugs. The frequency of clinical and biochemical relapse was 34% to 60% in four series encompassing a total of 277 patients.¹⁴³⁻¹⁴⁷ The rate of relapse was greater in PM patients,¹⁴³ but no specific features predisposing to relapse were identified. Fluctuations in muscle strength are less dramatic in IBM, and a surprising proportion (a third) of untreated patients were stable or improved after 6 months of observation.¹⁴⁸

Each episode of myositis may be followed by loss of muscle mass and strength, often varying according to the clinical classification and serum autoantibody. The best functional outcome occurs in DM, whereas the worst occurs in IBM and PM with anti-SRP antibody. Patients with ADM lack muscle involvement, but malignancy and aggressive ILD can develop.^{24,86,149}

In JDM, predictors of chronic active myositis include failure to achieve normal muscle strength after 4 months of glucocorticoid treatment, continued elevation of muscle enzymes beyond 3 months, increased plasma von Willebrand factor antigen after 10 months of treatment,¹⁵⁰ and anasarca with hypoalbuminemia.¹⁵¹ A nonunicyclic course in JDM was associated with persistent nail-fold changes on capillaroscopy.¹¹⁴

PROGNOSTIC CONSIDERATIONS

Survival

Studies published before the availability of glucocorticoids reported that up to 50% of untreated patients with PM-DM die of complications; the improved survival and functional outcome over the last 40 years have largely been attributed to glucocorticoids. During the 1960s, large series described mortality rates approximating 40% after 5 years, whereas reports in the 1970s revealed only a 19% mortality rate. A recent summary of mortality in IIM noted 5-year survival rates ranging from 75% to 95%, with the variation being attributed to patient selection factors.¹⁵² Shorter survival is associated with certain cohorts, including myositis-associated malignancy,^{153,154} whereas populations enriched with overlap myositis, juvenile myositis, and those with a lower mean age at onset have better survival.^{155,156} The reasons for improved survival probably include earlier diagnosis, detection of milder cases, better general medical care, and more judicious use of immunosuppressive drugs.

Beyond malignancy and older age at onset,¹⁵⁷⁻¹⁵⁹ factors associated with poor survival include delayed initiation of glucocorticoid treatment,

pharyngeal dysphagia with aspiration pneumonia, ILD, myocardial involvement, and treatment complications. Although poor survival in JDM relates to gastrointestinal vasculitis and sepsis, children do well, with mortality rates of just 2% to 3%.¹⁶⁰

Among the serum autoantibodies, anti-SRP is a marker for a poor prognosis,^{2,119} followed by the antisynthetase group, in which mortality is driven by the severity of ILD. The best survival occurs in patients with anti-PM-Scl and anti-Mi-2 autoantibodies.

Disability

The determinants of functional status in myositis are different from those of survival. For example, IBM has the worst functional outlook but good survival stemming from the lack of visceral involvement.

Overall, a number of disease-related sequelae may contribute to the functional impairment in IIM, including calcinosis (especially in JDM), arthropathy, pulmonary insufficiency as a result of interstitial fibrosis, pulmonary hypertension or respiratory muscle involvement, and myocardial involvement with congestive heart failure or ventricular arrhythmias.

The contribution of glucocorticoid and immunosuppressive drug toxicity to long-term disability has not been addressed adequately, but the most commonly encountered side effects include osteoporotic bone fractures, osteonecrosis, cataracts, and serious bacterial or fungal infections. Factors predisposing to infections include pharyngeal muscle involvement (aspiration pneumonia), weakness of the respiratory muscles, and cutaneous calcinosis. Coupled with early cytopenias predisposing to septicemia, late hematologic malignancies represent a very real concern in patients with myositis and require traditional immunosuppressive drugs or newer biologic agents, or both.

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149

Inflammatory muscle disease:
etiology and pathogenesis

■ INGRID E. LUNDBERG

- The major clinical features of myositis are muscle weakness and muscle fatigue.
- The major histopathologic findings of myositis consist of focal inflammation with T cells, macrophages, and dendritic cells, often together with injury, death, and repair of muscle cells (myocytes), and expression of major histocompatibility complex class I antigen on muscle fibers.
- Differences in the immunopathologic features with perivascular CD4+ T cells, B-cell infiltration, deposition of late complement components, and capillary loss, mainly in dermatomyositis, and endomysial infiltrates and activated CD8+ T cells and macrophage invasion of myocytes, mainly in polymyositis and inclusion body myositis, may reflect different etiologies and molecular pathways in different subsets of myositis.
- Myositis-specific autoantibodies, which target cytoplasmic molecules involved in protein synthesis, are associated with distinct clinical myositis subsets.
- The mechanisms that cause impaired muscle performance are likely to be a combination of cell-mediated muscle fiber necrosis, indirect effects of inflammatory cells by secretion of molecules that affect muscle fiber contractility, and an acquired metabolic myopathy secondary to loss of capillaries and local inflammation. Different molecular mechanisms may predominate in various phases of disease.

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) encompass a group of heterogeneous muscle disorders that share the clinical features of slowly progressive weakness of skeletal muscle, decreased muscle endurance, and muscle fatigue. Another common feature is the presence of inflammatory infiltrates, mainly composed of T cells, macrophages, dendritic cells, B cells, and plasma cells in muscle tissue. Autoantibodies are also frequently found in patients with inflammatory myopathies. The presence of infiltrating lymphocytes in the target organ and the muscles and the presence of autoantibodies suggest that the inflammatory myopathies are autoimmune diseases, but a target autoantigen has not been determined. On the basis of different clinical and histopathologic features, the IIMs can be subclassified into three major groups: polymyositis, dermatomyositis, and inclusion body myositis.¹ Another subclassification is based on the presence of autoantibodies, which are associated with distinctive clinical phenotypes such as antisynthetase syndrome.² The existence of these different clinical phenotypes, both those associated with different autoantibodies and those related to the categories of polymyositis, dermatomyositis, and inclusion body myositis, suggests that different pathogenic mechanisms are involved in the development of inflammatory myopathies. On the other hand, the predominating clinical symptoms of symmetric muscle weakness, mainly affecting proximal muscles, and decreased muscle endurance are shared by all the subsets of myositis, which indicates that some pathogenic mechanisms are shared.

Although muscle symptoms predominate in myositis patients, other clinical manifestations are common in polymyositis and dermatomyositis but not in inclusion body myositis. Besides skin rash, which by definition is present in dermatomyositis patients, interstitial lung disease is a frequently observed extramuscular manifestation, as are arthritis, Raynaud phenomenon, and gastrointestinal involvement (Table 149.1).^{1,3} Moreover, myositis is often observed in patients with other connective tissue diseases,

particularly in those with systemic sclerosis, mixed connective tissue disease, and Sjögren syndrome, and occasionally in patients with rheumatoid arthritis or systemic lupus erythematosus. These observations suggest that the IIMs are systemic inflammatory connective tissue disorders and that there could be etiologic factors or pathogenic mechanisms that are shared with other connective tissue diseases.

MUSCLE BIOLOGY AND PHYSIOLOGY

Skeletal muscle constitutes 40% of body weight and is instrumental for movements, joint protection, and maintenance in an upright position. Skeletal muscle is composed of striated muscle fibers, which are dependent on nerve and blood supply. The striated muscle fibers are multinucleated cells, and their length varies from a few millimeters to nearly 30 cm depending on body site.⁴ Each fiber is surrounded by a fine layer of connective tissue, the endomysium (Fig. 149.1). Several fibers, up to 150, form a fasciculus that is surrounded by another layer of connective tissue, the perimysium (see Fig. 149.1). Several fascicles form the muscle, which is surrounded by a fascia, epimysium.

Each muscle fiber is built up from ultrastructural functional units, myofibrils, that contain smaller units, myofilaments (see Fig. 149.1). In the myofilaments the contractile proteins myosin and actin make up 85% of all protein content.⁵ Other proteins that have structural functions or affect protein filament interactions are tropomyosin, troponin, desmin, and titin. The contractile unit in muscles is the sarcomere. The contraction is a Ca^{2+} -dependent process. Speed of contraction of a muscle depends on its myosin adenosine triphosphatase (mATPase) activity and is also correlated with specific isoforms of the contractile proteins. The speed-determining enzyme mATPase is associated with the myosin molecule. There are different isoforms of myosin with different contractile properties, depending on their heavy-chain isoform and mATPase activity. In adult muscle most individual muscle fibers are composed of only one myosin heavy-chain isoform. On the basis of mATPase activity or myosin heavy-chain isoform expression, three distinct fiber types have been described: slow type I, fast type IIA, and fast type IIB.⁶ Type IIB fibers are sometimes also called *type II X* or *type IID* in humans. A fourth fiber type, defined by mATPase reactivity, is an intermediate, undifferentiated, type IIC fiber. Type IIC fibers are regarded as transition fibers that can develop into either type I or type II fibers. Type I fibers contain the slow myosin heavy-chain isoform and type II fibers contain the fast myosin heavy-chain isoform. Type IIC fibers contain at least two different myosin isoforms (fast and slow) and developmental fetal myosin. Fiber types can also be differentiated using biochemical staining for mATPase at different pH values depending on the varying pH sensitivity of different mATPase reactivity. This information is used in clinical practice for histopathologic evaluation of muscle biopsy specimens from patients with neuromuscular problems (Fig. 149.2).

The different fiber types exhibit various physiologic properties. Thus type I fibers, slow twitch, are characterized by a relatively low mATPase reactivity and large and numerous mitochondria, which makes these fibers fatigue resistant and suitable for prolonged aerobic exercise and endurance work. Type II fibers, on the other hand, have a high mATPase activity, rely mainly on glycolytic systems for energy supply, and are important for quick, powerful actions. The specificity of fiber type in a muscle is established during development in the embryonic muscle and seems to be genetically determined.⁷

Each muscle is composed of a mixture of type I and II fibers, creating a checkerboard pattern (see Fig. 149.2). The ratio between the fiber types determines the physiologic properties of the muscle and differs between muscle groups. There are large interindividual variations in fiber type

TABLE 149.1
Affected organs and their evaluation in inflammatory muscle disease

Organ/system	Modalities of evaluation	Pathologic processes	Findings
Muscle	Biopsy	Myofiber degeneration-regeneration	Myofiber size variation; vacuolated, necrotic fibers
		Inflammation	Large central nuclei, basophilic sarcoplasm
		Fibrosis	Mononuclear cell infiltration
		Myofiber destruction	Increased interstitium and fatty replacement of muscle
Heart	EMG		Low-amplitude, short, polyphasic potential; spontaneous fibrillations; irritability
	MRI		
	T1 image	Fibrosis	Atrophy of muscle, scarring
	STIR image	Inflammation	Bright signal in inflamed muscle
Lungs	ECG, echo	Myocarditis, fibrosis	Arrhythmias, left ventricular hypertrophy
	Biopsy	Myocarditis, fibrosis	Myofiber size variation, mononuclear cell infiltrates, fibrosis
Gastrointestinal system	CXR, HRCT	Inflammation, fibrosis	Interstitial markings
	PFTs	Inflammation, fibrosis, restrictive lung disease	Decreased TLV and DLco
	Radionuclide scan	Inflammation, fibrosis	Ventilation-perfusion mismatches
	BAL	Inflammation, fibrosis	Abnormal leukocyte numbers and differentials
	Biopsy	Inflammation, fibrosis	Mononuclear cell infiltration, destruction of alveolar space and fibrosis
	Biopsy	Inflammation	Vacuolization of the basal layer; mononuclear cell infiltration
Skin	Biopsy	Inflammation	Vacuolization of the basal layer; mononuclear cell infiltration
Gastrointestinal system	Radiographic studies	Inflammation, fibrosis	Reflux and uncoordinated peristalsis

BAL, bronchoalveolar lavage; CXR, chest radiography; echo, echocardiography; DLco, diffusion capacity for carbon monoxide; ECG, electrocardiography; EMG, electromyography; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging; PFTs, pulmonary function tests; STIR, short tau inversion recovery; TLV, total lung volume.

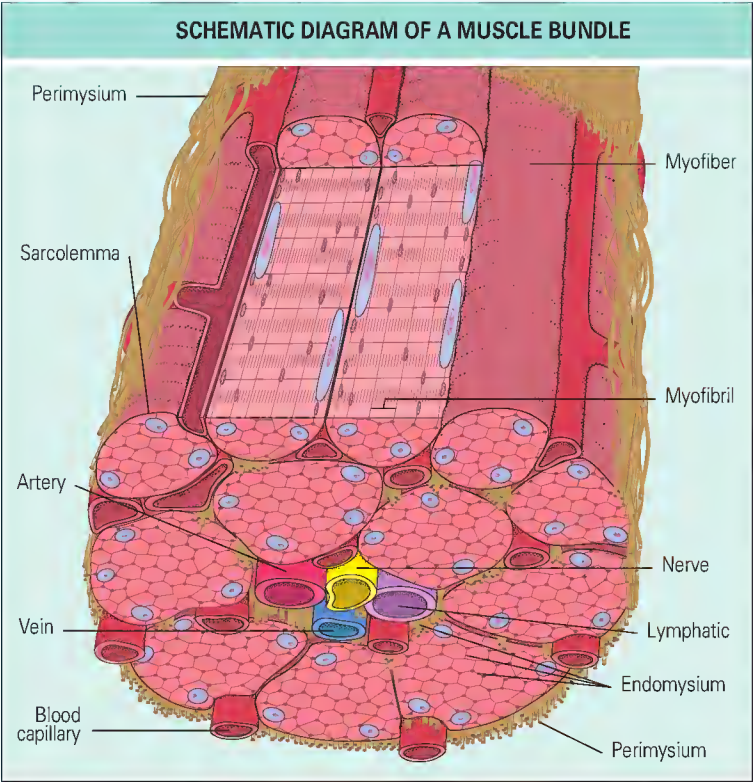


Fig. 149.1 Individual myofibers (muscle cells or myocytes) are each surrounded by an endomysial membrane. Groups of myocytes are arranged into a bundle or fascicle and surrounded by the perimysium. Muscle fascicles are arranged together as functional units surrounded by a membrane known as the epimysial membrane. The vascular bundle consists of the artery and vein supplying the muscle cells.

composition.⁴ In athletes certain patterns of fiber type composition seem to be advantageous for different purposes. For example, marathon runners have a predominance of slow-twitch, type I fibers, whereas athlete sprinters and ice-hockey players have a predominance of fast-twitch, type II fibers.⁴ There is a tendency toward a gender difference with more type I fibers and smaller type II fibers in women than in men.⁸ With increasing age there are fewer type II fibers in both men and women.⁹

Muscle development and regeneration

During development, muscles are composed of single nucleated myoblasts that fuse into multinucleated myotubes; these myotubes then differentiate into mature muscle fibers.¹⁰ The phenotype of a developing muscle fiber differs from that of mature muscle fibers in the expression of molecules on the cell surface and in the cytoplasm or sarcoplasm. One characteristic phenotype of mature, differentiated muscle fibers is absence of major histocompatibility complex (MHC) class I molecules (human leukocyte antigen [HLA] A, B, C). MHC class I molecules are expressed on all nucleated cells in the body with few exceptions such as nerve cells and muscle cells. One important function of MHC class I molecules is to present endogenous antigens to the immune system via interactions with T-cell receptors. What role MHC class I molecules play during the development of muscle fibers and why mature muscle fibers lose MHC class I expression during differentiation are not known.

Muscle has a regenerating capacity depending on satellite cells, a kind of reserve cells localized under the basal lamina of the muscle fiber.¹⁰ On appropriate stimulation these satellite cells can grow and fuse with the fiber or develop into new adult muscle cells, a process termed *regeneration*. Regenerating fibers are often found in muscle biopsy specimens from patients with inflammatory myopathies. Like myotubes, regenerating fibers express MHC class I molecules on the sarcolemma and in the sarcoplasm.

ETIOLOGY

The etiology of myositis is likely to involve both genetic and environmental factors, but their relative contributions are largely unknown.

Genetic factors

The best-known genetic risk factors are certain HLA alleles, but the HLA genes that are associated with inflammatory myopathies vary in different populations around the world. HLA DRB1*0301 and the linked DQA1*0501 are the strongest known risk factors for all major forms of sporadic and familial types of myositis in white adults and children in both the United States and Europe.^{11,12} These alleles are part of the 8.1 ancestral haplotype (AH) (HLA-B*08-DRB1*03-DQA1*05-DQB1*02, 8.1 AH), which has even stronger associations with the presence of certain autoantibodies, the anti-synthetase autoantibodies, particularly anti-histidyl-tRNA (transfer RNA) synthetase (anti-Jo-1) antibody (see Table 149.3).¹² Anti-Jo-1 positivity is also associated with HLA-DPB1*0101 genotype.¹² Similarly, the DRB1*07-DQA1*02-DQB1*02 haplotype is associated with dermatomyositis, but it is even more strongly associated with possession of the dermatomyositis-specific anti-Mi-2 antibody.¹² Other associations have been reported for

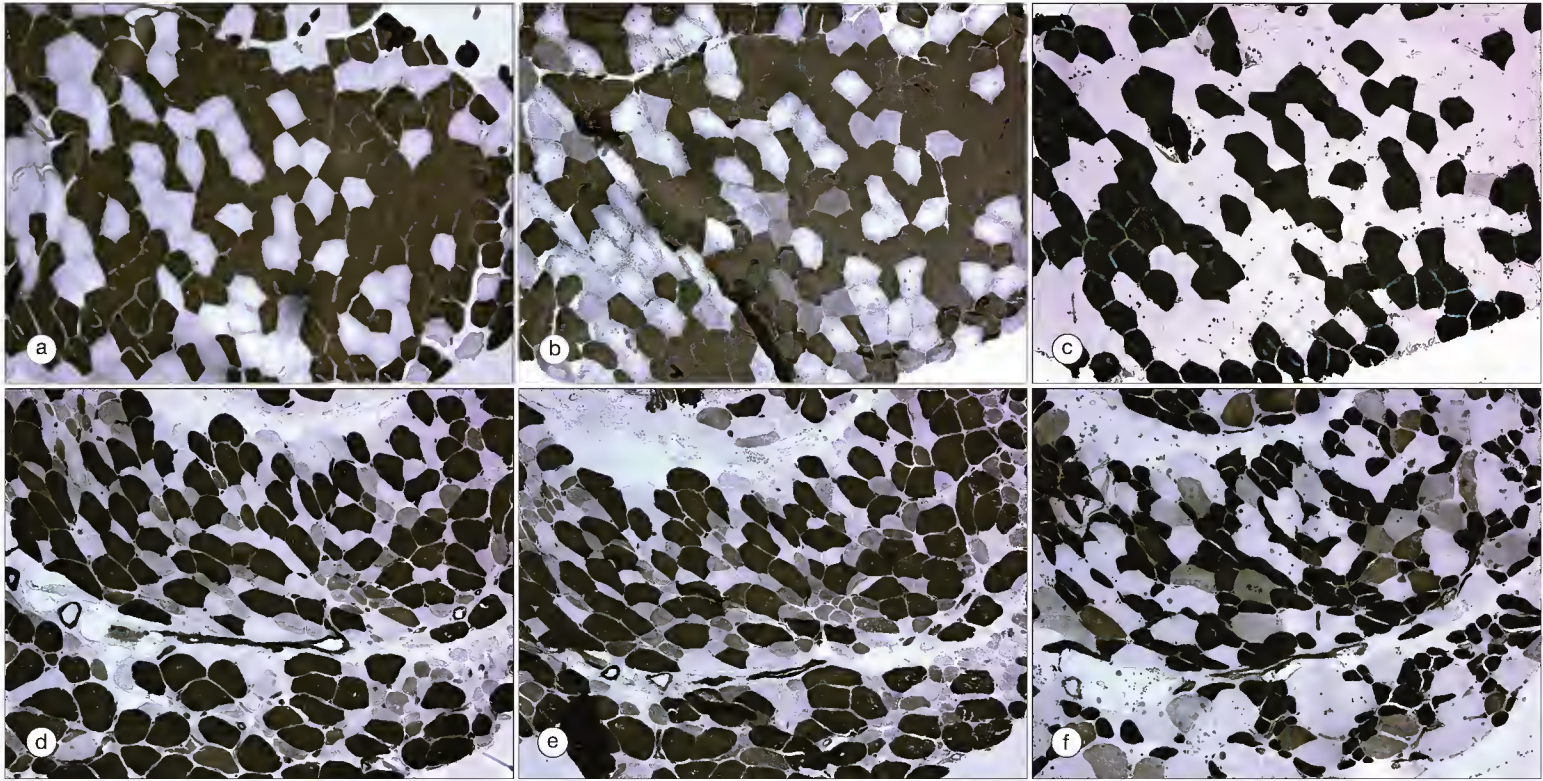


Fig. 149.2 Fiber types as defined by adenosine triphosphatase staining at different pH levels in musculus vastus lateralis from a healthy person (a through c) and from a patient with polymyositis (d through f). At pH 4.3 the type I fibers are dark and type IIA and IIB fibers are unstained (a, d). At pH 4.6 the type I fibers are dark, IIA fibers are unstained, and IIB fibers are gray (b, e). At pH 10.3 type I fibers are unstained and type IIA and IIB fibers are dark (c, f). The intermediate type IIC fibers are gray at all pH levels and are present only in the biopsy specimen from the polymyositis patient. (Courtesy Ingela Loell.)

other ethnic groups.¹² The association with certain HLA class II genotypes supports the role of a T cell–driven immune response because the only known function of MHC class II molecules is to present antigens to antigen-specific T-cell receptors.

There are also genetic associations between myositis and non-HLA genes, such as tumor necrosis factor (TNF) gene, -308TNFA genotype and a polymorphism in the protein tyrosine phosphatase (PTP) N22 gene, involved in T-cell regulation.¹² The -308TNFA gene is localized within the conserved ancestral haplotype on chromosome 6, mentioned earlier, and the TNF gene association is due to linkage disequilibrium with the extended ancestral haplotype.¹²

Although there is accumulating evidence that genetic factors are involved in the development of IIMs, it is clear that the genetics are complex as in other chronic inflammatory diseases. Furthermore, it is likely that environmental risk factors interact with genetic factors, but so far there is no information on such interactions in myositis.

Environmental factors

The environmental factors most frequently reported to be associated with muscle inflammation are drugs and infections. Other factors are ultraviolet (UV) light, vitamin D deficiency, and smoking.

Infections

Cases of muscle inflammation with histopathologic resemblance to polymyositis have been described in patients with specific infections. The most frequently reported cases have been in patients infected with the retroviruses human T-cell leukemia/lymphoma virus type 1 and human immunodeficiency virus and in those infected with the parasite *Trypanosoma cruzi*.¹³ However, there has been no success in detecting signs of a preceding or persisting infection in myositis cohorts, and thus solid evidence is still lacking for any role of continuing viral infections as a cause of the chronic muscle inflammation.

Ultraviolet light and vitamin D deficiency

An environmental factor that could be important in the cause and pathogenesis of myositis is UV radiation. The relative proportion of dermatomyositis cases, as well as the proportion of patients with anti-Mi-2 antibodies,

correlates with UV radiation intensity, with dermatomyositis clearly being more common close to the equator (Guatemala and Mexico) than close to the north pole (Iceland and Sweden).¹⁴ The association between UV light exposure and subtype of myositis suggests that UV light is an exogenous modifier that can influence the clinical phenotype in two closely related diseases, polymyositis and dermatomyositis.

Low serum levels of vitamin D have been reported in several autoimmune disorders including adult myositis, which suggests that vitamin D deficiency is a risk factor for the development of autoimmune diseases.¹⁵ Vitamin D has several roles in the regulation of the immune system, but the exact mechanisms in the development of autoimmunity is not known.

Drugs

Several drugs may induce myopathies with muscle weakness and increased serum levels of creatine phosphokinase resembling inflammatory myopathies (see Table 149.2). The most common cause of drug-induced myopathy in recent years is lipid-lowering agents, including statins, fibrates, and nicotinic acid.¹⁶ Predominating clinical features in statin-induced myopathy are muscle pain and cramps, but in rare cases severe rhabdomyolysis with a risk of renal failure may develop. Statin-induced myopathy is usually not characterized by inflammatory cell infiltrates in muscle tissue and in most cases is reversible after the drug is stopped. If muscle symptoms persist after the lipid-lowering drug is stopped, one should consider the possibility that the drug has triggered an underlying myopathy such as a metabolic myopathy. The mechanisms whereby these drugs cause myopathies have not been clarified, but statins are hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and this inhibition may interfere with energy production, which may give rise to symptoms in muscle fibers. Recently a necrotizing myopathy associated with autoantibodies directed against HMG-CoA reductase (anti-HMGCR [anti-200 kDa/100 kDa]), the target of statins, was reported.¹⁷ This myopathy is associated with the use of statins and HLA-DRB1*11:01 genotype.¹⁸ These observations may suggest a mechanistic link between statin exposure, increased HMGCR expression, and the possible presentation of HMGCR-derived peptide(s) by DRB1*11:01. These patients often respond to immunosuppressive agents. Tests for anti-HMGCR antibodies are not yet commercially available.

In general, drug-induced myopathies can be distinguished from inflammatory myopathies by the history of drug use, the absence of characteristic histopathologic changes in muscle biopsy specimens, and the occurrence of

TABLE 149.2

Drugs and toxins that may induce myopathy

Examples	Comments
Cimetidine	
Chloroquine	Vacuolar myopathy
Colchicine	Vacuolar myopathy
Emetine	
Ethanol	Acute rhabdomyolysis and chronic myopathy
Glucocorticoids	Type II fiber atrophy
Heroin	
Penicillamine	Typical polymyositis Mitochondrial myopathy
Statins and fibrates	Cases of necrotizing myopathy, polymyositis, rhabdomyolysis, and noninflammatory myopathies reported
Zidovudine (AZT)	
(Many others reported at the case level)	

clinical improvement when the drug is stopped. Also, glucocorticoids may induce a myopathy that, by itself, is not associated with any histopathologic changes reminiscent of inflammatory myopathy. The fact that glucocorticoid-induced myopathy may also be induced in patients with inflammatory myopathies during treatment with glucocorticoids raises an obvious diagnostic problem. The diagnosis of glucocorticoid-induced myopathy in patients with myositis thus can be established only when strength improves with lowered doses of prednisone.

An inflammatory myopathy with infiltration of inflammatory cells in muscle tissue resembling polymyositis or dermatomyositis has been reported in a few cases after treatment with interferon- α (IFN- α).¹⁹ There are also a few reports of signs of an inflammatory myopathy in patients with rheumatoid arthritis after treatment with TNF-blocking agents.²⁰ Whether these cases developed due to mere chance or whether the interference with the immune system caused by these agents triggered onset of a myositis needs to be further evaluated.

Smoking

An association between smoking and anti-Jo-1-positive myositis in patients with an HLA-DRB1*03 genotype was recently reported, which suggests a gene-environment interaction.²¹ Whether smoking is a risk factor for the development of myositis in general has not yet been investigated.

Malignancy

A strong association exists between malignancy and dermatomyositis, but the link is less clear with polymyositis.²² The increased risk involves different types of tumors.²³ Whether this association is due to a paramalignant phenomenon (i.e., development of myositis subsequent to the malignancy) or chronic inflammation contributing to the development of malignancies is not clear. Circumstantial evidence exists for a paramalignant phenomenon from reports of cases in which removal of the tumor has led to disappearance of the dermatomyositis. The clinical implication of the association, irrespective of the pathogenic mechanisms, is to search for tumors in patients with dermatomyositis. Recently a novel autoantibody, anti-transcriptional intermediary factor-1 γ (TIF-1 γ , or anti-p155/140), was reported to have a sensitivity of 78% and a specificity of 89% for diagnosing cancer-associated dermatomyositis.²⁴ An antibody test is not yet commercially available, but the autoantibody can be detected in serum by immunoprecipitation.

PATHOGENESIS

The presence of T lymphocytes in muscle tissue in a majority of patients with myositis and the frequent detection of autoantibodies indicate that immune mechanisms are involved in the pathogenesis of these disorders and that both T and B cells may have a pathogenic role (Box 149.1). The

BOX 149.1 IMMUNOLOGIC ABNORMALITIES IN PATIENTS WITH INFLAMMATORY MYOPATHIES

Cellular abnormalities

T-cell receptor restriction in inflamed muscle
Activated T and B lymphocytes expressing costimulatory molecules: CD86/CD80; CD28/CTLA4; CD40/CD40L in skeletal muscle
Increased peripheral mononuclear cell trafficking to muscle
Increased proportions of peripheral T and B lymphocytes bearing activation markers
High frequency of CD4+ CD28^{null} and CD8+CD28^{null} T cells in peripheral blood and muscle tissue
Type I interferon gene expression in muscle tissue and peripheral blood of dermatomyositis and polymyositis patients
High expression of proinflammatory cytokines and chemokines in muscle tissue (IL-1 α , IL-1 β , tumor necrosis factor, high-mobility group box 1, vascular endothelial growth factor, macrophage inflammatory protein 1 α)
Elevated serum levels of IL-1 α , IL-2, soluble IL-2 receptors, and soluble CD8 receptors
Decreased proliferative responses of peripheral mononuclear cells to T-cell mitogens
Increased proliferative responses of peripheral mononuclear cells to autologous muscle
Increased expression of cytokines and chemokines in infiltrating mononuclear cells and muscle cells
Increased expression of MHC class I (HLA-ABC), class II (HLA-DR), and intercellular adhesion molecule 1 on skeletal muscle fibers

Humoral abnormalities

Immunoglobulin and complement deposition in muscle vascular endothelium
Presence of myositis-specific autoantibodies (see Table 149.3)
Presence of myositis-associated autoantibodies (anti-U1RNP, anti-PM/Scl, anti-Ku)
Presence of other autoantibodies (anti-thyroid, anti-Sm, anti-Ro, anti-La, etc.)
Hypergammaglobulinemia, hypogammaglobulinemia, and agammaglobulinemia
Monoclonal gammopathy

HLA, human leukocyte antigen; IL, interleukin; MHC, major histocompatibility complex.

antigen specificities have not been clarified, and it is still not known whether muscle-specific immune reactions are involved and whether such reactions differ among various subsets of myositis.

Three major effector mechanisms have been proposed to be important for the development of chronic muscle inflammation and the major clinical symptoms, muscle weakness and muscle fatigue:

- Direct effects of infiltrating leukocytes, mainly T lymphocytes and macrophages, on muscle cells (e.g., by means of cytotoxicity)
- Indirect effects of molecules from the immune system (cytokines and others) on muscle metabolism and function
- Involvement of microvessels and a disturbed microcirculation, which could lead to acquired metabolic disturbances and thereby cause reduced muscle function

We could potentially learn about the operative pathogenic mechanisms in human diseases in several ways, through studies in animal models, through *in vitro* studies of cell or tissue cultures, or, most conclusively, from studies of the disease course and the target organ during administration of therapies targeting distinct molecules or mechanisms. Until recently, animal models have been of limited value in studies of myositis due to the lack of a model with a chronic muscle inflammation and associated histopathologic and clinical features resembling human polymyositis, dermatomyositis, or inclusion body myositis, but two promising animal models have now been developed, the MHC class I transgene and the C-protein myositis model, in which some aspects of myositis can be studied.^{25,26} Some information has also been gained from *in vitro* studies of cultured myoblasts and myotubes, which have demonstrated that the responsiveness and strength of cultured muscle cells are diminished after exposure to some cytokines, notably TNF.²⁷ The most informative studies have been performed in carefully characterized myositis patients with defined different clinical phenotypes and in different phases of their disease, as well as after different therapies. Such studies are based on characterization of the phenotypes of resident and infiltrating cells and distribution of molecules of potential pathogenic importance, as discussed next.

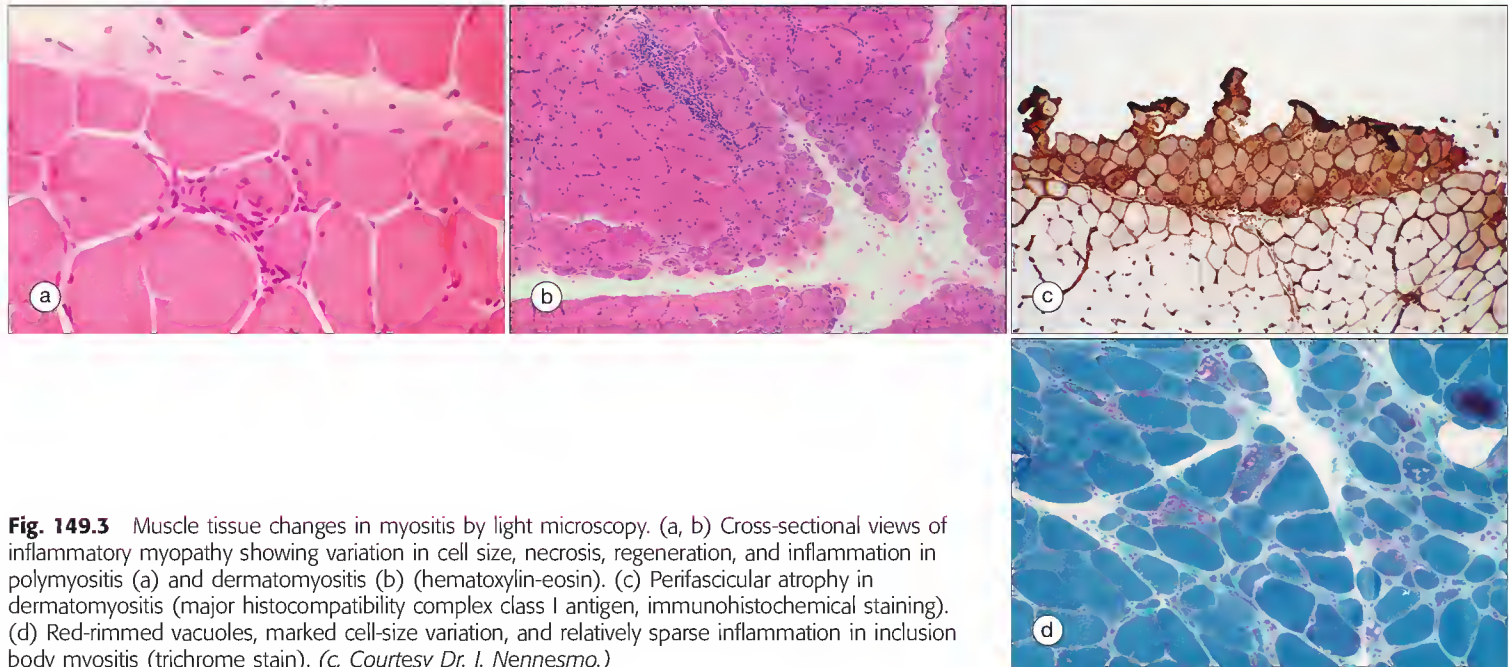


Fig. 149.3 Muscle tissue changes in myositis by light microscopy. (a, b) Cross-sectional views of inflammatory myopathy showing variation in cell size, necrosis, regeneration, and inflammation in polymyositis (a) and dermatomyositis (b) (hematoxylin-eosin). (c) Perifascicular atrophy in dermatomyositis (major histocompatibility complex class I antigen, immunohistochemical staining). (d) Red-rimmed vacuoles, marked cell-size variation, and relatively sparse inflammation in inclusion body myositis (trichrome stain). (c, Courtesy Dr. I. Nennesmo.)

Muscle histopathologic features

Characteristic histopathologic signs in patients with inflammatory myopathies are the presence of mononuclear inflammatory cell infiltrates in muscle tissue and degenerating, necrotic fibers, as well as regenerating muscle fibers (Fig. 149.3a and b).^{1,3,28} Atrophy of muscle fibers in a perifascicular fashion is found mainly in patients with dermatomyositis, often in a later phase of the disease (Fig. 149.3b and c). In inclusion body myositis, rimmed vacuoles are characteristic features that can be seen under a light microscope (Fig. 149.3d).¹ Nuclear or cytoplasmic inclusions are detected mainly by electron microscopy. None of these features in biopsy specimens is pathognomonic for myositis; all may also occur in other disorders, and they are not directly linked to muscle function. Importantly, these histopathologic features are often focal, and in some cases a muscle biopsy specimen can look normal despite clinically evident muscle weakness. Furthermore, the degree of histopathologic features is not correlated with the degree of muscle weakness. The focal nature of inflammation is also observed by magnetic resonance imaging, which can detect inflammation as a bright signal using the short tau inversion recovery (STIR) sequence (Fig. 149.4). The reasons for this heterogeneity of muscle inflammation are not known, but the heterogeneity suggests that not only does immune-mediated muscle fiber damage cause impaired muscle function but other mechanisms are also important, as discussed next.

Immunopathologic features

Careful characterization of human muscle tissue from patients with myositis using immunohistochemistry has revealed that there is a tendency for different lymphocyte subsets to accumulate in different regions of the muscle, which suggests that there are different targets of the immune reaction. The pattern of distribution of inflammatory cells also tends to vary for different clinical subsets of myositis.²⁹

Basically two different patterns of inflammatory cell infiltrates are found in muscle tissue in adult inflammatory myopathies. One is predominantly localized to the endomysium and is composed mainly of CD8+ and CD4+ T cells, macrophages, and dendritic cells.^{1,3,28,29} In some cases the infiltrates surround and seem to invade nonnecrotic muscle fibers (Fig. 149.5a).²⁸ This feature is seen predominantly in polymyositis and inclusion body myositis (see Fig. 149.5a).²⁸ The other pattern has a perivascular and perimysial localization and is composed mainly of CD4+ T cells, macrophages, dendritic cells, and B cells.^{1,3,28,29} This pattern is seen predominantly in dermatomyositis cases.^{28,29} These different immunohistopathologic features suggest that different pathogenic mechanisms could be involved in the different subsets of myositis, with a predominance of T cell-mediated muscle fiber damage in polymyositis and inclusion body myositis and a role for the microvessels in dermatomyositis (Fig. 149.5b). However, these changes are not strictly related to the presence or absence of skin rash. Recently further phenotyping of T cells has found CD28^{null} T cells of both CD4+ and CD8+

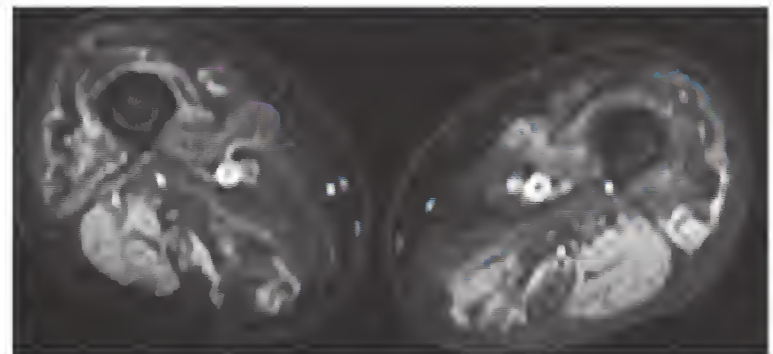


Fig. 149.4 Magnetic resonance images of the thigh. In cross section using the short tau inversion recovery technique, atrophy of the anterior muscles is evident. Inflammation shows up as bright areas in the posterior muscles. (Courtesy Dr. J. Frank and Dr. D. Fraser.)

phenotypes to dominate in both muscle tissue and peripheral blood in all three subsets of myositis.^{30,31} CD28^{null} T cells are proinflammatory, can be easily activated, and have cytotoxic capacity. Furthermore, they are apoptosis resistant and could contribute to the chronicity of disease, which makes them interesting as targets for therapy. CD28^{null} T cells have a restricted T-cell receptor (TCR) repertoire, which suggests that they are locally expanded.³¹ Another enigma in myositis is that in many patients the inflammatory cellular infiltrates are sparse and do not correlate with the degree of muscle symptoms, which suggests that other components of the immunopathology of inflamed muscle are also important for the disease. In contrast, the tissue distribution of signaling molecules produced in inflamed muscle tissues such as cytokines and chemokines does not seem to differ in various subsets of myositis, which indicates that some molecular mechanisms may be shared by different subsets of myositis.³²

Another feature of inflamed muscle tissue is expression of MHC class I and II molecules in muscle fibers, which normally do not express these antigens (Fig. 149.6).³³ MHC class I antigen expression is present in a majority of myositis patients both on regenerating fibers and on otherwise histopathologically normal-appearing muscle fibers. The MHC class I expression is localized to the muscle fiber membrane and often diffusely spread within the sarcoplasm. Furthermore, the MHC class I and class II expression on muscle fibers has been observed even in the absence of inflammatory cell infiltrates.³⁴ The MHC class II molecules are less consistently expressed, mainly on scattered muscle fibers. The mechanisms by which MHC class I and class II expression are induced on muscle fibers *in vivo* have not been clarified, but from *in vitro* studies it has been demonstrated that proinflammatory cytokines or chemokines may induce MHC class I and class II

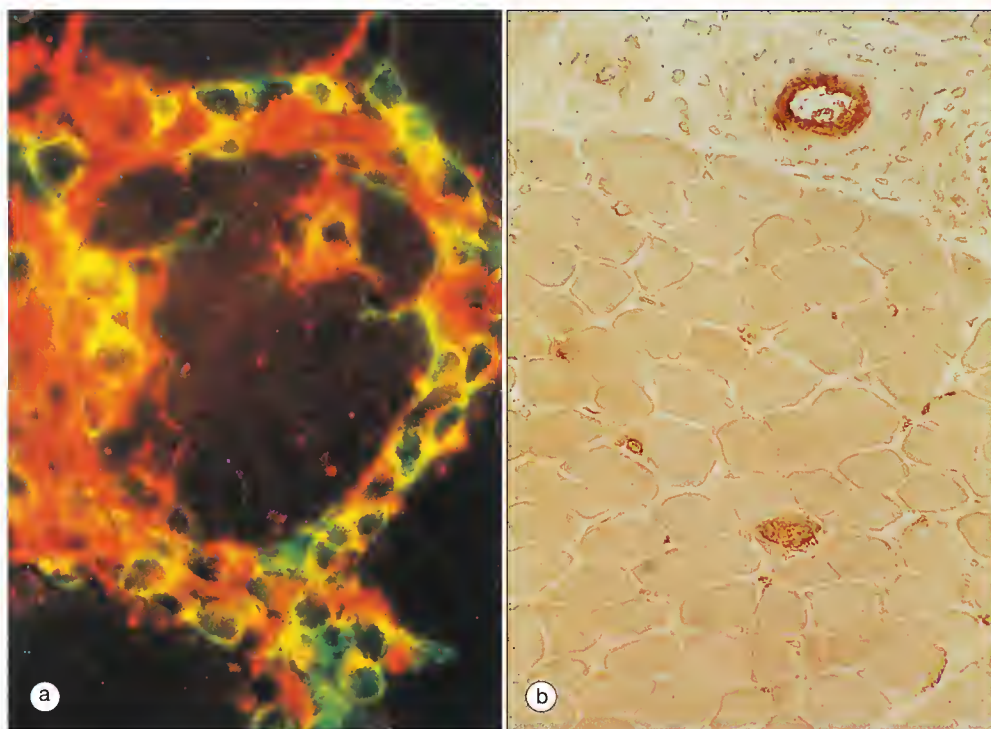


Fig. 149.5 (a) Lymphocytes invading a myocyte in a patient with myositis (double immunofluorescent staining with anti-CD8 [green] and anti-DR [red] antisera). Distribution of CD4+ and CD8+ lymphocytes in different clinical forms of myositis: In dermatomyositis inflammatory infiltrates consist predominantly of perivascular B and CD4+ T cells, and in polymyositis and inclusion body myositis they are mostly endomysial CD8+ T cells. (b) The complement membrane attack complex in the vessels of a muscle from a patient with dermatomyositis. (a, Courtesy Dr. J.T. Kissel; b, courtesy Dr. Andrew Engel.)

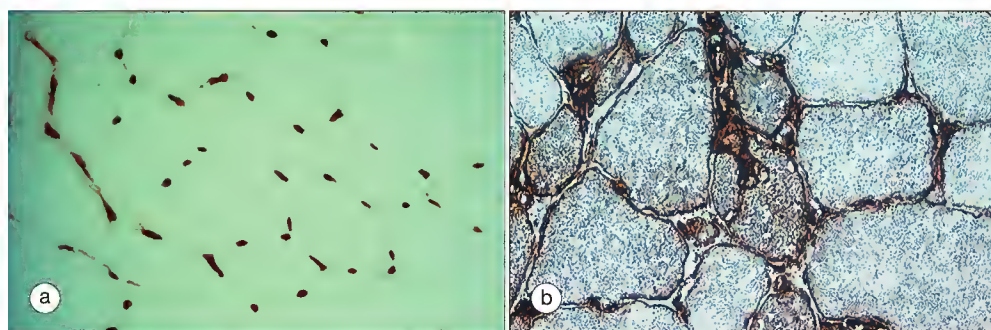


Fig. 149.6 Major histocompatibility complex (MHC) class I antigen expression detected by immunohistochemistry in muscle tissue. (a) In normal muscle, positive staining (brown) is seen mainly in capillaries. (b) In a patient with polymyositis, positive staining (brown) is localized to muscle fiber membranes, is seen diffusely in the sarcoplasm of several fibers, and appears on inflammatory cells localized in the endomysium.

expression on cultured muscle cells.³⁵ These include cytokines that have been detected in inflamed muscle tissue such as type I IFNs, IFN- γ , interleukin-1 α (IL-1 α) and IL-1 β , and TNF- α . A possible role of the induction of MHC class I molecules on muscle fibers in the pathogenesis of myositis is discussed in the following section. The MHC class I expression on muscle fibers, although not specific for myositis, could be helpful in diagnostic evaluation to distinguish affected muscles from normal muscle.³⁶

Cytokines and chemokines

A number of cytokines and chemokines that may play a role in the pathogenesis of myositis have been detected in muscle tissue from patients with these disorders. The most frequently reported cytokines in IIMs are the proinflammatory cytokines IL-1 α , IL-1 β , TNF- α , and type I IFNs and the alarmin high-mobility group box 1 (HMGB1).^{32,37,38} Other cytokines that have been found with increased expression in muscle tissue on the protein or messenger RNA level are IL-4, IL-6, IL-15, IL-17, and IL-18.³² The proinflammatory type I IFNs (IFN- α and IFN- β), which are produced mainly by plasmacytoid dendritic cells, were found with pronounced gene expression in muscle tissue and peripheral blood and with a suggestive association with disease activity in polymyositis and dermatomyositis.³⁹ A majority of these cytokines are present in inflammatory cells; some cytokines, such as TNF- α , IL-6, and IL-15, are also observed in the cytoplasm of muscle fibers, and still other cytokines (e.g., IL-1 α) are found mainly in endothelial cells, even when inflammatory cells are not detectable in the vicinity.³² Another prominent molecule in muscle tissue is transforming growth factor- β (TGF- β).^{32,37} TGF- β has antiinflammatory effects and could stimulate the development of fibrosis. Despite the different patterns of infiltrating inflammatory cells in different subtypes of myositis, the cytokine pattern in muscle tissue is with few exceptions similar in the different subsets of myositis.

Chemokines are inflammatory mediators that have chemotactic functions in attracting leukocytes to tissues. They are produced by a number of different cells including endothelial cells, fibroblasts, and lymphocytes and are secreted and bound to receptors on target cells (e.g., monocytes, lymphocytes). The main stimuli for chemokine production are proinflammatory cytokines such as IFN- γ , IL-1, TNF- α , bacterial products, and viral infections. The α -chemokines CXCL9 and CXCL10 and the β -chemokines CCL2, CCL3, CCL4, CCL19, and CCL21 are expressed in muscle tissue from myositis patients.⁴⁰ Some differences in chemokine expression have been observed between patients with dermatomyositis and those with polymyositis and inclusion body myositis. Dermatomyositis is characterized by high levels of CXCL12 and CCL2 in affected blood vessels and the B-cell activator CXCL13 is particularly prominent in the larger perimysial infiltrates of dermatomyositis,⁴⁰ whereas CXCL10 and CCL2 are expressed on infiltrating cells in muscle tissue in polymyositis and inclusion body myositis.⁴⁰

Immune mechanisms and muscle function

In addition to the previously described characteristic cellular infiltrations of T cells, restricted TCR use by muscle-infiltrating cells in polymyositis and inclusion body myositis provides additional support for a role of T cell-mediated muscle-specific immune reactivity. This restriction suggests that subpopulations of T cells are selected and expanded in muscle tissue in response to as yet uncharacterized antigens. In dermatomyositis the TCR patterns are more polyclonal. Although oligoclonal TCR patterns have been observed in polymyositis and inclusion body myositis, no consistent TCR repertoire has been identified to date.

The most common way to initiate an immune response is through professional antigen-presenting cells (e.g., dendritic cells or macrophages), which capture antigens in the peripheral tissue and then migrate to lymphoid

organs, where they present the antigenic peptides to antigen-specific T cells, initiating the expansion and maturation of helper (CD4+) and effector (CD8+) T cells.⁴¹ Both myeloid and plasmacytoid dendritic cells have been demonstrated in muscle tissue from patients with all subsets of myositis.⁴² Whether muscle fibers with MHC class I or class II expression may act as antigen-presenting cells and thereby interact with T cells is still uncertain. The muscle fibers may express additional cell-surface molecules (intercellular adhesion molecule 1 [ICAM-1] and CD40), but the costimulatory molecules (CD80/CD86) that customarily induce immune stimulation have not been demonstrated convincingly on muscle cells.⁴¹

Mechanisms of cell damage

The relationship between infiltrating inflammatory cells and muscle dysfunction is still unclear. One possibility is T cell-mediated muscle fiber death, but as mentioned earlier there is no clear evidence of an interaction between TCRs and MHC class I or II molecules on muscle fibers. Furthermore, the observation that the surface membrane of muscle fibers in the inflamed tissue remains intact (as indicated by both light microscopic and electron microscopic data), despite the close proximity of the inflammatory cells, argues against a direct cytotoxic effect of CD8+ T cells on muscle cells. Apoptosis of the muscle fibers has also been proposed as a mechanism for muscle fiber degeneration, but despite the efforts of several research groups, no one has succeeded in detecting signs of apoptosis of the muscle cells in muscle biopsy specimens from patients with myositis.⁴³ Some studies suggest that the resistance to undergoing Fas/TNF receptor-mediated apoptosis is due to expression in the muscle fibers of proteins that inhibit apoptosis; namely, Fas-associated death domain-like IL-1-converting enzyme inhibitory protein (FLIP), inhibitor of apoptosis protein-like protein (hILP), and Bcl-2.⁴⁴ Cytotoxic mechanisms mediated by perforin and granzyme were also suggested as mechanisms for cell damage in myositis, and perforin-containing granules within CD8+ T lymphocytes have been found oriented toward adjacent muscle fibers.⁴⁵ The expected porelike structures in the sarcolemma from perforin exposure could not be detected, however, so it is still uncertain whether this mechanism has any role in mediating direct T cell-mediated damage in myositis patients.

Indirect effects of molecules from the immune system (cytokines and others) on muscle metabolism and function

Because patients can have muscle weakness and decreased muscle endurance without detectable inflammatory infiltrates and muscle fiber cell apoptosis or necrosis, mechanisms other than direct cell-mediated muscle fiber damage could be involved in the disease mechanisms that cause impaired muscle function. Another possibility is that soluble factors such as cytokines or chemokines affect muscle fibers either by direct toxic effects that induce fiber degeneration or through effects on muscle fiber metabolism or contractility. As an example, TNF- α and HMGB1 may have profound effects on muscle function, causing muscle fiber contractile dysfunction.^{27,46} TNF also has a catabolic effect on muscle cells by mediating protein loss and insulin resistance; it inhibits regeneration of muscle fibers and is an important mediator of muscle atrophy associated with cachexia.²⁷ IL-1 α is known from *in vitro* studies to inhibit production of insulin-like growth factor, which leads to metabolic disturbances in nutrition supply. IL-1 α may also inhibit muscle regeneration through suppression of myoblast proliferation and myoblast fusion.³⁵

IL-1 α seems to be of particular interest in myositis because this cytokine was consistently found in endothelial cells of microvessels in muscle tissue from myositis patients who had muscle weakness in both the early and the late, chronic phase of disease as well as persisting muscle weakness after treatment with glucocorticoids. Furthermore, IL-1, IFN- α , IFN- γ , TNF and HMGB1 all have the capacity to induce expression of the MHC class I molecules on muscle fibers, a typical feature in myositis.^{33,34,35,46}

The results of studies targeting specific molecular pathways will provide more information on the relative role of these molecules in the disease mechanisms of inflammatory myopathies. The experience in using targeted therapies that block specific molecules in the inflammatory cascade is limited to date in myositis. Treatment with TNF blockade has had varying effects on muscle function and muscle tissue inflammation, which makes the role of TNF in the pathogenesis of myositis uncertain.⁴³ IL-1 is clearly a potential target for directed therapies in myositis, but limited data are available to date on the use of agents blocking this molecule.

The MHC class I antigen expression on muscle fibers may also have a direct effect on muscle function. This notion is supported by the observation of MHC class I expression on the muscle fibers of myositis patients with clinical muscle weakness even in the absence of detectable inflammatory infiltrates.³⁴ Another line of support comes from studies of an animal model in

which conditional upregulation of MHC class I molecules on muscle fibers causes transgenic mice to develop muscle weakness, which precedes the histopathologic inflammation.²⁴ The mechanism by which the MHC class I upregulation induces muscle weakness could be endoplasmic stress affecting the synthesis of proteins that are important for energy substrates and contractility.³⁷

Involvement of the microvasculature in inflammatory myopathies

A third possibility for disease mechanisms that affect muscle function in myositis is involvement of the microvessels. Clinical signs indicating microvessel involvement such as the presence of nail splinters are found mainly in patients with dermatomyositis. Histopathologic observations of a decreased number of capillaries in muscle tissue were initially reported in patients with dermatomyositis.⁴⁸ This was seen even in early cases with muscle symptoms but without inflammatory cellular infiltrates. Localization of the late components of the complement system (C5 to C9, the membrane attack complex) (see Fig. 149.6b) to the areas with fewer capillaries suggests a vascular injury, which may even precede the infiltration of inflammatory cells and lead to muscle fiber damage.

Other abnormal phenotypic changes of blood vessels have been observed in muscle tissue not only from patients with dermatomyositis but also from those with polymyositis and inclusion body myositis. These changes include thickening of the endothelial cells both of capillaries and venules to resemble the endothelial cells of high-endothelium venules (HEVs), which have a central role in lymphocyte homing. This endothelial phenotype together with increased expression of the adhesion molecules ICAM-1 and vascular cellular adhesion molecule 1 suggest that the endothelial cells are activated. The corresponding ligands, LFA-1 and VLA-4, are also present on inflammatory cells in muscle tissue in myositis patients. HEV-resembling endothelial cells with increased expression of IL-1 α have been observed in areas exhibiting cellular infiltration and areas without inflammatory cells and in both patients with new-onset polymyositis and dermatomyositis and patients with chronic disease who experience persisting muscle weakness after immunosuppressive treatment.³² Interestingly, these changes correlated better with the persisting decrease of muscle function than did the inflammatory infiltrates. The activated microvessels with expression of adhesion molecules could promote migration of inflammatory cells into the muscle tissue and thereby play a central role in pathogenesis not only in dermatomyositis, as was suggested earlier, but also in polymyositis and inclusion body myositis. Adhesion molecules could also be attractive molecules for targeted therapies in these conditions.

Another possible consequence of microvessel involvement is a secondary metabolic disturbance and muscle tissue hypoxia. This is indicated by reduced levels of adenosine triphosphate and phosphocreatine observed by magnetic resonance spectroscopy, which reflect an abnormal energy metabolism in muscle tissue.⁴⁹ Hypoxia could also be generated in chronically inflamed tissue, as has been demonstrated in the synovial tissue of patients with rheumatoid arthritis. Low oxygen tension was also observed *in vivo* in muscle tissue in a small study of myositis patients.⁵⁰ Another finding supporting the hypoxia hypothesis is that two of the most frequently detected cytokines in muscle tissue, IL-1 and TGF- β , could be induced by hypoxia. In addition, patients with polymyositis and dermatomyositis had a high level of expression of the potent proangiogenic peptide vascular endothelial growth factor in both muscle tissue and sera compared with healthy controls.⁵¹ Local tissue hypoxia could contribute to mitochondrial dysfunction as indicated by the increased number of ragged red fibers and cytochrome c oxidase-negative fibers observed in inflammatory myopathies, which is most pronounced in dermatomyositis and inclusion body myositis. In chronic polymyositis and dermatomyositis with persisting impaired muscle function, a low proportion of oxidative, type I fibers was detected in thigh muscles, which could be a consequence of local tissue hypoxia.⁵⁰ Interestingly, this was reversed by physical exercise, with improved muscle performance.⁵² A combination of factors, including both immune-mediated muscle cell death and activation of different molecular pathways with an acquired metabolic myopathy, are likely to contribute to muscle weakness and fatigue in polymyositis and dermatomyositis. Sufficient data support this combination of pathogenic pathways to support their consideration when treatment regimens are designed, but the key molecular pathways are still unclear and further research is needed.

Humoral mechanisms

Humoral mechanisms in the pathogenesis of IIMs are suggested on the basis of two observations. The first is the presence of autoantibodies, and the second is deposition of complement and immunoglobulins in microvessels

LABORATORY DEMONSTRATION OF MYOSITIS-SPECIFIC AUTOANTIBODIES

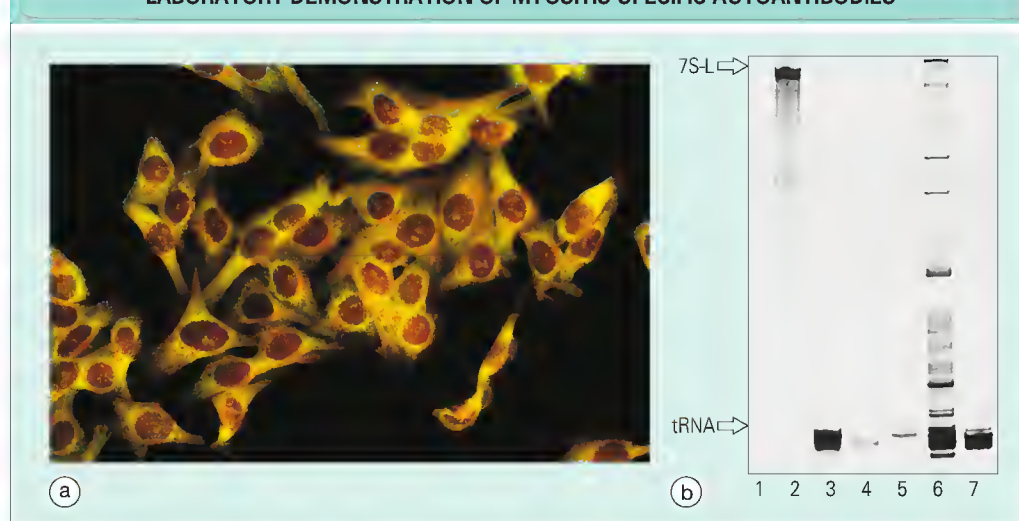


Fig. 149.7 (a) Cytoplasmic staining of cultured human cells by immunofluorescence using serum from a patient with anti-glycyl-transfer RNA (tRNA) synthetase antibodies. (b) Immunoprecipitation of cell extract by sera from patients with some myositis-specific autoantibodies. Only the RNA of the protein-RNA immunoprecipitate is shown. 1, normal; 2, anti-signal recognition particle (SRP); 3, anti-threonyl-tRNA synthetase (PL-7); 4, anti-histidyl-tRNA synthetase (Jo-1); 5, anti-isoleucyl-tRNA synthetase (OJ); 6, anti-alanyl-tRNA synthetase (PL-12), accompanied by anti-Ro, anti-La, and anti-RNP; 7, anti-glycyl-tRNA synthetase (EJ). (a, Courtesy D. Gracey; b, courtesy Dr. S. Cochran.)

in muscle biopsy specimens, as described earlier. Autoantibodies are present in 55% to 80% of myositis patients.⁵³ The most common autoantibodies are antinuclear antibodies, which are seen in all subsets of myositis but are less common in inclusion body myositis (30%).⁵³ No autoantibodies directed against muscle-specific antigens have been identified in myositis patients so far. Some of the autoantibodies detected are present in other inflammatory connective tissue diseases, even without signs of myositis, and are often called *myositis-associated autoantibodies* (e.g., antiribonucleoprotein [anti-RNP] antibodies), whereas others are found mainly in patients with IIM and therefore called *myositis-specific autoantibodies* (MSAs).²

The MSAs are particularly interesting in a pathogenic context not only because they are found almost exclusively in patients with myositis but also because they are associated with distinct clinical features and distinct genotypes. Because certain antibodies are associated with distinct extramuscular clinical features, their detection can be helpful to confirm a diagnosis of myositis and also to classify myositis patients into distinct clinical subgroups as described later. Interestingly, the presence of MSAs is associated with different HLA class II genotypes as described earlier in the discussion on genetics. The MSAs are often present at the first visit to the physician. In most patients they remain present during the disease course, although some (e.g., anti-Jo-1 antibodies) may vary with disease activity.⁵⁴ A common feature of these autoantigens is that they are cytoplasmic and thus do not induce the production of “antinuclear” antibodies; instead, they show a diffuse cytoplasmic pattern of staining of target cells when exposed to sera from patients with some MSAs (Fig. 149.7). These autoantigens are usually part of the protein synthesis machinery (Fig. 149.8).

The most frequently found MSAs are those directed against the aminoacyl-tRNA synthetases, a group of cytoplasmic enzymes that attach tRNAs to the corresponding amino acids (catalyze formation of aminoacyl-tRNA); these MSAs occur in 16% to 26% of patients with IIM.^{2,53} The most common of these is the anti-histidyl-tRNA synthetase antibody (anti-Jo-1), which targets histidyl-tRNA synthetase and is found in approximately 20% of patients with polymyositis or dermatomyositis. Other less common MSAs are listed in Table 149.3.⁵⁵ The presence of antisynthetase autoantibodies is associated with a distinct clinical phenotype, so-called *antisynthetase syndrome*, characterized by interstitial lung disease as the most prevalent clinical manifestation, myositis, arthritis, fever, Raynaud phenomenon, and roughened skin over the lateral and palmar surfaces of the index fingers, termed *mechanic's hands*.²

Anti-signal recognition particle (anti-SRP) autoantibodies are associated with a treatment-resistant myopathy and histopathologic features that include pronounced muscle fiber necrosis and little or no inflammation, termed *necrotizing myopathy*.⁵⁵ The clinical features associated with anti-Mi-2 antibodies are the typical skin rashes of dermatomyositis: Gottron papules, heliotrope rash, and a rash on the upper chest and shoulders—the so-called V-sign and shawl sign; this type has a good prognosis.^{2,55} Another autoantibody associated with dermatomyositis in both adults and children is directed against TIF-1 γ (a p155/p140 protein) and confers a high risk of malignancy in adult patients as mentioned earlier.^{24,55} Yet another novel autoantibody, anti-melanoma differentiation-associated gene 5 (anti-MDA5, or anti-CADM-p140, the clinically amyopathic dermatomyositis p140

antibody), has been found in about 20% of patients with clinical amyopathic myositis and is associated with rapidly progressive interstitial lung disease.⁵⁵ The anti-small ubiquitin-like modifier activating enzyme 1 (anti-SAE-1) antibody is also associated with dermatomyositis, characterized by severe skin involvement and interstitial lung disease.⁵⁵

The strong association between MSAs and distinct clinical features, as well as distinct HLA class II genotypes, implies a role for these autoantibodies in the pathogenesis of these subsets of myositis. However, some unanswered questions remain: First, how could these autoantigens, which are ubiquitously expressed intracellular proteins, elicit an immune response? And second, why are these autoantibodies associated with clinically distinct phenotypes? A few interesting possibilities regarding how these autoantigens could contribute to the immune response and the distinct clinical phenotypes have been suggested recently. The first comes from a demonstrated variation in autoantigen expression between tissues. An increased expression of the myositis autoantigens Mi-2 and histidyl-tRNA synthetase was recorded in regenerating muscle fibers compared with differentiated fibers, which suggests regenerating muscle fibers as a source of antigen in autoimmune myositis.⁵⁶ Some quantitative tissue variations in histidyl-tRNA synthetase expression were also observed, with a higher expression in normal lungs than in other healthy organs, which could possibly explain the frequent lung involvement associated with anti-histidyl-tRNA synthetase (anti-Jo-1) antibodies.

A second possibility is suggested by the interesting observation that the aminoacyl-tRNA synthetases targeted by the immune response in myositis may acquire chemotactic properties.⁵⁷ A possible role *in vivo* could be that these autoantigens may be exposed to the immune system during tissue damage and then act as chemokines to attract immune cells to aid repair as part of the innate immune response. In addition, sera from patients with anti-Jo-1 antibodies may induce type I interferon activity as in systemic lupus erythematosus, which also could be an important mechanism for a sustained immune reaction.⁵⁸

A third possibility relates to the hypothesis that autoantibodies are directed against modified self-proteins. Such modifications could occur during cell death or as a consequence of local inflammation. One such modification occurs through cleavage of proteins by granzyme B, a serine protease that is released by cytotoxic lymphocytes to kill virus-infected cells and tumor cells. Histidyl-tRNA synthetase (Jo-1 antigen) becomes immunogenic after cleavage by granzyme B.⁵⁹ This feature unifies a majority of autoantigens in myositis. Whether the granzyme B/perforin pathway has a role in the immune response *in vivo* in myositis still needs to be clarified.

Accumulating evidence thus suggests that MSAs have a role in the pathogenesis of myositis. However, to date it is not known whether these events are primary in the pathogenesis of disease or rather represent secondary phenomenon occurring as a consequence of tissue inflammation or damage.

INCLUSION BODY MYOSITIS

In inclusion body myositis there are specific features such as the rimmed vacuoles and inclusions of β -amyloid protein that have been the subject

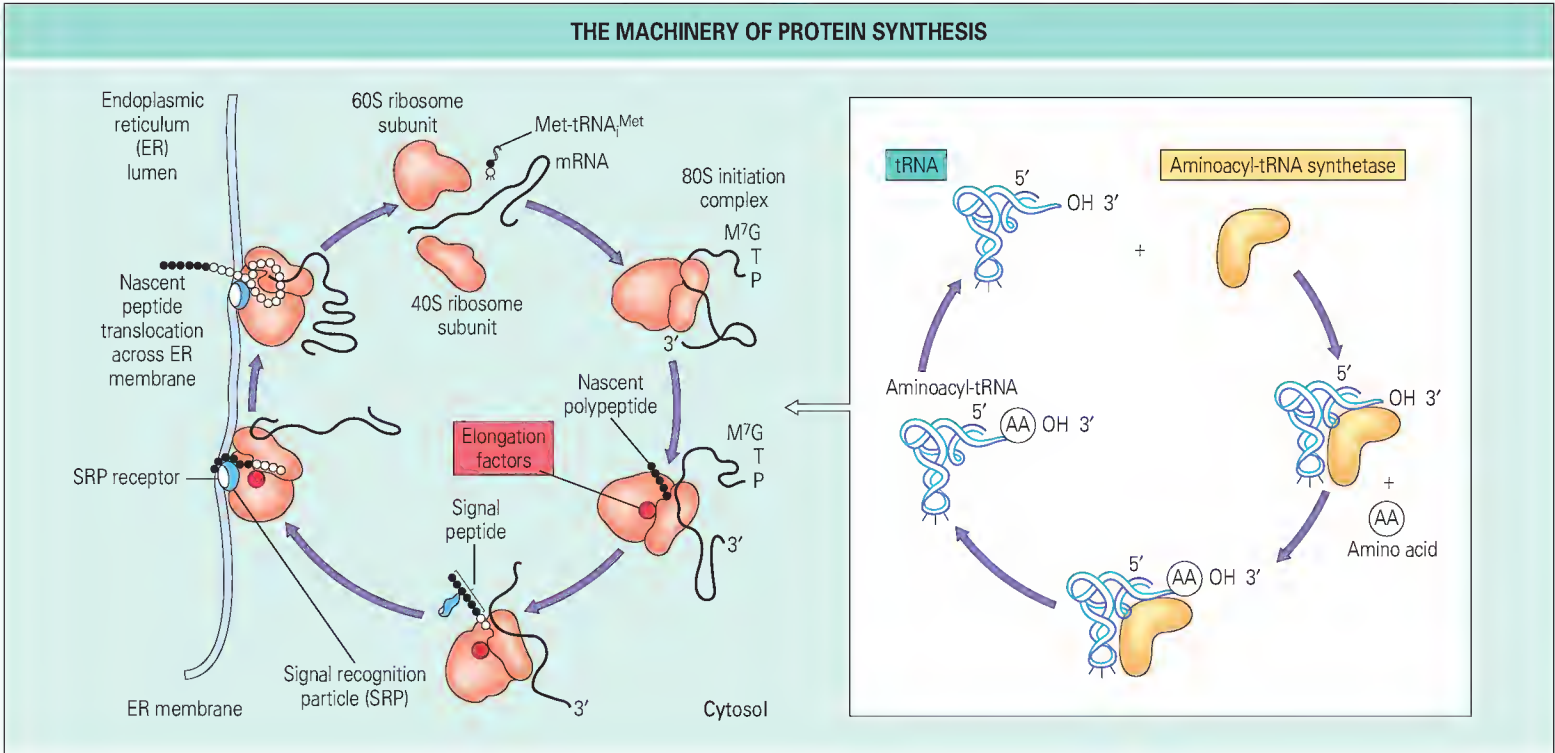


Fig. 149.8 Protein synthesis showing some of the targets of myositis-specific autoantibodies. Several of the myositis-specific autoantibodies target ubiquitous cytoplasmic antigens involved in protein synthesis—for example, the aminoacyl–transfer RNA (tRNA) synthetases—which are important enzymes that bind an amino acid to its tRNA. The ribosomes facilitate the linking of amino acids to form a polypeptide through binding of the tRNAs to messenger RNA (mRNA) templates (translation). This can take place in the cytosol or in the membrane of the endoplasmic reticulum (ER). Another target antigen, signal recognition particle (SRP) is essential for protein translocation across the membrane of the ER. GTP, guanosine triphosphate.

TABLE 149.3
Myositis-specific autoantibodies and their associated disease features

Autoantibody	Autoantigen	Prevalence in IIM (%)	Clinical association	HLA class II alleles
Antisynthetases				
Anti-Jo-1	HisRS	15-40	Antisynthetase syndrome [†]	DRB1*0301, [‡] DQB1*0201, [§] DQA1*0501, [‡] and/or DQA1*0401 [‡]
Anti-PL-7	ThrRS	<5	Antisynthetase syndrome [†]	
Anti-PL-12	AlaRS	<5	Antisynthetase syndrome [†]	
Anti-OJ	IleRS	<5	Antisynthetase syndrome [†]	
Anti-EJ	GlyRS	<5	Antisynthetase syndrome [†]	
Anti-Zo	PhenylRS		Antisynthetase syndrome [†]	
Anti-KS	AspRS		Antisynthetase syndrome [†]	
Anti-HA	ThyRS		Antisynthetase syndrome [†]	
Anti-SRP	SRP proteins	<5	Necrotizing myopathy	DR5, DQA1*0301, DRw52
Anti-KJ	Unidentified protein	<1	Interstitial lung disease	?
Anti-Mi-2	Nuclear helicase	<10	Classic dermatomyositis	DRB1*07, DQA1*0201
Anti-TIF-1γ (p155/140)	TIF-1γ		Juvenile dermatomyositis and dermatomyositis associated with malignancy	
Anti-MDA5 (CADM-140)	MDA5)	20% of CADM	Clinical amyopathic dermatomyositis, rapidly progressive interstitial lung disease	
Anti-SAE	SAE, A and B subunits		Dermatomyositis with interstitial lung disease	
Anti-p140	NXP-2—nuclear transcription	20% of JDM cases	JDM	
Anti-HMG-CoA reductase (anti-200 kDa/100 kDa)	HMG-CoA reductase		Statin-induced necrotizing myopathy	

[†]Antisynthetase syndrome is interstitial lung disease, fever, arthritis, Raynaud phenomenon, and mechanic's hands.
[‡]In black and Mexican American patients.
[§]In white patients.
^{||}Linked alleles.
Ala, alanyl; Asp, asparaginy; DM, clinical amyopathic dermatomyositis; Gly, glycyl; His, histidyl; HLA, human leukocyte antigen; HMG-CoA, hydroxymethylglutaryl-coenzyme A; IIM, idiopathic inflammatory myopathy; Ile, isoleucyl; JDM, juvenile dermatomyositis; MDA5, melanoma differentiation-associated gene 5; Phenyl, phenylalanyl; RS, tRNA synthetase; SAE, small ubiquitin-like modifier activating enzyme 1; SRP, signal recognition particle; Thr, threonyl; Thy, thyranyl; TIF, transcriptional intermediary factor.

of much interest.⁶⁰ Another characteristic of inclusion body myositis is the resistance to immunosuppressive treatment. Although some features are shared with polymyositis and dermatomyositis, as discussed earlier, there still is debate as to whether inclusion body myositis should be regarded as an inflammatory myopathy or as a degenerative myopathy with secondary inflammation.⁶¹ β -Amyloid, one of the degenerative proteins identified in muscle fibers of patients with inclusion body myositis, can stimulate human myoblasts to IL-6 production. This could imply that in muscle tissue of patients with inclusion body myositis there is a continual stimulation of IL-6 production, which could have a proliferative effect on the local immune response. Supporting a role for the humoral immune response at the site of tissue damage in inclusion body myositis is the recent observation that recombinant immunoglobulins reconstructed from single plasma cells derived from inclusion body myositis muscle tissue recognized desmin, a major intermediate filament protein.⁶² The role of the immune response in inclusion body myositis needs further investigation, however.

CONCLUSION

Both cellular and humoral immune mechanisms as well as nonimmune mechanisms are important in the pathogenesis of myositis. Muscle weakness and muscle fatigue, the major clinical features in myositis, could be caused by different mechanisms in different phases of the disease. In early disease the reversible changes that may affect muscle metabolism could play a major role, and in later disease irreversible changes that could be related to muscle fiber damage and replacement of muscle tissue by connective tissue and fat may be predominant factors. On the basis of the findings to date, it is likely that soluble factors such as cytokines, which are produced in muscle tissue by different sources such as inflammatory cells, endothelial cells, and muscle fibers, could affect muscle function and have an important role in pathogenesis. A better knowledge of key molecular pathways and the specific molecules affect muscle function will likely lead to new and more targeted therapies.

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150

Management of inflammatory muscle disease

■ FREDERICK W. MILLER

- A correct diagnosis, which almost always requires a muscle biopsy to rule out noninflammatory myopathies, is central to optimal treatment.
- Therapy for myositis is based more on anecdotal information and custom than on controlled trial data.
- Clinical remission, or elimination of all evidence of disease activity in all organ systems, is a realistic objective for most patients and should be pursued aggressively to optimize outcomes.
- Corticosteroids remain the most effective agents, but they should be supplemented by other drugs early in patients with poor prognostic features.
- For patients with dermatomyositis, sunscreens, sun avoidance, minimizing use of photosensitizers, topical corticosteroids, and hydroxychloroquine (Plaquenil) can be beneficial.
- Methotrexate and azathioprine are the most frequently used corticosteroid-sparing agents.
- Mycophenolate, cyclosporine, tacrolimus, cyclophosphamide, intravenous gamma globulin, anti-tumor necrosis factor agents, and rituximab are of benefit in some patients who do not respond to methotrexate or azathioprine.
- Most patients benefit from a graded rehabilitation program instituted as early as possible.
- Treatment of inclusion body myositis is unsatisfactory and controversial.
- Therapy needs to be individualized to the type of myositis, medical history, level of disease activity and disease damage, expectations, prognosis, and risk for adverse events in each patient.

GENERAL PRINCIPLES

The rarity and heterogeneity of the idiopathic inflammatory myopathies (IIMs), along with the few validated assessment tools, have limited the controlled trial data available to guide therapy and management. Few agents have been approved by the Food and Drug Administration for use in patients with myositis, and therapy remains challenging even for expert myologists. Nonetheless, a number of case series, some open-label trials, and a few randomized controlled studies have been performed in small groups of patients and can guide aspects of therapy (Table 150.1).¹⁻²⁵

The primary goal in the management of myositis is to improve function to as close as possible to the patient's predisease state. This is accomplished by (1) making an accurate diagnosis; (2) educating patients and their families about myositis; (3) defining and addressing patients' and families' major concerns; (4) enumerating the prognostic risk factors; (5) defining the extent of disease activity and disease damage in all affected systems; and (6) developing, with the patient's input, an individualized management approach that incorporates all of the above, as well as the patient's expectations and risk factors for adverse events with therapy. It is useful to think of the management of myositis in terms of that used for cancer patients, with initial induction therapy to rapidly decrease inflammation and achieve remission and later maintenance therapy to minimize the chance for relapse. Expert opinion is developing that in most cases, clinical remission, which is elimination of all evidence of disease activity in all organ systems, is a realistic objective and should be pursued aggressively to optimize outcomes.

Ensuring an accurate diagnosis is critical to all other aspects of management because there are so many mimics of the inflammatory myopathies

(see Chapter 148) and the therapeutic approaches differ greatly for many of them. Patients who were referred without an appropriate diagnostic evaluation, those who are not responding to adequate immunosuppressive therapy within the first several months, and those with atypical features should be reevaluated carefully to ensure a correct diagnosis. An important aspect of management involves the education of patients and their families about their disease (see "Additional Resources for Patients and Physicians").

Poor prognostic factors for myositis are not well defined, but a number of features have been suggested, as listed in Box 150.1.²⁶⁻²⁸ Despite few controlled studies to support a more aggressive approach in patients with poor prognostic factors, anecdotal information suggests that for those with poor prognostic features, adding additional immunosuppressive therapy to corticosteroids early in the disease course may improve outcomes.^{29,30} It is important to determine all the organ systems involved in these systemic disorders and to assess the degree of disease activity and damage that is present in each, and newly developed tools are useful in capturing this information.³¹ Integrating this information into a cohesive whole is the most difficult part of developing a comprehensive treatment strategy for patients with myositis. This should include an understanding of the expectations of the patient, as well as possible risk factors for adverse events with the therapies being considered.

Different groups of patients with myositis appear to have various degrees of disease activity at onset and to respond differently to therapeutic agents over time.^{26,32} Figure 150.1 presents the general disease courses for the major clinicopathologic and autoantibody groups of myositis and emphasizes that in certain groups of patients, disease activity is more likely to increase after reducing medications—for these groups, medications should be tapered more carefully.

Most of the focus of this chapter is on adult-onset IIM, but similar approaches should be considered for juvenile-onset disease and in those with dermatomyositis (DM) without significant muscle involvement (DM sine myositis).^{33,34}

PRIMARY DRUG THERAPIES

Even though just limited anecdotal information is available to guide therapy and no consensus has been reached on the best approaches, an algorithm for the treatment of inflammatory myopathies based on common clinical practices is proposed in Figure 150.2.

Corticosteroids

Daily oral corticosteroids are the primary initial therapy used to treat myositis. Despite the lack of controlled studies to support this practice, they are considered by most investigators to be the most effective treatment of polymyositis (PM) and DM.²⁷ Although the majority of patients have at least a partial response to corticosteroids, many do not respond adequately, many more experience increases in disease activity during steroid tapering, and most eventually suffer from the toxicities of corticosteroids. The initial dose and route of administration of corticosteroids are usually determined by disease severity, the number of poor prognostic factors present, and the risk factors for adverse events in each patient. A common practice is to begin with prednisone at 1 to 2 mg/kg/day. Prednisone is often begun as a single daily dose to minimize adverse effects; however, if an inadequate response is seen, it is frequently changed to a divided daily dose.

In patients with severe myositis and those with significant active pulmonary, cardiac, or gastrointestinal disease or other poor prognostic features, intravenous methylprednisolone 1 g/day for 3 consecutive days may be used

TABLE 150.1
Prospective trials in patients with idiopathic inflammatory myopathies
(in order of publication)

Trial (first author and reference)	Design	Agents	Efficacy	Grade of evidence
Polymyositis, dermatomyositis				
Bunch ¹	P, R, D-B	Aza-Pred vs. placebo-Pred	Possible	B
Bunch ²	Follow-up of Bunch ¹	AZA-Pred vs. placebo-Pred	Yes	B
Cherin ³	P, open	IVIg	Possible	B
Miller ⁴	P, R, D-B, P-C	PE vs. LPH vs. sham	No	A
Dalakas ⁵	P, R, D-B, P-C, crossover	IVIg vs. placebo	Yes	A
Cherin ⁶	P, open	IVIg	Possible	B
Cherin ⁷	P, retrospective	PE	Possible	C
Villalba ⁸	P, R, open, crossover	Oral MTX/Aza vs. IV MTX	Possible	B
Adams ⁹	P, open	Fludarabine	Possible	B
Oddis ¹⁰	P, open	Tacrolimus	Possible	C
Vencovsky ¹¹	P, R, controlled	CyA vs. MTX	Similar	B
Danieli ¹²	P, open vs. CyA/Pred/IVIg/PE	CyA/Pred vs. CyA/Pred/IVIg	Possible	C
Cherin ⁶	P, open	IVIg	Possible	C
Levine ¹³	P, open	Rituximab	Yes	B
van de Vlekkert ¹⁴	P, R, D-B	Pr vs. D	Similar	B
Muscle Study Group ¹⁵	P, R, D-B	Etanercept	Possible	B
Oddis ^{50a}	P, R, D-B	Rituximab	Likely	A
Inclusion body myositis				
Leff ¹⁶	P, R, open	MTX/Aza vs. IV MTX	Possible	B
Dalakas ¹⁷	P, D-B, P-C, crossover	IVIg vs. placebo	Possible	A
Walter ¹⁸	P, D-B, P-C, crossover	IVIg vs. placebo	Possible	A
Dalakas ¹⁹	P, R, D-B, P-C	IVIg/Pred	No	A
Muscle Study Group ²⁰	P, R, D-B, P-C	Avonex vs. placebo	No	A
Muscle study Group ²¹	P, R, D-B, P-C	Avonex vs. placebo	No	A
Barhon ²²	P, open	Etanercept	No	B
Polymyositis, dermatomyositis, inclusion body myositis				
Cronin ²³	P, R, open	IV Cyclo	No	B
Mastaglia ²⁴	P, open	IVIg	No	C
Dastmalchi ²⁵	P, open	Infliximab	No	C

Aza, azathioprine; Avonex, interferon beta-1a; CyA, cyclosporine A; Cyclo, cyclophosphamide; D, dexamethasone; D-B, double blind; IVIg, intravenous immunoglobulin; LPH, leukopheresis; MTX, methotrexate; P, prospective; P-C, placebo controlled; PE, plasmapheresis; Pr, prednisolone; Pred, prednisone; R, randomized.

Grade of evidence: A, randomized, controlled trial; B, observational studies; C, case series. Adopted from Oddis CV. Idiopathic inflammatory myopathy: management and prognosis. *Rheum Dis Clin North Am* 2002;28:979-1001; and Mastaglia FL, Zilko PJ. Inflammatory myopathies: how to treat the difficult cases. *J Clin Neurosci* 2003;10:99-101.

to achieve a more rapid response and avoid any question of inadequate oral adsorption. How rapidly to decrease the corticosteroid dose is determined by the patient's clinical response to therapy. A common error is to attempt too rapid a decrease in dose, which often results in increased disease activity requiring another course of higher-dose corticosteroids. The dose at which a disease flare occurs is fairly constant and predictable for a given patient.³⁵ To minimize the chance of disease flares during tapering, some investigators suggest maintaining an initial dose of prednisone at 1 mg/kg/day for at least a month and until the creatine kinase (CK) level returns to

GENERALIZED DISEASE COURSES FOR CLINICAL AND AUTOANTIBODY GROUPS OF MYOSITIS PATIENTS

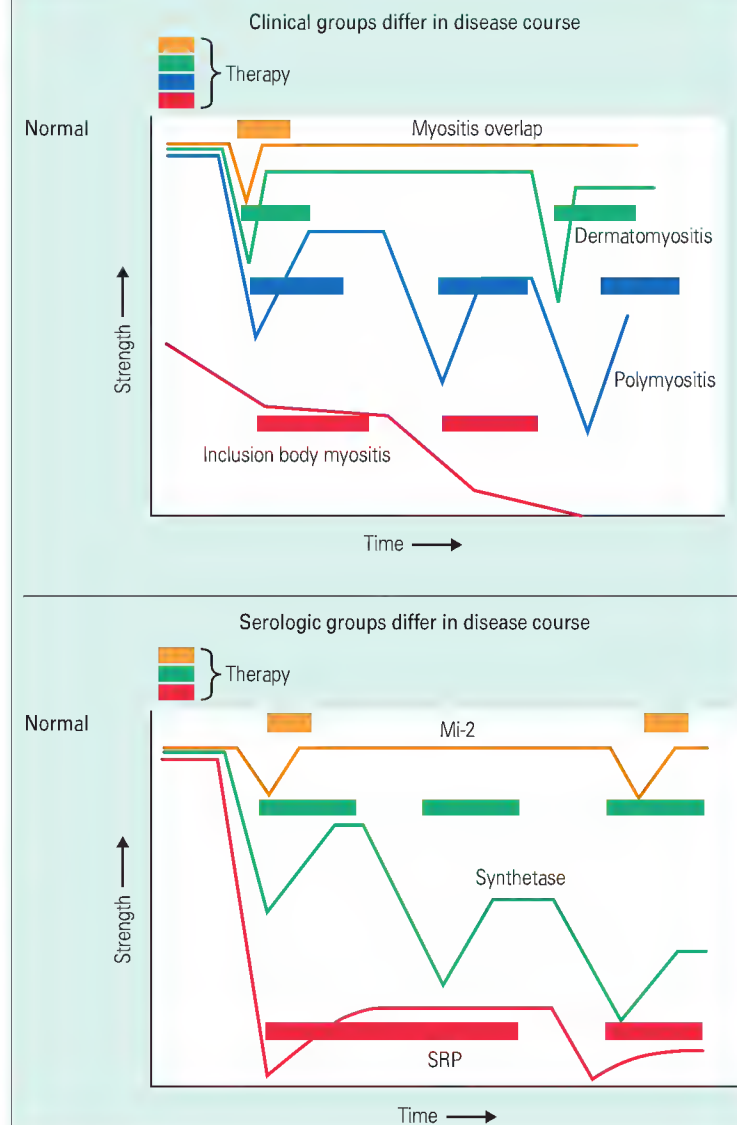


Fig. 150.1 Patients with myositis in association with other connective tissue diseases (myositis overlap) tend to have milder myositis that responds relatively well to therapy and infrequently return after withdrawal of therapy when compared with those with dermatomyositis. Polymyositis patients have more severe disease at onset with poorer responses to therapy and frequent exacerbations after tapering therapy. Patients with inclusion body myositis have slowly progressive disease that tends to be unresponsive, but some patients have the possibility of slowing of the rate of deterioration with therapy. A similar difference in myositis severity at onset, response to therapy, and disease exacerbation with withdrawal of therapy is seen in the serologic groups; patients with anti-Mi-2 autoantibodies have the best prognosis, followed by the antisynthetase and finally the anti-signal recognition particle (SRP) antibody groups. (Modified from Plotz PH, Rider LG, Targoff IN, et al. NIH conference. Myositis: immunologic contributions to understanding cause, pathogenesis, and therapy. *Ann Intern Med* 1995;122:714-24.)

normal and then reducing the prednisone dose by 25% monthly to a maintenance dose of 5 to 10 mg/day.²⁷ Other approaches include changing the prednisone to an alternate-day regimen once disease control has been achieved. There are few data to suggest how long corticosteroid maintenance therapy should continue after the initial clinical response and normalization of CK levels. A conservative approach is to continue with prednisone at 5 to 15 mg/day for a period of 6 months after achieving clinical remission.

Prolonged high-dose corticosteroid treatment should be avoided to minimize adverse effects and optimize outcomes. The many adverse events from

prolonged high-dose corticosteroid use include osteoporosis with vertebral collapse and osteonecrosis, hypertension, hyperglycemia, Cushing syndrome, cataracts, more frequent infections, and steroid myopathy. Patients must be advised about these potential problems and be evaluated carefully for their development at follow-up visits. Regarding steroid-induced myopathy, patients in whom increasing weakness develops while taking high-dose corticosteroids, with other evidence of decreasing disease activity, should be considered for empirical reductions in the corticosteroid dose. Calcium and

vitamin D supplements and bisphosphonates should be prescribed for those being treated long-term with corticosteroids.

Other agents

Even though previous approaches involved reserving additional immunosuppressive agents for those who failed corticosteroid therapy or had intolerable adverse effects, initial use of cytotoxic agents along with corticosteroids in patients with poor prognostic features is becoming more frequent. This more aggressive strategy has the advantage of minimizing the adverse effects of corticosteroids and offering the possibility of better outcomes in those who would otherwise be predicted to not do well.^{36,37}

Methotrexate

Because of its extensive history, safety record, and anecdotal efficacy, methotrexate is considered by many investigators to be the first choice as corticosteroid-sparing therapy for patients with inflammatory myopathy.²⁷ Retrospective data suggest that responses to methotrexate usually occur within 2 to 3 months and are better in men and those with antisynthetase syndrome.³⁵ A common practice is to begin dosing at 10 to 15 mg/wk and increase the dose by 5 mg/wk every month to a maximum of 25 to 30 mg/wk as needed. For those in whom gastrointestinal intolerance develops or adequate oral absorption is uncertain, subcutaneous administration may be used. The combination of methotrexate and azathioprine might benefit some patients who had not shown adequate responses to either agent alone.⁸

BOX 150.1 POOR PROGNOSTIC FACTORS IN INFLAMMATORY MYOPATHIES*

Older age at onset
Delay until diagnosis and treatment
Severe myositis
Significant pulmonary, cardiac, or gastrointestinal involvement
Previous lack of response to immunosuppressive therapy
Polymyositis versus dermatomyositis
Cancer-associated myositis
Inclusion body myositis
Antisynthetase, anti-signal recognition particle (SRP), anti-155/140, and anti-CADM-140 autoantibodies

*Information derived from references 26-28.

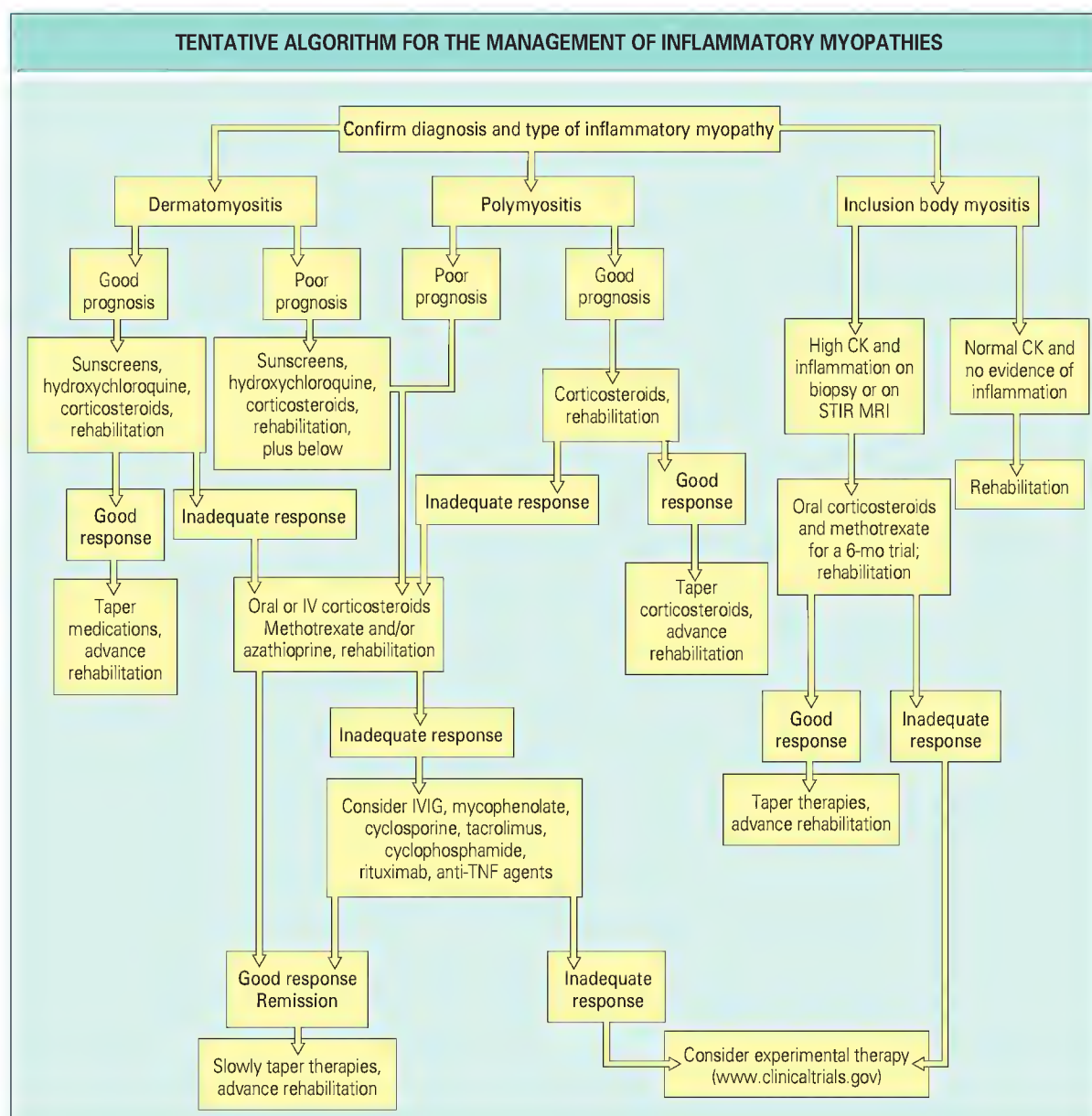


Fig. 150.2 CK, creatine kinase; IV, intravenous; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; TNF, tumor necrosis factor.

The primary toxicities of methotrexate, which are dose related, are gastrointestinal intolerance, fatigue or malaise for several days after the dose, cytopenia, and hepatic toxicity. The latter can be difficult to assess in patients with myositis, in whom elevations in serum transaminases and lactate dehydrogenase as a result of myoblast activation are common. Because serum levels of these enzymes usually correlate with serum CK levels, it is often useful to monitor the relative levels or ratios of transaminases and lactate dehydrogenase to CK levels to assess hepatic toxicity.³⁸ Although pulmonary toxicity from methotrexate can occur, it appears to be a less common problem in myositis than in rheumatoid arthritis and is one of the best agents for treating antisynthetase syndrome, in which lung disease is common.³⁹ Frequently, an empirical trial of decreasing or stopping the dose of methotrexate may be needed to fully assess the possible role of methotrexate as a contributor to new or unexplained signs or symptoms.

Azathioprine

Azathioprine is considered to be as effective as methotrexate in managing corticosteroid-resistant myositis, yet the time to response may be longer than that seen with methotrexate.³⁶ The usual effective dose is 150 to 200 mg/day. Controlled studies suggest that azathioprine plus corticosteroids improves functional ability over corticosteroids alone at 1 and 3 years of follow-up.^{2,40} The most frequent adverse effects are gastrointestinal intolerance, leukopenia, and liver toxicity.

Intravenous gamma globulin

Many studies suggest that intravenous gamma globulin (IVIG) is effective in adults and children with DM and PM.^{3,5,41,42} Because of its rapid onset of action and lack of immunosuppression, some experts suggest that IVIG is most useful as bridging therapy in patients with DM and those with severe myositis or serious infections. Studies regarding the use of IVIG for inclusion body myositis (IBM) have generally not shown effectiveness (see [Table 150.1](#)). Although a variety of doses have been used, a common approach is to give 1 g/kg/day for 2 consecutive days every month for a 3- to 6-month period.

Difficulties associated with the use of IVIG include its high cost, occasional scarcity, tachyphylaxis, and variations in effectiveness from lot to lot. Side effects include headaches, aseptic meningitis, flulike symptoms, rash, changes in blood pressure, and occasional thrombosis related to high blood viscosity. Many of these problems can be minimized by ensuring good patient hydration and slowing the rate of infusion of IVIG.

Mycophenolate

Small case series suggest that some patients with corticosteroid-resistant PM or DM respond to mycophenolate mofetil,^{43,44} although many myologists would use this agent after trials of methotrexate and azathioprine. Common starting doses are 500 mg twice per day, and this dosage may be titrated up to 1 g twice per day. Improvements in CK levels and strength often occur within 1 to 2 months. Side effects include gastric discomfort, diarrhea, cytopenia, and an increased rate of infections.

Cyclophosphamide

Cyclophosphamide appears to be less effective and more toxic than methotrexate or azathioprine when used for myositis, but it may be useful in patients with vasculitis and interstitial lung disease (ILD).^{23,27} Oral doses of 1 to 2 mg/kg/day, not to exceed 150 mg/day, are often prescribed. Monthly pulsed intravenous therapy may be helpful for ILD, as discussed later.

Cyclosporine/tacrolimus

Cyclosporine and tacrolimus work in similar ways to inhibit activation of CD4+ T cells. Small case series suggest that some corticosteroid-resistant adult and juvenile patients may benefit from cyclosporine or tacrolimus therapy.²⁷ Difficulties with the use of these drugs include interactions with grapefruit juice and other agents that influence their metabolism, a wide range of adverse effects, and a narrow therapeutic window that requires careful monitoring of drug levels.

OTHER DRUG THERAPIES

Antimalarials

Based on extensive anecdotal experience, antimalarials have been used for decades in children and adults with primary DM, DM sine myositis, and cancer-associated DM.⁴⁵ About a third of patients with DM may have an exacerbation of their skin disease after initial treatment, but this may resolve over time with continued treatment. Clinical experience suggests that in

patients with IIM, other nonmuscular manifestations of disease, including arthritis, fatigue, and subcutaneous inflammation (panniculitis), may benefit from antimalarial therapy. Most clinical reports involve hydroxychloroquine, usually given at 200 to 400 mg/day, but chloroquine and quinacrine have also been used with some benefit. One small case series suggested that some DM patients whose skin lesions have been unresponsive to a single antimalarial benefit from combination therapy consisting of hydroxychloroquine and quinacrine or chloroquine and quinacrine.⁴⁶

Anti-tumor necrosis factor agents

Infliximab has been reported to benefit some children with DM, as well as some adults with DM and PM; however, open-label trials have not been promising. One open-label trial of infliximab in 13 patients with PM, DM, or IBM resulted in 9 patients completing the 14-week study. Of these, three improved, four were unchanged, and two significantly worsened, thus suggesting to the authors that infliximab is not useful for treatment-resistant myositis.²⁵ Another open-label trial in patients with PM or DM treated with anti-tumor necrosis factor- α (TNF- α) and concurrent methotrexate therapy was discontinued prematurely because of a low inclusion rate and a high dropout rate as a result of disease progression and the development of an infusion reaction.⁴⁷ An open-label trial of etanercept in nine patients with IBM showed no evidence of improvement.²²

Concerns regarding anti-TNF agents as therapy for PM/DM include case reports of the development of myositis during their use for other diseases, as well as exacerbation of myositis after their use for established myositis.⁴⁸ Given the current data, more study is needed to determine the role of anti-TNF agents for myositis.

Rituximab

A number of case reports and case series of adult and children with DM and PM have reported positive responses to rituximab.^{13,49,50} In some cases retreatment has also resulted in positive responses. A recent large placebo phase design clinical trial did not show efficacy based on the primary end point, yet 83% of patients met the definition of improvement suggesting the usefulness of this agent.^{50a} Overall, little toxicity has been reported with this therapy.

Other agents

A variety of other treatments have been reported, usually in small numbers of myositis patients, with limited or no evidence that they are useful. Such therapies include apheresis, with a negative controlled trial in patients with PM/DM⁵¹; fludarabine, with some evidence of response in several patients in a pilot open-label trial of PM/DM⁵²; interferon beta, with two negative trials for IBM^{20,21}; total body irradiation, with several positive and several negative case reports in patients with PM, DM, and IBM; and case reports of responses to autologous stem cell transplantation, thymectomy, chlorambucil, alemtuzumab, extracorporeal photopheresis, or leflunomide for PM or DM.

Few studies have attempted to understand how to best combine the many immunosuppressive agents often used to treat myositis. One open-label trial suggested that combination methotrexate and azathioprine may be of benefit in patients who had not responded adequately to either agent alone.⁸ Given the complementary modes of action of many agents, this should be a promising area of research in the future.

NONMEDICAL TREATMENTS

Patient and family education

Optimal therapy is based on patients thoroughly understanding their disease. Patients and their families should be counseled and educated about myositis. Understanding the social and work environment of patients will also assist in best helping them adjust to their disease. Referrals to local and national myositis patient support groups should be made because they can be invaluable sources of information and support (see [“Additional Resources for Patients and Physicians”](#)).

Rehabilitation

A primary goal of therapy is to optimize the functional capacity of patients.²⁹ Rehabilitation is a critical aspect of this goal, yet it remains underused by most physicians and patients.⁵³ Graded rehabilitation that takes into account

BOX 150.2 AN APPROACH TO REHABILITATION OF PATIENTS WITH MYOSITIS**Acute phase—assess the patient for the possible needs below**

Massage and heat treatment of painful muscles.
 Fit with an appropriate collar for neck support.
 Use a balanced forearm orthosis on the wheelchair so that some independent feeding is possible.
 Support the wrists and ankles with resting splints to prevent flexion contractures.
 Instruct the patient in the use of a long-handled comb and toothbrush and a sponge to assist in self-care.
 Regular evaluations and treatment by a speech and language pathologist arranged as needed.
 Nurses and family should be trained in proper bed positioning, the appropriate position to facilitate feeding and prevent aspiration, techniques to facilitate breathing, and bed-to-chair transfers as needed.

Early recovery phase—assess the patient for the possible needs below

Begin muscle reeducation and strengthening.
 Give instructions in active range-of-motion exercises and begin a few isometric contractions of the major muscle groups (deltoids, biceps, quadriceps, hip abductors/extensors).
 Work on standing at the parallel bars and begin ambulation training.
 Occupational therapy as needed for dressing and bathroom care with appropriate bathroom devices (elevated toilet seat, bars, shower chair, hand-held shower).
 Assess vocational abilities and advise on-the-job retraining if necessary.
 As balance improves and strength becomes good (4/5 range), ambulation with only a straight cane can be initiated; some pelvic lurching may still be present because of gluteus medius muscle weakness, and the gait will be slow; work on negotiating stairs and ramps and practice walking outdoors, as well as car transfers.
 As enzyme levels decrease, increase the isometric exercise program to six contractions of each muscle group daily; pool therapy with range-of-motion and stretching exercises is permitted.
 Help the patient incorporate energy conservation strategies into the day.

Late recovery and chronic phase—assess the patient for the possible needs below

Isotonic exercise with low weights (2 to 4 kg) or a pool.
 Bicycle ergometry without resistance or walking in a pool or swimming.
 Gradual aerobic exercise (starting with 15-minute sessions and increasing to 30-minute sessions three times weekly).

the stage and severity—of the patient's disease is the optimal approach (Box 150.2). Although bed rest may be necessary during periods of severe myositis, even then passive range-of-motion exercises and stretching should be initiated to minimize or prevent the formation of contractures. Massage and heat treatment of painful muscles, collars, splints, or braces for support and assistive devices for self-care are often helpful. As patients respond to treatment, they should increase their activity through four stages: active assisted range-of-motion, followed by isometric, then isotonic, and finally aerobic exercise. If this graded approach is followed, there is little chance of disease flares developing.

ASSESSING DISEASE ACTIVITY AND DAMAGE

An important element in choosing appropriate therapy and monitoring responses to therapy for chronic systemic diseases such as myositis is careful assessment of all the disease manifestations over time. This includes determination of the type and degree of disease activity (evidence of active inflammation that is potentially reversible) and disease damage (persistent changes, including scarring and fibrosis that develop from previous active disease or complications of therapy) in all affected organ systems, and a number of tools have been developed for these purposes.³¹

Evidence of disease activity includes active rash; arthritis; elevation of serum CK, other muscle enzymes, or immunoglobulin levels; and recent alterations in muscle strength or function, energy level, muscle tenderness, dyspnea, or dysphagia. Evidence of disease damage includes joint contractures, muscle atrophy, hyperpigmentation or hypopigmentation, calcifications, and decreased serum creatinine.

The most common way of assessing disease activity and responses to therapy is to monitor serum CK, lactate dehydrogenase, or other muscle enzyme levels and muscle strength by manual muscle strength testing (Table 150.2). Because elevated muscle enzymes do not develop in some patients during periods of active disease and because disease activity in all organ

TABLE 150.2**Manual muscle strength testing grades**

0	No muscle contraction
1 (trace)	Palpable contraction, little or no motion
2 (poor)	Motion possible but not against gravity
3 (fair)	Motion against gravity possible
4 (good)	Motion possible against natural resistance
5 (normal)	Motion possible against considerable manual resistance

systems does not change over time in similar ways, other more comprehensive approaches have recently been developed. One way to systematically assess myositis disease activity and damage is through the use of core set measures and tools validated by the International Myositis Assessment and Clinical Studies Group (IMACS, available at <http://www.niehs.nih.gov/research/resources/imacs/abouttools/index.cfm>).⁵⁴ Although these approaches were developed for use in clinical trials, they also provide a comprehensive and sensitive way of tracking changes in clinical and laboratory parameters over time in the practice setting. The core set disease activity measures are patient and physician global assessment, manual muscle strength testing, serum levels of muscle enzymes, the health assessment questionnaire, and the myositis disease activity assessment tool. Significant clinical improvement can be defined as improvement of 20% or greater in three of any six of these core set measures, with no more than two becoming worse by 25% or greater (which cannot include manual muscle testing to assess strength).⁵⁵ Disease damage over time can be assessed in similar ways with the Myositis Damage Index.

Magnetic resonance imaging (MRI) of the thighs can be useful in long-standing cases to quantitate the degree of disease activity and damage in muscle, skin, and subcutaneous tissue. Bright signals on short tau inversion recovery (STIR) MRI represent increased water content, which is related to active inflammation, whereas bright signals on T1-weighted MRI represent fatty replacement. The T1 image also allows quantitative assessment of the degree of muscle atrophy present.

MANAGEMENT OF EXTRAMUSCULAR MANIFESTATIONS**Interstitial lung disease**

ILD develops in 30% to 40% of patients with PM/DM, is a major cause of morbidity and mortality, and is one of the most difficult myositis manifestations to assess and treat. ILD is most commonly seen in IIM patients with antisynthetase autoantibodies (see Chapter 149), and these patients may be more likely than ILD patients without autoantibodies to respond to therapy. Progression of ILD in patients with myositis may be acute, subacute, or chronic. Various approaches have been reported to be helpful in these patients, including high-dose intravenous corticosteroids, intravenous cyclophosphamide, cyclosporine, and tacrolimus.⁵⁶ Sequential follow-up examinations consisting of pulmonary function testing, high-resolution computed tomography of the chest, and careful monitoring for bacterial and viral infections are essential.

Cardiac involvement

Subclinical cardiac involvement is common with myositis, although it may not come to clinical attention unless symptomatic cardiac failure or arrhythmias occur. If these problems arise, myocarditis should be suspected and may be assessed by clinical measures and evaluation of serum troponin I levels. Because serum troponin T and CK-MB levels can be elevated as a result of activated myoblasts, they are better measures of disease activity than measures of cardiac involvement. Treatment of cardiac manifestations includes supportive care along with corticosteroids and other immunosuppressive therapy, depending on the severity of involvement.

Gastrointestinal involvement

Dysphagia, gastroesophageal reflux, abdominal bloating, and constipation or diarrhea are common problems in patients with myositis.

Severe dysphagia may lead to aspiration and requires careful evaluation and aggressive therapy with pulse corticosteroids, IVIG, and other immunotherapy. Cricopharyngeal myotomy or percutaneous gastrostomy tube feeding may be needed in severe cases.

Reflux esophagitis is a frequent complication with myositis and should be treated by the usual approaches of elevating the head of the bed and prescribing antacids or H₂-receptor antagonists. An unusual but life-threatening complication seen more commonly in children with DM is mucosal ulceration or perforation of the lower gastrointestinal tract from active vasculitis. This can lead to severe hemorrhage and secondary infections and often requires emergency surgery and aggressive treatment with high-dose intravenous corticosteroids, IVIG, and cytotoxic therapy.

Skin involvement

Myositis is associated with a wide variety of cutaneous manifestations that range from asymptomatic rash to life-threatening vasculitis and ulcerations (<http://dermatology-s10.cdlib.org/1502/reviews/photoessay/riderphotos.html>). Many DM skin lesions are photosensitive and respond at least partially to first-line treatments, such as avoidance of ultraviolet radiation and photosensitizers and the use of sunscreens or topical corticosteroids. Antimalarials are often the next therapy to consider for rash that does not respond to first-line treatment. Topical tacrolimus and systemic corticosteroids, methotrexate, mycophenolate, and IVIG have all been reported to be useful in treating the more severe skin lesions of DM.⁵⁷

Calcinosis

The best treatment of calcinosis is prevention through aggressive evaluation and treatment of skin and subcutaneous disease and avoidance of trauma. Once established, no therapies have proved to be effective, although some investigators have proposed the use of calcium channel blockers, vitamin K inhibitors, aluminum hydroxide, or colchicine. In severe cases in which the lesions produce chronic pain or impinge on critical structures, surgical removal may be necessary. When calcinosis lesions push out through the skin surface, they may drain “milk of calcium” and are at risk for infection (<http://dermatology-s10.cdlib.org/1502/reviews/photoessay/rideressay.html>).

Inclusion body myositis

Treatment of IBM is controversial and unsatisfactory. Some investigators do not think that immunosuppressive therapy is helpful for IBM. Nonetheless, anecdotal reports and retrospective reviews of corticosteroid and cytotoxic therapy, a prospective open-label trial of IVIG, and a randomized trial of combination oral methotrexate plus azathioprine versus high-dose methotrexate with leucovorin rescue all provide limited evidence that the rate of functional deterioration may be decreased or stabilized and strength

improved in a subset of patients with IBM (see [Table 150.1](#)). Characteristics that may identify those with IBM more likely to respond to immunosuppressive treatment are serum CK levels greater than five times the upper limit of normal, active inflammation noted on MRI or muscle biopsy, disease overlapping with other connective tissue diseases, and the presence of autoantibodies. Physical therapy and exercise, however, play the most important roles in the long-term care of patients with IBM.

FUTURE DIRECTIONS

Appropriately powered and long-term multicenter trials using validated outcome measures are needed to define the best treatment options for the IIMs. Given the growing number of distinct myositis phenotypes, each with probably different pathogenesis and response to therapy, it will be increasingly important to study these well-defined subgroups individually. Recent advances in genetics and molecular biology, the initial definition of environmental risk factors for myositis, novel therapies for other diseases, and new international collaborations and standards all promise the hope of not only inducing prolonged remissions but even the possibility of preventing the development of some cases of myositis in the future.

ADDITIONAL RESOURCES FOR PATIENTS AND PHYSICIANS

- The Myositis Association, www.myositis.org/—The largest myositis patient support group with annual meetings, newsletters, updates of recent research, and descriptions of ongoing clinical trials and research grants
- Muscular Dystrophy Association, www.mda.org/—A patient support group with a network of clinics, genetic testing facilities, and a helpful website
- Myositis Autoantibody Testing, Oklahoma Medical Research Foundation, Oklahoma City, <http://omrf.org/research-faculty/core-facilities/myositis-testing/>—Provides validated commercial testing for myositis autoantibodies
- Neuromuscular Disease Center, Washington University, St. Louis, <http://neuromuscular.wustl.edu/>—A clinically useful website for the differential diagnosis of muscle weakness with many informative tables and pathologic images
- International Myositis Assessment and Clinical Studies group (IMACS), <http://www.niehs.nih.gov/research/resources/imacs/>—a multidisciplinary consortium of experts interested in the assessment, treatment, and study of all forms of myositis
- <http://clinicaltrials.gov/>—A registry of federally and privately supported clinical trials conducted in the United States and around the world

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Metabolic, drug-induced, and other noninflammatory myopathies

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- The differential diagnosis of polymyositis and other inflammatory myopathies includes metabolic disorders and drug- or toxin-induced myopathies in addition to endocrine disorders, muscular dystrophies, and infectious etiologies.
- The primary metabolic myopathies are inherited disorders of muscle glycogen, lipid, or mitochondrial metabolism; they may cause episodic exercise intolerance along with myoglobinuria or progressive proximal muscle weakness.
- Drugs and toxins can induce myopathies through direct toxic effects on muscle, induction of autoimmune-mediated inflammatory myopathy, or metabolic derangements.

METABOLIC MYOPATHIES

Muscle contraction and relaxation are energy-dependent processes that derive energy from the hydrolysis of adenosine triphosphate (ATP). The supply of ATP is crucial, and several pathways have evolved, with each supplying energy under specific conditions to ensure a continuous supply of energy under a variety of circumstances. The processes responsible for maintaining a continual supply of ATP include glycogen and glucose metabolism, oxidative phosphorylation, the creatine kinase (CK) reaction by which phosphocreatine is converted to ATP, the purine nucleotide cycle, and lipid metabolism.¹

Glycogen/glucose metabolism (Fig. 151.1)

Anaerobic glycolysis is the main metabolic pathway used in the setting of limited oxygen supply during exercise. It is used during high-intensity, sustained, isometric muscle activity.¹ It is inefficient from an energetic standpoint and produces only two ATP molecules per glucose molecule, which is 19 times less than the full energy potential of a glucose molecule. Despite its inefficiency, it is a rapid process, approximately 100 times faster than oxidative phosphorylation. The final step in the pathway is conversion of pyruvate to lactate, which leads to accumulation of lactic acid.

Aerobic glycolysis is more efficient; however, the price needed to maintain this system is high: it requires functional mitochondria, a functioning circulatory system with a constant oxygen supply, and the ability to eliminate carbon dioxide. It is used as the main supply of energy during sustained, dynamic forms of exercise such as walking, but if short bursts of energy are needed, the system is often overwhelmed and anaerobic glycolysis takes over.

The phosphocreatine pathway acts as a “buffer” of ATP stores by limiting changes in ATP and allowing rapid formation of ATP during high-intensity exercise. The amount of phosphocreatine in muscle is small, and it is not able to sustain activity independently.

ATP can also be produced by the adenylate kinase reaction, which catalyzes the conversion of two adenosine diphosphate (ADP) molecules into one ATP and one adenosine monophosphate (AMP); however its clinical significance is limited.

The oxidative phosphorylation system (Fig. 151.2), present in the inner mitochondrial membrane, is the principal source of energy in muscle and other tissues. The flow of electrons from the reduced form of nicotinic adenine dinucleotide (NADH) to the last enzyme in the electron transport chain, cytochrome-c oxidase (complex IV), releases energy that is used in the synthesis of ATP.

Lipid metabolism

The major energy substrates used by resting muscle are fatty acids derived from very-low-density lipoprotein (VLDL) or from stored triglycerides. The metabolism of short-, medium-, and long-chain fatty acids is slightly different, yet these biochemical details have great clinical relevance.

Long-chain fatty acids are the major source of energy for prolonged, low-intensity exercise lasting longer than 40 to 50 minutes.¹ Unlike short- and medium-chain fatty acids, they are not able to freely cross the mitochondrial membrane and need to undergo a series of modifications. The first step is their conversion to coenzyme A (CoA) thioesters, which are then linked to carnitine by the enzyme carnitine palmitoyltransferase I (CPT-I), located on the inner side of the outer mitochondrial membrane. A translocase then transfers the acylcarnitine product across the inner mitochondrial membrane. Once in the mitochondrial matrix, CPT-II is required to convert the acylcarnitine molecule back into a CoA thioester and carnitine. Only then can the long-chain fatty acid derivative enter the β -oxidation pathway.

Short-chain and medium-chain fatty acids have a much less convoluted metabolic fate because they cross the mitochondrial membranes without difficulty and enter the β -oxidation pathway directly after activation to CoA thioesters. With each cycle of β -oxidation, a two-carbon fragment is cleaved and one acetyl-CoA molecule is generated. The acetyl-CoA then enters the citric cycle.

Part of the acetyl-CoA produced in the liver is used for ketone production at baseline. During periods of carbohydrate deprivation or fasting, ketone production is upregulated and it becomes an important source of energy for many tissues, including the brain.

General principles

The substrate used by muscle depends on the type of activity. Fatty acids are the predominant energy source at rest, whereas intense bursts of exercise will activate anaerobic glycolysis.² Mild exercise will initially use aerobic glycolysis but, if sustained, will gradually switch to fatty acid oxidation as the main energy source after 4 hours. Submaximal exercise of low intensity will use both glucose and fatty acids, and high-intensity exercise will use mainly aerobic glycolysis.^{3,4}

The metabolic myopathies are characterized, in general, by dynamic rather than static findings. This means that the symptoms and signs are usually triggered by activity. The most common phenotypes are exercise intolerance, exercise-induced weakness and muscle cramps, and only rarely, progressive, fixed weakness.¹ Importantly, patients with exercise-induced symptoms may not have any evident signs of muscle disease, such as weakness or muscle atrophy, and may have normal findings on electromyography (EMG) and routine laboratory values.

The diagnostic approach to the metabolic myopathies includes blood tests (serum CK [Box 151.1], lactate, ammonia, acylcarnitine, and amino acid profile), urine tests (organic acids and myoglobin), muscle biopsy (light and electron microscopy and biochemical assays), EMG, exercise testing, genetic testing, and magnetic resonance imaging (MRI).⁵ Before proceeding with expensive or invasive diagnostic modalities such as genetic testing and muscle biopsy, simple exercise tests may be used for screening purposes.

The ischemic forearm exercise test is a highly sensitive and specific diagnostic screening test for muscle glycolytic disorders. The protocol involves inflating a blood pressure cuff on the upper part of the arm to 20 mm Hg higher than systolic blood pressure. The patient is given a hand-grip dynamometer and told to squeeze it at maximum strength for 1 second followed by 1 second of rest. The cuff is released immediately after exercise. Blood samples from the tested arm are drawn at rest, during exercise, and

PATHWAYS OF CYTOSOLIC GLYCOGEN METABOLISM

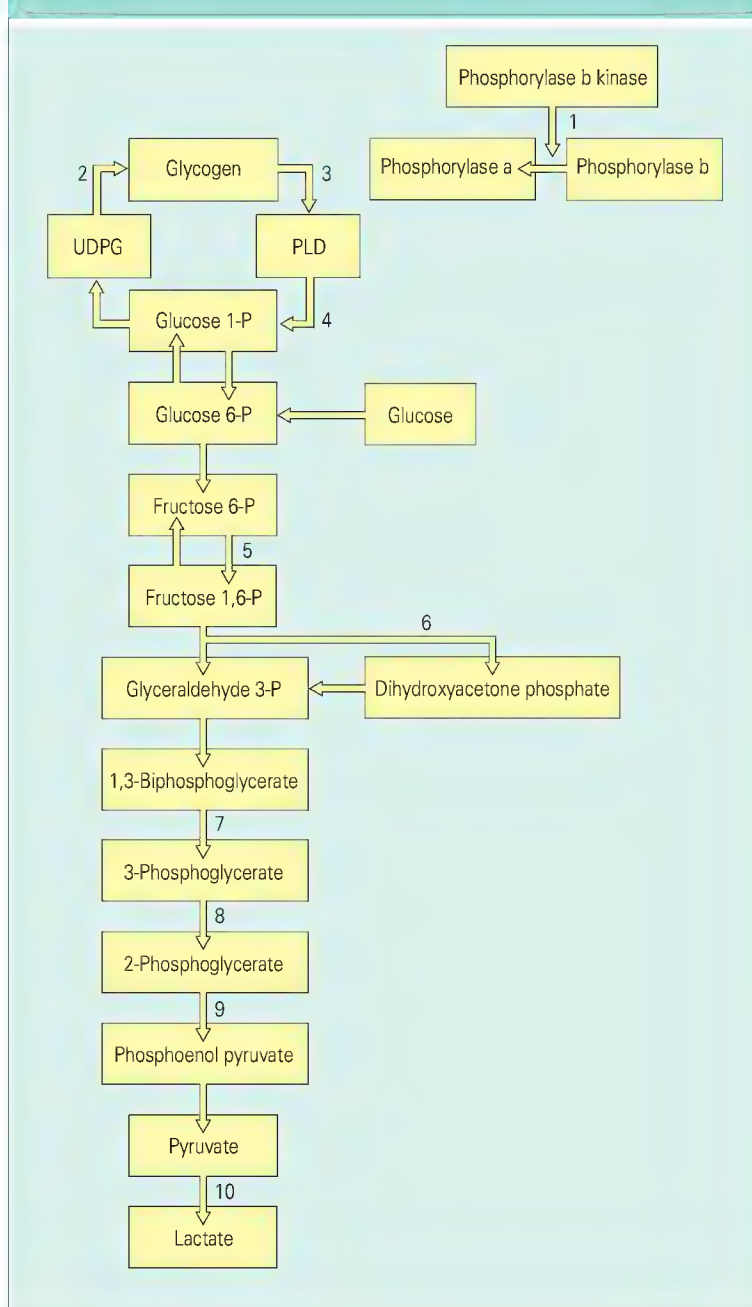


Fig. 151.1 Deficiencies in the numbered enzymes are recognized to cause a glycogen storage disease: 1, phosphorylase b kinase; 2, brancher enzyme; 3, myophosphorylase; 4, debrancher enzyme; 5, phosphofructokinase; 6, aldolase A; 7, phosphoglycerate kinase; 8, phosphoglycerate mutase; 9, β -enolase; 10, lactate dehydrogenase. Note that acid maltase is not included because it is a lysosomal enzyme. P, phosphate; PLD, phosphorylase limit dextran; UDPG, uridine diphosphate glucose.

during recovery, and blood levels of lactate and ammonia are measured.⁶ Normal subjects exhibit a threefold to fivefold rise in lactate and ammonia levels within 5 minutes after the end of the exercise, with a return to baseline about 10 to 15 minutes after cessation of the test.

If the lactate and ammonia responses are normal and suspicion for an underlying metabolic or mitochondrial myopathy persists, the next screening step is an aerobic exercise test. Patients with mitochondrial myopathies may have elevated resting lactate levels, but this finding is not universal. Cycle or treadmill ergometry is used to assess the cardiorespiratory response, arteriovenous oxygen difference, and lactate levels. Classically, patients with mitochondrial myopathies exhibit impaired oxygen extraction by the muscle, elevated lactate levels, and an intense cardiorespiratory response to exercise.⁷

BOX 151.1 CAUSES OF ELEVATED SERUM CREATINE KINASE LEVELS IN PATIENTS WITHOUT OVERT MUSCLE DISEASE

- Prolonged physical exercise
- Black race
- Frequent muscle trauma
- Sustained alcohol use
- Hypothyroidism
- Drugs causing subclinical myopathy
- Inflammatory myopathy
- Metabolic myopathy
 - McArdle disease
 - Acid maltase (α -glucosidase) deficiency
 - Phosphorylase b kinase
 - Periodic paralysis
 - Mitochondrial myopathy
- Muscular dystrophy
 - Dystrophinopathy
 - Caplain-3 gene mutation
 - Dysferlin gene mutation
 - Fukutin-related protein mutation
 - Malignant hyperthermia gene

The major categories of metabolic myopathies are defects in glucose/glycogen metabolism, disorders of fatty acid oxidation, mitochondrial diseases, and myoadenylate deaminase deficiency.⁵

Defects in glucose/glycogen metabolism

Depending on the specific enzyme deficiency, defects in glucose and glycogen metabolism can result in protean manifestations ranging from lethal, multiorgan involvement in infancy to isolated, dynamic or static muscle weakness in adulthood.

Patients with glycogen storage diseases affecting the muscles usually complain of random muscle aches and cramps at rest and easy fatigability with exertion and may occasionally have acute rhabdomyolysis induced either by brief, intense isometric exercise or by less intense but sustained dynamic exercise.⁸ Progressive muscle weakness mimicking polymyositis may occur. Serum CK levels may be elevated, EMG and histologic evaluation show myopathy with no inflammation, and even the Peter and Bohan criteria for polymyositis may be fulfilled.⁹ See Table 151.1 for an overview of glycogen storage diseases affecting skeletal muscle.

Myophosphorylase deficiency (McArdle disease, glycogenosis type V)

McArdle disease is an autosomal recessive disease in which phosphorylase, the enzyme catalyzing the removal of 1,4-glucosyl residues from the outer branches of the glycogen molecule, is deficient. It is the most common disorder of skeletal muscle carbohydrate metabolism and one of the most frequent genetic myopathies.²

Onset occurs in the second or third decade with exercise intolerance and muscle cramps. Half of the patients describe episodes of burgundy-colored urine following intense exercise (as a result of rhabdomyolysis). Patients have no difficulty performing moderate exercise at their own pace even for long periods. Crises are induced by brief, intense exercise episodes such as sprinting, as well as by less intense activities such as stair climbing for longer periods. Acute crises are characterized by muscle cramps accompanied by a certain degree of rhabdomyolysis. The pathognomonic sign of McArdle disease is the “second wind” phenomenon, defined as marked improvement in exercise tolerance about 10 minutes into aerobic exercise involving large muscles.¹⁰ During the early phase of moderate exercise, glycogen and anaerobic glycolysis are the main source of energy. After 10 to 15 minutes of moderate to intense exercise, fatty acid metabolism becomes the main energy source, thus leading to a second-wind phenomenon.

Serum CK levels are usually high, even between acute crises. The forearm ischemic test is an excellent screening test and shows a *flat venous lactate curve* with exaggerated elevations in blood ammonia in McArdle disease (Table 151.2). There is a common misconception in the literature regarding the specificity of this test. McArdle disease is, in fact, indistinguishable from phosphofructokinase or debrancher enzyme deficiencies based on results of the forearm ischemic test, and hence diagnostic confirmation is always required. EMG shows myotonic discharges, fibrillations, and positive waves.¹¹ Focal subsarcolemmal and intermyofibrillar accumulations of

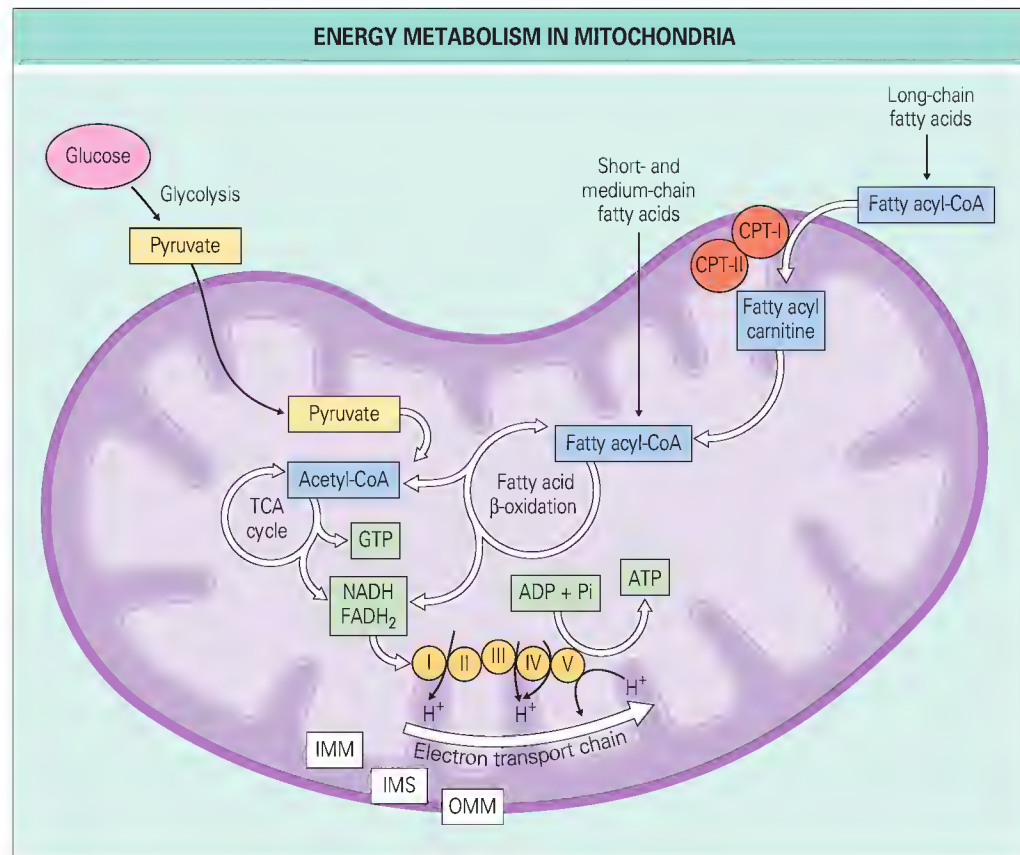


Fig. 151.2 Oxidative metabolism of both glucose and free fatty acids depends on converging enzymatic pathways in the cellular mitochondria. The key metabolic intermediate is acetyl coenzyme A (acetyl-CoA), derived both from pyruvate and as an end product of the mitochondrial β -oxidation of fatty acids. Pyruvate is generated from the glycolytic pathway in the sarcoplasm. It diffuses across the mitochondrial membrane and is then converted to acetyl-CoA by pyruvate dehydrogenase. The fatty acids are activated to fatty acyl-CoA derivatives by using adenosine triphosphate (ATP) as the energy source. This activation step occurs within the mitochondrion for short- and medium-chain fatty acids and in the sarcoplasm for long-chain fatty acids. Short- and medium-chain fatty acids enter the mitochondrion by passive diffusion, and long-chain fatty acids enter by facilitated transport via the carnitine shuttle. The carnitine shuttle transports long-chain fatty acids across the outer and inner mitochondrial membranes (OMM and IMM). The long-chain fatty acids are first transferred to carnitine by the enzyme carnitine palmitoyltransferase I (CPT-I), located in the outer membrane space. The fatty acid is then transferred into the mitochondrial matrix by a carnitine acylcarnitine translocase (not shown) located in the IMM. A second enzyme in the IMM, carnitine palmitoyltransferase II (CPT-II), regenerates the fatty acyl-CoA with the release of free carnitine. Within the mitochondrion, the fatty acyl-CoA is oxidized in a four-step cycle of reactions (β -oxidation) in which the β -carbon is oxidized to a ketone followed by cleavage between the α - and β -carbons to yield acetyl-CoA and a fatty acyl-CoA with two fewer carbon atoms. The four enzymes in this cycle include one of three acyl-CoA dehydrogenases (specific for short-, medium-, and long-chain fatty acyl-CoA), an enoyl-CoA hydratase, an oxidized nicotinamide adenine dinucleotide (NAD⁺)-dependent dehydrogenase, and a thiolase. Each cycle of β -oxidation yields 1 mole each of acetyl-CoA, reduced flavin adenine dinucleotide (FADH₂), and reduced NAD (NADH); for a 16-carbon fatty acid such as palmitate the cycle is repeated seven times, which yields 8 moles of acetyl-CoA and 7 moles of FADH₂ and NADH. Acetyl-CoA is oxidized in the tricarboxylic acid (TCA) cycle (Krebs cycle), a series of eight enzymatic reactions. Each mole of acetyl-CoA yields 3 moles of NADH and 1 mole of FADH₂. These reduced nucleotide coenzymes subsequently transfer electrons to molecular oxygen via the electron transport chain and in the process generate ATP from adenosine diphosphate (ADP). The electron transport chain consists of five large protein complexes (I to V) located in the IMM and two small independent components, cytochrome c and ubiquinone. Electrons move sequentially from one protein complex to the next (in the order of I to V) down an energy gradient. In the process, protons are pumped by complexes I, III, and IV across the IMM into the intermembrane space (IMS), thereby creating a membrane potential. GTP, guanosine triphosphate.

normally structured glycogen are seen in muscle biopsy specimens, but histochemical staining for phosphorylase reveals no activity.⁸

No specific treatment is available. Avoiding strenuous exercise is imperative. Glucose intake before exercise may diminish symptoms because the metabolic block is upstream of glucose metabolism.¹² This intervention does not lead to consistent improvement and almost invariably results in weight gain. A high-protein diet and creatine supplementation may increase muscle endurance.^{13,14}

Phosphofructokinase deficiency (glycogen storage disease type VII, Tarui disease)

Tarui disease is an autosomal recessive disease in which the key regulatory enzyme of the glycolytic pathway is deficient. Because of phosphofructokinase deficiency, the muscle is unable to use glucose as an energy source, so glucose intake in these patients leads to an “out-of-wind” phenomenon. The clinical features are similar to those of McArdle disease: muscle aches and cramps induced by exercise, as well as episodes of rhabdomyolysis. The characteristic features of Tarui disease include earlier onset, with the first symptoms occurring in childhood and more severe attacks frequently being associated with systemic symptoms such as nausea and vomiting. A

compensated hemolytic anemia is characteristic and occurs secondary to decreased erythrocyte 2,3-bisphosphoglycerate, which leads to a shortened erythrocyte life span.¹⁵ Serum CK is usually elevated between episodes. The forearm ischemic test shows no lactate elevation. Muscle biopsy demonstrates accumulation of normal glycogen. There is no effective therapy. A high-protein diet and aerobic conditioning have been used in case reports with variable success.¹⁶

Debrancher deficiency (Cori-Forbes disease, glycogenosis type III)

This is yet another autosomal recessive disease characterized by deficiency of the enzyme responsible for removal of the residual stubs of glycogen after digestion by phosphorylase. It is usually classified as a hepatic glycogenosis, but there are two subtypes: type IIIa, in which the enzyme deficiency affects both the liver and muscle, and type IIIb, in which only the liver is involved and debrancher activity in skeletal muscles is normal. The two subtypes can easily be distinguished with the forearm ischemic test, in which abnormal results are produced in type IIIa but not in type IIIb.

In contrast to McArdle and Tarui disease, muscle weakness in type IIIa is minimal in childhood and tends to become severe after the third or fourth

■ **TABLE 151.1**
Glycogen storage diseases affecting skeletal muscles

Type	Defect	Clinical features	Laboratory findings	Treatment
Type II (Pompe disease)	Lysosomal acid maltase	Proximal muscle weakness with pelvic girdle, paraspinal, and diaphragmatic weakness	↑ CK, ↑ AST Decreased or absent acid maltase activity in muscle or cultured skin fibroblasts	Enzyme replacement therapy with αglucosidase alfa, high-protein diet
Type V (McArdle disease)	Myophosphorylase deficiency	Exercise intolerance, muscle cramps, dark red urine after intense exercise Usually occurs in the 2nd or 3rd decade	Myoglobinuria, ↑ CK at rest and after exercise, ↑ NH ₃ and ↑ uric acid with exercise, abnormal enzyme assays in muscles	Ingestion of sucrose, glucose, or fructose immediately before exercise Low-dose creatine supplementation
Type VII (Tarui disease)	Phosphofructokinase	Same as McArdle disease plus severe exercise intolerance, compensated hemolytic anemia, acute exercise intolerance after a carbohydrate load	↑ CK and ↑ bilirubin, reticulocytosis, hyperuricemia Abnormal enzyme assays in muscles	Avoid strenuous exercise for prevention of muscle cramps and myoglobinuria
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	Same as McArdle disease plus hemolytic anemia and CNS dysfunction	↑ CK (not always), abnormal enzyme assays in muscles	Avoid strenuous exercise for prevention of muscle cramps and myoglobinuria
Lactate dehydrogenase deficiency	Lactate dehydrogenase, M subunit	Same as McArdle disease plus erythematous rash and obstetric difficulties because of uterine stiffness	↑ CK (not always)	Avoid strenuous exercise for prevention of muscle cramps and myoglobinuria
Fructose-1,6-biphosphate aldolase A deficiency	Fructose-1,6-biphosphate aldolase A	Same as McArdle disease plus hemolytic anemia	↑ CK (not always)	Avoid strenuous exercise for prevention of muscle cramps and myoglobinuria
Pyruvate kinase deficiency	Pyruvate kinase	Static symptoms, fixed muscle weakness, cramps	↑ CK (not always)	Avoid strenuous exercise for prevention of muscle cramps and myoglobinuria
Muscle phosphorylase kinase deficiency	Muscle phosphorylase kinase	Same as McArdle disease with muscle atrophy	↑ CK (not always)	Avoid strenuous exercise for prevention of muscle cramps and myoglobinuria

AST, aspartate aminotransferase; CK, creatine kinase; CNS, central nervous system; NH₃, ammonia.
Adapted from Khan M. Carbohydrates. In: McPherson R, editor. *Henry's clinical diagnosis and management by laboratory methods*. 22nd ed. Philadelphia: Saunders; 2011, p. 1543.

■ **TABLE 151.2**
The forearm ischemic test in metabolic myopathies

	Lactate	Ammonia
Cori disease (GSD type III, liver and muscle involvement)	Impaired response	Normal or enhanced response
Cori disease (GSD type III, liver involvement only)	Normal	Normal
McArdle disease (GSD type V)	Severely impaired response	Normal or enhanced response
Tarui disease (GSD type VII)	Severely impaired response	Normal or enhanced response
Myoadenylate deaminase deficiency	Reduced response	Severely impaired response

GSD, glycogen storage disease.

decade. The weakness is static and additive. Rarely, exercise intolerance may be present.¹⁷ Patients generally have elevated transaminase levels at rest and are at high risk for liver failure, cirrhosis, and hepatocellular carcinoma.¹⁸ The serum CK level is usually elevated. EMG shows myopathy, whereas muscle biopsy specimens show free glycogen accumulation. No effective treatment is available. A high-protein diet is commonly recommended but has not been proved to be of consistent benefit.¹⁴

Acid maltase deficiency (glycogenosis type II, Pompe disease)

In contrast to the other glycogenosis just described, Pompe disease is an autosomal recessive deficiency of the lysosomal enzyme acid maltase that leads to intralysosomal accumulation of glycogen in various tissues.¹⁹ In its infantile form it is universally fatal. In the adult form it may have an onset between the second and sixth decade with progressive, proximal weakness that may mimic polymyositis.²⁰ There is a wide range of phenotypic variability between these two forms. The serum CK level is elevated in all cases. There is no elevation in lactate levels with the forearm ischemic test, and EMG shows evidence of myopathic discharges with occasional myotonic

and complex repetitive discharges.⁸ Muscle biopsy shows periodic acid–Schiff–positive vacuolar myopathy with glycogen storage within lysosomes. Muscle acid maltase activity is decreased to less than 10% of normal. Enzyme replacement with recombinant human α-glucosidase has had some success in treating the infantile form. In adults, benefits have been observed with a high-protein and low-carbohydrate diet.²¹

Fatty acid oxidation disorders

Although these disorders have many overlapping features, three predominant phenotypes can be recognized: hepatic, cardiac, and muscular. A detailed discussion of the first two is beyond the scope of this chapter. The muscle phenotype is characterized by hypotonia and recurrent episodes of rhabdomyolysis. Muscle pain and myoglobinuria are the usual initial signs and are characteristically induced by infection, general anesthesia, or a low-carbohydrate, high-fat diet.²² Patients have no muscle cramps or contractions, and there is no second-wind phenomenon.¹

The major disorders of lipid metabolism that are manifested as isolated myopathy include (1) CPT-II deficiency, (2) very-long-chain acyl-CoA

dehydrogenase (VLCAD) deficiency, and (3) long-chain acyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiency.²³

Carnitine palmitoyltransferase II deficiency

CPT-II deficiency is the most prevalent disorder of lipid metabolism and the most common overall cause of hereditary, recurrent myoglobinuria.²⁴

CPT-II is located in the inner mitochondrial membrane and has the role of transporting long-chain fatty acids from the cytosolic compartment to the mitochondrial matrix so that they can undergo β -oxidation. A wide spectrum of phenotypes is noted in CPT-II deficiency, depending on the severity of the mutation.²⁵ Patients are asymptomatic between episodes. Symptomatic episodes usually develop after prolonged exertion (typically longer than 30 minutes), and patients tolerate brief, intense isometric exercise without difficulty. The typical symptoms and signs of CPT-II deficiency consist of myalgia, cramps, muscle stiffness and tenderness, weakness, and occasionally, myoglobinuria.²⁶ A second-wind or out-of-wind phenomenon is not seen. Similar crises may be induced by stress, fasting, viral infections, fever or exposure to cold, general anesthesia, use of nonsteroidal antiinflammatory drugs, and high doses of diazepam.⁸

A common laboratory finding that is used as a screening test in symptomatic patients is decreased total serum carnitine with an increased acylcarnitine fraction (elevated C16, C18:1, and C18:2). Findings on EMG and the ischemic forearm exercise test are normal. The diagnosis can be confirmed by whole blood DNA analysis, which detects known mutations in approximately 80% of patients.²⁷

The mainstay of treatment is lifestyle changes, which include avoiding prolonged aerobic exercise (longer than 30 minutes), prolonged fasting, and cold exposure, as well as specific dietary requirements, including the use of a high-carbohydrate, low-fat, low-protein diet along with extra carbohydrate intake before sustained exercise.²⁸

Very-long-chain acyl-CoA dehydrogenase deficiency

VLCAD deficiency involves the first step in the fatty acid oxidation of long-chain acyl-CoA intermediates of 20 to 12 carbons in length, thus affecting tissues dependent on fatty acid oxidation for cellular energy production, including the liver, heart, and skeletal muscle. The first symptoms usually occur in the neonatal period and consist of hypoglycemia and irritability. Affected patients have a high risk for recurrent rhabdomyolysis with exercise or other forms of stress, including illness. Dicarboxylic aciduria is universally present. The abnormal acylcarnitine profile is dominated by 5-cis-tetradecenoylcarnitine (C14:1).²⁸ Treatment is based on restriction of long-chain fatty acids in the diet, accompanied by medium-chain triglyceride supplementation.

Long-chain acyl-CoA dehydrogenase deficiency and trifunctional protein deficiency

LCHAD resides in a TFP bound to the inner mitochondrial membrane, along with 2-enoyl-CoA hydratase and 3-ketoacyl-CoA thiolase. Isolated LCHAD deficiency is a common fatty acid oxidation disorder characterized by long-term complications caused by cardiomyopathy, neuropathy, and retinopathy, with a high risk for rhabdomyolysis associated with stress or exercise.²⁹ The diagnosis is made by finding elevated hydroxyl long-chain acylcarnitines (OH-C16, OH-C18:1, and OH-C18:2) in the acylcarnitine profile.²⁸ Enzyme and mutation testing will differentiate isolated LCHAD deficiency from TFP deficiency.

TFP deficiency is more severe, with a high risk for early mortality.²⁹ It seems to be the only fatty acid oxidation disorder in which blood lactate levels are consistently elevated even when the patient is asymptomatic. Clinical features include hypoglycemia, hypotonia, dilated cardiomyopathy in the setting of hydroxydicarboxylic aciduria, and a normal blood acylcarnitine profile.²⁸ Because of their systemic manifestations, LCHAD and TFP deficiencies are unlikely to be confused with the inflammatory myopathies.

Mitochondrial myopathies

This clinically heterogeneous group of disorders results from impairment of oxidative phosphorylation. It has a prevalence of 9.2 per 100,000, which makes it one of the most common inherited neuromuscular disorders.³⁰ Primary mitochondrial myopathies may occur as a result of mitochondrial or nuclear DNA mutations. Those related to mitochondrial DNA mutations are inherited through maternal transmission and become apparent in late childhood or adult life. A smaller number are related to nuclear genes that encode proteins involved in the oxidative phosphorylation pathway, and they are manifested in early childhood. Secondary mitochondrial myopathies are caused by toxins, including zidovudine and clofibrate.

Clinically, they are well-defined syndromes associated with multisystem involvement and are not likely to be confused with the inflammatory myopathies.³¹ Mitochondrial myopathies include Kearns-Sayre syndrome; chronic progressive external ophthalmoplegia (CPEO); mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS); Leber hereditary optic neuropathy (LHON); neuropathy, ataxia, retinitis pigmentosa (NARP); myoclonic epilepsy with ragged red fibers (MERFF); mitochondrial neurogastrointestinal encephalomyopathy; and autosomal recessive cardiomyopathy-ophthalmoplegia.

An isolated mitochondrial myopathy may be accompanied by mild proximal limb weakness. Exercise intolerance marked by premature fatigue, headaches, nausea, and vomiting after submaximal exercise may be seen. Symptoms are worsened by fasting, minor illness, and stress.

The mitochondrial metabolic test battery includes CK, lactate and pyruvate, plasma carnitine, blood and urine amino acids, urine organic acids, and cerebrospinal fluid lactate and pyruvate.³² Fasting serum lactate levels are elevated in 70% of patients. The normal lactate-pyruvate ratio (<20:1) is increased. Serum CK is usually normal or mildly elevated. Carnitine levels are decreased with a relative increase in acylcarnitine levels. Muscle biopsy is often required for diagnosis. Histopathologic evaluation reveals characteristic ragged red fibers on Gomori trichrome stain (subsarcolemmal and intermyofibrillar accumulation of mitochondria that appear as bright red masses against the background of blue myofibrils).³² Confirmation of the diagnosis is achieved by molecular genetic testing for mutations most likely thought to be present based on the clinical and laboratory features. Treatment is mainly symptomatic, empirical, and palliative.³³

Myoadenylate deaminase deficiency

AMP deaminase 1 catalyzes the conversion of AMP to inosine monophosphate in skeletal muscle and plays an important role in the purine nucleotide cycle. Deficiency of this enzyme is seen in 2% of muscle biopsy specimens regardless of the indication for biopsy, and it is also found in 2% of healthy, white individuals.³⁴ The clinical manifestation of myoadenylate deaminase deficiency is thus heterogeneous, and it is most commonly asymptomatic. When symptomatic, exercise-induced fatigue, cramps, and myalgia are most common. Occasionally, myoglobinuria and rhabdomyolysis may occur after vigorous exercise. An increased serum creatine kinase level is seen in less than half of affected patients. The forearm ischemic test is highly sensitive and specific for the diagnosis of myoadenylate deficiency. AMP deaminase is the major ammonia-producing enzyme in muscle, so a flat ammonia response accompanied by a rise in plasma lactate is considered sufficient to ensure a reliable diagnosis.³⁵ Findings on EMG are usually normal, with minor abnormalities reported in a small subset of patients. The diagnosis can be confirmed by histochemical stains or enzymatic assays. Myoadenylate deaminase deficiency can subsequently be confirmed in muscle biopsy specimens by histochemical stains or direct enzymatic assay.

DRUG- AND TOXIN-INDUCED MYOPATHIES

A drug-induced myopathy is defined as an acute or subacute occurrence of myopathic symptoms, such as muscle weakness, myalgia, CK elevation, or myoglobinuria, in patients without muscle disease during or after exposure to therapeutic doses of certain drugs. Discontinuation of the offending agent leads to resolution of the symptoms in almost all cases.

The classification of drug- and toxin-induced myopathies according to the type of injury includes the following³⁶:

1. Necrotizing myopathy—the prototype of drug-induced muscle injury. Muscle biopsy specimens are characterized by widespread necrosis with macrophage invasion. Inflammatory infiltrates are not seen. The typical example is statin-induced myopathy.
2. Inflammatory myopathy, which is indistinguishable histologically from polymyositis. It can be caused by statins, interferon alfa, or intramuscular injections of genes.
3. Thick filament loss myopathy. Critical care myopathy is the classic example.
4. Type II muscle fiber atrophy. This is the underlying abnormality in steroid-induced myopathies.
5. Mitochondrial myopathies. Ragged red, cyclooxygenase-negative fibers are seen on histologic examination, as well as increased lipid accumulation. Zidovudine is the typical representative.
6. Lysosomal storage myopathy, which is caused by the accumulation of amphiphilic drugs in lysosomes. Hydroxychloroquine is the classic representative.

7. Antimicrotubule myopathy, which involves disruption of the cytoskeleton. Microtubule inhibition is the main mechanism of action of colchicine.
8. Fasciitis, which is of historical interest because its main representatives include toxic oil syndrome and L-tryptophan. Clinically, these disorders mimic eosinophilic fasciitis.

Statins

Statins are a class of lipid-lowering agents that inhibit hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase (HMGCR). Statin myopathy is defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to more than 10 times the upper limit of normal. According to the degree of muscle toxicity that they induce, the most myotoxic statin was cerivastatin, which was withdrawn from the market, followed by simvastatin, lovastatin, pravastatin, atorvastatin, and fluvastatin.³⁷

Several clinically relevant scenarios may occur with statin therapy:

1. Asymptomatic elevation of CK up to 10 times the upper normal limit is the most common finding. Based on expert opinion, in this scenario no further changes in treatment are needed as long as the patient remains asymptomatic and the CK elevation remains stable.
2. Myalgia may occur in up to 25% of patients and usually resolves after switching to a different statin or discontinuing therapy.
3. Muscle weakness with CK elevation. Besides the well-described myopathies, an intriguing recent discovery of antibodies against HMGCR in a subset of patients with necrotizing myopathy³⁸ highlighted the statins as the probable culprit of an immune-mediated necrotizing myopathy. If the myopathic symptoms and elevated CK persist with discontinuation of statin therapy, the possibility of an immune-mediated necrotizing myopathy must be considered. Nevertheless, this is a diagnosis of exclusion, and a meticulous workup for autoimmune, metabolic, paraneoplastic, or drug-induced myopathy should be pursued.
4. Rhabdomyolysis is a rare, but serious event characterized by highly elevated CK levels, myoglobinuria, and weakness. It may occur anytime during drug treatment, and the risk may be increased by a number of factors, including age, drug interactions, and renal dysfunction. The most important drug interactions that need to be avoided include the use of statins with amiodarone, cyclosporine, gemfibrozil, macrolides, and azoles.³⁹ Pravastatin is metabolized by a different cytochrome P450 enzyme and seems to be the safest in this group, alongside atorvastatin.

Colchicine

Myopathy, peripheral neuropathy, and rhabdomyolysis have been reported in patients taking colchicine. The myotoxicity of colchicine is thought to be related to disruption of the microtubular cytoskeletal network, which results in intracellular accumulation of autophagic vacuoles. This myopathy may mimic polymyositis and classically occurs in patients taking colchicine for prolonged periods, with proximal muscle weakness and elevated CK developing insidiously. Muscle biopsy specimens are characterized by a vacuolar myopathy without prominent necrosis or inflammation. The myopathy resolves fully 3 to 4 weeks after discontinuing use of the drug. An acute myopathy has also been described in the literature but is very rare. The risk for colchicine myopathy is increased by age, duration of therapy, drug interactions (cyclosporine), and inappropriate dosing in patients with renal insufficiency.

Hydroxychloroquine

Prolonged use of high-dose chloroquine or hydroxychloroquine may lead to a reversible myopathy. Clinically and histologically, this myopathy resembles acid maltase deficiency.³⁶ Progressive weakness and atrophy of proximal muscle groups may occur and be associated with mild sensory changes, tendon reflex depression, and abnormal nerve conduction. Importantly, serum CK levels are normal. Muscle biopsy specimens from patients with chloroquine- or hydroxychloroquine-induced myopathy demonstrate a vacuolar myopathy, often evident only on electron microscopy.⁴⁰ Periodic examination of knee and ankle reflexes should be undertaken and any signs of muscle weakness investigated. Use of hydroxychloroquine should be discontinued if weakness occurs. The myopathy is reversible, but the symptoms may take months to resolve.

Corticosteroids

Exogenous or endogenous glucocorticoid excess leads to weakness secondary to type II fiber atrophy. The mechanism responsible for the steroid effects has not been completely elucidated. Some degree of muscle weakness may eventually develop in the majority of patients treated with corticosteroids, usually after a period of at least 4 weeks. The weakness is more severe and may develop more rapidly in those treated with fluorinated corticosteroids, such as dexamethasone, triamcinolone, and betamethasone, than in those treated with nonfluorinated corticosteroids, such as prednisone and methylprednisolone.⁴¹ The weakness is proximal and accompanied by atrophy of the affected muscles. The distal extremities and oculobulbar and facial muscles are spared. EMG shows low-amplitude motor unit potentials and the absence of any spontaneous electrical activity. Selective atrophy of type II muscle fibers and the absence of inflammation or muscle necrosis are characteristic histologic features.⁴² The recommended treatment of steroid myopathy is reducing the steroid dose or switching to a nonfluorinated steroid and encouraging exercise to prevent disuse atrophy.³²

Toxicity from recreational drugs

Chronic alcoholism may lead to the development of both acute and chronic forms of myopathy. Chronic alcoholic myopathy is characterized by painless, progressive proximal muscle weakness and mild to moderate myopathic changes in muscle biopsy specimens (fiber necrosis, moth-eaten fibers, variability in fiber size, and type II fiber atrophy). Some long-term drinkers may experience an asymptomatic elevation in the serum CK level—as much as 20 times higher than normal levels—that is aggravated by physical activity.³⁶ Acute ethanol myopathy is characterized by severe myalgia, highly elevated CK levels, proximal muscle weakness, and myoglobinuria. Usually, the illness is not severe and patients note resolution of the muscle swelling and pain over a period of 2 weeks. Patients who resume alcohol consumption are particularly prone to subsequent attacks of this form of myopathy.⁴²

ENDOCRINE MYOPATHIES

Thyroid disorders

More than 75% of hypothyroid patients and 67% of hyperthyroid patients have neuromuscular symptoms.⁴³ Neuromuscular manifestations of hypothyroidism include proximal weakness, muscle stiffness and cramping, slow reflexes, and myoedema (local contracture after light percussion). Rarely, hypothyroidism may be accompanied by rhabdomyolysis. Another unusual finding that is sometimes seen in hypothyroid myopathy is muscular enlargement. Hoffman syndrome is defined as the combination of hypothyroidism with muscle stiffness, cramps, and muscular enlargement. Muscle enzymes are commonly high and rarely correlate with the weakness. EMG shows normal findings or mildly myopathic changes. The myopathy resolves with hormone replacement.

In hyperthyroidism, proximal muscular weakness with atrophy, brisk reflexes, and bulbar weakness may occur. Occasionally, distal weakness may be seen as well. Muscle enzymes are normal or low. EMG shows myopathic changes. The symptoms resolve a few months after normalization of thyroid hormone levels.⁴⁴ A rare manifestation of muscular disease in hyperthyroidism is thyrotoxic periodic paralysis. Patients exhibit rapidly progressing paralysis, greater in the lower extremities and often worse in the proximal musculature. The signs and symptoms are clinically identical to those of familial periodic paralysis.

Adrenal disorders

Iatrogenic steroid myopathy is manifested as an insidious, proximal muscular atrophy with weakness. Myalgia may be present. Fluorinated steroid preparations, such as dexamethasone and betamethasone, are most often the culprits. CPK levels are normal and EMG shows no evidence of irritable myopathy. Muscle biopsy specimens typically show evidence of type II fiber atrophy. Cushing disease classically causes proximal weakness and may be severe. Clinically, the myopathy is indistinguishable from iatrogenic steroid myopathies.

Diabetes

Diabetic amyotrophy is a distinctive form of diabetic neuropathy typified by an abrupt onset of pain and asymmetric proximal weakness and wasting of

the legs.⁴⁵ It characteristically affects elderly patients with type 2 diabetes ranging from poor to good control and is often associated with weight loss. EMG shows multifocal denervation in the paraspinal and lower extremity muscles. Nerve conduction studies show an axonal neuropathy. Treatment includes optimizing diabetic control and the use of corticosteroids and intravenous immunoglobulins.

Skeletal muscle infarction is a very rare complication of poorly controlled diabetes mellitus. Patients have an acute onset of painful swelling of the affected muscle and, occasionally, a palpable mass. Because this entity is frequently misdiagnosed clinically, increased clinical awareness is important for early recognition, particularly in a diabetic patient with a painful thigh or leg swelling.⁴⁶

MUSCULAR DYSTROPHIES

Muscular dystrophies are a heterogeneous group of inherited muscular disorders that affect the stability of the sarcolemmal membrane.³²

Duchenne muscular dystrophy

The prototypic example is Duchenne muscular dystrophy, an X-linked recessive disease characterized by the absence of dystrophin. Affected children are normal at birth, only to have a waddling gait, Gower sign (use of the arms to push oneself erect by moving the hands up the thighs), and calf pseudohypertrophy develop by 2 to 6 years of age. Because the stability of the sarcolemmal membrane is affected, there is ongoing degeneration and regeneration leading to elevated CK levels of up to 100 times normal. EMG shows myopathic changes. Muscle biopsy specimens with reduced or absent dystrophin staining are diagnostic. The diagnosis may be confirmed by demonstrating deletion of the dystrophin gene. No specific therapy is available. Death occurs at 14 to 20 years of age as a result of respiratory failure/cardiomyopathy.⁴⁷

Becker muscular dystrophy

Becker muscular dystrophy is very similar to the Duchenne type but has a less severe phenotype because of a partial loss of dystrophin. Patients are typically ambulating until 15 years of age, but otherwise the clinical features are identical, with the exception of muscle biopsy specimens, which may reveal normal dystrophin staining. Dilated cardiomyopathy necessitating heart transplantation may occur.⁴⁷

Emery-Dreifuss muscular dystrophy

Emery-Dreifuss muscular dystrophy is another X-linked recessive disorder that affects emerin. Emerin is an integral protein of the inner nuclear membrane in vertebrates and mediates anchorage of the membrane to the cytoskeleton. Clinically, patients have contractures of the elbows, neck, and spine, as well as scapulohumeroperoneal weakness. Cardiomyopathy and cardiac conduction defects are the most feared complications.⁴⁷

Limb-girdle muscular dystrophies

Limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of diseases characterized by mutations affecting various structural proteins and enzymes. Their nomenclature is straightforward, with type 1 LGMD being autosomal dominant and type 2 being autosomal recessive. Subclassification with letters denotes specific genetic mutations. They include LGMD2A (calpainopathy; CAPN), LGMD2B (dysferlinopathy; DYSF), LGMD2C (γ -sarcoglycanopathy; SGCG), LGMD2D (α -sarcoglycanopathy; SGCA), LGMD2E (β -sarcoglycanopathy; SGCB), LGMD2F (δ -sarcoglycanopathy; SGCD), LGMD2G (telethoninopathy; TCAP), LGMD2H (TRIM32), LGMD2I (FKRP), LGMD2J (TTN), and LGMD2K (POMT1).⁴⁷ Their prevalence approaches 1 in 100,000. The phenotypes cover the entire range between Duchenne and Becker muscular dystrophies. Patients generally have weakness and wasting restricted to the limb musculature, proximal greater than distal, with initial symptoms occurring in the second or third decade. Muscle biopsy specimens show muscle degeneration and regeneration. Muscle enzymes are typically elevated.⁴²

LGMD2A (calpainopathy) and LGMD2B (dysferlinopathy) are the most common recessive LGMDs in North America. Calpainopathy is frequently associated with profound shoulder-girdle weakness and sometimes scapular winging. Dysferlin deficiency may be accompanied by distal weakness and, in a purely distal form, is associated with severe calf wasting and elevated serum CK levels.⁴⁸ LGMD2B may be misdiagnosed as polymyositis because

of its onset in adult life, marked elevation of serum CK levels, and the presence of inflammatory infiltrates in muscle biopsy specimens.⁴⁹ Confirmation of the diagnosis begins with a muscle biopsy specimen, which demonstrates dystrophic changes, as well as reduced levels or absence of calpain or dysferlin on immunohistochemical staining. Molecular genetic studies are needed to confirm and define the character of the mutation.

The sarcoglycanopathies are forms of LGMD (types 2C, 2D, 2E, and 2F) caused respectively by mutations in the γ -, α -, β -, and δ -sarcoglycan genes, and they affect primarily white individuals. Onset is most often in early childhood, and loss of ambulation generally occurs before the age of 16 years. However, milder phenotypes do occur, with proximal muscle weakness first prompting medical attention in young adulthood. Muscle weakness is initially detectable in the pelvic girdle and later results in scapular winging in the shoulders. Respiratory muscle involvement occurs late in the disease and frequently leads to respiratory failure and death. Serum CK levels are elevated 10 to 100 times the upper limit of normal, typically higher than in the other forms of LGMD.

Myotonic dystrophy

Myotonic dystrophy (Steinert disease, myotonic dystrophy type I, dystrophia myotonica) is the most common adult dystrophy. It is an autosomal dominant disease caused by mutations in the gene that encodes for dystrophia myotonica protein kinase on chromosome 19 (DMPK). The mutation occurs in an untranslated region of the gene. Within the region are 5 to 30 repeating sequences of three nucleotides (CTG trinucleotide repeats). In myotonic dystrophy these CTG repeats expand into the hundreds or thousands. In general, the size of the expansion reflects the severity of the illness.

Clinically, slowly progressive limb weakness, distal more than proximal, is characteristic. The most commonly affected muscles are the facial muscles, distal muscles of the forearm, dorsiflexors of the foot, intrinsic muscles of the hand and feet, and the oropharyngeal and extraocular muscles.⁴⁷ The pelvic girdle, hamstrings, soleus, and gastrocnemius are spared. Myotonia can be elicited by percussing the thenar eminence or by observing delayed muscular relaxation after forceful contractions. CK is normal to mildly elevated and EMG shows myotonic discharges. The extramuscular features have diagnostic and prognostic significance. Smooth and cardiac muscle is most commonly involved, but the central nervous system, bone, and endocrine system may also be affected. Cataracts are almost universal. Testicular atrophy, reduced intelligence, depression, personality disorders, male pattern baldness, diabetes, and sleep apnea are common manifestations.

Proximal myotonic myopathy

Proximal myotonic myopathy (myotonic dystrophy type 2) is milder than myotonic dystrophy. Patients have a slowly progressive proximal myopathy that spares the face. Muscle pain and stiffness may be prominent. Myotonia is not as prominent as myotonic dystrophy on examination. CK is normal to mildly increased, and EMG shows myotonic discharges. Common manifestations include cataracts, cardiac conduction defects, fatigue, and obstructive sleep apnea. Proximal myotonic myopathy may be a close clinical mimic of idiopathic inflammatory myopathies.

INFECTIOUS MYOPATHIES

The musculature is inherently resistant to infections. Infectious myositis is rare and tends to occur in the setting of muscular injury, ischemia, or trauma. Numerous infections can cause myopathy. It is helpful to categorize infectious myositis on the basis of clinical manifestations.⁵⁰

Pyomyositis

Pyomyositis is a primary infection of skeletal muscle that is often associated with abscess formation. Intermuscular abscesses and abscesses extending into muscles by contiguous spread from nearby tissues are not classified as pyomyositis.

Pyomyositis is common in tropical areas and is responsible for up to 4% of hospital admissions in Africa. It is a rare diagnosis in the United States and most commonly described in human immunodeficiency virus (HIV)-infected and immunosuppressed patients, with approximately a third of cases occurring in previously healthy individuals.⁵¹

The most commonly identified etiologic agent is *Staphylococcus aureus* (75% in the United States), followed by group A streptococci, as well as rare cases of groups B, C, and G streptococci, *Pneumococcus*, *Haemophilus*, *Aeromonas*, *Pseudomonas*, *Klebsiella*, and *Escherichia*.

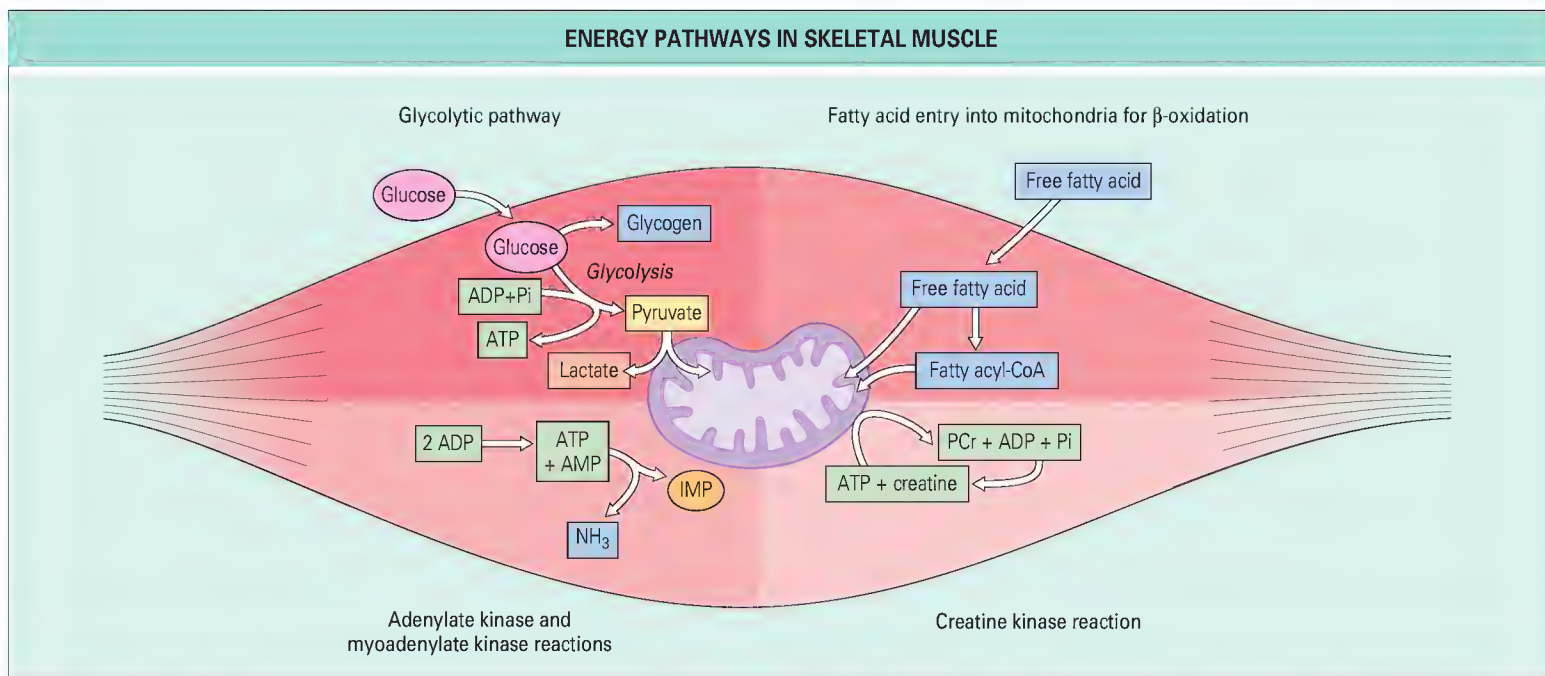


Fig. 151.3 Skeletal muscle uses adenosine triphosphate (ATP) as its fuel for contraction and relaxation. ATP can be generated via four separate metabolic pathways in skeletal muscle. The glycolytic pathway involves the metabolism of glucose derived from blood and the breakdown of muscle glycogen. The anaerobic metabolism of glucose yields pyruvate; in the presence of oxygen, the pyruvate can enter mitochondria and be metabolized further, and in anaerobic conditions, the pyruvate is converted to lactate. Free fatty acids derived from blood enter the mitochondria either as their fatty acyl-coenzyme A (acyl-CoA) derivatives (long-chain fatty acids) or as the intact molecule (short- and medium-chain fatty acids). Within the mitochondria, the fatty acids undergo β -oxidation to generate acetyl-CoA, which is then metabolized by the tricarboxylic acid cycle and the electron donors reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH₂). Phosphocreatine (PCr) is a high-energy storage compound that provides an immediate source for the regeneration of ATP via the creatine kinase reaction during the initial phases of muscular exertion. Creatine kinase activity is present in the inner mitochondrial membrane and in the sarcoplasm. PCr is regenerated from creatine within the mitochondria via oxidative phosphorylation. The adenylate kinase reaction generates ATP and adenosine monophosphate (AMP) from adenosine diphosphate (ADP). As the concentration of AMP increases during muscle exercise, it is converted to inosine monophosphate (IMP) and ammonia (NH₃) via the myoadenylate kinase reaction.

Most commonly, a single muscle is affected, but in up to 40% of cases, multiple muscles may be involved.⁵² The incidence of pyomyositis by body site may be reviewed in [Figure 151.3](#).

In the initial, invasive stage, local, tender swelling develops with no fluctuation or erythema. Aspiration yields no pus, but 2 or 3 weeks later, the occurrence of high spiking fevers associated with extreme pain and swelling of the affected muscle is the harbinger of the suppurative period. Imaging studies demonstrate an abscess and aspiration yields pus.

Serum CK is usually normal and blood culture results are positive in less than 50% of cases.^{53,54} Besides nonspecific laboratory markers of infection (leukocytosis, C-reactive protein, erythrocyte sedimentation rate, etc.), which are invariably elevated, the most important tool in diagnosis is imaging. Ultrasound is used as the initial screening imaging modality but may show normal findings in the early invasive phase. It may reveal muscle enlargement, or hypoechoic areas consistent with abscesses. Computed tomography may show low-density areas with a surrounding rim of contrast enhancement characteristic of pyomyositis. MRI gives greater anatomic detail and is the *de-facto* imaging “gold standard” for the diagnosis of pyomyositis.

Treatment consists of urgent drainage of any identified abscess, as well as empirical antibiotic coverage with vancomycin in an immunocompetent host or broad-spectrum antibiotic coverage targeting both gram-positive and gram-negative bacteria in immunosuppressed or HIV-infected patients.

Gas gangrene

Gas gangrene is a rapidly progressive life-threatening infection of skeletal muscle caused by clostridia (principally *Clostridium perfringens*). It is due to wound contamination in the setting of severe tissue trauma, inadequate surgical débridement, immunosuppression, and impaired blood supply. Rarely, nontraumatic gas gangrene caused by *Clostridium septicum* may occur in patients with occult gastrointestinal malignancies and lead to transient bacteremia.

Symptoms and signs may evolve over a period of 2 to 3 days, but they may also be fulminant and achieve a peak within 6 hours. Pain out of proportion to the findings on physical examination is followed by the rapid development of septic shock. There is a foul-smelling, serosanguineous,

dirty-appearing discharge with occasional gas bubbles. Crepitus on palpation is the classic hallmark described in the literature, but it may be masked by the massive surrounding tissue edema, and its absence does not rule out gas gangrene. Evidence of air in soft tissues on imaging or high clinical suspicion for gas gangrene is an absolute indication for urgent surgical intervention and débridement of nonviable tissues. Antibiotic therapy with penicillin G and clindamycin is an important adjunct to surgery.

Psoas abscess

A psoas abscess is defined as a purulent infectious collection within the psoas muscle. The psoas muscle is supplied by venous blood from the lumbar spine and has lymphatics from nearby intraabdominal organs overlying it. Secondary psoas abscesses develop as a result of spread of infection from contiguous structures, such as concurrent vertebral infections. Other routes may be from an intraabdominal source, most commonly gastrointestinal, including Crohn disease, cancer, appendicitis, or diverticulitis. Less commonly, psoas abscesses may develop in association with genitourinary infections, such as a perinephric abscess, vaginal delivery, cesarean surgery, abortion, or an infected retroperitoneal hematoma.

Myalgias without eosinophilia

Influenza

Influenza A and B viral myositis occurs most often in children. It is characterized by a sudden onset of calf pain and tenderness, which often results in difficulty walking. The myositis differs from the common initial complaint of myalgia by its later onset, more focal location, and more severe intensity.⁵⁵ CK levels are elevated. If EMG is performed, myopathic changes can be noted. Histopathologic examination of muscle reveals degeneration and necrosis and overall little inflammatory infiltrates. The myositis resolves within a few days with symptomatic treatment.

Human immunodeficiency virus

A slowly progressive myopathy that resembles polymyositis may develop in patients infected with HIV. Patients have myalgia, proximal symmetric

weakness, and elevation of serum CK levels. EMG may show an irritable myopathy indistinguishable from polymyositis.⁵⁶ Muscle biopsy specimens show endomysial, perimysial, or perivascular mononuclear cell infiltrates with muscle fiber necrosis and phagocytosis. Differentiating HIV myopathy from nucleoside reverse transcriptase inhibitor (NRTI) myopathy is a difficult clinical challenge that often requires a trial without NRTIs.

Myalgias with eosinophilia

Among the parasites that cause myositis, *Toxoplasma* is the most common in the United States. Toxoplasmosis can cause an inflammatory myopathy in immunocompromised hosts, often accompanied by fever, encephalitis, and other organ involvement. If isolated, treatment is not generally war-

ranted because the infection is usually self-limited. In severe cases, including progressive myositis, sulfadiazine and pyrimethamine are indicated.

Trichinosis occurs after the ingestion of undercooked pork or wild animal meat. The extraocular muscles are generally involved first, followed by the masseters and muscles of the diaphragm, neck, larynx, and limbs. Rarely, trichinosis can produce a clinical syndrome resembling polymyositis. Eosinophilia is an important diagnostic clue; serologic testing confirms the diagnosis.⁴²

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152

Overlap syndromes

■ ROBERT W. HOFFMAN

- Current nomenclature in rheumatology has advanced through the use of autoantibodies as biomarkers.
- Mixed connective tissue disease (MCTD) is widely recognized in children and adults and is characterized by the presence of overlapping clinical features and a high level of antiribonucleoprotein (anti-RNP) antibody.
- The core clinical features of MCTD include Raynaud phenomenon, arthralgia, arthritis, gastroesophageal reflux, and mild myositis.
- The Pm-Scl/PM-1-associated overlap syndrome is characterized by features of polymyositis and scleroderma in the presence of anti-Pm/Scl/PM-1 antibodies.
- Anti-Ku antibody syndrome can have features that overlap with those seen in MCTD, systemic lupus erythematosus (SLE), and Sjögren syndrome.
- Anti-RNA polymerase II antibody syndrome can have features of SLE overlapping with those of limited or diffuse scleroderma.

INTRODUCTION

Correct diagnosis and classification of a disease depend on knowledge of its etiology. The causes of all autoimmune connective tissue diseases are currently unknown, and their diagnosis depends on recognition of patterns of symptoms and signs. Internationally accepted criteria have been developed for the classification of some rheumatic diseases. Even though the use of classification criteria allows reasonably homogeneous patient populations to be selected for epidemiologic studies and clinical trials, it is of more limited value for determining precise treatment regimens in individual patients and for assessing prognosis. The challenges of diagnosis and classification are heightened in rheumatology in general and the autoimmune connective tissue diseases in particular by the tendency for one disease to merge with another. This results in an overlapping spectrum of clinical features among the rheumatic diseases, including the classically recognized entities such as systemic lupus erythematosus (SLE), systemic sclerosis, and polymyositis/dermatomyositis. Identification and characterization of specific antinuclear antibodies (ANAs) as biomarkers of disease have greatly assisted in the classification and diagnosis of systemic rheumatic diseases.

CLASSIFICATION AND DIAGNOSIS OF OVERLAP SYNDROMES

Nomenclature, taxonomy, disease classification, and diagnosis

The current classification scheme of disease can be dated back to Victorian England and pioneering work of the British epidemiologist William Farr, who is considered by many to be the founder of medical statistics. This system of disease classification, which is also known as disease taxonomy or disease nomenclature, is based on a hierarchic structure that uses consensus criteria. For a more complete discussion of this topic, see Chapter 1.

Classification criteria are essential for epidemiologic studies and clinical trials; they help ensure that the participants included both within a single study and across multiple studies are similar. The current system of disease classification is built on an anatomic focus of disease. This approach to classification, founded by William Farr, includes recognition of symptomatologic and epidemiologic patterns of disease. However, the focus on anatomic and symptomatologic patterns of disease rather than mechanisms of disease may not take full advantage of recent advances in science.

A focus on molecular mechanisms of disease, particularly when recent advances in immunology, imaging, and genetics are incorporated, has the potential to substantially advance disease classification. In rheumatology, all three of these modalities have been applied successfully to disease classification and diagnosis. For example, radiographic imaging is used for the classification of rheumatoid arthritis (RA) and ankylosing spondylitis. HLA-B27 genotyping combined with magnetic resonance imaging is used for the classification of ankylosing spondylitis. Measurements of rheumatoid factor and anti-citrullinated peptide antibodies (ACPAs) are criteria for the classification of RA; ANAs, anti-double-stranded DNA (dsDNA), and anti-Sm are criteria for the classification of SLE (see Chapters 91 and 130).

An important advance in the classification of rheumatic diseases has been the use of serologic immunologic testing for identification of autoantibodies and inclusion of these autoantibodies in the classification of many rheumatic diseases, including autoantibodies against ANA, dsDNA, Smith (Sm), U1-ribonucleoprotein (RNP), SSA (Ro), SSB (La), phospholipids, ACPA, and rheumatoid factor. These and other autoantibodies illustrate the value of immunologic testing and applying an understanding of disease pathogenesis to disease classification and diagnosis (see Chapters 91 and 130).

Finally, it is important to recognize the proper use and the limitations of classification criteria, as well as their distinction from diagnostic criteria. Classification criteria are designed for application in epidemiologic studies and clinical trials, and they are limited by current knowledge of disease. For example, unrecognized subsets of disease or multiple diseases may be included within a current classification scheme, which limits the validity of the criteria. Classification criteria differ from diagnostic criteria, and the two should not generally be used interchangeably. Diagnosis of any individual patient should incorporate knowledge of the disease as applied to the patient's specific circumstance. Disease at initial evaluation will often not encompass the full spectrum of clinical manifestations, which require time to develop fully. For many rheumatic diseases, including the entities reviewed in this chapter, validated and widely accepted diagnostic criteria are yet to be published.

Terms defined

Undifferentiated connective tissue disease

The term "undifferentiated connective tissue disease" (UCTD) was first applied by LeRoy and colleagues¹ to describe the early and often "undifferentiated" phase of a rheumatic disease at initial evaluation when a precise classification could not be made because the patient did not fulfill the recognized classification criteria. "UCTD" as applied by LeRoy and colleagues was not intended to describe a patient with an "overlap" syndrome who has features of two or more distinctly recognizable rheumatic diseases but rather one who lacks sufficient features to meet the criteria for any classification.¹ As LeRoy and associates described, many patients will have subsequent involvement of additional organs over time, and this often assists in correct disease classification. At a later time the patient may meet the classification criteria for a rheumatic disease.

TABLE 152.1
Autoantibodies as biomarkers for disease classification and diagnosis

Autoantibody specificity	Disease
U1-RNP	Mixed connective tissue disease
tRNA synthetase	Myositis with arthritis and pulmonary involvement
PM/Scl (PM-1)	Overlapping features of polymyositis and limited scleroderma
Ku	Polymyositis and systemic sclerosis
RNA polymerase II	Overlap with systemic lupus erythematosus
SSA (Ro)	Primary and secondary Sjögren syndrome

In the literature the term UCTD has also been used to describe a group of patients who despite careful observation over time will continue to fail to meet the classification criteria for any well-recognized rheumatic disease.² Notably, some authors have required that such UCTD patients have a positive fluorescent ANA test result. Recognition of these multiple uses of the term UCTD can assist in reading this sometimes confusing literature.

Overlap syndrome

A term that warrants definition is “overlap syndrome.” This term has been used to convey a variety of meanings by different authors. Frequently, the term has been used to describe patients exhibiting the features of more than one distinct clinical entity. Some have used the term to describe the predominance of selected clinical features, such as interstitial lung involvement or myopathy (i.e., myositis-pulmonary overlap), in patients with another widely recognizable rheumatic disease such as SLE or RA. The term is used here to describe the latter.

In the absence of pathognomonic clinical features or diagnostic laboratory test results, the correct diagnosis or classification of any patient may be challenging. The rheumatic diseases exhibit substantial overlapping clinical and immunologic features, which often makes classification difficult. Historic examples of diseases with overlapping signs and symptoms that are now considered distinct entities, including rheumatic fever, Lyme disease, calcium pyrophosphate deposition disease, RA, and ankylosing spondylitis, illustrate these challenges. As our understanding of the etiopathogenesis of the rheumatic diseases advances, there will certainly be increasing clarity in the classification and ease of diagnosis of apparent overlapping rheumatic entities. The focus of this chapter is on systemic autoimmune diseases with overlapping features of widely recognized multisystemic autoimmune diseases, including SLE, RA, scleroderma, polymyositis/dermatomyositis, and Sjögren syndrome.

Autoantibodies as a biomarker for classification

As early as the 1950s important advances were made in the use of serologic markers of disease, including the identification and characterization of autoantibodies, which can serve as markers for diagnosis and classification of the rheumatic diseases. This work began with the identification of rheumatoid factor and ANAs. Further identification and characterization of autoantibodies in the 1970s to 1980s, including the use of specific newly identified autoantibodies for classification, ultimately led to the recognition and classification of antiphospholipid (aPL) syndrome, mixed connective tissue disease (MCTD), and overlap syndromes with predominant muscle and lung involvement as distinctly identifiable entities. A summary of these conditions is presented in Table 152.1. The topic of aPL syndrome is reviewed elsewhere in this text (see Chapter 139); a comprehensive description of MCTD and overlap diseases characterized by the presence of specific autoantibodies accompanied by lung and muscle involvement is presented in this chapter.

MIXED CONNECTIVE TISSUE DISEASE

Introduction

MCTD was first described by Gordon C. Sharp and colleagues.³ It was characterized by overlapping features of SLE, scleroderma, and polymyositis in the presence of a newly identified antibody found at very high levels in

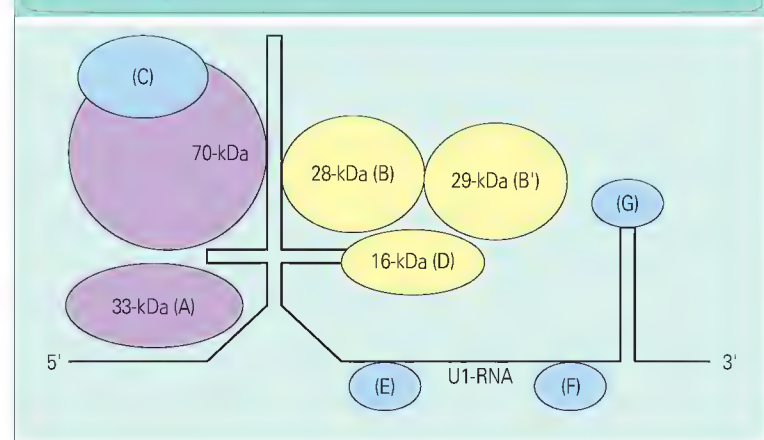
SCHEMATIC REPRESENTATION OF THE U1-RNP MOLECULE

Fig. 152.1 Polypeptides bound to U1-RNA. The polypeptides illustrated in purple (70-kDa and A) contain the epitopes that are predominantly recognized by anti-U1-RNP antibodies, and those shown in yellow contain the epitopes that are predominantly recognized by anti-Sm antibodies (B/B' and D). Also shown here is the other U1-associated C polypeptide that forms the U1-specific complex with 70-kDa and A, as well as the Sm polypeptides B/B', D, E, F, and G, which bind to U1, U2, U3, and U4/6 RNA (which are not shown).

TABLE 152.2
Clinical features of mixed connective tissue disease

Clinical feature	At diagnosis (%)	Cumulative findings (%)
Raynaud phenomenon	89	96
Arthralgia/arthritis	85	96
Swollen hands	60	66
Esophageal dysmotility	47	66
Pulmonary disease	43	66
Sclerodactyly	34	49
Pleuritis/pericarditis	34	43
Rash	30	53
Myositis	28	51
Renal disease	2	11
Neurologic disease	0	17

Data from Burdett MA, Hoffman RW, Deutscher SL, et al. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Arthritis Rheum* 1999;42:899-909.

patients' sera. This autoantibody, first called extractable nuclear antigen, is now known as anti-RNP. It has been demonstrated to be a nuclear RNP and is also known to be noncovalently associated with U1-RNA; in addition, it is known as U1-RNP (Fig. 152.1).^{4,5} All three terms are used interchangeably in the literature to describe this autoantibody.

History

Since the original description of MCTD by Sharp and colleagues more than 4 decades ago, the disease has become widely recognized around the world in both adults and children.³⁻¹³ The most common clinical features are listed in Table 152.2 and include Raynaud phenomenon, arthralgia, arthritis, and gastroesophageal reflux. Laboratory features include the presence of high levels of anti-RNP antibody, high-titer speckled-pattern fluorescent ANAs, leukopenia, hypergammaglobulinemia, and anemia. An example of diffuse hand swelling with typical sausage-shaped fingers in a patient with MCTD is illustrated in Figure 152.2.

Classification and diagnosis

Even though no diagnostic criteria have been widely accepted yet, at least four classification criteria have been proposed for MCTD. Among these



Fig. 152.2 Sausage-shaped fingers in a patient with mixed connective tissue disease, which is seen most often in the early edematous phase of the disease.

BOX 152.1 CRITERIA FOR MIXED CONNECTIVE TISSUE DISEASE

Serologic criteria

Anti-ribonucleoprotein antibody must be present at a moderate to high level in serum
AND

Clinical criteria

At least 3 of the following 5 clinical findings must be present:

- Edema of the hand
- Synovitis
- Myositis
- Raynaud phenomenon
- Acrosclerosis

AND these clinical criteria must include either synovitis or myositis

From Alarcon-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. *J Rheumatol* 1989;16:328-34.

criteria, those of Alarcon-Segovia and Cardiel are perceived to be the easiest to apply.¹⁴ A slightly modified form of the MCTD classification of Alarcon-Segovia and Cardiel is presented in [Box 152.1](#).

Clinical features

The clinical features of MCTD seen most frequently at initial evaluation and a summary of the cumulative clinical features observed over time from the longitudinal study of Burdt and colleagues⁷ that included follow-up for as long as 20 years are presented in [Table 152.2](#). Many studies from around the world in both adults and children have reported features of MCTD similar to those reported by Burdt and colleagues.⁷⁻¹³

Initially, the most common manifestations are Raynaud phenomenon, arthralgia, arthritis, diffusely swollen hands, and esophageal reflux.⁷ Other uncommon findings have also been described, including trigeminal neuropathy, seizure, psychosis, and pulmonary hypertension.

Diagnosis requires the presence of a high level of anti-RNP antibodies in serum, and other laboratory features often include leukopenia, lymphopenia, and mild anemia (see later for a detailed discussion of immunologic and laboratory testing in MCTD). Pleuritis, pericarditis, rash, and myositis may also develop over time in the typical patient as additional features of MCTD, in addition to the manifestations widely seen at initial evaluation (see [Table 152.2](#)). Among the most serious complications of MCTD is pulmonary involvement, including pulmonary hypertension, which is the most common disease-related cause of death.⁷

Skin

The most common skin manifestations of MCTD are Raynaud phenomenon and diffusely swollen hands (see [Fig. 152.2](#)), which may evolve into sclerodactyly ([Fig. 152.3](#)). Other rashes occur in approximately half of all patients and include photosensitivity rash, malar rash, and telangiectases over the face. Oral ulcers similar to those found in lupus may occur, and rashes



Fig. 152.3 Hands of a patient with mixed connective tissue disease showing features of both dermatomyositis (thickening and erythema of the dorsum of the fingers) and scleroderma (sclerodactyly and fixed flexion of the fingers).

typical of dermatomyositis, including Gottron papules or a heliotrope rash, have commonly been observed in MCTD.

Hands and joints

Arthralgia ultimately occurred in more than 90% of patients in the study of Burdt and associates,⁷ and inflammatory arthritis developed in approximately half of all patients. Rheumatoid factor is found in 25% to 50% of patients; however, erosions are uncommon. A Jaccoud-like arthritis, similar to that seen in SLE, has been described in MCTD.

Muscles

Myalgia occurs in 25% to 50% of patients, and myositis has been reported to be widely variable and variously reported in 25% to 75% of patients. The most common muscle-related findings appear to be muscle discomfort with elevated creatinine kinase levels in the absence of significant muscle weakness. This is typically an early feature of MCTD. Fibromyalgia has also been reported to occur in MCTD.

Pulmonary

Pulmonary hypertension is one of the most serious complications that can occur in MCTD. In the longitudinal study of Burdt and colleagues,⁷ pulmonary hypertension was the most common disease-related cause of death in patients with MCTD. It accounted for death in 13% during the follow-up period. In addition, interstitial lung disease can develop, with fibrosis occurring in approximately half of these patients. Pleural inflammation similar to that seen in SLE can also occur. Rare cases of pulmonary hemorrhage have been described.

Gastrointestinal

Symptomatic esophageal reflux is very common in patients with MCTD. Symptoms include heartburn, dysphagia, and less commonly, odynophagia and regurgitation of food. Other regions of the bowel, including the colon and small intestines, can be involved. In addition to esophageal dysmotility with reflux, the next most common gastrointestinal features of MCTD are bacterial overgrowth syndromes and malabsorption. Gastrointestinal involvement similar to that seen in scleroderma can occur.

Sicca

A study by Setty and coworkers¹⁵ found that secondary Sjögren syndrome occurs in approximately 25% of all patients with MCTD and is frequently accompanied by the presence of anti-SSA (Ro) antibodies. The presence of anti-SSA (Ro) antibodies was further correlated with photosensitivity and malar rash. Patients may have salivary or submandibular gland enlargement similar to that seen with primary Sjögren syndrome.

Cardiac

Cardiac involvement as detected by echocardiography or electrocardiography occurs in approximately a quarter of all patients with MCTD. Pericardial involvement is common and similar to that seen with lupus. Right heart involvement associated with pulmonary hypertension is among the most serious cardiac complication in MCTD.⁷ Less common manifestations that have been reported include various types of valvular abnormalities, septal hypertrophy, and myocarditis. Atherosclerotic heart disease, which is among

■ **TABLE 152.3**
Management of mixed connective tissue disease

Clinical feature	Treatment (mild vs. moderate to severe disease)
Arthralgia/arthritis	Mild—antimalarial, NSAIDs Moderate to severe—systemic corticosteroids, methotrexate, azathioprine while avoiding tumor necrosis factor–blocking agents because of potential risk for disease flare
Raynaud phenomenon	Mild—protective measures Moderate—calcium channel blockers may be of benefit Severe—scleroderma-like management
Rash	Mild—protective measures to avoid the sun, antimalarial, and topical corticosteroids Moderate to severe—systemic corticosteroids, immunosuppressant, including azathioprine
Esophageal reflux	Mild—avoidance measures Moderate to severe—proton pump inhibitor, endoscopy with screening for Barrett esophagus; dilatation rarely
Myositis	Mild—antimalarial, corticosteroids Moderate to severe—corticosteroids, methotrexate, and IVIG, similar to the management of polymyositis
Pulmonary involvement	Yearly screening with pulmonary function testing and pulmonary imaging may be beneficial for the identification of early disease or as clinically indicated*† Moderate to severe—cyclophosphamide immunosuppression or treatment as for primary pulmonary hypertension may be beneficial (see the references cited*†)
Cardiovascular	Modify risk factors Yearly screening with ECG and echocardiography may be beneficial for the identification of early disease or as clinically indicated
Sicca	Symptomatic treatment
Sexual dysfunction	Treat erectile dysfunction as indicated and identify and treat androgen deficiency in men; treat vaginal dryness; counsel
Pregnancy and contraception	Monitor as for a high-risk pregnancy; SSA (Ro) and RNP have been associated with congenital heart block in neonates; pregnancy outcomes reported to be favorable from experienced centers Counsel on risk for sexually transmitted diseases, contraceptive options, risk and potential teratogenicity of medications; avoid estrogen-containing contraceptives
General	Antimalarial unless contraindicated; appropriate vaccines for age and risk; modify cardiovascular risk; promote healthy lifestyle, including exercise, diet, and risk avoidance; monitor and treat depression when present; suicidality may be a risk

*Jais X, Launay D, Yaici A, et al. M. Immunosuppressive therapy in lupus- and mixed connective tissue disease–associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008;58:521-31.
†McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009;119:2250-94.
ECG, electrocardiography; IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug; RNP, ribonucleoprotein.

T cells.¹⁹ Innate immune signaling through Toll-like receptors 7 and 3 appear to be involved.

Management

Currently, no treatment of MCTD has been approved by the U.S. Food and Drug Administration or the European Medical Agency. Therefore, all treatments recommended are for off-label use of medication and are based on best practices and expert opinion.^{20,21} A summary of the management of MCTD is presented in Table 152.3.

Pm-Scl (PM-1)-ASSOCIATED OVERLAP SYNDROME

Patients with antibodies against the Pm-Scl antigen have features of both polymyositis and scleroderma, including sclerodactyly, proximal scleroderma, Raynaud phenomenon, and pulmonary involvement.²²⁻²⁴ These patients generally do not progress to widespread or diffuse sclerodermatous involvement of the skin, but renal involvement similar to what can occur in scleroderma with hypertensive crisis has been reported.

RARE OVERLAP SYNDROMES: Ku AND RNA POLYMERASE

The initial report of patients with anti-Ku antibodies described them to have features of polymyositis and scleroderma; Ku is an 80-kDa DNA binding protein. Subsequent reports documented that Ku antibody–positive patients may have a wide range of clinical signs and symptoms, including features seen in MCTD, SLE, and Sjögren syndrome.²⁵

Patients with SLE and both limited and diffuse scleroderma have been reported to have antibodies reactive with RNA polymerase I and III. Patients

with selective reactivity against RNA polymerase II antibodies have been reported who exhibit an SLE overlap syndrome. Patients with selective RNA polymerase II reactivity have also been reported to have reactivity with Ku, RNP, and topoisomerase I.²⁶

CONCLUSION

Although diagnosis and classification of all the rheumatic diseases ultimately will be determined by increased understanding of their etiology, the fact remains that currently the causes of all autoimmune connective tissue diseases are unknown and their diagnosis depends on recognition of patterns of symptoms and signs. The challenges of diagnosis and classification are heightened in the autoimmune connective tissue diseases by the overlapping spectrum of clinical features among these diseases. Identification and characterization of specific ANAs as biomarkers of disease have, however, greatly assisted in classification and diagnosis of these systemic rheumatic diseases. MCTD is now widely recognized in adults and children as a distinct disease entity by physicians around the world. The use of autoantibodies as biomarkers for the diagnosis and classification of MCTD, SLE, and RA is widely accepted. Specific autoantibodies can also be useful for the diagnosis of tRNA synthetase–, Pm-Scl/PM-1–, Ku–, and RNA polymerase–associated overlap syndromes.

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THE VASCULITIDES

153

Classification and epidemiology of vasculitis

■ PETER A. MERKEL ■ ALFRED D. MAHR

- The vasculitides are a heterogeneous group of diseases linked by common clinical, laboratory, and pathophysiologic features.
- Classification and diagnostic criteria have substantial implications for clinical practice and clinical research in vasculitis.
- The American College of Rheumatology Criteria for the Classification of Vasculitis and the definitions of the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides are widely used for clinical research in vasculitis.
- Epidemiologic studies have helped advance hypotheses regarding the causes of many vasculitides.
- Both genetic and environmental factors have been shown to play roles in the pathogenesis of vasculitis.

INTRODUCTION

The term *vasculitis* refers to several diseases involving inflammation of blood vessels with subsequent tissue destruction and/or organ failure. The systemic vasculitides can be considered as a group of disorders because they have in common inflammatory vascular disease as the primary or a substantive pathologic process and also have overlapping clinical features.

All types of primary or idiopathic vasculitis are considered rare diseases, reaching “orphan” status in the United States (i.e., they affect fewer than 200,000 persons). However, the prevalence of different forms of vasculitis varies greatly both geographically and ethnically, which raises intriguing questions about specific genetic and environmental influences on the pathogenesis.

Diagnostic and classification criteria have substantial implications for clinical practice as well as for clinical and epidemiologic research. This chapter reviews and discusses the implications of these concepts for our understanding of vasculitis.

Classification, definitions, and diagnostic criteria for vasculitis

A number of systems have been proposed for the classification and diagnosis of the vasculitides. It is recognized that such systems are imperfect, and the classification and diagnosis of vasculitis is an ever-evolving process. Nonetheless, these systems are used in most of the clinical research, are applied to treatment guidelines, and are used in daily communication among clinicians.

History and evolution of vasculitis classification systems

The first classification system for the vasculitides was proposed by the pathologist Pearl Zeek in 1952 and included only five entities. Although this system clearly omitted many diseases now recognized as vasculitis, it was a major advance in the field, and all subsequent attempts at classification have essentially evolved from her original format.

Many other vasculitis classification schema have been proposed.¹ Most are modifications of prior systems incorporating newly described separate entities (e.g., Kawasaki disease), removing entities no longer considered to be vasculitis (e.g., lymphomatoid granulomatosis), or adapting the terminology to reflect better understanding of pathophysiology and new diagnostic tests (e.g., antineutrophil cytoplasmic antibodies, or ANCA). The central organizing themes of these classification systems vary from predominant vessel size, to associated diseases, to putative pathophysiology/causality, to clinical manifestations, or, most commonly, to some amalgamation of all these factors.

Antineutrophil cytoplasmic antibody-associated vasculitis

The term ANCA-associated vasculitis is now widely used to cover granulomatosis with polyangiitis (formerly known as *Wegener granulomatosis*), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as *Churg-Strauss vasculitis*). However, this term may cause confusion since patients may have these diagnoses even if tests for ANCA are negative. Nonetheless, “ANCA-associated vasculitis” has become an accepted subclassification for vasculitis, as formalized in the 2012 revision of the Chapel Hill nomenclature.²

Table 153.1 provides an outline of the major forms of vasculitis with reference to the factors listed earlier.

CONCEPT OF DEFINITIONS, CLASSIFICATION SYSTEMS, AND DIAGNOSTIC CRITERIA FOR VASCULITIS

It is important to distinguish the terms *disease classification*, *disease definitions*, and *diagnostic criteria*, because they are obviously related but provide unique contributions to the field.

Classification systems for vasculitis aim to differentiate among patients correctly known to have a form of vasculitis to create homogeneous subsets for clinical research. Classification criteria can be inappropriately used for diagnosis.

Definitions for vasculitis aim to provide a standard name that is linked to the fundamental pathologic features inherent in the given disease and aim for inclusion of pathognomonic findings. Such definitions of diseases need to be widely accepted and applied within a field of study.



TABLE 153.1
The systemic vasculitides

	Predominant vessel size			ANCA-associated	Granuloma
	Large	Medium	Small		
Primary vasculitides					
Giant cell arteritis	Yes				Yes
Takayasu arteritis	Yes				Yes
Isolated aortitis					Yes
Polyarteritis nodosa		Yes			
Kawasaki disease		Yes			
Granulomatosis with polyangiitis (Wegener granulomatosis)		Possible	Yes	Yes	Yes
Microscopic polyangiitis		Possible	Yes	Yes	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)		Possible	Yes	Yes	Yes
Immunoglobulin A vasculitis (Henoch-Schönlein purpura)			Yes		
Cryoglobulinemic vasculitis			Yes		
Behçet disease	Yes	Yes	Yes		
Anti-glomerular basement membrane disease (Goodpasture syndrome)			Yes		
Buerger disease		Yes	Yes		
Cogan syndrome	Yes	Yes	Yes		
Relapsing polychondritis	Yes	Yes	Yes		
Urticarial vasculitis		Yes	Yes		
Primary angiitis of the central nervous system		Yes	Yes		Yes
Secondary vasculitides					
Rheumatoid arthritis			Yes		
Systemic lupus erythematosus			Yes		
Other connective tissue diseases			Yes		
Infection	Yes	Yes	Yes		
Drugs		Yes	Yes	Possible	
Malignancies	Yes	Yes	Yes		

ANCA, antineutrophil cytoplasmic antibody.

Data from Mahr AD, Merkel PA. Vasculitis. In: Creager M, editor. Atlas of vascular medicine. 3rd ed. Philadelphia: Current Medicine Group/Springer; 2007.

Diagnostic criteria for vasculitis aim to allow clinicians to determine if a specific disease is present; they are usually more detailed than classification criteria and include both general and specific data elements. Diagnostic criteria are crucial for practicing clinicians to help them direct diagnostic evaluations and thus provide proper care.

The 1990 American College of Rheumatology vasculitis classification system

By far the most widely used classification system is the 1990 American College of Rheumatology (ACR) Criteria for the Classification of Vasculitis (Table 153.2, Table e153.1).³ The stated purpose of these criteria is to provide guidance for clinical research studies of a selected set of seven types of vasculitis.

Strengths of the ACR classification system include the imprimatur of the ACR, the data-driven approach, and its simplicity of use since the criteria are based mostly on clinically relevant and commonly obtained information items. The wide adoption of this system is evidence both that it is useful and that it addressed an unmet need in the field.

The ACR classification criteria for vasculitis also have some important limitations:

1. The criteria include only seven diseases, and alternative systems are needed to study other types of primary vasculitis and all secondary forms.
2. The criteria were produced without a gold standard for any of the diagnoses under study; this limitation would be common to any classification system.
3. There was no attempt to group or link diseases in any manner, a positive feature of other classification systems.

There are also limitations common to any such system that is now 20 years old, including that the criteria do not incorporate newer diagnostic tests, especially testing for ANCA, and that specific forms of vasculitis have subsequently been suggested either for adoption for use in clinical practice (microscopic polyangiitis) or for elimination from use (hypersensitivity vasculitis). Similarly, patients with vasculitis may fulfill more than one set of ACR criteria. To address some of these issues, a hierarchic algorithm was proposed to supplement the ACR criteria and Chapel Hill definitions (see later) that includes additional histologic and laboratory data (Fig. e153.1).⁴ Similarly, positive results on ANCA testing was an added item in the “modified” ACR criteria for granulomatosis with polyangiitis used in some recent clinical studies.⁵

Nonetheless, the ACR classification criteria are the most commonly applied criteria in the field, and any attempt to revisit the classification of the vasculitides will be compared with the ACR system.

Classification of childhood vasculitides

The Pediatric Rheumatology European Society (PReS) and the European League Against Rheumatism (EULAR) formed a group to develop separate classification criteria for five types of childhood vasculitides, including Kawasaki disease (not included in the ACR criteria).⁶ The resulting criteria include, but are not restricted to, data elements found in both the ACR classification and the Chapel Hill definitions (see later). The resulting overall classification system is outlined in Box e153.1 and the detailed criteria for the five specific forms of vasculitis are presented in Box e153.2.

Although it is important to ensure that those vasculitides that are either unique to childhood or more common during childhood are recognized by classification and nomenclature systems, creating a full set of separate criteria for vasculitis in childhood creates a new set of challenges. Most

■ TABLE e153.1

American College of Rheumatology 1990 classification criteria for vasculitis

Disease	Criteria	Definition
Giant cell (temporal) arteritis ¹⁴⁰ (need 3 of 5 criteria for classification)	Age at disease onset ≥50 yr New headache Temporal artery abnormality Elevated erythrocyte sedimentation rate Abnormal temporal artery biopsy	Development of symptoms or findings beginning at age 50 or older New onset of or new type of localized pain in the head Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries Erythrocyte sedimentation rate ≥ 50 mm/hr by Westergren method Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells
Takayasu arteritis ¹⁴¹ (need 3 of 6 criteria for classification)	Age at disease onset ≤40 yr Claudication of extremities Decreased brachial artery pulse Blood pressure (BP) difference > 10 mm Hg (between arms) Bruit over subclavian arteries or aorta Arteriogram abnormality	Development of symptoms or findings related to Takayasu arteritis at age ≤40 yr Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities Decreased pulsation of one or both brachial arteries Difference of >10 mm Hg in systolic blood pressure between arms Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental
Polyarteritis nodosa ¹⁴² (need 3 of 10 criteria for classification)	Weight loss ≥4 kg Livedo reticularis Testicular pain or tenderness Myalgias, weakness, or leg tenderness Mononeuropathy or polyneuropathy Diastolic BP > 90 mm Hg Elevated blood urea nitrogen (BUN) or creatinine Hepatitis B virus Arteriographic abnormality Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils	Loss of ≥4 kg body weight since illness began, not due to dieting or other factors Mottled reticular pattern over the skin of portions of the extremities or torso Pain or tenderness of the testicles, not due to infection, trauma, or other causes Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy Development of hypertension with the diastolic BP > 90 mm Hg Elevation of BUN > 40 mg/dL or creatinine > 1.5 mg/dL, not due to dehydration or obstruction Presence of hepatitis B surface antigen or antibody in serum Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or noninflammatory causes Histologic changes showing the presence of granulocytes and mononuclear leukocytes in the artery wall
Wegener granulomatosis ¹⁴³ (granulomatosis with polyangiitis) (need 2 of 4 criteria for classification)	Nasal or oral inflammation Abnormal chest radiograph Urinary sediment Granulomatous inflammation on biopsy	Development of painful or painless oral ulcers or purulent or bloody nasal discharge Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities Microhematuria (>5 red blood cells per high-power field) or red cell casts in urine sediment Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)
Churg-Strauss syndrome ¹⁴⁴ (allergic granulomatosis and angiitis, eosinophilic granulomatosis with polyangiitis) (need 4 of 6 criteria for classification)	Asthma Eosinophilia Mononeuropathy or polyneuropathy Pulmonary infiltrates, nonfixed Paranasal sinus abnormality Extravascular eosinophils	History of wheezing or diffuse high-pitched rales on expiration Eosinophilia > 10% on the white blood cell differential Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution), attributable to systemic vasculitis Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to systemic vasculitis History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses Biopsy including artery, arteriole, or venule, showing accumulation of eosinophils in extravascular areas
Henoch-Schönlein purpura (immunoglobulin A vasculitis) ¹⁴⁵ (need 2 of 4 criteria for classification)	Palpable purpura Age ≤20 yr at disease onset Bowel angina Wall granulocytes on biopsy	Slightly raised "palpable" hemorrhagic skin lesions, not related to thrombocytopenia Patient ≤20 yr at onset of first symptoms Diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhea Histologic changes showing granulocytes in the walls of arterioles or venules
Hypersensitivity vasculitis ¹⁴⁶ (need 3 of 5 criteria for classification)	Age at disease onset ≥16 yr Medication at disease onset Palpable purpura Maculopapular rash Biopsy including arteriole and venule	Development of symptoms after age 16 Medication was taken at the onset of symptoms that may have been a precipitating factor Slightly elevated purpuric rash over one or more areas of the skin; does not blanch with pressure and is not related to thrombocytopenia Flat and raised lesions of various sizes over one or more areas of the skin Histologic changes showing granulocytes in a perivascular or extravascular location

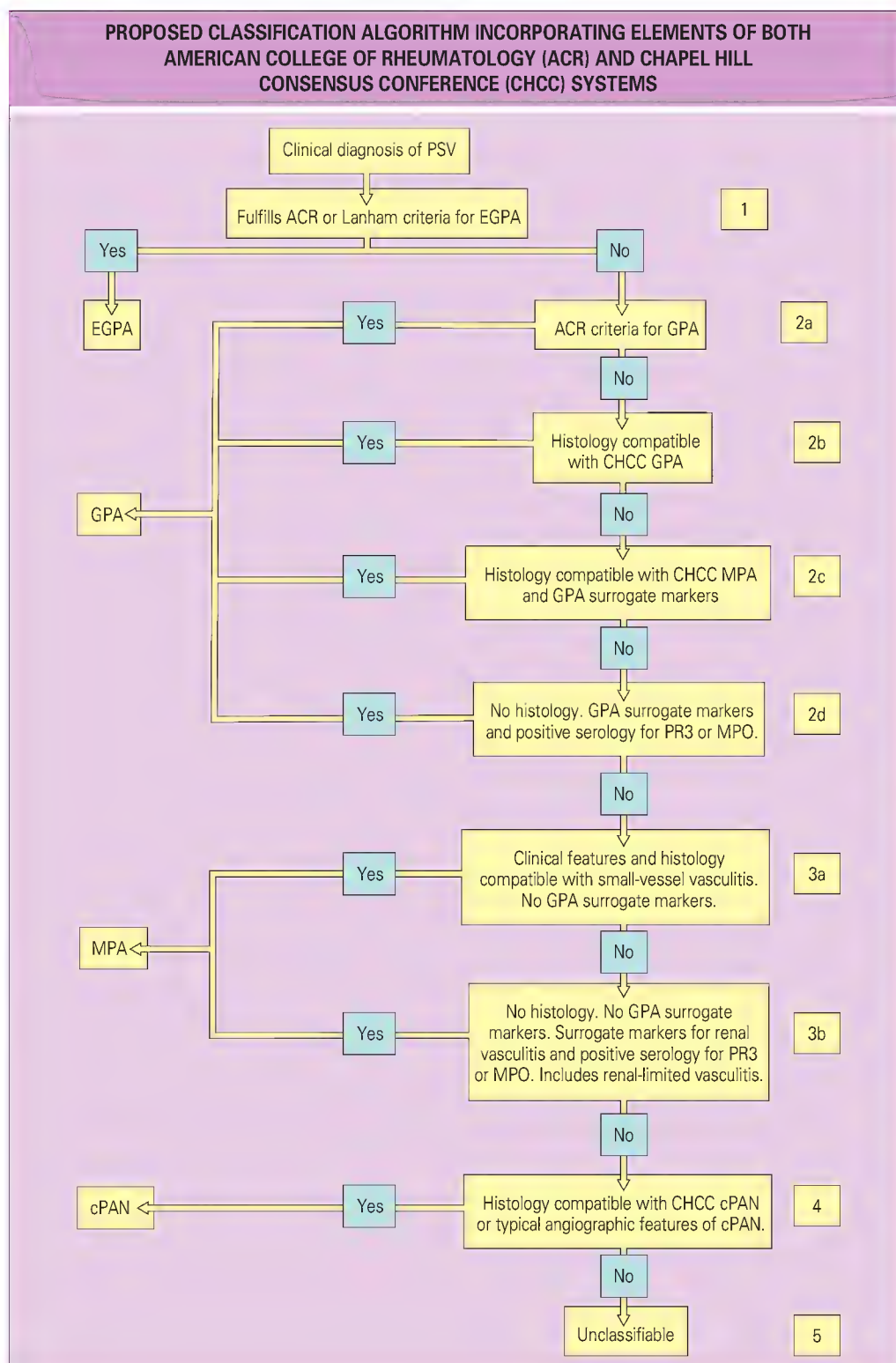


Fig. e153.1 European Medicines Agency classification algorithm for ANCA-associated vasculitis and polyarteritis nodosa. cPAN, classic polyarteritis nodosa; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; PSV, primary systemic vasculitis. (Adapted from Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007;66:222-7.)

BOX e153.1 EULAR/PreS CLASSIFICATION OUTLINE OF CHILDHOOD VASCULITIS**I. Predominantly large-vessel vasculitis**

- Takayasu arteritis

II. Predominantly medium-sized-vessel vasculitis

- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

III. Predominantly small-vessel vasculitis**A. Granulomatous**

- Granulomatosis with polyangiitis (Wegener)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

B. Nongranulomatous

- Microscopic polyangiitis
- Immunoglobulin A vasculitis (Henoch-Schönlein)
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV. Other vasculitides

- Behçet disease
- Vasculitis secondary to infection (including hepatitis B-associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue diseases
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

EULAR, European League Against Rheumatism; PreS, Pediatric Rheumatology European Society.

Adapted from Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PreS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936-41.

BOX e153.2 EULAR/PreS CLASSIFICATION CRITERIA OF CHILDHOOD VASCULITIDES**Classification criteria for immunoglobulin A vasculitis (Henoch-Schönlein)**

Palpable purpura (mandatory criterion) in the presence of at least one of the following four features:

- Diffuse abdominal pain
- Any biopsy showing predominant immunoglobulin A deposition
- Arthritis* or arthralgia
- Renal involvement (any hematuria and/or proteinuria)

Classification criteria for Kawasaki disease

Fever persisting for at least 5 days (mandatory criterion) plus four of the following five features:

- Changes in peripheral extremities or perineal area
- Polymorphous exanthema
- Bilateral conjunctival injection
- Changes of lips and oral cavity: injection of oral and pharyngeal mucosa
- Cervical lymphadenopathy

In the presence of coronary artery involvement (detected on echocardiography) and fever, fewer than four of the remaining five criteria are sufficient (the exact number of criteria required is to be defined in the validation phase).

Classification criteria for childhood polyarteritis nodosa

A systemic illness characterized by the presence of either a biopsy showing small and mid-size artery necrotizing vasculitis OR angiographic abnormalities[†] (aneurysms or occlusions) (mandatory criteria), plus at least two of the following:

- Skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions)
- Myalgia or muscle tenderness
- Systemic hypertension, relative to childhood normative data
- Mononeuropathy or polyneuropathy
- Abnormal urine analysis and/or impaired renal function[‡]
- Testicular pain or tenderness
- Signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary, or central nervous system)

Classification criteria for granulomatosis with polyangiitis (Wegener)

Three of the following six features should be present:

- Abnormal urinalysis[§]
- Granulomatous inflammation on biopsy[¶]
- Nasal sinus inflammation
- Subglottic, tracheal, or endobronchial stenosis
- Abnormal chest x-ray or CT
- PR3 ANCA or C-ANCA staining

Classification criteria for Takayasu arteritis

Angiographic abnormalities (conventional, CT, or MR) of the aorta or its main branches (mandatory criterion), plus at least one of the following four features:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference >10 mm Hg between arms
- Bruits over aorta and/or its major branches
- Hypertension (related to childhood normative data)

*Acute, any joint.

[†]Should include conventional angiography if magnetic resonance angiography is negative.

[‡]Glomerular filtration rate of <50% normal for age.

[§]Hematuria and/or significant proteinuria.

[¶]If a kidney biopsy is done, it characteristically shows necrotizing pauci-immune glomerulonephritis.

ANCA, antineutrophil cytoplasmic antibodies; CT, computed tomography; EULAR, European League Against Rheumatism; MR, magnetic resonance; PR3, proteinase 3; PreS, Pediatric Rheumatology European Society.

Adapted from Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PreS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936-41.

TABLE 153.2
American College of Rheumatology 1990 classification criteria for vasculitis

Disease	Criteria
Giant cell (temporal) arteritis (need 3 of 5 criteria for classification)	Age at disease onset ≥ 50 yr New headache Temporal artery abnormality Elevated erythrocyte sedimentation rate Abnormal temporal artery biopsy
Takayasu arteritis (need 3 of 6 criteria for classification)	Age at disease onset ≤ 40 yr Claudication of extremities Decreased brachial artery pulse Blood pressure (BP) difference > 10 mm Hg between arms Bruit over subclavian arteries or aorta Arteriogram abnormality
Polyarteritis nodosa (need 3 of 10 criteria for classification)	Weight loss ≥ 4 kg Livedo reticularis Testicular pain or tenderness Myalgias, weakness, or leg tenderness Mononeuropathy or polyneuropathy Diastolic BP > 90 mm Hg Elevated blood urea nitrogen or creatinine Hepatitis B virus Arteriographic abnormality Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils
Wegener granulomatosis (granulomatosis with polyangiitis) (need 2 of 4 criteria for classification)	Nasal or oral inflammation Abnormal chest radiograph Urinary sediment Granulomatous inflammation on biopsy
Churg-Strauss syndrome (allergic granulomatosis and angiitis; eosinophilic granulomatosis with polyangiitis) (need 4 of 6 criteria for classification)	Asthma Eosinophilia Mononeuropathy or polyneuropathy Pulmonary infiltrates, nonfixed Paranasal sinus abnormality Extravascular eosinophils
Henoch-Schönlein purpura (immunoglobulin A vasculitis) (need 2 of 4 criteria for classification)	Palpable purpura Age ≤ 20 yr at disease onset Bowel angina Wall granulocytes on biopsy
Hypersensitivity vasculitis (need 3 of 5 criteria for classification)	Age at disease onset ≥ 16 yr Medication at disease onset Palpable purpura Maculopapular rash Biopsy including arteriole and venule

Data from Hunder GG, Arend WP, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. *Introduction. Arthritis Rheum* 1990;33:1065-7.

importantly, there is the potential for different classification or diagnostic systems for the same diseases in children and adults; this could lead to confusion clinically and problems with including or comparing data from clinical trials across age groups. The field should work toward development and adoption of comprehensive sets of classification and diagnostic criteria applicable to the range of vasculitides seen in both childhood and adulthood.

Other classification criteria for vasculitides

Many other systems have been developed or proposed to classify or diagnose single vasculitides. The International Study Group for Behçet's Disease "diagnostic" criteria⁷ (Table e153.2) and the Japanese Behçet's Disease Research Committee criteria^{8,9} for Behçet disease, the American Heart Association¹⁰ "diagnostic" criteria for Kawasaki disease (Box e153.3), and classification criteria for mixed cryoglobulinemic vasculitis¹¹ each refer to vasculitides that were not included in the ACR Classification Criteria.

Additionally, other systems are used either to complement or to replace the ACR classification criteria, including the Lanham criteria for eosinophilic granulomatosis with polyangiitis,¹² the "diagnostic" criteria for Takayasu arteritis of Ishikawa¹³ (subsequently revised by Sharma and

colleagues¹⁴), the criteria for the "diagnosis" of immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura),^{15,16} and "diagnostic" criteria for polyarteritis nodosa.¹⁷

The Chapel Hill Consensus Conference definitions

In 1994 an international group of medical experts in vasculitis from various medical disciplines met as the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis (CHCC) and published their conclusions and proposals.¹⁸ The goals of the conference were, through a modified nominal group process, to agree upon the names of several forms of vasculitis and "construct root definitions for the vasculitides so named." The group stated that they were specifically *not* aiming to create a new classification scheme or diagnostic criteria for vasculitis; the CHCC definitions are meant to complement existing classification systems. In 2012 an expanded set of experts, including several members of the original 1994 group, revised the nomenclature to include new insights gained over the two intervening decades, added more forms of vasculitis and addressed issues surrounding eponyms.

The CHCC process has established a set of names and definitions for 10 forms of vasculitis (Table 153.3). Although these definitions emphasize specific pathologic findings, it was recognized that histologic criteria may be appropriately replaced by surrogate indicators. For example, although "granulomatous inflammation of the aorta and its major branches" is the definition of Takayasu arteritis, angiographic abnormalities may be assumed to indicate such aortitis.

Important advances of the CHCC proposals include the incorporation of the testing of ANCA and the inclusion of the name *microscopic polyangiitis*, which helped solidify the use of this term to define a disease now considered separate from polyarteritis nodosa. The 2012 revision extended the number and scope of vasculitides addressed by the nomenclature and should help standardize how vasculitis is referred to in the medical literature.

The CHCC proposal also has some weaknesses. The definitions were derived from consensus of expert opinion without formal validation and reliability testing and still rely on some partially subjective data elements since even histologic findings are not fully objective. For example, pathologists may view the same set of slides from a lung biopsy specimen but differ as to whether "granulomatous inflammation" is present.

The CHCC approach has had unintended consequences in that these definitions are regularly, and many feel, inappropriately applied in clinical research studies as both classification and diagnostic criteria. For example, the application of either the CHCC definitions or ACR criteria to patients with clinical diagnoses of polyarteritis nodosa or ANCA-associated vasculitides has been shown to result in substantial discordances in categorization.¹⁹

Changes regarding the use of eponyms to name vasculitides

The use of eponyms to name diseases occurs in vasculitis perhaps more so than in any other group of rheumatic diseases and has led to problems and controversies. *Wegener granulomatosis* has recently been replaced with *granulomatosis with polyangiitis* due to Dr. Wegener's association with the Nazi regime.²⁰ In keeping with the movement to replace honorific eponyms with more scientifically descriptive names, the 2012 CHCC nomenclature proposed new names for some other vasculitides (see Table 153.3).

Diagnostic criteria for vasculitis

Despite 50 years of increasingly intense study of vasculitis and multiple attempts at creating systems to describe these diseases, a generally accepted cohesive and complete set of diagnostic criteria has never been established for the vasculitides.

Neither the ACR criteria nor the CHCC definitions are ideal for use in establishing a diagnosis of vasculitis.

When formally tested for use as diagnostic criteria, the ACR classification criteria did not perform well.²¹ Similarly, the CHCC definitions were found to have poor sensitivity for the diagnosis of granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis.²²

Current status of classification, nomenclature, and diagnostic criteria for vasculitis

Classification criteria, disease definitions, and diagnostic criteria for the vasculitides have been in a state of continued evolution for more than 50 years, and the current systems, despite the shortcomings outlined earlier,

■ **TABLE e153.2**
International Study Group diagnostic criteria for Behçet disease

<i>Recurrent oral ulceration</i>	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-mo period
Plus two of:	
<i>Eye lesions</i>	Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination or Retinal vasculitis observed by ophthalmologist
<i>Skin lesions</i>	Erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions or Acneiform nodules observed by physician in postadolescent patients not receiving corticosteroid treatment
<i>Positive pathergy test</i>	Read by physician at 24-48 hr

*Findings applicable only in the absence of other clinical explanations.
From International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078-80.*

BOX e153.3 AMERICAN HEART ASSOCIATION DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE

- Fever of at least 5 days' duration
- Presence of four of the following principal features:
 - Changes in extremities
 - Polymorphous exanthem
 - Bilateral conjunctival injection
 - Changes in the lips and oral cavity
 - Cervical lymphadenopathy
- Exclusion of other diseases with similar findings*

*Include measles, scarlet fever, drug reactions, Stevens-Johnson syndrome, other febrile viral exanthemas, Rocky Mountain spotted fever, Staphylococcal scalded skin syndrome, toxic shock syndrome, juvenile rheumatoid arthritis, leptospirosis, mercury poisoning. Patients with fever and fewer than four principal clinical features can be diagnosed as having Kawasaki disease when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography.
From Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993;87:1776-80.

■ TABLE 153.3

Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference (CHCC) on the nomenclature of systemic vasculitis

CHCC 2012 name	CHCC 2012 definition
Large vessel vasculitis (LVV)	Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected.
Takayasu arteritis (TAK)	Arteritis, often granulomatous, predominantly affecting the aorta and its major branches. Onset usually in patients younger than 50 yr.
Giant cell arteritis (GCA)	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 yr and often associated with polymyalgia rheumatica.
Medium vessel vasculitis (MVV)	Vasculitis predominantly affecting medium arteries defined as the main visceral arteries and their branches. Any size artery may be affected. Inflammatory aneurysms and stenoses are common.
Polyarteritis nodosa (PAN)	Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCA).
Kawasaki disease (KD)	Arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries. Coronary arteries are often involved. Aorta and large arteries may be involved. Usually occurs in infants and young children.
Small vessel vasculitis (SVV)	Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium arteries and veins may be affected.
ANCA-associated vasculitis (AAV)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries). Associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCA-negative.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (Wegener) (GPA)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common.
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.
Immune complex vasculitis	Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent.
Anti-glomerular basement membrane (anti-GBM) disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.
Cryoglobulinemic vasculitis (CV)	Vasculitis with cryoglobulin immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved.
Immunoglobulin A vasculitis (Henoch-Schönlein) (IgAV)	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur.
Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)	Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common.
Variable vessel vasculitis (VVV)	Vasculitis with no predominant type of vessel involved that can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries).
Behçet's disease (BD)	Vasculitis occurring in patients with Behçet's disease that can affect arteries or veins. Behçet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur.
Cogan syndrome (CS)	Vasculitis occurring in patients with Cogan syndrome characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis (affecting small, medium, or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis.
Single-organ vasculitis (SOV)	Vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a system vasculitis. The involved organ and vessel type should be included in the name (e.g., cutaneous small vessel vasculitis, testicular arteritis, central nervous system vasculitis). Vasculitis distribution may be unifocal or multifocal (diffuse) within an organ. Some patients originally diagnosed as having SOV will develop additional disease manifestations that warrant redefining the case as one of the systemic vasculitides (e.g., cutaneous arteritis later becoming systemic polyarteritis nodosa).
Vasculitis associated with systemic disease	Vasculitis that is associated with and may be secondary to (caused by) a systemic disease. The name (diagnosis) should have a prefix term specifying the systemic disease (e.g., rheumatoid vasculitis, lupus vasculitis).
Vasculitis associated with probable etiology	Vasculitis that is associated with a probably specific etiology. The name (diagnosis) should have a prefix term specifying the association (e.g., hydralazine-associated microscopic polyangiitis, hepatitis B virus-associated vasculitis, hepatitis B virus-associated cryoglobulinemic vasculitis).

From Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum* 2013;65:1-11.

have proved quite useful for clinicians and clinical researchers. However, there is still room for progress. The existence and use of multiple such systems leads to confusion, and the resulting heterogeneity may hamper clinical research and comparison of clinical studies in vasculitis.

There is a need to continue to work toward a set of classification and diagnostic criteria that are inclusive, are comprehensive, are meaningful to both researchers and clinicians, include both children and adult patients, incorporate readily available and reliable clinical data, are derived more through a data-driven process than expert opinion, reflect current understanding of the pathophysiology of the various diseases, and achieve international acceptance. Furthermore, the classification and diagnostic systems should ideally share common data elements and avoid contradictions. The international vasculitis community is currently conducting a large collaborative project aimed at readdressing both classification and diagnostic criteria for the vasculitides.

EPIDEMIOLOGY OF VASCULITIS

The principles of epidemiology are described in Chapter 1. Both descriptive and analytic epidemiologic research techniques have been applied to the study of vasculitis.

Epidemiologic research in vasculitis

Several intriguing clinical observations have stimulated epidemiologic research in vasculitis. Observations of racial, geographic, periodic, or seasonal variations in disease frequency for some vasculitides raise fascinating issues and generate hypotheses about the underlying causes of these diseases. However, epidemiologic research also faces several challenges. Because all vasculitides are rare diseases and substantial resources are required to collect data for larger numbers of patients, the quality of the epidemiologic data accumulated for the vasculitides is heterogeneous. Although some disorders have been well studied, for others epidemiologic characteristics remain poorly understood. Furthermore, differences in diagnostic classification, as discussed in the previous section, are also an important concern.

The following section summarizes the knowledge on epidemiology for the most common vasculitides. Some primary vasculitides (e.g., central nervous system vasculitis or anti-glomerular basement membrane disease) and the secondary vasculitides are not covered.

Vasculitides predominantly affecting large vessels *Giant cell arteritis*

Giant cell arteritis (GCA) is the most common among the primary vasculitides with an annual incidence (in the population of individuals at least 50 years of age) between 2.4 and 32.8 cases per 100,000 people.²³⁻⁴⁰ [Table e153.3](#) summarizes the available incidence data for GCA. Studies strongly suggest that GCA affects primarily populations of Northern European ancestry and rarely occurs outside of white populations.⁴¹ There is evidence that the incidence of GCA has increased over the last 50 years by a factor of 2 to 5,⁴² a trend at least partly explained by an increased awareness of the disease by clinicians and identification of patients with negative findings on temporal artery biopsy.^{42,43}

The role of genetic factors is indirectly suggested by observations of familial cases of GCA⁴⁴ and by occurrence of GCA in monozygotic twins.⁴⁵ There is also a well-established association between GCA and the HLA class II genes and particularly the HLA-DRB1*04 allele, which is carried by more than 50% of patients according to case series.^{25,40,46-51} Various other genetic polymorphisms have been described in the context of GCA; for example, the genes encoding tumor necrosis factor, ICAM-1, RANTES, MICA, interleukin-1 (IL-1) receptor antagonist,⁵² and IL-10.⁵³

An infectious cause of GCA has been suggested by periodic and seasonal variations in its incidence, as well as by the observation that the initial development of GCA is often preceded by infectious episodes^{24,26,32,39,54}; however, neither sets of initial findings have been able to be reproduced.^{28,39,55} Furthermore, studies seeking to identify a causal infectious agent for GCA have yielded mixed results.^{34,56-61}

Other environmental factors associated with GCA include smoking,^{62,63} hormonal factors (as suggested by the negative association between number of pregnancies and GCA),⁶⁴ a history of previous atherosclerotic vascular disease,^{62,63} and sun exposure.⁵⁴

Takayasu arteritis

Epidemiologic data on Takayasu arteritis are scarce. The clinical observation that Takayasu arteritis might predominantly affect nonwhite

populations—for example, Asians or South Americans—is not yet well substantiated by the scarce descriptive population-based studies. The annual incidence of Takayasu arteritis has been estimated in different geographic regions quite uniformly with rates (per million inhabitants) of 0.4 in Denmark,⁶⁵ 0/4 to 0.8 in the United Kingdom,⁶⁶ 0.8 in Sweden,⁶⁷ 1 to 2 in Japan,⁶⁸ 2.2 in Kuwait,⁶⁹ and 2.6 in the United States.⁷⁰ In contrast, prevalence estimates suggest that Takayasu arteritis might indeed be several-fold more common in Japan (40 per million inhabitants)⁶⁶ compared with the United Kingdom (4.7 to 7.1)⁶⁶ or Sweden (6.4).⁶⁷

A genetic predisposition to Takayasu arteritis is suggested by findings of an association between Takayasu arteritis and HLA alleles, particularly HLA-B52^{71,72} and HLA-B39.⁷¹ A genomewide association study identified further susceptibility loci within the HLA region and within the *FCGR2A/FCGR3A* locus.⁷³ The long-suggested hypothesis that infection with *Mycobacterium tuberculosis* might play a role in the pathogenesis of Takayasu arteritis⁷⁴ remains unconfirmed.

Vasculitides predominantly affecting medium-sized vessels *Polyarteritis nodosa*

Epidemiologic data referring to polyarteritis nodosa (PAN) must be interpreted cautiously in light of the wide variability that exists in the diagnostic and classification criteria for PAN. The prevalence and annual incidence of PAN were estimated, respectively, at 2 to 33 per million inhabitants⁷⁵⁻⁷⁹ and 0 to 16 per million inhabitants.⁸⁰⁻⁸⁵

There is circumstantial evidence that PAN is associated with chronic hepatitis B virus infection,⁸⁵⁻⁸⁷ and this association is now well accepted. Data from case series suggest that in the 1970s and 1980s, approximately half of the patients diagnosed with PAN were chronically infected with the hepatitis B virus.⁸⁸ Over the past 20 years, the percentage of patients with PAN associated with hepatitis B virus in Western nations has become much smaller, likely as a consequence of large vaccination campaigns against hepatitis B virus.⁸⁸ It is commonly believed that PAN affects white people almost exclusively.⁷⁷

Kawasaki disease

Kawasaki disease (KD) is the most common form of vasculitis in children. The annual incidence (per 100,000 children younger than 5 years of age) is estimated at 216 in Japan⁸⁹ and at 113 in Taiwan.⁹⁰ To date, more than 180,000 cases have been recorded in Japan,⁹¹ with three notable peaks in incidence occurring in 1979, 1982, and 1986. Seasonal variation in the onset of KD has been described, with outbreaks occurring in the winter and the spring.⁹²

Outside of Asia, KD is much less common, with an approximately 10-fold to 20-fold lower incidence than that reported by studies in Asia.⁴¹ In addition, in the United States, KD affects children of Asian descent much more than African American or white children.⁹³

Genetic studies using candidate gene approaches have not been able to convincingly demonstrate a genetic predisposition to KD, and KD does not seem to be associated with any specific HLA antigen. One study suggested a possible role for genes involved in the synthesis of immunoglobulins.⁹⁴ Much stronger evidence for a genetic underpinning to KD was provided by recent genomewide association studies, which identified *FCGR2A* and several other loci as putative contributors to KD susceptibility.⁹⁵⁻⁹⁸

Several factors point strongly toward an infectious cause of KD, including the onset in early childhood, the clinical manifestations, the existence of secular peaks in the incidence, and seasonal variations. An association between KD and a history of a previous respiratory infection has been demonstrated⁹⁹; however, no specific microorganism has yet been linked to KD. Other associations with KD reported include exposure to rug shampoo¹⁰⁰ and residence in a home near water.⁹³

Vasculitides predominantly affecting small vessels *Granulomatosis with polyangiitis*

Among the three ANCA-associated vasculitides, granulomatosis with polyangiitis (GPA) is the best studied with respect to epidemiology. Prevalence and annual incidence rates of GPA, which have been reported mostly for Europe, were estimated at 24 to 160 per million inhabitants and 2.1 to 15 per million inhabitants, respectively¹⁰¹ ([Fig. 153.1](#) and [Table e153.4](#)). These data suggest a rise in the frequency of GPA over the last several decades, which can be at least partially explained by the introduction and widespread availability of ANCA testing since the late 1980s.¹⁰¹

The results of descriptive studies support a decreasing north-to-south gradient in the incidence of GPA in the Northern Hemisphere¹⁰² (see



TABLE e153.3

Population-based annual incidence estimates (per 100,000 people aged ≥ 50) for giant cell arteritis in various countries

Study	Country of study	Study period	Incidence (per 100,000)
United States			
Salvarani et al ²⁶	United States	1950-1991	17.8
Salvarani et al ⁴²	United States	1950-1999	18.8
Smith et al ³¹	United States	1971-1980	1.58
Northern Europe			
Baldursson et al ²³	Iceland	1984-1990	27
Rajala et al ⁴⁰	Finland	1969-1989	4.5-9.2
Haugeberg et al ³⁷	Norway	1992-1996	29.1-32.8
Gran et al ³⁶	Norway	1987-1994	29.0
Petursdottir et al ³⁹	Sweden	1976-1995	22.2
Elling et al ³⁴	Denmark	1982-1994	20.4
Jonasson et al ²⁴	Scotland	1964-1977	4.2
Smeeth et al ²⁹	United Kingdom	1990-2001	22
Reinhold-Keller et al ²⁷	Germany	1998-2002	2.5-4.6
Barrier et al ³⁰	France	1970-1979	9.4
Southern Europe			
Salvarani et al ²⁵	Italy	1980-1988	6.9
Gonzales-Gay et al ²⁸	Spain	1981-1998	10.2
Sonnenblick et al ³²	Israel	1980-1991	10.2

TABLE e153.4

Population-based prevalence estimates (per 1,000,000) for GPA, MPA, and EGPA in various countries

Study	Country	Study period	GPA	MPA	EGPA
North America					
Cotch et al ⁴⁷	United States	1986-1990	26-32		
Europe					
Koldingsnes et al ¹⁴⁸	Norway	1994-1998	95		
Mohammad et al ⁷⁸	Sweden	2002	160	94	14
Haugeberg et al ⁷⁶	Norway	1996	53		13
Watts et al ⁸⁴	United Kingdom	1988-1997	63		
Watts et al ¹⁴⁹	United Kingdom	2005	65		
Reinhold-Keller et al ⁷⁹	Germany	1994	42-58	0-9	2-7
Mahr et al ⁷⁷	France	2000	24	25	11
Oceania					
Ormerod et al ⁷⁵	Australia	1995-2004	64-95	18-39	12-22
Gibson et al ¹⁵⁰	New Zealand	2003	112	37	

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

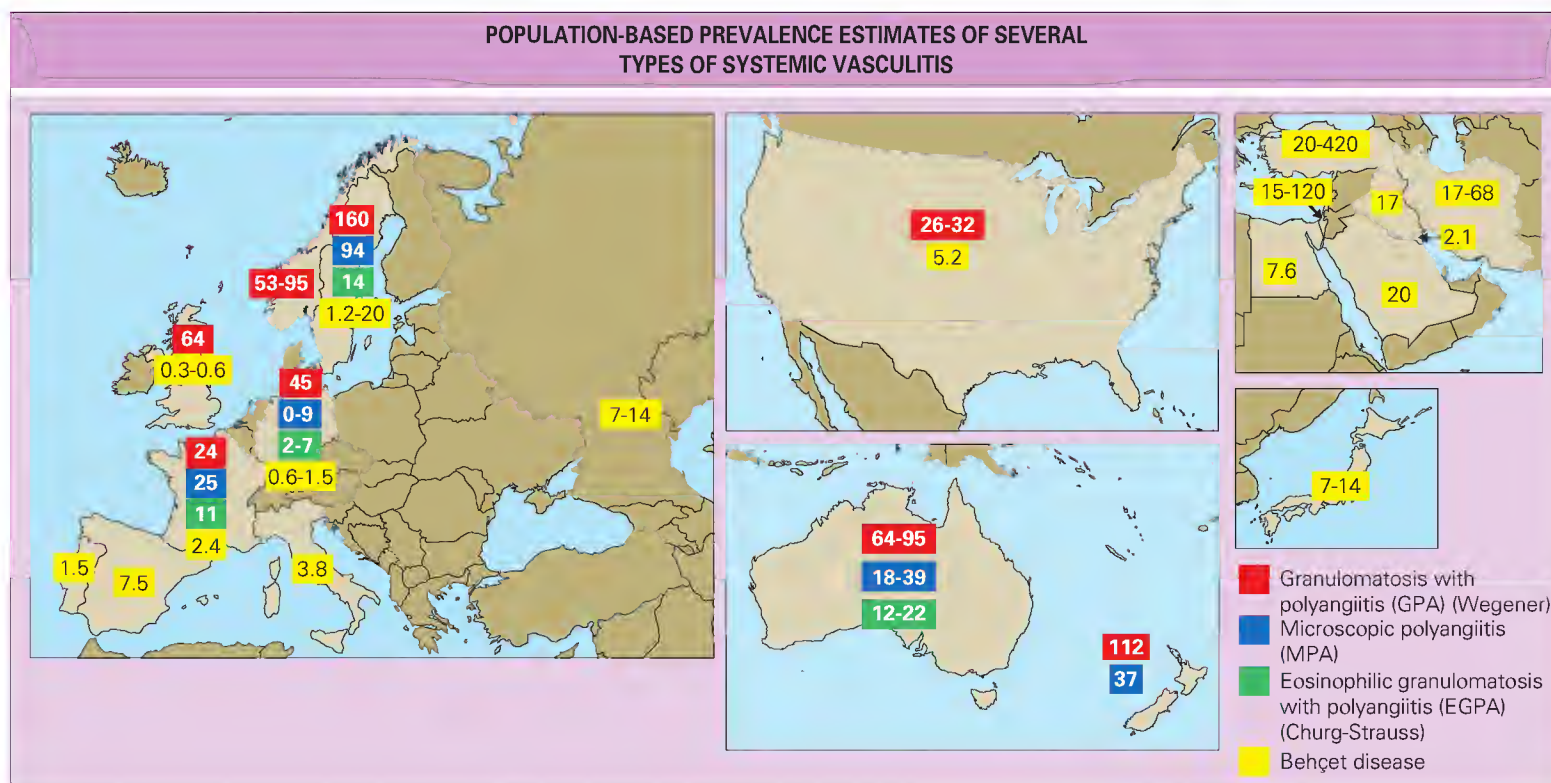


Fig. 153.1 Prevalence of systemic vasculitides per 1,000,000 persons (for GPA, MPA, and EGPA) or per 100,000 persons (for Behçet disease) in various countries. Values represent ranges from several studies with some averaging/rounding performed. Map is not perfectly to scale.

Fig. 153.1). The increased frequency in higher latitudes could point to a protective role of sunlight exposure.¹⁰³ Evidence is also increasing with respect to the low risk of GPA in Asian or African populations.^{77,104} A comparative analysis of populations in the United Kingdom and Japan found similar incidence rates for ANCA-associated vasculitis, but GPA was seven times less commonly seen in the Japanese population.¹⁰⁴

The knowledge of the role of genetics in the development of GPA has increased substantially in recent years. The most widely reproduced genetic link to GPA identified by case-control studies using a candidate gene approach relates to the Z allele of the gene encoding α_1 -antitrypsin (*SERPINA1*).¹⁰⁵ Associations of GPA with HLA antigens and other genes, including those encoding PTPN22, proteinase 3, and CTLA-4, have been reported by candidate gene studies.¹⁰¹ Some of these association were recently replicated by two genomewide association studies, which yielded associations of GPA with the HLA-DPB region,^{106,107} *SERPINA1*, and the gene encoding proteinase 3.¹⁰⁶

Compared with the effect of genetic factors, the role of environmental factors in causing GPA remains relatively poorly investigated. Exposure to silica is the most consistently reported risk factor and confers a risk increase (odds ratio) of between 2 and 14.¹⁰¹ The results of case-control studies suggested other environmental risk factors; for example, farming and exposure to livestock, organic solvents, industrial pollutants, or pesticides.¹⁰¹ The hypothesis of an infectious origin of GPA has been long emphasized, but no causal microorganism has yet been identified. Nasal carriage of *Staphylococcus aureus* has been linked to an increased risk of disease relapses.¹⁰⁸ Studies focusing on seasonal variations in the onset of GPA have yielded conflicting results.¹⁰⁹

Microscopic polyangiitis

The epidemiology of microscopic polyangiitis (MPA) is less well described than that of GPA (see Fig. 153.1 and Table e153.4). Based on reported estimates, the prevalence of MPA varies from 0 to 94 per million inhabitants and the annual incidence varies from 1 to 10.1 per million inhabitants in Europe.¹⁰¹ In Kuwait and Japan, the annual incidence of MPA has been estimated to be 24.5 and 18.2 per million inhabitants, respectively.^{101,104} Comparisons of incidence rates have raised the possibility that MPA is more common in Asian than in European populations¹⁰⁴ and has a frequency gradient inverse to the one seen in GPA, with a greater frequency in the countries in the south of Europe¹⁰² (see Fig. 153.1). However, the existence of such a gradient remains to be confirmed and is called into question by recent Swedish studies that reported high prevalence and incidence figures for MPA.¹⁰¹

Only a few genetic studies have specifically focused on MPA. Most studies examined MPA together with GPA or within a combined set of ANCA-positive vasculitides with antimyeloperoxidase specificity. MPA has been associated with a polymorphism of a gene coding for IL-10.¹¹⁰ In Japan, a link has been shown between MPA and the HLA-DRB*0901 allele,^{111,112} the I-haplotype DRB1*0901-DQB1*0303,¹¹³ and killer cell immunoglobulin-like receptor genotypes.¹¹³ A link has also been shown between the number of copies of the FCGR3B gene and the risks of MPA or GPA in European patients.¹¹⁴ More recently, a genomewide association study in Europe found that MPA was associated with HLA-DQ.¹⁰⁶

As is true for GPA, silica exposure was shown to be a risk factor for MPA.¹⁰¹

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is the least common of the ANCA-associated vasculitides. The few descriptive investigations carried out in Europe and Australia indicate that EGPA prevalence ranges between 2 and 22 per million inhabitants¹⁰¹ (see Fig. 153.1 and Table e153.4). The annual incidence (per million inhabitants) has been estimated at 0 to 3.7 in Europe, 2.2 to 2.3 in Australia, 0.8 to 2.8 in New Zealand,¹⁰¹ and 2.4 in Japan.¹⁰⁴

Genetic candidate gene association studies suggest that HLA-DRB1*04 and DRB1*07 are potential susceptibility factors for EGPA.^{115,116} Another study found an association of the functional variant of IL-10 gene in ANCA-negative cases of EGPA.¹¹⁷

Because EGPA usually occurs in association with asthma and allergy symptoms, including rhinitis and sinusitis, a hypersensitivity response has been proposed for the pathogenesis of EGPA. Many observations were reported of the occurrence of EGPA following exposure to various medications, vaccination, or desensitization,¹¹⁸ but none of these studies was definitive or accounted for the majority of cases. Much attention has focused on the potential causal or triggering role of leukotriene receptor antagonists (e.g., montelukast, zafirlukast, and pranlukast). However, results of pharmacoepidemiologic studies suggest that the association between this class of asthma medications and the development of EGPA is likely confounded by the severity of the asthma associated with EGPA.¹¹⁹ As is the case with GPA and MPA, a possible link also exists between EGPA and exposure to silica.¹⁰¹

Immunoglobulin A vasculitis (Henoch-Schönlein purpura)

IgA vasculitis is the most common vasculitis encountered in children in Western countries. Its annual incidence is estimated at between 6.1 and

26.7 per 100,000 children.¹²⁰ These studies suggest that IgA vasculitis is more frequent among children of Asian ancestry (24 per 100,000 infants per year) than in white children (17.8 per 100,000 infants per year) or black children (6.2 per 100,000 infants per year).¹²¹ IgA vasculitis is much rarer in adults than in children, with an annual incidence of 1.1 to 1.8 per 100,000 adults.¹²⁰

A genetic predisposition for IgA vasculitis is suggested by the unequal ethnic distribution and by the association of IgA vasculitis with HLA-DRB1*01, DRB1*11, B35, and A11; the familial Mediterranean fever (MEFV) gene; and the angiotensin-converting enzyme insertion/deletion gene.¹²⁰

Among environmental factors, infections are the leading presumed cause of IgA vasculitis. IgA vasculitis occurs more readily during the winter¹²² and is frequently preceded by an upper or lower airway infection. Several viral and bacterial agents have been implicated in the etiology of IgA vasculitis, but none seems to be the universal cause.¹²⁰ Antigenic stimulations in response to medications, toxins, or food products have been described as preceding the onset of IgA vasculitis,¹²³ but this remains to be confirmed and is not consistently supported by epidemiologic surveys.¹²⁰ In adults, an association of IgA vasculitis with cancers has been described, with a relative risk of concurrent or preceding cancer of 5.3 among patients with IgA vasculitis compared with a matched control group.¹²⁴

Vasculitides affecting vessels of various size

Behçet disease

The epidemiology of Behçet disease (BD) is characterized by a striking geographic disparity with more frequent occurrences in an area spanning from East Asia to the Mediterranean Sea. Therefore BD is sometimes also called the *Silk Road disease*, but the idea that the environmental or genetic cause of BD might have been disseminated throughout this ancient trade route is hypothetical.



Table e153.5 summarizes the many prevalence studies conducted in BD. The highest prevalence of BD has been reported for areas in Turkey, with estimates ranging from 20 to 420 per 100,000 inhabitants.¹²⁵ Studies carried out in populations in Southeast Asia and the Middle East show a prevalence between 2.1 and 120 per 100,000 inhabitants.¹²⁵ In the United States and in Western European countries, prevalence of BD is much lower, with rates between 0.27 and 7.50 per 100,000 inhabitants.¹²⁵⁻¹²⁷

Several studies have addressed the question of risk of BD in migrant populations. Among Turks living in West Berlin, Germany, the prevalence of BD is approximately 40 times higher than in their peers of German descent.¹²⁸ Similarly, in Paris, France, BD is approximately 17 times more frequent among people of Northern African background than among the population with French or other European origins,¹²⁹ and in Sweden it is 7 times more frequent among non-Swedish individuals.¹²⁶ Although a microenvironmental or socioeconomic factor cannot be excluded, these observations support the view that genetic factors play a central role in the development of BD.

There are additional lines of evidence to support the idea that genetic factors are critical in determining susceptibility to BD, including a high familial recurrence rate,^{129,130} concordance for BD between monozygotic twins,^{131,132} and the phenomenon of “genetic anticipation.”¹³³ For pediatric BD, results of a segregation analysis are in keeping with a possible autosomal recessive inheritance pattern.¹³⁴ Additionally, the HLA class I allele B51 is a well-established genetic marker tightly associated with BD.¹³⁵ A meta-analysis found that this allele is carried by 34% to 64% of patients and increases the risk of developing BD by a factor of 5.8.¹³⁵ The results of genomewide association studies further suggested *IL23R-IL12RB2*, *IL10*,^{136,137} *CCR1*, and *STAT4*¹³⁸ as susceptibility loci for BD.

In contrast to the effect of genetic factors, the potential role of environmental determinants in the development of BD remains poorly studied, although infectious causes have been proposed.¹³⁹

Current status of epidemiologic research in the vasculitides

In spite of their rarity, which considerably hampers the conduct of large-scale studies, there has been much progress in the field of epidemiologic research for several of the vasculitides. These studies have helped advance hypotheses regarding the etiologies of many vasculitides. It now seems clear that the different entities have different underlying pathogenic mechanisms which combine, to various extents, with specific genetic backgrounds and environmental factors. Further epidemiologic studies and large-scale genetic association studies will help discern the relative contributions and interactions of genetics and environment to the pathogenesis of these diseases and help unravel the relationships among the individual vasculitides and between the vasculitides and nonvasculitic disorders.

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■ TABLE e153.5

Population-based prevalence estimates (per 100,000) for Behçet disease in various countries

Study	Country of study	Prevalence
North America		
O'Duffy (1978) ¹⁵¹	United States	0.3
Calamia et al (2009) ¹²⁷	United States	5.2
Europe		
Chamberlain (1977) ¹⁵²	England	0.6
Jankowski et al (1992) ¹⁵³	Scotland	0.3
Crespo et al (1993) ¹⁵⁴	Portugal	1.5
Ek et al (1993) ¹⁵⁵	Sweden	1.2
Zouboulis et al (1997) ¹²⁸	Germany	0.6
Sanchez Burson et al (1998) ¹⁵⁶	Spain	7.5
Papoutsis et al (2006) ¹⁵⁷	Germany	1.5
Salvarani et al (2007) ¹⁵⁸	Italy	3.8
Mahr et al (2008) ¹²⁵	France	2.4
Mohammad et al (2013) ¹²⁶	Sweden	2.0
Asia		
Yamamoto et al (1974) ¹⁵⁹	Japan	7.0-8.5
Demirhindi et al (1981) ¹⁶⁰	Turkey	80
Mousa et al (1986) ¹⁶¹	Kuwait	2.1
Yurdakul et al (1988) ¹⁶²	Turkey	370
Davatchi et al (1997) ¹⁶³	Iran	16.7
Al-Dalaan et al (1997) ¹⁶⁴	Saudi Arabia	19.5
Nakae et al (1993) ¹⁶⁵	Japan	13.5
Idil et al (2002) ¹⁶⁶	Turkey	110
Jaber et al (2002) ¹⁶⁷	Israel	120
Al-Rawi et al (2003) ¹⁶⁸	Iraq	17
Azizlerli et al (2003) ¹⁶⁹	Turkey	420
Cakir et al (2004) ¹⁷⁰	Turkey	20
Krause et al (2007) ¹⁷¹	Israel	15.2
Davatchi et al (2007) ¹⁷²	Iran	68
Africa		
Assaad-Khalil et al (1997) ¹⁷³	Egypt	7.6

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Biology and immunopathogenesis of vasculitis

■ CEES G.M. KALLENBERG

- The endothelium is an active player in inflammatory processes in general and in the pathogenesis of vasculitis in particular.
- Cytokine-induced endothelial cell activation and leukocyte-endothelium interaction are coordinated processes underlying differential leukocyte recruitment to sites of inflammation.
- Immune complex formation and deposition underlie the small-vessel vasculitides in immunoglobulin A vasculitis (Henoch-Schönlein purpura), anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, and hypocomplementemic urticarial vasculitis.
- Clinical and experimental data suggest but do not prove that antineutrophil cytoplasmic antibodies (ANCA) directed against proteinase 3 and myeloperoxidase are pathogenic in the ANCA-associated small-vessel vasculitides.
- Cell-mediated immunity—in particular, a helper T type 1 and helper T type 17 CD4+ T-cell response to as yet undefined antigen(s)—is the major pathogenic event in the medium- and large-vessel vasculitides.

INTRODUCTION

Vasculitis is a condition characterized by inflammation of blood vessels. Its clinical manifestations depend on the location and size of the involved vessels as well as on the nature of the inflammatory process. The vasculitides are localized or systemic diseases with a variable clinical expression. At the Chapel Hill Consensus Conference (CHCC) in 1993 a classification of vasculitides was proposed based largely on the size of the vessels involved, the histopathologic features of the lesions, and clinical findings.¹ By consensus, definitions were proposed for the individual diseases, but it was not the aim of the conference to develop classification criteria (see Chapter 153). Nevertheless, these definitions have been used since then for classifying vasculitis into specific categories. Recently, the nomenclature of the vasculitides has been revised, with inclusion of various conditions not mentioned in the original CHCC nomenclature and an attempt to classify vasculitides also based on underlying condition and probable etiology (Box 154.1).²

As mentioned, vasculitis concerns inflammatory reactions of the blood vessel wall. The vascular endothelium, being at the interface of the circulating bloodstream and the structural components of vascular and perivascular tissue, plays a major role in vasculitis. Cells from the innate and adaptive immune system have to adhere to and pass the endothelium to evoke inflammation in the vessel wall. The endothelium is an active player in this process. Endothelial cells differ in morphology and function depending on their location in the body. Macrovascular endothelial cells are different from microvascular endothelial cells, and various artery-derived endothelial cells are not identical to venous endothelial cells. Because various forms of vasculitis differ in their involvement of the vascular tree, characteristics of the respective endothelia may be relevant for our understanding of the systemic vasculitides.

Therefore, first a discussion is presented of the role of endothelial cells in inflammation. Next, the immunopathogenesis of the major vasculitides is discussed; that is, the vasculitides of the large and medium-sized vessels in which immune deposits are generally absent, the small-vessel vasculitides characterized by immune deposits, and the so-called pauci-immune small-vessel vasculitides that are frequently associated with antineutrophil cytoplasmic autoantibodies (ANCA).

THE ENDOTHELIUM IN INFLAMMATION

The endothelium constitutes a single layer of cells that covers the inner side of blood vessels. It functions as a passive lining of the vasculature and is also actively involved in many physiologic and pathophysiologic processes. The endothelium is not a homogeneous layer of cells throughout the body, but its characteristics and functions differ depending on the size and location of the vessels. In addition, it may change in function and activity after contact with stimuli that are generated locally or systemically.

Larger blood vessels consist of endothelial cells, smooth muscle cells, connective tissue, and elastic elements. The endothelium in these vessels actively participates in the regulation of vascular tone, which determines blood flow to specific organs. Vasodilating effects mostly originate from the production of prostacyclin and nitric oxide by endothelial cells, whereas vasoconstriction is brought about in large part by endothelin-1 and arachidonic acid metabolites, in particular thromboxane A₂ and prostaglandin H₂.³ Particular attention has been paid to dysfunction of endothelial cells in regulating vascular tone as an early manifestation of atherosclerosis.⁴ Also in systemic autoimmune diseases, including systemic vasculitis, endothelial cell dysfunction has been implicated as a major factor underlying early atherosclerosis in these diseases.⁵ *In vitro* studies of endothelial cell function in health and disease using human umbilical vein endothelial cells are frequently used as a model for macrovascular endothelium or for endothelium in general. Their characteristics and functions are not always representative of endothelial cell function *in vivo*. Nevertheless, studies on human umbilical vein endothelial cells have contributed greatly to our knowledge of the endothelium. Presently, microvascular endothelial cells of a different origin (e.g., glomerular endothelial cells) are available for *in vitro* studies and may be more relevant for the investigation of endothelial function in specific disease processes.⁶

In the microvascular bed, endothelial cells reside on a basal lamina with sparsely distributed pericytes around them. These pericytes have important functions in maintaining the integrity of the microvasculature. Loss of pericytes results in endothelial hyperplasia and increased permeability of the endothelium.⁷

The endothelium has the following main functions:

- Providing a semipermeable barrier for transport of soluble molecules
- Maintaining hemostatic balances
- Controlling local blood flow (e.g., via nitric oxide and endothelin-1)
- Regulating coordinated recruitment of leukocytes
- Participating in neovascularization

Although the molecular base of these functions differs, changes in these functions occur in a coordinated way upon stimulation, in particular via proinflammatory cytokines, during inflammation.

Endothelial cell activation during inflammation

Local, or sometimes systemic, recruitment of proinflammatory cytokines results in receptor-mediated activation of endothelial cells. The main representatives are tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and IL-17. In addition, thrombotic agonists such as thrombin and, less frequently, oxidants and traumatic stimuli can activate endothelial cells. The first step that follows is the rapid translocation of constitutively present P-selectin from storage granules, the so-called Weibel-Palade bodies. The next step is the transcriptionally regulated synthesis of E-selectin, which is expressed on the endothelial cell surface. In a timely coordinated way a number of other adhesion molecules are produced and expressed on the endothelial cell membrane that are differentially involved in the recruitment



BOX 154.1 NAMES FOR VASCULITIDES ADOPTED BY THE 2012 INTERNATIONAL CHAPEL HILL CONSENSUS CONFERENCE ON THE NOMENCLATURE OF VASCULITIDES
Large-vessel vasculitis (LVV)

Takayasu arteritis (TAK)

Giant cell arteritis (GCA)

Medium-vessel vasculitis (MVV)

Polyarteritis nodosa (PAN)

Kawasaki disease (KD)

Small-vessel vasculitis (SVV)

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Microscopic polyangiitis (MPA)

Granulomatosis with polyangiitis (Wegener granulomatosis) (GPA)

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis) (EGPA)

Immune complex SVV

Anti-glomerular basement membrane (anti-GBM) disease

Cryoglobulinemic vasculitis (CV)

Immunoglobulin A vasculitis (Henoch-Schönlein purpura) (IgAV)

Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Variable-vessel vasculitis (VVV)

Behçet disease (BD)

Cogan syndrome (CS)

Single-organ vasculitis (SOV)

Cutaneous leukocytoclastic angiitis

Cutaneous arteritis

Primary central nervous system vasculitis

Isolated aortitis

Others

Vasculitis associated with systemic disease

Lupus vasculitis

Rheumatoid vasculitis

Sarcoid vasculitis

Others

Vasculitis associated with probable etiology

Hepatitis C virus-associated cryoglobulinemic vasculitis

Hepatitis B virus-associated vasculitis

Syphilis-associated aortitis

Drug-associated immune complex vasculitis

Drug-associated ANCA-associated vasculitis

Cancer-associated vasculitis

Others

of various subsets of leukocytes (see later). These molecules include vascular cell adhesion molecule 1 (VCAM-1); intercellular adhesion molecule 1 (ICAM-1), ICAM-2, and ICAM-3; and receptors for leukocyte integrins, such as very late antigen 4 (VLA-4).⁸ In addition, endothelially displaced chemoattractants, called *arrest chemokines*, are produced that induce conformational changes in certain leukocyte integrins that allow their interaction with endothelial adhesion molecules.⁹ Besides producing and upregulating adhesion molecules that regulate leukocyte recruitment, endothelial cell-activating stimuli also affect hemostatic balance. In particular, they induce the production and expression of tissue factor by endothelial cells resulting in a procoagulant state during inflammation. During inflammation, proangiogenic factors—that is, vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2)—also are produced that interact with endothelial cells, which results in angiogenesis, particularly during chronic inflammatory responses. Hypoxic conditions at the site of inflammation induce the expression of hypoxia-inducible factor 1 (HIF-1), a transcription factor expressed in many cells that leads to the expression of genes involved in angiogenesis.¹⁰ For this reason, HIF-1 could be a target for treatment in chronic inflammatory diseases.

Several signal-transducing pathways are involved in endothelial cell activation, and insight into these pathways has stimulated the development of drugs that interfere with these pathways.¹¹ The pathways mostly studied *in vitro* are the TNF- α - and IL-1-mediated signal transduction routes. Soluble TNF- α is released as a trimer and interacts with the TNF receptors TNFR1 and TNFR2. TNFR1 is present on endothelial cells. Interaction of TNF- α with TNFR1 results in a cascade of reactions (as shown in Fig. e154.1). Via nuclear factor- κ B activation the endothelial cells express the adhesion molecules E-selectin, ICAM-1, and VCAM-1; the proinflammatory cytokine

IL-6; the polymorphonuclear neutrophil (PMN) recruiting and activating chemokine IL-8; inducible nitric oxide synthase (iNOS); cyclooxygenase-2; and others. At the same time, protective genes are expressed with antiapoptotic and downregulatory activity. This prevents the activated endothelial cells from going into apoptosis.

Nevertheless, activated endothelial cells, probably in an early apoptotic state, may detach and be present in the bloodstream as circulating endothelial cells. Increased levels of circulating endothelial cells have been reported in active cytomegalovirus infection and in different forms of vasculitis. In ANCA-associated vasculitis their level correlates with disease activity.¹² These circulating endothelial cells were also shown to inhibit endothelial progenitor cells and, for this reason, to contribute to vascular damage, because these endothelial progenitor cells play a major role in repairing injured vessels.¹³ Also, endothelial microparticles have been demonstrated in increased numbers in peripheral blood in patients with active vasculitis. These microparticles are released from endothelial cells and express E-selectin; they should be distinguished from platelet microparticles that express CD42a and are also increased in active vasculitis, and from neutrophil microparticles that are released *in vitro* from ANCA-stimulated neutrophils and activate endothelial cells.^{14,15}

In addition to the TNF- α /TNFR1 pathway, IL-1 is also operative in activating endothelial cells. Endothelial cells express one type of receptor for IL-1, the IL-1R, which binds IL-1 α with higher affinity than IL-1 β . IL-1 β is the soluble form of IL-1 derived from biologically inactive pro-IL-1 β by enzymatic cleavage via caspase-1 and next released. The signal transduction routes involved in endothelial cell activation by IL-1 largely follow the pathways described for TNF- α (see Fig. e154.1).

The effects seem synergistic, however. This may be relevant in view of pharmacologic intervention in both pathways—that is, TNF- α - and IL-1-mediated endothelial cell activation—in vasculitis.

Leukocyte-endothelium interaction

Local recruitment of cells participating in the immune response is essential for immune homeostasis. As mentioned earlier, the coordinated upregulation of adhesion molecules on activation of endothelial cells is instrumental in starting an inflammatory reaction. P-selectin, constitutively present in Weibel-Palade granules, is rapidly translocated to the endothelial cell membrane. This allows the first interaction with circulating neutrophils via P-selectin glycoprotein ligand 1 (PSGL-1), the principal ligand for P-selectin on the neutrophil membrane. This interaction results in tethering of the PMN on the endothelial cell surface. This is rapidly followed, within a couple of hours, by transcription and translation of E-selectin, which appears next on the endothelial cell membrane. E-selectin interacts with sialyl Lewis^x on the PMN. This interaction, together with the binding of L-selectin on PMNs to its ligands on activated endothelial cells, results in a state of rolling of PMNs over the endothelial surface (Fig. e154.2). The rolling neutrophil is now locally activated by signaling molecules, produced by the locally activated endothelium, that bind to G protein-coupled receptors on the neutrophil. These molecules include platelet-activating factor, which is rapidly synthesized and has a phospholipid structure, and the chemokines IL-8 and epithelial neutrophil-activating peptide-78, in addition to the arrest chemokines mentioned earlier.⁹ As part of this activation process of PMNs, β_2 integrins, ligands for a group of adhesion molecules that next appear on activated endothelial cells, undergo conformational alterations resulting in changes in avidity and affinity and are now able to interact with these adhesion molecules that 4 to 12 hours after activation appear on the endothelial cell membrane. The β_2 integrins on leukocytes include the CD11a/CD18 and lymphocyte function-associated antigen 1 (LFA-1) complex that interacts with ICAM-1 and ICAM-2 on activated endothelial cells (see Fig. e154.2). Together with VCAM-1, these molecules belong to the immunoglobulin superfamily. VCAM-1 is the ligand for VLA-4, also indicated as the α_4 integrins, which is expressed on lymphocytes. After these latter ligand-ligand interactions, leukocytes adhere firmly to the endothelium in an activated state.⁸

The next step is when the leukocyte squeezes itself through the endothelium into the surrounding tissue where it follows its way guided by chemokine concentration gradients. This process of diapedesis through the endothelium requires active involvement of molecules located at the junctions of endothelial cells. At least six molecules are involved in junctioning two endothelial cells by homophilic interaction. These include vascular endothelial cell-specific cadherin (VE-cadherin); the junction adhesion molecules JAM-A, JAM-B, and JAM-C; platelet-endothelial cell adhesion molecule-1 (PECAM-1); and CD99.¹⁶ Partial redistribution of these adhesion molecules induced by cytokine stimulation of endothelial cells loosens the junctions and allows the leukocyte to enter the space between the

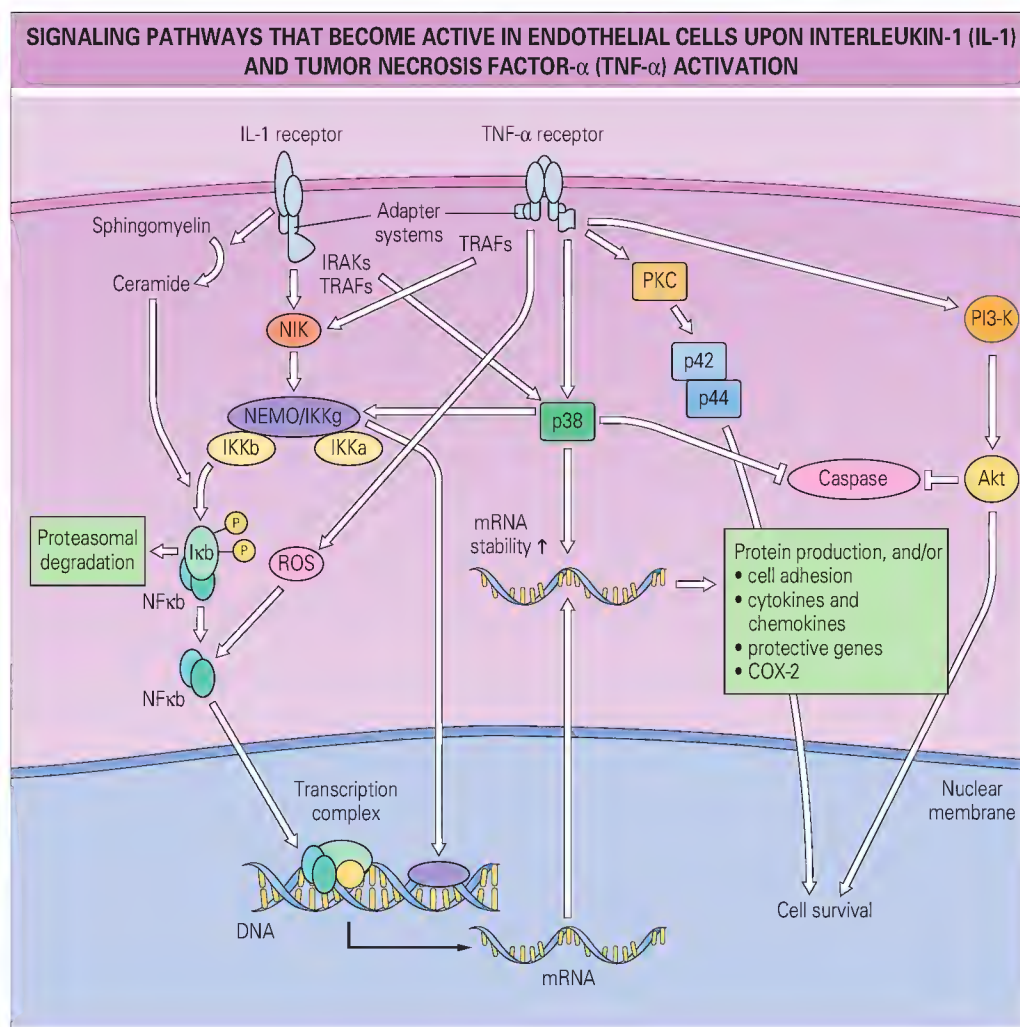


Fig. e154.1 The activation of interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) leads to the expression of proinflammatory genes, including those for cell adhesion molecules, cytokines, and chemokines, as well as cell survival genes. Several pathways result in the activation of the transcription factor nuclear factor- κ B (NF- κ B). At the same time, antiapoptotic signals are generated that prevent apoptosis of the activated endothelial cell. COX-2, cyclooxygenase-2; IKK, I κ B kinase; I κ B, inhibitor of NF- κ B; IRAK, IL-1 receptor-associated kinase; mRNA, messenger RNA; NEMO, NF- κ B essential modulator; NIK, NF- κ B-inducing kinase; PI3-K, phosphatidylinositol 3'-kinase; PKC, protein kinase C; ROS, reactive oxygen species; TRAF2, TNF receptor-associated factor 2. (From Kuldo JM, Ogawara KI, Werner N, et al. Molecular pathways of endothelial cell activation for [targeted] pharmacologic intervention in chronic inflammatory diseases. *Curr Vasc Pharmacol* 2005;3:11-39.)

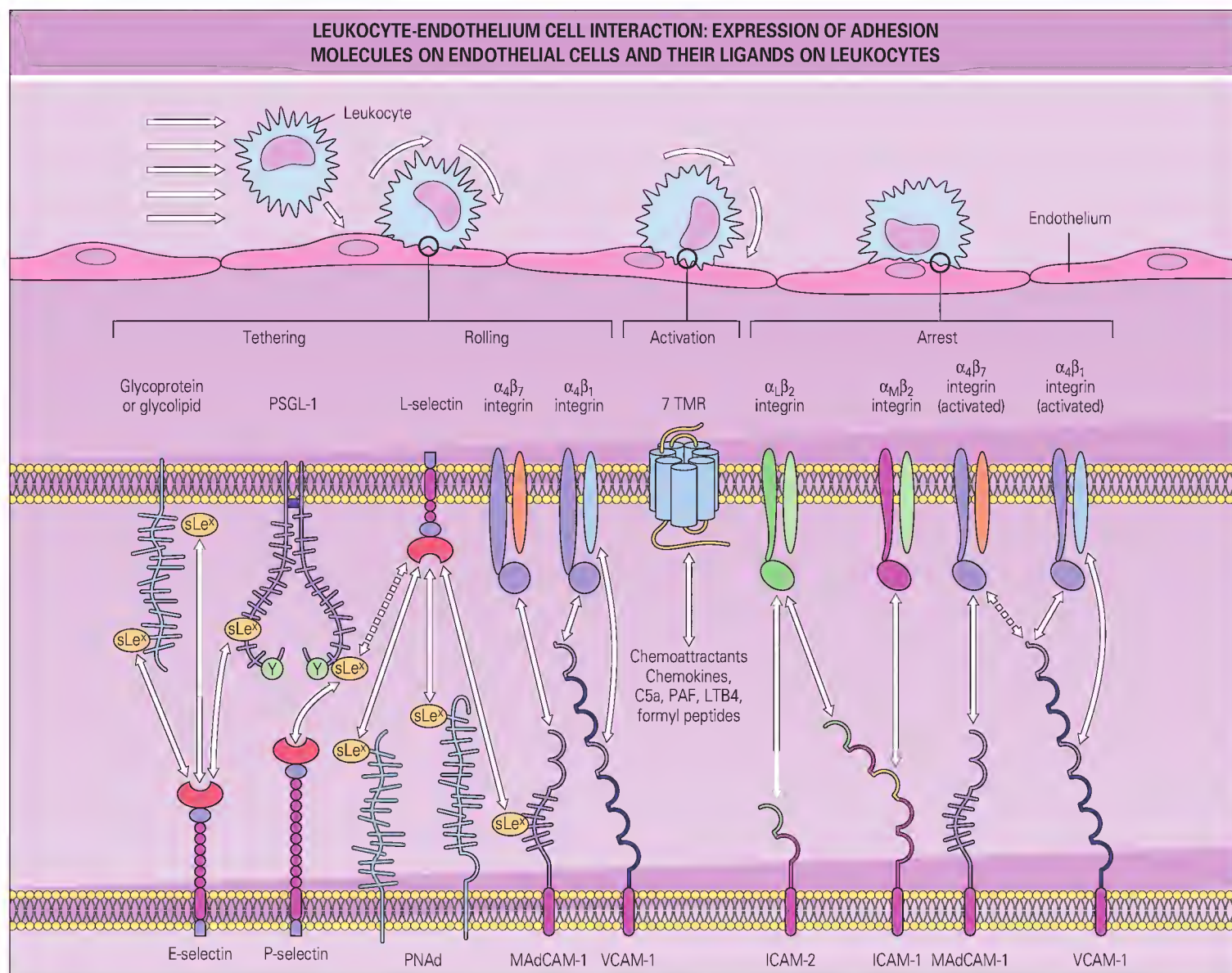


Fig. e154.2 The four distinct steps in adhesion that leukocytes must undergo to accumulate in a blood vessel are shown at the top of the diagram. Also shown are the predominant molecular determinants of each step with respect to leukocytes (middle of the diagram) and endothelial cells (bottom of the diagram). The arrows in the middle portion indicate the various interactions possible between molecules. Leukocytes in the bloodstream (the graduated set of arrows at the top of the diagram) symbolize the laminar flow profile in blood vessels, where the velocity of blood is fastest in the center and approaches zero at the vessel wall) become tethered to endothelial cells and roll slowly downstream. Tethering is greatly facilitated by leukocyte receptors that occur at high density on the tips of microvillous surface protrusions (L-selectin, P-selectin glycoprotein ligand 1 [PSGL-1], and α_4 integrins), whereas subsequent rolling is not influenced by the topography of adhesion receptors. The most efficient tethering molecules are L-selectin and P-selectin. L-selectin recognizes sulfated sialyl Lewis^x (sLe^x)—like sugars, called *peripheral-node addressin* (PNAd), in high endothelial venules. L-selectin also interacts with other ligands on inflamed endothelial cells (not shown) and with PSGL-1 on adherent leukocytes (indicated by the dashed arrow). The binding of PSGL-1 to L-selectin and P-selectin requires an sLe^x-like sugar to be close to an N-terminal motif containing three tyrosines (Y) that must be sulfated. E-selectin can also interact with PSGL-1, but it does not require tyrosine sulfation. E-selectin also recognizes other sLe^x-bearing glycoconjugates. E-selectin and the α_4 integrins can tether some leukocytes, but their predominant function is to reduce the velocity of rolling. Rolling leukocytes respond to chemoattractants on endothelial cells because they express specific receptors with seven transmembrane domains (7 TMR), which transmit intracellular signals through G proteins. The most prominent chemoattractants that bind to 7 TMR are listed in the figure. Some of these molecules, such as chemokines, are presented on the endothelial surface; others are secreted or diffuse freely into the vessel lumen. The activating signal induces rapid activation of β_2 integrins, α_4 integrins, or both, which bind to members of the endothelial immunoglobulin superfamily. The α_4 integrins can mediate activation-independent rolling interactions as well as arrest rolling leukocytes. However, the latter function requires the activation of α_4 integrins (illustrated by the more open conformation of the integrin heterodimer, compared with that of α_4 integrins that mediate rolling). C5a, activated C5; ICAM-1, ICAM-2, intercellular adhesion molecules 1 and 2; LTB₄, leukotriene B₄; MAdCAM-1, mucosal addressin cell adhesion molecule type 1; PAF, platelet-activating factor; VCAM-1, vascular cell adhesion molecule 1. (Reproduced with permission from von Adrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. *N Engl J Med* 2000;343:1020-34.)

endothelial cells. It should be mentioned that PECAM-1, CD99, JAM-A, and JAM-C are found also on leukocytes and that homophilic interactions between leukocytes and endothelial cells certainly play a role in transmigration of leukocytes as well. This process of transmigration is an active process also for the endothelial cell because calcium influx in endothelial cells is required for effective diapedesis. Recent data suggest that, in addition to engaging in this so-called paracellular transmigration, leukocytes may also follow a transcellular route of transmigration in which cytoskeletal remodeling and membrane fusion events play a major role.¹⁷

Leukocyte-endothelial cell interaction preferentially occurs in postcapillary venules. It is noteworthy that many forms of small-vessel vasculitis are manifested by leukocytoclastic vasculitis localized in postcapillary venules, particularly in the skin. Here, PMNs do not pass the vascular wall but become fully activated, followed by apoptosis and necrosis within the vessel wall. The role of immune complexes and ANCAs in this process is discussed later in the section on small-vessel vasculitis.

Endothelium, coagulation, and inflammation

Tissue factor is upregulated in endothelial cells activated by, among others, proinflammatory cytokines. Tissue factor is a transmembrane protein that initiates coagulation. It can be expressed by malignant cells and macrophages as well and plays a role in angiogenesis, particularly in tumor development. In the resting state, endothelium has antithrombotic characteristics based on the expression of thrombomodulin, heparan sulfate proteoglycans that bind and activate antithrombin III, prostacyclin, ecto-adenosine diphosphatase, and receptors for fibrinolytic agents, such as plasminogen and tissue plasminogen activator. One of the first steps in endothelial cell activation is the translocation of P-selectin from the Weibel-Palade bodies to the membrane of endothelial cells. Interaction of P-selectin with PSGL-1 on leukocytes induces the upregulation of tissue factor, which initiates the coagulation cascade. In addition, it leads to the formation of platelet-leukocyte aggregates and the production of procoagulant microparticles that are tissue factor positive as well. Furthermore, P-selectin on activated platelets contributes to the recruitment of these microparticles to thrombi. Thus P-selectin expression plays a major initiating role in the development of the procoagulant state of endothelium in inflammation. The prothrombotic state of activated endothelial cells is further highlighted by the loss of thrombomodulin and heparan sulfate proteoglycans. Indeed, elevated levels of serum thrombomodulin occur in many forms of vasculitis and have been proposed as markers of disease activity.

Damage and repair: angiogenesis

In chronic inflammatory conditions such as rheumatoid arthritis angiogenesis is part of the inflammatory process.¹⁸ Three different processes are involved in angiogenesis: angiogenic sprouting, intussusceptive growth, and seeding of endothelial progenitor cells in newly formed blood vessels.

Sprouting from endothelial cells occurs in the presence of hypoxemia. It first requires degradation of the endothelial cell basement membrane via production of metalloproteinases and gelatinases by the activated endothelial cell. Sprouting endothelial cells need a new basement membrane as well as pericytes for their further development. Locally produced platelet-derived growth factor (PDGF) and transforming growth factor- β are major players in this process. Endothelial cell proliferation itself is under the control of angiogenic factors called *angiopoietins*. The best characterized are VEGF and FGF. Both factors are produced by a variety of cells, and HIF-1 (see earlier) is the major transcription factor involved.¹⁰ Receptors for VEGF, which itself occurs in various forms, are expressed on endothelial cells but also on monocytes and smooth muscle cells. Binding of VEGF to its receptor on the endothelial cell leads to a cascade of signal transduction steps that finally result in vessel hyperpermeability via production of platelet-activating factor, cell proliferation with inhibition of apoptosis after activation, and actin reorganization and cell migration.¹⁹ As mentioned earlier, endothelial progenitor cells also play a role in neovascularization and repair. Endothelial progenitor cells, derived from stem cells, constitute 0.01% of peripheral blood mononuclear cells and are characterized by the surface markers CD34 and VEGF receptor type 2, although there is still controversy on their characterization.²⁰ Under the influence of several factors, among which are VEGF, granulocyte-macrophage colony-stimulating factor, erythropoietin, tissue ischemia, and, interestingly, hydroxymethylglutaryl-coenzyme A reductase inhibitors, these cells can be mobilized and induced to proliferate. Different sources of endothelial progenitor cells have been identified, and their role in chronic inflammatory conditions is not yet well defined,^{11,19} although they have been suggested to contribute to vascular repair in vasculitis.¹⁴

IMMUNOPATHOGENESIS OF SMALL-VESSEL VASCULITIDES

Based on the 2012 CHCC classification,² the small-vessel vasculitides show vasculitic involvement of arterioles, capillaries, or venules. Larger vessels may be involved as well. Within this category two groups are identified: the immune complex-mediated small-vessel vasculitides and the ANCA-associated vasculitides. The former group encompasses IgA vasculitis (Henoch-Schönlein purpura) and cryoglobulinemic vasculitis as the two most prevalent conditions and, in addition, anti-glomerular basement membrane (anti-GBM) disease and hypocomplementemic urticarial vasculitis (anti-C1q vasculitis); the second group consists of granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

Immune complex-mediated small-vessel vasculitides

Since 1970, immune complexes have been considered as pathogenic factors in many forms of vasculitis. In some of the vasculitides associated with probable etiology (see Box 154.1) in particular, immune complexes consisting of microbial antigens or drugs and their cognate antibodies may be operative in pathogenesis. Although immune deposits, that is, immunoglobulin and complement, have been detected by direct immunofluorescence in vessel walls, the antigens supposedly involved in the complexes have been identified only in a minority of cases. Nevertheless, small-vessel vasculitis in the presence of immune deposits should always raise suspicion of an underlying disorder, either one of the connective tissue diseases or an infectious disorder. In particular, infective endocarditis may mimic idiopathic small-vessel vasculitides. Chronic immune stimulation during infections may even result in polyclonal B-cell stimulation with production of autoantibodies such as rheumatoid factor (RF), antinuclear antibodies, and ANCA, the last frequently but not always of unspecified antigenic specificity. Within the spectrum of idiopathic vasculitides, the 2012 CHCC classification defined IgA vasculitis, anti-GBM disease, cryoglobulinemic vasculitis, and hypocomplementemic urticarial vasculitis as disorders that are characterized by the presence of immune deposits within the vessel wall.

Immunoglobulin A vasculitis (Henoch-Schönlein purpura)

IgA vasculitis is defined by the CHCC as “a vasculitis with IgA1-dominant immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles); often involves skin and gastrointestinal tract and frequently causes arthritis; glomerulonephritis indistinguishable from IgA nephropathy may occur.”²² This definition implies that IgA1-containing complexes are the primary pathogenic factor in this disease. Indeed, deposition of polymeric IgA1 in combination with complement C3 has been found in capillaries and postcapillary venules in skin, gastrointestinal tract, and glomeruli in IgA vasculitis (Fig. 154.1). Within the kidney, IgA1 deposits are found in the glomerular capillary wall and in the mesangium, with the mesangium being the main location of IgA1 deposits. Data relating to the pathogenesis of IgA vasculitis are derived also from studies of IgA nephropathy because no major biologic differences have been found between the two diseases.^{21,22} The origin of polymeric IgA1 that is deposited in the vessel wall in IgA vasculitis has not been fully clarified. Serum IgA consists mainly of monomeric IgA1, and IgA from mucosal surfaces consists of 60% of polymeric IgA2 (two IgA2 molecules connected by a J protein). Total serum IgA level is increased in around 50% of patients with IgA vasculitis, and this increase involves both monomeric IgA1 and polymeric IgA1.^{21,22} Increase in IgA level has been related to increased production due to stimulation of the mucosal immune system. However, no consistent antigen(s) have been detected in the immune deposits. Otherwise, precipitation and induction of relapse of IgA vasculitis has been associated with microbial infections, drugs, and food antigens.²²

Whether primary disturbances in immunoregulation underlie increased IgA production in IgA vasculitis is not clear. Besides increased production, impaired clearance of IgA1 has been demonstrated. It should be noted that high levels of IgA1 in themselves do not result in IgA vasculitis. In patients with IgA1 myeloma or human immunodeficiency virus infection with increased IgA levels, precipitation of IgA vasculitis has not been observed. Abnormal glycosylation of IgA, particularly in the hinge region of the molecule, has been implicated as a causal factor for abnormal clearance and formation of complexes of IgA with fibronectin, lectin, IgG, and IgA1 itself (resulting in polymeric IgA1). Abnormal glycosylation of IgA is particularly present in patients with nephritis as part of IgA vasculitis.²¹ It has been suggested that this abnormal glycosylation constitutes neopeptides on IgA1

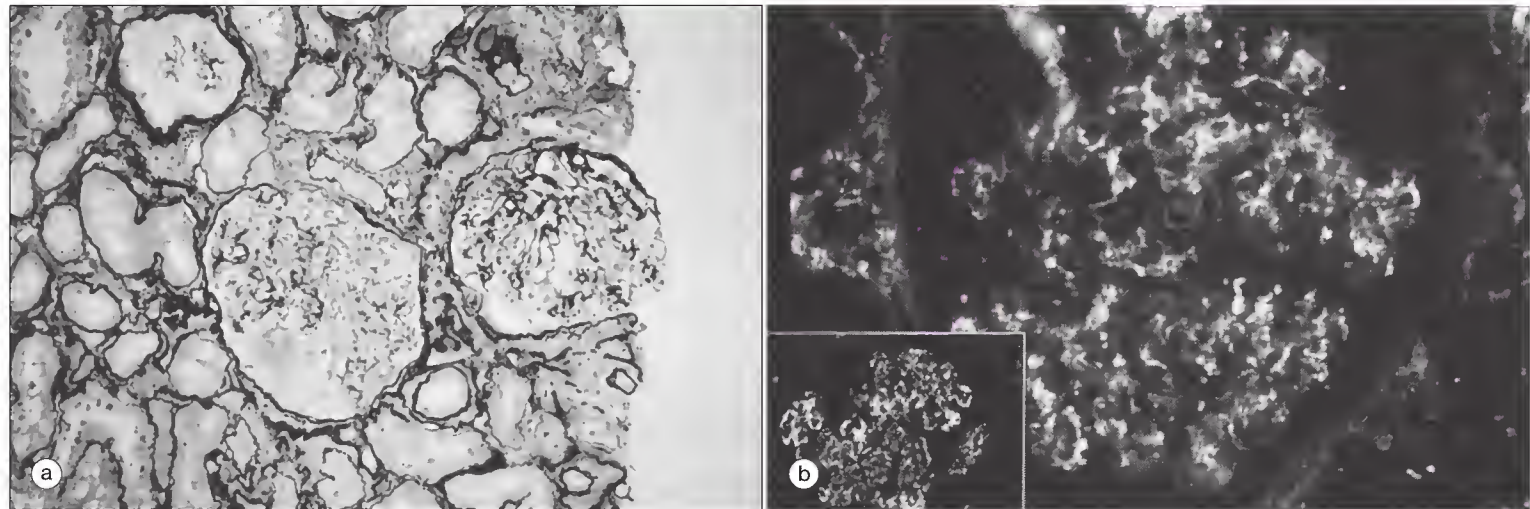


Fig. 154.1 Nephritis in immunoglobulin A (IgA) vasculitis (Henoch-Schönlein nephritis). (a) Renal biopsy was performed in a 45-year-old woman with recurrent cutaneous vasculitis and episodes of gastrointestinal vasculitis of 2 years' duration because of recent-onset erythrocyturia and severe proteinuria. Specimen shows a focal and segmental extracapillary crescentic glomerulonephritis of recent origin (silver methenamine, hematoxylin-eosin, $\times 50$). (b) Staining with monoclonal anti-IgA1 antibodies shows diffuse glomerular and granular deposits in the mesangia and locally in the capillary wall. Inset: staining for C3 shows a similar pattern (immunofluorescence, anti-IgA, $\times 125$).

that induce IgG class antibodies that complex with abnormally glycosylated IgA. These complexes could be pathogenic factors in nephritis as part of IgA vasculitis and IgA nephropathy by activating mesangial cells²¹ (Fig. 154.2). A genetic basis of aberrant glycosylation has been suggested.²³

How do increased levels of IgA and/or abnormally structured IgA result in immune complex-mediated vasculitis? Both immune complex deposition from the circulation and *in situ* complex formation may play a role, because in 50% of patients circulating immune complexes are not demonstrated to be present. Polymeric IgA1 can interact with Fc α receptors on mesangial cells and activate these cells, which results in mesangial glomerulonephritis. Otherwise, subendothelial deposition or *in situ* complex formation can result in complement activation either via the alternative pathway with deposition of properdin and/or via the mannan-binding lectin pathway. Coprecipitation of IgG and/or IgM may incidentally lead to complement activation via the classical pathway as well. Subendothelial deposition results in endocapillary proliferation and crescent formation in the kidneys.²¹

Leukocytoclastic vasculitis in the skin and gastrointestinal tract in IgA vasculitis is induced by subendothelial immune deposition, which results in endothelial activation with upregulation of adhesion molecules. Recruitment of neutrophils is further stimulated via production of chemokines such as IL-8 by activated endothelial cells. Polymeric IgA or IgA complexes may activate these neutrophils additionally.

Anti-glomerular basement membrane disease

Anti-GBM disease is defined by the CHCC as “vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti-basement membrane autoantibodies; lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.”²² The clinical syndrome of pulmonary hemorrhage and necrotizing crescentic glomerulonephritis is designated also as *Goodpasture syndrome*. This syndrome can be due to anti-GBM disease but can also be present in ANCA-associated vasculitis and other forms of small-vessel vasculitis. For this reason the term *renopulmonary syndrome* is preferred to avoid the use of *Goodpasture syndrome* as synonymous with anti-GBM disease.

The autoantibodies in anti-GBM disease are directed against the C-terminal globular (NC1) domain of a tissue-specific type IV collagen chain, the $\alpha 3$ chain, or $\alpha 3(\text{IV})\text{NC1}$ in abbreviation.²⁴ The same epitopes are recognized in all patients. In direct immunofluorescence testing of renal tissue from patients with anti-GBM disease a linear pattern of GBM staining is seen for IgG and complement C3. The pathogenicity of these autoantibodies has been demonstrated by eluting IgG class antibodies from kidneys of patients with anti-GBM disease and injecting the eluates in monkeys. This resulted in deposition of the antibodies and complement at the GBM and glomerulonephritis but without crescent formation. Further studies, both in experimental animals and in humans, demonstrated that cellular immunity as well is required for lesion development, including crescent formation in human anti-GBM disease.²⁵

MAJOR STEPS IN THE PATHOGENESIS OF NEPHRITIS AS PART OF IGA VASCULITIS AND IGA NEPHROPATHY

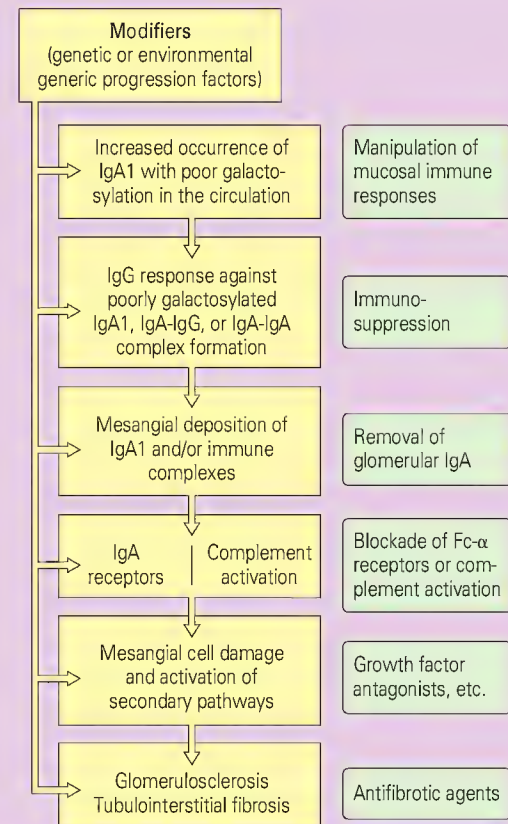


Fig. 154.2 Each of the key steps (center) in the pathogenesis of nephritis in immunoglobulin A (IgA) vasculitis and IgA nephropathy likely is affected by potent genetic or environmental modifiers. Potential therapeutic consequences are shown on the right. (Reproduced with permission from Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? *Am J Kidney Dis* 2011;58:992-1000.)

Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis is defined according to the 2012 CHCC classification as “vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum; skin, glomeruli and peripheral nerves are often involved.”²

The main element in the pathogenesis of this disorder is the presence of cryoglobulins that are cold-precipitable immunoglobulins. Three types of cryoglobulins are detectable:

Type I, found in 10% to 15% of patients, consists of monoclonal IgM-RF and originates in the context of a lymphoproliferative or myeloproliferative disease.

Type II, occurring in 50% to 60% of patients, consists of monoclonal IgM-RF and polyclonal IgG.

Type III, found in 30% to 40% of patients, consists of polyclonal IgM-RF and polyclonal IgG.

Type II and type III cryoglobulins are collectively referred to as *mixed cryoglobulins*. These mixed cryoglobulins have been detected during chronic bacterial and viral infections and as part of (systemic) autoimmune diseases, in particular in Sjögren syndrome. The remaining idiopathic cases are designated as *essential mixed cryoglobulinemia*. It has become apparent, however, that many cases of essential mixed cryoglobulinemia are related to hepatitis C virus (HCV) infection.²⁶ The percentage of HCV-related cases differs among geographic areas, ranging from 40% to 100%, with a 90% association in the Mediterranean countries.

The etiopathogenesis of essential mixed cryoglobulinemia without HCV infection has not been clarified, but polyclonal B-cell activation and/or antigen/superantigen-driven B-cell activation have been suggested. More insight has been obtained into the etiopathogenesis of mixed cryoglobulinemia associated with HCV infection. Various explanations have been proposed for HCV-induced cryoglobulin production. The HCV envelope protein E2 can bind to CD81, which is present on hepatocytes and lymphocytes as well, and trigger a polyclonal B-cell response. Also, IgG with anti-HCV reactivity can induce IgM-RF molecules with a particular cross-idiotype. At that stage, low-titer type III cryoglobulins are present. Next, a single dominant clone-producing monoclonal IgM-RF emerges, which results in the production of high-titer type II cryoglobulins. This event can result in progression into a malignant B-cell lymphoma. B-cell proliferation particularly occurs within the CD5-positive subtype, which is a dominant B-cell type in other autoimmune diseases as well. Thus it seems that IgG anti-HCV core antibodies select a particular RF repertoire. This explains the presence of HCV-related proteins in the skin blood vessels of patients with type II mixed cryoglobulinemia.²⁷

The clinical manifestations of (HCV-related) mixed cryoglobulinemia are purpura, arthritis/arthralgia, peripheral neuropathy, and nephritis. The full-blown spectrum of the disease is seen in association with type II cryoglobulins. HCV proteins are present in the dermis and epidermis, but vascular damage develops in the presence of IgM and IgG molecules only, in

conjunction with complement deposition. Endothelial activation with upregulation of adhesion molecules attracts neutrophils, which leads to leukocytoclastic vasculitis. Within the kidney, subendothelial cryoglobulin deposition results in membranoproliferative glomerulonephritis type I, occurring in 20% to 30% of patients (Fig. 154.3). Here also, HCV core proteins can be detected. Vasculitis of small- and medium-sized renal arteries occurs in one third of patients. Focal, immune complex-mediated glomerulonephritis may occur in type III cryoglobulinemia and is much milder than in type II cryoglobulinemia. Neuropathy has been considered to result from vasculitis of the vasa nervorum.

Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Hypocomplementemic urticarial vasculitis is defined by the 2012 CHCC as “vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels and associated with anti-C1q antibodies; glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common.”² Lesions show leukocytoclastic vasculitis with deposition of immunoglobulins and complement. The disease can be idiopathic or associated with systemic autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome; infectious diseases, in particular hepatitis B and C; use of medication; malignancies; and other conditions. Autoantibodies to the collagenous part of C1q are invariably present in patients with the idiopathic variety of the disease. Anti-C1q autoantibodies are, however, far from specific for the disease, and their primary pathogenic role in hypocomplementemic urticarial vasculitis has not been proven.²⁸

Antineutrophil cytoplasmic antibody-associated vasculitides

Unlike in IgA vasculitis and cryoglobulinemic vasculitis, in ANCA-associated vasculitides—that is, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)—immune deposits are generally, but not always, absent at the lesional sites. These disorders are characterized by the presence of autoantibodies against cytoplasmic constituents of neutrophils and monocytes, designated as ANCAs (Fig. 154.4). ANCAs in the vasculitides are directed either against proteinase 3 (PR3), a third serine protease besides elastase and cathepsin G that is found in neutrophil granules, or against myeloperoxidase (MPO).^{29,30} Three lines of evidence suggest, but do not prove, that PR3-ANCAs and MPO-ANCAs are involved in the pathogenesis of their associated disorders.

First, PR3-ANCA and MPO-ANCA are closely associated with GPA, MPA, and EGPA. Diagnostic sensitivity and specificity, as derived from several studies, are given in Table 154.1. In EGPA, MPO-ANCAs are associated with typical vasculitic lesions, whereas in the absence of ANCAs, eosinophilic infiltration, generally without apparent small-vessel vasculitis, predominates.³¹ Furthermore, increase in levels of ANCAs has been shown to precede relapses of the associated disease. The predictive value of an increase in ANCA titer in patients with GPA as measured by

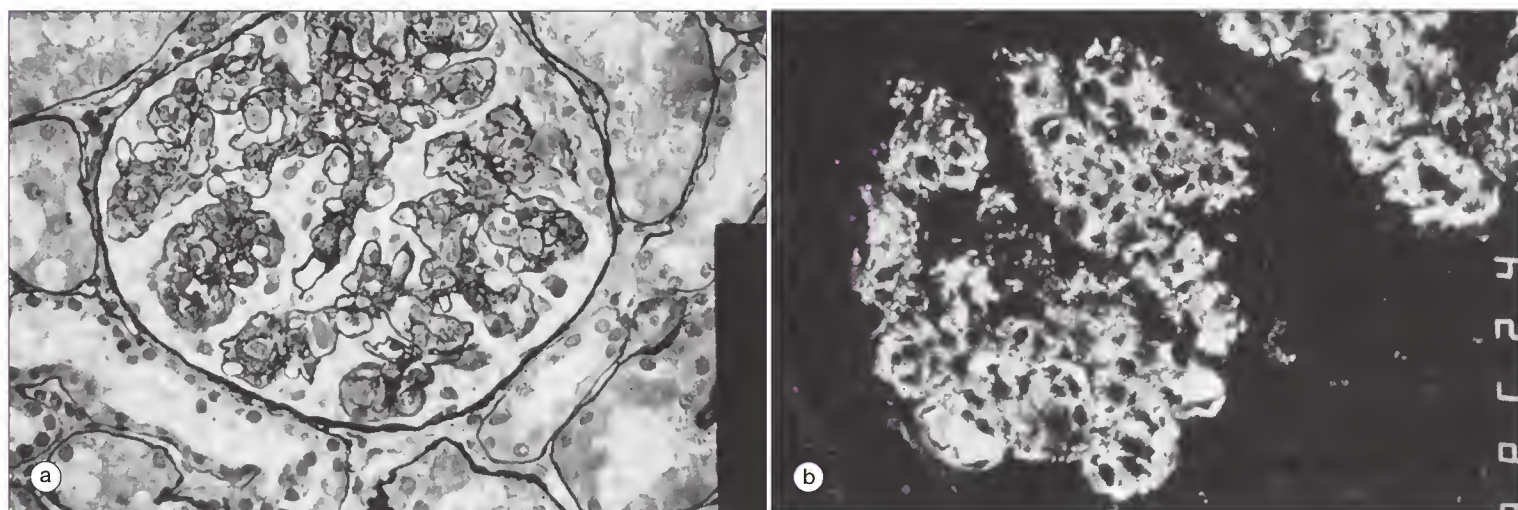


Fig. 154.3 Essential type II cryoglobulinemia. (a) Diffuse proliferation of mesangial cells and subendothelial deposition of eosinophilic material with or without mesangial (matrix) interposition (silver methenamine, hematoxylin-eosin, $\times 125$). (b) Anti-C3 polyclonal antibodies. Diffuse glomerular granular deposition of immune complexes consisting of immunoglobulin G (IgG), IgM, and C1q (not shown) as well as C3 in the mesangial area is seen as well as subendothelial deposition and occasionally intracapillary aggregates (immunofluorescence, $\times 125$).

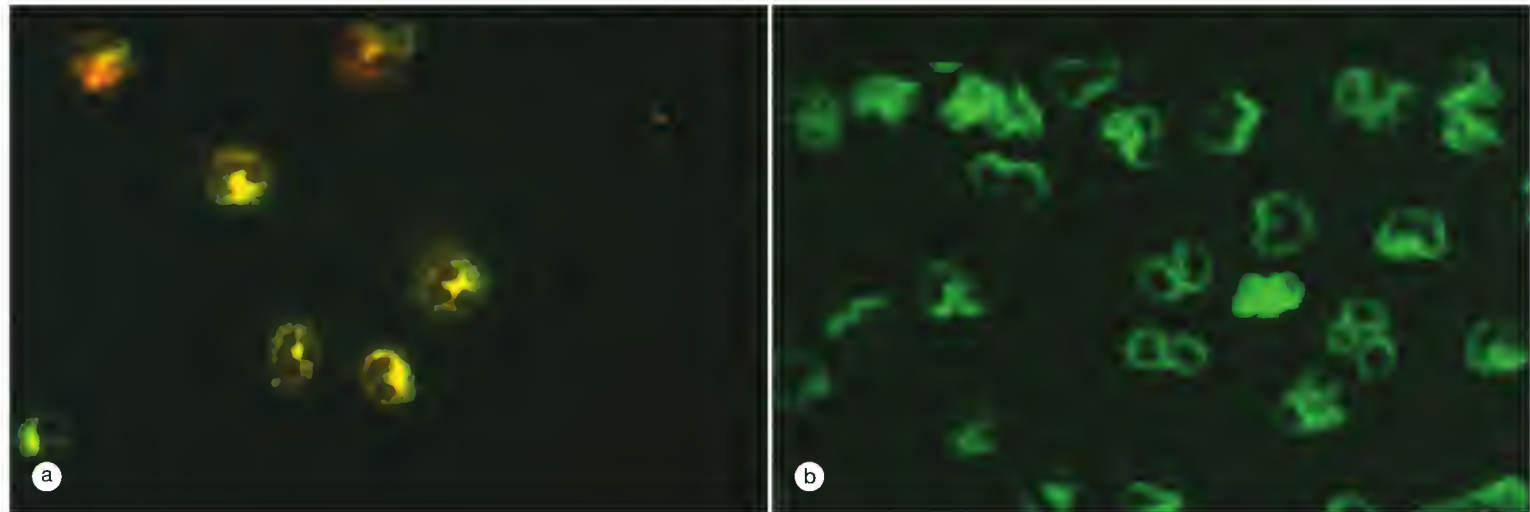


Fig. 154.4 Staining of cytoplasmic components of ethanol-fixed neutrophils by indirect immunofluorescence using a serum sample from a patient with active antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis and antibodies to proteinase 3. (a) A characteristic granular pattern of fluorescence (c-ANCA) is seen, (b) This fluorescence pattern is different from the perinuclear pattern that can be produced by serum samples from patients with antimyeloperoxidase antibodies (p-ANCA).

TABLE 154.1
Disease associations of PR3-ANCA and MPO-ANCA

Disease entity	Sensitivity of	
	PR3-ANCA (%)	MPO (%)
Granulomatosis with polyangiitis	66	24
Microscopic polyangiitis	26	58
Idiopathic crescentic glomerulonephritis	30	64
Eosinophilic granulomatosis with polyangiitis	<5	40

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

indirect immunofluorescence (IIF) was reported as 57% and for PR3-ANCAs measured by enzyme-linked immunosorbent assay (ELISA) as 71%.³² Otherwise, 43% of patients with a rise in ANCAs by IIF and 29% with a rise in PR3-ANCAs by ELISA did not experience relapse.³² These data, however, have not been confirmed in other studies.³³ Also, patients who persistently test positive for PR3-ANCAs after induction of remission have a higher chance of ensuing relapses.³⁰ Thus PR3-ANCAs and MPO-ANCAs are certainly associated with GPA, MPA, and, to a lesser extent, EGPA, but this association, particularly in relation to relapsing disease, is far from absolute. Two other observations support a pathogenic role for ANCA *in vivo*. First, pulmonary hemorrhage and renal involvement were reported in a neonate with MPO-ANCA in cord blood and a mother who had a history of previous MPO-ANCA vasculitis and at the time of delivery had preeclampsia and tested positive for MPO-ANCA.³⁴ Second, a large genomewide association study demonstrated the association of PR3-ANCA with HLA-DP genes as well as with genes encoding for PR3 and α_1 -antitrypsin as well as the association of MPO-ANCA with HLA-DQ genes; these associations were stronger for the autoantibodies than for the associated diseases—that is, GPA and MPA.³⁵

Second, *in vitro* studies showed that ANCAs are able to stimulate neutrophils, primed with low doses of proinflammatory cytokines, to produce reactive oxygen species and release lytic enzymes. In various *in vitro* systems, ANCAs are able to induce adherence of neutrophils to endothelial cells and to stimulate neutrophils to lyse endothelial cells or to induce detachment of these cells. The interaction between ANCAs and neutrophils occurs via binding of their F(ab')₂ fragment to PR3 or MPO expressed on the neutrophil surface as well as by binding of their Fc fragments to Fc γ receptors on the neutrophils. The pathways and signal transduction routes involved in ANCA-induced neutrophil activation have been further elucidated as possible targets for treatment. A percentage of peripheral blood neutrophils express PR3, with or without priming, and this percentage differs among individuals and seems genetically determined. Interestingly, this percentage is higher in patients with GPA than in healthy control subjects, and within a cohort of patients with GPA higher expression is associated with more

frequent relapses. Thus both availability of the autoantigens on the surface of neutrophils, in particular PR3, and the neutrophil activating potential of ANCA appear to be involved in necrotizing vasculitis based on *in vitro* studies.³⁰

The third and strongest argument for pathogenicity of ANCAs is derived from experimental studies in animals. In these studies, an MPO-directed immune response was induced by immunizing MPO-deficient mice with mouse MPO. IgG or splenocytes of these mice were transferred into immunodeficient mice or wild-type mice. This resulted in the development of (focal) necrotizing glomerulonephritis and pulmonary capillaritis, which was augmented by the simultaneous injection of lipopolysaccharide (Fig. 154.5). Furthermore, the alternative pathway of complement has been demonstrated to be an essential factor for lesion development because mice deficient in factor B or factor C5 of the complement system did not develop lesions. This model strongly suggests a direct pathogenic effect of MPO-ANCAs. Also, a rat model of anti-MPO-associated vasculitis demonstrated the *in-vivo* potential of anti-MPO to interfere with leukocyte-endothelial interaction and to cause microvascular damage. However, an approach comparable to that described earlier for anti-MPO-associated vasculitis but using PR3-deficient mice did not result in necrotizing vasculitis but in augmentation of a locally induced inflammatory response only.³⁶ A more recent model,^{36a} in which human hematopoietic stem cells were injected into immunodeficient mice followed by injection with human PR3-ANCA, did result in glomerulonephritis and pulmonary capillaritis in part of the mice but not in granulomatous lesions, which are characteristic for PR3-ANCA associated GPA.

In summary, although it is difficult to prove, the currently available data certainly suggest that ANCAs are pathogenic (Fig. 154.6).

Recently, a new autoantibody has been described in patients with pauci-immune necrotizing crescentic glomerulonephritis (NCGN), the renal manifestation of ANCA-associated vasculitis.³⁷ This antibody is directed against lysosomal membrane protein-2 (Lamp-2) and seems both sensitive and specific for pauci-immune NCGN, although these data are still controversial.³⁸ Anti-Lamp-2 antibodies are able to induce pauci-immune focal NCGN in an animal model. Furthermore, an epitope of human Lamp-2 shows 100% homology with a bacterial adhesin from gram-negative bacteria.³⁷ These data suggest that bacterial peptides may induce a pathogenic autoantibody that results in the renal manifestations of ANCA-associated vasculitis.

Immunopathogenesis of major small-vessel vasculitides

Granulomatosis with polyangiitis

The cause of GPA is not known. The initial phase of the disease is frequently characterized by ongoing (destructive) inflammation in the upper airways. This localized form of the disease may persist, but the disease may also progress to (or directly manifest as) a generalized form. Relapses also frequently start with otorhinolaryngologic symptoms, and grumbling disease is mostly apparent in this region as well. This suggests that the initial trigger is localized in the upper airways. Friedrich Wegener, after whom the disease

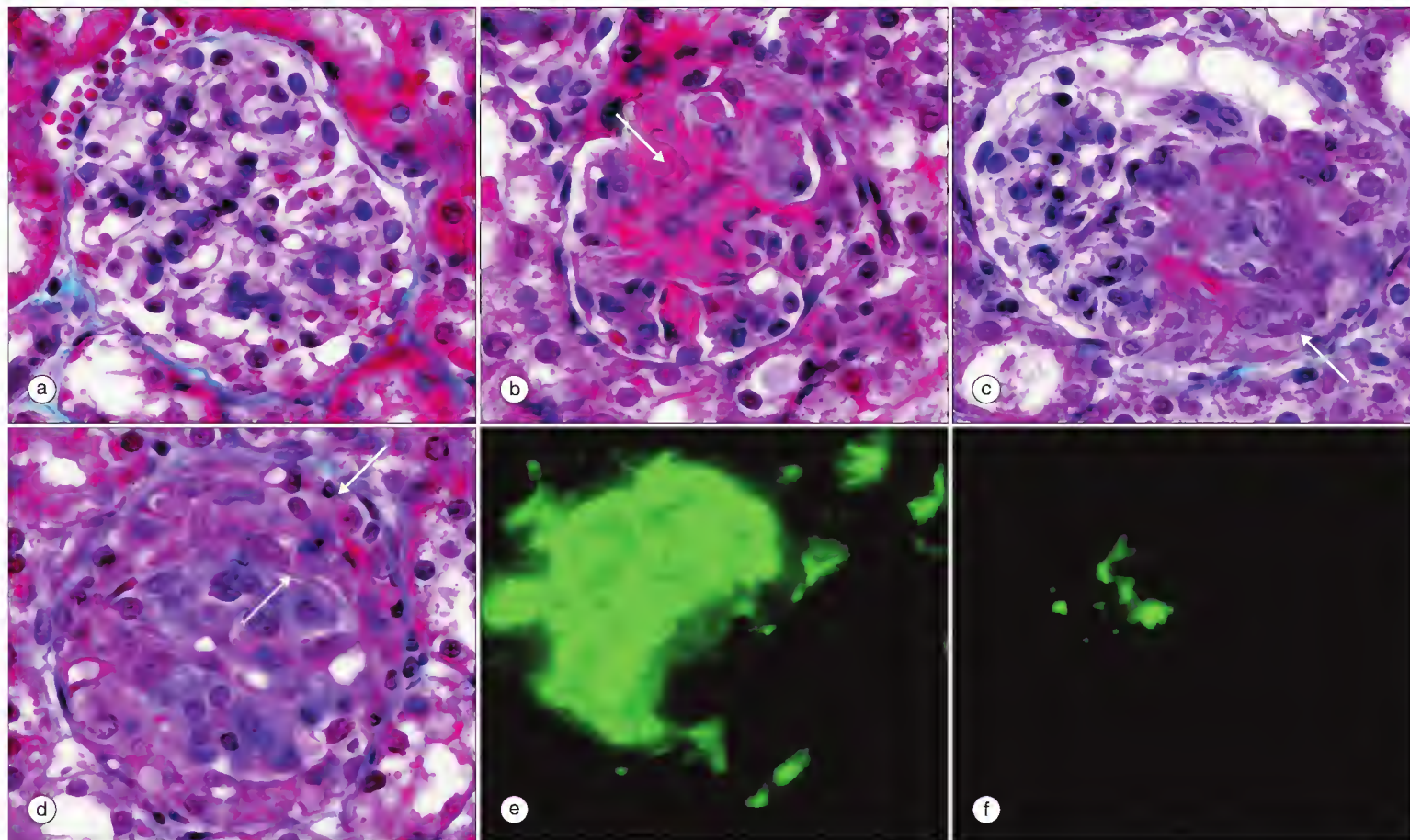


Fig. 154.5 Glomerular lesions in Rag2⁻ mice 6 days after receiving antimyeloperoxidase immunoglobulin G (IgG). (a) Glomerulus with no lesions. (b) Segmental fibrinoid necrosis (arrow). (c) Segmental fibrinoid necrosis with an adjacent small cellular crescent (arrow). (d) Large circumferential cellular crescent (between arrows) completely surrounding a glomerulus. (e) Immunofluorescence microscopy for fibrin showing prominent staining corresponding to segmental necrosis and crescent formation. (f) Immunofluorescence microscopy for IgG showing a paucity of segmental staining corresponding to an area of segmental necrosis. (Masson trichrome staining for light microscopy.) (From Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest* 2002;110:955-63, with permission.)

was previously named, considered the disease to be a pathergic reaction to an environmental factor. This factor has not yet been identified, but chronic nasal carriage of *Staphylococcus aureus* is present in 60% of patients with GPA compared with 20% of control subjects and is associated with a relapsing course.³⁹ If this association is based on a causal relationship, it is presently not clear. GPA is strongly associated with the presence of PR3-ANCAs (see Table 154.1). Recently, peptides encoded by RNA that shows complementarity to RNA encoding for PR3 have been shown to induce PR3-ANCAs by as yet unknown mechanisms. Peptides from this so-called complementary PR3 (cPR3) showed homology to several microbial peptides, among which are peptides from *S. aureus*.⁴⁰ Also, other observations connect upper airway inflammation with *S. aureus* carriage and PR3-ANCAs. Analysis of the immunoglobulin gene repertoire as present in granulomatous lesions in the upper airway showed a predominance of V_H³-positive B cells with affinity for both PR3 and the *S. aureus*-derived B-cell superantigen staphylococcal protein A. Thus several lines of evidence suggest that upper airway inflammation with persistence of *S. aureus* may induce germinal center formation with affinity maturation of PR3-ANCA-producing B cells.

PR3-ANCAs are strongly associated with GPA, although MPO-ANCAs may occur as well (see Table 154.1). Within cohorts of patients with ANCA-associated vasculitis, patients who test positive for PR3-ANCAs show more granulomatous inflammation, more widespread organ involvement, and a faster decline in renal function than patients who test positive for MPO-ANCA. In addition, data from animal experiments suggest a direct pathogenic effect of MPO-ANCAs but not of PR3-ANCAs (see earlier). Furthermore, the genetic background of PR-ANCA is different from that of MPO-ANCA (see earlier). Thus, both clinically and experimentally, PR3-ANCA-associated disease differs from MPO-ANCA-associated vasculitis. However, this clinical distinction between PR3-ANCA- and MPO-ANCA-associated disease is far less apparent in cohorts from east Asian countries.

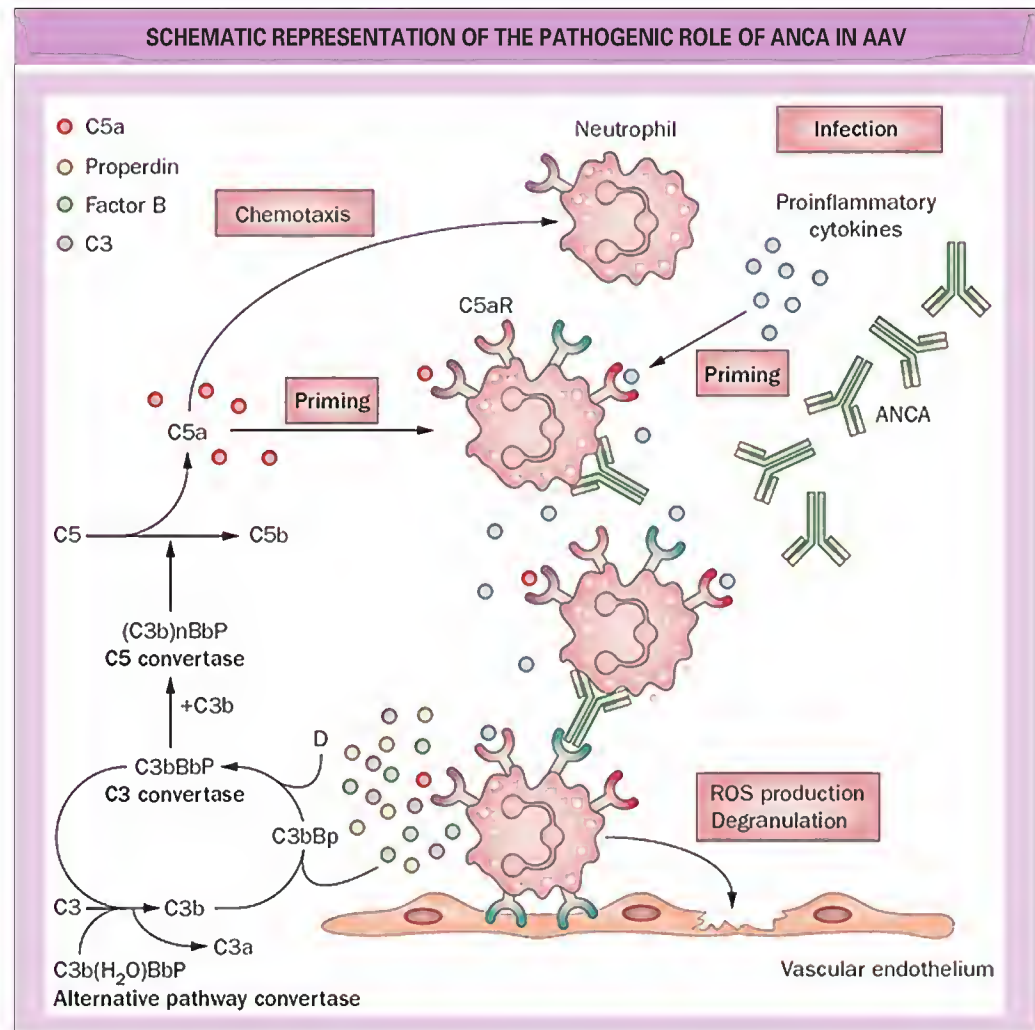
The granulomatous inflammatory lesions in GPA indicate involvement of cellular immune responses. Although the targets of these immune

responses are not yet known, persistent T-cell activation with predominance of effector memory T cells is present in GPA also during remission. Relapses coincide with an increase in levels of soluble IL-2R, which reflects increase in T-cell activation. In terms of cytokine production, type 1 helper T (Th1) cells seem to predominate, although this has not been consistently found. More recent studies show that effector memory T cells, probably with a cytokine pattern consistent with Th17 cells, are continuously present also during quiescent disease and localize in target tissues such as the kidneys when the disease becomes active. Furthermore, functional deficiencies in regulatory T cells have been suggested in GPA. In conclusion, current data suggest an exogenous trigger as the inducing agent in GPA followed by immune activation with generation of PR3-ANCAs as well as effector T cells.^{30,41}

Microscopic polyangiitis

MPA, in contrast to classic polyarteritis nodosa, is an ANCA-associated disease characterized by small-vessel vasculitis with frequent involvement of the kidneys (pauci-immune NCGN) and, somewhat less frequently, the lungs (pulmonary capillaritis). Their combined involvement results in a renopulmonary syndrome. ANCAs are directed against MPO in the majority of patients (see Table 154.1). There is increasing evidence from experimental animal models that MPO-ANCAs are pathogenic, as discussed earlier.³⁶ With respect to the mechanisms involved, a recent rat model of MPO-ANCA-induced renopulmonary syndrome showed that MPO-ANCAs induce leukocyte firm adhesion and transmigration, which leads to microvascular injury. After injection of immunoglobulin fractions with MPO-ANCAs into naive rats, endothelial injury with postcapillary venular hemorrhage was observed.³⁶ All of these data strongly suggest a direct pathogenic role for MPO-ANCAs in MPA based on studies that show similarities between clinical and histopathologic findings in MPA and lesion development in *in-vivo* experimental models. Also, the occurrence of MPA in a neonate born to a mother with MPO-ANCAs strongly suggests that transplacental transfer of IgG-class MPO-ANCAs can induce this disease.³⁴

Fig. 154.6 In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), local infection, such as with *Staphylococcus aureus*, results in priming of neutrophils via proinflammatory cytokines. This results in the surface expression of the ANCA antigens allowing ANCAs to bind to and further activate neutrophils that are rolling along the endothelium. Activation results in firm binding to the endothelium and release of lytic enzymes and reactive oxygen species (ROS), which damage the vessel wall. Also, the alternative pathway of complement is activated with generation of the powerful neutrophil chemoattractant C5a. This amplification loop contributes to the necrotizing inflammation of the vessel wall. (From Chen M, Kallenberg CG. ANCA-associated vasculitides—advances in pathogenesis and treatment. *Nat Rev Rheumatol* 2010;6:653-66, with permission).



Interestingly, anti-GBM antibodies are found in around 30% of patients with MPO-ANCA-associated vasculitis. This subset of patients has more severe renopulmonary disease and a poorer prognosis than patients with MPO-ANCAs only.⁴² The direct pathogenic effect of anti-GBM antibodies has been proven in clinical and experimental studies. In all likelihood, both anti-GBM antibodies and MPO-ANCAs contribute to lesion development in this subset.

Eosinophilic granulomatosis with polyangiitis

Within the spectrum of ANCA-associated vasculitides, ANCAs occur less frequently in EGPA. Around 40% of patients test positive, in most cases for MPO-ANCAs.³¹ The presence of ANCAs in EGPA is associated with small-vessel vasculitis clinically apparent as purpura, mononeuritis multiplex, necrotizing glomerulonephritis, and pulmonary hemorrhage. This suggests that EGPA includes two disease entities, one associated with ANCAs and characterized by small-vessel vasculitis and the other being ANCA negative and characterized by tissue infiltration by eosinophils. In the former subset, pathogenic events follow pathways as mentioned earlier for MPO-ANCA-associated MPA. The latter subset more resembles the hypereosinophilic syndrome in which clonal or T cell-driven polyclonal expansion of eosinophils with tissue infiltration and release of toxic products by these cells plays a major role in pathogenesis.³¹

IMMUNOPATHOGENESIS OF VASCULITIDES OF MEDIUM- AND SMALL-SIZED ARTERIES

Among the vasculitides of medium- and small-sized arteries, classic polyarteritis nodosa and Kawasaki disease are the major disorders.

Polyarteritis nodosa

The 2012 CHCC defined classic polyarteritis nodosa (PAN) as “necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCA.”²

This definition excludes any vasculitic condition in which arterioles, capillaries, and venules are involved. For this reason, many conditions previously described as PAN are now designated as MPA, which makes classic PAN a very rare disorder. Classic PAN is characterized by segmental necrotizing arterial lesions frequently with microaneurysm formation and resulting in ischemia, infarction, and hemorrhage.⁴³ Not infrequently, it presents as an isolated finding (e.g., as small bowel infarction). Hepatitis B virus (HBV)-related PAN, formerly observed in one third of patients with PAN, is now rare. This condition presents as an acute disease occurring within 6 months of an HBV infection. Abdominal signs, malignant hypertension with renal failure, and orchitis are predominant. The immunopathogenesis of classic PAN, including HBV-related PAN, has been studied to a limited extent. ANCAs are absent; immune deposits are detected particularly in HBV-related PAN. Once viral replication has stopped and seroconversion has occurred, the disease does not progress or relapse.⁴⁴ This strongly suggests that HBV-related PAN is caused by immune complex formation in antigen excess. In HBV-negative PAN, immune deposits are frequently absent, and its immunopathogenesis is presently unclear. Shear stress at arterial bifurcation points may be involved in the location of the lesions and microaneurysm formation.

Kawasaki disease

Kawasaki disease is an acute, self-limiting form of vasculitis occurring in childhood. It starts with fever, conjunctivitis, erythema of the lips and oral mucosa, and cervical lymphadenopathy, together with an acute-phase response. Without treatment, coronary vasculitis with aneurysm formation develops in 25% of patients.⁴⁵ Prompt treatment with intravenous immunoglobulin reduces this percentage to less than 5%. The clinical presentation as well as the epidemiology of the disease strongly suggests an infectious origin, but despite many efforts a particular microbial pathogen has not been identified. A few pathologic observations, obtained from postmortem studies, show endothelial activation with subendothelial infiltration of mononuclear cells, in particular cytotoxic T cells and monocytes/macrophages in the coronary arteries, which are a site of predilection in this

medium-sized artery vasculitis. This contrasts with the fibrinoid necrosis and neutrophil infiltration seen in classic PAN and suggests a viral origin. The finding of oligoclonal IgA-producing plasma cells around inflamed coronary arteries also suggests a microbial cause, more specifically a respiratory virus. Previous studies have pointed toward a role for superantigens in Kawasaki disease. Superantigens are able to cross-link major histocompatibility complex (MHC) molecules on antigen-presenting cells with particular V β regions of the T-cell receptor and thereby activate subsets of T cells that carry that particular V β region. During the acute phase of the disease, T cells from the peripheral blood show an expansion of V β 2 and V β 8 T-cell receptor families, suggesting stimulation by staphylococcus- or streptococcus-derived superantigens. These superantigens *in vivo* can bridge MHC class I- and II-expressing endothelial cells with CD8+ and CD4+ T cells. However, levels of antibodies to staphylococcal and streptococcal superantigens have not been found to differ between patients with Kawasaki disease and healthy control subjects. As mentioned earlier, intravenous immunoglobulin is an effective treatment in the acute phase to reduce the occurrence of coronary artery aneurysms. The efficacy of intravenous immunoglobulin might give a clue to the immunopathogenesis of Kawasaki disease, but no consistent explanations have been given. Thus, at present, Kawasaki disease is considered to arise from an aberrant immune response to as yet undefined microorganisms in a genetically susceptible host.⁴⁶

IMMUNOPATHOGENESIS OF LARGE-VESSEL VASCULITIDES

In contrast to the necrotizing vasculitides affecting the small and medium-sized vessels, the large-vessel vasculitides are not dominated by polymorphonuclear cell infiltration but show a cellular immune response with infiltration of monocytes/macrophages and T cells. The two major diseases in this group are giant cell arteritis, also designated as *temporal arteritis*, and Takayasu arteritis.

Giant cell arteritis

Giant cell arteritis (GCA) is defined by the 2012 CHCC as “arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries; often involves the temporal artery; onset usually in patients older than 50; often associated with polymyalgia rheumatica.”²

GCA is characterized histopathologically by mononuclear infiltrates in all layers of the arterial wall in conjunction with activated T cells. Macrophages and T cells are present in granuloma formation, and multinucleated giant cells are localized close to the fragmented internal elastic lamina. Proliferation of the intima results in occlusive vasculopathy.

Insight into the immunopathogenesis of GCA stems mainly from the pioneering work of Weyand and Goronzy.^{47,48} These researchers attributed an initiating and central role to dendritic cells in the immunopathogenesis of GCA. Immature dendritic cells, lacking the costimulatory molecules CD80 and CD86, are present in the adventitia of arteries and, due to lack of costimulation, tolerize T cells that recognize (auto)antigens presented by these dendritic cells localized in the adventitial area. Immature dendritic cells can be activated *in vitro* and *in vivo* by stimulants such as lipopolysaccharide, which results in, among others, the expression of costimulatory molecules (CD80/86) and the capacity to activate T cells. Whereas dendritic cells in the adventitia of arteries from healthy controls are immature, temporal arteries from patients with polymyalgia rheumatica without inflammatory changes display mature dendritic cells in their adventitia. These dendritic cells, in contrast to adventitial dendritic cells from control

subjects, are able to activate T cells derived from GCA lesions, as shown in experiments in mice with severe combined immunodeficiency in which the respective temporal arteries were implanted and T cells adoptively transferred.⁴⁹ Thus *in situ* maturation of dendritic cells in the adventitia seems an initial event in the immunopathogenesis of GCA. How these dendritic cells get activated is presently unknown. The second element is constituted by CD4+ T cells that interact with these mature dendritic cells. The crucial question of what these T cells recognize has not been answered. Autoantigens and various microorganisms—in particular parvovirus, varicella-zoster virus, and *Chlamydia*—have been suggested but not substantiated. Mature dendritic cells in the adventitial layer of the temporal artery produce the chemokines CCL19 and CCL21 and express receptors for these chemokines as well. This causes the dendritic cells to remain *in situ* instead of migrating into regional lymph nodes and allows the local interaction with CD4+ T cells.⁴⁹

Activation of T cells leads to a Th1- and Th17-type response via dendritic cell-derived IL-18, with massive production of interferon- γ (IFN- γ) and IL-17, followed by the generation of granulomas that mainly localize in the media. Here, macrophages are activated by IFN- γ and produce reactive oxygen species, nitric oxide via upregulation of iNOS, and metalloproteinases. IFN- γ also induces the generation of multinucleated giant cells that contribute to the production of PDGF and, in particular, VEGF. Th1 and Th17 immunity seems responsible for the early phase and Th1 immunity for the more chronic smoldering inflammation.⁵⁰ The response to injury of the arterial vessel wall determines the level of occlusion of affected arteries and the occurrence of ischemic lesions. VEGF production results in neovascularization in the media and intima, which allows further proliferation of myofibroblasts, a process that is also dependent on PDGF production (Fig. e154.3).

Besides this cellular immune response that results in arteritis of the extracranial branches of the aorta, a systemic inflammatory response is characteristic of GCA as well. This inflammatory response is comparable to that occurring in polymyalgia rheumatica in which large-vessel arteritis is, as far as we know, lacking. It is initiated by proinflammatory cytokines, in particular IL-1 and IL-6, and is apparent in the production by the liver of acute-phase proteins such as C-reactive protein. There is evidence that these proinflammatory cytokines are mainly produced by circulating monocytes, but how these cells are stimulated in GCA and polymyalgia rheumatica is presently unknown.

Takayasu arteritis

Takayasu arteritis is defined by the 2012 CHCC as “arteritis, often granulomatous, affecting the aorta and its major branches. Onset usually in patients younger than 50.”² This disease, which is in several ways comparable to GCA, occurs far more frequently in people from Japan, Southeast Asia, India, and Mexico than in whites, in whom GCA predominates. These racial differences suggest genetic factors, but specific genes have not been identified beyond weak human leukocyte antigen associations. Immunohistopathologic analysis of the infiltrates in acute phases of the disease points toward a cellular immune response with infiltration of both Th1 and Th17 cells, natural killer cells, and CD8+ cytotoxic T cells. Th1 cells induce activation of macrophages and the formation of giant cells. Th17 cells contribute to the inflammatory lesions by activating neutrophils. Natural killer cells and $\gamma\delta$ T cells interact via their NKG2D receptor with MICA antigens on vascular smooth muscle cells, which results in cytotoxicity via their production of perforin.⁵¹ Further analysis shows a restricted use of T-cell receptor $\alpha\beta$ genes in lesional tissue. This may suggest that a specific antigen or a superantigen is operative in this disease. The nature of this (super) antigen, however, has not been identified.

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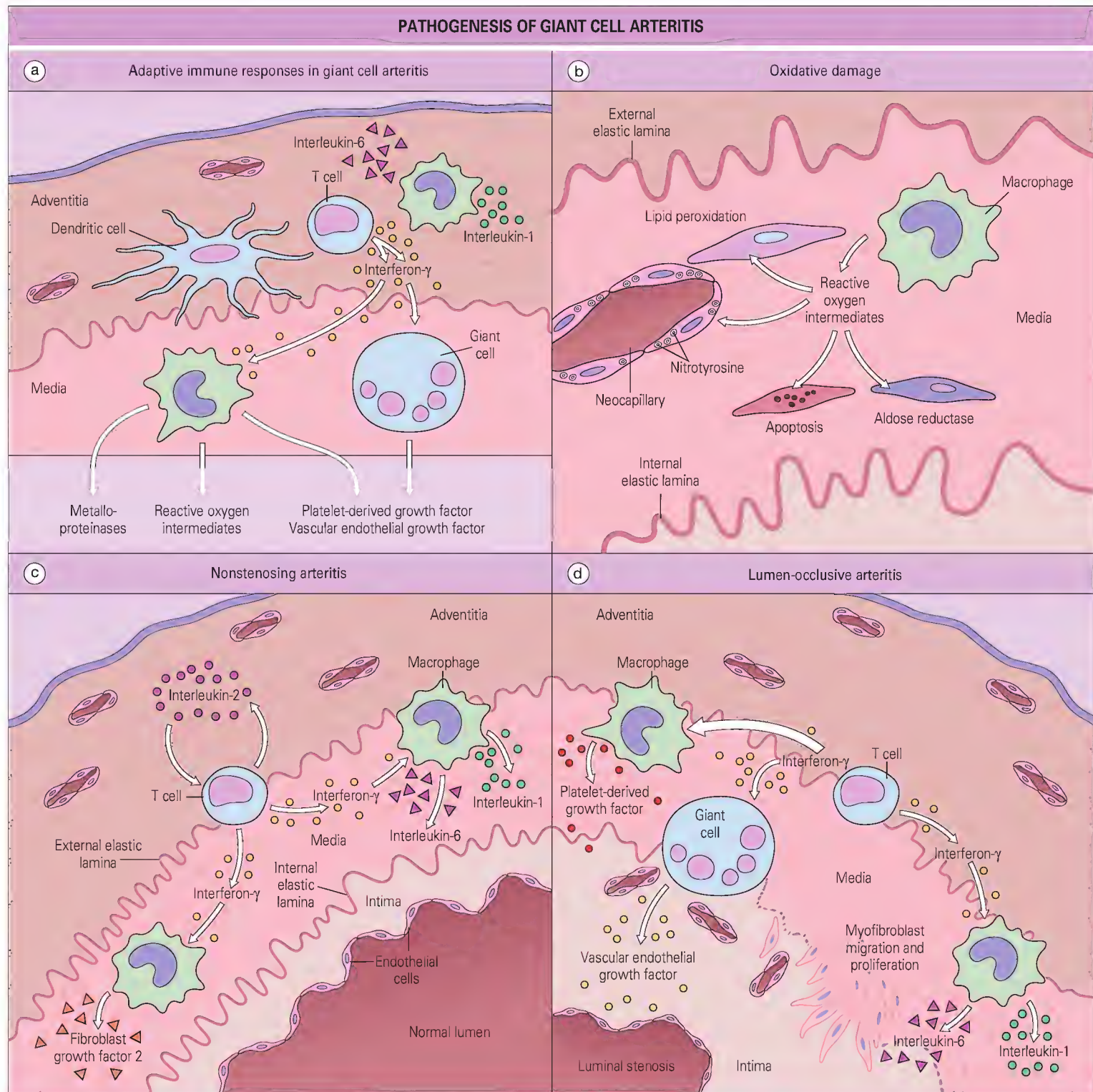


Fig. e154.3 (a) Activation and trapping of dendritic cells in the arterial adventitia generate the conditions required for the recruitment and stimulation of antigen-specific T cells. CD4⁺ T cells that enter the microenvironment of the arterial wall interact with dendritic cells and begin secreting cytokines. Interferon- γ is a critical cytokine that regulates the differentiation and function of macrophages. The functional commitment of the macrophages in the vascular infiltrates is closely linked to their location in the arterial wall. Macrophages in the adventitial layer supply the inflammatory cytokines interleukin-1 and interleukin-6. Macrophages in the media secrete metalloproteinases and play a critical part in oxidative injury through the production of reactive oxygen intermediates. (b) Three aspects of oxidative damage in the media are shown. Protein nitration occurs in endothelial cells lining neocapillaries. Toxic aldehydes are formed in the process of lipid peroxidation, and smooth muscle cells undergo apoptosis. In parallel, reactive oxygen intermediates also trigger cellular activation, as exemplified by the induction of aldose reductase. (c and d) The response of the artery to injury is shown. Arteritis does not necessarily result in luminal stenosis and may proceed without compromising blood flow (c). In patients with ample production of platelet-derived growth factor and vascular endothelial growth factor, rapid and exuberant intimal hyperplasia ensues, causing lumen-occlusive arteritis (d). Accordingly, the clinical presentation of arteritis may or may not include ischemic complications. (Reproduced with permission from Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med* 2003;349:160-9.)

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Polyarteritis nodosa and Cogan syndrome

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- Polyarteritis nodosa is a necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and is not associated with anti-neutrophil cytoplasmic autoantibodies. It is a rare disease but more common in areas endemic for hepatitis B virus infection. Patients typically have systemic symptoms, and organs involved include the kidneys, skin, joints, muscles, nerves, and gastrointestinal tract. Testicular involvement, though characteristic, is less common, as is cardiac involvement. The lungs are usually spared.
- Polyarteritis nodosa is a monophasic self-limited disease that tends to not recur once remission is induced. It is treated with corticosteroids, but strategy options vary according to the underlying etiology and disease severity. Therapeutic options include cyclophosphamide, plasma exchange for severe cases, and antiviral medications for patients with hepatitis B virus-associated polyarteritis nodosa.
- Cogan syndrome is a rare, chronic inflammatory disease of unknown etiology that predominantly affects the eye and inner ear and is reported mostly in young white adults. It can be associated with vasculitis and aortitis. The hallmarks of Cogan syndrome are interstitial keratitis and recurrent Ménière-like episodes that can result in deafness. Infections and inflammatory conditions that affect the ears and eyes need to be considered in the differential diagnosis.
- Cogan syndrome is treated with corticosteroids for acute flares and recurrences of ocular or auditory inflammation. Other immunosuppressive drugs such as cyclophosphamide, azathioprine, methotrexate, and cyclosporine can be used when corticosteroid treatment fails. The prognosis varies according to disease activity. Ocular outcomes are good, but deafness is the most common long-term consequence.

INTRODUCTION

The systemic vasculitides are a heterogeneous group of multisystem disorders characterized by inflammation and necrosis of small and medium-sized blood vessels. The first cases of vasculitis were reported in the mid-1800s with the description of peri(poly)arteritis nodosa (PAN), a term later used collectively to describe a whole spectrum of vasculitic diseases, particularly until the mid-20th century.¹ The development during the last 30 years of different classification systems and the introduction of classification criteria have further broadened our understanding of these conditions. The American College of Rheumatology (ACR) classification criteria (1990),² however, did not recognize microscopic polyangiitis (MPA), in contrast to most other vasculitides, including PAN. The introduction of antineutrophil cytoplasmic antibodies (ANCA) in the late 1980s with their strong links to a group of vasculitides (sometimes called ANCA-associated vasculitis [AAV]) also helped develop our understanding of the potential for separating and classifying these diseases by recognizing that PAN is not associated with ANCA.

The Chapel Hill Consensus Conference in 1994 (CHCC 1994) defined the typical features of many of the vasculitides, including Wegener granulomatosis (WG), MPA, and Churg-Strauss syndrome (CSS) (also closely associated with ANCA).³ The CHCC 1994 used the term “classic (c)” PAN to help differentiate MPA from cPAN³ because we now recognize these diseases to be very different clinicopathologic conditions. MPA is usually restricted to relatively small blood vessels; it is strongly linked to ANCA and is much more common than PAN, which is a disease of mainly

medium-sized arteries that is rarely associated with ANCA and not infrequently linked to infection with hepatitis B virus (HBV). With evolving knowledge and understanding of the different vasculitides, a further Chapel Hill meeting was conducted in 2011 (published in 2012, the so-called CHCC 2012) to improve and develop definitions and classification of the different vasculitic diseases, as well as to introduce an updated nomenclature that includes WG, or granulomatosis with polyangiitis (GPA), and CSS, or eosinophilia with granulomatosis and polyangiitis (EGPA).⁴ They also included Cogan syndrome (CS) when associated with vasculitis (Cogan vasculitis) in recognition of the association of CS with vasculitis involving large and medium-sized arteries, sometimes similar to that seen with PAN. CHCC 2012 dropped the “c” from PAN as the ensuing years from 1994 had firmly established MPA as a separate disease entity.

The position of PAN and CS within the constellation of the vasculitides is described in Chapter 153.

POLYARTERITIS NODOSA

Definition

PAN is defined as “a necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules; and not associated with anti-neutrophil cytoplasmic autoantibodies (ANCA).”⁴ In CHCC 2012, specifying that ANCA are not associated with PAN and the addition of a category for AAV reflect advances in knowledge gained about ANCA since CHCC 1994. Although the role of ANCA in the pathogenesis of vasculitis has not been fully elucidated, many studies have confirmed that ANCA are a reliable marker for a clinically and pathologically distinct category of small-vessel vasculitis and that they are typically absent in patients with PAN. Such a discriminator is useful because PAN and AAV can exhibit clinically and pathologically indistinguishable necrotizing arteritis of medium and small arteries.

Classification

Classification of the vasculitides remains confusing and controversial because of overlap in clinical expression of the different vasculitic syndromes. For practical purposes, classification generally reflects dominant vessel size and the presence or absence of ANCA. PAN, being predominantly a disease of medium vessels lacking association with ANCA, is placed in a group distinct from the AAVs (see Chapter 153).

In 1990 the ACR produced classification criteria for seven types of systemic vasculitis, including PAN but not MPA. The ACR classification criteria for PAN are presented in Table 155.1. The sensitivity of these criteria was 82.2% with a specificity of 86.9%.⁵ The criteria are not without problems; they were validated in patients known to have vasculitis but not in patients before the diagnosis of vasculitis or other systemic illnesses. Their reliability when used in patients in whom vasculitis is only suspected is poor. Furthermore, they did not consider ANCA.

The CHCC (1994 and 2012) provided definitions for PAN (and MPA). PAN was defined as a disease predominantly affecting medium or small arteries, whereas MPA was a condition affecting smaller microscopic vessels.^{3,4} A consequence of this distinction is that PAN has become very uncommon. The CHCCs provided only definitions and not formal classification criteria; the lack of criteria for MPA has resulted in the CHCC definitions being used to classify patients in epidemiology studies.

A further problem is that the criteria were developed for use in adults. A Paediatric Rheumatology European Society/European League Against Rheumatism working group published classification criteria for pediatric PAN in

TABLE 155.1
ACR 1990 criteria for the classification of polyarteritis nodosa*

Criterion	Definition
1. Weight loss >4 kg	Loss of 4 kg or more body weight since the illness began that is not due to dieting or other factors
2. Livedo reticularis	Mottled reticular pattern over the skin of portions of the extremities or torso
3. Testicular pain or tenderness	Pain or tenderness of the testicles not attributable to infection, trauma, or other causes
4. Myalgias, weakness, or polyneuropathy	Diffuse myalgias (excluding the shoulder and hip girdle)
5. Mononeuropathy or polyneuropathy	Development of mononeuropathies, multiple mononeuropathies, or polyneuropathy
6. Diastolic BP >90 mm Hg	Development of hypertension with a diastolic BP >90 mm Hg
7. Increased BUN or creatinine	Increase in BUN >40 mg/dL (14.3 mmol/L) or creatinine >1.5 mg/dL (132 mmol/L) not attributable to dehydration or obstruction
8. Hepatitis B virus	Presence of hepatitis B surface antigen or antibody in serum
9. Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries that is not due to arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes
10. Biopsy of small or medium-sized artery	Histologic changes showing the presence of a small or medium-sized artery containing PMN granulocytes or granulocytes and mononuclear leukocytes in the artery wall

*The traditional format. For classification purposes, a patient with vasculitis shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are present. The presence of any three or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%. ACR, American College of Rheumatology; BP, blood pressure; BUN, blood urea nitrogen; PMN, polymorphonuclear leukocytes (granulocytes). Adopted from Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088-93.

2010.⁶ These criteria do not include HBV infection because it is rarely a cause of PAN in children as a result of improved vaccination protocols.

The French study group recently developed criteria for PAN and introduced exclusion or negative criteria⁷ (Table 155.2). Of the original 10 ACR criteria, only 3 were maintained (presence of HBV antigen, arteriographic abnormalities, and neuropathy). The negative criteria were considered to not be features of PAN and, if present, to be indicative of another type of vasculitis. The sensitivity of these criteria was 70.6% with a specificity of 92.3%.

It is worth stressing that validated diagnostic criteria for PAN are still not available.

Epidemiology

PAN is uncommon. Estimates before the introduction of modern classification systems showed an annual incidence in a general population ranging from 9.0 to 77 per million.⁸ The highest figure was observed in a hepatitis B–endemic Alaskan Eskimo population.⁹ These figures included MPA, PAN, connective tissue disease–associated vasculitis, and EGPA (CSS). PAN, however, is much less common than previously reported because of the current, more strict CHCC definitions. In U.K. epidemiology studies, PAN is very rare and occurs much less frequently than MPA at a rate of probably less than 1 per million per year. In Kuwait the annual incidence was much higher at 16.4 per million.¹⁰ PAN occurs at all ages and is more common in men. The mean age at the onset of PAN is 51 years.¹¹

Environmental factors

The major environmental risk factor is HBV infection, which has been firmly associated with PAN for 40 years. In areas endemic for HBV infection, up to 95% of cases are associated with it. In France, falling HBV infection rates have correlated with a decrease in HBV-associated PAN.¹² In Alaska,

TABLE 155.2
The French Vasculitis Study Group minimal set of low-redundant predictive criteria for polyarteritis nodosa

Criterion	Polyarteritis nodosa association
HBV infection	Positive
ANCA positivity	Negative
Asthma	Negative
ENT signs	Negative
Cryoglobulin positivity	Negative
Glomerulonephritis	Negative
Arteriographic abnormalities	Positive
Mononeuropathy/polyneuropathy	Positive

ANCA, antineutrophil cytoplasmic antibody; HBV, hepatitis B virus; ENT, ear, nose, and throat. Data from Henegar C, Pagnoux C, Puechal X, et al. A paradigm of diagnostic criteria for polyarteritis nodosa: analysis of a series of 949 patients with vasculitides. *Arthritis Rheum* 2008;58:1528-38.

HBV-associated PAN has disappeared from the population following the introduction of a vaccination program. In this population, infection was associated with D genotype HBV.¹³ Other viruses such as human immunodeficiency virus (HIV), parvovirus B19, and hepatitis C virus (HCV) have also been associated with PAN.¹⁴

Clinical features

PAN has a spectrum of severity from mild, limited disease to progressive disease, which may be fatal. Virtually any organ may eventually be affected. Typically, patients experience the constitutional features of fever, malaise, weight loss, and diffuse aching, along with manifestations of multisystem involvement such as peripheral neuropathy and an asymmetric polyarthritis. Visceral involvement, such as the kidney or gut, may occur coincidentally with these features or may appear later. Table 155.3 describes the clinical findings in a large group of patients with PAN, including those with HBV-related disease.

Cutaneous lesions

Cutaneous lesions, including infarctions, ulcerations, livedo reticularis, subcutaneous nodules, and ischemic changes in the distal ends of digits (Fig. 155.1), occur in 25% to 60% of patients. The frequency of skin lesions in PAN is not different from that in MPA. Biopsy does not necessarily help distinguish MPA from PAN.¹⁵

Musculoskeletal features

Arthralgia or arthritis is present in as many as 60% of patients. Patients may also initially be seen with or early in the course of the disease have a polymyalgia rheumatica–like syndrome. An asymmetric, episodic, nondeforming polyarthritis involving the larger joints of the lower extremity may occur in up to 20% of cases, most commonly early in the disease.

Neurologic features

Peripheral neuropathy may occur in up to 85% of patients with PAN and might be the initial manifestation.¹¹ It is more common in patients with HBV-related PAN. The neuropathy affects the lower extremities somewhat more often than the upper extremities. Its onset is often very acute, with pain and paresthesias radiating in the distribution of a peripheral nerve, followed in hours by a motor deficit of the same peripheral nerve. This may progress asymmetrically to involve other peripheral nerves and produce mononeuritis multiplex or multiple mononeuropathy. With additional nerve damage, the final result may be a symmetric polyneuropathy involving all sensory modalities and motor functions. Less commonly, a slowly evolving distal sensory neuropathy or cranial nerve palsy may occur. Clinical manifestations suggestive of central nervous system (CNS) involvement are much less common than those of peripheral nerve involvement, but the two may appear together. CNS involvement includes headache, seizures, cranial nerve dysfunction, cerebral hemorrhage, and stroke.

Renal involvement

PAN is usually characterized by vascular nephropathy, without glomerulonephritis, in about 35% of patients.¹¹ Multiple renal infarcts, the consequence of vascular nephropathy, produce renal failure. Renal angiography

TABLE 155.3

Main clinical characteristics at diagnosis of 348 patients with PAN by HBV status

Characteristic	All patients (N = 348)	Non-HBV-related PAN (n = 225)	HBV-related PAN (n = 123)	P
No. of men/women (ratio)	220/128 (1.7)	137/88 (1.6)	83/40 (2.1)	
Age at diagnosis (yr, mean $\pm$ SD)	51.2 $\pm$ 17.3	50.9 $\pm$ 17.8	51.7 $\pm$ 16.4	
Time from first symptom to diagnosis (mo, mean $\pm$ SD)	7.4 $\pm$ 23.2	8.9 $\pm$ 27.3	4.7 $\pm$ 12.4	*
General symptoms	324 (93.1)	209 (92.9)	115 (93.5)	
Fever	222 (63.8)	136 (60.4)	86 (69.9)	
Weight loss	242 (69.5)	149 (66.2)	93 (75.6)	
Weight lost (kg, mean $\pm$ SD)	6.3 $\pm$ 6.5	5.4 $\pm$ 5.9	7.9 $\pm$ 7.2	†
Myalgias	204 (58.6)	139 (61.8)	65 (52.8)	
Arthralgias	170 (48.9)	106 (47.1)	64 (52.0)	
Neurologic manifestations	275 (79.0)	167 (74.2)	108 (87.8)	†
Peripheral neuropathy	258 (74.1)	153 (68.0)	105 (85.4)	†
Mononeuritis multiplex	246 (70.7)	145 (64.4)	101 (82.1)	†
Central nervous system	16 (4.6)	11 (4.9)	5 (4.1)	
Urologic and renal manifestations	176 (50.6)	100 (44.4)	76 (61.8)	†
Hematuria	53 (15.2)	34 (15.1)	19 (15.4)	
Proteinuria (>0.4 g/24 hr)	75 (21.6)	46 (20.4)	29 (23.6)	
Recent-onset hypertension	121 (34.8)	61 (27.1)	60 (48.8)	†
Severe hypertension	24 (6.9)	11 (4.9)	13 (10.6)	*
Orchitis or testicular tenderness	38 (17.3)	18 (13.1)	20 (24.1)	*
Cutaneous manifestations	173 (49.7)	130 (57.8)	43 (35)	†
Nodules	60 (17.2)	53 (23.6)	7 (5.7)	†
Purpura	77 (22.1)	55 (24.4)	22 (17.9)	
Livedo	58 (16.7)	45 (20.0)	13 (10.6)	†
Peripheral limb edema	85 (24.4)	50 (22.2)	35 (28.5)	
Gastrointestinal manifestations	132 (37.9)	70 (31.1)	62 (50.4)	†
Abdominal pain	124 (35.6)	62 (27.6)	62 (50.4)	†
Bleeding	12 (3.4)	8 (3.6)	4 (3.3)	
Perforations	15 (4.3)	8 (3.6)	7 (5.7)	
Cholecystitis	13 (3.7)	5 (2.2)	8 (6.5)	
Appendicitis	4 (1.1)	2 (0.9)	2 (1.6)	
Pancreatitis	13 (3.7)	6 (2.7)	7 (5.7)	
Gastrointestinal manifestations requiring surgery	48 (13.8)	24 (10.7)	24 (19.5)	
Cardiac and vascular manifestations	78 (22.4)	46 (20.4)	32 (26.0)	
Vasculitis-related cardiomyopathy	26 (7.5)	10 (4.4)	16 (13.0)	†
Pericarditis	19 (5.5)	11 (4.9)	8 (6.5)	
Digital ischemia (without necrotic lesions)	21 (6.0)	12 (5.3)	9 (7.3)	
Distal necrotic lesions and/or limb arterial claudication	22 (6.3)	14 (6.2)	8 (6.5)	
Ophthalmologic manifestations	30 (8.6)	17 (7.6)	13 (10.6)	
Retinal vasculitis/exudate	15 (4.3)	8 (3.6)	7 (5.7)	
Pulmonary manifestations [§]				
Cough	20 (5.7)	14 (6.2)	6 (4.9)	
Lung infiltrates	12 (3.4)	10 (4.4)	2 (1.6)	
Pleural effusions	12 (3.4)	7 (3.1)	5 (4.1)	
Periostitis	3 (0.9)	3 (1.3)	0	
FFS = 0	208 (59.8)	150 (66.7)	58 (47.1)	†
FFS = 1	78 (22.4)	41 (18.2)	37 (30.1)	
FFS $\geq$ 2	62 (17.8)	34 (15.1)	28 (22.8)	
BVAS at diagnosis (mean $\pm$ SD)	16.5 $\pm$ 8.3	15.1 $\pm$ 7.6	19.1 $\pm$ 9.1	†

Except when indicated otherwise, values are the number (%) of patients.

* $P \leq 0.05$.† $P \leq 0.001$.‡ $P \leq 0.01$.

§Pulmonary manifestations were nonspecific and caused by cardiac or renal insufficiency, or both.

BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; HBV, hepatitis B virus; PAN, polyarteritis nodosa; SD, standard deviation.

Adapted and modified from Pagnaux C, Serar R, Henegar C, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis* 2010;62:616-26.

will frequently show several aneurysms and infarcts. Ureteral stenosis and perinephric hematomas (microaneurysm rupture) can occur. Hypertension develops as a result of renal artery or, less commonly, renal parenchymal involvement. Hypertension, usually mild, develops in 20% to 50% of patients and is particularly associated with HBV infection.¹¹

Gastrointestinal involvement

Abdominal pain occurs in up to 70% of patients and is more common in those with HBV-related disease.¹¹ Other features of gastrointestinal involvement include diarrhea, gut hemorrhage, and abnormal liver enzyme test results. Liver involvement is not common clinically, except if associated with



Fig. 155.1 Cutaneous lesion of polyarteritis nodosa.

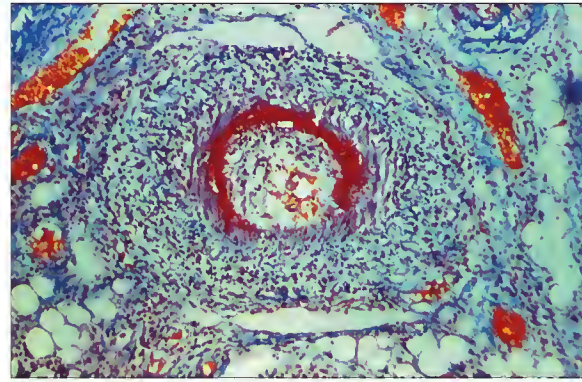


Fig. 155.2 Histopathology of polyarteritis nodosa.

HBV infection. Gastrointestinal involvement is among the most serious features of PAN and is associated with a poor prognosis. Abdominal pain secondary to vasculitis may be the first manifestation of vasculitis and presents a particular challenge.

Cardiac involvement

Cardiac involvement in patients with PAN is common pathologically but is recognized less often clinically. Myocardial infarction, when it occurs, is generally silent and due to coronary arteritis. The use of cardiac magnetic resonance imaging (MRI) to evaluate for coronary arteritis has been suggested as a less invasive means of assessing the extent of myocardial damage.¹⁶ Cardiomegaly occurs in about 20% of patients. Congestive heart failure develops as a result of coronary insufficiency or severe hypertension (or both). Cardiomyopathy is predictive of increased mortality. Endocarditis is not observed in patients with PAN, and its occurrence should alert the clinician to an alternative diagnosis.

Orchitis

Testicular involvement is manifested as pain, but clinical involvement as indicated by swelling or induration occurs in approximately 20% of patients. Orchitis is one of the most characteristic features of cPAN¹¹ and is more common in polyarteritis complicated by gastrointestinal involvement and vasculitis associated with HBV infection. It is rarely the first manifestation of the disease, is generally unilateral, and is caused by ischemia of the testicular artery.

Other features

Pulmonary involvement is uncommon in PAN, so other causes should be considered, especially infection.¹¹ Diffuse involvement of skeletal muscle arteries may cause ischemic pain and intermittent claudication. Myalgias occur in about 50% of patients with polyarteritis, but generalized myopathy and increased creatine kinase concentrations are unusual. Venous thromboembolism is less common than in AAV and occurs in 2.8% of patients.¹⁷

Secondary polyarteritis nodosa

Vasculitis of medium-sized vessels mimicking polyarteritis may be a manifestation or complication of other diseases. This secondary vasculitis occurs in patients with rheumatoid arthritis, Sjögren syndrome, hairy cell leukemia, myelodysplastic syndrome, and other hematologic malignancies. Secondary vasculitis is histopathologically and clinically indistinguishable from the primary forms.

Viruses, including HIV, are particularly inclined to cause small-vessel vasculitis, whereas bacterial infections have been associated with inflammation of all sizes of blood vessels. The association of PAN with HBV infection is particularly strong. Patients with HBV-associated PAN have more severe disease than do those with non-HBV-associated PAN, with greater weight loss and more frequent peripheral nerve involvement, abdominal pain, gastrointestinal manifestations requiring surgery, specific cardiomyopathy, orchitis, hypertension, and elevated transaminase levels¹¹ (see Table 155.3). The evaluation of every patient with vasculitis should include HBV serology. PAN is usually manifested within the first 6 months of HBV infection. Hepatitis is rarely diagnosed before the onset of PAN, which can therefore be the first manifestation of HBV infection.

HCV is also associated with PAN.¹⁴ Among a cohort of 161 patients with HCV-related vasculitis studied by the French group, PAN was diagnosed in 31 patients chronically infected with HCV, with both the ACR and Chapel Hill criteria being fulfilled. When compared with HCV-associated mixed cryoglobulinemic vasculitis, HCV-related PAN was associated with more

severe and acute clinical findings, such as more frequent fever and weight loss, severe hypertension, involvement of the gastrointestinal tract, severe acute sensory-motor multifocal mononeuropathy, and kidney and liver microaneurysms. Patients with HCV-related PAN had a higher rate of clinical remission. The overall 5-year survival rate was 86% for the entire cohort, regardless of the type of vasculitis. Patients with skin involvement and PAN-type vasculitis had a better chance for a complete clinical response than did patients with renal involvement, which had the opposite association.¹⁴

Limited forms of polyarteritis

Isolated polyarteritis of the appendix, gallbladder, uterus, or testis is well recognized, though uncommon. Vasculitic peripheral neuropathy can occur without other systemic or constitutional symptoms. A cutaneous form of polyarteritis that affects predominantly the lower extremities is distinguished from systemic polyarteritis by its lack of visceral involvement and benign course.¹⁸ Although the chronic, relapsing, nonlethal nature of the condition has been stressed by some, other investigators have documented the refractory nature of chronic cutaneous vasculitis and the significant cumulative morbidity related to skin, muscle, joint, and nerve involvement and the effects of therapy.

Pathology

The pathology of polyarteritis consists of focal, necrotizing inflammatory lesions that extend through the wall of small and medium-sized arteries (Fig. 155.2). The inflammation is characterized by fibrinoid necrosis and pleomorphic cellular infiltration predominantly by macrophages and lymphocytes and variable numbers of neutrophils and eosinophils. A significant eosinophilic infiltrate favors the diagnosis of EGPA (CSS). The normal architecture of the vessel wall, including the elastic lamina, is disrupted. Thrombosis or aneurysmal dilation may be present at the site of the lesion. Healed areas of arteritis show proliferation of fibrous tissue and endothelial cells, which may lead to occlusion of the vessel. Lesions at all stages of progression and healing may be seen pathologically if sufficient tissue is available for study. The focal nature of the inflammation increases the risk for a false-negative biopsy result when the tissue sample is small. The finding of perivascular inflammation or intimal proliferation without fibrinoid necrosis of the arterial wall suggests, but does not confirm the diagnosis of polyarteritis. In autopsy studies of patients with PAN, inflammation is frequently found in the arcuate and interlobar arteries and arterioles of the kidney, along with evidence of infarction.

Investigations

The systemic inflammatory nature of PAN is reflected in the nonspecific findings of an increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, normochromic normocytic anemia, thrombocytosis, and diminished concentrations of serum albumin. Eosinophilia is not common and is generally associated with pulmonary involvement in EGPA (CSS).

ANCAs are generally considered to not be present in PAN. Rheumatoid factor, other than when present in rheumatoid arthritis, is frequently associated with cryoglobulins. Low-titer antinuclear antibodies are not seen often. Hypocomplementemia is more common in secondary polyarteritis.

Angiography is useful in patients with suspected polyarteritis, particularly if the symptoms and laboratory abnormalities do not direct the choice of biopsy. Angiography may be the diagnostic procedure of choice in patients with HBV-associated polyarteritis. The typical angiographic appearance



Fig. 155.3 Angiography of polyarteritis nodosa showing microaneurysms.

includes long segments of smooth arterial stenosis alternating with areas of normal or dilated artery, smooth tapered occlusions, thrombosis, and a lack of significant atherosclerosis (Fig. 155.3). The dilated segments include saccular and fusiform aneurysms, which strongly suggests PAN. The most frequently involved vessels are the renal, hepatic, and mesenteric vessels. When angiography is performed, it is important that all intraabdominal vessels be studied, including the celiac axis and the mesenteric, renal, and hepatic arteries. The angiographic appearance may regress after treatment. A number of uncommon conditions can mimic the visceral angiographic appearance of vasculitis, including bacterial endocarditis, atrial myxoma, drug abuse, pancreatitis, abdominal malignancy, and disorders of connective tissue.

Although most reported data are derived from conventional contrast-enhanced angiography, magnetic resonance angiography (MRA) can be used as an alternative to classic angiography. A small study looking at imaging of renal involvement in PAN suggested that in the absence of microaneurysms, differentiation between PAN and pyelonephritis with computed tomography (CT) and MRI is difficult. The authors concluded that plain dynamic abdominal imaging, though diagnostically helpful, is often inconclusive and that angiography is therefore required for a definite diagnosis.¹⁹ MRA and contrast-enhanced MRI can also be used to assess for coronary arteritis and myocardial dysfunction and may reveal coronary ectatic disease in patients with MPA and PAN.¹⁶

Muscle biopsy specimens are positive in around 50% of patients with PAN who have muscle pain or claudication. The yield of muscle biopsy is lower in asymptomatic cases.

Assessment of disease activity and damage

Modern therapy for the systemic vasculitides has dramatically altered the prognosis from an acute fulminating life-threatening condition to a chronic disease, with considerable morbidity arising from either disease activity or therapy. Several systems have been developed to assess disease activity and damage, including the Birmingham Vasculitis Activity Score (BVAS), the Groningen Index, and the Vasculitis Activity Index. The BVAS is the most widely applicable to different types of necrotizing vasculitis and has been systematically validated.²⁰ The BVAS is a comprehensive scoring system that includes nine organ systems. Clinical features that are attributable to active vasculitis and that have occurred anew and been present within the previous 4 weeks are recorded. Organ involvement associated with a worse prognosis is given greater weighting. The BVAS has also been used to develop definitions of remission and relapse, which are now being used in multicenter trials.

Vasculitis results in organ damage from either the disease itself or therapy. Damage is defined as an irreversible process that is the result of scars and

not due to acute inflammation or persistent disease activity. The Vasculitis Damage Index (VDI) is also an organ-based system and is scored after 3 months. The VDI is comprehensive, permits assessment of the accumulation of damage with time, and has been validated²¹; however there are concerns that it may not adequately determine the full spectrum of damage experienced by patients with vasculitis of small- and medium-sized vessels. An ongoing international initiative (OMERACT Vasculitis Working group) is aiming to create an evidence-based unified approach to assessment of disease for the primary systemic vasculitides by revising and improving damage assessment tools.²²

The final component of patient assessment is quality of life. The Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36) has been validated for use in patients to assess vasculitis. An emerging patient-reported outcome is health-related quality of life, which is the component of a patient's quality of life that is thought to be attributable to health status rather than education or socioeconomic status.

Differential diagnosis

To establish a diagnosis of PAN, other causes of systemic illness (infection such as endocarditis) and pseudo-vasculitic syndromes such as cholesterol emboli, atrial myxoma, and antiphospholipid syndrome should be excluded, as well as other types of vasculitis that can also involve medium-sized arteries, including the AAVs. Secondary PAN and limited PAN forms should also be considered in the differential diagnosis.

Management

The natural history of untreated PAN is a rapidly progressive, usually fatal disease. The introduction of corticosteroids resulted in an improvement in the survival rate of patients with PAN to 50% at 5 years.²³ A number of randomized controlled trials have been performed, but they included patients with CSS and preceded introduction of the CHCC definitions for PAN and MPA.

The French group analyzed the results from four of their prospective trials, including patients with PAN, that were carried out between 1980 and 1993²⁴:

- Corticosteroids and plasma exchange versus corticosteroids and plasma exchange plus oral cyclophosphamide (CYC) in patients with PAN, CSS, or MPA
- Corticosteroids alone versus corticosteroids and plasma exchange in patients with PAN (without HBV), MPA, or CSS
- Corticosteroids and pulse CYC versus corticosteroids, pulsed CYC, and plasma exchange in patients with poor-prognosis PAN (without HBV), CSS, and MPA; good-prognosis patients received corticosteroids and either pulsed or continuous CYC
- Corticosteroids and antiviral therapy in patients with PAN associated with HBV

The 278 patients were reclassified according to the current definitions of PAN, MPA, and CSS. Overall survival was the same in the 215 patients who received CYC plus corticosteroids or corticosteroids alone. Stratification for disease severity suggested that patients with more severe disease had prolonged survival when treated with CYC. In this analysis, 15 of the 22 patients who died of severe vasculitis had not received corticosteroids. CYC did not, however, appear to reduce the relapse rate. The authors concluded that CYC should be used only in patients with severe disease at initial evaluation.

A recent prospective, multicenter trial by the same group recruited 124 patients with newly diagnosed PAN or MPA from 1993 to 2005 and assessed the efficacy of systemic corticosteroids alone as first-line treatment of PAN and MPA without poor-prognosis factors (as defined by the Five-Factors Score [FFS]). It also compared the efficacy and safety of azathioprine versus pulsed CYC as adjunctive immunosuppressive therapy for patients experiencing treatment failure or relapse. At the time of treatment failure or relapse of disease, patients were randomized to receive 6 months of therapy with oral azathioprine or six pulses of CYC. The overall 5-year survival rate was good (92%), but first-line corticosteroid treatment was able to achieve and maintain remission in only about half the patients, and 40% required additional immunosuppressive therapy. Azathioprine or pulsed CYC was fairly effective in treating corticosteroid-resistant disease or major relapses. Disease-free survival was found to be significantly lower in patients with MPA than in those with PAN.²⁵

The best treatment strategy for patients with systemic vasculitis associated with viral infection should take into account the etiology of the disease and be adapted to the pathogenesis.²⁶ The combination of plasma

exchange and antiviral treatment has been shown to be effective in HBV-associated PAN. Antiviral drugs that have been used with benefit include vidarabine, interferon alfa, and lamivudine,²⁶ the latter giving the best results. Lamivudine 100 mg/day is used with plasma exchange after a few days of steroids treatment (the dose should be reduced in patients with renal impairment), and this regimen is associated with 90% recovery and 60% seroconversion to anti-HBe. The French group used plasma exchange four times per week for 3 weeks, three times per week for 2 to 3 weeks, and then progressive lengthening between sessions. The response clinically can be very rapid, with recovery within 3 weeks. Plasma exchange should be stopped if anti-hepatitis B antibodies are detected (to avoid clearance of them as well).

Rituximab, a chimeric monoclonal antibody, induces selective depletion of B lymphocytes by targeting the CD20 surface antigen. Although good evidence supports the use of rituximab both for induction of remission and for maintenance therapy, especially with refractory AAV, not much evidence other than isolated case reports supports its use for PAN.²⁷

Similarly, there is a lack of robust scientific evidence to guide treatment of the limited variant “cutaneous PAN.” Most experts recommend less aggressive therapy with nonsteroidal antiinflammatory drugs or with other agents such as colchicine or dapsone.²⁸

Prognosis

PAN can be considered to be a monophasic self-limited disease that tends to not recur once remission is induced. In a series of patients with HBV-associated PAN, around 6% relapsed and the relapse rate is thought to be similar to that in those with non-HBV-associated PAN.¹²

The FFS at initial encounter is a useful guide to prognosis. The following parameters are assessed: proteinuria greater than 1 g/day, creatinine level higher than 140 $\mu\text{mol/L}$, cardiomyopathy, gastrointestinal symptoms, and CNS involvement. An FFS of greater than 2 in patients with PAN is associated with greatly increased mortality. The major cause of death in HBV-related PAN is gastrointestinal tract involvement.¹² A large systematic retrospective study of 348 patients with PAN between 1963 and 2005 showed that survival rates differed significantly between patients with an FFS of 0 and those with an FFS of 1 or 2 and between patients with HBV-related PAN and patients with non-HBV-related PAN. Patients in whom PAN was diagnosed after 1995 had better outcomes. Clinical parameters associated with increased risk for death in multivariate analysis were age older than 65 years, recent-onset hypertension, or gastrointestinal manifestations requiring surgery at diagnosis. A higher risk for relapse was associated with non-HBV-related PAN and the presence of skin manifestations, especially nodules.¹¹

COGAN SYNDROME

Definition

CS is characterized by ocular inflammatory lesions, including interstitial keratitis (IK), uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis (affecting small, medium, or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis.⁴ The primary ocular vascular target for inflammation in CS is small vessels in the vascularized layers of the anterior part of the globe, specifically, from outer to inner, the conjunctiva (conjunctivitis), episclera (episcleritis), sclera (scleritis), and uvea (uveitis). Inflamed small blood vessels invade the adjacent normally avascular corneal stroma and cause the very distinctive IK of CS.

Classification

The vasculitis occurring in patients with CS is classified as a variable-vessel vasculitis. The diagnosis of CS is based on the characteristic involvement of both the eye and the inner ear in a young adult. As in PAN, no validated diagnostic criteria have been established.

CS was first described as a separate medical entity in 1945 by David Cogan, an ophthalmologist from the Massachusetts Eye and Ear Infirmary in Boston. He described four patients with a combination of nonsyphilitic IK and vestibuloauditory symptoms that resembled Ménière disease.²⁹ In differentiating these cases from the IK and hearing loss that occur in congenital and tertiary syphilis, Cogan emphasized that both the results of clinical examination and the course of the disease and its sequelae were distinguishable. The onset of eye disease in CS is gradual, and the cornea is not affected much, even after months of follow-up. On the other hand,

syphilitic disease begins abruptly, peaks within a fortnight, and then gradually improves. In syphilis, deafness occurs with a significant delay of months or years and usually in patients with severe IK.

Typical and atypical Cogan syndrome

In 1980, Haynes and colleagues³⁰ divided CS into “typical” and “atypical” after reviewing 13 new cases of CS seen at the National Institutes of Health. The “atypical” forms were characterized by more serious inflammatory disease of the eye, such as scleritis and posterior uveitis, and a higher degree of association with systemic vasculitis. In 2004 a French case series³¹ describing 17 typical and 15 atypical cases of CS concluded that caution should be exercised before endorsing a diagnosis of atypical CS because it may share common manifestations with other systemic diseases such as sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, Sjögren syndrome, inflammatory bowel disease, and AAVs. The biggest case series to date, from Mayo Clinic in 2006, also concluded that division of CS into two forms was no longer relevant,³² mainly because an increasing number of patients with typical CS and vasculitis had been described in the literature, thus making this distinction redundant.

Epidemiology

CS is predominantly a disease of white adults with the peak incidence occurring in the 20- to 30-year-old age group. CS is not associated with any gender or geographic predominance. Although around 250 patients with CS have been reported in the literature, there is considerable publication overlap, with some cases being reported more than once. It is also likely that many cases remain unrecognized or labeled inaccurately as “idiopathic” autoimmune ear disease, hearing loss, or keratitis.³³ Therefore, the actual incidence and prevalence are unknown, but overall, CS is considered a rare disease.

Environmental factors

The etiology of CS is unknown but it is thought to result from an environmental trigger interacting with a genetically predisposed host. Infection may act as a precipitator.³⁴ This is supported by observations that 25% to 33% of patients with CS have an antecedent flulike illness.^{30,32} Despite several attempts to link CS with a variety of infectious agents, including *Borrelia burgdorferi* and various *Chlamydia* species, there have been no conclusive results showing any significant associations. Furthermore, antibiotic treatment has never proved effective.³¹

A few patients exhibit reactivity against inner ear antigens that have sequence homology with Ro/SSA autoantigen and a core protein antigen of reovirus type III.³⁵ Based on animal studies in which passive transfer of the autoantibodies reproduced the features of CS, it is speculated that infection with reovirus type III may be a trigger for CS through the mechanism of molecular mimicry.

Cigarette smoking is considered an additional trigger.³² Among the 60 patients seen in the Mayo Clinic between 1940 and 2002, 31 (52%) were smokers, a rate approximately twice that in the general population.

Clinical features

The combination of ocular and vestibular symptoms in a young adult should raise suspicion for CS. Either of these organs is almost equally likely to be the cause of the initial symptoms.

Nonspecific systemic symptoms such as fever, weight loss, and fatigue may occur before any ocular or audiovestibular manifestations in less than 5% of patients.^{30,32} However, to establish a diagnosis of CS it is necessary to have either eye or inner ear disease manifestations, which are rare in PAN. Other systemic features such as lymphadenopathy, organomegaly, serositis, musculoskeletal symptoms, and urticaria have also been described.³¹⁻³³

Ocular

The predominant ocular feature is IK, which is typically manifested as a painful red eye, photophobia, and blurred vision. Diplopia, tearing, visual field defects, and a sensation of a foreign body in the eye also occur as initial findings.³⁰

Because the ocular manifestations may be intermittent and fleeting, close monitoring with repetitive eye examinations is necessary to monitor for ocular inflammatory disease, particularly IK.³⁶ Slit-lamp examination will demonstrate a patchy, deep, granular corneal infiltrate in most cases (Fig. 155.4). Other ocular manifestations include conjunctivitis, iridocyclitis, scleritis/episcleritis, corneal ulceration, or more rare pathology such as vitritis, choroiditis and subretinal neovascular membrane, pars planitis, orbital pseudotumor, and cotton-wool spots. Retinal vasculitis can also occur

and is a serious complication that may lead to visual impairment; it thus requires urgent ophthalmologic intervention and aggressive treatment.

Vestibuloauditory

Vestibuloauditory dysfunction in CS is typically manifested as sudden unilateral involvement, but gradually progressive sensorineural hearing loss. Vestibular features include sudden-onset vertigo, nausea, vomiting, ataxia, and tinnitus.^{30,31} These symptoms may mimic attacks caused by Ménière disease with or without hearing loss and can also cause nystagmus and oscillopsia (the perception of objects jiggling backward and forward following abrupt turning of the head from side to side).

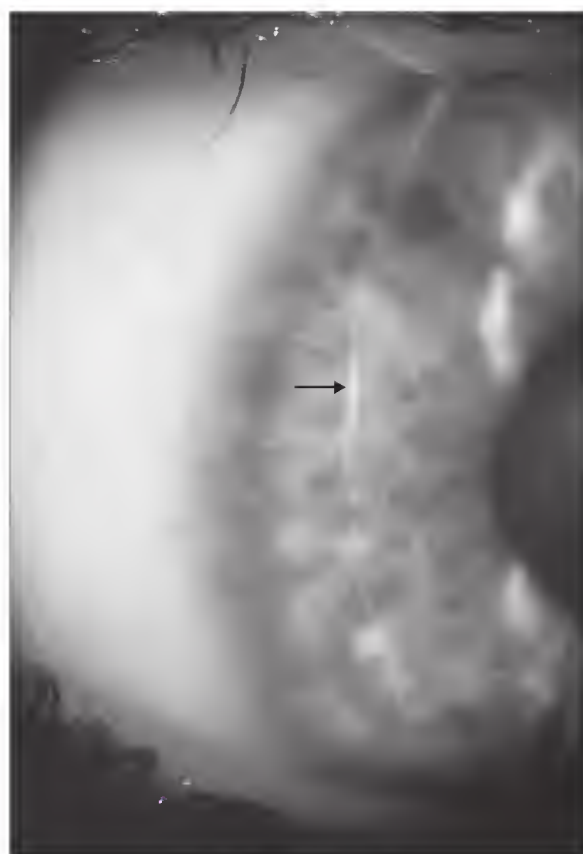


Fig. 155.4 Slit-lamp findings from a patient with Cogan syndrome and interstitial keratitis. A subtle stromal infiltrate (arrow) typical of early interstitial keratitis is demonstrated in the narrow band of light. (Reproduced with permission from McCallum RM, St. Clair EW, Haynes BF. Cogan's syndrome. In: Hoffman GS, Weyand CM, editors. *Inflammatory diseases of blood vessels*. New York: Marcel Dekker; 2002, p. 491-509.)

Recurrent episodes of inner ear disease can lead to cochlear hydrops and also to profound hearing loss, which occurs suddenly and affects both ears in 75% of patients.^{30,32} The resultant downward fluctuation of hearing related to cochlear hydrops can be secondary to changes in cochlear pressure rather than the inflammatory process alone.³⁷

Audiometry testing will typically show sensorineural hearing loss, predominantly affecting the low and high range of frequencies, and sometimes poor speech discrimination.

Vasculitis

Vasculitis occurs in approximately 15% to 20% of patients with CS.³³ CS-related vasculitis may affect any size of vessel, but it most commonly causes large-vessel vasculitis resembling Takayasu arteritis, with the typical histology characterized by infiltration of the walls with polymorphonuclear cells, mononuclear cells, and multinucleated giant cells; intimal proliferation; fibrinoid necrosis; and disruption of the elastic lamina.³⁸ Symptoms, including upper or lower limb claudication (or both) or renal artery stenosis may occur in patients with CS and mimic Takayasu-like large-vessel vasculitis.

Aortitis occurs in 10% of patients^{30,31} and can develop within weeks to years of the onset of CS. Proximal aorta involvement and aortic valve regurgitation are not uncommon. Thoracic and abdominal aortic aneurysms have also been described.³¹ Angiography shows occlusive disease of the major branches of the aorta in different levels³⁹ (Fig. 155.5). Small- and medium-vessel vasculitis similar to PAN has also been described with renal, gastrointestinal, musculoskeletal, and even neurologic manifestations. Coronary arteritis has likewise been reported.³⁹

Other systemic features

Nonspecific systemic symptoms often develop in patients with CS. Neurologic involvement is uncommon but may be manifested in the CNS as meningitis, encephalitis, psychosis, and seizures, as well as peripheral nerve involvement such as mononeuritis multiplex and cranial neuropathy. Musculoskeletal symptoms include nonspecific myalgia and arthralgia.³³

Associations with other disease

Other systemic diseases such as Crohn disease,³⁰ ulcerative colitis, sarcoidosis, hypothyroidism, and interstitial nephritis have occurred in association with CS.

Assessment of disease activity and investigations

Investigation is aimed at establishing the diagnosis and assessing the severity of organ involvement.

Blood and cerebrospinal fluid

Similar to PAN, the inflammatory nature of CS is reflected in the increase in CRP and ESR and the presence of leukocytosis. Hematologic examination may reveal anemia and leukocytosis with relative lymphopenia. In the context of suspected systemic vasculitis, in addition to routine hematologic and biochemical tests, urinalysis should be performed to look for proteinuria, hematuria, and red cell casts.

Serologic investigations, including ANCA, antinuclear antibodies, rheumatoid factor, anticardiolipin antibodies, complement, and cryoglobulins, are typically negative in CS but should be checked to exclude other systemic

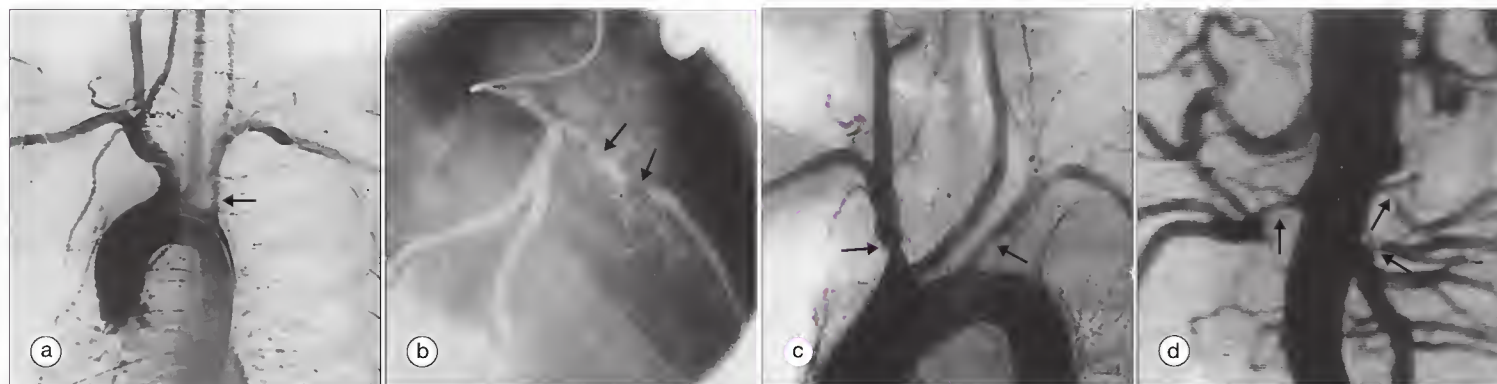


Fig. 155.5 Large-vessel vasculitis in Cogan syndrome. (a) Stenotic lesion of the left subclavian artery (arrow). (b) Stenotic lesions in the left anterior descending coronary artery (arrows) with poststenotic dilatation. (c) Stenotic lesions in the right innominate artery (left arrow) and the left subclavian artery (right arrow). (d) Multiple lesions in the single right and duplicated left renal arteries (arrows). (Reproduced with permission from Allen NB, Cox CC, Cobo M, et al. Use of immunosuppressive agents in the treatment of severe ocular and vascular manifestations of Cogan's syndrome. *Am J Med* 1990;88:296-301.)

disease. Virologic and microbiologic investigations to exclude syphilis and Lyme disease or hepatitis should also be considered.

Inner ear autoantibodies such as anti-hsp70 and anti-68 kDa are often used as a marker of autoimmune sensorineural hearing loss; however, they have no specificity for CS.^{34,40} There are autoantibodies more specific to CS that target a peptide antigen (called Cogan peptide) that shares sequence homology with CD148 and connexin 26, which are expressed on inner ear endothelial cells. These autoantibodies have been found in sera from patients with CS and are able to transfer the disease to animals in laboratory conditions. Although their presence confirms the autoimmune nature of CS, they are not routinely used in clinical practice.³⁴

Cerebrospinal fluid examination might reveal pleocytosis and increased protein and gamma-globulin.³⁰

Assessment of organ involvement

Ocular

Slit-lamp examination is used to evaluate and observe for the presence of IK, which is found in 70% of patients (see Fig 155.4). The typical earliest findings are giant corneal infiltrates 0.5 to 1 mm in diameter. A thorough ophthalmologic examination should also assess for the presence of scleritis or episcleritis, iridocyclitis, conjunctivitis, and any evidence of anterior or posterior ocular inflammation. Ophthalmic photography may be used for follow-up of any affected segments. Fluorescent angiography may help in assessing for retinal vasculitis or retinochoroiditis.

Vestibuloauditory

Otologic examination with an audiogram is necessary to document any hearing loss (occurs in 95% of patients). Audiometry will typically reveal relative sparing of the middle range, a pattern similar to that of Ménière syndrome. The presence of oscillopsia or nystagmus should be evaluated. Brainstem evoked potentials are abnormal in patients with cochlear damage. Caloric responses are abnormal with vestibular injury.

Cardiovascular

Symptoms of aortitis range from an asymptomatic murmur to exertional dyspnea, chest pain, and congestive heart failure with severe aortic regurgitation.^{39,41} A thorough physical cardiovascular examination should be performed in all patients with CS (including bilateral blood pressure assessment to identify any discrepancy suggestive of large-vessel arteritis). In the presence of evidence suggestive of myocardial infarction,²⁹ pericarditis,³⁹ left ventricular hypertrophy, or arrhythmias, further cardiovascular investigations such as electrocardiography, echocardiography, and cardiac angiography should be considered.

Echocardiography may show signs of aortic regurgitation such as “fluttering” of the anterior mitral valve leaflet, thickening of the valve cusps,⁴² paradoxical movement of the ascending aorta during systole,⁴¹ and left ventricular enlargement.^{41,42} Cardiac catheterization helps in the evaluation of hemodynamics^{38,41,43} and in the diagnosis of aortic valvular disease. Coronary angiography may reveal ostial coronary stenosis^{39,41} and distal coronary arteritis, whereas visceral angiography can demonstrate the typical lesions of Takayasu-like or polyarteritis-like vasculitis^{38,41,42} (see Fig 155.5).

Positron emission tomography is an emerging modality for the diagnostic workup of other types of large-vessel involvement such as Takayasu vasculitis. However, its role remains to be determined in CS-related large-vessel vasculitis.^{33,44}

Neurologic

MRI is typically useful in excluding the presence of an acoustic neuroma, other brain stem lesions, or a tumor in the cerebellopontine angle. In some patients with CS, brain MRI and CT have shown soft tissue and calcified obliteration of vestibular and cochlear structures. With gadolinium-enhanced MRI, disruption of the blood-labyrinthine barrier may be seen as enhancement of the vestibular and cochlear structures.⁴⁵

Differential diagnosis

CS should be considered in patients with ocular inflammation and evidence of audiovestibular dysfunction. The differential diagnosis of CS is broad and depends on the clinical findings, but CS should be distinguished mainly from other types of vasculitis that may cause scleritis or uveitis (i.e., GPA, PAN, Behçet disease). Furthermore, infectious causes of IK should also be considered and excluded with serologic testing and cultures. Several disorders produce ocular inflammation and vestibuloauditory dysfunction similar to CS. Examples include syphilis, Lyme disease, Vogt-Koyanagi-Harada syndrome, toxic exposures, and Ménière disease. Finally, nonocclusive, nonvasculitic vasculopathy should also be considered.

TABLE 155.4

Treatment of Cogan syndrome

Disease manifestations	Recommended treatment
Ocular	
Interstitial keratitis	Topical ocular corticosteroids and mydriatics (atropine)
Iridocyclitis	Low-potency topical corticosteroids such as 1% prednisolone acetate (3-7 days)
Anterior uveitis	Systemic corticosteroids (only in the case of failure of topical therapy)
Suspected chlamydial infection	Treatment with a tetracycline antibiotic (doxycycline) (200 mg daily for 2-3 wk)
Posterior-segment ocular inflammation	Systemic steroids DMARDs as steroid-sparing agents
Audiovestibular	
Acute vestibular symptoms	Diuretics, antihistamines, bed rest
Chronic vestibular symptoms	Vestibular exercises
Hearing loss	
Hearing loss	Corticosteroids: prednisolone 1 mg/kg daily (up to 60 mg) for 2 wk and then taper. Duration of initial treatment, 4-6 mo. Consider immunosuppressant therapy with steroid-sparing agents
Severe hearing loss unresponsive to medical treatment	Cochlear implant
Systemic vasculitis	
Cogan syndrome with large-vessel vasculitis	Corticosteroids and cyclosporine or cyclophosphamide
Cogan syndrome with medium-vessel vasculitis	Corticosteroids and cyclophosphamide as per treatment of polyarteritis nodosa

DMARD, disease-modifying antirheumatic drug.

Management

Patients with CS may go to different specialists, depending on their symptoms, and may initially be managed in an eye or an ear, nose, and throat clinic. However, these patients are best managed by a multidisciplinary team that includes ophthalmologists, otolaryngologists, audiologists, and rheumatologists. A summary of treatment options is outlined in Table 155.4.

Main principles

- The mainstay treatment of acute flares and recurrences if ocular and auditory inflammation is present is glucocorticoids.
- Keratitis and anterior uveitis usually respond to topical steroids. However, posterior scleritis and retinitis may require oral glucocorticoids.
- Audiovestibular disease requires high-dose oral steroids (1 to 2 mg/kg/day of prednisolone).
- Resistant disease or systemic disease with vasculitis requires immunosuppression.

Ocular disease

IK and iridocyclitis/anterior uveitis are treated with topical ocular corticosteroids and mydriatics to control inflammation and prevent synechiae. Low-potency topical corticosteroids such as 1% prednisolone acetate are often adequate for treating IK, and the symptoms tend to improve within a week.³⁰ Systemic corticosteroids are not generally indicated but may be used in the rare case of failure of topical therapy.^{30,46}

In nonresponding patients, chlamydial infection should be considered as a possible cause of the inflammation, and a trial of treatment with a tetracycline antibiotic such as doxycycline should be considered (200 mg daily for 2 to 3 weeks).⁴⁶ Conjunctivitis, scleritis, and episcleritis can also be treated with topical corticosteroids. Nodular scleritis warrants more aggressive therapy with systemic corticosteroids or other potent immunosuppressive drugs. Episcleritis and scleritis can be managed with topical or systemic nonsteroidal antiinflammatory therapy.

Posterior-segment ocular inflammation that is progressive or persistent or interferes with vision requires systemic corticosteroid therapy with prednisolone 1 mg/kg.^{30,37} Progression of posterior ocular inflammation despite systemic corticosteroids or failure to respond after 2 to 3 weeks of high-dose steroids should prompt the clinician to add immunosuppressive drugs such as methotrexate, azathioprine, CYC, or cyclosporine.^{33,41,47}

Cataracts may develop as a result of topical and systemic corticosteroid therapy. Surgical extraction and correction should be encouraged, especially in patients with hearing impairment from CS because they may depend on lip reading or sign language for communication.³⁷

Vestibuloauditory disease

A trial of systemic corticosteroid therapy is indicated for a patient in whom CS and hearing loss are newly diagnosed.^{30,33,48} Systemic corticosteroids are initiated at a dose of 1 to 2 mg/kg/day of prednisone or its equivalent (up to 60 mg)³³ for 2 weeks and then tapering of the dose in decrements of 5 to 10 mg every 1 to 2 weeks according to the patient's response. The dose can then be tapered to discontinuation over the next 3 to 4 months, provided that auditory acuity remains stable. Patients with refractory disease and recurrent episodes of hearing loss may require long-term daily corticosteroid therapy to maintain auditory function. Ideally, the dose of prednisone should be kept to 10 mg/day or less in these cases.

The use of immunosuppressive drugs as steroid-sparing agents is not uncommon. CYC, methotrexate, azathioprine, tacrolimus, leflunomide, and biologic drugs have been used successfully as adjunctive immunosuppressive therapy; however, their efficacy remains uncertain.³³ There are very few controlled trials, with the exception of a double-blind, placebo-controlled, randomized trial in which methotrexate therapy showed no significant efficacy in ameliorating autoimmune hearing loss.⁴⁹ Most evidence for the use of other disease-modifying antirheumatic drugs, including anti-tumor necrosis factor (TNF) and rituximab, is anecdotal and based on isolated case reports.⁵⁰⁻⁵² Some evidence indicates that infliximab can be effective in the treatment of hearing loss secondary to CS.⁵³ Etanercept is not effective in preserving or improving hearing loss, but it may improve word identification and recognition.⁵⁴

Hearing loss related to cochlear hydrops may respond to a course of diuretic therapy.^{37,46} Control of the symptoms of acute vestibular dysfunction can be facilitated with antihistamine or benzodiazepines and bed rest. In chronic cases, vestibular therapy with exercise activity may also prove useful.^{37,46} Cochlear implantation is the most successful surgical approach for end-stage hearing loss in patients with CS who have not responded to medical therapy or conventional hearing augmentation.³³

Systemic vasculitis

CS-related systemic vasculitis is treated with systemic glucocorticoids (prednisolone 1 mg/kg) in the same protocols as for any systemic vasculitis.

Medium-vessel vasculitis is treated with the same CYC regimen used for PAN.

For large-vessel vasculitides, cyclosporine (4 mg/kg/day or less) for a year or CYC (2 to 3 mg/kg orally) has been recommended. Methotrexate (15 to 25 mg/wk) has also been used.

Although biologic agents have been used in isolated case reports (anti-TNF, tocilizumab, rituximab), there is no convincing evidence to prove their efficacy.

Prognosis

The natural progression of the disease consists of an initial flare, which may last several weeks to months, followed by a chronic, slowly progressive phase. Ocular outcomes in patients with CS are excellent. Blindness occurs in less than 5% of eyes. In contrast, deafness is a frequent and debilitating outcome in CS and occurs in up to 52% of cases.⁵⁵ Corticosteroid therapy may improve the auditory outcomes. The vestibular manifestations improve in most patients with CS. However, some patients are left with persistent oscillopsia. Finally, although systemic vasculitis can be treated successfully, CS with vasculitis can be associated with a poor prognosis, especially in the context of large-vessel vasculitis with aortic incompetence.

CONCLUSION

PAN and CS are rare vasculitides with potential multisystem involvement. They are not associated with the presence of ANCA, and both require corticosteroid therapy in association with immunomodulators, depending on disease activity and severity. A high degree of clinical suspicion in patients with typical features, in conjunction with targeted investigations and confirmative histopathology or angiography, is helpful in distinguishing these two conditions from the large number of possible differential diagnoses. The main principles of managing patients with systemic vasculitis with regard to assessment of disease activity and damage, as well as the therapeutic paradigms involving CYC regimens for severe disease, are applicable to both these conditions. However, there is still a low level of evidence for therapeutic strategies because of the lack of large randomized controlled trials and the rarity of these important diseases.

ACKNOWLEDGMENTS

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Polymyalgia rheumatica and giant cell arteritis

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POLYMYALGIA RHEUMATICA

- Polymyalgia rheumatica (PMR) is characterized by proximal muscle pain and stiffness that affects the neck, shoulders, and pelvic girdle.
- It is a forme fruste of giant cell arteritis (GCA) with molecular evidence of vascular inflammation yet absence of wall-infiltrating lymphocytes; PMR occurs in the same patient population that is at risk for GCA.
- Laboratory abnormalities (elevated erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and interleukin-6 [IL-6]) reflect an activated acute-phase response. Autoantibody assays are negative.
- Synovial inflammation, particularly of large joints, can occur but should raise suspicion for seronegative polyarthritis.
- Vascular symptoms necessitate temporal artery biopsy.
- Small doses of corticosteroids (10 to 20 mg/day) are sufficient to induce prompt and marked improvement of stiffness and pain.

GIANT CELL ARTERITIS

- This panarteritis of medium and large arteries is combined with an intense systemic inflammatory syndrome. Vasculitic lesions cause luminal occlusion and tissue ischemia or aortic aneurysm.
- Preferentially targeted vascular beds include branches of the external carotid, subclavian, common carotid, and vertebral arteries and the aorta.
- The major risk factor is age; patients are older than 50 years and the incidence continues to increase further with age.
- Typical features include new-onset headaches, scalp tenderness, jaw claudication, polymyalgia, fever, malaise, anorexia, and weight loss. Vascular occlusion is manifested as loss of vision, stroke, and ischemia of the upper extremities.
- Laboratory abnormalities include highly elevated acute-phase proteins (ESR, CRP, IL-6) and anemia.
- The diagnostic procedure of choice is temporal artery biopsy.
- Imaging of the aortic arch and the large vessels can be informative.
- Symptoms of systemic inflammation are explicitly sensitive to corticosteroid therapy, with dramatic improvement seen within 48 hours.

INTRODUCTION

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two closely related inflammatory syndromes.^{1,2} In GCA, inflammatory infiltrates occupy the walls of medium-sized and large arteries and cause mural injury, luminal occlusion, and vascular stenosis. PMR is associated with intense muscle pain and stiffness affecting the shoulder and pelvic girdle; mild synovial and periarticular inflammation of proximal joints may be present in some patients, whereas in others the tissue site of inflammation remains unidentified. Both syndromes share laboratory abnormalities that reflect a vigorous acute-phase response and are critical for diagnosis and monitoring of affected patients.

PMR and GCA occur in the same patient population, thus suggesting common risk factors and pathogenic pathways. Significant progress has been made in discerning the molecular events of the vasculitic component. Vessel wall indigenous dendritic cells (DCs) that sense immunostimulatory danger signals have a checkpoint function and regulate the recruitment and

in situ activation of vasculitic T cells. The intense acute-phase response has prompted speculation that PMR and GCA are sequelae of infection, but attempts to implicate a single pathogen in the arterial tissue have not yet been successful, which raises the possibility of a diverse set of instigators.

The most significant risk factor for both syndromes is age; PMR and GCA are restricted to those 50 years and older, thus suggesting a critical role for aging, as well as for environmental and acquired factors, in the pathogenesis of the disease.

Over the past decades our ability to diagnose GCA accurately has improved, patient management has become more individualized, and the overall prognosis is good.

POLYMYALGIA RHEUMATICA

PMR is a syndrome of pain and stiffness that typically affects the proximal muscles of the shoulder and pelvic girdle. The muscles supporting the neck can be involved; myalgia of the torso is less common. PMR is frequently encountered in patients with GCA, in whom it may precede, follow, or accompany the manifestations of vasculitis. A small proportion (<10%) of patients with PMR and no clinical evidence of vasculitis are found to have frank vascular inflammation on biopsy. Laboratory tests show elevated acute-phase reactants, including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6).^{3,4} An almost pathognomonic characteristic of the disease is prompt response to corticosteroids. For most patients, treatment can be discontinued after 1 to 2 years, although smoldering disease activity may persist.

The major diagnostic challenge in PMR is the lack of a pathognomonic test. Provisional diagnostic criteria (Box 156.1) have been developed that rely on nonspecific symptoms such as proximal muscle aching and stiffness and an acute-phase response, but these symptoms can occur in many other diseases.⁵ Abnormal ultrasound findings, particularly subdeltoid bursitis, were slightly more frequent in patients with PMR than in controls. In many patients PMR remains a diagnosis of exclusion that is made by minimizing the likelihood of other inflammatory conditions associated with a polymyalgia syndrome (Box 156.2). Some experts prefer a broad diagnostic definition of PMR and include patients with seronegative polyarthritis who have arthritis of the proximal joints or swelling and pitting edema on the dorsa of the hands and wrists; however, the outcome in these patients is different from that of the more narrowly defined PMR and resembles the outcome of seronegative rheumatoid arthritis (RA).

A critical aspect of diagnosing PMR lies in excluding GCA because these syndromes are so closely associated. Temporal artery biopsy should be performed in patients with suspicious vascular symptoms. Findings of GCA, as demonstrated by temporal arteritis on biopsy or typical vascular involvement on imaging studies, override a diagnosis of PMR. In any case, patients with PMR should be monitored for the emergence of vasculitis because GCA may develop even years later.

Clinical features

Ninety percent of patients with PMR have a sudden onset of muscle aching and stiffness affecting the neck, shoulders, and upper part of the arms. Frequently, they describe the pain as severe and disabling. Isolated discomfort in the pelvic girdle and thighs is less frequent. Symmetric myalgia is typical but not mandatory. Classically, the medial and distal parts of extremities are not affected, but the pain can radiate to the elbow and knee regions. The myalgia is most severe during the early morning hours; morning stiffness can be long lasting and incapacitating. Typically, the muscle pain is exacerbated by movement, such as using the arms or trying to rise from a

sitting position. On clinical examination, active range of motion of the proximal joints is restricted by pain and stiffness, but passive range of motion of the shoulders and hips is maintained. Little evidence exists for joint swelling or tenderness. Also, patients with PMR rarely lose muscle strength, a manifestation that warrants a workup for myositis.

Accompanying constitutional symptoms are frequent (>50% of patients) and include fatigue, malaise, anorexia, weight loss, and subfebrile temperatures.^{1,2} Fever, chills, and night sweats should prompt evaluation for underlying infection, malignancy, and vasculitic involvement.

BOX 156.1 POLYMYALGIA RHEUMATICA: PRELIMINARY DIAGNOSTIC CRITERIA

Required:

Age ≥50 years
Bilateral shoulder aching
Abnormal CRP and/or ESR

Major (2 points):

Morning stiffness >45 minutes
Absence of RF or ACPA

Minor (1 point):

Hip pain or limited range of motion
Absence of other joint involvement
Ultrasound findings of subdeltoid bursitis, biceps tendinitis, glenohumeral synovitis, trochanteric bursitis, or hip synovitis
Ultrasound findings in both shoulders

A score of 4 (or 5 if ultrasound is included) is suggestive for PMR.

ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

From Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 Provisional classification criteria for polymyalgia rheumatic: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Arthritis Rheum* 2012;64:943-54.

BOX 156.2 DISEASE ENTITIES WITH POLYMYALGIA SYMPTOMS

Rheumatoid arthritis
Rotator cuff syndrome
Osteoarthritis of the shoulder and hip joints
Fibromyalgia
Polymyositis/dermatomyositis
Spondyloarthritis
Systemic lupus erythematosus
Vasculitides
Paraneoplastic myalgias
Infection-associated myalgias
Statin therapy
RS3PE (remitting seronegative symmetric synovitis and pitting edema)
Parkinson disease
Hypothyroidism

Etiology and pathogenesis

Age is the major risk factor for PMR. The disease develops in individuals 50 years and older, and incidence rates continue to increase with advancing age.⁶ Two thirds of patients are female. Risk for the disease varies with geographic region, possibly reflecting environmental factors or clustering of risk genes in selected populations. The highest incidence rates have been reported in northern Europe, particularly the Scandinavian countries. In Olmsted County, Minnesota, a region enriched with immigrants from Scandinavia, yearly incidence rates have been estimated to be 59 per 100,000 people 50 years and older.⁶ Even higher incidence rates have been reported from the United Kingdom, up to 84 per 100,000 person-years.⁷

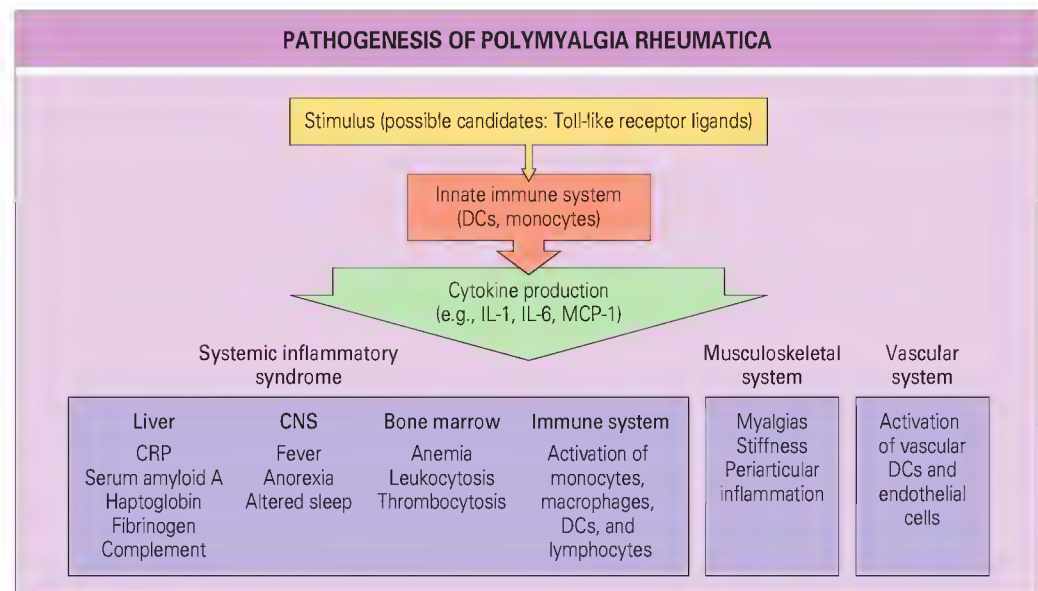
PMR is almost certainly a multigenic disease. Association with the HLA-DR4 haplotype has been reported in several populations, with variable results on whether this major histocompatibility complex class II haplotype confers only disease susceptibility or also plays a role in disease severity.

Central to the pathogenesis of PMR is the location where the inflammation occurs. This issue of tissue involvement remains unresolved, however. Systemic activation of the innate immune system is a key component of PMR, and a disease model of a primary defect triggering innate immunity is strongly supported by the presence of highly elevated acute-phase proteins (Fig. 156.1).² Patients with PMR have a high frequency of circulating activated monocytes/macrophages that produce proinflammatory cytokines such as IL-6.⁸ Because the frequency of cytokine-producing monocytes/macrophages in the circulation is indistinguishable from that in patients with GCA, systemwide monocyte activation is probably one of the early events in both diseases and not a consequence of local inflammation. Abnormal cytokine concentrations are found in the interstitial fluid of muscles, possibly a correlate of the myalgia characteristic of the disease.⁹ In addition, the temporal arteries of patients with PMR show evidence of local production of some inflammatory mediators even in the absence of an obvious inflammatory infiltrate by histomorphology.¹⁰ DCs in the adventitia of normal temporal arteries are activated and differentiated in patients with PMR.¹¹ They secrete chemokines, which are potent attractors of T cells, and can initiate adaptive immune responses in the vessel wall. When normal temporal arteries, arteries from PMR patients, and arteries from GCA patients were co-implanted into immunodeficient mice, vascular DCs in PMR arteries recruited and activated CD4+ T cells, whereas DCs in normal temporal arteries failed to promote T-cell stimulation (i.e., T cells from the GCA arteries moved into the PMR arteries but avoided the normal arteries). These experiments suggest that activation of vascular DCs is an initial step in establishing the vasculitis that has already occurred in PMR patients. The stimuli that activate vascular DCs in PMR are unknown, but these findings have reinitiated discussion about the role of infectious organisms, generally the most potent activators of DCs.

Laboratory studies

Acute-phase responses are examined by measuring the ESR or levels of CRP or IL-6. Other acute-phase reactants, including fibrinogen, serum amyloid A protein, and von Willebrand factor, are also elevated but do not appear to be more useful than CRP for diagnostic purposes or as biomarkers to

Fig. 156.1 CNS, central nervous system; CRP, C-reactive protein; DC, dendritic cell; IL, interleukin; MCP-1, monocyte chemoattractant protein-1. (From Weyand CM, Goronzy JJ. *Giant-cell arteritis and polymyalgia rheumatica*. *Ann Intern Med* 2003;139:505-15.)



monitor disease activity. Not all patients display abnormal findings with the standard inflammatory markers; about 10% have a normal ESR.⁴

Most patients have mild to moderate normochromic or hypochromic anemia. Frequently, platelet counts are elevated. Elevation of liver enzymes, particularly alkaline phosphatase, is part of the inflammatory syndrome. Serum creatinine levels and urinary sediments are normal. Despite intense muscle pain, muscle enzymes, electromyographic studies, and muscle biopsy do not show any evidence of muscle injury.

A useful diagnostic finding is the absence of autoantibodies. Antineutrophil cytoplasmic antibodies (ANCA) are rarely detected. Complement levels are normal. Antinuclear antibodies should prompt reassessment for an underlying connective tissue disease. Rheumatoid factors or antibodies to citrullinated peptides are not more frequent than expected in a population of healthy elderly individuals. Serum immunoglobulin concentrations are normal.

Imaging studies

Vascular imaging studies are performed primarily to exclude the vasculitic manifestations of GCA. They are indicated only if vasculitis is suspected clinically. The issue is particularly relevant for GCA of the distal subclavian arteries. Frequently, these patients come to clinical attention because of signs and symptoms of PMR, but about 50% have a negative temporal artery biopsy result.¹² Positron emission tomography with fluorine-18-labeled fluorodeoxyglucose (FDG-PET) has been reported to show enhanced metabolic turnover in the aortic wall and its large branches in a subset of PMR patients.¹³ Although this finding emphasizes vascular inflammation as a component of PMR, the specificity and clinical implications remain unclear. It is unknown whether the metabolic changes in patients with vasculitic inflammation are sufficiently distinct from those in atherosclerotic disease and whether PMR patients with vascular involvement based on PET should be managed differently.

In the subset of PMR patients with inflammation of periarticular structures, ultrasonography and magnetic resonance imaging (MRI) are sensitive diagnostic approaches.¹⁴ The most prominent findings are subdeltoid and subacromial bursitis; rarely, bicipital tenosynovitis and glenohumeral joint synovitis are found. Ultrasonography rapidly reveals accumulation of fluid in the bursae. Soft tissue thickening and edema can be visualized on MRI with a focus on axial T2-weighted sections.

Differential diagnosis

Polymyalgic syndromes are diagnosed frequently and require careful evaluation (see Box 156.2). The current diagnostic criteria (see Box 156.1) are only moderately helpful in identifying patients with “true” PMR. In a significant proportion of patients seen initially with polymyalgia, the diagnosis is revised at follow-up.¹⁵ PMR and some forms of RA are particularly difficult to distinguish. Patients with late-onset RA tend to have preferential involvement of the proximal joints, particularly in early stages of the disease, thus making it almost impossible to separate them from patients with PMR. With progression of the disease, peripheral and erosive arthritis often develop in RA, but not in PMR.

Closely related to PMR is the remitting seronegative symmetric synovitis and pitting edema (RS3PE) syndrome, a variant of seronegative RA characterized by symmetric peripheral synovitis and tenosynovitis causing pitting edema on the dorsa of the hands and wrists and, less frequently, the ankles and feet. Patients with RS3PE respond explicitly well to low doses of corticosteroids. Imaging studies demonstrate the intense tenosynovitis component of this polyarthritis. The disease usually remains nonerosive.

A combination of muscle pain, stiffness, and inflammatory markers is fairly common in patients with systemic lupus erythematosus; identification of antinuclear antibodies and organ manifestations typical of connective tissue disease (especially skin, lung, or kidney disease) makes it relatively easy to distinguish these syndromes. Marked constitutional symptoms, including fever, weight loss, depression, and malaise, in combination with muscle soreness is common in many vasculitic syndromes, including GCA.

Inflammatory myopathies typically cause loss of muscle mass and strength. Elevated muscle enzyme levels should prompt further evaluation by electromyography and muscle biopsy.

Patients with diffuse muscle pain and stiffness need to be interviewed carefully for their medication history. Myalgia, muscle weakness, and cramping develop in 1% to 5% of patients taking statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors).¹⁶ In general, the pain is more diffuse, lacks preference for proximal muscle groups, and does not display a circadian rhythm; muscle enzyme levels can be normal or elevated. The myalgia can persist after withdrawal of statin therapy.

Physicians should be alert to the possibility of paraneoplastic myalgia. Profound weight loss, drenching night sweats, and an incomplete response to corticosteroids provide clues for further assessment. An elevated ESR because of a paraprotein can be the first indication of lymphoproliferative disease. Also, patients should be examined for an underlying infection that may be causing fatigue, malaise, fever, muscle pain, weight loss, and inflammatory markers.

Treatment

A typical feature of PMR is a prompt, profound response to corticosteroids. For most patients, initial prednisone doses of 10 to 20 mg or equivalent are sufficient to control the myalgia.^{3,4} Infrequently, patients require higher doses. Almost complete resolution of symptoms is usually experienced within 2 to 3 days, but clinical responses to lower prednisone doses can be delayed. Incomplete responses or recurrence of symptoms during the early treatment phase should increase suspicion about the diagnosis or raise the possibility of GCA.

The initial doses are maintained for 2 to 4 weeks, followed by careful tapering. Normally, the corticosteroid dose can be reduced by 10% every 2 to 4 weeks. About 50% of patients experience disease flares as the dosage of corticosteroids is decreased. Monitoring of the ESR and CRP can help in assessing the inflammatory burden. With improvement, the ESR returns to the normal range and the CRP level improves but frequently does not completely normalize, a finding suggesting continuous smoldering disease activity. Clinical symptoms (especially muscle soreness and malaise) are used as the main indicators for therapy. Recurrent myalgia or a rise in acute-phase markers frequently require only minute increases in corticosteroid doses. Unresolved questions are whether smoldering systemic inflammation beyond 1 to 2 years requires treatment and, if so, which immunosuppressive method can be safely administered long-term. Very low dosages of corticosteroids (prednisone 1 to 3 mg/day) are often sufficient for adequate control of symptoms in these chronically treated patients.

Use of methotrexate (MTX) as a corticosteroid-sparing agent has been addressed in a randomized, doubled-blind, placebo-controlled trial. Prednisone (25 mg/day starting dose) was tapered off within 24 weeks with dose adjustment in the event of flare-up. Patients were randomized to receive 10 mg of MTX per week for 48 weeks or placebo. Outcome was assessed after 18 months. Significantly more patients in the MTX group were not taking corticosteroids, and significantly fewer experienced any flare-ups. However, the rate and severity of adverse effects were similar and the corticosteroid-sparing effect was modest (cumulative 2.1 g of prednisone in the MTX group and 2.9 g in the placebo group), which raises the question of whether the benefits from MTX are clinically meaningful.¹⁷ Although in a long-term follow-up study 65% of patients had at least one corticosteroid-related adverse effect, mortality rates in PMR patients are not increased, and even longer than expected survival has been reported in a Scandinavian cohort.¹⁸ Efforts should concentrate on ensuring that patients receive the minimally effective corticosteroid doses. Given the age and comorbid conditions of individuals at risk for PMR, the use of aggressive immunosuppressants should be considered with great caution. Since patients with PMR experience increased bone turnover, even before corticosteroid therapy,¹⁹ management should include calcium and vitamin D supplementation and other bone-sparing treatments if indicated by bone mineral density measurements.

GIANT CELL ARTERITIS

GCA is an inflammatory vasculopathy that affects large and medium-sized arteries.²⁰ Almost all patients have signs and symptoms of systemic inflammation manifested as nonspecific constitutional symptoms with an intense acute-phase response, including highly elevated ESR and CRP values and anemia. Diagnostic criteria have been developed to distinguish GCA from other vasculitides²¹; however, they were intended for investigative studies and not for establishing the diagnosis in individual patients (Box 156.3).

The vascular component of GCA results from a granulomatous arteritis that elicits a response to injury in the affected vessel wall.²² In medium-sized arteries, this leads to hyperplasia of the intima, luminal occlusion, and ischemia. In the aortic wall, inflammation causes structural damage that eventually results in aneurysm formation and dissection. Selected vascular territories, such as the aorta and its upper branches, are most susceptible to GCA. Typically, branches of the external carotid, including the temporal arteries, are involved. The most severe complications of GCA are loss of vision and stroke. Blindness is potentially preventable if the disease is recognized and treated promptly, thus emphasizing the need for a high index

BOX 156.3 AMERICAN COLLEGE OF RHEUMATOLOGY 1990 CRITERIA FOR THE CLASSIFICATION OF GIANT CELL ARTERITIS

The presence of 3 or more of the following 5 criteria assigns a vasculitis patient to the diagnosis of GCA

- Age at disease onset ≥ 50 years
- Headache of new onset or new type
- Tenderness or decreased pulsation of the temporal artery
- Elevated erythrocyte sedimentation rate (>50 mm/hr)
- Histologic changes of arteritis (either granulomatous lesions, usually with multinucleated giant cells, or diffuse mononuclear cell infiltration)

From Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122-8.

of clinical suspicion and familiarity with the typical and atypical manifestations of this vasculitis.

The overall prognosis of patients with GCA is good. Survival rates of patients with GCA are equivalent to those of an age-matched population.²³ Notably, acceleration of atherosclerosis, which complicates the course of many rheumatic diseases, has not been found in patients with GCA.

Clinical features

GCA is a disease of the elderly and does not usually occur before the age of 50 years. The mean age at diagnosis is 70 to 75 years, and two thirds of patients are female. Frequently, the disease begins insidiously, with symptoms gradually increasing in severity over a period of weeks or months. In some cases the onset is abrupt and the first manifestation is a major complication, such as loss of eyesight. Symptoms can wax and wane and resolve temporarily, even in the absence of treatment. The spectrum of initial disease manifestations is broad (Table 156.1),^{1,2} and physicians need to be alert to not miss subtle manifestations of vascular insufficiency or clinical symptoms.

Most patients come to clinical attention because of headaches, scalp tenderness, and PMR; fever, malaise, anorexia, and weight loss are also frequent manifestations.²⁴ If the arteritis involves the cranial vasculature, headaches and ischemia of the eye, brain, and cranial muscles dominate the findings. If extracranial arteries are the primary target, patients often have an aortic arch syndrome characterized by impaired blood flow to the upper extremities.¹² If the major disease component is systemic inflammatory syndrome, vascular complications may be minimal and the clinical features are those of a wasting syndrome or fever of unknown origin. Manifestations of vascular inflammation are helpful for the clinician in predicting whether a patient has GCA. Signs of systemic inflammation are obviously less specific but are a useful hint in screening for suspected cases (Fig. 156.2).

Cranial arteritis

The former names of GCA, temporal arteritis and cranial arteritis emphasized the inflammatory stenosis of distal branches of the thoracic aorta. Because the disease targets branches of the external carotid artery, patients complain of headaches, scalp tenderness, jaw claudication, and tongue claudication. The blood supply to the orbit can become compromised and cause visual loss.²⁵ Stenotic lesions in the vertebral and basilar arteries produce central nervous system ischemia, vertebrobasilar insufficiency, transient ischemic attacks, and strokes.²⁶

Patients describe their headaches as being diffuse or localized, usually in the temporal, occipital, or periorbital areas. The headaches can be severe, may be refractory to standard analgesics, and can interfere with sleep. Scalp tenderness is frequent and at times localized over the temporal and occipital arteries, but it can also be distributed diffusely. The pressure from wearing glasses may be intolerable. Insufficient blood flow to the masseter and pterygoid muscles causes jaw claudication, a rather specific finding for GCA. Talking or chewing elicits muscle cramping and pain that forces the patient to interrupt conversations or meals. A similar mechanism can lead to tongue claudication, rarely complicated by frank gangrene. A sore throat and painful dysphagia may indicate ischemia of the pharynx.

The true incidence of ocular involvement in GCA is poorly defined, but it is estimated that up to 15% of patients experience ophthalmic complications.²⁵ Ischemia in the territory of the ophthalmic artery is the leading cause of ocular problems, but ischemia anywhere along the visual pathways can threaten eyesight. The visual loss is pain free, can be partial or complete, be unilateral or bilateral, and is generally irreversible. The most common cause is anterior ischemic optic neuropathy secondary to occlusion of the

TABLE 156.1
Clinical features of giant cell arteritis

Clinical feature	Overall frequency	Seen predominantly in
Manifestations of vascular injury		
Headaches:		
Different patterns; often severe, sometimes throbbing; can be localized	+++	CA
Scalp tenderness:		
Often temporal; elicited by combing or by touching or wearing glasses; the temporal artery can be thickened, tender, or nodular	++	CA
Jaw claudication:		
Induced by chewing and prolonged talking	++	CA
Ocular symptoms:		
Partial or complete visual loss, amaurosis fugax, or ocular motor deficit; blindness, unilateral or bilateral; usually permanent	+	CA
Dysphagia:		
Sore throat, painful swallowing	+	CA
Respiratory symptoms:		
Dry, nonproductive cough	+	CA
Limb claudication:		
Ischemic pain with use of the arms, paresthesias, color changes, rarely lower extremity claudication	+	
Absent or asymmetric pulses	+	LVA
Asymmetric blood pressure readings	+	LVA
Ischemia of the central nervous system:		
Vertebrobasilar insufficiency, dizziness, imbalance, cortical blindness, confusion	+	CA
Tongue claudication	+	CA
Aortic dilation and regurgitation	+	LVA
Myocardial infarction	+	
Peripheral neuropathy	+	
Tissue gangrene:		
Scalp, tongue, or digits	+	
Manifestations of systemic inflammation		
Intense acute-phase response:		
Elevated erythrocyte sedimentation rate; elevated levels of C-reactive protein, interleukin-6, and other acute-phase proteins; thrombocytosis; elevated liver function test results	+++	CA, SISA, LVA
Normocytic, normochromic anemia	++	SISA, CA
Polymyalgia rheumatic:		
Stiffness and pain in the muscles of the shoulders, pelvic girdle, and neck; rarely the torso	++	CA, SISA, LVA
Wasting syndrome:		
Anorexia, weight loss, fever, malaise, night sweats, depression	++	SISA
Synovitis of peripheral joints:		
Mostly the wrists	+	

CA, cranial arteritis; LVA, large vessel arteritis; SISA, systemic inflammatory syndrome with arteritis.

Data from Weyand CM, Goranzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003;139:505-15.

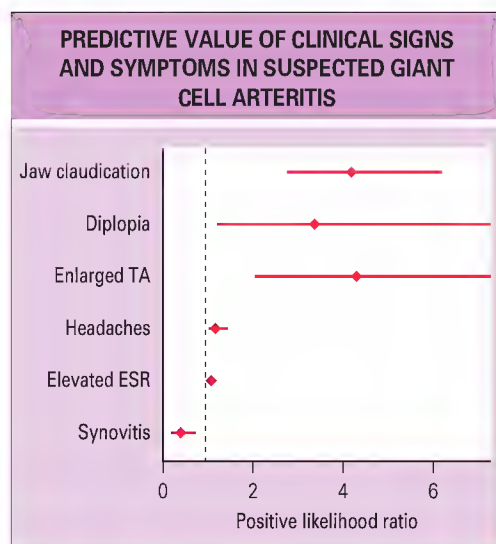


Fig. 156.2 Jaw claudication, diplopia, and an enlarged temporal artery (TA) are helpful findings in distinguishing patients likely to have giant cell arteritis. Likelihood ratios near 1 (black dotted line) indicate that the characteristic occurred equally in patients with positive and negative TA biopsy results. Synovitis occurred more frequently when biopsy specimens were negative. (From Smetana GW, Shmerling RH. Does this patient have temporal arteritis? *JAMA* 2002;287:92-101.)

ophthalmic artery or the posterior ciliary arteries supplying the optic nerve. Ophthalmologic examination finds a pale disc edema resulting from ischemic damage to the optic nerve head. Preceding symptoms may include amaurosis fugax or fleeting visual blurring with exercise, but the loss of vision is frequently sudden. Patients with facial pain, periorbital pain, and swelling may be at higher risk for ischemic ophthalmic complications. Diplopia and ocular motor imbalance are recognized manifestations of GCA that have been estimated to occur in 2% to 15% of patients and sometimes precede the visual loss.²⁷ The ophthalmoplegia can be unilateral or bilateral; most commonly involved is the oculomotor nerve, which leads to third nerve palsy.

Arteritis of the vertebral and basilar arteries can cause brain stem ischemic episodes or strokes, often complicated by dizziness, balance problems, vertigo, and oculomotor defects. Infrequent neurologic manifestations of GCA include mononeuropathies and peripheral neuropathies.

Pulmonary symptoms occur less frequently, but ischemia of the bronchial tree can result in a dry, nonproductive cough.

Large-vessel arteritis and aortitis

A large-vessel pattern of GCA can overlap with a cranial pattern or be the dominant manifestation of the disease.²⁸ Stenotic lesions in the distal subclavian arteries, the axillary arteries, and the brachial arteries are typical of GCA and are relatively easy to distinguish from the more proximal lesions of Takayasu arteritis and from atherosclerotic disease. Lower extremity arteries are infrequently affected.²⁹

Large-vessel GCA leads to aortic arch syndrome, with ischemia of the upper extremities sometimes being manifested as pulseless disease.¹² Activities involving the arms, such as brushing the teeth, working overhead, or playing the piano, induce ischemic pain and force the patient to rest. Blood pressure readings may be asymmetric, bilaterally diminished, or absent. Raynaud phenomenon-like symptoms consisting of paleness, a bluish discoloration, and dysesthesias of the hands are common. Tissue gangrene, predominantly affecting the fingertips, can also occur. Bilateral manifestations are common, but unilateral involvement or asymmetric patterning is possible. About 50% of patients with subclavian-axillary GCA have negative temporal artery biopsy findings and also lack cranial clinical signs and symptoms, such as headaches, jaw claudication, and visual symptoms.¹²

Aortitis has been estimated to complicate GCA in 10% to 20% of patients, but this figure is probably underestimated. In particular, subtle forms of aortic wall inflammation remain clinically silent. The thoracic part of the aorta is more commonly affected than the abdominal part.²⁹ In contrast to medium-sized arteries, the aorta responds to GCA with loss of the medial layer, destruction of the elastic membrane, luminal dilation, and eventually, aneurysm formation. Late clinical features such as aortic valve insufficiency, aortic dissection, and rupture of an aortic aneurysm can each be the first sign of GCA aortitis. Histomorphologic features of giant cell vasculitis in resected aortic aneurysms may also lead to the diagnosis.

In view of the potentially life-threatening complications of GCA aortitis, patients with established GCA should be monitored for aortic involvement. Modern imaging modalities, including computed tomography (CT) and MRI, offer fast information about the diameter of the aorta, wall irregularities, dissection, and wall thickness.³⁰ In contrast to Takayasu arteritis, GCA aortitis causes less pronounced wall thickening.

Systemic inflammatory syndrome with arteritis

Forty percent to 50% of patients with GCA exhibit fever, malaise, fatigue, weakness, anorexia, weight loss, and depression. In a specific patient subset these constitutional symptoms were found to be the major disease manifestations.³¹ Frequently, these patients are not initially seen by a rheumatologist but are referred when a workup for malignancy and chronic infection has remained negative. In about 15% of cases, fever of unknown origin is the initial manifestation. In such patients, physical examination of scalp arteries may provide normal results. Nevertheless, GCA should be suspected if the patient falls into the at-risk age group. The preferred diagnostic procedure is temporal artery biopsy even if clinical symptoms of vascular ischemia are lacking. Histomorphologic evaluation may demonstrate vessel wall inflammation without intimal hyperplasia. Patients with this variant of GCA may be at lower risk for the development of blindness.³²

Polymyalgia rheumatica

PMR symptoms develop in approximately 50% of patients with GCA; 25% already have proximal myalgia at the time of initial diagnosis. In an estimated 10% of patients with isolated PMR, GCA will subsequently be diagnosed. Disease flares in patients with GCA undergoing prednisone taper are frequently manifested as myalgia, not as ischemic complications.

In a meta-analysis that examined clinical symptoms for their sensitivity and specificity in predicting the results of temporal artery biopsy, synovitis was a negative predictor of arteritis.²⁷ This study emphasizes the fact that joint inflammation is not a manifestation of GCA and indicates a different diagnosis (see Fig. 156.2).

Etiology and pathogenesis

GCA is an immune-mediated disease with abnormalities in the innate and adaptive arms of the immune system.²⁰ No single instigator of the chronic immune response in the vascular wall has been identified, nor has a single abnormality in the host's immune system been found. Multiple risk factors predispose individuals to this inflammatory vasculopathy. The major risk factor is age, and incidence rates increase after the age of 50 years over the ensuing decades.³³ The immune system changes dramatically with age, and immune regeneration and function decline steeply during later life. How immunosenescence affects risk for GCA is not known.

Geographic variations in incidence rates point toward Scandinavian ancestry as an important risk factor.³⁴ Incidence rates are the highest in Iceland, followed by Sweden, Norway, and Denmark; rates in the United States correlate with northern European immigration patterns. Disease susceptibility in blacks is low. Takayasu arteritis, another type of granulomatous vasculitis, is more likely to develop in individuals of Asian origin.

Genetic polymorphisms that would explain the ethnic predisposition have not been identified. Like many other autoimmune syndromes, GCA is an HLA class II-associated disease.³⁵ PMR and GCA display a similar association with the HLA-DR4 haplotype, thus suggesting a role of HLA-DR4-linked genes in predisposing individuals to the systemic inflammatory syndromes but not in facilitating pathways of vessel wall inflammation.

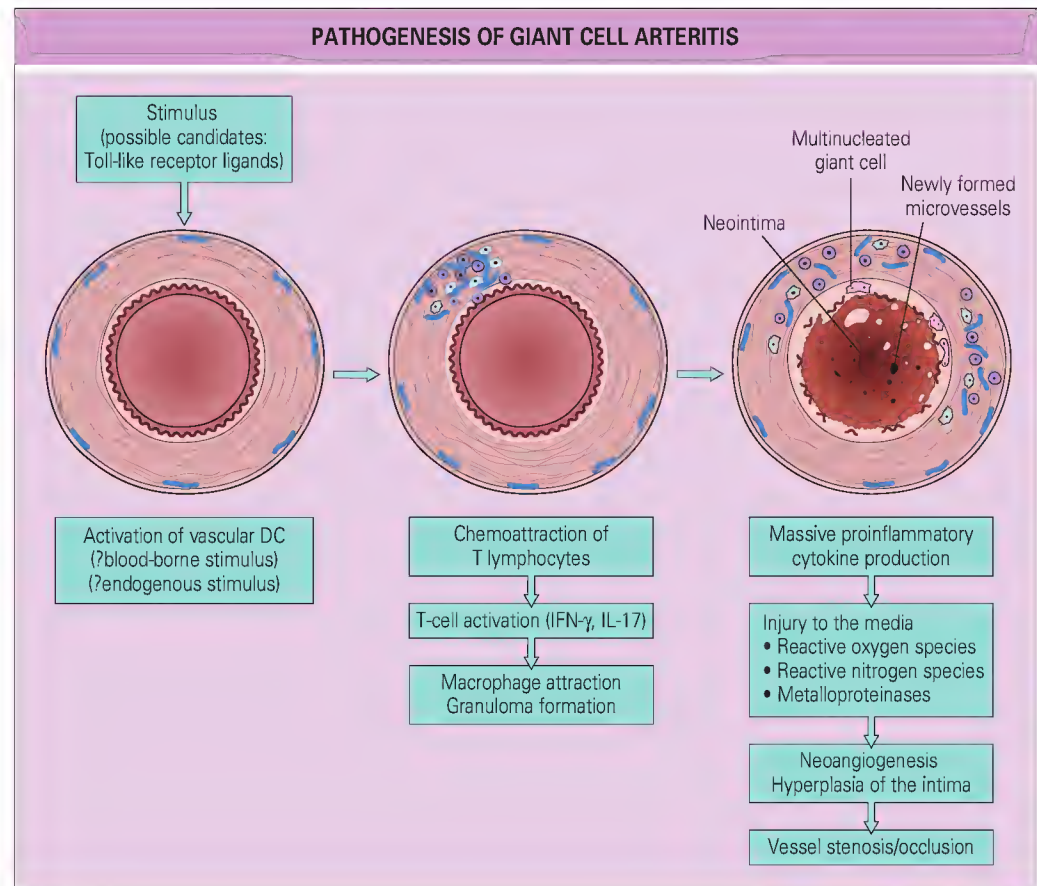
Efforts to identify infectious organisms in the inflamed arteries have not yielded consistent results.³⁶ Studies describing the identification of microbial gene sequences in affected arteries have generally not been confirmed in subsequent research.

Pathogenic mechanisms

Over the past decade, pathogenic pathways for the vasculitic process have been dissected.^{20,37} The emerging disease model proposes three critical checkpoints: innate immune cells in the vessel wall facilitate the early steps of immune system activation, adaptive immune responses mediate *in situ* CD4+ T-cell stimulation, and structural parameters of the vessel wall provide the microenvironment for deregulated innate and adaptive immunity (Fig. 156.3).

In normal, noninflamed temporal arteries, the wall not only consists of endothelial cells, vascular smooth muscle cells, fibroblasts, and matrix but also harbors a DC population in the adventitia at the media-adventitia border. DCs form a ringlike structure around the circumference of the vessel in a discontinuous, skipping pattern. Their phenotype identifies them as specialized tissue DCs with both similarities to and differences from Langerhans cells and DCs in lymphoid tissue.

Fig. 156.3 DC, dendritic cell; IFN- γ , interferon- γ .



DCs function primarily as sentinels that sense disturbances in the tissue microenvironment and report this to the immune system. DCs are equipped with many kinds of receptors through which they recognize molecular patterns shared by infectious microbes. They also respond to tissue damage and are suspected to have a broad role in tissue homeostasis. The functional properties of vascular DCs have been studied in an experimental model in which human temporal arteries were implanted into immunodeficient mice. Injection of bacterial products such as lipopolysaccharides into the artery-mouse chimeras triggers vascular DCs to initiate the production of chemokines and recruit T cells to the artery wall.¹¹ The recruited T cells undergo activation in the adventitia,³⁸ proliferate, and produce CD40L and interferon- γ (IFN- γ). This model recapitulates the early steps in vasculitis and defines the wall-residing DCs as gatekeepers. Vascular DCs have emerged as a prime candidate in determining why some blood vessels are more prone to be targeted by GCA and why the inflammatory infiltrates are often arranged in a skipped distribution. Each vascular bed expresses a unique profile of Toll-like receptors (TLRs), which not only assigns pathogen-sensing function to arteries but also gives each vascular territory an immunologic identity.³⁹

Signals recognized by vascular DCs critically determine the architecture of emerging vasculitis. TLR4 ligands induce a pattern of panarteritis, whereas stimulation of TLR5 results in perivasculitis.⁴⁰ Studies of temporal artery biopsy specimens have also suggested two distinct inflammatory patterns, thus supporting the concept of GCA subtypes related to differences in initial disease instigators.⁴¹

In fully developed GCA, dense infiltrates of CD4+ T cells, macrophages, and DCs crowd the wall structure. CD4+ T cells release IFN- γ and undergo clonal expansion, with identical T-cell clones growing in both temporal arteries of the patient. These T cells orchestrate an immune response that eventually leads to wall damage and an arterial response to injury. At least two T-cell differentiation pathways, type 1 helper T cell (Th1) and Th17, have been implicated in vasculitic T-cell responses.⁴² Cytokine patterns can be quite diverse and correlate with the clinical manifestations.⁴³ Patients with high tissue IFN- γ levels often have intense intimal hyperplasia and, accordingly, exhibit tissue ischemia, including visual symptoms and jaw claudication. Patients with a predominance of systemic inflammation, often with minimal luminal occlusion, typically produce large amounts of IL-2 but less IFN- γ in the tissue. In longitudinal studies the cytokine pattern was not stable over time. In early untreated GCA, a broad array of cytokines characteristic of the Th1 and Th17 pathways were found, including

macrophage-derived IL-1, IL-6, IL-12, and IL-23 and T cell-derived IFN- γ and IL-17. Six months after initiation of treatment, 80% of all patients still had evidence of vascular inflammation, but only the Th1 and not the Th17 response persisted.⁴²

Recruitment of CD4+ T cells to the adventitia of the blood vessel by activated DCs is a condition *sine qua non* for amplifying and maintaining the inflammation. Depletion of T cells in mice implanted with GCA-affected temporal arteries disrupts the disease process, inhibits macrophage activity, and leads to resolution of the granulomatous infiltrates.⁴⁴ T-cell recruitment or function (or both) is at least in part dependent on signals involving the NOTCH pathway. Treatment of the human tissue-mouse chimera with a NOTCH cleavage inhibitor or a soluble NOTCH ligand, Jagged1-Fc, abrogated the T-cell response in the artery.⁴⁵ DCs are necessary to continuously support T-cell activation; depletion of DCs in GCA tissue very effectively abrogates the vasculitis.¹¹

Macrophages settle in distinct microenvironments of the arterial wall.⁸ Depending on their positioning in the adventitia, media, or intima, they commit to different functional profiles resembling differentiation into M1 and M2 macrophages. Adventitial macrophages specialize in producing IL-6 and IL-1. Medial macrophages actively secrete reactive oxygen intermediates. Oxidative stress contributes to the destruction of endothelial and vascular smooth muscle cells. Medial macrophages also produce metalloproteinases, which are probably relevant in digesting elastic membranes and would explain the typical finding of fragmented elastic membranes in affected arteries. These macrophages and the macrophage-derived multinucleated giant cells that are typically localized at the media-intima border release growth and angiogenesis factors, such as platelet-derived growth factor and vascular endothelial growth factor, and support the maladaptive arterial response that eventually results in outgrowth of the intimal layer and vessel occlusion.²²

Intimal hyperplasia requires mobilization, migration, and proliferation of myofibroblasts. Growth factors facilitate these essential steps and thus have a direct impact on the degree of intimal obstruction. Intimal layer outgrowth is possible only if sufficient oxygen is supplied. Under physiologic conditions, the arterial intima and media are avascular structures, whereas the adventitia contains a vasa vasorum network. GCA-affected temporal arteries often show a newly formed microvessel network commonly arranged in the distal part of the intima but also extending into the media. The degree of neovascularization in the inflamed vessel wall is closely correlated with the amount of IFN- γ produced by activated CD4+ T cells.²²

Investigations

Pathology

Arterial biopsy remains the most specific diagnostic procedure (see Box 156.3). Temporal artery biopsy, if done correctly, is a low-risk procedure with high diagnostic yield. Therefore, a clinical diagnosis should always be confirmed by tissue biopsy. Patients in whom the diagnosis of GCA is based on only laboratory abnormalities and clinical features often become challenges when long-term therapy is required because their diagnosis remains uncertain. Guided by clinical examination, the side with more abnormal findings (headaches and tenderness or nodularity of temporal vessels) should be sampled first. Because GCA can produce skip lesions, an arterial segment 2 to 3 cm in length should be harvested. Immediate evaluation of frozen sections from this segment enables one to make the decision whether to proceed with biopsy of the second side. However, in large case series the yield of biopsy of the second side has been low, thus providing the rationale for sparing the second side for possible future biopsy if suspicion for GCA persists or arises again.⁴⁶ In selected cases the occipital artery is sampled.

Histomorphologic evaluation of inflamed temporal arteries finds T-cell and macrophage infiltrates in the wall. Lymphocytes usually accumulate in the media. Multinucleated giant cells are found in about 50% and are not required for the diagnosis. Classically, such giant cells localize at the media-intima border, near fragments of the internal elastic lamina. Hyperplastic intima can occlude the vascular lumen, but in some cases it remains completely uncompromised. Isolated adventitial lymphocytic infiltrates can be a significant finding and be sufficient for a diagnosis of vasculitis. Some pathologists describe “healed arteritis” when finding thickened intima, fragmented elastic membranes, and medial scarring. Arteritis in the temporal artery may represent a vasculitis other than GCA. Fibrinoid necrosis is unusual for GCA and suggests another vasculitic entity, such as panarteritis nodosa or ANCA-associated vasculitis, which needs to be confirmed further by appropriate studies.

An important question relates to the timing of arterial biopsy and whether corticosteroid therapy can lead to false-negative findings. Preferably, biopsy should be performed as early as possible in an untreated patient. However, therapy should not be postponed in patients at risk for loss of vision or other serious complications. Retrospective studies examining biopsy specimens from corticosteroid-treated patients have reported persistence of inflammatory infiltrates.⁴⁷ Studies of mice implanted with inflamed temporal arteries have also demonstrated that eliminating vascular inflammation is exquisitely difficult and requires very high doses of corticosteroids.⁴⁸ Repeated biopsies in a small longitudinal study have shown persistence of the inflammation for more than 6 months in the majority of patients.⁴² Biopsies should therefore be performed in patients already receiving therapy if indicated. Whether corticosteroids can lead to the resolution of more subtle findings is unknown.

Laboratory studies

Acute-phase proteins are helpful markers in diagnosing and managing GCA. Although acute-phase proteins are nonspecific markers of immune system activation, high ESR values in an elderly individual can prompt consideration of GCA. Not all patients have high or even abnormal ESR results. Up to 25% of patients with biopsy-confirmed GCA have a normal ESR before corticosteroids are started.⁴⁹ Normal ESR results do not exclude the diagnosis and the need for tissue biopsy in clinically suspected patients.

Other acute-phase reactants, such as CRP, may be helpful biomarkers. IL-6, a cytokine that induces the production of acute-phase proteins, is highly elevated in patients with GCA and PMR and may be more sensitive in detecting low-grade inflammation⁴⁹; however, circadian rhythm makes it more difficult to interpret. Numerous other acute-phase proteins, including fibrinogen, haptoglobin, orosomucoid, α_1 -antitrypsin, serum amyloid A, and von Willebrand factor, have all been reported to be elevated in GCA with no evidence of disease specificity. A normochromic, normocytic anemia can be an initial feature. Thrombocytosis occurs frequently. In addition, elevated liver function test results, especially for alkaline phosphates, is seen in many GCA patients. Serum albumin levels can be decreased.

No autoantibody is pathognomonic of GCA, and therefore autoantibody studies are useful only for excluding other diseases. Rheumatoid factors and antibodies to citrullinated peptides are negative. ANCAs have value in differentiating GCA from other arteritides. Reports of an increased frequency of antiphospholipid antibodies are of unknown significance.

Imaging studies

Blood vessel imaging has gained importance as a method for assessing the extent of vasculitis or even for making a diagnosis of GCA. Even though the vast majority of patients with GCA and cranial symptoms have positive

temporal artery biopsy findings, histology is negative in about 50% of patients with an extracranial distribution.¹² In these patients the subclavian, axillary, vertebral, and occasionally the carotid arteries are the primary targets. Imaging of these vessels in biopsy-negative patients can establish the diagnosis. Detection and monitoring of aortic arch involvement depend heavily on imaging procedures. Typical findings include long-segment narrowing of the vascular lumen of primary and secondary branches, often with smooth tapering at both ends (Fig. 156.4).³⁰ The pattern of involvement provides crucial hints. Lesions in the distal subclavian, the axillary, and the proximal brachial arteries are typical of GCA. Patients with cerebral ischemia need evaluation for stenotic lesions of the vertebral and basilar artery system. GCA does not affect intracerebral arteries.

Conventional radiographic angiography remains superior for detailed assessment of vessel anatomy and luminal status, but it is usually required only for preoperative evaluation. Digital subtraction angiography, formerly used for quick assessment, has been replaced by magnetic resonance angiography (MRA). Not limited by axial, coronal, and sagittal planes, MRA is the preferred procedure for assessing the aortic branches and neck vessels. CT angiography can give rapid information about aortic dimensions, as well as wall irregularities and thickening. Contrast media-induced nephrotoxicity is a disadvantage of this approach.

High-resolution MRI or duplex ultrasonography can be applied to evaluate the temporal artery directly for signs of inflammatory changes. A dark halo around the lumen of the temporal artery on ultrasound has been associated with inflammatory edema and wall thickening. However, both imaging procedures are not sufficiently sensitive and may miss the more challenging patients with subtle vasculitis. The sensitivity of detecting GCA with MRI is only about 80%.⁵⁰ In a prospective study, ultrasonography did not increase the diagnostic accuracy of a careful physical examination, thus indicating that it cannot replace temporal artery biopsy.⁵¹ A large recent meta-analysis of 17 studies with close to 1000 patients estimated a sensitivity of just 75% with a specificity of 83%.⁵²

A critical issue in the management of GCA is how to quantify disease burden and activity. Much hope has been placed on T2-weighted MRI as a means of imaging wall thickness, wall edema, and potentially, blood flow in the inflamed wall as an indirect marker of inflammation. However, studies in patients with Takayasu arteritis have questioned the value of MRI as a means of measuring disease activity.⁵³ FDG-PET indicates inflammatory activity in the vessel wall in GCA and PMR.⁵⁴ Increased uptake of labeled glucose by inflammatory cells provides the underlying mechanisms of detection, but no properly designed studies have been conducted to assess this procedure's specificity and sensitivity. Specifically, it is unknown whether subtle inflammation in atherosclerotic lesions can be distinguished from active arteritis in an elderly patient population expected to have an increased atherosclerotic burden.

Treatment

Corticosteroids

Corticosteroids are highly effective in suppressing both the vascular and systemic components of GCA. The incidence of blindness, the most feared complication of GCA, declined considerably when corticosteroid therapy was introduced. Corticosteroid therapy should be started promptly at diagnosis and not be delayed in patients with progressive disease or impending visual loss. In almost all patients with GCA, corticosteroids induce such rapid symptomatic relief that the response to corticosteroid therapy has been considered a diagnostic criterion. Disease manifestations related to the systemic inflammation and PMR respond within 48 to 96 hours, often with dramatic relief. Manifestations related to impaired blood flow, such as jaw claudication, extremity claudication, and visual complications, may show delayed or no response because luminal occlusion of blood vessels by intimal hyperplasia is irreversible. However, corticosteroids may reduce tissue edema, enhance some blood flow, and restore some function.

Almost all patients respond to 40 to 60 mg of prednisone (or equivalent) per day given as a single morning dose. Higher starting doses are sometimes used in patients with visual loss or transient amaurosis. Once all the reversible symptoms resolve, usually after about 1 month of therapy, and the ESR and CRP improve by at least 50%, the corticosteroid doses are tapered. Patients initially need to be evaluated at 2- to 4-week intervals and should be monitored for clinical symptoms and laboratory evidence of inflammation. Corticosteroid doses are titrated according to disease activity; in nearly all cases prednisone can be tapered by 10% every 2 weeks. Once patients reach a daily dose of 10 mg, further tapering should be very gradual, about 1 mg per month. Alternate-day dosing is unsuccessful and should not be attempted. Recurring symptoms and rising levels of acute-phase proteins often complicate corticosteroid tapers that are too rapid. Most often, disease flares require

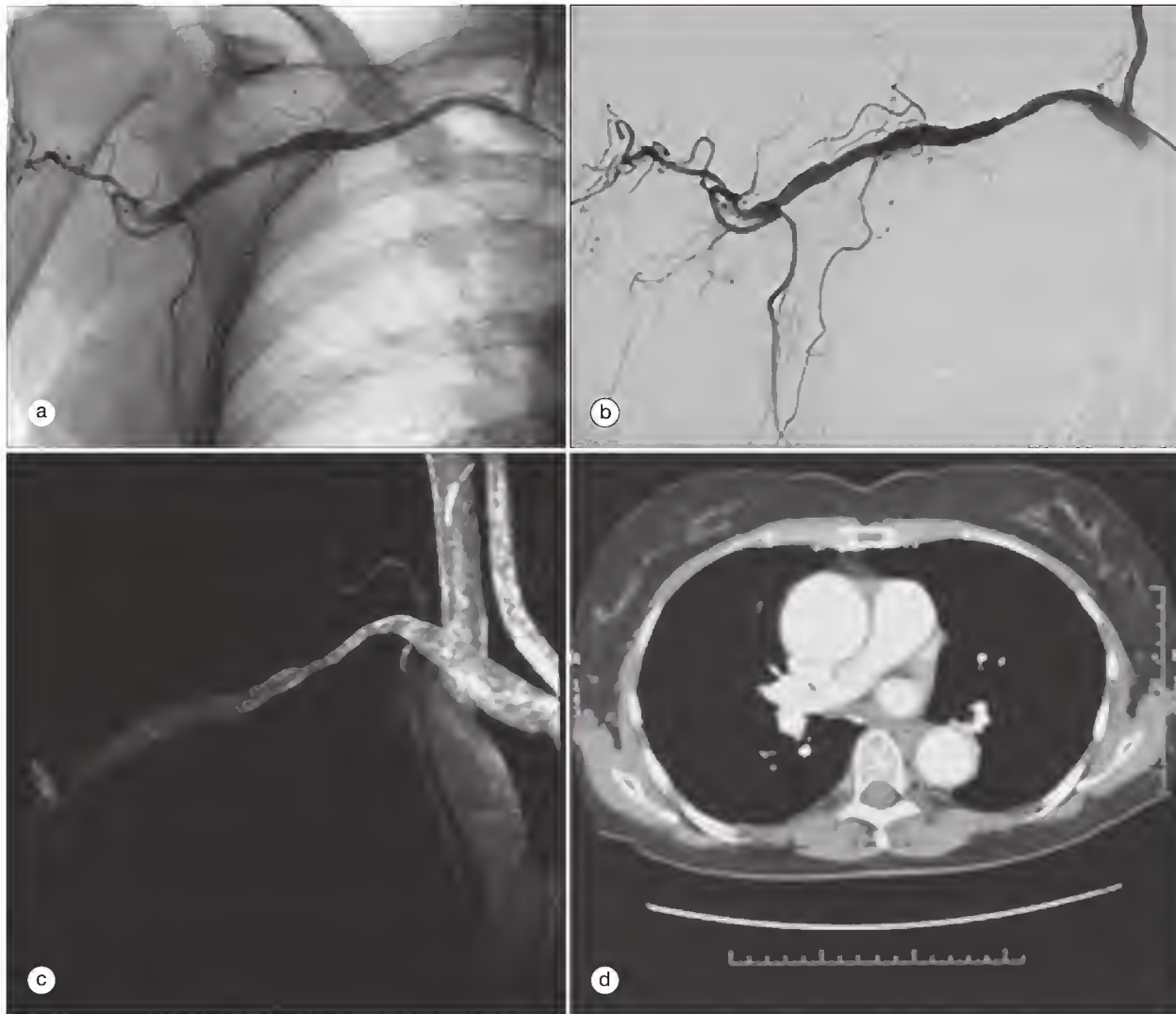


Fig. 156.4 Imaging studies for giant cell arteritis. (a) Occlusion of the axillary-brachial junction. The angiogram shows irregularity of the right subclavian artery with occlusion at the axillary-brachial junction and formation of collateral vessels. (b) Digital subtraction image. (c) A magnetic resonance angiogram of the great vessels shows narrowing of the subclavian artery distal to the origin of the vertebral artery. (d) A contrast-enhanced computed tomographic image of the chest shows pronounced ectasia of the ascending aorta, minimal thickening, and irregularity of the wall.

only moderate increases in corticosteroid doses.⁴⁹ Fortunately, disease recurrence is manifested mostly as PMR or constitutional symptoms. Once adequate corticosteroid therapy is implemented, the risk for visual loss is low.

Throughout corticosteroid tapering, monitoring of the ESR can be helpful in assessing disease activity, but values frequently remain normal even in a clinical flare (Fig. 156.5).⁴⁹ Measurement of CRP and IL-6 appears to be more sensitive in detecting inflammation; however, studies have demonstrated that IL-6 levels remain elevated in many patients who are clinically asymptomatic.^{4,49} Thus, mildly elevated acute-phase markers alone may not justify increased treatment.

GCA is not a self-limited disease; smoldering disease activity may persist even after 2 years of corticosteroid treatment. Some patients require long-term low-dose corticosteroid treatment, but the need for high doses for prolonged periods is infrequent and should be assessed carefully. Whether low-grade inflammation, detected by sensitive markers such as CRP or IL-6, warrants continued immune system suppression is unknown. Findings of aortic dissection/aneurysm a decade after initial diagnosis signal the chronicity of the disease process and may encourage long-term treatment to control the inflammatory activity.²⁸ This issue needs to be approached in appropriately designed clinical trials to weigh its risks and benefits.

A recent randomized controlled trial examined the therapeutic efficacy of initial pulse corticosteroids.⁵⁵ The goal was to explore whether initial high doses of corticosteroids (15 mg/kg methylprednisolone intravenously, or approximately 1000 mg/day for an average 70-kg patient) on 3 consecutive days would shorten the disease course and reduce long-term corticosteroid requirements. The induction regimen allowed rapid tapering of oral prednisone to less than 5 mg/day within 36 weeks. Most importantly, the percentage of patients off treatment was higher in the pulse corticosteroid group, thus suggesting induction of lasting remission.

Other immunosuppressive drugs

Most immunosuppressive drugs used by rheumatologists as corticosteroid-sparing agents have been considered for GCA without solid evidence that the antiinflammatory activity of corticosteroids can be replaced. Azathioprine has been used with little success. Two studies have explored MTX as a corticosteroid-sparing therapy. One found possible benefit in patients managed with a combination of corticosteroid and MTX.⁵⁶ However, a double-blind, placebo-controlled trial of adjuvant MTX treatment in 98 patients with GCA failed to show an effect on control of disease activity or cumulative corticosteroid doses.⁵⁷ A phase 2 study evaluating the safety and efficacy of infliximab showed no significant benefit of blockade of tumor necrosis factor. Patients receiving corticosteroids alone or combined with relatively high doses of infliximab (5 mg/kg) had similar relapse rates and cumulative corticosteroid doses over the 22-week study period.⁵⁸ In one case series, IL-6 receptor blockade rapidly controlled systemic disease activity; however, it is unclear whether it controls the vasculitic inflammation.⁵⁹

Adjuvant therapy

Retrospective analysis of one patient cohort has suggested that low-dose aspirin reduces rates of visual loss and cerebrovascular accidents,⁶⁰ probably because of its antiplatelet action. While being maintained on chronic corticosteroid therapy, patients should be monitored for changes in bone mineral density, hypertension, and diabetes mellitus. Measures to prevent osteoporosis include calcium and vitamin D supplements and, if necessary, bone protective therapy. Patients should be encouraged to remain active. In patients with prolonged corticosteroid requirements, an exercise program is often required to prevent and manage proximal myopathy.

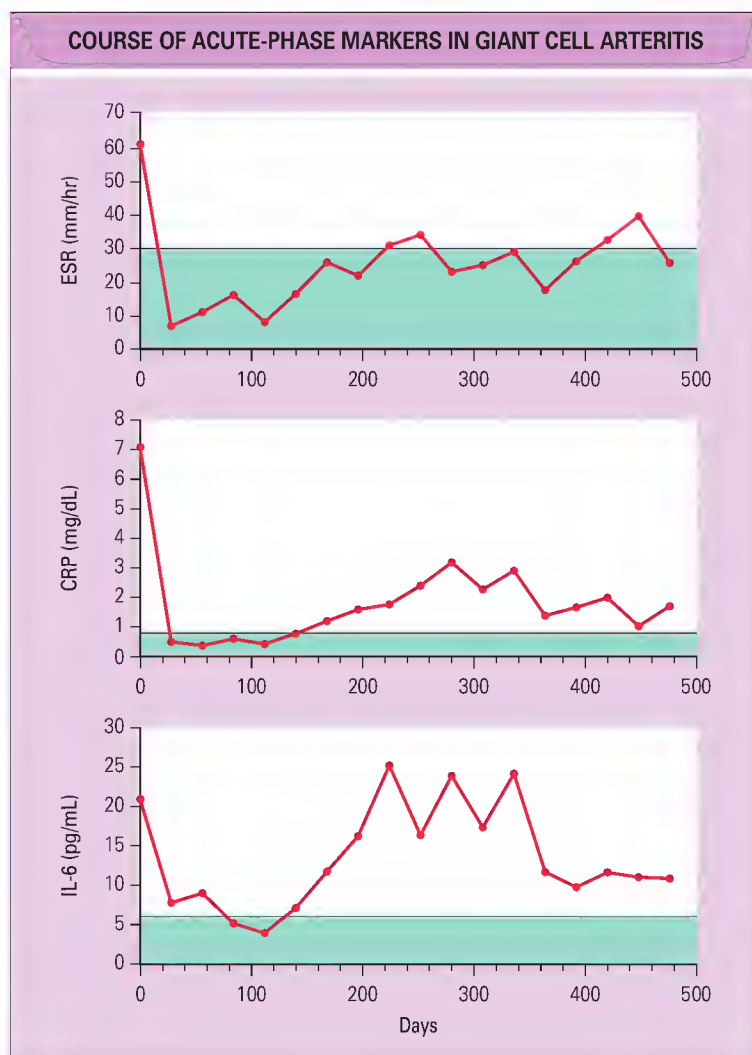


Fig. 156.5 Patients with biopsy-proven giant cell arteritis were treated with corticosteroids (initial dose: 1 mg/kg), and the acute-phase markers erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) were monitored longitudinally. With the initial high doses of corticosteroids, all three markers improved markedly. IL-6 reached the normal range (shaded blue-green area) only briefly after 90 days of therapy. With decreasing doses of corticosteroids, IL-6 and CRP returned to elevated levels, whereas ESR remained mostly within the normal range. (From Weyand CM, Fulbright JW, Hunder GG, et al. *Treatment of giant cell arteritis: interleukin-6 as a biological marker of disease activity*. *Arthritis Rheum* 2000;43:1041-8).

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Antineutrophil cytoplasmic antibody–associated vasculitis

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- Granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis) is a form of vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) directed against serine proteinase 3 (PR3). GPA is characterized by granulomatous inflammation and variable degrees of focal necrotizing vasculitis in small and medium-sized blood vessels. This disease has a tropism for the respiratory tract and kidneys. Respiratory manifestations include erosive rhinosinusitis, septal perforation, saddle nose deformity, subglottic stenosis, pulmonary nodules, and diffuse alveolar hemorrhage.
- Microscopic polyangiitis (MPA) is another form of ANCA-associated vasculitis (AAV) characterized by the presence of ANCA directed against myeloperoxidase (MPO) in the serum and focal necrotizing vasculitis of small and medium-sized blood vessels on histopathologic analysis of affected organs. MPA tends to involve the kidneys, lungs, skin, and peripheral nerves. The classic respiratory manifestation of MPA is pulmonary capillaritis, which can lead to diffuse alveolar hemorrhage.
- Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome) is a disease characterized by granuloma formation, tissue infiltration by eosinophils, and variable degrees of focal necrotizing vasculitis in small and medium-sized blood vessels. EGPA targets the upper and lower respiratory airways, peripheral nerves, gastrointestinal tract, and heart, and is associated with MPO-ANCA in approximately 50% of affected patients. The respiratory features of EGPA are asthma, fleeting pulmonary infiltrates, and chronic rhinosinusitis. Cardiac involvement is a major risk factor for death in EGPA.
- The most common renal manifestation of AAV is a pauci-immune focal and segmental glomerulonephritis with crescent formation (necrotizing and crescentic glomerulonephritis). This complication is seen eventually in approximately 70% to 80% of patients with GPA or MPA but in only a minority of EGPA cases (approximately 20%).
- Migratory oligoarthritis are common in AAV.
- Serious eye manifestations of AAV include necrotizing scleritis and peripheral ulcerative keratitis. These are most typical of GPA rather than MPA or EGPA. Patients with GPA can also develop inflammatory orbital pseudotumors.
- The differential diagnosis for AAV is broad and includes infectious, oncologic, and other rheumatologic diseases. EGPA must also be differentiated from other eosinophilic disorders. Histopathologic analysis remains the gold standard for the diagnosis of AAV.
- ANCA testing plays a major role in diagnosis, and positive results on ANCA assays are often helpful in suggesting the disease when presenting features are nonspecific. However, ANCA testing has limited value in monitoring disease activity and guiding therapy.
- Immunosuppressive therapy is effective in the induction of disease remissions in most cases of AAV. However, these disorders often flare during or after treatment reduction, and require therapy augmentation. Current treatments are associated with mortality and substantial morbidity.
- Glucocorticoid-dependent asthma in EGPA patients is often difficult to control with currently available therapies.

DEFINITION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAVs) are composed of granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). This group of multi-organ system diseases of unknown cause shares the histopathologic features of necrotizing inflammation in small and medium-sized blood vessels, substantial overlap in the types of organs involved, and varying associations with the presence of ANCA in serum.

HISTORY

In 1866 Adolf Kussmaul and Rudolf Maier noted nodular inflammatory lesions of the medium-sized and small arteries during the autopsy of a 27-year-old journeyman tailor who had developed fever, myalgias, abdominal pain, and oliguria.¹ Their report is considered to be the first case on record of “periarteritis nodosa” (now termed *polyarteritis nodosa*, or PAN), the archetype for all forms of primary systemic vasculitis. GPA was first described by Heinz Klinger² in 1931, and 5 years later, similar findings were reported by Friedrich Wegener.³ These cases were all considered to be *grenzformen* (variants) of PAN. In 1951 EGPA was differentiated from PAN by Jacob Churg and Lotte Strauss.⁴ In contrast, MPA was not separated widely from PAN until 1994, when its tropism for small blood vessels and its tendency to cause glomerulonephritis and pulmonary capillaritis, neither of which is typical of PAN, were emphasized.⁵ Validation of the pathologic links between these diseases became clearer with the discovery of ANCA in the 1980s and the finding that most patients with GPA, MPA, and (to a lesser extent) EGPA have these autoantibodies in their blood.

EPIDEMIOLOGY

Ethnic and geographic variations have been described in the AAVs. In the United States and northern Europe, GPA is approximately twice as common as MPA, but in Japan, China, and the south of Spain, the converse is true.⁶ Large cohort studies demonstrate a predilection for white populations, and whites account for more than 90% of all AAV cases.⁷⁻⁹

Except for a possible female predominance in cases of limited GPA,¹⁰ no sex-specific risk has been clearly demonstrated in these disorders. In terms of age, AAVs have been described from childhood to old age, but the onset of GPA and EGPA peaks in the fifth decade of life and the mean age for the presentation of MPA is somewhat older, in the range of 65 to 75 years. Population-based studies in the last decade have reported incidences of 6.5 to 11 per million for GPA, 3 to 15 per million for MPA, and 0.15 to 3 per million for EGPA. Improved survival has increased the estimated prevalences of these disorders, which now range between 65 and 160 per million for GPA, 39 and 94 per million for MPA, and 11 and 46 per million for EGPA.⁶

CLINICAL FEATURES

Pattern of onset

Common individual organ manifestations of the AAVs are depicted in [Fig. 157.1](#). The onset of GPA and MPA may be insidious, acute, or even fulminant. Substantial overlap of clinical features (including ANCA positivity) sometimes makes the distinction between these entities challenging, but the



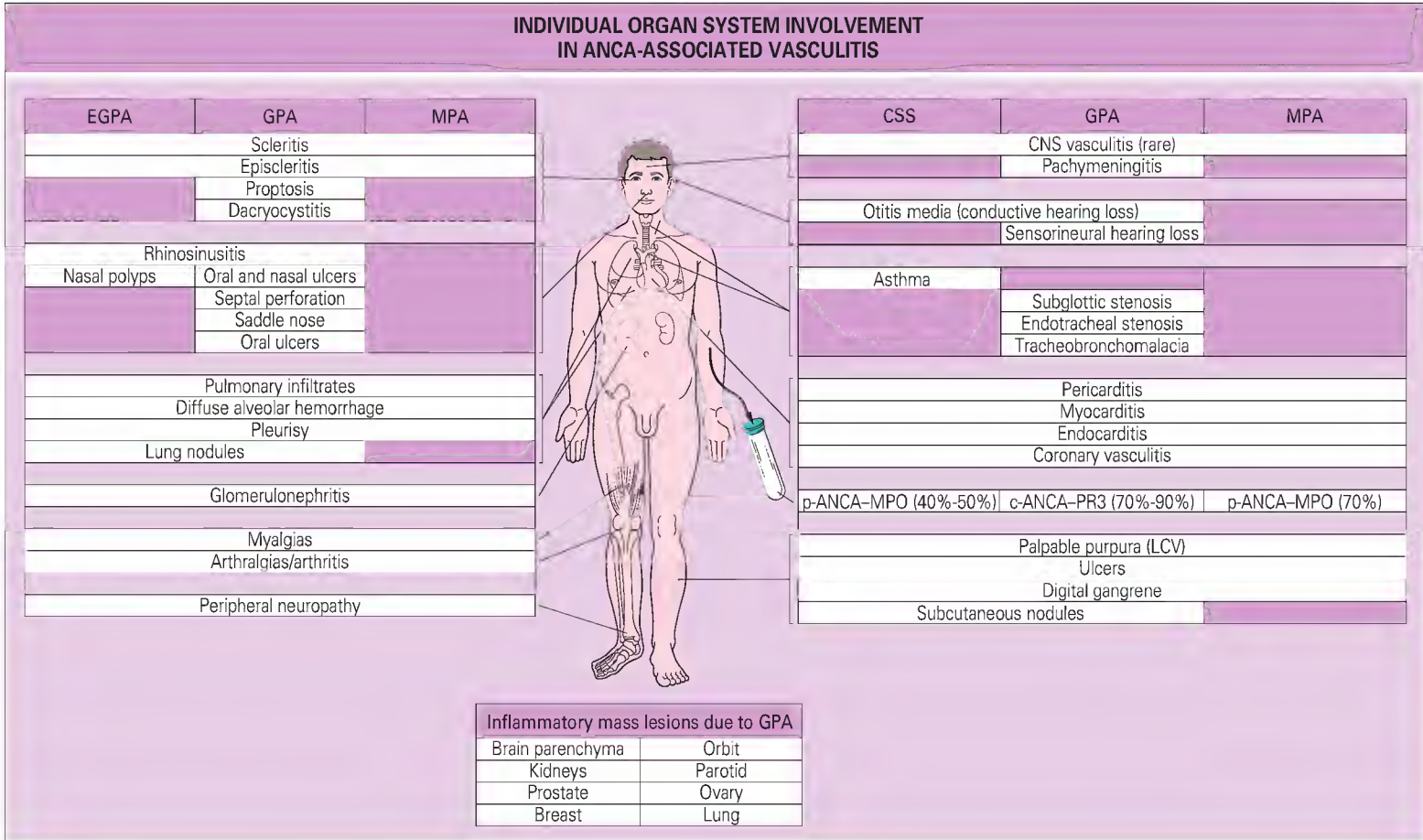


Fig. 157.1 Characteristic organ system involvement in eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). ANCA, antineutrophil cytoplasmic antibody; c-ANCA, ANCA with a cytoplasmic staining pattern; CNS, central nervous system; LCV, leukocytoclastic vasculitis; MPO, myeloperoxidase; p-ANCA, ANCA with a perinuclear staining pattern; PR3, proteinase 3. (Redrawn from Hoffman GS, Weyand C, editors. *Inflammatory diseases of blood vessels*. New York: Marcel Dekker; 2002, with permission.)

appearance of classic syndromes often allows rapid diagnoses. Thus the constellation of persistent bloody rhinorrhea, pulmonary nodules, and glomerulonephritis suggests GPA, whereas an acute pulmonary-renal disease with absent ear, nose, and throat (ENT) manifestations makes MPA more likely. When insidious in onset, GPA and MPA may evolve into an immediate threat to either the patient's life or the function of a vital organ after months or years of smoldering symptoms (e.g., upper respiratory tract disease in GPA).

The classic presentation of EGPA is a three-stage unfolding: a prodrome of rhinosinusitis and asthma, followed by a second period of blood and tissue eosinophilia (e.g., eosinophilic pneumonia), and finally a third phase dominated by vasculitis.¹¹ The latency between the prodromal phase and the overt angitis can be as long as several years. Some patients do not follow this clear-cut stepwise progression and have allergic, eosinophilic, and vasculitic symptoms in different orders or all together.

Upper respiratory tract and ears

Granulomatosis with polyangiitis and microscopic polyangiitis

Nasal, sinus, oral, pharyngolaryngeal, tracheal, and/or ear abnormalities are seen in more than 90% of all GPA cases.¹² In about one quarter of MPA patients, ENT complaints arise, but these are generally mild. Sinonasal symptoms in GPA include pain, congestion, persistent purulent and/or bloody rhinorrhea, recurrent epistaxis, and nasal crusting. Inflammation may lead to mucosal erosions as well as bone and cartilage destruction resulting in septal perforation and, in many cases, nasal bridge collapse, or saddle nose deformity (Fig. 157.2 and Fig. e157.1). Painful tongue ulcerations and a characteristic gingivitis known as *strawberry gums* (Fig. 157.3) can occur in a minority of GPA patients.

Conductive, sensorineural, or mixed hearing loss may develop in GPA. Conductive hearing loss results from involvement of the middle ear cavity (e.g., granulomatous inflammation or serous otitis media) or from eustachian tube malfunction due to nasopharyngeal disease. Of poorly understood pathophysiology, inner ear disease may be associated with

sensorineural hearing loss and/or vestibular symptoms (e.g., nausea and vertigo). Rarely, the cartilaginous structures of the external ears become inflamed, mimicking relapsing polychondritis.

Subglottic stenosis resulting from tracheal inflammation and scarring is a serious complication of GPA.¹³ Subglottic involvement can present subacutely with respiratory stridor, but is often an insidious process that may manifest as hoarseness or chronic cough. With time, airway scarring can cause tracheal stenosis (Fig. e157.2) or tracheomalacia. Pulmonary function tests (flow-volume loops) may provide a useful, noninvasive means of quantifying the airway obstruction, but the most accurate method of assessing tracheal disease in GPA is by direct laryngoscopy.

Eosinophilic granulomatosis with polyangiitis

Allergic rhinosinusitis is the earliest manifestation of EGPA in up to 80% of the cases and typically precedes the vasculitic symptoms by months or years.^{11,14} Nasal polyps, when present, can cause chronic airway obstruction. As in GPA, nasal crusting and conductive hearing loss due to granulomatous middle ear inflammation may also occur in this disorder, but destructive sinonasal disease is atypical of EGPA and characteristic of GPA.

Eyes

A variety of ocular manifestations are more likely to occur in GPA than in other AAVs. Necrotizing scleritis, which causes eye pain and conjunctival injection (Fig. e157.3), may lead to scleromalacia perforans and blindness. Peripheral ulcerative keratitis may also threaten the vision of patients if the progression to perforation ("corneal melt") is not halted by prompt treatment.¹⁵ Other ocular manifestations include conjunctivitis, episcleritis, keratitis, uveitis, retinitis, optic neuritis, and occasionally occlusion of the retinal vessels.

Retrobulbar inflammatory lesions are observed in GPA. These orbital pseudotumors may cause proptosis, ocular pain, diplopia, or vision loss due to optic nerve compression or interference with the optic nerve blood supply (Fig. 157.4). GPA patients may also develop epiphora secondary to nasolacrimal duct obstruction.



Fig. e157.1 Saddle nose deformity resulting from collapse of the nasal cartilage in granulomatosis with polyangiitis.



Fig. e157.2 Subglottic stenosis. A web of scar tissue is evident just below the vocal chords.

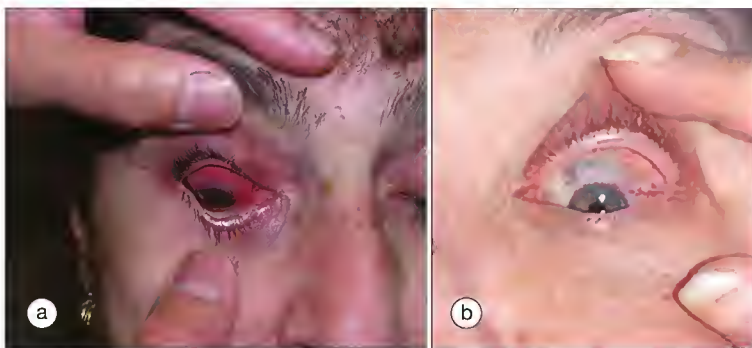


Fig. e157.3 Scleritis. (a) Active scleral inflammation, associated with substantial eye pain. (b) Healed scleritis, with resultant scleral thinning. The bluish choroid is evident beneath the scleral layer.

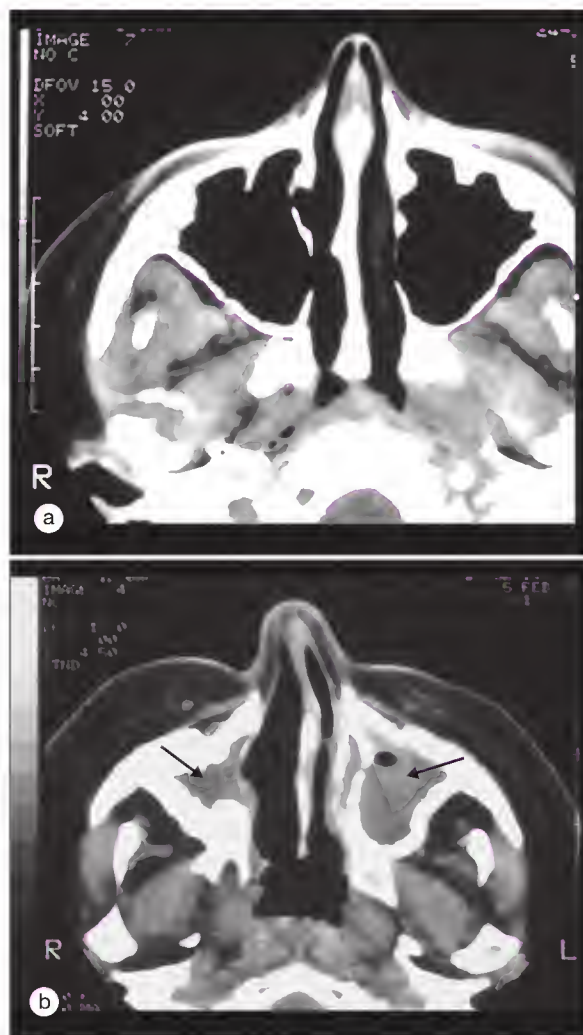


Fig. 157.2 (a) Computed tomographic (CT) image showing normal maxillary sinuses in a patient recently diagnosed with granulomatosis with polyangiitis (GPA). (b) CT image for a patient with longstanding GPA showing nasal septal deviation, destruction of the medial walls of the right maxillary sinus, opacification of both sinuses (arrows), and neo-ossification of all maxillary bony structures due to chronic inflammation.



Fig. 157.3 Oral manifestations of granulomatosis with polyangiitis. "Strawberry gums" due to gingival inflammation.

Lungs

Granulomatosis with polyangiitis and microscopic polyangiitis

Patients with either GPA or MPA may have pleuroparenchymal lung involvement causing cough, dyspnea, hemoptysis, and/or pleuritic chest pain. The pulmonary manifestations of GPA range from asymptomatic lung nodules



Fig. 157.4 Computed tomographic image for a patient with granulomatosis with polyangiitis showing a left orbital mass.

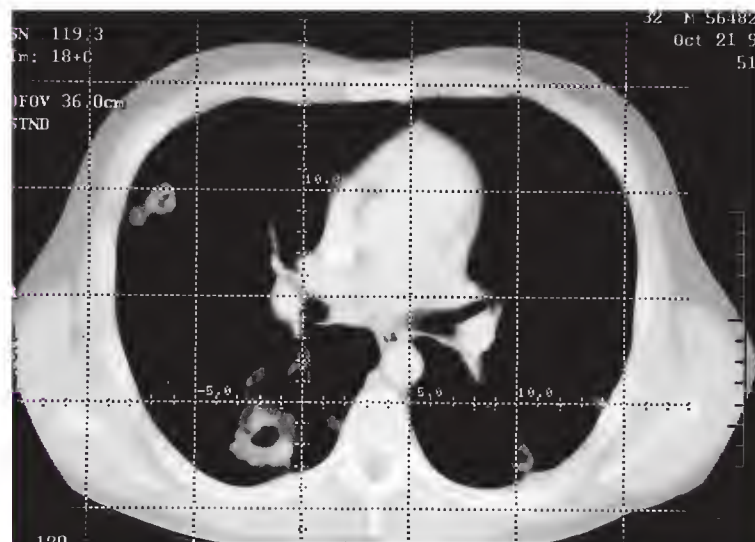


Fig. 157.5 Computed tomographic image of the chest for a patient with granulomatosis with polyangiitis. Multiple bilateral pulmonary nodules can be seen, many of which have cavitated.

and pulmonary infiltrates to fulminant pulmonary bleeding (see later). The pulmonary nodules (Fig. 157.5) are usually multiple and bilateral and may cavitate, raising concern for malignancy and mycobacterial and fungal infection. Radiographic infiltrates, which may wax and wane, are often initially misdiagnosed as pneumonia.

In about 10% to 15% of MPA and GPA patients, capillaritis leads to diffuse alveolar hemorrhage (DAH),⁸ a life-threatening complication characterized by hemoptysis, falling hematocrit, rapidly changing alveolar infiltrates, and acute respiratory failure (Fig. 157.6). DAH must be differentiated from other causes of hemoptysis (e.g., bronchial artery erosion by a lung nodule).

In GPA, large-airway inflammation and scarring can lead to bronchial stenosis and/or bronchomalacia. In this scenario, respiratory symptoms may become refractory to medical treatment, and recurrent postobstructive pneumonias can occur. Other possible lung manifestations are pleurisy, interstitial lung disease (associated with ANCAs against myeloperoxidase [MPO] rather than ANCAs against proteinase 3 [PR3]),¹⁶ pulmonary arterial hypertension, and pulmonary embolism.¹⁷

Eosinophilic granulomatosis with polyangiitis

Asthma is the hallmark of EGPA and is seen in more than 95% of cases.¹⁴ Obstructive airway disease usually persists over time and often becomes difficult to treat. The long latencies observed between the onset of asthma and the development of angitis are explained in part by the fact that corticosteroids, often used to treat refractory or relapsing bronchospasm, may



Fig. 157.6 Chest radiograph showing extensive air space infiltrates corresponding to diffuse alveolar hemorrhage in a patient with antineutrophil cytoplasmic antibody-associated vasculitis.

delay or mask the early stages of vascular inflammation. The putative link between some asthma treatments (e.g., leukotriene modifiers) and EGPA probably reflects the fact that effective inhaled therapies for asthma permit corticosteroid tapering, which opens the way for the emergence of more ominous inflammatory disease.¹⁸

As a result of either tissue eosinophilia or vasculitis, nearly half of EGPA patients develop transient patchy alveolar infiltrates. Bronchoalveolar lavage in these cases reveals increased eosinophil counts. Less frequently, eosinophil-rich pleural effusions, noncavitary nodules, and DAH also occur.^{19,20}

Kidneys

Nearly 80% of patients with GPA and MPA and approximately 20% of those with EGPA develop renal disease at some point during the course of their disease.^{8,12,14} Kidney involvement is a major source of morbidity in GPA/MPA but tends to be milder in EGPA. The most feared clinical presentation is a rapidly progressive glomerulonephritis (RPGN) that manifests as proteinuria (usually nonnephrotic), dysmorphic hematuria, urine cellular casts, and rapidly rising serum creatinine level. The histologic correlate of RPGN is a necrotizing, focal and segmental glomerulonephritis with crescent formation (see later section on **pathologic features**). Without appropriate therapy, this lesion may lead to irreversible loss of renal function within days to weeks. Thus the appearance of an active urine sediment or the deterioration of renal function in AAV patients signals the need for prompt workup and aggressive treatment.

Other less common renal manifestations include nephritic and nephrotic syndromes, tubulointerstitial nephritis, and slowly progressive chronic kidney disease. An isolated form of crescentic glomerulonephritis, often associated with perinuclear ANCA (p-ANCA) or MPO-ANCA, has traditionally received the name of *renal-limited vasculitis*.²¹ Some authors consider this entity to represent a forme fruste of MPA.

Musculoskeletal system

More than half of patients with AAV have prominent musculoskeletal symptoms. Arthralgias are more frequently reported, but true synovitis with joint effusions may occur. The typical pattern of involvement is migratory and oligoarticular, and large joints tend to be affected. Myalgias are common, but true myositis is very rare.

Skin

Approximately half of AAV patients develop cutaneous manifestations, and palpable purpura is the usual presentation (approximately 50%). In both GPA and EGPA, erythematous cutaneous nodules with or without

superficial crusting may occur on the scalp, elbows, hands, and feet (termed *cutaneous extravascular necrotizing granulomas* or *Churg-Strauss granulomas*; Fig. e157.4). Other dermatologic lesions include subcutaneous nodules, skin ulcers, subungual splinter hemorrhages, digital gangrene, livedo reticularis, and, mainly in EGPA, urticarial rash.^{8,12,22} The cutaneous vasculitis of AAV is nearly always less diffuse than that of immune complex-mediated conditions, such as mixed cryoglobulinemia. However, small dots of purpura in AAV may herald the development of more dangerous disease in other organs.

Nervous system

EGPA targets the peripheral nervous system (PNS) in 70% to 80% of the cases, more frequently than in MPA or GPA (15% to 60% of cases).^{8,11,14,19,20,23} Sudden-onset weakness (e.g., of the foot), paresthesias, or neuropathic pain may represent the initiation of mononeuritis multiplex or, less frequently, a distal symmetric (purely sensory or sensorimotor) polyneuropathy. Electromyography with nerve conduction study can be useful to characterize different patterns of PNS injury (e.g., mononeuropathy vs. polyneuropathy). Sural nerve biopsy, the gold standard test to demonstrate vasculitic neuropathy, commonly shows axonal degeneration. However, more specific findings such as necrotizing vasculitis of the vasa nervorum, granulomas, and/or perineural infiltration by eosinophil are seen in only half of the cases.

Central nervous system (CNS) manifestations are comparatively less common than PNS disease. CNS complications include cranial neuropathies, CNS vasculitis leading to stroke or brain hemorrhage,²⁴ and, in patients with GPA, intraparenchymal mass lesions and pachymeningitis. All three forms of AAV can infrequently present with prominent headaches and necrotizing vasculitis of the temporal arteries, mimicking giant cell arteritis.

Heart

Pericarditis, valvular lesions, and coronary vasculitis may occasionally be seen in patients with GPA and MPA. In contrast, cardiac involvement is far more common in EGPA (approximately 50%), and represents a leading cause of death.^{11,25} By mechanisms that include vasculitis, coronary vasospasm, tissue eosinophilic and/or granulomatous infiltration, and the (fibrotic) end result of those processes, patients with EGPA may develop acute coronary syndromes, myocarditis, pericarditis, valvulopathy, and endomyocardial fibrosis. Restrictive and dilated cardiomyopathy (sometimes rapidly evolving to heart failure), conduction and rhythm disturbances, and sudden cardiac arrest can arise. In addition to common cardiac testing (e.g., electrocardiography, echocardiography, coronary angiography), advanced heart imaging such as cardiac magnetic resonance and positron emission tomography might be of particular diagnostic utility in this setting.^{26,27} Heart biopsy is performed only rarely, when noninvasive tools fail to provide an accurate diagnosis.

Gastrointestinal tract

Vasculitis seldom affects the gastrointestinal (GI) system in GPA. However, mesenteric angiitis, potentially leading to ischemia-induced bowel perforation, can be seen in up to 20% to 40% of EGPA and MPA patients.^{8,14} GI manifestations include abdominal pain, nausea, vomiting, enterorrhagia, diarrhea, and intestinal occlusion. Mild transaminase elevation is detected in some cases.

Eosinophilic infiltration can affect the GI wall at different levels in EGPA, causing a variety of problems. In the lower tract, serosal disease may produce peritonitis with eosinophil-rich ascites; muscular or submucosal infiltrates can lead to dysmotility or obstructive nodular masses; and mucosal inflammation may result in bleeding. When EGPA involves the esophagus and stomach, it can cause odynophagia, dysphagia, vomiting, chest pain, and dyspepsia. Finally, pancreatitis, acalculous cholecystitis, appendicitis, and granulomatous or eosinophilic hepatitis have occasionally been reported.

Angiography lacks sensitivity to detect aneurysms and stenosis of the mesenteric circulation in AAV.⁸ Therefore, when GI tract compromise is suspected in these patients, endoscopic procedures may be used to identify mucosal ischemic changes, and mucosal-submucosal biopsy may show the presence of characteristic lesions (e.g., vasculitis, granulomas, or eosinophilic infiltration).

Blood

Several nonspecific abnormalities found on routine analysis of the peripheral blood are surrogates of an underlying inflammatory process in AAV



Fig. e157.4 Cutaneous extravascular necrotizing granulomas (Churg-Strauss granulomas) over the extensor surface of the olecranon region.

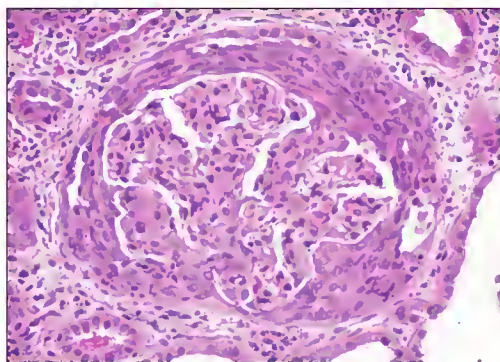


Fig. 157.7 Renal histopathologic features in antineutrophil cytoplasmic antibody-associated vasculitis (AAV). A segmental necrotizing glomerulonephritis with crescent formation is the classic kidney lesion in AAV. Immunofluorescence studies in these diseases show a paucity of immunoglobulin and complement deposition.

patients. The erythrocyte sedimentation rate and C-reactive protein level are often elevated during disease activity. The complete blood count may demonstrate mild to moderate degrees of normocytic anemia and thrombocytosis, which occasionally can be striking. The white blood cell (WBC) count can be normal or elevated. Whereas patients with GPA may have mildly increased eosinophil numbers, prominent hypereosinophilia (more than 10% on differential WBC count) is one of the diagnostic criteria for EGPA. Of note, eosinophil counts reflect disease activity in EGPA and tend to decline with adequate treatment (e.g., glucocorticoid therapy). Finally, in correspondence with a type 2 helper T-cell (Th2) polarization, the serum immunoglobulin E levels are frequently elevated in EGPA.

Other manifestations

Constitutional symptoms such as fatigue, fever, and weight loss, common in AAV, often serve as indicators of an underlying inflammatory process. These symptoms, however, rarely occur in isolation. On the other hand, granulomatous inflammation can cause pseudotumors in GPA and EGPA. These lesions may be found in potentially every organ, including the heart, parotid gland, GI tract, breast, bone, and genitourinary organs, and when they are present, the exclusion of comorbid processes (e.g., malignancy) is imperative.

PATHOLOGIC FEATURES

The discovery of ANCA (see later) has facilitated the identification of AAV. Nevertheless, in the majority of cases, a definitive diagnosis relies on the adequate interpretation of biopsy specimens. All too often, by the time clinicians recognize the pattern of organ dysfunction as suggestive of AAV and perform appropriate tissue sampling, substantial damage has already occurred.

The typical renal lesion of GPA, MPA, and EGPA is a necrotizing, focal and segmental glomerulonephritis accompanied by crescent formation (Fig. 157.7). Immunofluorescence studies of renal biopsy specimens demonstrate scant or complete absence of immunoglobulin and complement deposition, hence the term *pauci-immune glomerulonephritis*.²⁸ In GPA and EGPA, the finding of granulomatous inflammation in renal biopsy specimens is unusual.

Larger biopsy specimens from the lungs obtained by open or thoracoscopic procedures may capture the entire histologic spectrum of AAV. Pulmonary vasculitis in GPA may involve arteries, veins, and capillaries, with or without granulomatous features.²⁹ Vascular necrosis begins as clusters of neutrophils within the blood vessel wall, which degenerate and become surrounded by histiocytes. This neutrophilic debris coalesces into irregularly bordered microabscesses that, when extensive, are referred to as *geographic necrosis* (Fig. 157.8a). Well-formed granulomas contain CD4 T cells, macrophages, scattered neutrophils, multinucleated giant cells, and B cells (see Fig. 157.8b). The range of granulomatous inflammation includes either palisading or poorly formed granulomas. Of note, the vasculitic and granulomatous features of GPA may not always coexist in the same area.

In patients with MPA, which typically presents as DAH, lung biopsy often demonstrates pauci-immune vasculitis with fibrinoid necrosis of the interalveolar septal capillaries (pulmonary capillaritis) (Fig. 157.9). In contrast with lesions in the lung parenchyma, upper respiratory tract lesions in GPA

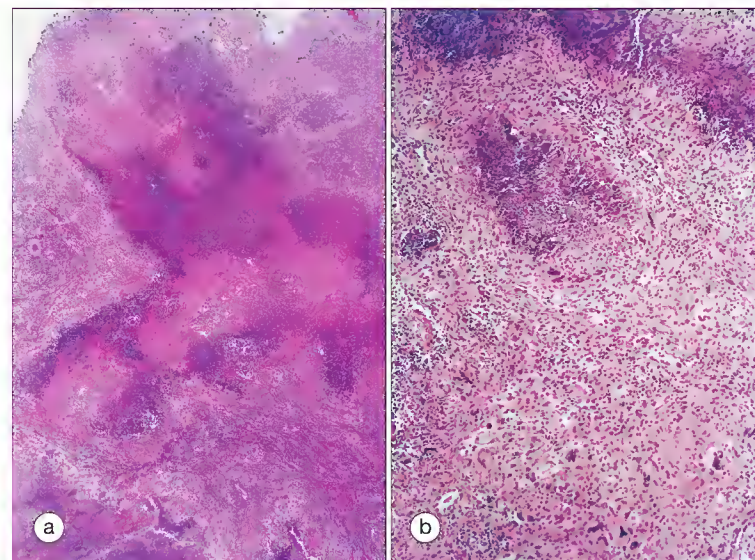


Fig. 157.8 Pulmonary histopathologic features in granulomatosis with polyangiitis. (a) Extensive coalescent areas of necrosis in a biopsy specimen from a pulmonary nodule. This pathologic finding is termed *geographic necrosis*. (b) Numerous multinucleated giant cells surrounding an ovoid region of necrobiosis.

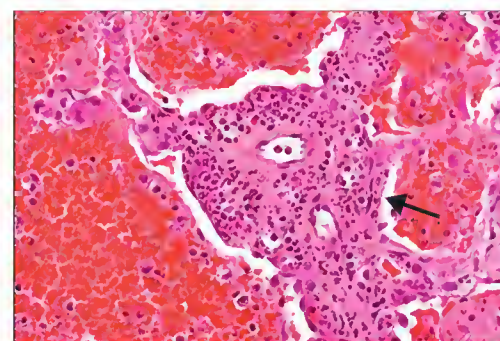


Fig. 157.9 Pulmonary histopathologic features in microscopic polyangiitis. There is abundant extravasation of red blood cells into the alveolar space. Inflammatory cells infiltrate the wall of the capillary vessels and the interstitial space of the alveolar septa.

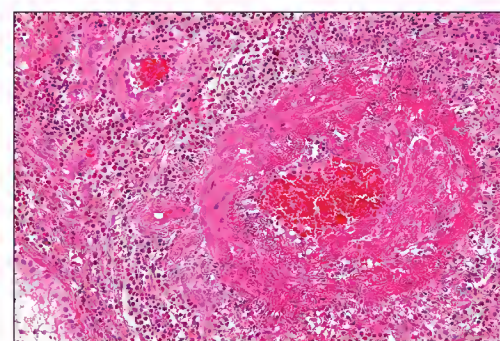


Fig. 157.10 Histopathologic features of eosinophilic granulomatosis with polyangiitis (EGPA). Small-vessel vasculitis with marked angiocentric infiltrates of eosinophils in a patient with EGPA.

frequently have a nondiagnostic histologic appearance, showing only signs of unspecific acute and chronic inflammation.³⁰

The anatomic-pathologic hallmarks of EGPA are necrotizing angitis of small and medium-sized blood vessels, extravascular necrotizing granulomas, and tissue eosinophilic infiltration (Fig. 157.10).^{11,31} These lesions may occur in isolation or coexist. As in GPA, vasculitis in EGPA can display granulomatous or nongranulomatous features and involve arteries, capillaries, and veins. A perivascular cuff of eosinophils may be present as well, and eosinophil-rich granulomas tend to locate near to the small vasculature. A less specific interstitial infiltrate of eosinophils may be present within the

BOX 157.1 CLINICAL UTILITY OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA) TESTING

- Combined testing using immunofluorescence (IF) assays and enzyme immunoassays (EIAs) for antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO) is recommended. The most reliable results are positivity for ANCAs by both IF and EIA. However, positive serologic test results alone are not diagnostic of ANCA-associated vasculitis (AAV).
- Even with rigorous serologic evaluations, not all patients with AAV test positive for ANCAs. ANCAs are seen in 90% to 95% of individuals with generalized granulomatosis with polyangiitis (GPA), 70% to 80% of those with limited GPA forms, 70% of those with microscopic polyangiitis, 40% to 50% of those with eosinophilic granulomatosis with polyangiitis, and 70% to 80% of patients with renal-limited vasculitis.
- A host of systemic illnesses (which may mimic AAV), including infections, malignancies, and systemic rheumatic conditions, may be associated with the presence of ANCAs.
- Although the sensitivities of the two testing techniques are comparable, EIA has a higher specificity than IF.
- Even in patients who are ANCA positive, the titers are unreliable indicators of disease activity. As a rule, predicating treatment decisions on ANCA titers is a mistake.
- The direct role of ANCAs in the pathogenesis of human AAV remains unclear. Most current evidence suggests that ANCAs may be one of the effector pathways of tissue injury in these disorders, because ANCAs enhance the degranulation of cytokine-primed neutrophils *in vitro*, and anti-MPO and anti-PR3 antibodies trigger the development of crescentic glomerulonephritis and pulmonary capillaritis in animal models.

lungs or occupy extrapulmonary sites including the heart, upper airway, skin, GI tract, kidneys, and peripheral nerves.^{11,19,31}

When AAV involve the small blood vessels of the skin dermis, biopsy specimens reveal leukocytoclastic vasculitis. Cutaneous extravascular necrotizing granulomas with or without eosinophil predominance may also occur in EGPA and GPA, respectively.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

ANCAs are autoantibodies directed against MPO, PR3, or other constituents (e.g., the LAMP-2 protein) of the primary granules of neutrophils and monocyte lysosomes. Since their discovery in 1982,³² ANCA testing has become an essential part of the diagnostic evaluation of patients with small-vessel vasculitis.³³ Two types of assays for these antibodies, immunofluorescence (IF) and enzyme immunoassay (EIA), are now in common use. The current role of ANCA testing in the diagnosis and management of AAV is summarized in Box 157.1.

Different factors contribute to the variation in sensitivity, specificity, and positive and negative predictive value of ANCA testing. These determinants include the method of detection used, the vasculitis type (i.e., GPA, MPA, or EGPA) and extension (e.g., limited vs. generalized GPA), and the disease activity at the time of sampling. With IF, three principal patterns of fluorescence are recognized: cytoplasmic (c-ANCA), perinuclear (p-ANCA), and atypical (x-ANCA) (Fig. 157.11). In patients with vasculitis, the c-ANCA pattern usually corresponds to the presence of anti-PR3 antibodies (PR3-ANCA) and the p-ANCA pattern typically correlates with anti-MPO antibodies (MPO-ANCA), which can be detected by EIA.

When IF and EIA results are considered together, ANCAs are seen in approximately 90% to 95% of generalized GPA cases during active disease, and in around 70% to 80% of cases of the limited forms.³⁴ Although a negative ANCA test result does not preclude the diagnosis of GPA, the detection of a c-ANCA pattern on IF in combination with PR3-ANCA detection by EIA strongly suggests this disorder. In contrast, the p-ANCA/MPO-ANCA combination is more prevalent in MPA (70% of cases), EGPA (40% to 50%), and renal-limited vasculitis (70% to 80%); however, it also occurs in a minority of GPA patients (approximately 10%). Of note, it has been suggested that the presence of ANCAs in EGPA^{19,20,31} is associated with vasculitic manifestations (e.g., glomerulonephritis, peripheral neuropathy, palpable purpura, DAH), whereas ANCA-negative cases more often tend to develop eosinophilic features (e.g., cardiomyopathy).

Atypical ANCA patterns are found in a wide variety of disorders, such as inflammatory bowel disease, systemic immune-mediated diseases, and infections.³³ These atypical patterns are sometimes difficult to distinguish from the p-ANCA pattern. Thus, regardless of the pattern revealed by IF,

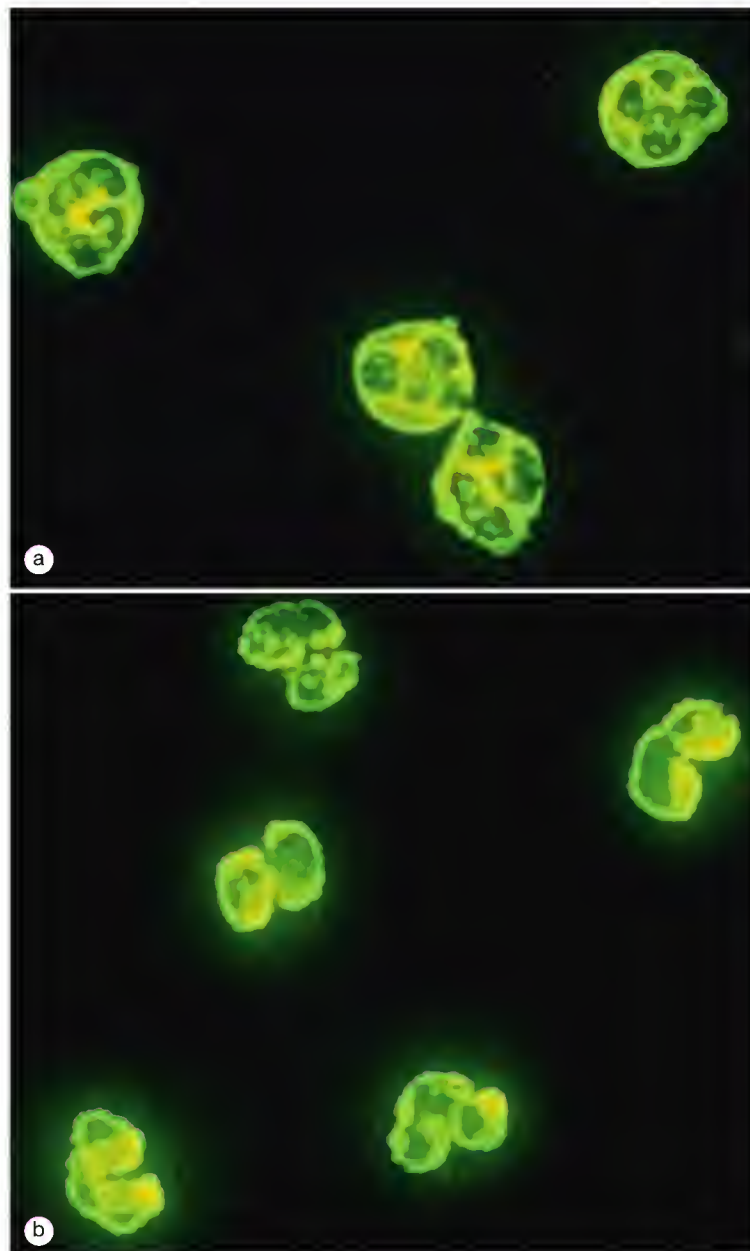


Fig. 157.11 Antineutrophil cytoplasmic antibodies (ANCAs) demonstrated by immunofluorescence. (a) Cytoplasmic pattern (c-ANCA). (b) Perinuclear pattern (p-ANCA).

positive results on IF assays should be confirmed by EIAs, which also determine the specific antigen targeted by the ANCA (e.g., PR3, MPO).

In general, ANCA levels have correlated imperfectly with disease activity.³⁵ Titers of antibodies tend to decline following the institution of immunosuppressive therapy, but approximately half of patients who achieve complete clinical remission remain ANCA positive to some degree, albeit usually with a much lower titer than at the start of treatment. The period between the rise in ANCA titers and the appearance of renewed disease activity may be up to several years. Thus ANCA titers are poor predictors of the timing of disease flares, and in a significant minority of cases the direction of serial ANCA titers is misleading, with disease flares occurring in the absence of a rise or even in the setting of declining ANCA titers. Thus, for most patients, treatment should not be guided by ANCA titers in the absence of clinically evident disease.

Despite advances in ANCA testing techniques, the cornerstone of diagnosis in AAV remains the combination of typical clinical features and histopathologic findings. When the diagnosis is uncertain, all reasonable avenues should be pursued to obtain biopsy specimens to confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

The histologic distinction between GPA, MPA and EGPA can often be challenging. Renal features of AAV are frequently indistinguishable, and in

TABLE 157.1

Nomenclature and classification criteria for antineutrophil cytoplasmic antibody–associated vasculitides

Chapel Hill Consensus Conference nomenclature*	
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). <i>Necrotizing glomerulonephritis is common.</i>
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). <i>Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.</i>
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels and associated with asthma and eosinophilia.
1990 American College of Rheumatology classification criteria for granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis †	
Granulomatosis with polyangiitis	Eosinophilic granulomatosis with polyangiitis
1. Nasal or oral inflammation Painful or painless oral ulcers, or purulent or bloody nasal discharge	1. Asthma History of wheezing or diffuse high-pitch rales on expiration
2. Abnormal chest radiograph Nodules, fixed infiltrates, or cavities	2. Eosinophilia Eosinophilia of >10% eosinophils on white blood cell differential count
3. Urinary sediment Microhematuria or red cell casts	3. Mononeuropathy or polyneuropathy Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to systemic vasculitis
4. Granulomatous inflammation on biopsy specimen Granulomatous inflammation within the wall of an artery or in the perivascular area	4. Pulmonary infiltrates, nonfixed Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates) attributable to systemic vasculitis
	5. Paranasal sinus abnormality History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
	6. Extravascular eosinophils Biopsy including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas

*From Jennette JC, Falk RJ, Androssy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187-92.

†From Leavitt RY, Fucci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33:1101-7; and Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990;33:1094-100.

addition, all these patients may develop musculoskeletal symptoms, peripheral neuropathy, skin manifestations, and the life-threatening complication of alveolar hemorrhage.

Typical features of GPA, MPA and EGPA are contrasted in Fig. 157.1, and the classification criteria for the AAVs are shown in Table 157.1. GPA can be differentiated from MPA essentially by the presence of conspicuous upper respiratory tract symptoms, the finding of granulomas as part of the histologic lesion, and its strong association with c-ANCA/PR3-ANCA. Although EGPA is also a granulomatous disease that affects the upper airway, virtually all EGPA patients have asthma and significant hypereosinophilia (both absent in GPA and MPA). Furthermore, whereas biopsy specimens from patients with GPA sometimes demonstrate a mild degree of eosinophil infiltration, striking tissue eosinophilia is highly characteristic of EGPA. Finally, unlike GPA, EGPA does not usually cause destructive upper airway disease or cavitary pulmonary nodules and tends to affect the heart, peripheral nerves, and GI tract more often.

More important in terms of treatment implications is distinguishing AAVs from a myriad of disorders of varied etiologies that can mimic GPA, MPA, or EGPA. Other forms of vasculitis presenting with skin lesions (e.g., palpable purpura), arthralgias, and/or glomerulonephritis should be considered. In this regard, Henoch-Schönlein purpura, cryoglobulinemia, and systemic rheumatoid vasculitis or systemic lupus erythematosus (SLE) can at times be misleading. However, each one of these rheumatic diseases may have other clinical manifestations (e.g., malar rash, erosive synovitis), laboratory findings (e.g., circulating cryoglobulins, anti-cyclic citrullinated protein antibodies, antinuclear antibodies), and pathologic features (e.g., immune deposits on tissue biopsy specimens) that shift the balance during the differential process.

AAVs must be distinguished from pulmonary-renal syndromes such as anti-glomerular basement membrane (anti-GBM) disease, immune complex-mediated disorders, sepsis with disseminated intravascular coagulation, and others. In anti-GBM disease, the relevant antibodies can be

measured in the blood or observed as linear staining in indirect IF studies of lung or kidney tissue. Patients with SLE and most other immune complex-associated diseases have hypocomplementemia, specific serologic markers (e.g., double-stranded DNA antibodies), and a characteristic granular IF staining pattern on renal biopsy specimens.

Immunoglobulin G4–related disease can mimic both GPA and EGPA closely in its tendency to form mass lesions, its ability to affect many of the same organs (particularly the orbital region, lungs, and kidney), and its common association with mild to moderate eosinophilia. Levamisole, an adulterant commonly used in cocaine, can induce a vasculitic condition associated with a variety of autoantibodies, including ANCAs, antiphospholipid antibodies, and others, leading to diagnostic confusion.

GPA limited to the respiratory tract may pose a difficult diagnostic problem. Infection (mycobacterial or fungal infection, actinomycosis, syphilis), malignancy (squamous cell carcinoma, extranodal T-cell lymphoma), or illicit drug use (intranasal cocaine) can present with destructive ENT lesions. Because granulomatous infections of the lung (e.g., with mycobacteria or fungi) may also cause vasculitis and necrosis, a diagnosis of GPA should not be rendered based on lung biopsy specimens until special stains and cultures have yielded negative results. Lymphomatoid granulomatosis, an angiocentric immunoproliferative disorder, may be difficult to differentiate from GPA (and certain chronic infections like tuberculosis) because it can present with constitutional symptoms, lung nodules, and a polymorphic inflammatory infiltrate associated with tissue necrosis.

Finally, hypereosinophilia and a marked association with atopic manifestations bring up a particular group of differential diagnoses that are pertinent to consider when EGPA is suspected. Obstructive lung disease in the presence of fleeting pulmonary infiltrates and other classic organ manifestations (e.g., mononeuritis multiplex) make straightforward the distinction of EGPA from uncomplicated asthma or allergic rhinosinusitis; however, long latencies between different EGPA phases can sometimes delay a definite diagnosis considerably. Conditions associated with blood and/or tissue

eosinophilia such as drug reactions, parasitic infections, allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, and eosinophilic esophagogastritis may at times enter the differential diagnosis of EGPA. Unlike EGPA, these problems are not characterized by granulomatous inflammation. Moreover, although the histologic findings in eosinophilic pneumonia and eosinophilic esophagogastritis may be indistinguishable from those in EGPA, these organ-restricted eosinophilic disorders are not systemic and remain confined to the respiratory and GI tract, respectively. Finally, idiopathic hypereosinophilic syndrome may be particularly difficult to differentiate from EGPA, and some cases meet criteria for both disorders. Clues to separate these entities are the virtual absence of asthma in idiopathic hypereosinophilic syndrome and the presence of vasculitis and/or granulomas in EGPA.

ETIOLOGY AND PATHOGENESIS

Environmental influences are thought to interplay with genetic and epigenetic factors in the origination of AAVs, but the ultimate cause of these disorders remains elusive. The striking white predominance in AAVs indicates that genes probably play an important role. However, the rare occurrence of familial cases suggests that heritable factors alone are not sufficient. A genomewide association study of GPA and MPA patients showed major histocompatibility complex (MHC) and non-MHC associations. PR3-ANCA polyangiitis (mostly GPA) was associated with single-nucleotide polymorphisms at the HLA-DPB1 (confirming prior studies), SERPINA1 (α_1 -antitrypsin), and PRTN3 loci, whereas an association with HLA-DQ was observed in MPO-ANCA vasculitis (mostly MPA).³⁶ Fine mapping and functional studies are required to define the specific roles of these genetic variants. Candidate gene studies have reported susceptibility polymorphisms associated with HLA-DR, interleukin-10 (IL-10), CTLA-4, CD226, CD18, PTPN22, and Fc γ receptor genes, but many of these associations need further research.^{37,38}

Environmental exposures represent other potential etiologic factors in AAV. Inhaled materials (e.g., silica) can induce a delayed-type hypersensitivity reaction and therefore may play a role in GPA. Different triggers including allergens and drugs (e.g., leukotriene receptor antagonists, omalizumab, antithyroid agents, levamisole) have been linked to the initiation of EGPA and MPA.^{39,40} Moreover, since the original descriptions of GPA by Klinger² and Wegener,³ microbial pathogens have been considered as possible precipitants of this disease, and *Staphylococcus aureus* has been implicated as the cause of an autoimmune response against PR3.⁴¹

Regardless of the initiating event(s), three main pathogenic mechanisms can be recognized within the complex network of adaptive and innate immune cells involved in the pathophysiology of AAV (Fig. 157.12). First, neutrophils, macrophages, dendritic cells, and T and B lymphocytes have different roles in the process of *vasculitic damage* (e.g., crescentic glomerulonephritis) in GPA, MPA, and EGPA. Second, in GPA (and less prominently in EGPA), there is tissue disruption by invasive *granulomatous inflammation* (e.g., orbital pseudotumor, lung nodules). Third, *eosinophil-mediated injury* is regarded as a prominent effector pathway in EGPA (e.g., eosinophilic myocarditis). In this setting, cytokines (e.g., tumor necrosis factor- α [TNF- α], IL-17, interferon- γ [IFN- γ], IL-5), chemokines (e.g., IL-8, eotaxin-3, CCL17), components of the complement cascade, and ANCAs themselves (see later), orchestrate and amplify different aspects of the inflammatory response. A schematic representation of the proposed molecular events involved in GPA, MPA, and EGPA is shown in Fig. 157.12.

The cellular branch of the adaptive immune system, fundamental for the origination of autoimmunity, also contributes to the perpetuation of the self-reacting process and provides additional effectors of tissue damage. Changes in the composition and activation status of the CD4 T-cell subsets have been described in AAV.⁴² Whereas a Th17 response appears to contribute to this group of diseases in general, GPA and MPA also feature the upregulation of the Th1 axis (TNF- α , IFN- γ),⁴³ and a Th2 polarization (IL-4, IL-5, IL-13) has been demonstrated primarily in EGPA.⁴⁴ More recently, numerical reduction and/or functional defects in the regulatory T-cell compartment have been reported in AAV as well.⁴²

Clinical trials of B-cell depletion have provided the most conclusive evidence for a pathogenic role of B cells in AAV.^{45,46} Besides differentiating into ANCA-producing plasmocytes, B cells have an extended spectrum of antibody-independent actions that include regulatory and antigen-presenting functions and the expression of costimulatory molecules and soluble mediators that can modulate effector T-cell responses and maintain T-cell memory.

PR3 and MPO are enzymes expressed in the leukocyte granules that can shuttle to the cytoplasmic membrane upon cellular activation. Experimental evidence suggests that ANCA activation of primed neutrophils in the

microcirculation may be an important common effector mechanism in AAV.⁴⁷ Neutrophils of patients with GPA have higher expression of membrane-bound PR3 than healthy controls,⁴⁸ and this phenomenon is increased during disease relapse.⁴⁹ *In vitro*, ANCAs can induce cytokine-stimulated neutrophils not only to degranulate and produce reactive oxygen species⁵⁰ but also to adhere to and damage bystander endothelial cells.^{51,52} *In vivo*, passive transfer of MPO⁵³ and PR3⁵⁴ autoantibodies can trigger crescentic glomerulonephritis and pulmonary capillaritis in animal models, and one case of transplacental passage of ANCAs followed by neonatal pulmonary-renal syndrome has been reported.⁵⁵ Of note, ANCA-stimulated neutrophils become a source of proinflammatory mediators⁵⁶ and also release neutrophil extracellular traps (NETs).⁵⁷ Neutrophil-derived IL-6, IL-23, and IL-17 may stimulate B and T cells, therefore integrating the innate and adaptive systems.⁵⁸ NETs, on the other hand, are chromatin-rich structures that also contain the PR3 and MPO. It is hypothesized that in AAV, increased neutrophil NET formation (“NETosis”) could fuel the immune system with autoantigens and also stimulate B lymphocytes and dendritic cells in a Toll-like receptor 9-dependent manner.

Because patients are normocomplementemic and the end-organ damage is pauci-immune, the participation of the complement cascade was not suspected in AAV until recently. Complement depletion, genetic ablation of specific proteins (factor B, factor C5 and C5a receptor), and pharmacologic inhibition of C5 signaling have been shown to protect animals from a challenge with anti-MPO antibodies.⁵⁹⁻⁶¹ Human neutrophils bridged by ANCAs are able to activate the alternative complement pathway on their surfaces, possibly through the release of properdin or reactive oxygen species.^{60,62} The anaphylatoxin C5a generated by this mechanism is a potent inflammatory molecule that not only amplifies the process by targeting other cells (e.g., endothelium) but also chemoattracts and furthers primes other neutrophils, which upregulate their membrane expression of MPO and PR3 antigens; therefore a vicious cycle is created.^{60,63}

Granulomatous inflammation, the hallmark of GPA, is a cell-mediated immune reaction. PR3 has been shown to induce maturation of dendritic cells and endow them with the capacity to shape a Th1 response.⁶⁴ During disease remission, effector memory CD4 T cells with natural killer–like properties are expanded in peripheral circulation. These cells, which represent an important source of IFN- γ and TNF- α , probably migrate to the target tissues during active disease and represent the driving force for monocyte accumulation, epithelioid differentiation and fusion, and granuloma formation.⁶⁵ On the other hand, granulomatous lesions in GPA could function as a (tertiary) lymphoid-like tissue in which autoreactive B cells expand, mature, and sustain the production of anti-PR3 antibodies.⁶⁶

In EGPA, endothelial and epithelial cells produce chemotactic molecules (e.g., eotaxin-3, CCL17) that regulate the trafficking of eosinophils into the foci of inflammation.^{67,68} Eosinophils are found not only in vasculitic lesions and necrotizing granulomas but also in developing interstitial infiltrates.^{4,11} The expansion of the eosinophil compartment in EGPA is considered to be modulated by cytokines produced by Th2-polarized cells (e.g., IL-4, IL-5, IL-13) with a possible contribution of the IL-23/Th17 axis. IL-5, levels of which are increased in EGPA during active disease,⁶⁹ selectively intervenes in the mobilization, maturation, and survival of eosinophils and is considered the most potent stimulator of eosinophil function. Upon homing into the target organs, eosinophils degranulate and release cytotoxic enzymes (e.g., major basic protein, eosinophil-derived neurotoxin, eosinophil cationic protein). It has been suggested that in EGPA, eosinophil-derived IL-25 is responsible for the differentiation of naive CD4 cells toward the Th2 lineage, therefore closing a cross-talk loop that could perpetuate hypereosinophilia and organ infiltration.

TREATMENT

Overview

Data from the 1950s indicate that, in the absence of appropriate treatment, patients with fully expressed GPA have a mean survival of only 5 months and 82% mortality at 1 year.⁷⁰ The prognosis of AAV is not nearly so grim in the modern era because the use of glucocorticoids and immunosuppressants has dramatically improved the short-term survival of these patients (the actual remission induction rate is 80% to 95%).^{12,45,71-73} However, decreased mortality has made evident the chronic morbidity burden associated with these disorders (see later).

Current choices for the treatment of GPA/MPA and EGPA are based on the classification of specific cases into the category of “severe, generalized disease or poor prognosis” versus “localized, early systemic disease or good prognosis.”^{74,75} Severe and generalized GPA/MPA constitute a threat to the

PROPOSED MOLECULAR EVENTS IN THE PATHOGENESIS OF AAV

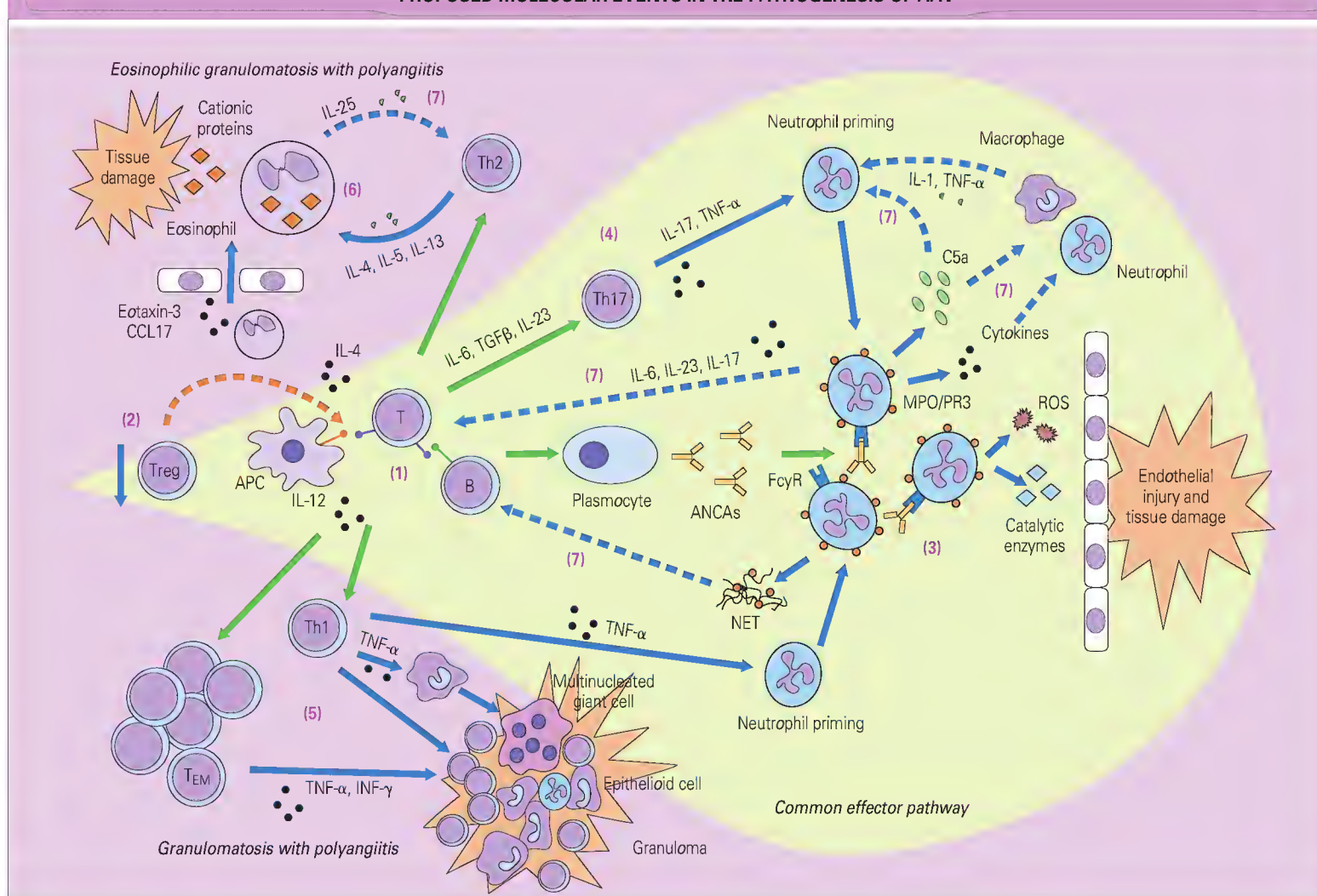


Fig. 157.12 Pathogenic mechanisms in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). (1) Antigen-presenting cells (APCs) interact with helper CD4 T cells and B cells for the production of ANCAs. (2) The process of tolerance break may be permitted by numerical or functional defects in the regulatory T cells (Treg), which also may limit subsequent effector pathways insufficiently. (3) ANCAs cross-link Fcγ receptor (FcγR) and myeloperoxidase (MPO) or proteinase 3 (PR3) on the surface of primed neutrophils, which leads to cellular degranulation, production of reactive oxygen species (ROS), vascular endothelial damage, and tissue injury. (4) Type 17 helper T (Th17) cells promote neutrophil recruitment to the foci of inflammation and may provide additional effector mechanisms. (5) In granulomatosis with polyangiitis, Th1 cells and effector memory T cells (T_{EM}), which are an important source of tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), further prime neutrophils and drive the formation of granulomatous inflammation. Granulomas are composed of activated CD4 T cells, macrophages, giant cells, neutrophils, and B cells. (6) In eosinophilic granulomatosis with polyangiitis, eosinophils are recruited to the sites of inflammation, and cytokines produced by Th2 cells (e.g., interleukin-5 [IL-5]) promote their activation with degranulation of cationic proteins (e.g., major basic protein) that cause tissue damage. (7) Positive feedback and amplification loops operate in AAV at different levels, perpetuating and augmenting the self-reacting process (e.g., neutrophil extracellular nets [NETs], cytokines [IL-6, IL-23, IL-17, TNF- α , IL-25], complement factors [C5a]). TGF- β , transforming growth factor- β .

function of vital organs or to the patient's life (e.g., RPGN, DAH, intestinal ischemia, necrotizing scleritis, vasculitic neuropathy). Conversely, localized or early systemic disease does not pose such threats in the short term (e.g., ENT disease, cutaneous lesions, arthritis). A five-factor score (FFS) is used to classify EGPA patients according to the presence or absence of clinical manifestations associated with poor prognosis (creatinine level of more than 1.58 mg/dL [140 μ mol/L], proteinuria of more than 1 g protein per day, cardiomyopathy, severe GI involvement, and CNS manifestations).⁷⁵ The presence of one or more of these features reflects severe disease and warrants aggressive treatment.

Generalized and severe granulomatosis with polyangiitis and microscopic polyangiitis

The classic National Institutes of Health (NIH) treatment,¹² which consisted of 1 year of oral cyclophosphamide (CYC) (2 mg/kg daily) in combination with prednisone (1 mg/kg daily tapered over 6 to 12 months), has been modified in the last decade in an attempt to spare glucocorticoids and minimize the exposure to alkylating agents. Furthermore, controlled trials have demonstrated that CYC-based and rituximab (RTX)-based regimens have comparable efficacy for the treatment of generalized GPA and MPA.

Current CYC-based strategies consist of a short and aggressive phase of induction of remission (e.g., 3 to 6 months of CYC), followed by lower-intensity therapy with agents such as azathioprine (AZA) (CYCAZAREM trial⁷¹) or methotrexate (MTX) (WEGENT trial⁷³) to prevent disease exacerbations (maintenance of remission). Mycophenolate mofetil was found to be inferior to AZA in a randomized study (IMPROVE trial⁷²), but its use in specific settings (e.g., MPO-associated AAV) may need further investigation.^{76,77} A wide array of other therapies including intravenous immunoglobulin (IVIG), calcineurin inhibitors, and leflunomide have been employed in small numbers of patients, but so far insufficient data exist to judge their efficacy. Of note, etanercept was ineffective for the maintenance of disease remission in a placebo-controlled trial,⁷⁸ and small studies of infliximab and adalimumab did not show significant results either.

The optimal length of maintenance therapy is not clear, but continuation of immunosuppression for longer than 12 to 18 months after remission is reasonable because the majority of disease exacerbations occur after therapy discontinuation.^{71,79} The REMAIN trial designed to evaluate the safety and efficacy of long-term maintenance treatment with AZA and low-dose glucocorticoids is currently ongoing. Before the initiation of AZA therapy, testing of the individual's phenotype for the thiopurine methyltransferase (TPMT) enzyme is advised to avoid potentially serious complications.⁷¹

In clinical practice, the use of either daily oral or intermittent intravenous (IV) CYC varies from center to center. In the CYCLOPS trial,⁸⁰ which compared IV pulse CYC with oral CYC, the two treatment regimens produced similar remission rates even though the group given IV CYC received half the cumulative dose of CYC of the orally treated group. Extended follow-up for a median duration of 4.3 years revealed comparable survival rates (approximately 80%) and adverse effect profiles for both approaches; however, patients treated with pulse therapy had a higher risk of relapse.⁸¹ Long-term data focused on the incidence of malignancy associated with each strategy may shift the balance toward IV or oral administration. Regardless of the route employed, induction of neutropenia is not required to achieve therapeutic effects, and meticulous monitoring of the WBC count is essential to avoid life-threatening infections. Oral CYC should be withheld temporarily and the IV dose should be adjusted if the WBC count falls below 4.0×10^9 per liter.

Since 2010, B-cell depletion strategies have emerged as a strongly preferable alternative to CYC for treatment of GPA and MPA. In two controlled studies,^{45,46} a single course of RTX demonstrated efficacy and short-term safety equivalent to that of CYC followed by AZA for remission induction and maintenance; all patients also received glucocorticoids. In the RAVE trial,⁴⁶ RTX induced disease remission at 6 months and permitted the discontinuation of prednisone in 64% of patients, compared with 53% of those given CYC. Of note, among patients with relapsing disease at baseline, RTX was more efficacious than CYC. Extended follow-up in this trial showed that at 12 months, 42% of the patients in the RTX arm and 38% of those in the CYC arm remained in remission without glucocorticoids.⁸² In the RITUXVAS study,⁴⁵ a similar percentage of patients in the RTX and CYC groups had their disease brought under control within 3 months (91%) and remained free of relapse at 12 months of follow-up (85% to 90%). Controlled studies exploring the long-term safety and efficacy of B-cell depletion as a maintenance strategy, including serial retreatment, and comparisons with oral immunosuppression (e.g., AZA) are required. Nevertheless, the RAVE data indicate that among patients newly diagnosed with either GPA or MPA, approximately 45% of patients will be in remission and not receiving glucocorticoids for longer than 1 year if treated with remission induction regimens that involve either RTX or CYC.

RTX was superior to CYC with regard to the short-term occurrence of selected adverse events such as neutropenia and had led to fewer cases of pneumonia at 18 months of follow-up in the RAVE trial. However, the combination of RTX and high-dose glucocorticoids also increases the risk of treatment-related morbidity, and patients must be followed closely. Nevertheless, RTX-based regimens are likely to be considerably safer over long-term follow-up with regard to malignancy induction, bladder toxicity, and infertility, which makes this approach the optimal current strategy for remission induction (and possibly maintenance) in most patients.

Localized and early generalized granulomatosis with polyangiitis and microscopic polyangiitis

Localized or early generalized GPA/MPA may respond to the combination of MTX and glucocorticoids.⁸³ In the NORAM trial,⁷⁹ MTX and CYC were compared for remission induction in patients with newly diagnosed disease. At 6 months, remission was achieved in approximately 90% of patients in both groups. On withdrawal of therapy after remission, however, relapse rate was significantly higher in the MTX group,⁸⁴ and many of these patients ultimately require CYC therapy. Of note, MTX should be avoided when the serum creatinine concentration is more than 2.0 mg/dL, because renal dysfunction significantly heightens the potential for myelotoxicity.

Trimethoprim-sulfamethoxazole has a limited or no role in the treatment of active localized GPA, but this antibiotic may decrease the risk of relapse.⁸⁵

Eosinophilic granulomatosis with polyangiitis

Patients with EGPA without poor prognostic factors (FFS = 0) achieve disease remission with glucocorticoids alone in more than 90% of cases. Although one third of these patients experience relapse upon glucocorticoid tapering, the long-term survival of this population is excellent.³¹ In the presence of poor prognostic factors, a regimen of 12 pulses of IV CYC is superior to 6 pulses (both in combination with glucocorticoids) in terms of disease-free survival, but no differences are seen in induction of remission, occurrence of early adverse events, major relapse rate, and 5-year mortality (approximately 10%).⁸⁶ Upon CYC discontinuation, flares are frequent in the absence of maintenance therapy (more than 70% of cases). Although high-quality data favoring a staged approach to treatment are lacking in EGPA, extrapolation of results from GPA/MPA trials suggests that a lower-intensity regimen for remission maintenance (e.g., AZA) may prevent

exacerbations and decrease the long-term adverse effects associated with prolonged CYC exposure.

In refractory and relapsing EGPA, different treatment modalities have been used with mixed results. In an attempt to spare glucocorticoids, these patients often receive AZA, MTX, mycophenolate mofetil, TNF- α antagonists, IVIG, and plasma exchange. Unfortunately, the rate of response with these approaches has been highly variable, so that any strong recommendation is inadequate. Moreover, successful treatment with RTX has been described in small series and case reports,^{87,88} but controlled studies are lacking.

Better understanding of the pathophysiology of EGPA has focused attention on Th2- and eosinophil-targeted therapies. IFN- α , a cytokine that inhibits eosinophil degranulation and the production of Th2 cytokines by CD4 cells (including IL-5), might have a role in inducing remission in refractory cases,⁸⁹ but the long-term use of this agent seems to be ineffective.⁹⁰ More recently, encouraging results were obtained with the anti-IL-5 monoclonal antibody mepolizumab in two pilot trials in patients with refractory disease. During mepolizumab therapy, blood eosinophilia declined and patients maintained disease remission while being able to taper glucocorticoid use. After drug discontinuation, relapses occurred mostly in patients in whom the eosinophil count returned to pretreatment levels, which suggests that continuous therapy might be required in some cases.^{91,92}

NONPHARMACOLOGIC INTERVENTIONS

Upper airway disease in granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis

In GPA, subglottic stenosis and sinonasal disease may respond incompletely to immunosuppressive therapy. Once scarring is well established in the subglottic region, airway narrowing may be secondary to the progression of fibrosis rather than to GPA-related inflammation. In such cases, surgical dilation is required for the airway stenosis. GPA often leads to chronic nasal and sinus dysfunction from damage caused by the disease itself, superinfection of devitalized tissues, and/or surgical procedures performed for either diagnosis or treatment. Regardless of disease activity, most patients require daily (or more frequent) saline irrigations to minimize the accumulation of secretions and crusts and to reduce the incidence of secondary infections. Distinguishing between worsening sinus disease caused by active GPA and that caused by superimposed infection may be difficult, and sometimes both are present simultaneously. In the absence of a prompt response to antibiotics, surgical drainage and biopsy are often required for a more definitive diagnosis. Nasal polyps develop in up to 80% of EGPA patients. A subset of these patients require polypectomy to relieve the symptoms of nasal airway obstruction.

Plasma exchange

Data demonstrating the pathogenicity of ANCA in animal models has led to the investigation of plasma exchange in human disease. Besides eliminating ANCAs, plasma exchange could theoretically exert beneficial effects in AAV by extracting cytokines and activated complement and coagulation factors from the bloodstream. In the MEPEX trial,⁹³ AAV patients with severe renal failure (creatinine concentration of more than 5.7 mg/dL) received induction therapy with glucocorticoids and CYC, and were randomly assigned either to undergo seven plasma exchange sessions or to receive three IV methylprednisolone pulses. Although the progression to end-stage renal disease (ESRD) was reduced by 24% at 12 months in the plasma exchange group, there was no survival benefit, and the initial advantage of plasma exchange in promoting renal recovery was not appreciated on long-term follow-up.⁹⁴ Although the ongoing PEXIVAS trial may definitely clarify the effects of plasma exchange on ESRD and mortality, in the meantime, plasma exchange remains an experimental therapy with potentially serious adverse effects (e.g., line-associated infections) that may be considered in patients with life-threatening complications of AAV such as severe acute renal failure and DAH that are not responding to immunosuppressive therapy.

Dialysis

The requirement for acute dialysis in AAV does not necessarily indicate irreversible loss of renal function, because more than 50% of patients with AAV who undergo acute renal replacement therapy become dialysis independent with prudent use of aggressive therapy for active disease. Recovery

of native renal function usually occurs within 2 to 3 months of initiation of dialysis. Given that ESRD and dialysis represent risk factors for infection in themselves, clinicians should remember to dose CYC appropriately in patients with lower glomerular filtration rates to avoid increasing the rate of infectious complications beyond that already seen in this population.

Renal transplantation

ESRD has been estimated to occur in up to 20% of some AAV cohorts. Although studies of AAV patients who have undergone renal transplantation are small, results to date suggest that the rates of both allograft and patient survival are similar to those in the nonvasculitic, nondiabetic transplant population. ANCA status at the time of transplantation is not a useful prognostic marker, and its presence should not preclude consideration of transplantation in a patient who is otherwise in apparent remission.⁹⁵

DISEASE ASSESSMENT

Tools used for measuring disease activity and extension in AAV include the Birmingham Vasculitis Activity Score (BVAS)⁹⁶ and its variant for GPA (BVAS/WG),⁹⁷ a physician global assessment, the Disease Extent Index (DEI), and the FFS. The BVAS is the most widely used in GPA and MPA and consists of nine groups of organ system–based items. Remission is defined in the BVAS as the absence of active disease in any organ system (BVAS = 0). Patients with EGPA are frequently classified using the FFS.⁷⁵ Long-term damage attributed to the disease and its treatment is usually measured with instruments such as the Vasculitis Damage Index (VDI) and the Combined Damage Assessment Index (CDAI).⁹⁸

MORBIDITY AND MORTALITY

Descriptions of large cohorts of GPA patients (the longitudinal NIH cohort [n = 158], the Lübeck cohort [n = 155] and the WGET cohort [n = 180])^{12,78,99} confirm common themes with regard to morbidity and prognosis. Median follow-up times in the NIH and German cohorts were 8 and 7 years, respectively. The majority of patients in both series received daily CYC and glucocorticoids as treatment. As noted, 54% to 75% of patients achieved complete remission, but 50% to 60% of these ultimately experienced relapse (at periods ranging from 3 months to 16 years). Recent clinical trials have shown that 80% to 96% of GPA/MPA patients may experience remission with current therapies. Studies have not been homogeneous in terms of clinical definitions (e.g., of “minor disease flare”), the percentage

of patients with GPA and MPA enrolled, and the long-term use of low doses of glucocorticoids as part of the maintenance regimen; overall, however, the flare rate has been around 10% to 20% at 12 to 18 months and 30% to 70% at 24 to 36 months.^{45,71-73,78,80} Most of the exacerbations occurred after the discontinuation of maintenance therapy, which argues for the necessity of extended immunomodulation. Of note, patients with MPA seem to experience a lower rate of relapse than those with GPA.¹⁰⁰

Mortality at 1 year in GPA/MPA exceeds 15%. Infection (due to pharmacologic immunosuppression) and active vasculitis are the most important causes of early death. Eighty-six percent of the NIH patients experienced permanent disease-related morbidity, including chronic renal insufficiency (42%), hearing loss (35%), nasal deformity (28%), tracheal stenosis (13%), and visual loss (8%).¹² ESRD is seen in about 20% of these patients within 10 years.¹⁰⁰

Immunosuppressive treatments also contribute to morbidity and mortality. In the NIH series, serious infections occurred in 46% of the patients.¹² Despite the use of shorter CYC courses and new remission induction strategies with RTX, infectious complications continue to influence the prognosis of GPA/MPA patients. Other treatment-related adverse events includes CYC-induced cystitis,^{12,80,99} increased risk of malignancy (particularly bladder cancer, myelodysplastic syndrome, leukemia, and lymphoma),^{12,78} infertility,¹² and a host of adverse effects related to the use of glucocorticoids (e.g., cataracts, bone fractures, diabetes).¹² The incidence of bladder injury (cystitis) and cancer has become much lower since numerous centers have adopted induction remission strategies using shorter courses of CYC (3 to 6 months) for patients with severe disease, followed by attempts to maintain remission with AZA or MTX.

In EGPA, the presence of one risk factor (FFS = 1) and two or more risk factors (FFS ≥ 2) is associated with a 5-year mortality of 25% and 45%, respectively, and such cases warrant more aggressive therapy, whereas a FFS of 0 is associated with a mortality of 3% to 12% after the same period of time. With adequate treatment, survival in EGPA is 95% at 1 year and 60% to 97% at 5 years.¹⁰⁰ However, the use of CYC in EGPA patients is also associated with significant complications.⁸⁶

Regardless of the initial disease severity and the therapy received, nearly 80% of EGPA patients continue to have asthma that is difficult to treat. This population therefore requires continuous therapy with low to moderate doses of systemic glucocorticoids, which make a substantial contribution to the development of treatment-induced morbidity (e.g., bone fractures).^{31,86}

Patients taking immunosuppressants should receive prophylaxis against *Pneumocystis jiroveci* pneumonia; in addition, all patients who require long-term glucocorticoid therapy are at risk of osteoporosis, and treatment with calcium, vitamin D, and bisphosphonates should be prescribed according to national guidelines (e.g., those of the National Osteoporosis Foundation).

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158 Takayasu arteritis

■ CAROL A. LANGFORD

- Takayasu arteritis is an inflammatory disease of unknown etiology characterized by granulomatous vasculitis affecting the aorta, its main branches, and the pulmonary arteries. It occurs most often in women of childbearing age.
- Physical examination will show absent pulses, bruits, and asymmetric blood pressure.
- Hypertension is an important contributor to morbidity and mortality.
- Common symptoms include claudication, headaches, dizziness, syncope, visual changes, dyspnea, palpitations, and vessel tenderness (carotidynia).
- Systemic symptoms may be absent but include fever, night sweats, fatigue, arthralgia, and myalgia.

HISTORY

The first descriptions of Takayasu arteritis may date from the 1700s and 1800s when several patients were reported with pulselessness and aortic disease. In 1905, Mikito Takayasu presented the case of a young woman with a wreathlike arteriovenous anastomosis around the optic disc. Caccamise and Whitman in 1952 referred to this entity as “pulseless or Takayasu disease,” and in 1962, Judge and colleagues introduced the term *Takayasu arteritis*. Although Takayasu arteritis has become the most widely used name for this disease in the United States, it is known in other countries as aortic arch syndrome, pulseless disease, middle aortic syndrome, occlusive thromboaropathy, and nonspecific aortoarteritis.

EPIDEMIOLOGY

Takayasu arteritis has often been characterized as an illness affecting young women of Eastern ethnic background. However, descriptions from diverse regions have supported the fact that it occurs throughout the world but may have a varying spectrum in different populations (Tables 158.1 and 158.2).¹⁻⁶ Although Japanese series have demonstrated a female preponderance of 9:1, nearly equal representation in men and women has been reported in Israel and India. Similarly, although Takayasu arteritis is most commonly diagnosed between the ages of 15 and 25 in Japan, it has been diagnosed in patients from Italy and Sweden at a mean age of 41 years. In Olmsted County, Minnesota, the incidence is estimated to be 2.6 cases per million.

CLINICAL FEATURES

At the time of diagnosis, 10% to 20% of patients with Takayasu arteritis are clinically asymptomatic, with the disease being detected incidentally as a result of abnormal vascular findings on examination.⁵ The remaining 80% to 90% of patients seek medical attention because of symptoms that are systemic or vascular. Systemic symptoms include fatigue, malaise, weight loss, night sweats, fever, arthralgia, or myalgia, but they may be absent in

up to 60% to 80% of patients.^{5,7,8} Vascular symptoms occur as a direct result of either active vasculitis or vascular damage from previous disease. Active inflammation may result in tenderness over the vessel, and carotidynia occurs in 2% to 32% of patients. Vessel inflammation typically results in either stenosis (Figs. 158.1 and 158.2) or aneurysm formation (Fig. 158.3). The frequencies of common symptoms, which vary between different series, are listed in Table 158.1.¹⁻⁶ Decreased circulation in the extremities is often manifested as intermittent claudication. Stenosis or occlusion of the two carotid and two vertebral arteries or the vessels proximal to their origin may be asymptomatic or be manifested as transient ischemic attacks, stroke, dizziness, syncope, headache, or visual changes. Although mesenteric involvement is common, gastrointestinal symptoms such as nausea, diarrhea, vomiting, and abdominal pain occur infrequently.

Retinal disease occurs in 14% of patients and results from compromise of the internal carotid circulation with central retinal hypoperfusion. Aortic valvular regurgitation secondary to dilation of the aortic root occurs in 5% to 55% of patients (see Fig. 155.3). Coronary vessel stenosis may develop in up to 25% of patients,⁴ with other manifestations including mitral valve regurgitation, cardiomyopathy, and myocarditis. In arteriographic studies, pulmonary artery disease may occur in 50% to 86% of patients (Fig. 158.4).^{2,3} Although it is usually mild and asymptomatic, patients may have features of pulmonary hypertension. Findings on ventilation-perfusion scans are often abnormal in this setting and may be mistaken for thromboembolic disease. Cutaneous manifestations occur in 3% to 28% of patients, with the most common lesions being erythema nodosum, pyoderma gangrenosum, erythema induratum, and ulcerative lesions. Renovascular hypertension can result in nonspecific glomerular disease secondary to arterial narrowing.

INVESTIGATIONS

Diagnosis and monitoring of disease activity

Takayasu arteritis is diagnosed by the presence of characteristic arterial lesions in the aorta and its branches, for which other causes of large-vessel abnormalities have been excluded. The American College of Rheumatology proposed classification criteria in 1990 for the purpose of providing a standard way to describe patients with Takayasu arteritis in studies.

Laboratory and radiographic investigations are initially used diagnostically and thereafter for the purpose of assessing disease activity. An inability to accurately assess disease activity in Takayasu arteritis has been a critical limitation in managing individual patients and evaluating therapeutic regimens. Currently, disease activity is typically assessed by evaluating the collective information gained from imaging, from clinical assessment of the symptoms and signs, and from laboratory studies. Despite this approach, active arteritis has been found in up to 44% of surgical bypass specimens taken from patients judged to be quiescent by current methods.⁵

Laboratory investigations

No laboratory study is diagnostic of Takayasu arteritis or correlates with active arteritis. The disease is not associated with antineutrophil cytoplasmic antibodies. Complete blood cell counts may reveal normochromic, normocytic anemia, leukocytosis, and thrombocytosis. Some series have found the erythrocyte sedimentation rate to be a useful marker for assessing active inflammatory disease,⁹ whereas others have not found it to be uniformly reliable.^{5,8} C-reactive protein can also be a marker of active inflammation in some patients, although no data are available regarding its overall utility in Takayasu arteritis.

TABLE 158.1
Common symptoms and signs (%) in Takayasu arteritis

Symptom/sign	Study					
	Japan ¹ (N = 52)	India ² (N = 106)	China ³ (N = 530)	Korea ⁴ (N = 129)	USA ⁵ (N = 60)	Mexico ⁶ (N = 107)
Fatigue/constitutional	27	—	—	34	43	78
Weight loss	—	9	—	11	20	22
Musculoskeletal	6	5	—	—	53	53
Claudication	13	—	25	21	90	29
Headache	31	44	—	60	42	57
Visual changes	6	12	10	20	30	8
Syncope/dizziness	40	26	14	36	35	13
Palpitations	23	19	—	23	10	43
Dyspnea	21	26	11	42	—	72
Carotidynia	21	—	—	2	32	—
Hypertension	33	77	60	40	35	72
Bruit	—	35	58	37	80	94
Decreased pulses	62	—	37	55	60	96
Asymmetric blood pressure	—	—	—	—	47	—

TABLE 158.2
Pattern of vessel involvement in Takayasu arteritis

Vessel	Study						Symptoms
	Japan ¹ (N = 52)	India ² (N = 95)	China ³ (N = 105)	Korea ⁴ (N = 129)	USA ⁵ (N = 60)	Mexico ⁶ (N = 107)	
Subclavian							
Right	21	28	46	41	8	13	Upper extremity claudication, Raynaud phenomenon
Left	56	59	78	61	55	25	
Carotid							
Right	31	7	23	12	7	7	Visual changes, syncope, transient ischemic attacks, stroke
Left	40	21	26	32	27	19	
Vertebral	—	—	13	10	35	19	Visual changes, dizziness
Ascending aorta	46	13	—	1	—	27	
Aortic arch or root	—	19	—	2	35	27	Aortic insufficiency, congestive heart failure
Thoracic aorta	31	26	25	37	17	—	
Abdominal aorta	33	72	55	46	47	67	
Celiac axis	—	3	4	5	18	—	Rarely abdominal pain, nausea, vomiting
Inferior mesenteric	—	8	3	7	—	14	Rarely abdominal pain, nausea, vomiting
Superior mesenteric	—	12	24	16	18	14	Rarely abdominal pain, nausea, vomiting
Renal							
Right	23	53	34	30	17	18	Hypertension, renal failure
Left	15	52	32	33	2	16	
Iliac							
Right	—	15	10	—	2	1	Lower extremity claudication
Left	—	12	8	—	5	6	
Pulmonary	—	49	53	—	—	14	Atypical chest pain, dyspnea
Coronary	—	—	—	23	—	9	Chest pain, myocardial infarction, dyspnea

—, Not specified.



Fig. 158.1 Magnetic resonance arteriogram demonstrating diffuse moderate stenosis of the proximal left common carotid and proximal occlusion of the left subclavian artery coming off the aortic arch along with the development of an extensive collateral network.



Fig. 158.2 Irregularity and stenosis of the infrarenal abdominal aorta and right renal artery seen on a magnetic resonance arteriogram.

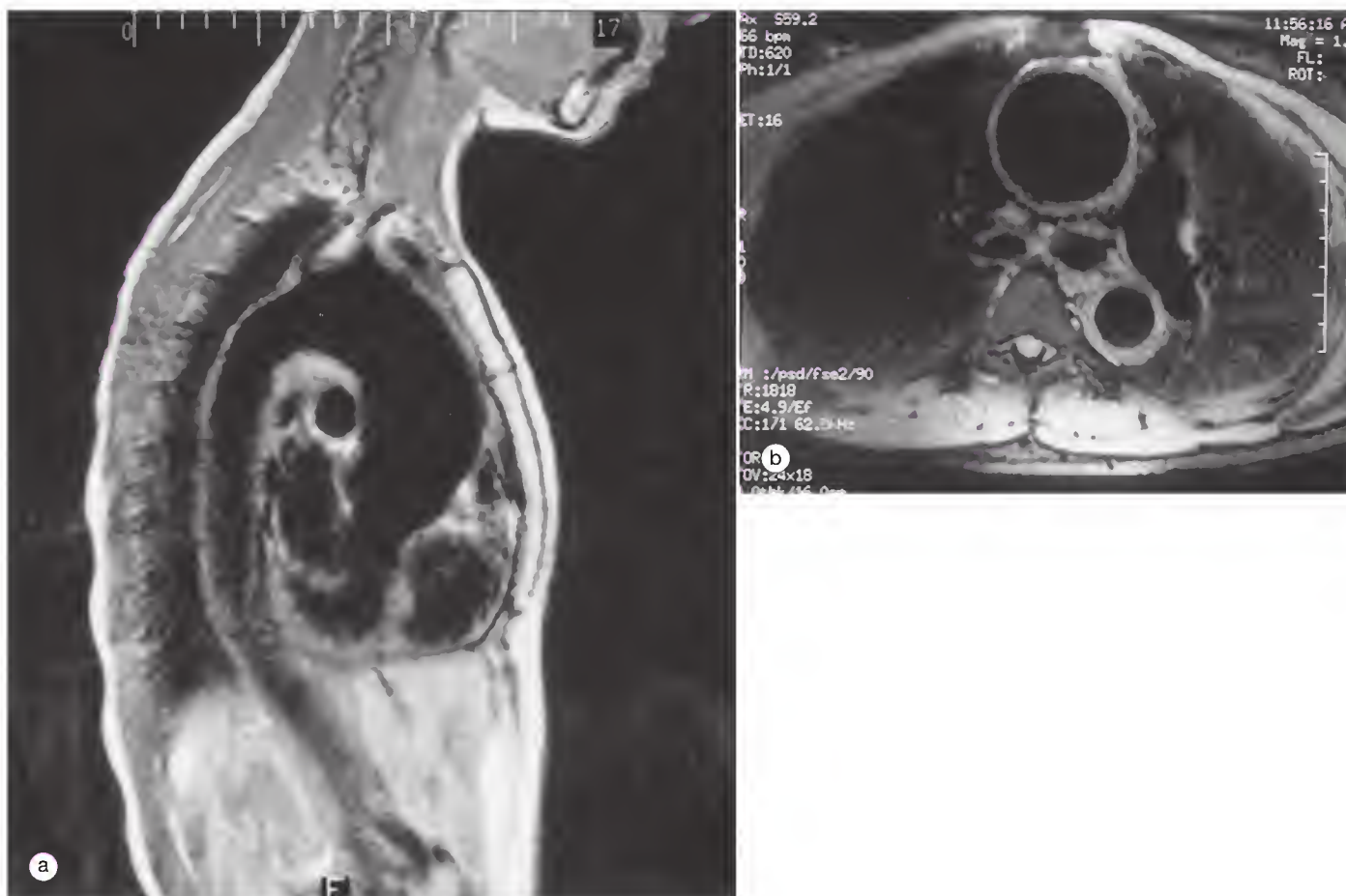


Fig. 158.3 (a and b) Aneurysm of the aortic root seen on magnetic resonance imaging (T1-weighted images). The ascending aorta measures 5.0 cm and can be compared with the normal diameter of the descending aorta.



Fig. 158.4 Pulmonary arteriogram in a patient with Takayasu arteritis. Abrupt termination of a proximal branch to the lingula is seen, as well as a vessel with irregularity and narrowing.

Radiographic studies

Diagnostic imaging is fundamental to the diagnosis of Takayasu arteritis and plays an essential role in monitoring the disease. Arteriography with catheter-directed intravascular injection of contrast dye, magnetic resonance imaging (MRI), or computed tomographic angiography (CTA) provides information on vascular luminal dimensions. Complete imaging of the aorta and its major branches should be performed in all patients at the time of diagnosis and during serial evaluation because such studies can detect clinically occult vascular disease and provide information important to diagnosis and future disease management. The noninvasive ability to look at a vessel with MRI or CTA provides a useful means of serial monitoring. In the absence of contraindications, such imaging is typically performed at 6- to 12-month intervals in those with Takayasu arteritis to monitor for the development of new vascular lesions.

Vessel stenosis is present in 85% or more of patients at the time of diagnosis and is the most common arteriographic finding (see Figs. 158.1 and 158.2). Aneurysms may be saccular or fusiform and typically affect the aorta rather than its branches (see Fig. 158.3). Various patterns of vessel involvement have been observed in different populations (see Table 158.2). Comparative studies of vessel disease across different regions have been aided by the use of arteriographic classification systems that focus on the distribution of vessel involvement (Fig. 158.5).¹⁰ After diagnosis, the development of new lesions in new vascular territories is considered by most investigators to be indicative of active disease. However, progression of previous vascular lesions may also result from noninflammatory fibrosis.

Catheter-directed dye arteriography has remained the “gold standard” for detecting and measuring the luminal dimensions of involved vessels in Takayasu arteritis. It also allows assessment of central blood pressure, which may be important in patients in whom vascular disease in the extremities does not allow accurate peripheral measurement. Limitations of dye arteriography are the risk for thromboembolism and significant exposure to contrast agent and radiation.

Magnetic resonance angiography (MRA) and CTA are safe and noninvasive techniques for assessing vessel patency in Takayasu arteritis.¹¹ The use

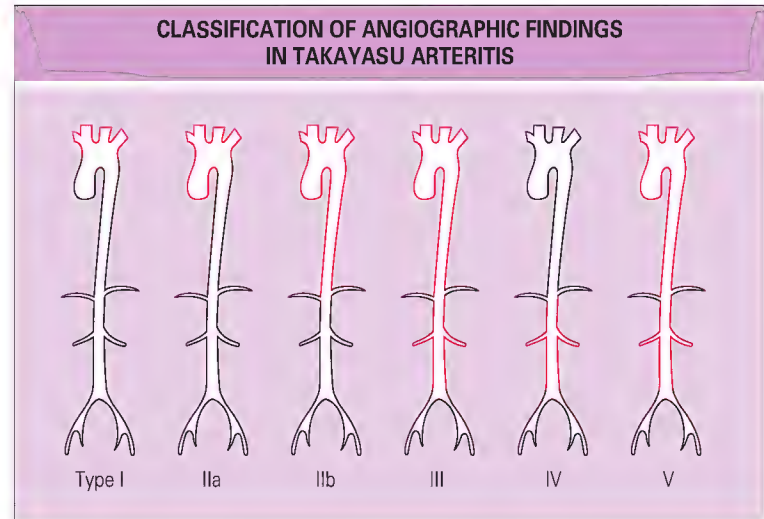


Fig. 158.5 (Redrawn from Hata A, Noda M, Moriwaki R, et al. Angiographic findings of Takayasu arteritis: new classification. *Int J Cardiol* 1996;54[suppl]:S155-63.)

of CTA requires exposure to radiation, and both CTA and MRA are contraindicated in the setting of renal insufficiency. In contrast to conventional arteriography, MRI also provides information on arterial wall thickness and edema with fast spin-echo sequences, although its correlation with active disease is unclear.¹¹

Ultrasonography has been reported to provide useful information, but this technique is operator dependent and additional study is required to determine its applicability.¹² The results with ¹⁸F-fluorodeoxyglucose-labeled positron emission tomography (FDG-PET) have been mixed, with some studies concluding that FDG-PET is useful for the detection of active inflammation and others finding no association between vascular intensity and clinical disease activity.^{13,14}

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Takayasu arteritis includes atherosclerotic, inflammatory, infectious, and hereditary diseases that affect the large vessels. IgG4-related disease has emerged as a potential cause of aortitis and peri-aortitis and is histologically differentiated from Takayasu arteritis by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, a storiform pattern of fibrosis, and obliterative phlebitis.¹⁵

PATHOLOGY

Tissue biopsy plays little or no role in the diagnosis of Takayasu arteritis because histologic examination of the great vessels is usually possible only at the time of vascular procedures or after death. Takayasu arteritis is a panarteritis that typically occurs as focal “skip lesions.” During active disease, the inflammatory infiltrate is predominantly lymphocytic with granuloma formation and giant cells involving the media and adventitia. Later, degeneration of the internal elastic lamina of the media, adventitial fibrosis, and neovascularization are seen.

The pathophysiology and etiology of Takayasu arteritis remain poorly understood. The presence of granulomatous inflammation, blood vessel inflammatory infiltrates consisting of T cells and monocyte/macrophages, and high tumor necrosis factor (TNF)-producing T cells suggests that type 1 helper T-cell (Th1) mechanisms play a role in pathogenesis of the disease. Analysis of cytokine gene transcription in peripheral blood mononuclear cells has demonstrated increased constitutive mRNA expression of TNF and interleukin-4 (IL-4) and a decrease in the induced expression of IL-10 mRNA.¹⁶ In other studies, evidence of cell-mediated cytotoxicity has been provided by the demonstration of increased numbers of $\gamma\delta$ T lymphocytes with a restricted T-cell receptor, as well as $\gamma\delta$ T lymphocytes, natural killer cells, and cytotoxic T cells in aortic tissue.¹⁷ Extension of this work has found that $\gamma\delta$ T cells in patients with Takayasu arteritis are reactive to 60-kDa heat shock protein (hsp60) and cytotoxic to aortic endothelial cells, thus suggesting a role for hsp60 and $\gamma\delta$ T cells in disease pathogenesis.¹⁸ In studies from Japan, Korea, and Turkey, an association of Takayasu arteritis with HLA-B*52 has been described.¹⁹ In Indian patients, Takayasu arteritis

is associated with HLA-B*51, whereas analysis of HLA genes in North America has not revealed any association.⁵

MANAGEMENT

General principles

Treatment of active disease is based on the rationale that interruption of active inflammation before the development of significant vessel damage improves the prognosis. However, the role of immunosuppressive treatment in lessening morbidity and mortality has been difficult to assess. In a series of 30 longitudinally observed patients, 93% achieved remission but only 28% had a sustained remission, defined as the absence of clinical, laboratory, and radiographic evidence of new vascular lesions for more than 6 months while taking less than 10 mg of prednisone daily; relapses occurred in 96% of those who had achieved remission.⁷ To date, therapeutic data on Takayasu arteritis have come from open-label trials, observational studies, and case series. Therapeutic decisions are often guided by the location and severity of lesions, collateral circulation, and medication toxicity. Effective care of patients with Takayasu arteritis includes not only treatment of active disease but also nonmedical management of fixed vascular lesions or aneurysms, as well as control of comorbid features.

Conventional immunosuppressive agents

Glucocorticoids are the foundation of treatment of Takayasu arteritis. Combination therapy is considered primarily in patients who have severe disease or persistent disease activity despite glucocorticoids treatment or when remission cannot be maintained with acceptable doses of glucocorticoids. Because combination therapy increases the risk for infection, care should be taken to monitor for cytopenia and provide prophylactic treatment of *Pneumocystis jiroveci*.

Glucocorticoids

Glucocorticoids are the therapeutic mainstay for Takayasu arteritis. Resolution of systemic symptoms occurs in 25% to 100% of glucocorticoid-treated patients,^{5,6,20} and some reports have demonstrated improvement in arteriographic blood flow and return of previously absent pulses. No comparative trials have been conducted to determine the optimal dose and length of glucocorticoids treatment. In retrospective series, initial prednisone doses ranging from 20 to 100 mg/day have been used.^{6,20} In a retrospective analysis of 150 patients who had received 30 mg/day prednisolone, 51% had improved quality of life, 37% experienced no change, and 12% worsened, although the definitions of these outcome measures were not stated.²⁰ In the largest prospective standardized experience with glucocorticoids for Takayasu arteritis, in which patients initially received prednisone at a dosage of 1 mg/kg/day (60 mg daily) for the first 1 to 3 months, which was then tapered, 52% achieved remission.⁹ Although current data support the use of an initial prednisone dosage of 1 mg/kg/day, a lower starting dosage may be considered in selected individuals at high risk for glucocorticoids toxicity, provided that immediate tissue ischemia is not a threat.

Methotrexate

A prospective standardized trial evaluated the use of methotrexate (MTX) in a glucocorticoids-resistant population.²¹ In this study of 16 patients, MTX at 15 to 25 mg/wk combined with prednisone led to remission in 81%. However, remission was followed by relapse in 54%, and 19% of patients had progressive disease. Toxicities of MTX include elevated hepatic transaminase levels, stomatitis, pneumonitis, teratogenicity, and bone marrow suppression. Although this study has limitations, these data support that MTX may be an effective means of inducing remission and minimizing glucocorticoids toxicity in patients with Takayasu arteritis.

Cyclophosphamide

Cyclophosphamide (CYC) was the first cytotoxic agent studied for Takayasu arteritis; however, data regarding its use are limited.²² CYC has the potential for serious short- and long-term toxicity, including bone marrow suppression, infection, infertility, bladder injury, transitional cell carcinoma of the bladder, and myeloproliferative disease. Given the predilection for relapse and the predominantly young female population affected, CYC is rarely used for Takayasu arteritis.

Azathioprine

Valsakumar and colleagues²³ used azathioprine (AZA) combined with prednisolone to treat 15 patients with active Takayasu arteritis for 1 year.

All patients showed improvement in systemic symptoms and laboratory measures of disease activity within 3 months, and arteriograms 1 year later revealed no changes. AZA can be associated with cytopenia, infection, allergic reactions, and leukemia. Use of AZA concomitantly with glucocorticoids can be considered in patients who cannot receive MTX or who have experienced relapse after previous MTX treatment.

Other conventional immunosuppressive agents

Mycophenolate mofetil,^{24,25} leflunomide,²⁶ and minocycline²⁷ have been used in a limited number of patients, but further study will be required for their efficacy to be determined.

Biologic therapies

The use of TNF inhibitors in patients with Takayasu arteritis has been explored in a number of case series because of evidence suggesting a role of Th1 mechanisms in the development of large-vessel granulomatous vasculitis.²⁸⁻³¹ Molloy and colleagues²⁹ used TNF-modulatory agents to treat 25 patients with refractory Takayasu arteritis. Remission was achieved and prednisone was discontinued in 15 patients (60%) and tapered to a dosage lower than 10 mg daily in another 7 patients (28%); major relapses occurred in 4 patients and 4 experienced adverse events. Schmidt and associates³⁰ retrospectively studied 20 patients with refractory Takayasu arteritis treated with TNF inhibitors. Disease remission occurred in 18 patients (90%) and sustained remission in 10 (50%). Ten patients of 12 patients receiving at or above prednisone 10mg daily (83%) were able to taper the prednisone dosage to below 10 mg daily, with 7 being able to stop glucocorticoids treatment. However, 6 of 18 patients experienced relapse, 20% discontinued treatment because of adverse events, and six infections occurred in 5 patients. Although the results from these studies are encouraging, it remains difficult to determine the efficacy and relative safety of anti-TNF therapy for Takayasu arteritis in the absence of a randomized controlled trial.

Other biologic agents have prompted interest for investigation in treating Takayasu arteritis, including several case reports of use of the anti-IL-6 receptor antibody tocilizumab^{32,33} and an ongoing randomized trial of the T-cell co-stimulation modulator abatacept. However, the evidence on either of these agents is insufficient to currently support their use in clinical practice.

Antiplatelet therapy

In a retrospective study of 48 patients with Takayasu arteritis, De Souza and coworkers³⁴ found that the use of antiplatelet therapy was associated with a lower frequency of ischemic events and had a protective effect with a low frequency of bleeding complications. Even though this study is small, it suggests that in patients without contraindications, aspirin 100 to 200 mg daily may reduce the risk for acute ischemic events in patients with Takayasu arteritis.

Nonmedical interventions

Nonmedical interventions are important for the revascularization of stenosed or occluded vessels that produce significant ischemia or for the treatment of aneurysms. Up to 70% of patients with Takayasu arteritis may require nonmedical interventions, with the most frequent indications including cerebral hypoperfusion, renovascular hypertension, limb claudication, repair of aneurysms, and valvular insufficiency.

The safety and potential benefits of vascular reconstructive surgery in patients with Takayasu arteritis have been favorable, but occlusion and complication rates vary greatly between series.³⁵⁻³⁸ Although surgery is more invasive than other forms of vascular intervention, current studies suggest that it results in a higher rate of patency over time.^{35,37} Ideally, vascular reconstruction should be deferred until the acute inflammation is controlled medically because aneurysm formation, graft dehiscence, or graft occlusion may be more likely in the setting of active arteritis.^{36,38} The role of perioperative glucocorticoids in clinically quiescent patients remains unclear. The site of revascularization is also important with regard to the long-term outcome, and care should be taken to avoid placing surgical connections to vessels that are frequently known to become involved during the course of disease. Bypass grafts for involved cervicobrachial vessels should ideally originate from the ascending aorta because this segment rarely becomes stenotic.

Percutaneous transluminal angioplasty (PTCA) can be effective in acutely improving blood flow. In settings in which renal artery PTCA is undertaken, care must be taken to minimize sudden drops in blood pressure

in patients who have severe stenoses across critical vascular beds. The ability of PTCA to acutely reduce stenosis has varied widely, but it transiently improved blood pressure in the majority of patients. However, the longevity of results is variable, with some studies suggesting a substantial restenosis rate.³⁵

Percutaneously placed stents have also been used for Takayasu arteritis. Similar to the experience with PTCA, the short-term results have been encouraging, but some series have found a high rate of restenosis or occlusion over extended follow-up.^{35,37} A recent report has described the use of stent grafts for Takayasu arteritis.³⁹ Although this intervention appears to be associated with better results than can be achieved with bare metal stents, longer-term patency data will be needed to understand the durability and role of this endovascular therapy in these patients.

Management of comorbid features

Hypertension has been reported to occur in 32% to 93% of patients¹⁻⁶ and it contributes to renal, cardiac, and cerebral injury. Because the subclavian arteries are a frequent site of vessel stenosis, blood pressure measurements in one or both arms may not be representative of aortic root pressure, and therefore four-extremity blood pressure measurements should be taken at each clinic visit. When treating hypertension, care should be taken to avoid precipitous drops in blood pressure, particularly in patients with compromised cerebral blood flow. Because evidence supports the finding that patients with Takayasu arteritis have a high rate of plaque formation,

proactive assessment and effective control of traditional atherosclerotic risk factors are also essential.

OUTCOME

The long-term outcome of patients with Takayasu arteritis has varied between studies. Although North American reports found overall survival rates to be 94% or greater,^{5,7} the 5-year mortality rate has been as high as 35%.^{3,9} Disease-related mortality can occur as a result of congestive heart failure, cerebrovascular events, myocardial infarction, aneurysm rupture, or renal failure.^{1,3,4,8,9} Takayasu arteritis is associated with substantial morbidity. In one series, 74% of patients exhibited compromised function in activities of daily living and 47% were permanently disabled.⁵

Pregnancy

For women not being treated with cytotoxic therapy, pregnancy is not contraindicated, but careful perinatal care is important to optimize outcomes in both the mother and child. Although the amount of data is still limited, most series have reported favorable maternal and fetal outcomes.^{5,40} Hypertension is the most common cause of complications and must be monitored closely. Induction of labor or cesarean section is not mandatory for women with Takayasu arteritis, although advanced planning for the method of delivery is important.⁴⁰

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159 Behçet syndrome

■ SEBAHATTIN YURDAKUL ■ VEDAT HAMURYUDAN ■ HASAN YAZICI

- Behçet syndrome is a systemic vasculitis of unknown etiology that is characterized by recurrent mucocutaneous manifestations and chronic relapsing uveitis with the potential threat of blindness. It may involve veins and arteries of all size.
- A marked geographic distribution exists along the "Silk Route," with the greatest prevalence rates found in Turkey, Iran, and Japan.
- Behçet syndrome occurs most commonly in the second or the third decades and has an undulating course that generally abates in intensity with the passage of time.
- Men and those in whom the disease develops at a young age have a more severe disease course.
- Frequent recurrent oral and genital ulcerations and a variety of other skin manifestations occur, including the "pathergy" phenomenon.
- Other complications include musculoskeletal, large-vessel, neurologic, and gastrointestinal involvement.

HISTORY AND EPIDEMIOLOGY

In 1937 Hulusi Behçet from Istanbul described three patients with oral and genital ulcerations, hypopyon-related uveitis, and erythema nodosum.¹ Additional clinical manifestations, including musculoskeletal, neurologic, vascular, and gastrointestinal involvement, were recognized later and added to the disease spectrum.^{2,3} The underlying pathology includes an inflammatory process of arteries and veins.

The usual onset of Behçet syndrome occurs in the third decade. Onset is rare in people 50 years or older and before puberty. Both genders are affected equally, but men and the young have a more severe disease course.⁴

The global distribution suggests a geographic pattern coincident with the ancient Silk Route, with the highest incidence found in the Middle and Far East. The prevalence of Behçet syndrome has been reported to be between 20 and 421 per 100,000 adults in five field surveys in Turkey. These figures compare with 17 in Iraq, 80 in Iran, and 120 per 100,000 in an Arab community in Israel. Estimated prevalence ranges are 0.64 in the United Kingdom, 6.4 in Spain, and 5.2 in the United States per 100,000 population. Similar low frequencies are seen in indigenous Germans (1.47/100,000), whereas Turks living in Berlin, Germany, still have a distinctly high rate of 77 per 100,000.⁵

Even with the low figures in Europe, in the suburbs of Paris the frequency of Behçet syndrome was higher (7.1/100,000) than the frequencies of Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyarteritis nodosa taken individually and close to the frequency of all three diseases combined (9/100,000).⁵

Disease prevalence shows ethnic variation even in the same city: ethnic Armenians living in Istanbul have a lower frequency of Behçet syndrome (110/100,000) than the general population does (420/100,000).⁶ Immigrant Turks in Berlin have a higher frequency than ethnic Germans do, indicative of a genetic load, but have a lower frequency than Turks living in Turkey do, indicative of an environmental influence. Similarly, the higher frequency of Behçet syndrome in Arabs in Israel might signify both genetic and environmental factors, with the latter perhaps related to lower social strata.

ETIOLOGY

Genetic and environmental factors play a role, although the exact contribution of each is unknown.

Genetic factors

The syndrome does not show mendelian inheritance. The increased prevalence of the disease along the Silk Route, an increased sibling recurrence rate (λ_s , 11 to 53) in Turkey, and the involvement of another family member (1/10) in endemic areas suggest a genetic element. A meta-analysis showed that the most frequent association is with HLA-B51/B5, which has been validated in various ethnic groups.⁷ A whole-genome analysis has recently identified 16 additional loci and 2 other non-HLA loci such as interleukin-10 (IL-10) and IL23R-IL12RB2, thus pointing to a true complex genetic disorder.^{8,9}

Several other genes such as the major histocompatibility complex class I chain-related genes (MIC), tumor necrosis factor (TNF), and the heat shock proteins¹⁰ and their various polymorphisms have been identified, but it is not clear whether they are in linkage disequilibrium with HLA-B51 or independently affect susceptibility.

Environmental factors

The hypersensitivity to *Streptococcus sanguis* antigens, their sequence homology with various heat shock proteins, and their potential cross-reactivity suggest a pathogenetic role. Herpes simplex virus type 1, *Staphylococcus aureus*, and *Prevotella* species, which are found in nonsterile pustular skin lesions, have also been suggested as potential candidates.¹¹ However, no infectious agent has yet been causally linked to Behçet syndrome.

CLINICAL FEATURES

The manifestations of Behçet syndrome tend to recur either alone or in combination (Table 159.1). Mucocutaneous lesions constitute the hallmark of Behçet syndrome, but uveitis and neurologic and large-vessel manifestations are the most serious.

Mucocutaneous lesions

Oral aphthous ulcerations (Fig. 159.1a) are usually the first and most frequent manifestation. The oral ulcers of Behçet syndrome are generally indistinguishable from ordinary canker sores; however, they are generally multiple and recur more frequently. Minor aphthous ulcers (<10 mm in diameter) are the most common type ($\approx 90\%$) and heal without scarring; major or herpetiform ulcers are less frequent. Major ulcers can leave scars.

Genital ulcerations (see Fig. 159.1b) typically develop on the scrotum (90%) and less frequently on the penis in men and on the labia majora (70%) followed by the labia minora in women. They heal with scarring in about two thirds of patients when they are large (≥ 1 cm in diameter).¹² Urethritis and dysuria are not usually present.

Mainly three types of skin lesions are found:

1. Erythema nodosum-like lesions (see Fig. 159.1c) are confined to the lower extremities and commonly heal with residual pigmentation, as distinct from idiopathic erythema nodosum or lesions secondary to other causes. Histologic examination of these lesions shows more



Fig. 159.1 Mucocutaneous findings in Behçet syndrome. (a) Oral aphthae. (b) Genital ulceration. (c) Erythema nodosum–like nodular lesions. (d) Multiple positive pathergy tests.

TABLE 159.1
Frequency of the clinical manifestations of Behçet syndrome and classification criteria of the International Study Group

Manifestation	Frequency (%)
Oral ulcers	97-99
Genital ulcers	≈85
Papulopustular lesions	≈85
Erythema nodosum	≈50
Pathergy reaction	≈60 (Mediterranean countries and Japan)
Uveitis	≈50
Arthritis	≈50
Subcutaneous thrombophlebitis	25
Deep vein thrombosis	≈10
Arterial occlusion/aneurysm	≈4
Central nervous system involvement	10
Epididymitis	≈10
Gastrointestinal lesions	1-30 (more prevalent in Japan)

*In the absence of other clinical explanations, patients must have the following:
Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient at least three times in a 12-month period plus two of the following:*

- Recurrent genital ulceration*
- Eye lesions: anterior uveitis, posterior uveitis, cells in the vitreous by slit-lamp examination, or retinal vasculitis observed by an ophthalmologist*
- Skin lesions: erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules in postadolescent patients not treated with corticosteroids*
- Positive pathergy test read by a physician at 24 to 48 hours*

vasculitic elements than occurs with idiopathic erythema nodosum or other causes.¹³

2. Superficial thrombophlebitis (Fig. 159.2) may also appear as a nodular skin lesion mimicking erythema nodosum. Superficial thrombophlebitis may be associated with deep vein thrombosis.



Fig. 159.2 Superficial thrombophlebitis.

3. The acne-like lesions are usually indistinguishable from ordinary acne.¹⁴ They occur not only at the usual sites of acne but also at uncommon sites such as the legs and arms.

In addition, papular lesions, consistent with cutaneous vasculitis and Sweet syndrome (neutrophilic dermatosis), can also be associated with Behçet syndrome.

The pathergy reaction

The pathergy reaction (see Fig. 159.1d) represents hyperreactivity of the skin to trauma. Typically, it is characterized by erythematous papule or pustule formation at a skin site 24 to 48 hours after insertion of the needle. This phenomenon is quite specific for Behçet syndrome. However, wound healing after biopsy-induced trauma is normal. The frequency of pathergy positivity is 60% to 70% in Turkey and Japan, but it is rarely observed in patients from northern Europe or the United States.¹⁵



Fig. 159.3 Hypopyon uveitis.

Eye involvement

Eye involvement occurs in 50% of patients. It is more frequent and more severe in men and the young. This chronic, relapsing uveitis is mostly bilateral, involves both the anterior and posterior uveal tracts, and leads to significant morbidity. Anterior uveal tract inflammation frequently leads to photophobia and red eye, whereas posterior tract inflammation is characterized by visual loss. Hypopyon-related uveitis (**Fig. 159.3**) is seen in 20% and indicates a poor prognosis because it is almost always associated with severe retinal disease. Isolated anterior uveitis is infrequent, and conjunctivitis is rare.

Posterior uveal inflammation with involvement of the retina can be severe. Retinal lesions consist of exudates, hemorrhages, papilledema, and macular disease. Postinflammatory structural changes, including synechiae and retinal scars, are important determinants of the prognosis of the eye disease.

Musculoskeletal involvement

Behçet himself described “rheumatoid pains” in 1938, 1 year after the original description. Seen in up to 50% of patients, the typical features of joint involvement include a nondeforming, nonerosive peripheral monoarthritis or oligoarthritis that lasts not more than a few weeks. The knees are involved most frequently, followed by the ankles, wrists, and elbows. Synovial fluid is commonly inflammatory, but a good mucin clot is usual. Synovial histology shows nondiagnostic, nonspecific synovitis.^{16,17}

Occasionally, chronic arthritis and osteonecrosis can be seen. Back pain is uncommon, and properly conducted studies of sacroiliac joint involvement have not demonstrated an increased prevalence in Behçet syndrome.¹⁷

Patients with Behçet syndrome and arthritis also have more acne lesions. Furthermore, patients with arthritis and acne have significantly more enthesopathy. Behçet syndrome with arthritis and acne forms a distinct cluster that was significantly more common in familial cases, thus interestingly suggesting genetic predisposition for a particular disease cluster.¹⁸ However, sacroiliitis and HLA-B27 were not increased in this cluster.

Fibromyalgia can develop, especially in female patients. Local or systemic myositis occurs rarely in both the proximal and distal ends of extremities in patients with Behçet syndrome.

Neurologic disease

Neurologic involvement is observed in 5% to 10% of patients. Parenchymal involvement (80%), commonly involving the brain stem, is manifested by pyramidal, cerebellar, and sensory signs and symptoms along with sphincter disturbances and behavioral changes. Isolated cerebellar involvement is unusual. Nonparenchymal involvement (20%) is characterized by dural sinus thrombi, with intracranial hypertension being manifested as headaches and papilledema. Simultaneous parenchymal and nonparenchymal involvement is unusual. Parenchymal involvement has a more severe course. Cerebrospinal fluid examination is nonspecific, with a high protein or cell count implying a more guarded prognosis. Peripheral nerve disease, seen frequently in other vasculitides, is uncommon.¹⁹



Fig. 159.4 Pulmonary artery aneurysms on a chest radiograph.

Venous and arterial lesions

Vascular lesions develop in a fourth to a third of patients, mostly in males. Thrombophlebitis of superficial (see **Fig. 159.2**) or deep veins is most frequent in the legs. Thrombosis of major vessels, such as vena cava obstruction and occlusion of the suprahepatic veins (Budd-Chiari syndrome), occurs less frequently. Despite the frequent occurrence of venous involvement, thromboembolism is rare because of the tight adherence of thrombi to the diseased endothelium.

The entire arterial tree can be affected, with aneurysms or occlusions (or both) in the abdominal aorta and the carotid, femoral, and popliteal arteries.²⁰ Behçet syndrome is the only vasculitis that can cause pulmonary artery aneurysms, which are the leading cause of death.²¹ Recurrent hemoptysis is the main manifestation. The aneurysms are seen as noncavitating opacities on chest radiographs (**Fig. 159.4**). The diagnosis can be confirmed by computed tomography or magnetic resonance imaging.

Cardiac involvement

Valvular lesions, myocarditis, pericarditis, coronary vasculitis, coronary and ventricular aneurysms, and intracardiac thrombus formation have been reported infrequently (6%) and portend a poor prognosis.²² A study that compared the clinical, electrocardiographic, and echocardiographic findings of patients with Behçet syndrome and healthy control subjects did not find a difference between the two groups.²³ Unlike many other chronic vasculitides, increased atherosclerosis is not a major problem with Behçet syndrome.²⁴

Lung disease

Apart from pulmonary artery aneurysms, isolated thrombosis of peripheral segments of the pulmonary arteries with or without aneurysms can be seen. Both types of involvement can occur together and have similar clinical findings and prognosis. Nodules, cavities, and consolidations are frequently confused with secondary infections in an immunocompromised patient. Mediastinal lymphadenopathy and pleural and pericardial effusions may be observed. Patients may have pulmonary artery hypertension.²⁵

Gastrointestinal involvement

Mucosal ulcerations, primarily in the ileum²⁶ and colon, cause colicky abdominal pain, diarrhea, and bleeding. Ileocecal lesions are prone to perforation. Gastrointestinal involvement is seen in about a third of patients from Japan but is less common in those from the Mediterranean basin.

Other clinical findings

Glomerulonephritis has been reported sporadically. Amyloidosis of the AA type can accompany and cause nephrotic syndrome. Epididymitis (10%) is

a well-recognized feature of Behçet syndrome. Bladder involvement can result in voiding dysfunction.² Patients exhibiting features consistent with coexistent Behçet syndrome and relapsing polychondritis (mouth and genital ulcers with inflamed cartilage—MAGIC syndrome) have been described. These patients have various combinations of oral and genital ulcerations, thromboembolic disease, ocular inflammation, and gastrointestinal ulcerations along with nasal and auricular chondritis.

Finally, auditory and vestibular lesions, presumably caused by vasculitis, are more frequently recognized in patients with Behçet syndrome.

PROGNOSIS

A recent survey of the 20-year outcome of a cohort of 427 patients with Behçet syndrome revealed that men and those young in age at onset of the disease have a more stormy course and increased mortality. Mortality was highest in patients 14 to 24 years of age at their first visit,²⁷ similar to a recent report from France.²⁸ It decreased, however, as time passed. Exacerbations of the undulating course become less frequent as the patients aged. On the other hand, about 60% of patients would not have fulfilled any set of criteria for diagnosis at the end of 20 years, which means that the majority of patients go into a remission once they pass the initial, active disease years.²⁷

Ruptured pulmonary and peripheral aneurysms and neurologic and gastrointestinal involvement are the major causes of mortality.²⁷ Budd-Chiari syndrome and amyloidosis also carry a guarded prognosis.²⁸

INVESTIGATIONS

Laboratory findings are nonspecific. A moderate anemia of chronic disease and leukocytosis are seen in about 15% of patients. The erythrocyte sedimentation rate and C-reactive protein value may be mildly elevated. However, these parameters are not good indicators of disease activity. Autoantibodies such as rheumatoid factor, antinuclear antibody, anticardiolipin, and antineutrophilic antibodies are absent.

DIFFERENTIAL DIAGNOSIS

A set of classification criteria have been developed (see Table 159.1).²⁹ Using recurrent aphthous ulceration as an obligatory feature, these criteria require the presence of two other sets of organ involvement for diagnosis.

Patients with recurrent aphthae in addition to only one organ manifestation are considered to have “incomplete” disease and present a diagnostic challenge. Diseases in the differential diagnosis and their characteristic features are presented in Table 159.2. The seronegative arthritides and inflammatory bowel disease constitute the main difficulties in the differential diagnosis, especially in the West. Without the help of extraintestinal manifestations it might be impossible to differentiate Behçet syndrome from Crohn disease.

PATHOGENESIS

Behçet syndrome is an inflammatory vasculitis of unknown etiology that can involve all types and sizes of arteries and veins. The absence of typical necrotizing vasculitis and giant cell formation in histology specimens coupled with the propensity for venular involvement and the presence of pulmonary and arterial aneurysms is unique (Fig. 159.5).³⁰

A type 1 helper T (Th1) cell–mediated immune response and hypersensitivity to nonspecific trauma as exemplified by the pathergy test are characteristic. A proinflammatory innate immune system–derived activation that is sustained by adaptive immune responses is thought to be important in pathogenesis.³¹ The observation of a potential genetic impairment in the production of IL-10,^{8,9} an inflammation-suppressing molecule, and an augmented IL-21–driven Th17 pathway³² are recent considerations in pathogenesis.

A coagulation abnormality, though extensively sought, has not been found to explain the high frequency of venous thrombosis. A decrease in fibrinolysis is probably the most consistent finding.

Neutrophil hyperreactivity has also been an important issue. However, it is not clear whether the activity is inherent in the neutrophil or is due to the priming cytokines that are abundant in the circulation.

Behçet syndrome does not easily fit into any proposed classes because the disease does not have the classic group characteristics, such as urethritis,

TABLE 159.2
Differential diagnosis of Behçet syndrome

Disease	Features not seen in Behçet syndrome
Reactive arthritis	Urethritis, penile lesions on the glans penis, conjunctivitis
Seronegative arthropathies	Mainly psoriatic skin lesions, aortic insufficiency, frequent axial involvement
Inflammatory arthropathies	Serologic abnormalities
Inflammatory bowel disease	Inflammatory lesions throughout the bowel
Multiple sclerosis	Intranuclear ophthalmoplegia, optic neuritis
Sarcoidosis	Bilateral hilar adenopathy, parenchymal pulmonary disease
Other systemic vasculitides	Microaneurysms, mononeuritis multiplex, antineutrophil cytoplasmic antibodies
Vogt-Koyanagi-Harada syndrome	Peliosis, alopecia, vitiligo
Stevens-Johnson syndrome	Blisters, corneal involvement
Venereal diseases	Glans lesions, specific serologic studies
Coxsackievirus and echovirus infections	Subacute course
Relapsing polychondritis	Nasal and auricular chondritis

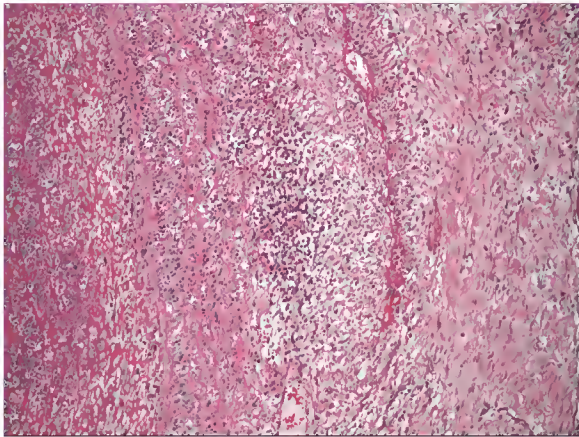


Fig. 159.5 This high-power photomicrograph shows fresh thrombus formation and prominent lymphoplasmacytic infiltration in the entire wall of the elastic artery. Perivascular inflammatory infiltration of adventitial tissue is also present together with vasa vasorum arteritis (hematoxylin-eosin, x100). (Courtesy Dr. Buge Oz.)

balanitis, sacroiliitis, and HLA-27 association for the seronegative spondyloarthritis; female preponderance, Raynaud phenomenon, Sjögren syndrome, and specific antibodies for autoimmune diseases; and the predominance of fever and pediatric involvement, gene mutations such as the TNF receptor or pyrin, and the CARD/NOD gene associations of Crohn disease for autoinflammatory disorders.³³ Clinical observations have suggested that there are clusters of disease expression in Behçet syndrome. One such cluster consists of superficial and deep vein thrombosis, dural sinus thrombi, and pulmonary arteries, and another is the cluster of acne, arthritis, and enthesitis.³³ These clusters suggest that more than one disease mechanism may be operative in the pathogenesis of Behçet syndrome.

MANAGEMENT

The aim of the treatment is to prevent organ damage. The type and severity of symptoms along with prognostic factors determine the therapeutic strategy. Prophylactic immunosuppressive therapy with azathioprine might be considered for young men during the initial years of the disease because they carry the highest risk for the development of severe complications in the long term.^{34,35}

TABLE 159.3
EULAR recommendations for the management of Behçet syndrome

Manifestation	Recommended therapy
Eye involvement	Azathioprine combined with corticosteroids is recommended as the first-line agent for all patients with posterior uveitis.
Refractory eye involvement	In the case of visual loss (>2-line drop in visual acuity on a 10-scale chart) or retinal involvement (retinal vasculitis or macular involvement), the addition of cyclosporine or infliximab to azathioprine and corticosteroids is recommended. Interferon alfa with or without corticosteroids may be another alternative.
Vascular involvement	Immunosuppressives such as corticosteroids, azathioprine, cyclosporine, and cyclophosphamide are recommended for venous involvement. Cyclophosphamide along with corticosteroids is recommended for arterial involvement. However, firm evidence for these recommendations is lacking.
Thrombophilia	No data, even uncontrolled, support the use of anticoagulant, antiplatelet, or fibrinolytic agents for the management of deep vein thrombosis or arterial lesions.
Gastrointestinal involvement	Sulfasalazine, corticosteroids, azathioprine, TNF- α antagonists, and thalidomide should be considered before surgery, except in emergencies.
Arthritis	Colchicine will be effective for most patients. Azathioprine, interferon alfa, and TNF- α antagonists may be considered for refractory cases.
CNS involvement	For parenchymal involvement, corticosteroids, azathioprine, interferon alfa, cyclophosphamide, methotrexate, and TNF- α antagonists are recommended. Dural sinus thrombosis can be managed with corticosteroids.
CNS involvement and cyclosporine	Cyclosporine should not be used in patients with CNS involvement unless definitely necessary for ocular inflammation.
Mucocutaneous involvement	Mild oral or genital ulcers may be managed with topical measures (corticosteroid- or lidocaine-containing creams, sucralfate suspension). Erythema nodosum can be managed with colchicine. Azathioprine, interferon alfa, and TNF- α antagonists are recommended for refractory cases.

CNS, central nervous system; EULAR, European League Against Rheumatism; TNF, tumor necrosis factor.

Adapted from Hotemi G, Silmon A, Bong D, et al. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008;67:1656-62.

Controlled trials are limited to mucocutaneous manifestations and eye involvement, but no formal evidence is available for treatment of the vascular, neurologic, and gastrointestinal manifestations. An European League Against Rheumatism task force proposed nine recommendations for the management of Behçet syndrome (Table 159.3).³⁶

Mucocutaneous lesions are treated according to their severity. Topical cream (e.g., triamcinolone acetonide cream) may provide symptomatic relief. Colchicine (1 to 2 mg/day) is recommended for mild to moderately severe manifestations and especially for erythema nodosum and genital ulcers.³⁷ Thalidomide (100 mg/day) is highly effective in treating severe oral and genital ulcers, but severe adverse effects such as teratogenicity and polyneuropathy prevent prolonged use of this drug.³⁸ Azathioprine is effective in suppressing frequent recurrences of oral and genital ulcers. Uncontrolled studies of infliximab and adalimumab and one short-term randomized controlled trial of etanercept suggest that TNF- α inhibitors are effective in controlling refractory mucocutaneous manifestations.^{39,40}

Arthritis can be often managed with colchicine.³⁷ Short courses of corticosteroids and nonsteroidal agents may provide symptomatic relief. Sulfasalazine, azathioprine, TNF- α antagonists, and interferon alfa may be considered for long-lasting or frequently recurring arthritis attacks.

Azathioprine combined with corticosteroids is the first-line treatment of uveitis, which most frequently involves the entire globe.^{36,41,42} The presence of retinal involvement or a significant drop in visual acuity necessitates the addition of either cyclosporine or a TNF- α antagonist to the combination of azathioprine and corticosteroids. Interferon alfa, alone or with corticosteroids, is another alternative. The daily dose of azathioprine is 2.5 mg/kg, and a minimum of 3 months is required for commencement of its effect. Cyclosporine is rapidly effective in reducing the frequency and severity of ocular attacks, as well as in improving visual acuity, but relapses of uveitis have been reported after cessation of cyclosporine. The daily dose of

cyclosporine should not be higher and should preferentially be lower than 4 to 5 mg/kg, with close monitoring for adverse effects, especially nephrotoxicity. Use of cyclosporine is not recommended in patients with central nervous system involvement unless absolutely indicated.³⁶ Infliximab, even with a single dose, may rapidly suppress attacks of uveitis.⁴⁰ However, its effect is not long-lasting and thus continuous treatment is required. Adalimumab is another alternative, and switching from one TNF- α antagonist to another when required appears to be effective.⁴³ The effect of interferon alfa starts rapidly, and it may induce long-lasting drug-free remission.⁴⁴ The optimal dose of interferon alfa has not been determined yet.⁴⁵

The use of anticoagulants for the management of venous thrombosis is still a matter of debate. New information suggests that treatment with azathioprine and corticosteroids significantly reduces recurrences of venous thrombosis.⁴⁶ Cyclophosphamide combined with high-dose corticosteroids is used for arterial aneurysms. Pulmonary aneurysms are generally bilateral and multiple and tend to recur; surgery should thus be the last choice. Endovascular embolization can replace surgery in an emergency, but the very frequent coexistence of venous thrombosis may render this intervention technically difficult. Surgery for peripheral aneurysms should always be supported with immunosuppressive agents to prevent relapses.⁴⁷

The course of gastrointestinal involvement is not infrequently complicated by relapses requiring resection of large bowel segments. Sulfasalazine, 5-aminosalicylic acid, azathioprine, corticosteroids, thalidomide, and TNF- α antagonists have been used anecdotally to prevent recurrences.³⁶

Parenchymal central nervous system involvement is initially treated with pulsed corticosteroids. TNF- α antagonists, azathioprine, cyclophosphamide, methotrexate, and interferon alfa are used to prevent relapses. Dural sinus involvement usually responds to treatment with corticosteroids. Blockade of IL-1 and IL-6 appears to be on the horizon as a promising target.

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160 Kawasaki disease

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- Kawasaki disease (KD) is the most common cause of acquired heart disease in children in the United States, Western Europe, and Japan.
- KD is not a rare disease, with more than 5000 and 12,000 new cases diagnosed each year in the United States and Japan, respectively.

HISTORY

Historical investigation suggests that the systemic vasculitis that we now call *Kawasaki disease* (KD) was new in the East and old in the West.¹⁻³ Records from Western Europe and the United States from the late 19th and early 20th centuries document a pathologically indistinguishable vasculitis in infants that was called *infantile periarteritis nodosa* and was diagnosed only at autopsy.⁴ In 1967 Dr. Tomisaku Kawasaki reported on a series of 50 patients in Japan with a syndrome that he named *mucocutaneous lymph node syndrome*.⁵ Not until a nationwide epidemiologic survey was performed in 1970 in Japan was it appreciated that this clinical syndrome was associated with coronary artery aneurysms that could lead to myocardial infarction and death. An English-language version of Kawasaki's original patient series report was published in 1974, and the term *Kawasaki disease* was proposed in 1977 by Landing and Larson.^{4,6} Today, KD is recognized as the most common cause of acquired pediatric heart disease in nations across the globe and has been identified in all ethnic groups and races.^{7,8}

EPIDEMIOLOGY

In Japan, the country of highest incidence, there were 240 cases per 100,000 children (younger than 5 years of age) in 2010.⁹ In the United States, there is no effective active surveillance program, and incidence estimates are extrapolated from insurance databases. The incidence in the United States in 2000 based on hospital discharge diagnoses was 17.1 per 100,000 children younger than 5 years of age.¹⁰ Important regional differences in incidence within the United States suggest a genetic influence on disease susceptibility, and rates per 100,000 children younger than 5 years are 210 for Japanese American children in Honolulu, 43 for children of Filipino descent in San Diego, and 15 for a largely African American population in Detroit.¹¹⁻¹³ Familial occurrence is increasingly being reported.^{14,15} Based on a 2009-2012 nationwide survey in Japan, there was a 3.6% recurrence risk, 1.6% occurrence of sibling cases, and 0.7% occurrence in children with a history of KD in one or both parents.⁹

KD cases cluster in both time and space, which lends support to the theory that there is an infectious trigger for the disease.¹⁶ In both Japan and the United States there is a biphasic occurrence of the disease with peaks in the winter/spring and again in midsummer.^{17,18} A recent analysis has linked fluctuations in KD case numbers with tropospheric wind patterns that originate in Central Asia.¹⁹

CLINICAL FEATURES

No laboratory test exists to confirm the diagnosis of KD, and the clinician must use clinical criteria in conjunction with supportive laboratory data to establish the diagnosis. Updated guidelines for the diagnosis of complete and incomplete KD are available from the American Heart Association²⁰ (Box 160.1).

The exanthem can take many different forms but is never frankly bullous or vesicular (Fig. 160.1). Micropustules (less than 1 mm) may occur over extensor surfaces, genitals, and the upper buttocks.²¹ The rash is accentuated in the groin in 50% of patients.²² Unlike in bacterial toxin-mediated illnesses such as scarlet fever, there is rarely generalized desquamation of the rash. In general, the rash is not pruritic except in children with a history of eczema. Both psoriasis and eczema are associated with KD, and the first flare of these chronic skin conditions may occur during the convalescent phase of KD.^{23,24}

Injection of the bulbar conjunctiva with associated perilimbal sparing is noted in the majority of patients (Fig. 160.2). Unlike in viral conjunctivitis, there is no conjunctival inflammation and no exudate or tearing, and both eyes become injected at the same time.^{25,26} Anterior uveitis is seen in over 80% of patients examined by slit lamp during the first week after fever onset.²⁷

Changes in the oropharynx include fissured red lips, strawberry tongue, and oropharyngeal erythema without discrete lesions or ulcers. The fissuring of the lips usually occurs in the center portion of the vermillion border. Tonsillar exudate is not a feature of KD.²⁸

Changes in the extremities include edema of the dorsa of hands and feet and palm and sole erythema, which is distinct from the rash (Fig. 160.3). Periungual desquamation in the convalescent phase may occur on the fingers or toes or both and is noted in approximately two thirds of patients (Fig. 160.4).²⁹ Transverse grooves across the nail bed (Beau lines) appear 4 to 6 weeks after fever onset. Arthritis was prospectively documented in 30% to 40% of patients in the preimmunoglobulin era, and more recently arthritis or arthralgia was noted in 7.5% to 15% of patients in retrospective studies.³⁰⁻³² Arthritis of the small joints of the fingers is common and is often associated with a bluish discoloration over the proximal interphalangeal joints. Axial arthropathy with frank arthritis or arthralgia may be associated with joint effusions with a neutrophil predominance and cell counts of 20,000 to 200,000 cells/mm³.³¹

A painful, unilateral cervical lymph node mass is noted in approximately one third of patients.²⁸ A misdiagnosis of bacterial cervical lymphadenitis frequently delays the diagnosis of KD and appropriate treatment.³³ Imaging studies show a "cluster of grapes" appearance of the node mass, in contrast with the more common single, hypodense node associated with localized bacterial infection.³⁴ KD patients with cervical node enlargement tend to be older and have higher levels of inflammatory markers than patients with bacterial infection.³⁵

The most serious clinical findings are associated with the cardiovascular system. Although myocarditis is universally present based on biopsy studies, a gallop rhythm is noted only in approximately one third of patients and frank congestive heart failure is rare during the acute phase. A new clinical presentation with high-output shock associated with hypotension has been described.^{36,37}

Other clinical manifestations of KD may include the following: gastrointestinal manifestations including hydrops of the gallbladder and pancreatitis, urethritis, facial nerve palsy (rare), and sensorineural hearing loss (fewer than 1% of cases). Minor associated symptoms are frequent and, in a recent series, included gastrointestinal symptoms (vomiting, diarrhea, or abdominal pain; 61% of cases) and respiratory tract symptoms (cough or rhinorrhea; 35% of cases).³²

LABORATORY ASSESSMENTS

Laboratory testing is used to document high levels of systemic inflammation and to rule out other rash/fever syndromes as appropriate based on the history and findings of the physical examination (Fig. 160.5).³⁸ A minimum laboratory evaluation should include the following: complete

BOX 160.1 CLINICAL CRITERIA FOR CLASSIC KAWASAKI DISEASE

Fever persisting at least 4 days in the presence of four of five principal clinical criteria:

1. Polymorphous rash
2. Bilateral conjunctival injection without exudate
3. Changes in the oropharynx, including red fissured lips, strawberry tongue, and red pharynx without exudate
4. Changes in the extremities, including edema of the dorsa of the hands and feet, palm and sole erythema, and periungual desquamation during the convalescent stage (usually 2 to 3 weeks after fever onset)
5. Enlarged cervical lymph node of at least 1.5 cm (usually unilateral)



Fig. 160.1 Polymorphous exanthem over the limbs and trunk of an infant with acute Kawasaki disease.



Fig. 160.2 Conjunctival injection, red fissured lips, and left cervical lymphadenopathy in a patient with acute Kawasaki disease.



Fig. 160.3 Edematous, erythematous feet in a patient with acute Kawasaki disease. (Courtesy the Kawasaki Disease Foundation.)



Fig. 160.4 Periungual desquamation of the fingers and toes 2 to 3 weeks after fever onset in a patient with Kawasaki disease.

blood cell count with manual differential count, erythrocyte sedimentation rate (ESR), C-reactive protein level, alanine aminotransferase level, γ -glutamyltranspeptidase level, albumin level, and urinalysis.^{28,39}

Echocardiographic assessment and electrocardiography should be performed according to the guidelines of the American Heart Association, and the internal diameter of the right coronary artery and left anterior descending coronary artery and aortic root should be expressed as standard deviations from the mean normalized for body surface area (z score).^{20,40-43} Tissue Doppler imaging is useful to detect diastolic dysfunction.⁴⁴

PATHOLOGIC FEATURES

KD is a systemic vasculitis that primarily affects medium-sized, extraparenchymal musculoelastic arteries and shows a predilection for the coronary

LABORATORY ABNORMALITIES DURING THE FIRST 10 DAYS AFTER FEVER ONSET AND BEFORE TREATMENT IN PATIENTS WITH ACUTE KAWASAKI DISEASE

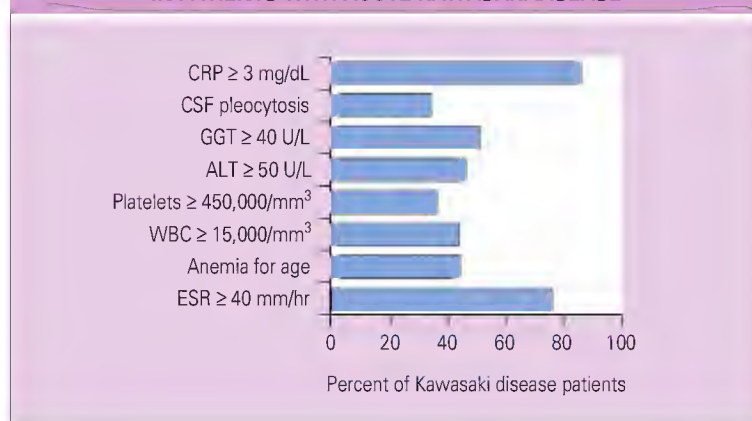


Fig. 160.5 Abnormal laboratory results seen in patients with acute Kawasaki disease. ALT, alanine aminotransferase; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate. GGT, γ -glutamyltranspeptidase; WBC, white blood cells.



Fig. 160.6 Selective coronary angiogram showing a giant aneurysm of the left coronary artery.

arteries.⁴⁵ Myofibroblast infiltration with secretion of proinflammatory cytokines, matrix metalloproteinases, and elastases destroys the structural integrity of the vessel wall and can result in aneurysm formation (Fig. 160.6).⁴⁶ Three linked vasculopathic processes characterize the acute and chronic pathologic changes in the vessel wall and include an acute, self-limited necrotizing arteritis, a subacute or chronic vasculitis, and luminal myofibroblastic proliferation.

The necrotizing arteritis, which occurs during the first 2 weeks after onset of fever, is characterized by infiltration with neutrophils from the lumen of the vessel. Myocarditis is universal at this stage and can progress to fibrosis and scarring in the later stages.⁴⁷

During the subacute/chronic vasculitis, which may begin within the first 2 weeks after fever onset, there is an infiltration of small lymphocytes, plasma cells, and eosinophils from the adventitial vasa vasorum, which progresses toward the lumen. Aneurysms of the coronary arteries with or without thrombosis can occur. Immunohistochemical testing shows a predominance of CD8⁺ T cells and macrophages infiltrating the vessel wall with secretion of matrix metalloproteinases during this stage.^{48,49} Infiltration of immunoglobulin A-secreting plasma cells is also noted.⁵⁰

A different vasculopathic process involves a progressive, asynchronous intraluminal stenosis mediated by vascular smooth muscle cell-derived myofibroblasts. This process is associated with intimal thickening, remodeling of aneurysms, thrombotic occlusion, and stenosis in the medium-sized arteries.

ETIOLOGY AND PATHOGENESIS

Most investigators agree that a microbial agent triggers the immune response that characterizes acute KD. Many infectious agents have been proposed and discarded as candidates for the causative agent of KD.⁵¹ Intracytoplasmic inclusions that stain with a synthetic antibody constructed from sequences derived from KD plasma cells have been proposed as evidence of a viral cause.⁵² It is possible that multiple agents trigger the syndrome in genetically susceptible hosts.

An understanding of the complex genetics of KD has been pursued through candidate gene studies, family linkage studies, and genomewide association studies.⁵³⁻⁵⁶ A functional polymorphism in the inositol-1,4,5-trisphosphate 3-kinase gene that affects interleukin-2 signaling through the NFAT/calcineurin pathway confers increased susceptibility and also increased risk of aneurysm formation.⁵⁷ Genetic variation in the transforming growth factor- β signaling pathway confers increased risk of aneurysm formation.⁵⁸ Further studies are necessary to capture the sum of the genetic diversity that influences KD susceptibility and outcome.

TREATMENT AND MANAGEMENT

Based on large-scale clinical trials in the 1980s, the current recommended treatment for KD patients is a single intravenously administered dose of immunoglobulin (IVIG, 2 g/kg) in conjunction with high-dose aspirin (80 to 100 mg/kg/day).⁵⁹ After cessation of fever, most centers reduce the aspirin dosage to a low antiplatelet dosage of 3 to 5 mg/kg/day. The aspirin is continued until the ESR and platelet count have returned to the normal range. This approach, if implemented within the first 10 days after fever onset, reduces the incidence of coronary artery aneurysms from 25% to 5%.

IVIG resistance, defined as persistent or recrudescence fever (temperature of 38.0°C or higher) at least 36 hours after the end of the initial IVIG infusion, can occur in patients at highest risk of coronary artery damage.⁶⁰ Originally described as affecting only 10% to 15% of KD patients, IVIG resistance has now increased to 20% to 30% of patients in some regions of the United States and Japan.^{61,62} Strategies to treat IVIG resistance have included a second infusion of IVIG, a single infusion of infliximab, corticosteroids, cyclosporine, and plasmapheresis.⁶³⁻⁶⁶ Prospective identification of patients at risk of IVIG resistance would allow intensification of initial treatment.⁶⁷ Risk scores have been devised in Japan, but their application to populations outside of Japan has not been successful, possibly due to the mixed ethnic composition of the population.^{60,68} A large, prospective, randomized multicenter trial in the United States examined the addition of pulsed methylprednisolone to IVIG in the initial treatment of KD patients, but no benefit was demonstrated.⁶⁹ In contrast, a prospective, randomized, open-label study of the addition of a 15-day course of steroids to primary therapy with IVIG in Japan in risk score-selected KD patients demonstrated improved coronary artery outcomes.⁶⁴ The use of corticosteroids at any point during the treatment of acute KD remains controversial.⁷⁰ In a retrospective study, patients treated with infliximab for IVIG-resistant KD had faster resolution of fever and fewer days of hospitalization but no difference in coronary artery outcome compared with patients treated with a second dose of IVIG.⁷¹ A randomized, double-blind, placebo-controlled trial of infliximab plus IVIG for initial treatment of KD patients has completed enrollment, and data are currently being analyzed.

Arthritis persisting after treatment with IVIG usually responds well to naproxen or a single dose of infliximab. It is rare for patients to require treatment for arthritis beyond the subacute phase.

Management of cardiovascular complications should be undertaken by pediatric and adult cardiologists familiar with evolving treatment guidelines. Studies using historical controls suggest a benefit of warfarin therapy (to an international normalized ratio of 2.0 to 2.5) for patients with giant aneurysms (8 mm or more in internal diameter).^{72,73} Antiplatelet therapy with aspirin and/or clopidogrel is recommended for all patients with persistent dilatation or aneurysms, although prospective trials have not been performed.²⁰

Some centers perform echocardiography at 5-year intervals in all children and young adults after KD owing to the emerging recognition of arrhythmia, sudden death, myocardial fibrosis, and congestive heart failure in individuals with no documented coronary artery lesions during the acute phase of the illness.⁷⁴ Because arterial calcification is a common feature of KD vascular lesions, obtaining a computed tomographic coronary artery calcium score several years after acute KD may help identify individuals with significant vasculopathy.⁷⁵ Evidence-based guidelines for the long-term care and management of KD patients into adulthood are evolving.

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161

Henoch-Schönlein purpura/
immunoglobulin-A vasculitis

■ SEZA OZEN ■ YELDA BILGINER

- Henoch-Schönlein purpura is currently termed immunoglobulin A (IgA) vasculitis now that the role of IgA in its pathogenesis is more apparent.
- A set of classification criteria have been newly developed for children and may help pediatricians in making the diagnosis as well.
- Evidence-based data are desperately needed for the treatment of kidney involvement, although this is one of the most common childhood vasculitides.

DEFINITION

Henoch-Schönlein purpura (HSP), a primary vasculitis of childhood that predominantly affects small vessels, is characterized by a characteristic purpura, abdominal pain, arthritis, and renal involvement. It is the most common childhood vasculitis in most parts of the world. HSP has been defined by the Chapel Hill Consensus Criteria 2012 (CHCC2) as a vasculitis with IgA1-dominant immune deposits that affect small vessels (predominantly capillaries, venules, or arterioles), often involves the skin and gut, and frequently causes arthritis.¹ Thus HSP will be termed HSP/IgA vasculitis in this chapter. The CHCC2 also stated that glomerulonephritis indistinguishable from IgA nephropathy may occur and suggested the new name to be IgA vasculitis.¹

Although the first description is attributed to Heberden in 1896,² Schönlein proposed the diagnostic triad of purpuric rash, arthritis, and abnormalities in the urinary sediment and called the disease “*peliosis rheumatica*” in 1837.³ Subsequently, his student Henoch described the gastrointestinal and renal manifestations of the disease.⁴

EPIDEMIOLOGY

HSP/IgA vasculitis occurs most often in children between the ages of 3 and 10 years, and the peak age at onset occurs between 4 and 6 years.^{5,6} It has a slight male preponderance (1.5:1), unlike other rheumatologic diseases.⁷ Though rare, it is also seen in infants, adolescents, and adults. In North America the incidence of HSP is 13.5 to 18 per 100,000, but a large population-based survey from a multiethnic region of the United Kingdom reported an annual incidence of 20.4 per 100,000.^{5,6} HSP has also been reported to have an incidence of 12.9 per 100,000 children in Taiwan and 10.2 per 100,000 children in the Czech Republic.^{8,9} Most cases occur in the winter and are often preceded by an upper respiratory tract infection.¹⁰

The incidence in adults, however, is only 1.3 per 100,000 with a mean age at diagnosis of about 50 years.¹¹ The disease is known to have a more severe course in adults.

CLASSIFICATION

The American College of Rheumatology (ACR) defined criteria for the classification of HSP in 1990. The ACR criteria require the presence of at least two of the following: (1) 20 years or younger at onset, (2) palpable purpura, (3) bowel angina, and (4) histologic changes showing granulocytes in the small walls of arterioles and venules.¹² In 2006 pediatricians suggested a new set of criteria, which were later revised based on a large multinational registry.¹³ The new criteria, published as the Ankara 2008 criteria, were endorsed by the European League Against Rheumatism, the Pediatric Rheumatology European Society, and the Paediatric Rheumatology International

Trials Organisation (Table 161.1). According to these criteria, palpable purpura is a mandatory feature, age as a criteria has been removed, arthritis/arthralgia was added, and the finding of granulocytes in biopsy specimens was replaced by IgA deposition. This new classification provides 100% sensitivity and 87% specificity for the classification of HSP.^{13,14}

ETIOLOGY AND PATHOGENESIS

HSP/IgA vasculitis is a multifactorial immune complex disease. The exact etiology of HSP remains unknown; however, a number of concepts are important in the pathogenesis of the disease.

Environmental factors

Infectious agents, drugs, and vaccinations have been implicated as possible triggers of HSP. A seasonal distribution of the disease, a frequent history of a preceding upper respiratory tract infection, and a higher incidence in childhood point to an infectious etiology. Although group A streptococci have been studied the most, other viral and bacterial pathogens have been postulated, such as parvovirus B19, *Bartonella henselae*, *Helicobacter pylori*, varicella, rubella, rubeola, hepatitis A and B, and *Mycoplasma pneumoniae*.¹⁵⁻²²

In adults, drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (losartan), antibiotics (clarithromycin), nonsteroidal antiinflammatory drugs (NSAIDs), vaccinations, insect bites, and food allergies have been reported as precipitating factors for HSP.²³⁻²⁶

Immunologic factors

IgA has a key role in the pathogenesis of HSP. The clinical manifestations of HSP are due to deposition of IgA1 in vessel walls and the renal mesangium. It has been hypothesized that introduction of microbes through respiratory tract or gastrointestinal mucosa leads to activation of the mucosal immune system, which increases an abnormally glycosylated polymeric IgA production.^{27,28} The subsequent formation of IgA immune complexes in target organs leads to a series of inflammatory events that result in vasculitis in the respective tissues. IgA may also bind to endothelial cells and either induce endothelial cell lysis by activation of complement or directly activate endothelial cells to produce interleukin-8 (IL-8).²⁷

In HSP nephritis, levels of aberrantly glycosylated IgA1 (galactose deficient O-linked glycans) are increased, similar to patients with IgA nephropathy.^{29,30} This shed light on the pathogenesis of HSP nephritis, and it has been suggested that polymeric galactose-deficient IgA1 is recognized by naturally occurring antiglycan IgA1 or IgG, and circulating immune complexes are formed.^{28,31} Once deposited in the mesangium, the IgA immune complexes initiate the ensuing glomerular inflammation.²⁸

Although IgA has a key role in its pathogenesis, HSP is a systemic inflammatory disease, and research is ongoing to determine the role of specific inflammatory markers in the pathogenesis of the disease. Cellular immunity is also increasingly being implicated. Some proinflammatory cytokines such as tumor necrosis factor- α , IL-6, IL-8, and recently, IL-17 have been found to be increased in children with acute HSP.³²⁻³⁶

Genetic background

Increased occurrence in family members supports a genetic predisposition for this vasculitis.³⁷⁻³⁹ Several reports suggest that HLA class II polymorphisms can be a risk factor for HSP.^{39,40} An association between HLA-B35

TABLE 161.1
EULAR/PRINTO/PRES (Ankara, 2008) criteria for Henoch-Schönlein purpura*

Criterion	Definition
Purpura (mandatory)	Palpable purpura or petechiae with lower limb predominance and at least 1 of 4 of the following:
Abdominal pain	Diffuse, acute, colicky pain. Intussusception and gastrointestinal bleeding may be seen
Histopathology	Leukocytoclastic vasculitis with predominantly IgA deposition or proliferative glomerulonephritis with predominantly IgA deposition
Arthritis or arthralgias	Acute joint swelling or pain with limitation of motion or acute joint pain without joint swelling or limitation on motion
Renal involvement	Proteinuria >0.3 g for >24 hr or spot albumin-to-creatinine ratio >30 mmol/mg on a spot morning sample; hematuria or red blood cell casts >5 red blood cells/high-power field or ≥2+ on dipstick

*If the purpura has an atypical distribution, demonstration of IgA deposits on a biopsy specimen is required.

EULAR, European League Against Rheumatism; PRES, Pediatric Rheumatology European Society; PRINTO, Paediatric Rheumatology International Trials Organisation.
 From Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. *Ann Rheum Dis* 2010;69:798-806.

and risk for nephritis has also been suggested.⁴¹ The association with ACE gene polymorphisms remains controversial, although it may have a role in selected patients.⁴² Mutations in the gene associated with familial Mediterranean fever have been associated with the disease in certain ethnic groups.⁴³

CLINICAL FINDINGS

HSP/IgA vasculitis is an acute, systemic disease, and the classic signs and symptoms of the disease include purpura, arthralgia/arthritis, abdominal pain, and glomerulonephritis. Symptoms may be experienced within several days or weeks.⁵ An upper respiratory infection usually precedes the disease.^{15,16,17,22} Low-grade fever and fatigue are often present.^{44,45} Clinical characteristics of patients with HSP/IgA vasculitis are presented in Box 161.1.

Cutaneous involvement

The predominant cutaneous finding in patients with HSP is palpable purpura, which is also mandatory for diagnosis¹⁴ (Fig. 161.1). The purpuric rash is most prominent on dependent areas such as the extensor surface of the lower extremities, the belt line, and the buttocks, but it may also be seen on the arms, face, and ears.^{15,46} In addition, skin lesions may be found on the scrotum, penile shaft, and glans penis.⁴⁷ Rarely, petechiae, ecchymoses, and hemorrhagic bullae can be seen. The cutaneous lesions progress in color from red to purple to brown before fading. In children the eruption is characterized by its polymorphism, whereas in adults it is frequently monomorphic.^{15,23} Hemorrhagic necrotic lesions are more often seen in adults.⁴⁸ Especially in young children, subcutaneous edema may develop in the scalp, face, dorsa of the hands and feet, scrotum, or elsewhere.⁴⁹

Joint involvement

Arthralgia and arthritis occur in 60% to 80% of patients and may precede the rash in up to a quarter of patients with HSP.^{15,45} The arthritis is often monoarthritis and is characterized by periarticular swelling and pain and limitation of motion. The joint disease is nonmigratory and transient and resolves without residual abnormalities.⁴⁵

Gastrointestinal involvement

Gastrointestinal involvement, including colicky abdominal pain, vomiting, and gastrointestinal bleeding, occurs in 50% to 75% of children, usually within a week after onset of the rash. Gastrointestinal signs and symptoms may rarely precede the purpura.^{15,50} Abdominal pain is the most common

BOX 161.1 CLINICAL CHARACTERISTICS OF PATIENTS WITH HENOCCH-SCHÖNLEIN PURPURA/IGA VASCULITIS: ITEMIZED STARTING FROM THE MOST FREQUENT TO THE MOST RARE

Skin (involvement is present in all patients)

Palpable purpura
 Petechiae
 Ecchymoses
 Bullae
 Ulceration
 Maculopapular lesions
 Urticarial lesions
 Subcutaneous edema

Joints (up to 82%)

Arthritis/arthralgia

Gastrointestinal system (50% to 75%)

Abdominal pain
 Gastrointestinal hemorrhage
 Bowel infarction
 Bowel perforation
 Duodenal obstruction
 Intussusception
 Acute pancreatitis
 Hepatobiliary involvement
 Protein-losing enteropathy

Renal (20% to 60%)

Microscopic hematuria
 Proteinuria
 Macroscopic hematuria
 Acute nephritic or nephritic syndrome
 Hypertension
 Acute renal failure

Urogenital

Orchitis
 Scrotal edema
 Ureteral stenosis
 Testicular torsion

Neurologic

Central nervous system vasculitis
 Headache
 Seizures
 Visual abnormalities and verbal disability
 Facial palsy
 Peripheral neuropathy

Pulmonary

Alveolar hemorrhage
 Intestinal infiltrates



Fig. 161.1 Purpura involving the lower extremities in a child with Henoch-Schönlein purpura/IgA vasculitis.

gastrointestinal symptom and is often periumbilical and epigastric and worsens after meals.⁵¹ Intestinal bleeding manifested as gross or occult blood occurs in approximately a third of children. Intussusception develops in 1% to 5% of children and is mostly ileoileal in location.^{45,46} Perforations, usually ileal, may occur spontaneously or be associated with intussusception.⁵² Less common involvement includes acute pancreatitis, hepatobiliary involvement, and enteropathy.^{45,53-55}

Renal involvement

Renal involvement has been reported to occur in 20% to 60% of children.^{15,46,56} Clinical findings range from the more common transient, isolated microscopic hematuria and mild proteinuria to the less common nephrotic syndrome, nephritic syndrome, rapidly progressive glomerulonephritis, and renal failure. Nephritis rarely develops before appearance of the characteristic rash.^{15,50}

Renal disease develops in most children within the first 6 weeks and in the remaining within 6 months.⁵⁷ Age older than 7 years at onset, severe abdominal symptoms, persistent purpuric lesions, and decreased factor XIII activity are associated with increased risk for nephritis.^{45,58-60} Renal manifestations are less likely to develop in children younger than 2 years.⁶¹ In longitudinal studies of unselected patients, the risk for chronic renal impairment is 2% to 15% and that for end-stage renal disease is lower than 1%.⁵⁶

Renal involvement is detected in 45% to 85% of cases of adult-onset HSP, with a 30% risk for progression to renal insufficiency.⁶² It has been reported that patients older than 20 years with gastrointestinal involvement at onset and persistent eruption are more likely to progress to renal disease.^{63,64}

Genitourinary involvement

Orchitis occurs in 10% to 20% of boys with HSP and may mimic testicular torsion.^{15,50} There are also single reports of ureteral stenosis in patients with HSP.⁶⁵

Neurologic involvement

Neurologic involvement has been reported in 1% to 8% of children and affects mostly those with either severe kidney disease or uncommon features.^{66,67} Central nervous system dysfunction results from vascular obstruction, intracerebral hemorrhage, or severe hypertension.⁶⁸ Possible neurologic findings include headache, altered level of consciousness, seizures, focal neurologic deficits, visual abnormalities, verbal disability, peripheral neuropathy, and facial palsy.^{66,67}

Pulmonary involvement

Although pulmonary hemorrhage is a very rare complication of HSP, especially in children, it is associated with high morbidity and mortality. Clinical symptoms of pulmonary hemorrhage include hemoptysis, dyspnea, chest pain, and anemia.^{69,70}

Malignancy

HSP has been associated with malignancy, most commonly with solid tumors in adult patients⁷¹ but not in children.

Pregnancy

Onset of HSP has been reported both during pregnancy and in the postpartum period. Establishing a diagnosis of HSP in pregnancy can be difficult because of the importance of distinguishing other vasculitides (skin involvement), obstetric emergencies, acute abdomen, labor (abdominal pain), and preeclampsia (nephritis). Women who had HSP as a child are more likely to have proteinuria or hypertension during pregnancy.⁶⁸

DIAGNOSIS

No specific laboratory test is available for the diagnosis of HSP. Moderate leukocytosis and mild anemia as a result of gastrointestinal bleeding can be identified in some children. Acute-phase reactants may be elevated. Urinalysis might reveal hematuria, proteinuria, or both. In patients with renal disease and urinary abnormalities, the degree of proteinuria should be defined and renal function tests should be performed. Stool should be examined for frank or occult blood.⁷² An increase in IgA is seen in 50% of cases, and circulating IgA-containing immune complexes may be present in some patients, but

TABLE 161.2

Laboratory features of Henoch-Schönlein purpura/IgA vasculitis

Investigations	Possible findings
Initial investigations	
Complete blood count	May reveal leukocytosis and/or anemia
Acute-phase reactions (erythrocyte sedimentation rate/C-reactive protein)	Normal or elevated
Urinalysis	Normal, hematuria, and/or proteinuria
Stool guaiac examination	Normal, positive
Secondary investigations (indicated according to clinical features and abnormal results of the above)	
Urine protein/creatinine	Normal, increased, nephrotic range
Renal functional tests	Normal, elevated creatinine, hypoalbuminemia
Plain abdominal supine radiograph and chest radiograph	Normal, air leak
Abdominal ultrasonography	Thickened bowel wall, intussusception
Tests for differential diagnosis	
Blood culture	Specific infections
Imaging procedures and relevant biopsies	To differentiate from PAN
Antineutrophil cytoplasmic antibody (ANCA)	ANCA-associated vasculitis
Antinuclear antibodies, anti-double-stranded DNA, complement 3	SLE, hypocomplementemic urticarial vasculitis
PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus.	

these findings are not specific for the diagnosis.^{45,72} Other laboratory studies are useful to exclude diseases that should be included in the differential diagnosis. Platelet number and clotting test results are normal. Serologic tests such as antinuclear antibodies and rheumatoid factor are negative, and C3 and C4 are normal and need not be studied for diagnosis.

Abdominal ultrasonography or computed tomography is the preferred diagnostic modalities for imaging intussusception in children with HSP because barium enemas may miss the ileoileal location.⁵² Ultrasonography may show asymmetric bowel wall thickening secondary to vasculitis involving the gastrointestinal system, mainly the jejunum and ileum.¹⁵ Scrotal ultrasonography could be helpful if scrotal involvement is suspected (Table 161.2).

Skin biopsy is helpful if the rash is atypical; it reveals leukocytoclastic vasculitis involving the capillaries and venules of the mid and upper dermis and, with direct immunofluorescent studies, shows perivascular deposition of IgA, C3, and fibrinogen in the affected vessel wall.^{15,73}

Indications for renal biopsy in children are (1) nephritic/nephrotic proteinuria; (2) raised creatinine, hypertension, or oliguria; (3) heavy proteinuria (urinary albumin-to-creatinine ratio persistently >100 mg/mmol) on an early morning urine sample at 4 weeks; (4) persistent proteinuria after 4 weeks; and (5) impaired renal function.^{45,74}

HSP/IgA vasculitis-associated nephritis is characterized by mesangial damage with different degrees of hypercellularity ranging from isolated mesangial proliferation to focal and segmental proliferation and severe crescentic glomerulonephritis. Mesangial diffuse IgA deposits are the hallmark of the disease. IgA1 is the dominant subclass. C3 is deposited in 75% to 85% of cases⁷⁶ (Figs. 161.2 and 161.3).

DIFFERENTIAL DIAGNOSIS

HSP/IgA vasculitis should be distinguished from acute hemorrhagic edema of infancy, immune thrombocytopenic purpura, hemolytic-uremic syndrome, systemic lupus erythematosus, disseminated intravascular coagulation, infections, hypersensitivity vasculitis, and other type of vasculitis.^{45,46} It should be borne in mind that the gastrointestinal symptoms can mimic a surgical abdomen, infectious enteritis, or inflammatory bowel disease in the absence of the characteristic rash (see Table 161.2).

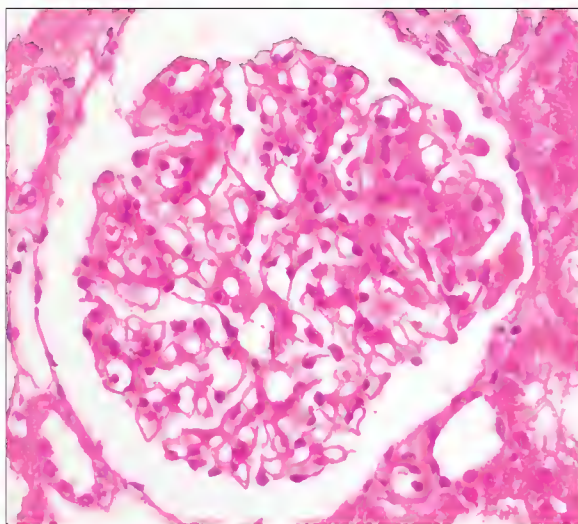


Fig. 161.2 Renal biopsy specimen showing segmental mesangial proliferation and expansion of the mesangial matrix.

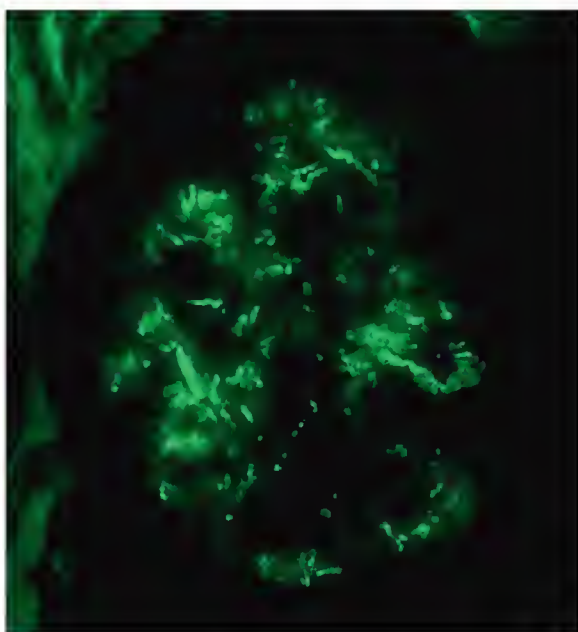


Fig. 161.3 Immunopathology—mesangial IgA deposition.

TREATMENT

Because HSP is a self-limited disease, the external manifestations of the disease are managed with appropriate symptomatic measures. For those with joint involvement and painful inflammatory soft tissue edema, analgesics such as acetaminophen and NSAIDs can be used (Table 161.3).⁷⁷⁻⁸⁴ To date, however, no study has examined the efficacy of NSAIDs for HSP. One should be aware of the gastrointestinal and renal side effects of these drugs, albeit rare in children.

The use of steroids is reserved for patients with gastrointestinal involvement. Prednisone is generally taken at dose of 1 mg/kg/day for 2 weeks, with weaning over the subsequent 2 weeks. However, in patients who need to be admitted to the hospital, steroids must be administered intravenously.⁸⁵ A randomized double-blind placebo-controlled study confirmed that short-term steroid therapy decreased the intensity and duration of gastrointestinal symptoms and the severity of joint symptoms.^{78,79}

Despite the lack of evidence-based data for the management of severe cutaneous lesions or extensive bullae in patients with HSP, steroid and dapsone are recommended therapies for these patients.⁸⁰ Scrotal and testicular involvement is another HSP manifestation that can benefit from a short-term course of steroids.^{5,86}

Severe or life-threatening disease is rare; however, if pulmonary or central nervous system involvement or the kidney disease is progressing

TABLE 161.3

Treatment of Henoch-Schönlein purpura/IgA vasculitis

Evidence-based recommendations	Evidence
Arthritis/arthralgia with NSAIDs	D
Severe skin bullous lesions with steroids	D
Gastrointestinal involvement with steroids	
Reduces the intensity of abdominal pain	B
Reduces the mean resolution time	A
Renal involvement	
Early prednisone treatment does not prevent renal disease	A
Moderate nephritis	
Prednisone, ACE inhibitors, tonsillectomy	D
Rapidly progressive glomerulonephritis	
Pulse and oral steroids, cyclophosphamide, azathioprine, MMF, cyclosporine, plasma exchange	D

ACE, angiotensin-converting enzyme; MMF, mycophenolate mofetil; NSAIDs, nonsteroidal antiinflammatory drugs.

Data from references 78 to 84.

rapidly, heavy immunosuppressive drugs and plasma exchange are indicated, just as for any severe systemic vasculitis.

Treatment of Henoch-Schönlein purpura-associated nephritis

Management of HSP nephritis is still controversial because we lack prospective, randomized controlled studies that have investigated the treatment of HSP in patients with renal involvement. Furthermore, it is difficult to interpret the efficacy of treatment because spontaneous recovery can occur in patients with severe initial findings. More importantly, long follow-up is required because late progression to chronic kidney disease can be seen in patients with mild symptoms.

We have a good level of evidence that the use of steroids early in the course of the disease does not prevent the development of nephritis.^{78,81-83} However, we lack such data for the treatment of kidney disease once it develops.

Moderate nephritis

This group would include patients with less than 50% crescents on renal biopsy, no renal failure, and the presence of heavy proteinuria. Zoffenalla and Fanos⁸⁴ reviewed the management of HSP nephritis and concluded that there was insufficient firm evidence to guide best practice in the management of HSP nephritis. Corticosteroids have been advocated for these patients either alone or in combination with immunosuppressive agents. Various treatment regimens have been proposed, including ACE inhibition, tonsillectomy, cyclophosphamide, and azathioprine.^{45,75,87,88} In view of the similarities with IgA nephropathy, ACE inhibitors should be prescribed for all patients with persistent proteinuria.⁸⁹

Rapidly progressive glomerulonephritis

More than 50% crescents and heavy proteinuria are poor prognostic factors for HSP/IgA vasculitis-associated nephritis, and therefore treatment is aimed at preventing long-term morbidity in high-risk patients. Although we lack well-designed controlled studies for such patients, intensive therapy should be considered, including steroids and cyclophosphamide with or without plasma exchange.^{90,91} A recent study failed to show additional benefit of cyclophosphamide in adults with severe HSP over steroids alone.⁹² However, more prospective data are needed. Other options recommended for the treatment of severe HSP nephritis are cyclosporine, azathioprine, and mycophenolate mofetil.⁹³⁻⁹⁵ Very rare case reports suggest the use of rituximab for resistant cases.⁹⁶

Renal transplantation

IgA mesangial deposition frequently recurs after renal transplantation, even though recurrence of the clinical symptoms of HSP is unusual. The disease status of the recipient and other factors may affect IgA production and its deposition in the newly grafted kidney.⁷⁶ Although risk for recurrence had been reported to be as high as 35% and risk for graft loss secondary to recurrence to be 11%,⁹⁷ Kanaan and colleagues⁹⁸ found recurrence rates to be lower than previously reported. The actuarial risk for recurrence in a first

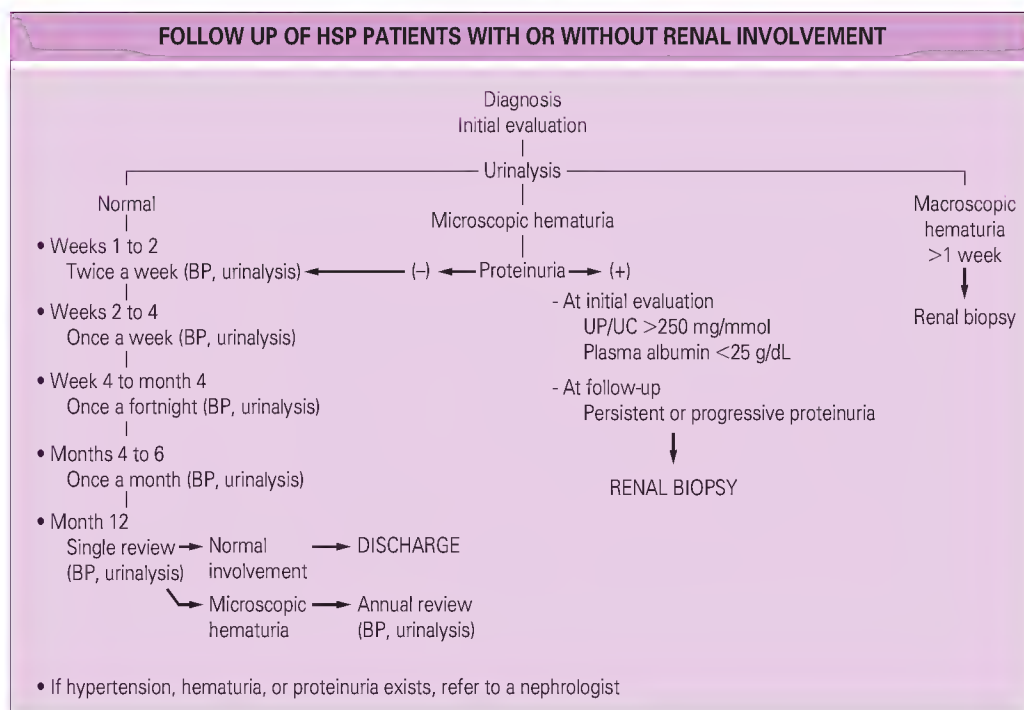


Fig. 161.4 BP, blood pressure; UC, urinary creatinine; UP, urinary protein.

graft was 11%, and the risk for graft loss as a result of recurrence was 7.5% at 10 years.

OUTCOME AND PROGNOSIS

If severe gastrointestinal or renal complications are not present, HSP/IgA vasculitis is a self-limited disorder. The duration of the disease is less than 14 days in approximately a third of patients, 2 to 4 weeks in a third, and longer than 4 weeks in the remaining third.^{99,100} Patients should be described as having prolonged disease if the symptoms persist for longer than 12 weeks.^{15,49} A variety of infections can precipitate HSP. Recurrence develops in around a third of cases, generally within 4 months of resolution of the symptoms.¹⁰¹

The prognosis is good for most children. Gastrointestinal involvement causes early morbidity, whereas renal disease causes late morbidity. In general, patients with microscopic hematuria have an excellent prognosis.⁵⁷ Nephritis complicated by nephrotic syndrome, a histologic finding of crescents in more than 50% of glomeruli on renal biopsy, and heavy proteinuria during follow-up were associated with a poor prognosis.^{46,101,102} A multicenter study of 443 patients with HSP/IgA nephritis from Turkey reported

that although all the patients in whom end-stage renal disease developed (1.1%) had nephritic-nephrotic syndrome at initial evaluation, logistic regression analysis did not show any association of the initial symptoms and histology with outcome.¹⁰³ Thus, although heavy proteinuria and deterioration of renal function seem to affect the outcome adversely, we lack evidence-based data for clinical or biopsy findings to serve as precise predictors of the ultimate outcome in all patients. On the other hand, Narchi⁵⁷ reviewed 12 studies that included 1133 children, which provided important data on the subject. Renal impairment occurred in 1.6% of those with isolated urinary abnormalities and in 19.5% of those in whom nephritic or nephrotic syndrome had developed. Thus patients with nephrotic proteinuria need to be treated and monitored closely. Patients with microscopic hematuria should be assessed annually because of the possibility of late renal deterioration. Narchi⁵⁷ recommended that because no long-term renal impairment occurred if the findings on urinalysis were normal, there is no need for follow-up after the first 6 months in those whose urinalysis results remain normal. A practical pathway to guide patients with renal involvement is presented in Figure 161.4. It has been recommended that patients with normal findings on urinalysis undergo follow-up for at least 1 year. Patients who have had clinical nephritis should be monitored closely for at 5 five years, and those with significant proteinuria or deteriorating renal function should undergo biopsy.

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162

Cutaneous vasculitis and panniculitis

■ JEFFREY P. CALLEN ■ LUIS REQUENA

- Cutaneous vasculitis is characterized by polymorphonuclear inflammation of small to medium-sized vessels in the skin. Although circulating immune complexes are involved in its pathogenesis, a complex interaction of cytokines and vasoactive amines with endothelial cells is necessary for disease expression.
- Panniculitis represents an inflammation within adipose tissue, most commonly the subcutaneous fat, and is classified as septal, lobular, or mixed form.
- A variety of associated systemic diseases and clinical syndromes occur in patients with vasculitis or panniculitis.
- Therapy depends on the severity of the disease and the presence of systemic involvement or associated conditions.

CLASSIFICATION

Vasculitis

Many classification systems have been proposed for all forms of vasculitis, beginning with that of Pearl Zeek in the 1950s and extending most recently to those of the American College of Rheumatology and the Chapel Hill Consensus Conference.¹ Unfortunately, most of these systems do not satisfy the needs of dermatologists because small-vessel disease may occur in many of the entities.² Therefore the presence of dermatologic features such as palpable purpura, urticarial lesions, nodules, ulcers, or livedo reticularis with histologic evidence of leukocytoclastic vasculitis (LCV) indicates the likelihood that a vasculitic process will affect the skin and possibly internal organs.

Panniculitis

Panniculitis is defined as an inflammatory reaction affecting the subcutaneous tissue, which consists primarily of fat. The panniculitides are traditionally divided into four categories based on histopathologic criteria (Box 162.1): (1) mostly septal panniculitis without vasculitis, (2) mostly septal panniculitis with vasculitis, (3) mostly lobular panniculitis without vasculitis, and (4) mostly lobular panniculitis with vasculitis.³

Erythema nodosum is primarily a septal panniculitis without vasculitis that is a reactive process secondary to a variety of underlying disorders, most commonly sarcoidosis, infections, or exposure to certain drugs. Weber-Christian disease is a lobular panniculitis, but this term is outmoded because many of the patients so described have been found to have an associated abnormality such as pancreatic disease or factitial disease.

PATHOLOGIC, CLINICAL, AND SYSTEMIC FEATURES

Cutaneous vasculitides

The lesions observed in patients with cutaneous vasculitis can vary from transient urticaria-like lesions to necrosis of wide areas of skin.² The type of lesion, in general, reflects the size of the vessel involved and thus varies somewhat with the specific vasculitic syndrome. The most common

cutaneous findings in patients with vasculitis is palpable purpura (Fig. 162.1), followed by urticaria-like lesions.

Histopathologic features

Histopathologically, in the cutaneous lesions of either palpable purpura or urticaria-like lesions there is involvement of the postcapillary venules of the superficial plexus, which demonstrate necrosis of endothelial cells, fibrin deposits with the vessel walls, extravasation of erythrocytes, and infiltration of neutrophils, including their breakdown, with leukocytoclasia manifested as the presence of nuclear dust (Fig. 162.2). In some patients, eosinophils might also be present in the infiltrate, which might indicate that the disease is drug induced.⁴

Palpable purpura

The development of palpable purpura is dynamic, often beginning as non-palpable purpura. As the process progresses, some lesions become papular, nodular, bullous, infarctive, or ulcerative.⁵ The lesions fade as the reparative processes begin. These lesions most frequently occur on dependent surfaces, such as the legs. Palpable purpura is characterized by smooth, discrete papules with relatively uniform lesional hemorrhage. When the lesions are arranged in a retiform (netlike) pattern and are superficial purpuric plaques with multifocal areas of hemorrhage and necrosis, an immunoglobulin A–associated vasculitis may be more common (Fig. e162.1).⁶ The lesions of vasculitis can, on occasion, become generalized.

Urticarial lesions

Urticarial lesions of vasculitis are the second most common cutaneous manifestation (Fig. 162.3). These lesions differ from those of common urticaria, which is associated with transient pruritic lesions that last for no longer than several hours and resolve without any residual alteration, in the following ways: the individual lesions are most often long-lived, lasting between 6 and 72 hours; the lesions may resolve with some residual pigmentation or ecchymosis (Fig. 162.4); the lesions are often characterized by pain or burning rather than pruritus; and the patients tend to have symptoms or signs of multisystem disease, such as arthralgia, fever, gastrointestinal pain, lymphadenopathy, or abnormal urine sediment. The lesions of urticarial vasculitis are usually generalized. Demonstration of the long-lived nature of these lesions can be achieved by circling several lesions and evaluating them for the onset of resolution.

Other cutaneous lesions

A wide array of other cutaneous lesions can also occur, including erythematous plaques, erythema multiforme-like lesions, annular lesions, nodules, ulcerations (Fig. e162.2), necrosis, and livedo reticularis. Table 162.1 lists the varying, yet overlapping, cutaneous manifestations that occur in the traditional vasculitic syndromes. The occurrence of palpable purpura, the hallmark of LCV, in all syndromes except large-vessel vasculitis has resulted in some of the controversy surrounding the classification.

Systemic manifestations

The systemic manifestations correlate with the syndrome and the size of the vessel involved (Box 162.2). This section focuses on small-vessel vasculitis. Henoch-Schönlein purpura is considered in Chapter 161, and polyarteritis nodosa, granulomatosis with polyangiitis (Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) are covered in Chapters 155 and 157.

The most common systemic manifestation of vasculitis is involvement of organs with a rich vascular supply, such as the gut, the kidneys, the lungs, and the musculoskeletal system. In a study of 82 patients selected for





Fig. e162.1 Retiform purpuric plaques in a patient with immunoglobulin A-associated vasculitis.



Fig. e162.2 Leukocytoclastic vasculitis with ulceration in a patient with rheumatoid arthritis.

BOX 162.1 CLASSIFICATION OF THE PANNICULITIDES**Mostly septal panniculitis without vasculitis**

- Erythema nodosum
- Vilanova disease: subacute nodular migratory panniculitis

Mostly lobular panniculitis without vasculitis

- Idiopathic neutrophilic panniculitis
- Subcutaneous fat necrosis of the newborn
- Postcorticosteroid panniculitis
- Calcifying panniculitis
- Pancreatic panniculitis
- α_1 -Antitrypsin deficiency
- Physical or factitial panniculitis
- Histiocytic cytophagic panniculitis
- Lipodystrophy syndromes
- Connective tissue panniculitis
- Subcutaneous panniculitis–like T-cell lymphoma
- Sclerosing panniculitis: lipodermatosclerosis

Mixed panniculitis

- Lupus profundus: lupus erythematosus panniculitis
- Erythema nodosum–like lesions of Behçet syndrome

Panniculitis with vasculitis

- Small-vessel vasculitis (postcapillary venule), also known as *leukocytoclastic vasculitis*
- Medium-sized-vessel vasculitis (arterioles or small arteries): *polyarteritis nodosa*
- Erythema induratum, also known as *nodular vasculitis*



Fig. 162.1 Palpable purpura representing a small-vessel vasculitis that on histopathologic study was shown to be a leukocytoclastic vasculitis.

cutaneous LCV, only about 50% had any systemic manifestations that were clinically evident, and in general this group of patients had involvement that was not life threatening.⁷ Similarly, Blanco and colleagues⁸ found that in a majority of patients with cutaneous vasculitis the disease had a relatively benign course. However, their data for adults differed from those for children.

Vasculitic syndromes with prominent cutaneous disease**Acute hemorrhagic edema of infancy**

Acute hemorrhagic edema of infancy is a rare condition that occurs in infants younger than 2 years of age.⁹ It has an acute onset, often following an upper respiratory tract infection or drug ingestion. The rash begins as urticarial plaques but rapidly becomes intensely purpuric (Fig. e162.3), frequently with annular lesions. Fever and generalized edema are common. Acute hemorrhagic edema of infancy has been distinguished from Henoch-Schönlein purpura by clinical and immunologic differences.

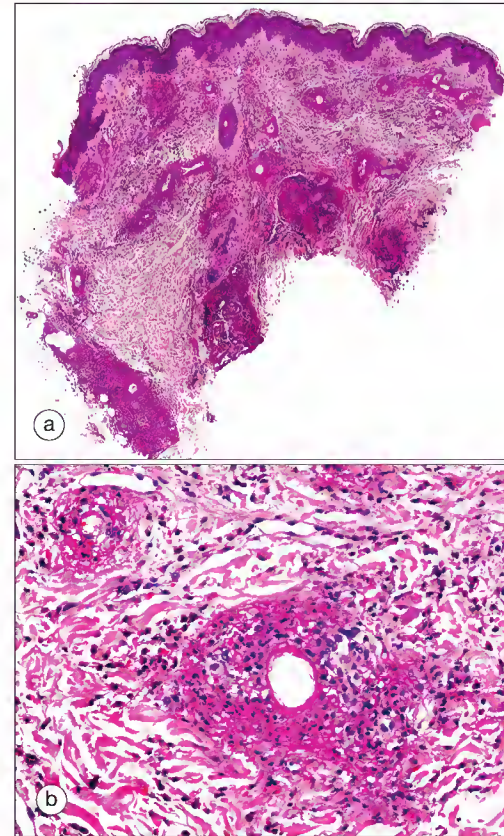


Fig. 162.2 Leukocytoclastic vasculitis. (a) Inflammatory reaction surrounding the small dermal vessels. (b) Fibrinoid necrosis of the vessel wall with a neutrophilic infiltrate; leukocytoclasia is present.



Fig. 162.3 Hypocomplementemic urticarial vasculitis.

Hypocomplementemic urticarial vasculitis

McDuffie and coworkers¹⁰ first described hypocomplementemic urticarial vasculitis when they reported on four patients with recurrent attacks of erythematous urticarial and hemorrhagic skin lesions associated with synovitis and, sometimes, abdominal distress. Their patients did not have lupus erythematosus or paraproteinemia but did have hypocomplementemia; two had nephritis.

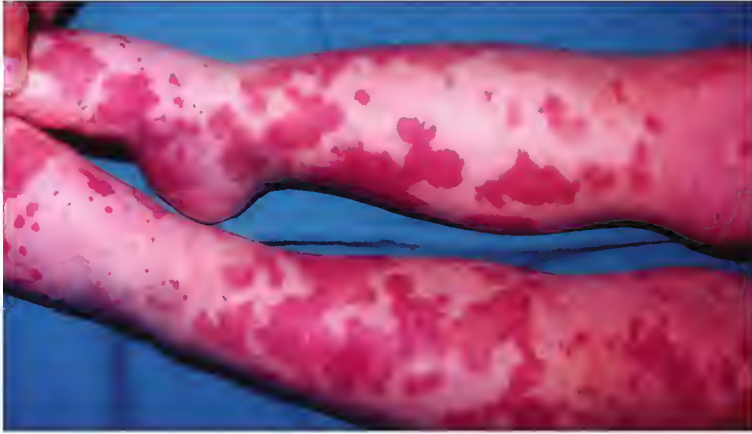


Fig. e162.3 Acute hemorrhagic edema of infancy. In this patient palpable purpura is accompanied by edema of the legs.



Fig. 162.4 Residual bruising evident in a patient with urticarial vasculitis.

TABLE 162.1

Relationship between vasculitic syndrome and its predominant cutaneous manifestation

Clinical syndrome	Predominant cutaneous morphology
Leukocytoclastic vasculitis	Palpable purpura
Henoch-Schönlein purpura	Retiform purpuric plaques
Hypocomplementemic urticarial vasculitis	Urticarial lesions of long duration that resolve with purpura or ecchymosis
Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)	Ulcerative nodules, palpable purpura, peripheral gangrene
Polyarteritis nodosa	Subcutaneous nodules, livedo reticularis, ulcerations, peripheral gangrene

BOX 162.2 SYSTEMIC DISEASES ASSOCIATED WITH LEUKOCYTOCLASTIC VASCULITIS (SMALL-VESSEL VASCULITIS)

Other vasculitic syndromes: Granulomatosis with polyangiitis, polyarteritis nodosa, microscopic polyarteritis

Rheumatic disorders: Systemic lupus erythematosus, rheumatoid arthritis, idiopathic inflammatory myopathy, Sjögren syndrome

Infections: Hepatitis C virus infection, hepatitis B virus infection, human immunodeficiency virus infection, infection with β -hemolytic streptococci, subacute bacterial endocarditis

Paraprotein disorders: Cryoglobulinemia (usually mixed, often hepatitis C virus related), macroglobulinemia, hyperglobulinemia

Other disorders: Inflammatory bowel disease, neoplasia (hairy cell leukemia, lymphoma, or rarely solid tumors), cystic fibrosis, bowel bypass syndrome, deficiency of the second component of complement, α_1 -antitrypsin deficiency

Urticarial lesions may also be an early clinical manifestation of lesions that become typical palpable purpura. The spectrum of urticarial vasculitis has also grown, in recent years, to include the presence of lung manifestations characterized by asthma or obstructive lung disease.¹¹ Patients with hypocomplementemic urticarial vasculitis often have or develop obstructive disease, whereas most patients with normal complement levels, chronic urticaria, and vasculitis have little or no systemic involvement.¹²

Vasculitis associated with paraproteinemia

Almost any clinical lesion, from urticarial lesions through palpable purpura to necrosis and ulceration, can occur in patients with an abnormal circulating protein. In patients with cryoglobulins there may be a predilection for acral disease affecting the toes, fingers, ears, and nose; otherwise these patients have lesions and distributions similar to those of patients without a paraprotein. The presence of a paraproteinemia in patients with vasculitis has therapeutic implications; thus almost all patients with chronic or recurrent cutaneous vasculitis should undergo evaluation for a paraprotein, including testing for cryoglobulins and immunofixation electrophoresis. In many of the patients with mixed cryoglobulinemia, a link with hepatitis C virus infection has been noted.¹³ These patients may have noninflammatory occlusive disease or a small-vessel vasculitis. Treatment with interferon

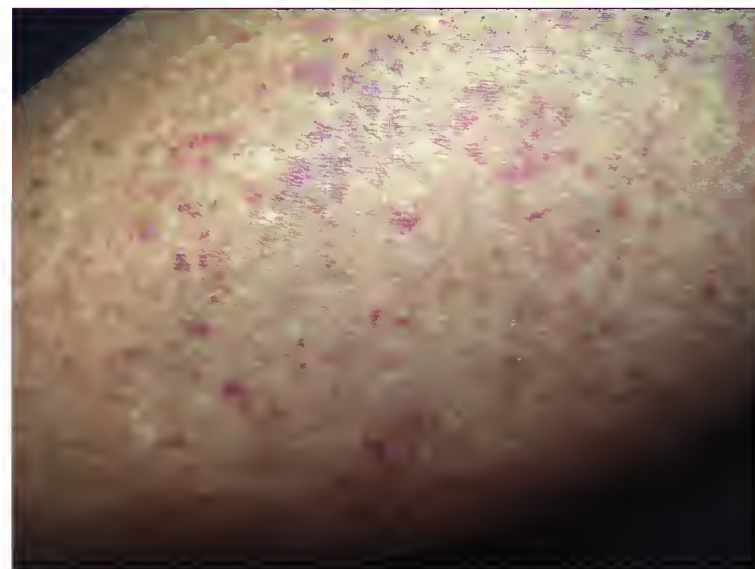


Fig. 162.5 Nonpalpable lesions of hyperglobulinemic purpura in Waldenström hypergamma globulinemia.

alfa-2a and/or ribavirin with or without rituximab has led to disease control in many of these patients.¹⁴

Hyperglobulinemic purpura has been separated from other vasculitides¹⁵ because some of the lesions of hyperglobulinemic purpura are nonpalpable (Fig. 162.5) and do not reveal LCV on biopsy. However, this may indicate that these lesions are early or late manifestations, and in the authors' experience, if the skin biopsy is timed appropriately, the specimens usually reveal LCV. Hyperglobulinemic purpura has recently been associated with Sjögren syndrome and lupus erythematosus. These patients commonly demonstrate the anti-Ro (anti-SS-A) antibody.

Paraneoplastic vasculitis

Cutaneous or systemic vasculitis, or both, have been reported on several occasions in patients who have or have had malignancies.¹⁶ Sanchez-Guerrero and colleagues¹⁷ reported that 11 of a series of 222 patients newly diagnosed with vasculitis of any form had what was judged to be "paraneoplastic vasculitis." In most of these patients (9 of 11), the vasculitis was limited to the small cutaneous vessels and was histologically characterized as LCV. In 3 patients, the vasculitis was the presenting manifestation of neoplasia (squamous cell carcinoma of the esophagus, T-cell lymphoma, and myeloblastic leukemia). A recent report from Northwest Spain^{17b} suggested that the incidence of malignancy is perhaps as high as 3.8% of adult patients.

The occurrence of solid organ malignancies with cutaneous vasculitis has been considered to be rare. However, Podjasek and coworkers¹⁸ identified a group of 17 such patients seen at the Mayo Clinic over a 14-year period. These patients were found through a review of 812 charts, which represents something around a 2% occurrence rate. The vasculitis occurred before the malignancy in 3 patients, concurrently in 3 patients, and after the malignancy in 11 patients. It was not clear from their report whether a paraneoplastic course occurred in any patient. Many of the patients were treated with prednisone and some were treated with immunosuppressive or cytotoxic agents, often successfully.

The mechanisms underlying paraneoplastic vasculitis are unknown. The vasculitis can at times be directly related to tumor treatment, but in many cases the occurrence appears to be coincidental. The exact incidence of neoplasia with vasculitis is not known, and thus extensive evaluation for malignancy cannot be recommended; unexplained symptoms, however, should be investigated. Lymphoreticular malignancies—in particular, hairy cell leukemia and non-Hodgkin B-cell lymphoma—have been the most frequently reported type of neoplasia, but a wide variety of solid tumors also have occurred in patients with vasculitis.^{16,19}

Cutaneous polyarteritis nodosa

Cutaneous polyarteritis nodosa is characterized clinically by nodules, livedo reticularis, ulcerations, or a combination of these lesions (Fig. 162.6).^{20,21} Histopathologically, the lesions are characterized by LCV of the arterioles, often in the subcutaneous tissue, occasionally with a surrounding panniculitis (Fig. 162.7). The nodular lesions must be differentiated from erythema nodosum or other panniculitides. Livedo reticularis can occur with thrombotic disorders of several causes, including acquired disorders such as

antiphospholipid antibody syndrome and inherited thrombophilic disorders including factor V Leiden mutation and methylenetetrahydrofolate reductase polymorphisms. Cutaneous polyarteritis nodosa is generally associated with a good prognosis, but patients with ulcerations tend to have neuropathy more frequently.²¹ A variety of systemic disease associations, including inflammatory bowel disease, rheumatoid arthritis, and paraproteinemia, have been reported in patients with cutaneous polyarteritis nodosa. The cutaneous and systemic forms of polyarteritis nodosa have been linked to exposure to several drugs, including propylthiouracil use and the prolonged use of minocycline.²² Systemic polyarteritis nodosa may manifest skin lesions similar to those of the cutaneous form but shows involvement of muscular arteries in other organs. A more detailed discussion of systemic polyarteritis nodosa is provided in Chapter 155.

Erythema elevatum diutinum

Erythema elevatum diutinum is a rare form of LCV that has its major manifestation in the skin.²³ The lesions begin as red-purple or yellow papules that coalesce to form plaques. The most prominent involvement occurs on the extensor surfaces, such as the knees, elbows, and dorsa of the hands (Fig. 162.8). The only systemic manifestation is arthralgia, which occurs in 20% to 40% of patients. Some of the patients with erythema elevatum diutinum are found to have an immunoglobulin A paraprotein. Histopathologically, the characteristic finding of concentric perivascular fibrosis around the involved vessels is found in longstanding lesions.

Cutaneous vasculitis in patients with rheumatic diseases

Cutaneous vasculitis, as manifested by palpable purpura, urticarial lesions, or ulcerations, is commonly observed in systemic lupus erythematosus,

rheumatoid arthritis, and Sjögren syndrome. The appearance of cutaneous vasculitis is usually associated with active systemic disease.

Cocaine/levamisole-associated vasculitis/vasculopathy syndrome

A recent “epidemic” of vasculitis/vasculopathy syndrome related to the use of levamisole as an adulterant for cocaine has been seen at various medical centers and reported in the medical literature.²⁴ These patients have acral necrotic/purpuric lesions and may have widespread necrotizing livedo or ulcers (Fig. 162.9) along with positivity for perinuclear antineutrophil cytoplasmic antibodies and antiphospholipid antibodies, leukopenia, and thrombocytopenia. Patients have findings of LCV as well as an occlusive vasculopathy on biopsy. Recovery occurs with cessation of levamisole use but recurs if the patient begins to use the product again. The pathogenesis of this process is not understood.

Panniculitides

Erythema nodosum

Erythema nodosum (EN) is a relatively common process that is usually acute and self-limited. The typical clinical presentation is the sudden onset of one or more tender, erythematous nodules on the anterior legs that are more easily palpated than visualized (Fig. 162.10). The eruption is often preceded by a prodrome of fever, malaise, and/or arthralgias. As the lesions age they may develop an ecchymotic appearance. Over a 4- to 6-week period they eventually heal without scar formation. Ulceration of the primary process is rare. Although EN is usually an acute process, patients with chronic or recurrent disease have been described using terms such as *chronic EN*, *EN migrans*, *subacute nodular migratory panniculitis* (Vilanova disease), or *septal granulomatous panniculitis*. Chronic or recurrent EN most commonly occurs in middle-aged women. The disease is often present for several years and is most common on the legs.

Biopsy of characteristic acute lesions is usually not needed to confirm a diagnosis but, when performed, specimens reveal a predominantly septal panniculitis without vascular inflammation but with scattered radial Miescher granulomas within the connective tissue septa. The presence of the granulomas might be predictive of an associated granulomatous disease such as sarcoidosis.

Causative or associated conditions are present in about 50% of patients with EN.²⁵ The associated conditions can be divided into three broad categories: infections, drug exposures, and systemic diseases (usually inflammatory disorders). A partial list of the known associations is given in Box 162.3. The infectious agents associated with EN tend primarily to affect the respiratory or gastrointestinal tract and are most often bacterial or fungal. The drugs most commonly associated with EN are antibiotics and oral contraceptives. Pregnancy, particularly in its second trimester, is a known association, and the EN will recur with subsequent pregnancies or with the administration of oral contraceptives. EN-like lesions may occur in Behçet disease and are accompanied by oral and genital ulcerations, pathergy, uveitis, and/or central nervous system disease or other systemic manifestations. A specific variant of sarcoidosis associated with EN is known as *Löfgren syndrome*.^{25,26} This disorder is an acute, self-resolving process in which EN occurs with bilateral hilar lymphadenopathy, arthritis, and



Fig. 162.6 Cutaneous polyarteritis. Retiform necrosis with background livedo reticularis.

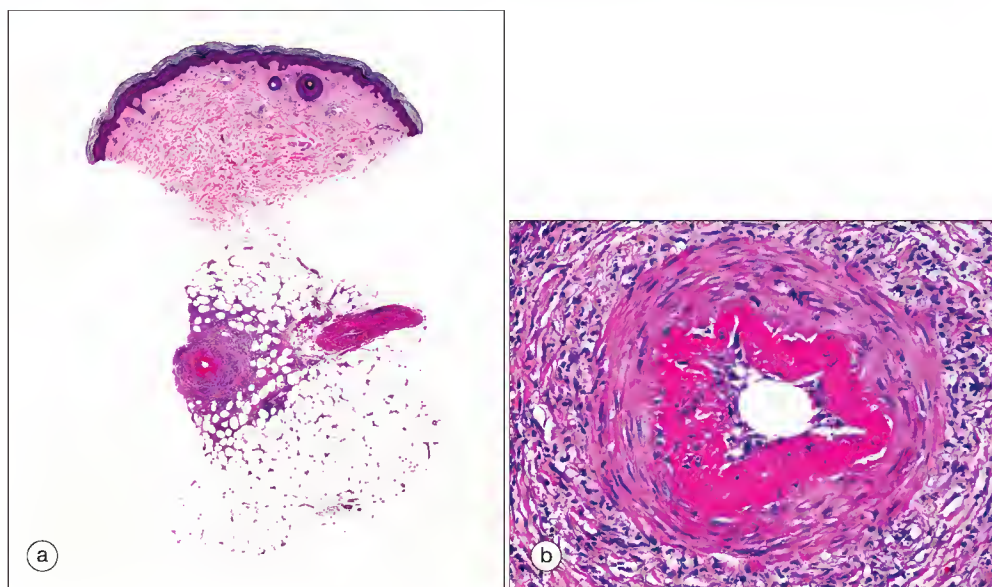


Fig. 162.7 (a) Cutaneous polyarteritis nodosa. Note that the vessel involved is in the subcutaneous tissue. It is imperative to perform a biopsy that is deep enough to sample the subcutaneous tissue in such patients. (b) Close-up of the affected vessel revealing vessel wall destruction with intimal proliferation and surrounding inflammatory reaction.



Fig. 162.8 Erythema elevatum diutinum.



Fig. 162.9 Reticulated necrotizing purpura in a patient with vasculitis/vasculopathy syndrome induced by levamisole-contaminated cocaine. (a) Shoulder lesions. (b) Acral lesions on the ears.

anterior uveitis. Granulomatous colitis (Crohn disease), regional enteritis, and ulcerative colitis have been associated with EN.²⁷ In patients with inflammatory bowel disease, it appears that the EN parallels the activity of the bowel disorder. At least half of cases of EN are not found to have an associated or underlying process.

Idiopathic neutrophilic lobular panniculitis

Idiopathic neutrophilic lobular panniculitis was formerly known as *Weber-Christian disease* (WCD). Thus in the past a diagnosis of WCD would be given when patients had multiple recurrent subcutaneous nodules with



Fig. 162.10 Erythema nodosum secondary to acute sarcoidosis.

BOX 162.3 SOME CAUSES OF AND ASSOCIATIONS WITH ERYTHEMA NODOSUM

Infections

- Streptococcal pharyngitis
- Tuberculosis
- Valley fever (coccidioidomycosis)
- Blastomycosis
- Histoplasmosis
- Psittacosis
- *Yersinia* colitis
- *Salmonella* gastroenteritis
- Cat-scratch fever
- Leprosy

Systemic diseases

- Sarcoidosis
- Inflammatory bowel disease
- Collagen vascular disorders: dermatomyositis, lupus erythematosus, scleroderma
- Malignancy (rare)
- Sweet syndrome
- Behçet disease

Pregnancy

Idiopathic

Drugs

- Antibiotics: penicillin, sulfonamides
- Birth control pills

accompanying fever and a biopsy specimen that revealed a lobular panniculitis with an early neutrophilic infiltrate with fat degeneration, foamy histiocytes, and giant cell formation. However, increasingly, many such patients are found to have other disease associations, and the number of patients with WCD has progressively decreased. White and Winkelmann²⁸ suggest that when patients with WCD are observed, many can be reclassified as having another panniculitic syndrome.

α_1 -Antitrypsin deficiency-associated panniculitis

Not infrequently, patients with panniculitis have a deficiency of α_1 -antitrypsin. Thus, in a study of 96 patients, Smith and associates²⁹ found 15 patients with such deficiency. These patients were more likely to have ulceration and drainage and correspondingly had greater amounts of fat necrosis and elastic tissue destruction. It was suggested that induction of lesions by trauma was more likely in these patients, and thus débridement should be avoided in such patients. They should also be evaluated for pulmonary and liver disease and counseled to avoid smoking; treatment with α_1 -proteinase inhibitor concentrate may be helpful.

Pancreatic panniculitis

Patients with pancreatic diseases may develop subcutaneous fat necrosis (lobular panniculitis) (Fig. e162.4) with accompanying polyarthritides and osseous intramedullary fat necrosis. A variety of pancreatic pathologic changes have been implicated in the development of this process, including pancreatitis, pancreatic carcinoma (acinar cell), pancreatitis secondary to





Fig. e162.4 Pancreatic panniculitis manifesting as erythematous tender nodules on the anterior legs.

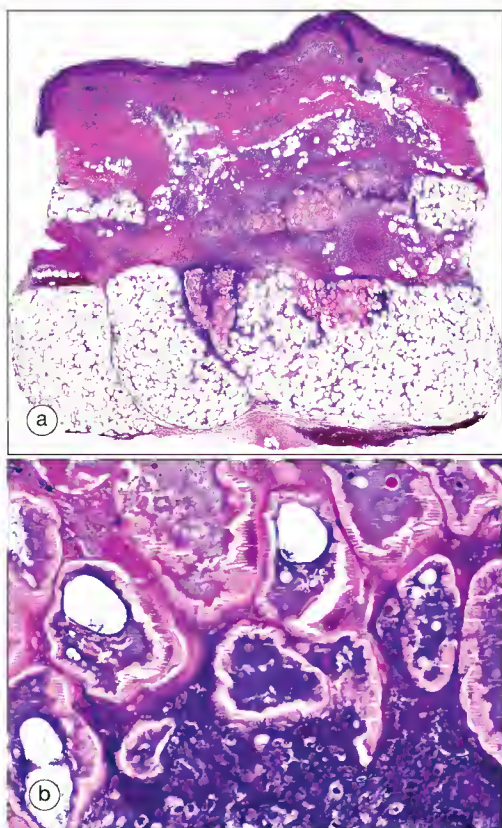


Fig. 162.11 Pancreatic panniculitis with extensive necrosis and ghost lipocytes.

cholelithiasis, posttraumatic lesions, pancreatic ischemia, pancreatic pseudocyst, and pancreas divisum (a congenital pancreatic abnormality).³⁰⁻³² The pathogenesis of pancreatic panniculitis is not well understood. It is possible that pancreatic enzymes directly destroy fat and that the inflammation follows, as demonstrated by Dhawan and associates³⁰; however, elevations of pancreatic enzymes, particularly lipase, do not occur in all pancreatic diseases that have been associated with pancreatitis. Histopathologically, there is extensive fat necrosis with a basophilic alteration of lipocytes (Fig. 162.11). Ghost cells with absent nuclei are also common.

Calcifying panniculitis of renal failure

Patients with renal failure often have abnormal calcium and phosphorus metabolism. These patients may develop acute, erythematous, tender, indurated nodules as a manifestation of calciphylaxis, more recently termed *calcific uremic arteriopathy*.³³ The panniculitis lesions can progress to necrosis (Fig. 162.12) and ulceration. The prognosis is poor, and treatment should consist of attempts to correct the calcium-phosphorus imbalance. Parathyroidectomy with or without renal transplantation may be helpful. Recently the use of intravenous sodium thiosulfate or oral cinacalcet has been reported to be of benefit in individual patients and small case series.³⁴

Poststeroid panniculitis

Panniculitis after withdrawal of corticosteroid therapy is a rare entity that seems to be limited to children.³⁵ Patients have been treated with corticosteroids for a wide array of problems, including leukemia, nephrotic syndrome, rheumatic carditis, and encephalopathy. Interestingly, the panniculitis may clear on readministration of the corticosteroids. The pathogenesis of this rare complication is not understood. The histopathologic features of this condition are identical to those of subcutaneous fat necrosis of the newborn, which is characterized by needle-shaped crystals within a histiocytic infiltrate.

Lipoatrophic panniculitis

Several conditions have been described in children that often result in lipoatrophy after the inflammatory reaction. There exists a spectrum that perhaps includes lipogranulomatosis subcutanea (previously known as *Rothman-Makai syndrome*), lipoatrophic panniculitis, lipophagic panniculitis of childhood, subcutaneous fat necrosis of the newborn, and localized lipoatrophy (atrophic connective tissue disease panniculitis).³⁶ These children tend to have multiple erythematous lesions, most commonly on the extremities, that resolve with subcutaneous atrophy. The patients often also



Fig. 162.12 Calcific uremic arteriopathy (calciphylaxis). This patient has a reticulated necrosis.

manifest fever. They may have associated autoimmune phenomena, such as juvenile rheumatoid arthritis, Hashimoto thyroiditis, or diabetes mellitus. There is no known effective therapy, although some patients have responded to oral corticosteroids, oral antimalarial agents, or oral dapsone.

Histiocytic cytophagic panniculitis/subcutaneous panniculitis-like T-cell lymphoma

Histiocytic cytophagic panniculitis was described by Crotty and Winkelmann³⁷ as a chronic histiocytic disease of the subcutaneous fat, with accompanying inflammatory panniculitis, fever, serositis, and "reticuloendotheliomegaly." Craig and coworkers³⁸ have suggested that there are two, perhaps distinct, patterns of disease: one that is benign and is termed *cytophagic histiocytic panniculitis* and one that is malignant and is termed *subcutaneous T-cell lymphoma*. In both instances the hemophagocytic syndrome may occur, but in cytophagic histiocytic panniculitis there is often a response to prednisone and/or cyclosporine. Some of these patients perhaps have Epstein-Barr virus within their lesions. There are some patients who initially appear to have a connective tissue panniculitis, but with time it becomes evident that the correct diagnosis is subcutaneous panniculitis-like T-cell lymphoma.³⁹⁻⁴³ The World Health Organization has recently reclassified subcutaneous panniculitis-like T-cell lymphoma into those with an $\alpha\beta$ T-cell subtype and those with a $\gamma\delta$ phenotype. The $\alpha\beta$ subtype, when it occurs without an associated hemophagocytic syndrome, appears to be steroid responsive and to have an indolent course.⁴⁴ Therefore the diagnosis of subcutaneous panniculitis-like T-cell lymphoma should be reserved only for subcutaneous T-cell lymphomas with CD3+, CD4-, CD8+, and β F1+ immunophenotype ($\alpha\beta$ T-cell subtype).

Lupus erythematosus panniculitis (lupus profundus)

Lupus erythematosus panniculitis (LEP) is a rare cutaneous manifestation of lupus erythematosus (LE) occurring in 1% to 3% of patients with LE.^{45,46} The lesions are tender, red-blue, subcutaneous nodules that may eventually ulcerate. They tend to occur on the face (Fig. 162.13), upper arms, thighs, and/or buttocks. The lesions may underlie a typical lesion of discoid LE. Histopathologic changes include a panniculitis that is both lobular and septal (Fig. 162.14). When the overlying epidermis and/or dermis demonstrate changes of LE, the diagnosis of LEP can be histologically confirmed. The activity of the panniculitic lesion does not seem to follow the course of the systemic disease.

Sclerosing panniculitis (lipodermatosclerosis)

Jorizzo and colleagues⁴⁷ coined the term *sclerosing panniculitis* to describe panniculitis with well-circumscribed, indurated, inflammatory plaques of the lower extremity; others have used the term *lipodermatosclerosis* to



Fig. 162.13 Lupus erythematosus panniculitis manifesting as multiple atrophic, calcified lesions on the arm.

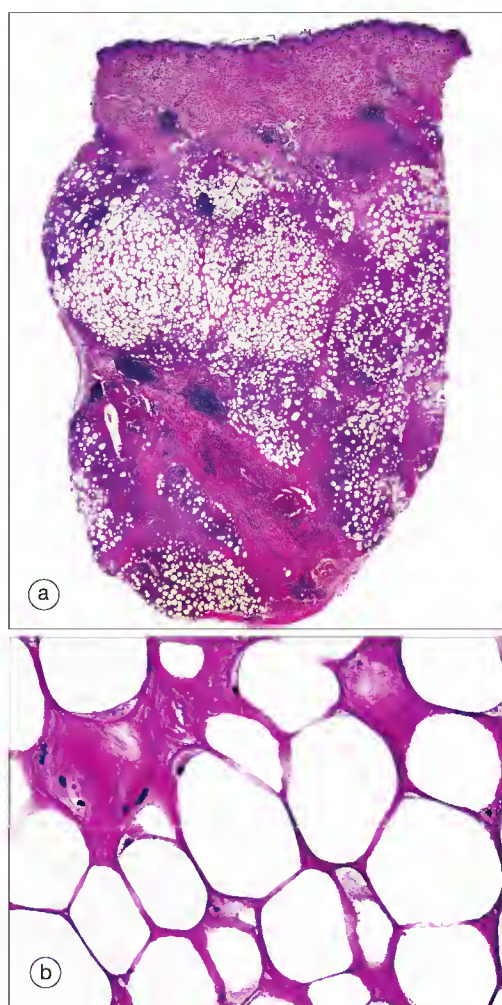


Fig. 162.14 Mixed lobular and septal panniculitis.

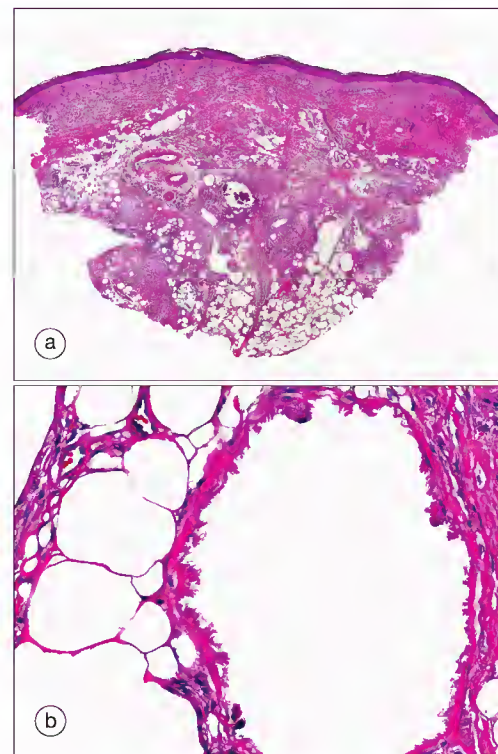


Fig. 162.15 Sclerosing panniculitis. (a) Extensive lobular panniculitis with fibrosis. (b) Close-up of characteristic fat microcysts with foci of membranous fat necrosis.

Because sclerosing panniculitis is a manifestation of venous insufficiency, therapy should include the use of support stockings, leg elevation, and rest. Measures for the prevention of phlebitis are also warranted. Low doses of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) may be helpful. In patients with factor V Leiden mutation, the use of warfarin or heparin might be beneficial, and in those with a polymorphism of methylenetetrahydrofolate reductase the use of folic acid and other B vitamins might help. Intralesional injection of triamcinolone acetonide may also be beneficial.

Factitial panniculitis

Factitial panniculitis caused by external trauma or the injection of foreign substances is not common but should be considered in patients with unusual clinical or histopathologic features of panniculitis. In traumatic lesions an organizing hematoma may be demonstrated histologically, whereas with injections one encounters refractile bodies or a “Swiss cheese” effect. Occasionally, spectroscopic and/or chromatographic techniques are necessary to identify the causative injected material.

INVESTIGATIONS

Cutaneous vasculitis

The purpose of evaluation is, first, to identify a cause or an associated condition and, second, to assess the presence and severity of systemic involvement.⁴⁹ The evaluation begins with a careful history taking and physical examination. **Box 162.4** presents the basic workup recommended for patients with cutaneous vasculitis. In patients with acute disease in whom there is an obvious cause such as a drug or infection, the evaluation is streamlined and need not assess for all possible causes. Skin biopsy of an early lesion is necessary to confirm the presence of LCV but often is not performed in children with typical lesions.⁸ In patients with chronic disease or those in whom there is not an obvious cause, the workup is more extensive. An assessment for paraproteins is necessary in this group of patients, but evaluation for malignancy is probably not necessary unless there are other symptoms or signs. Immunofluorescence testing of a cutaneous biopsy specimen can be useful when Henoch-Schönlein purpura is considered.

Panniculitis

As in patients with cutaneous vasculitis, the evaluation of patients with panniculitis should include taking a careful history and performing physical



describe this condition. Often the leg looks like an inverted soda bottle due to the sclerosis of tissue around and immediately above the ankle (**Fig. e162.5**). These lesions most frequently occur in women and are usually accompanied by signs of venous insufficiency. Some patients have known prior thrombophlebitis, and evidence of venous insufficiency may be present. Patients with this entity are sometimes found to have a tendency toward thrombophilia, as evidenced by the presence of factor V Leiden mutation or methylenetetrahydrofolate reductase polymorphisms. Histopathologically this disorder is characterized by fat necrosis, sclerosis, and a lobular panniculitis.⁴⁸ Fat microcysts with foci of membranous fat necrosis are also commonly observed in the later stages of the disease (**Fig. 162.15**).



Fig. e162.5 Sclerosing panniculitis characterized by tender, indurated, hyperpigmented plaques overlying the medial malleoli.

examination. The possibility of infection of the upper respiratory tract should be considered, and a throat swab for a rapid streptococcal screening, skin tests for tuberculosis, and a chest radiograph should be obtained. In general, neither inflammatory bowel disease nor infectious enteritis is asymptomatic, and thus it is not necessary to perform endoscopic or radiographic procedures in these patients. Tests for enzymatic abnormalities, such as amylase, lipase, or α_1 -antitrypsin deficiency, should be ordered. The

possibility of a coexistent collagen vascular disease should also be considered.

DIFFERENTIAL DIAGNOSIS

Cutaneous vasculitis

The differential diagnosis of cutaneous vasculitis differs with each clinical lesion. Palpable purpura must be differentiated from traumatic purpura, capillaritis (also known as *chronic pigmented purpura*), insect bites, embolic phenomena, and a variety of infections. Embolic processes that can mimic vasculitis include atheromatous emboli and emboli from a left atrial myxoma. In addition, endocarditis may mimic cutaneous vasculitis.⁴⁹

Urticarial lesions must be differentiated from “garden variety” urticaria, bites, erythema multiforme, and drug eruptions. Ulcerations can occur from noninflammatory vessel occlusion such as atherosclerosis, malignant processes, or bites, or from nonvascular inflammatory conditions such as pyoderma gangrenosum. Livedo reticularis usually occurs with involvement of medium-sized vessels and secondary to atherosclerosis, emboli, or occlusive vasculopathy associated with antiphospholipid antibody syndrome.

Panniculitis

The differential diagnosis of panniculitis involves distinguishing it primarily from insect bites, thrombophlebitis, and cellulitis. Insect bites may be tender, red, infiltrated lesions. The distribution is dependent on the type of bite, and in general the patient is otherwise asymptomatic. Often there is a puncture site within the lesion. Cellulitis rarely manifests as subcutaneous nodules. When the diagnosis is in question, wedge biopsy or deep punch biopsy that includes subcutaneous fat is helpful.

MANAGEMENT

Cutaneous vasculitis

The treatment of cutaneous vasculitis depends on whether there is clinical evidence of systemic disease and how severe the cutaneous disease is. Table 162.2 highlights some of the treatments that might be considered for various cutaneous vasculitic syndromes. The patient with severe systemic necrotizing vasculitis should be treated rapidly and aggressively with systemic corticosteroids and possibly an immunosuppressive agent. Pulsed treatment

BOX 162.4 EVALUATION OF THE PATIENT WITH CUTANEOUS VASCULITIS

History

- Infections?
- Drug ingestion?
- Prior occurrence of one of the associated disorders?
- Any systemic symptoms?

Physical examination

- General appearance
- Vital signs
- Type and distribution of lesions
- Evidence of arthritis?

Skin biopsy

- Routine skin biopsy should be performed on a fresh lesion in all patients
- Immunofluorescence microscopy is optional; may be useful when Henoch-Schönlein purpura is considered

Laboratory studies

Necessary

- Complete blood cell count
- Urinalysis
- Chest radiograph
- Tests for collagen vascular diseases: antinuclear antibody, anti-Ro (SS-A), rheumatoid factor
- Hepatitis C antibody, hepatitis B surface antigen
- Paraproteins: cryoglobulin assay, immunofixation electrophoresis
- Antineutrophil cytoplasmic antibodies

When appropriate or under special circumstances

- Total hemolytic complement
- Circulating immune complexes
- Erythrocyte sedimentation rate and/or C-reactive protein level
- Blood cultures

TABLE 162.2

Treatment of cutaneous vasculitis based on syndrome

Syndrome	First choice	Alternative choices	Comments
Hypersensitivity vasculitis	Identify and remove the antigen. Consider dietary therapy. Treat any associated disorder.	Colchicine, dapsone, immunosuppressive agent (methotrexate, azathioprine, etc.), rituximab, corticosteroids	A thorough evaluation is needed to exclude other vasculitic syndromes that may manifest as palpable purpura.
Henoch-Schönlein purpura	Observation	Corticosteroids, immunosuppressive agent, or both	There are no data demonstrating that treatment alters the outcome. Often this condition is self-limiting. Hypertension, preeclampsia in women, and renal failure are possible long-term sequelae.
Urticarial vasculitis—normocomplementemic	Antihistamines	Colchicine, dapsone, corticosteroids, immunosuppressive agents, intravenous immunoglobulin	Chronic urticaria, particularly when associated with vasculitis, is probably an immune-mediated disorder.
Urticarial vasculitis—hypocomplementemic	Dapsone, corticosteroids, immunosuppressive agents	Intravenous immunoglobulin	This disorder is difficult to treat. Associated pulmonary disease may occur and there is no known effective therapy.
Vasculitis with hepatitis C virus	Interferon with or without ribavirin	Corticosteroids	Suppression of the viral load may decrease the manifestations of vasculitis.
Vasculitis in a patient with B-cell lymphoma (or a history of lymphoma)	Colchicine, dapsone	Rituximab, intravenous immune globulin	
Cutaneous polyarteritis nodosa	Corticosteroids or immunosuppressive agents (methotrexate or azathioprine)	Intravenous immunoglobulin	Although there is a primary focus on the skin, patients may develop ulcers or may have associated inflammatory bowel disease, mononeuritis multiplex, and/or arthritis.
Erythema elevatum diutinum	Dapsone	Corticosteroids	

with either methylprednisolone or cyclophosphamide can result in rapid control of the disease.

Patients with chronic cutaneous vasculitis tend to be frustrated and frequently desire treatment for symptomatic relief or for cosmetic reasons. In some cases, small recurrent purpuric lesions with superficial ulceration can compromise the patient's ability to work. In patients with acute disease such as Henoch-Schönlein purpura, no treatment may be necessary other than agents for symptomatic relief.

It is important to identify and remove any offending antigen that may be present. Some examples are ingestants such as a drug, food, or food additive that can be avoided. Lunardi and colleagues⁵⁰ described five patients with chronic cutaneous vasculitis in whom dietary factors were found to be causative. Some patients with paraneoplastic vasculitis whose tumors are removed experience resolution of the vasculitis. Patients with paraproteinemia may be good candidates for treatment with an immunosuppressive agent to suppress the formation of the abnormal protein, and in the case of hepatitis C virus-associated cryoglobulinemic purpura, interferon alfa-2a with or without ribavirin and with or without rituximab has been useful.^{18,51} Patients with erythema elevatum diutinum seem to respond extremely well to oral dapsone therapy. Finally, patients with a lymphoma or a history of a lymphoma may respond to rituximab.

Patients without an identifiable cause or associated phenomenon who require therapy can be treated with a variety of agents. A therapeutic ladder can be designed from which treatments can be selected sequentially until an appropriate and effective agent is identified. Because the postulated mechanism for cutaneous vasculitis involves immune complex-mediated disease, complement activation, chemotaxis of polymorphonuclear leukocytes, lysosomal release, and resultant cell destruction modulated by vasoactive substances, agents that interfere with any of these processes may be beneficial. Agents such as antihistamines, NSAIDs, antimalarials, and sulfones have been reported to be therapeutic in individual cases, but they have not been uniformly effective in the authors' experience. Corticosteroids, if given at a sufficiently high dosage, are almost always effective. In open-label trials, colchicine was effective in 75% to 80% of patients with cutaneous vasculitis⁵²; however, in the only published double-blind, placebo-controlled trial, colchicine failed to demonstrate efficacy.⁵³ In the authors' view, that trial was compromised by biases that favored a response in the placebo group. Immunosuppressive agents such as azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, and cyclosporine are also often effective. Recently developed biologic agents such as rituximab have benefited some patients.⁵⁴

The burning or itching of the lesions most often irritates patients with urticarial vasculitis. The patient should be treated first with antihistamines. Histamine 1 (H₁) receptor antagonists can be combined with H₂ antagonists, but the dosages required often result in drowsiness. In some cases, the use of doxepin, which has effects on both H₁ and H₂ receptors, is effective. Finally, the newer, less-sedating agent cetirizine or nonsedating agents such as fexofenadine or loratadine can be used during waking hours and a soporific agent given before retiring.

Panniculitis

There are few randomized, controlled clinical trials to guide treatment decisions in the panniculitis group of disorders. The treatment of EN and other panniculitides first involves the search for a causative disease and its treatment if present. In the absence of a treatable disorder, therapy is symptomatic. Acute EN is often self-limited; thus nontoxic therapies are advised. Bed rest and leg elevation are very helpful in controlling symptoms. In patients who need to be ambulatory, use of support stockings or tights may be helpful. Aspirin or other NSAIDs may be effective. Sometimes, however, treatment with aspirin does not produce results before toxicity is reached, and oral indomethacin (25 to 75 mg/day) is therefore recommended.

In patients with chronic EN or frequent recurrences, oral potassium iodide (300 to 900 mg/day) has been useful in open clinical trials. When the drug is stopped or the dose is lowered, the disease often relapses, only to respond again with reinstitution of therapy. Other therapies that may be considered are oral corticosteroids, colchicine, hydroxychloroquine, or an immunosuppressive agent. Cyclosporine has been used successfully in some patients. One adjunctive therapy that can be helpful is intralesional injection of triamcinolone acetonide.

There is no specific therapy for patients with idiopathic neutrophilic lobular panniculitis. Reports have centered on the use of antiinflammatory agents (aspirin, other NSAIDs), oral corticosteroids, antimalarial agents, and immunosuppressive agents (cyclophosphamide and cyclosporine). In addition, colchicine, dapsone, and potassium iodide may be effective in some individual cases. There is no information regarding the role of biologic therapy in these patients.

Patients with $\alpha\beta$ subcutaneous panniculitis-like T-cell lymphoma who do not have an associated hematophagocytic syndrome are often steroid responsive, and the prognosis is generally good. Those with a $\gamma\delta$ phenotype have a more aggressive form and referral to an oncologist is recommended.

Patients with LEP may respond to antimalarial agents or to intralesional injections of triamcinolone. Corticosteroids and/or immunosuppressive agents are rarely necessary in LEP.

CONCLUSION

The cutaneous vasculitides and panniculitides form a wide array of syndromes that often can be separated on the basis of clinical features, associated disorders, and/or histopathologic findings. The newest lesion should be sampled. Evaluation for an underlying process should include investigation for ingestants, infections, malignancy, and autoimmune disorders. In the absence of an underlying disease, treatment is aimed at control of the inflammatory reaction with NSAIDs, corticosteroids, dapsone, potassium iodide, antimalarial agents, colchicine, or cytotoxic or immunosuppressive agents.

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163 Cryoglobulinemia

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- Cryoglobulinemia is characterized by the presence in the serum of one or more immunoglobulins that precipitate at temperatures below 37°C and redissolve on rewarming.
- Three types of cryoglobulins are recognized: type I, an isolated monoclonal immunoglobulin; type II, immunoglobulin G (IgG) and an IgM rheumatoid factor (RF) of monoclonal origin; and type III, IgG and a polyclonal IgM RF. The presence of Types II and III is considered mixed cryoglobulinemia.
- This disease predominantly affects middle-aged women. A hepatitis C virus infection is the cause in the majority of mixed cryoglobulinemia cases (60%-90%).
- Histologically cryoglobulinemia is a small-vessel leukocytoclastic vasculitis.
- Clinically, dependent purpura is evident in almost all patients. Other common features include weakness, arthralgias, liver involvement, Raynaud phenomenon, and multiplex mononeuritis.

HISTORY

The term *cryoglobulinemia* refers to the presence in the serum of one or more immunoglobulins that precipitate at temperatures below 37°C and redissolve on rewarming.

According to Brouet and associates,¹ the cryoglobulins can be subdivided into three subgroups: type I contains an isolated monoclonal immunoglobulin, type II comprises immunoglobulin G (IgG) and an IgM rheumatoid factor (RF) of monoclonal origin, and type III comprises IgG and a polyclonal IgM RF.

Type I cryoglobulins are frequently of the IgG isotype; less frequently they may be composed of IgM, IgA, or light chains.² Type I cryoglobulinemia is frequently associated with immunoproliferative disorders.

Mixed cryoglobulins (types II and III) are composed of IgG, plus an IgM (rarely of either IgA or IgG) with RF activity. They represent up to 80% of all cryoglobulins and are generally present in lower concentrations than monoclonal cryoglobulins. Mixed cryoglobulinemia (MC) has been described in association with chronic infections and autoimmune disorders.³

In 1966, Meltzer and Franklin described for the first time a syndrome characterized clinically by the triad of weakness, arthralgias, and Raynaud phenomenon and by the presence of mixed cryoglobulins without any known precipitating factor; this condition was termed *essential MC*.²

However, the frequent finding of liver involvement in patients with MC, which is much less common in other immune complex-mediated diseases, suggested the hypothesis that an environmental factor, possibly a hepatotropic virus, might be the actual trigger of the disease. An association with the hepatitis B virus (HBV) was suggested, but this was not confirmed by subsequent studies, in which HBV antigenemia was only occasionally detected in individuals with antibodies against the HBV surface antigen.⁴

Studies in the 1990s on large series of patients with MC definitively eliminated HBV as a causative agent in most cases of MC, and the hypothesis of a hepatotropic virus as a causal agent became less convincing.⁵

Subsequently, however, the identification of hepatitis C virus (HCV) as the main causative agent of non-A, non-B hepatitis⁶ provided fresh support for this hypothesis. Because HCV is a hepatotropic virus that can cause

chronic infection with liver involvement, its prevalence was evaluated in a small series of patients with MC. With the use of first-generation tests, antibodies against HCV were initially demonstrated in 30% to 54% of all patients with MC.⁷⁻⁹ With newer tests, the prevalence was found to be even higher, ranging from 70% to 100%. Increasing evidence suggested that this association also has pathogenetic significance. In particular, the demonstration of the specific concentration of HCV in type II cryoglobulins, immunohistochemical evidence of HCV-associated antigens in vasculitic skin biopsy specimens, and the presence of HCV RNA in serum and plasma samples and of HCV infection in the peripheral mononuclear cells of patients with MC all lend support to the etiopathogenetic role of HCV in MC. Because this role has been universally accepted, the term *essential MC* should be dropped, and in the majority of cases the disease should be referred as to *HCV-related MC*.^{2,10} HCV-negative MC accounts for about 5% to 10% of cases.¹¹

EPIDEMIOLOGY

The prevalence of MC is not homogeneous across countries; it is more frequent in southern Europe than in northern Europe or North America. The geographic distribution of MC seems to be closely related to the endemic presence of HCV infection. Among the different HCV genotypes, genotype 2a has been described to be more frequent in patients with MC than in chronic HCV carriers without MC. Different prevalences of serum cryoglobulins, ranging from 19% to 50%, have been reported in HCV-infected patients. Clinical overt cryoglobulinemic syndrome seems to be evident in 15% to 30% of these subjects and in 5% to 10% of all HCV-infected patients.¹²

CLINICAL FEATURES

MC shows a slow progression with periods of exacerbation and remission and rare acute flares.

Purpura

Purpura almost always occurs in patients with MC, often as the presenting feature. It is characteristically nonpruritic, is intermittent, and involves the lower extremities because venous stasis favors the precipitation of cryoglobulins. In widespread and severe forms of the disease, however, it can also involve the abdomen and chest (Figs. 163.1 and 163.2). An association of leg ulcers with purpura is the presenting symptom in 22% of patients (Fig. 163.3). Histologically, it is characterized by dermal vasculitis with a variable degree of involvement of the subcutaneous interstitium.⁴

Raynaud phenomenon

Raynaud phenomenon, usually mild and nonnecrotizing, is present in 25% of patients at diagnosis.

Joint involvement

Arthralgias are present in the majority of cases and usually recur intermittently during the course of the disease. Occasionally, a frank arthritis can occur.⁴ During chronic HCV infection two different clinical subsets of arthritis have been described to occur: (1) a monoarticular or oligoarticular intermittent arthritis involving large and medium-sized joints (almost always with the presence of cryoglobulins), and (2) a polyarticular symmetric arthritis closely resembling rheumatoid arthritis (RA). Differentiating



Fig. 163.1 Patient with cryoglobulinemic purpura involving the lower limbs. The right limb is more involved than the left because venous stasis favors the precipitation of cryoglobulins (the patient had venous insufficiency on the right side).



Fig. 163.2 In widespread cutaneous vasculitis the purpura involves limbs, abdomen, and chest. This photograph shows the dorsum of a patient with diffuse purpura.

between true RA and HCV-related RA-like arthritis can be particularly challenging because there are no reliable clinical parameters that can distinguish between the two conditions. In general, HCV-related arthritis is less serious and nonerosive than classical RA. Recently, anti-cyclic citrullinated peptide antibodies, which are always absent in MC, have been suggested as a useful tool in distinguishing between the two disorders.^{13,14}

Renal involvement

Renal involvement is one of the most serious complications of MC and affects approximately one third of patients. Histologically, it almost



Fig. 163.3 Skin ulceration is the final result of severe cutaneous vasculitis.

invariably takes the form of type I membranoproliferative glomerulonephritis with a varying degree of interstitial and vascular damage.¹⁵ Clinically, renal involvement ranges from isolated proteinuria to nephritic syndrome. The disease course is generally characterized by periods of remission and exacerbation, and if not adequately treated, the renal disease eventually leads to renal failure in 14% of cases.^{16,17}

Peripheral nerve involvement

Another common feature in patients with MC is peripheral neuropathy. However, the real frequency of this manifestation is often underestimated, owing to its smoldering clinical course. Subjective symptoms suggesting peripheral neuropathy were present in over 90% of patients with MC,¹⁸ whereas objective manifestations as well as sensory motor conduction velocity abnormalities were detected in half the patients. There were electrophysiologic abnormalities in 82%. Pure motor neuropathy is a rarer finding (about 5%) but, when present, is a disabling condition.

The nerve injury may have a number of underlying causes, including immunologically mediated demyelination, vasculitis, or occlusion of the vasa nervorum by cryoglobulin precipitation. Histologic studies have shown inflammatory vessel damage with axonal degeneration. The correlation found between serum cryoglobulin levels and various neurologic findings suggests that an immune complex-mediated mechanism might be responsible for this nerve damage.^{2,10,16}

Liver involvement

Liver involvement is present in more than two thirds of patients with MC and is predominantly revealed on biochemical testing. Clinically, it is generally asymptomatic and laboratory evidence of cell damage is usually mild or absent. However, the correlation between clinical liver disease and histologic findings is low, because the latter shows in all instances various degrees of periportal inflammation, with fibrosis, architectural derangement, and evidence of cirrhosis in one third of cases.^{2,4}

Lymphoproliferative disorders

HCV infection, independent of concomitant MC, carries an increased risk of development of lymphoma,¹⁸ but this risk is higher in patients with HCV-positive MC syndrome.¹⁹ Some of these cases appear to be highly responsive to antiviral therapy, which provides clinical evidence for a pathogenetic association. HCV-associated lymphomas represent a variety of histologic subtypes, most frequently non-Hodgkin B-cell lymphomas.¹⁸ MC is frequently associated with a benign lymphoproliferative disorder that takes the form of distinct lymphoid infiltrates with B cells bearing surface monoclonal RF (IgMκ) in the portal tracts, spleen, and bone marrow. This disorder, which is responsible for the monoclonal RF in type II cryoglobulins, can evolve in 5% to 10% of patients to frank non-Hodgkin B-cell lymphoma. The risk of developing lymphoma is about 35 times higher in patients with MC than in the general population. Comparison of North American and European series show a clear-cut south-north gradient of prevalence

(reflecting the prevalence of HCV infection), which suggests the intervention of further environmental and/or genetic factors.²⁰

In clinical practice it is possible to observe a sudden decrease or disappearance of serum cryoglobulins or RF, sometimes associated with abnormally high levels of C4, as the presenting symptom of complicating B-cell malignancy.²¹ In addition, a low level of γ -globulin in the setting of HCV-related MC syndrome could predict the diagnosis of Non-Hodgkin lymphoma.²²

Hyperviscosity syndrome

Although increased blood viscosity and reduced blood filtration can be demonstrated in a high percentage of patients with MC, a frank hyperviscosity syndrome is relatively uncommon.^{23,24}

Other manifestations

Other manifestations are dryness of eyes and mouth, bilateral parotid swelling, generalized lymphadenopathy, recurrent abdominal pain, and central nervous system involvement.⁴ In some patients with acute abdomen, laparoscopy discloses a vasculitis of the small mesenteric vessels. Lung involvement has been frequently observed, particularly at the level of the small airways and the pulmonary interstitial spaces.²⁴⁻²⁶ In rare instances patients with MC have cardiovascular involvement with coronary vasculitis, heart failure, and pericarditis²⁷ or isolated gynecologic involvement with vasculitis of the female genital tract.²⁸

OUTCOME

Mortality

Patients with MC have higher mortality rates than the general population.^{29,30} Table 163.1 shows the acute causes of death in patients with MC, the most frequent being renal involvement and widespread vasculitis (most often involving the gastrointestinal tract). Other frequent causes of death are liver involvement and infections. In a significant number of cases, the cause of death remains unknown.²⁹

On the whole, research data on mortality in patients with MC give heterogeneous results, which might be explained by methodologic differences, such as differences in the stage of disease in the patients recruited, time of enrollment, and length of follow-up. However, a number of prognostic factors have been almost invariably associated with a higher mortality; in particular, increasing age, renal involvement, intestinal vasculitis, more severe vasculitis, immune-suppressive treatment, and certain types of cryoglobulins are generally associated with poorer outcome.^{30,31} By contrast, the presence of some clinical features, such as sicca syndrome³⁰ and the use of antiviral agents, has been found to be associated with a better outcome.³¹

■ TABLE 163.1

Acute causes of death in mixed cryoglobulinemia

Mortality rate 16%-66%	
Acute cause of death	%
Stroke	5-25
Hepatocellular carcinoma	10-12
Liver involvement	13-18
Lymphoma	13-21
Pulmonary involvement	10-21
Renal involvement	21-33
Gastrointestinal involvement	12.5
Infection	25-26
Vasculitis	13-31
More than one cause	25-36
Miscellaneous	25
Unknown	18-43

INVESTIGATIONS

The key laboratory parameters for the diagnosis of MC as specified in the preliminary classification criteria for cryoglobulinemic vasculitis³² are (1) the presence of cryoglobulins, (2) the presence of RF, (3) reduced serum levels of C4, and (4) the presence of a serum monoclonal component (Box 163.1).

The laboratory hallmark of MC is the presence of type II or type III cryoglobulins with RF activity. High levels of circulating immunocomplexes and low levels of complement (primarily via activation of the classical pathway) are characteristic findings in MC. Patients with MC may have a monoclonal component in their sera, usually IgM κ ; this reflects the presence of clones of lymphoid cells in the portal tracts of the liver, spleen, and bone marrow.

Detection of cryoglobulins

A 20-mL blood sample should be stored at 37°C until completely coagulated, centrifuged at 37°C at 2500 rpm for 5 minutes, and then stored at 4°C for 1 week. A white precipitate in the bottom of the tube indicates the presence of cryoglobulins. When the tube is rewarmed to 37°C, the precipitate will dissolve.

To quantify the amount of cryoglobulins present in the serum sample, cryocrit should be determined. Briefly, the serum is centrifuged at 2500 rpm in a graduated tube at 4°C and the percentage of cryoglobulins is calculated.

To characterize the cryoglobulins, a variety of immunologic methods can be performed, although immunodiffusion and immunofixation are the methods of choice for the typing of cryoglobulins and for the accurate assessment of clonality. Combining the two procedures may be particularly helpful in determining the oligoclonality of each component of the complex.³³

BOX 163.1 PRELIMINARY CLASSIFICATION CRITERIA FOR CRYOGLOBULINEMIC SYNDROME

Satisfied if findings are positive on at least two of the three items (questionnaire, clinical, laboratory).

The patient must test positive for serum cryoglobulins on at least two determinations at ≥ 12 -week interval.

(i) Questionnaire item: at least two of the following:

- Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?
- Have you ever had red spots on your lower extremities that leave a brownish color after their disappearance?
- Has a doctor ever told you that you have viral hepatitis?

(ii) Clinical item: at least three of the following four (present or past)

- Constitutional symptoms
 - Fatigue
 - Low-grade fever (37°-37.9°C for >10 days with no cause)
 - Fever (>38°C) with no cause
 - Fibromyalgia
- Articular involvement
 - Arthralgias
 - Arthritis
- Vascular involvement
 - Purpura
 - Skin ulcers
 - Necrotizing vasculitis
 - Hyperviscosity syndrome
 - Raynaud phenomenon
- Neurologic involvement
 - Peripheral neuropathy
 - Cranial nerve involvement
 - Vasculitic central nervous system involvement

(iii) Laboratory item: at least two out of the following three (present)

- Reduced serum C4 level
- Presence of serum rheumatoid factor
- Presence of a serum monoclonal component

Detection of rheumatoid factor

RF may be detected by means of either enzyme-linked immunosorbent assay or laser nephelometry.³⁴

Detection of C3 and C4

Antigenic analysis of complement proteins makes use of several tests, such as electrophoresis, immunofixation, immunoelectrophoresis, and nephelometric and immunoturbidimetric quantification. At present, laser nephelometric and immunoturbidimetric analysis are the most commonly employed techniques.³⁵

Detection of hepatitis C virus

Anti-HCV antibodies can be detected in the sera of cryoglobulinemia patients by means of commonly employed immunoassays, immunoblot assays, and, more recently, immunochromatography-based rapid tests. Qualitative and quantitative HCV nucleic acid assays in routine use are based on polymerase chain reaction, branched DNA signal amplification, and transcription-mediated amplification. In addition, assays for HCV genotyping are available, based variously on direct sequencing, reverse hybridization to genotype-specific oligonucleotide probes, and restriction fragment length polymorphism analysis.³⁶

DIFFERENTIAL DIAGNOSIS

Systemic vasculitides

HCV infection may be associated with different types of systemic vasculitides. Polyarteritis nodosa (PAN), although most frequently associated with hepatitis B infection, in a limited number of cases is associated with HCV infection. However, because the prevalence of this infection among PAN patients is low (5% to 10%), the significance of the association is unclear. Moreover, in a small number of patients with PAN, cryoglobulins are also detectable, and this makes the differential diagnosis with MC even more difficult. At presentation, patients with PAN more often have life-threatening systemic vasculitis, malignant hypertension, cerebral angiitis, and ischemic abdominal pain than do patients with MC. Moreover, kidney and liver microaneurysms involving the medium-sized vessels are a hallmark of PAN, whereas small-vessel involvement occurs in MC. Finally, peripheral nerve involvement almost always takes the form of a severe multifocal sensorimotor neuropathy in PAN, whereas distal moderate sensory neuropathy is more frequent in MC.³⁶

Leukocytoclastic vasculitis has been claimed to be associated with HCV infection. Whether this condition is a separate entity or represents an incomplete form of cryoglobulinemia is an unresolved issue. However, the presence of HCV infection in a patient affected by leukocytoclastic vasculitis makes the search for cryoglobulins mandatory.³⁷

Sjögren syndrome

MC and Sjögren syndrome share a number of clinical and serologic features. The prevalence of HCV infection among European patients with primary Sjögren syndrome ranges from 5% to 19%. A small number of patients with MC have anti-Ro/SSA and anti-La/SSB antibodies. Therefore, at least in some instances, a true overlap between the two conditions may exist. In the other cases, differentiating between the two disorders can be unusually difficult. Moreover, it should be stressed that HCV is a sialotropic virus and can cause a true Sjögren syndrome secondary to the infection, even in the absence of cryoglobulins. Features distinguishing between the primary disorder and HCV-related Sjögren syndrome might include a lower prevalence of symptoms of dryness, a significant increase in the prevalence of liver involvement, cryoglobulinemia and hypocomplementemia, a lower prevalence of anti-Ro/SSA and anti-La/SSB autoantibodies, and a milder expression of lymphocytic infiltrates on the salivary glands in HCV-positive patients.^{13,38,39} Recently, the new diagnostic criteria for primary Sjögren syndrome have included HCV infection as an exclusion criterion.⁴⁰

ETIOPATHOGENESIS

MC is a complex disorder with a broad spectrum of clinical manifestations representing an interaction between autoimmune disorders, immune complex-mediated disorders, and lymphoproliferative processes. It is now

clear that HCV plays a central role in the etiopathogenesis of MC.^{2,10,20} Vasculitic lesions are not identical in different organs as far as their pathogenetic mechanisms are concerned. Whereas palpable purpura results from the deposition of complexes of HCV, IgM RF, IgG, and complement components, which are all easily detectable in cutaneous vasculitis, HCV-related proteins are found less often in the kidney and have never been demonstrated in peripheral neuropathy.^{41,42}

HCV, like other RNA viruses, is characterized by a high degree of genetic heterogeneity.² Mutation of HCV during replication favors the escape from the immune system and the persistence of the virus in the host. Chronic HCV infection represents, in turn, a chronic stimulus for the immune system and is one of the main pathogenetic steps in MC. The mechanism leading to the formation of autoantibodies during HCV infection remains obscure. HCV recognizes different binding molecules on the cell surface that are not completely identified. Among them, the most known are CD81, scavenger receptor class B type I and low-density lipoprotein receptor.⁴³ The engagement of HCV with CD81 lowers the B-cell threshold for polyclonal activation, which leads to the formation of autoantibodies and cryoglobulins; however, other factors must also be involved because a large proportion of patients with autoantibodies do not have cryoglobulins. A different mechanism involving intracellular B-lymphocyte infection by HCV seems to underlie HCV-associated monoclonal gammopathy and non-Hodgkin B-cell lymphoma.²⁰

After the initial activation, the continuous exposure to antigen pressure may result in a positive selection of B cells with the emergence of a B-cell population producing a monoclonal IgM rheumatoid factor. These B clones can be found within peripheral blood, bone marrow, and liver of patients with HCV infection; their presence is usually considered as an indolent lymphoproliferative disorder that evolves into a frank malignant lymphoma in a minority of cases.²⁷

The monoclonal IgM molecules secreted by B-cell clones have the peculiarity of bearing a cross-reacting idiotype called WA that binds immunoglobulins directed against anti-HCV core proteins.⁴⁴ A recent study demonstrated that WA B cells can be detected not only in all patients with cryoglobulinemic vasculitis but also in nearly 10% of asymptomatic patients with HCV infection. This discovery suggests that WA B cells may be a marker for the development of cryoglobulinemic vasculitis and for B-cell lymphomas in patients with HCV infection.⁴⁵

Although many steps forward have been made in the knowledge of cryoglobulinemic vasculitis, several aspects of its etiopathogenesis have yet to be clarified, for example, why only some HCV-infected patients develop the cryoglobulinemic syndrome. Recent studies suggest that the host's genetic background plays an important role in determining the susceptibility to cryoglobulinemic vasculitis of some HCV-infected patients. On the basis of this hypothesis some investigators focused their attention on this aspect. They established that the abnormal presence of large immune complexes in MC may be due either to the reduced uptake of immunoglobulins by the reticuloendothelial system or to the excessive production of immunoglobulins by B cells, so they analyzed allelic variants of the low-affinity Fcγ receptor (FcγR) genes and of BAFF promoter. Indeed, low-affinity FcγRs mediate the clearance of circulating cryoglobulins, whereas BAFF, a tumor necrosis factor-α family member, regulates immunoglobulin secretion and B-cell differentiation and survival. From this study no significant differences emerged in the distribution of FcγR genotypes, whereas a greater prevalence of BAFF promoter's T-allele homozygosity was observed in patients with cryoglobulinemic vasculitis than in HCV-infected patients without cryoglobulinemic syndrome. It has been observed that T allele is associated with elevated serum BAFF levels and with the presence of cryoglobulinemic vasculitis.⁴⁶ The host immune response against HCV is not always protective against infection; indeed, viral clearance is not associated with an immunization against reinfection. Immune response in long-term HCV carriers seems to exert a selective pressure on the virus that favors the emergence of viral strains more prone to escape from it. In particular, a substantial divergence between humoral and cell-mediated response to the virus has been unveiled; humoral response is responsible for extrahepatic manifestations and seems to be of no effect in controlling infection. Cell-mediated immune response is of greater importance in the production of antiviral cytokines but seems also to have a role in cytotoxic damage.⁴⁷ In this regard, recently a substantial divergence in cytokine production has been claimed between individuals with HCV infection not associated with cryoglobulinemic syndrome and those with HCV-related cryoglobulinemic vasculitis. In particular, an emerging role for chemokines and type 1 cytokines in the pathophysiology of this vasculitis has been claimed.^{48,49}

The possible etiopathogenesis of MC may be summarized as follows. Among the different possible noxious agents, HCV either alone or in combination with other still unknown factors plays an important role.

Autoimmunity may be a virus-triggered epiphenomenon perpetuated by a variety of factors, including genetic susceptibility, environmental factors, and host and viral factors (e.g., genotype, superinfection with unrelated strains, escape from the immunologic system). The persistence of the virus represents a continuous challenge for the host, and the chronic stimulation of the immune system on the one hand triggers the appearance of autoantibodies through molecular mimicry or other unidentified mechanisms and on the other hand favors the emergence of clones protected against apoptosis; in this way, the pathway of autoimmunity is possibly maintained through a vicious cycle.^{2,10,13} The vascular deposition of immunocomplexes composed of cryoglobulins, with the involvement of viral markers and autoantigens, is responsible for the organ damage observed in MC and in the vasculitis associated with HCV infection. HCV acts as a long-term stimulus on the immune system and infects blood mononuclear cells. Monoclonal or polyclonal B-cell expansion is the most important consequence of this process. Autoantibody production is another result. The activation of oncogenes leads to the emergence of clones protected against apoptosis. This, as previously mentioned, possibly favors the persistence of autoreactive clones and the promotion of lymphoproliferative disorders.^{2,10,11,20,43,47}

MANAGEMENT

MC is a complex multisystem disease. The treatment of this disorder is still a challenge, and different specialists should ideally cooperate to get a better result. The three main aims of any rational therapeutic approach are to eradicate HCV (etiologic therapy), to limit or suppress B-lymphocyte proliferation (pathogenetic therapy), and to ameliorate symptoms and reduce the damage caused by circulating immune complexes (symptomatic therapy).^{27,50} Treatment should be tailored to the individual patient focusing on the clinical history, disease manifestations, possible comorbidities, and previous therapies.^{42,43,47,50}

In cryoglobulinemic patients with life-threatening manifestations (abdominal vasculitis, hemorrhagic alveolitis, hyperviscosity syndrome, and sometimes acute motor neuropathy and rapidly progressive glomerulonephritis) the first-line intervention is a high dose of corticosteroids and plasmapheresis. Concomitant immunosuppressive therapy with cyclophosphamide might be needed to prevent a cryoglobulin rebound after plasmapheresis.^{2,47,50} The possible persistence or onset of cryoglobulinemic vasculitis in patients with persistently negative serum HCV RNA findings suggests that the autoimmune process can become independent of viral triggering and play a predominant pathogenetic role in some disease stages. Therefore antiviral therapy cannot be considered as a first step in more severe cases.^{47,50} Rituximab was recently used successfully in patients with cryoglobulinemic syndrome and severe vasculitis refractory to conventional therapies.^{51,52}

The common manifestations of severe cryoglobulinemic vasculitis are skin ulcers, peripheral neuropathy (motor or sensory neuropathy refractory to symptomatic therapy), and active glomerulonephritis. In these cases the best therapeutic option is rituximab; it destroys CD20+ cells, which may harbor HCV and play an important pathogenetic role in cryoglobulin

production. Indeed, rituximab decreases serum cryoglobulin and RF levels and increases C4 levels with the disappearance of bone marrow B-cell clonal expansion. Glomerulonephritis responds to rituximab within the first 3 months; skin ulcers usually improve within 3 months, but complete healing requires longer. Both sensory and motor neuropathy improve within 1 to 5 months with stable or improved electromyographic findings.⁵⁰ Rituximab can increase HCV viral load but without leading to significant liver impairment; it has been given to cryoglobulinemic vasculitis patients with liver cirrhosis and has led to an improvement in both MC symptoms and liver function.⁵³ By contrast, it may induce a severe reactivation of HBV, so it should be used in patients positive for hepatitis B surface antigen and in occult HBV carriers (patients with anti-hepatitis B core antigen antibodies) only when strictly needed and in combination with antiviral therapy.⁵⁴ The duration of the response to a single cycle of rituximab is difficult to define; long-term responses (more than a year) have been observed most frequently, and retreatment with rituximab after relapses has proved to be effective in most cases.⁵⁰

It has recently been suggested that patients with serious clinical manifestations may receive a combination therapy consisting of rituximab and synchronous or metachronous administration of antiviral therapy. This approach seems to reduce the time to clinical remission and to be more effective than the standard therapies.^{54,55} Antiviral therapy remains a cornerstone in the management of cryoglobulinemic vasculitis in HCV-related cases, and it should be used in patients in more stable condition, particularly those with nonsevere manifestations of cryoglobulinemic vasculitis, such as constitutional features, purpura or arthritis, and very mild renal and neurologic features. The current standard antiviral treatment is the combination of pegylated interferon- α (PEG-IFN- α) and ribavirin. The decision to treat patients with chronic hepatitis C depends on multiple factors including a precise assessment of the severity of liver disease, the presence of absolute or relative contraindications to therapy, and previous treatment failure or intolerance. The HCV genotype is systematically determined before treatment because it determines the duration of treatment (up to 48 weeks for HCV genotype 2 or 3 and 72 weeks for 1 or 4)⁵⁴ as well as the dose of ribavirin.⁵⁵⁻⁵⁸ Treatment with PEG-IFN- α combined with ribavirin led to a sustained antiviral response in 41% to 54% of patients infected with HCV genotype 1 and approximately 80% of those infected with HCV genotypes 2 and 3.⁵⁹ When antiviral therapy is not effective, is contraindicated, or is not tolerated, treatment with rituximab should be considered.⁵⁰⁻⁵²

In the future the treatment of HCV-associated cryoglobulinemic vasculitis may be improved by the administration of an antiviral triple therapy in which the standard PEG-IFN- α and ribavirin may be combined with one of the new protease inhibitors (telaprevir or boceprevir), especially in patients infected by HCV genotype 1.^{56,43}

The treatment of non-HCV-related cryoglobulinemic vasculitis usually is similar to that of other vasculitis, with steroids and immunosuppressive drugs used in most severe cases. In these cases treatment with rituximab also seems effective.^{59,60}

Additional therapies for MC have been proposed, such as imatinib, thalidomide, bortezomib, and interleukin-2, but future controlled studies are necessary to assess their effectiveness and tolerability in this disease.^{43,61,62}

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Primary angiitis of the central nervous system

■ JAMAL A. MIKDASHI

- Primary angiitis of the central nervous system is a rare syndrome characterized by inflammatory cell infiltration and necrosis of small and medium-sized blood vessel walls of the brain parenchyma, spinal cord, and leptomeninges.
- Headache, seizure, and cognitive impairment are the predominant symptoms, although various multifocal or diffuse neurologic symptoms with a remitting or progressive course may be present, including ischemic stroke and hemorrhage.
- The diagnosis is confirmed by either brain biopsy or cerebral angiography. Angiographic changes indicating an irregular course of vessels with characteristic segmental narrowing can be observed, but angiographic findings are normal at times and may not predict the pathologic findings. Cerebrospinal fluid and magnetic resonance imaging findings support the diagnosis of primary angiitis of the central nervous system.

HISTORY

Cerebral vasculitis was first reported in 1922 by Harbitz as an unusual type of arteritis associated with multinucleated giant cell arteritis of the small meninges and cerebrum.¹ Other documented cases of cerebral vasculitis described as noninfectious granulomatous angiitis with a predilection for the nervous system were reported by Newman and Wolf in 1952² and later by Cravioto and Fegin in 1959.³ Hughes and Brownell in 1966 described a progressive fatal form of vasculitis that is limited to the central nervous system (CNS) and was named primary angiitis of the CNS (PACNS) of unknown etiology.⁴

CASE DEFINITION AND CRITERIA

Problems with nomenclature and case definitions (isolated, primary, granulomatous angiitis) have evolved since the early description of cerebral vasculitis. It was difficult to separate polyarteritis and syphilitic endarteritis because of the occasional presence of similar pathologic findings of vascular necrosis, giant cells, and epithelioid cells in these disorders. Granulomatous formations may also occur in association with varicella-zoster virus infection, lymphoma, sarcoidosis, giant cell arteritis, amyloid angiopathy, and human immunodeficiency virus (HIV) infection. In addition, the heterogeneity of their clinical features and the lack of accurate and sensitive diagnostic tests have made categorization of these disorders uncertain.

No valid classification criteria have been established for the diagnosis of PACNS. Recommended criteria for the diagnosis of PACNS include the following⁵⁻⁷:

1. Clinical pattern of headaches and multifocal neurologic deficits that may remit or be present for at least 6 months unless the deficits are severe at onset or rapidly progressive
2. Cerebral angiography demonstrating segmental arterial narrowing and vessel occlusion affecting many cerebral vessels in the absence of proximal vessel atherosclerosis
3. Exclusion of systemic inflammation, vasculitis, and infection
4. Leptomeningeal/parenchymal biopsy specimen demonstrating vascular inflammation and exclusion of alternative diagnoses

PACNS is recognized as an inflammatory granulomatous disorder of small and medium-sized blood vessels of the arterial and venous system (angiitis) of the brain or spinal cord; it does not involve blood vessels or organs beyond the CNS. PACNS remains a diagnostic challenge. The clinical syndrome is rare, with poorly defined risk factors and varied clinical symptoms that may be identical to those produced by infection, occlusive vascular disease, and malignancy. Cerebral and leptomeningeal biopsy is the "gold standard" for the diagnosis of PACNS. Cerebrospinal fluid (CSF) and brain magnetic resonance imaging (MRI) findings support the diagnosis of PACNS, but neither laboratory tests nor neuroimaging allows a definite diagnosis to be made.

A definite diagnosis of PACNS is based on confirmed pathologic findings, whereas a probable diagnosis of PACNS is based on abnormal brain MRI and angiographic features of vasculitis with abnormal CSF studies in the absence of tissue confirmation. Atypical or possible PACNS refers to patients with a high probability of angiographic findings of vasculitis and normal CSF studies in the absence of a clear suspicion for reversible cerebral vasoconstriction syndrome (RCVS). Even though this categorization is based on tissue diagnosis, neuroimaging, angiographic findings, and CSF studies, it may not reflect differences in the validity of the diagnosis or response to treatment, and large multicenter prospective studies are necessary to establish these observations.

CLINICAL SYNDROMES OF CEREBRAL VASCULITIS

When vasculitis is clinically and pathologically restricted to the CNS, it is referred to as primary CNS vasculitis or PACNS and as secondary when associated with various other disorders (Box 164.1). The CNS may be involved as a single organ in systemic vasculitis, usually Behçet disease, polyarteritis nodosa (PAN), granulomatosis with polyangiitis (Wegener granulomatosis), systemic lupus erythematosus (SLE) and other connective tissue diseases, HIV infection, cutaneous herpes zoster infection, illicit drug use, lymphoma, amyloid angiopathy, and graft-versus-host disease.

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS**Clinical findings**

The epidemiology of PACNS is poorly understood; it occurs predominantly in men in the fourth and fifth decades but may involve patients of all ages ranging from children to the elderly. PACNS in children is not addressed in this chapter. In the Mayo Clinic experience, the incidence of primary CNS vasculitis in Olmstead County, Minnesota, was estimated to be 2.4 cases per 1,000,000 person-years, with reduced long-term survival being associated with cerebral infarction and large-vessel involvement.⁸

Most case reports and clinical series of PACNS have described the findings to be insidious and slowly progressive, cumulative, and associated with multifocal neurologic dysfunction.^{9,10} At times the mode of onset is acute or subacute.

The typical manifestation consists of nonfocal symptoms such as headache and intermittent confusion and focal neurologic symptoms such as hemiparesis. Ataxia of limbs or gait, focal cortical dysfunction, including aphasia, and seizures are less frequent. Virtually every neurologic symptom has been reported at least once. Nonspecific visual complaints occur in approximately 15% of patients, but disorders of specific ocular motor nerves

or the optic nerve and visual field defects are much less common. Systemic symptoms such as fever or weight loss are generally absent.

Stroke occurs in approximately 15% of patients at one point during the illness and is mainly due to intracerebral hemorrhage.⁹ The disease rarely causes ischemic strokes or transient ischemic attacks in the absence of widespread inflammation, as verified by CSF studies (pleocytosis). Occasionally, patients may have multiple sclerosis–like symptoms involving the spinal cord or cerebellum with early relapses and partial remissions.¹¹ CNS vasculitis may develop in patients with rapidly progressive multiple sclerosis¹² or in those treated with biologic therapy for active relapsing multiple sclerosis.¹³

Spinal cord involvement is uncommon in PACNS.¹⁴ It may occur before cerebral symptoms, coincide with cortical involvement, or be manifested as an isolated neurologic syndrome of inflammatory myelopathy. Progressive paraparesis, acute transverse myelitis, and subdural hemorrhage secondary to multiple microaneurysms have been recorded. In most cases reported, PACNS is diagnosed after death and is associated with granulomatous histopathology. MRI of the spinal cord may reveal enhanced lesions over the

thoracic and lumbar vertebrae and the conus medullaris. Spinal cord involvement with PACNS features has also been reported in patients with Hodgkin disease, Behçet syndrome, SLE, and sarcoidosis. Thorough evaluation of the spinal cord is recommended in all patients with PACNS.

A tumorlike mass lesion has been recognized in PACNS.¹⁵ Clinical features include headache, focal and nonfocal neurologic syndromes, and seizures. The mass lesions are identified on brain MRI, and most patients have abnormal findings on CSF studies. Cerebral angiography shows a mass effect and not cerebral vasculitis. Excision biopsy is required for the diagnosis. The histopathologic findings of the mass lesion are described as being those of granulomas, granulomatous angiitis, lymphocytic angiitis, and amyloid-related angiitis. Even though excision of the mass lesion may be curative, aggressive immunosuppressive therapy is associated with a favorable outcome.

Pathogenesis

Despite advances in cellular and molecular immunology and genetics and improved understanding of the cerebral blood vessel damage, the pathogenic mechanism of PACNS remains unknown. There is little support for an immune complex process. The nature of the inflammatory infiltrate is not well studied. Immunophenotype testing has indicated the presence of memory/inducer CD45RO+ T cells, CD20+ B cells, and CD8+ T cells.¹⁶⁻¹⁸

The rarity of PACNS and the limited brain tissue obtained from patients have delayed progress in this complex syndrome. Understanding the role of triggering factors such as infections, in particular, *Mycoplasma gallisepticum*, varicella-zoster virus, West Nile virus, and HIV, may help in identifying specific clues to factors that mediate the neurovascular inflammation in PACNS. Elucidation of the role of amyloid deposition as a trigger of cerebral vascular inflammation might identify the link between primary CNS vasculitis and cerebral amyloid angiopathy.

Pathology

The characteristic pathologic findings include multiple small foci of infarction and hemorrhage, segmental necrotizing granulomatous inflammation of small and medium-sized leptomeningeal and cortical arteries, and Langhans or foreign body giant cells.^{7,19} A mixture of epithelioid cells, plasma cells, macrophages, scattered granulomas, and giant cells is often present (Fig. 164.1). Fibrinoid necrosis and eosinophilic infiltration may occur. Acute lesions frequently coexist with healing or healed lesions. Though present in most autopsy cases, giant cells are not required to make a diagnosis of PACNS.

The histopathology of PACNS is quite variable, and different patterns are recognized, including granulomatous, lymphocytic, and necrotizing vasculitis. Granulomatous vasculitis, a common pattern, is characterized by vasocentric destructive mononuclear inflammation associated with well-formed granulomas, multinucleated giant cells, or both. Amyloid deposition is frequent.

Lymphocytic vasculitis is characterized by lymphocytes with occasional plasma cells, typically in multiple layers, extending through the vascular wall, and causing vascular distortion or destruction. The presence of lymphocytic infiltrates is reported in children with PACNS and those with cocaine-associated CNS vasculitis. Lymphocytic infiltrates within blood vessel walls can be found in the context of various CNS pathology, including infections and malignancy.

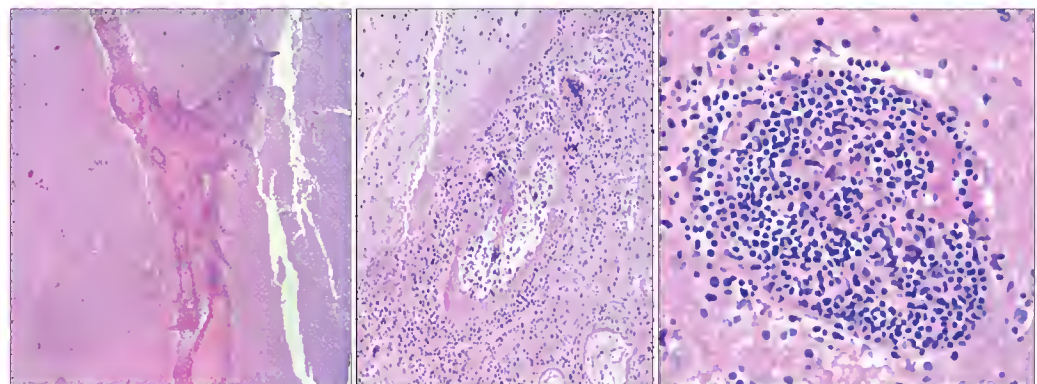
Necrotizing vasculitis is less frequent and characterized by transmural fibrinoid necrosis similar to that seen in PAN. Necrotizing vasculitis involves predominantly small muscular arteries and is associated with disruption of

BOX 164.1 CLINICAL SYNDROMES OF CEREBRAL VASCULITIS

- I. Primary central nervous system vasculitis/primary angiitis of the nervous system
 1. Granulomatous angiitis of the central nervous system
- II. Secondary central nervous system vasculitis
 1. Systemic vasculitis
 - a. Behçet disease
 - b. Necrotizing arteritis of the polyarteritis type (PAN)
 - c. Systemic granulomatous vasculitis/ANCA-associated vasculitis (GPA, CSS)
 - d. Giant cell arteritis
 - e. Hypersensitivity vasculitis and cryoglobulinemic vasculitis
 - f. Kawasaki disease
 2. Connective tissue diseases
 - a. Systemic lupus erythematosus
 - b. Sjögren syndrome
 - c. Rheumatoid arthritis
 - d. Mixed connective tissue disease/overlap syndrome
 - e. Scleroderma
 - f. Sarcoidosis
 3. Infection-associated cerebral vasculitis
 - a. Virus (varicella-zoster virus, West Nile virus, cytomegalovirus, hepatitis B and C viruses)
 - b. Retroviral infection/HIV-1
 - c. Spirochete (*Treponema pallidum*, *Borrelia burgdorferi*)
 - d. Fungi (*Aspergillus*, *Coccidioides*, *Histoplasma*)
 - e. *Bartonella*
 - f. *Rickettsia*
 - g. Bacterial meningitis
 - h. *Mycoplasma*
 - i. *Mycobacterium tuberculosis*
 - j. Protozoal, amebiasis, cysticercosis
 4. Cerebral vasculitis associated with amyloidosis, amyloid angiitis
 4. Cerebral vasculitis associated with paraneoplastic disorders, paraneoplastic angiitis

ANCA, antineutrophil cytoplasmic antibody; CSS, Churg-Strauss syndrome; GPA, granulomatosis with polyangiitis; HIV, human immunodeficiency virus.

Fig. 164.1 Brain biopsy findings of granulomatous vasculitis include a mixture of epithelioid cells, plasma cells, macrophages, and scattered granulomas (hematoxylin-eosin staining).



the internal elastic lamina. Intracerebral and subarachnoid hemorrhage is common.

PACNS involves medium-sized arteries and small vessels, including arterioles, capillaries, veins, and venules. The inflamed vessels may become narrowed, occluded, and thrombosed and are associated with tissue ischemia and necrosis in the territories of the involved vessels (Fig. 164.2). The presence of aneurysms should raise suspicion for a mycotic inflammatory reaction, and an infectious etiology needs to be identified.

Laboratory investigations

No laboratory data are specific for PACNS. General medical laboratory data are unremarkable, including acute-phase reactants such as the erythrocyte sedimentation rate and C-reactive protein. Inflammatory markers of systemic vasculitis such as antineutrophil cytoplasmic antibodies may be encountered and indicate systemic vasculitis with CNS disease. Examination of CSF is essential given that it is abnormal in most documented autopsy cases of PACNS.⁷ The characteristic CSF findings in PACNS, though nonspecific, are those of aseptic and chronic meningitis with mild lymphocytic pleocytosis and mild to moderate protein elevation. Eosinophilic pleocytosis is rarely seen. The presence of oligoclonal bands with an elevated immunoglobulin G index is reported. The major role of CSF examination is to exclude infections and malignancy. Abnormal CSF findings are an indication for angiography.

Brain imaging

No computed tomography (CT) findings are typical of PACNS. CT is less sensitive than MRI in evaluating the changes caused by cerebral vasculitis except for cerebral hemorrhage. CT angiography or multislice CT is useful for the evaluation of large-vessel vasculitis. MRI is the most sensitive technique in detecting changes in cerebral vasculitis involving large, medium,

and small vessels, but it lacks specificity in histopathologically confirmed cases. Brain MRI almost always has abnormal findings in PACNS. Serial brain MRI may be required to increase its sensitivity. Digital subtraction angiography should be considered when findings on brain MRI are normal and clinical suspicion for cerebral vasculitis remains high. Areas of stenosis, dilatation, and occlusion in medium and small arteries are suggestive of cerebral vasculitis.

The most common findings of vasculitis on brain MRI are focal areas of high signal intensity. Multiple and often bilateral infarcts of various age in more than one vascular territory are suggestive of vasculitis. Mural thickening, hemorrhages, leukoencephalopathy, and gadolinium-enhanced lesions in the cortex, deep white matter, or leptomeninges can also be demonstrated.²⁰ A single tumorlike lesion or isolated myelopathies are also described.

High-resolution contrast-enhanced MRI of the vessel wall may help in differentiating reversible cerebral vasoconstriction disorders from cerebral vasculitis. Fat-suppressed T1-weighted images are sensitive for vessel wall enhancement.²¹ Vessel wall thickening and intramural enhancement, particularly of the large arteries, are specific for CNS vasculitis.

Magnetic resonance angiography (MRA) provides complementary findings to conventional brain MRI. MRA is the principal modality for investigating patients thought to have intracranial stenosis, but only in large to medium-sized brain arteries that can be imaged with a high diagnostic accuracy, and it is generally of little use in small-vessel PACNS. High field strength (7 T) offers the possibility of directly evaluating small vessels. The changes induced by vasculitis seen on MRA are similar to those seen on conventional angiography and include stenosis with occlusion (Fig. 164.3). MRA may overestimate the severity of stenosis at points of vessel branching or vascular occlusion.

Advanced MR techniques, including MR perfusion scans, can demonstrate the microscopic flow of blood through tissue. They provide measures of cerebral blood flow, cerebral blood volume, and the mean transit time of

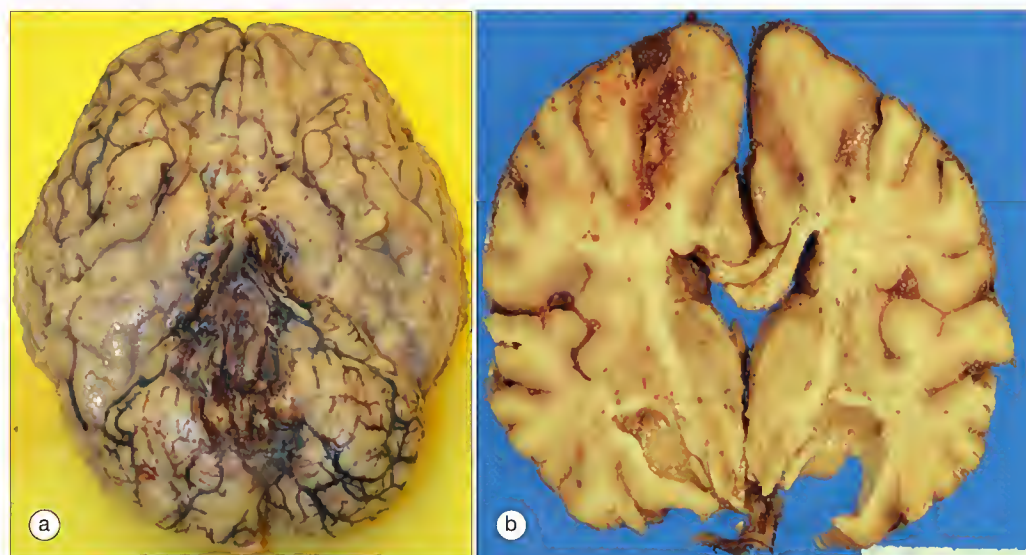


Fig. 164.2 (a) Brain stem destruction secondary to cerebral vasculitis with swelling and opacification of the meninges. (b) Cerebral vasculitis with bilateral parasagittal hemorrhagic lesions and left subfalcine herniation.

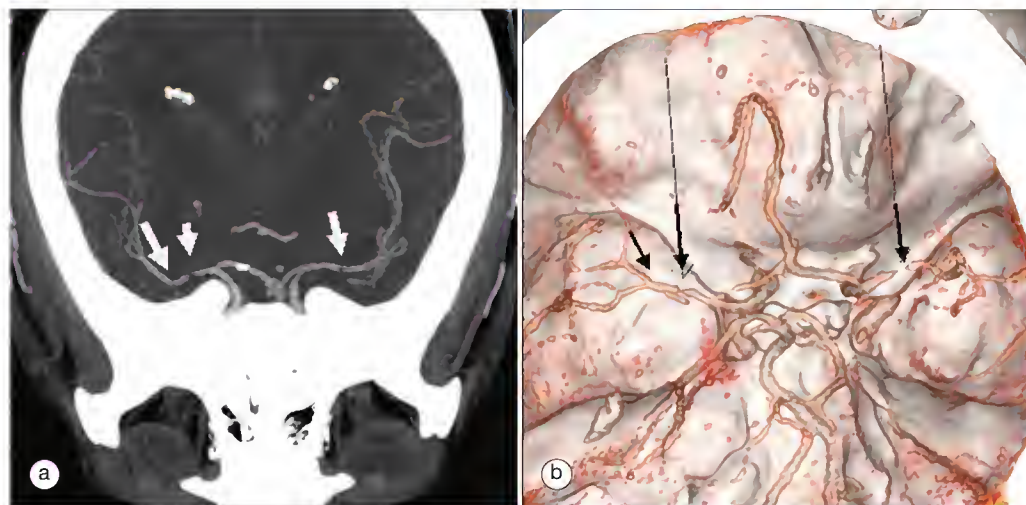


Fig. 164.3 Magnetic resonance imaging (a) and computed tomographic angiography (b) of cerebral artery branches with focal arterial narrowing (arrows) in cerebral vasculitis. The inflamed vessels may become narrowed, occluded, and thrombosed and are associated with tissue ischemia and necrosis in the territories of the involved vessels.

a unit of blood through a unit of tissue. Cerebral vasculitis is characterized by a decrease in cerebral blood volume consistent with hypoperfusion. These methods are well suited to measure treatment efficacy with serial examinations.

Diffusion weighted imaging (DWI) measures diffusion of water through the brain. The apparent diffusion coefficient (ADC) can be used to measure the integrity of structures in the brain. Although the restriction of diffusion seen with acute infarction is a marker of loss of tissue integrity, an increase in the ADC has been reported in cerebral vasculitis with normal findings on conventional brain MRI. DWI may allow earlier detection of breakdown of structures and may help in prognosis and monitoring of treated patients.

Magnetic resonance spectroscopy can be used to measure in vivo metabolism. Several studies have shown a decrease in *N*-acetylaspartate in vasculitis, a marker of neuronal and cell wall integrity. Fluorodeoxyglucose-labeled positron emission tomography (FDG PET) can detect glucose utilization and demonstrate areas of hypometabolism and hypermetabolism. Although FDG PET can visualize inflammatory changes in vessels larger than 4 mm, its use is limited, however, to large vessels. What is more important is that the abnormal diffuse and focal perfusion patterns seen on FDG PET or single-photon emission computed tomography do not always correlate with neurologic symptoms or distinguish vasculitis from nonvasculitic vasculopathy.

Currently, cerebral angiography with its anatomic and hemodynamic data and three-dimensional capability of demonstrating bilateral large- or small-vessel changes consistent with angiitis is frequently used as the basis for establishing the diagnosis of PACNS. The “typical” findings of cerebral vasculitis on four-vessel catheter angiography are widespread segmental changes in the large, intermediate, and small arteries of several territories of the cerebral circulation, microaneurysmal dilatation, vessel irregularities, and multiple occlusions with sharp cutoffs (Fig. 164.4). Occlusion of large cerebral vessels is rare. Small aneurysms, usually on vessels more distal than those bearing congenital saccular aneurysms, are occasionally present but cannot be distinguished from aneurysms complicating atrial myxoma or infective endocarditis.

The “typical” angiographic features of cerebral vasculitis have low sensitivity and specificity. Such features are found in approximately a third of patients with histopathologically confirmed PACNS and may be seen in those with CNS infection, atherosclerosis, cerebral embolism, and vasospasm of diverse causes.²² In addition, the changes induced by cerebral vasculitis are less apparent in large vessels during early phases of the illness. Small-vessel vasculitis is not detected in vessels smaller than 0.2 mm because they are below the resolution of cerebral angiography. Thus, many patients with histopathologically documented PACNS have entirely normal angiographic or nonspecific vascular findings.²³

Biopsy findings

Brain, spinal cord, and leptomeningeal biopsy remains the gold standard for the diagnosis of PACNS. The procedure of choice is open-wedged biopsy of the tip of the nondominant temporal or frontal lobe with excision of 1 cm³ of the overlying leptomeninges and gray and white matter of the underlying cortex. Directing the biopsy to an area of leptomeningeal enhancement or a focal or mass lesion when present may increase the diagnostic yield. False-negative biopsy findings occur in up to 25% of autopsy cases because of focal lesions and sampling errors.²⁴

The role of biopsy is not only to provide proof of the diagnosis of PACNS but also to exclude alternative diagnoses, including infection and malignancy. Findings on brain or leptomeningeal biopsy suggestive of nonspecific gliosis, perivascular inflammation, and parenchymal ischemic damage should be interpreted with caution and correlated with the clinical context and imaging studies. Although tissue biopsy is the most reliable approach, the presence of vasculitis in the biopsy specimen may reflect a primary infectious process with secondary vascular inflammation. A negative biopsy tissue culture remains a crucial element for the diagnosis of PACNS.

Differential diagnosis

Certain disorders that are not vasculitis in origin but that mimic PACNS and pose a challenge to the diagnosis of PACNS are listed in Box 164.2. A substantial number of patients will be found to have the clinical syndrome of PACNS but may have cerebral vasospasm with no clear evidence of cerebral vasculitis.

Reversible Cerebral Vasoconstriction Syndromes

RCVSs comprise a group of disorders characterized by multifocal reversible segmental vasoconstriction of the cerebral vessels and lack of vasculitic

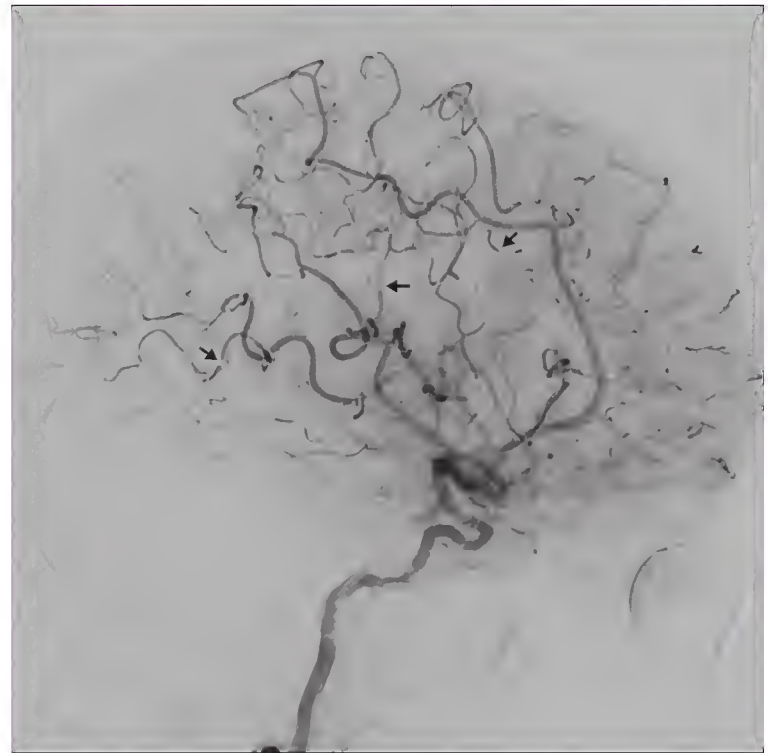


Fig. 164.4 Oblique lateral four-vessel angiography of cerebral vasculitis. Characteristic focal cerebral arterial narrowing (arrows) with segmental changes, occlusions, and a sharp cutoff are seen in several territories.

BOX 164.2 NONINFLAMMATORY VASCULOPATHIC DISORDERS THAT MIMIC PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

- Reversible cerebral vasoconstriction syndromes
- Intracranial atherosclerosis
- Cerebral embolism
- Hypercoagulable state
- Intracranial vertebral artery dissection
- Neurofibromatosis
- Fibromuscular dysplasia
- Susac syndrome
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Moyamoya disease
- Acute multifocal placoid pigment epitheliopathy
- Mitochondrial encephalopathy, lactic acidosis, and strokelike illness (MELAS)
- Progressive multifocal leukoencephalopathy
- Reversible posterior leukoencephalopathy syndrome
- Demyelinating syndrome

changes on brain biopsy.²⁵ RCVSs include Call-Fleming syndrome; thunderclap headache; postpartum angiopathy; migraine cerebral vasospasm; benign angiopathy of the CNS; exposure to vasoactive substances, including adrenergic or serotonergic drugs; and less commonly, severe hypertension, pheochromocytoma, metabolic disorders, brain tumors, and brain surgery. In very rare instances, vasculitis has been reported with amphetamine and cocaine use.^{26,27}

RCVS has a female preponderance with a mean age at onset of around 45 years. A provocative factor can be identified in 12% to 60% of patients. The pathogenic mechanism of RCVS is largely unknown and is supposedly due to a transient alteration in cerebrovascular tone.

The clinical course of RCVS is uniphasic and may vary from pure cephalgia to rare catastrophic events associated with several hemorrhagic and ischemic strokes, brain edema, and death. The initial feature is acute severe “thunderclap” headaches, which may be recurrent over a 1- to 3-week period, followed at times by focal neurologic symptoms and seizures. Major clinical complications include localized cortical subarachnoid hemorrhage, watershed infarcts, and posterior reversible leukoencephalopathy. Ischemic

stroke with transient ischemic strokes and cerebral infarcts or microscopic hemorrhage occurs a few days after the initial normal findings on neuroimaging, and cerebral vasoconstriction may arise 2 to 3 weeks after clinical onset.

The diagnosis of RCVS should be suspected (Table 164.1) in a patient with an acute onset of symptoms in a specific clinical setting, such as in the postpartum period, in the context of migraine headache, or following the ingestion of a drug that causes cerebral vasospasm. CSF examination shows normal to mild involvement. No specific brain MRI findings accompany RCVS; high-resolution contrast-enhanced MRI of the vessel wall may enable differentiation between RCVS and CNS vasculitis. The key diagnostic element is reversibility of the angiographic changes within 12 weeks after onset, which is typical of RCVS. When cerebral vasculitis resolves spontaneously or with a short course of glucocorticoid therapy, a form of RCVS should be suspected. Nimodipine seems to reduce thunderclap headaches with 48 hours but has no definite effect on the outcome of hemorrhagic or ischemic stroke. Relapses are rare.

TABLE 164.1
Demographic characteristics, clinical features, and imaging studies distinguishing PACNS from RCVS

Feature	PACNS	RCVS
Demographics		
Age at onset (yr)	40-50	20-40
Gender predilection	Men	Women
Clinical features	Variable	Cephalgia Catastrophic stroke/edema
Onset of symptoms	Insidious	Acute/subacute
Provocative factors	None	Vasoactive medication Eclampsia/postpartum status Migraine
Headache	Progressive	Thunderclap
Stroke, onset	During the course of illness	Early, a few days after initial normal imaging
Course	Progressive	Uniphasic Rapid dynamic nature
Diagnosis		
CSF	Abnormal	Normal
High-resolution MRI of the vessel wall	Arterial wall enhancement	Lack of contrast enhancement
Treatment	Glucocorticoids/ immunosuppressives	Calcium channel blockers/ nimodipine Magnesium
Resolution at follow-up angiography	Months	Within 3 mo

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PACNS, primary angiitis of the central nervous system; RCVS, reversible cerebral vasoconstriction syndrome.

Amyloid angiitis

Cerebral amyloid angiopathy (CAA) is a nonvasculitic inflammatory disorder that is defined by the accumulation of amyloid in the walls of small and medium-sized cerebral arteries; it is often recognized by spontaneous and recurrent hemorrhages in the brain, spinal cord, and leptomeninges. Intracerebral lobar hemorrhage is sometimes silent, and patients may have progressive dementia and spastic paraparesis. Recently, a few case reports have described granulomatous angiitis in patients with sporadic, amyloid beta peptide (A β)-related CAA.²⁸

Inflammatory amyloid angiopathy is associated with subacute cognitive decline, headaches, seizures, focal neurologic deficits, and hallucinations. Most patients are found to have white matter hyperintensities and microhemorrhages on imaging studies that are of similar appearance to those in PACNS. CSF examination usually shows modest elevation of protein and lymphocytic pleocytosis; rarely, eosinophilic pleocytosis is reported. The histopathology of brain lesions includes vasculitic features with angiodestructive inflammation that is often granulomatous and associated with meningeal lymphocytosis (Fig. 164.5). A β is consistently present in abundance in affected blood vessels but is usually scanty within the parenchyma of the cerebral cortex.

Paraneoplastic angiitis

Hodgkin disease, non-Hodgkin lymphoma, and intravascular lymphomatous and angio-immunolymphoproliferative diseases may be accompanied by paraneoplastic angiitis manifested as granulomatous angiitis of the CNS or recurrent cerebral venous thrombosis,²⁹ and such conditions have a poor outcome. CNS lymphomas may have imaging studies that are characteristic of vasculitis of the CNS and spinal cord and, histologically, may be indistinguishable from vasculitis. Necrotizing arteritis and microvasculitis have also been described in patients with breast cancer and occult small cell lung cancer with related anti-Hu-associated paraneoplastic encephalomyelitis and sensory neuropathy. Molecular genetic testing and immunohistochemical staining are indispensable diagnostic tools for verification.

Diagnostic approach

The major consideration in the approach to a patient with possible PACNS is to decide whether the clinical manifestations are restricted to the nervous system or whether they are part of a more active systemic disease. A careful history and physical examination of the skin, eyes, paranasal sinuses, testicles, kidneys, and lungs is critical in the process of the differential diagnosis of PACNS.

Correct diagnosis of PACNS requires a high index of suspicion coupled with knowledge of disorders that may masquerade as PACNS. An algorithmic approach with a flow sheet containing questions has been used when encountering a patient with a possible diagnosis of PACNS (Box 164.3), but a definite diagnosis is made only after extensive investigation.^{30,31}

PACNS should be suspected in the setting of chronic meningitis; recurrent focal neurologic symptoms such as atypical strokes; unexplained diffuse neurologic symptoms such as headache, seizure, and cognitive abnormalities; or spinal cord dysfunction not associated with systemic disease or any other process.

General laboratory and serologic evaluation is helpful in the differential diagnosis of PACNS (Box 164.4). CSF studies are crucial for eliminating infections, malignancy, or alternative process. In such circumstances,

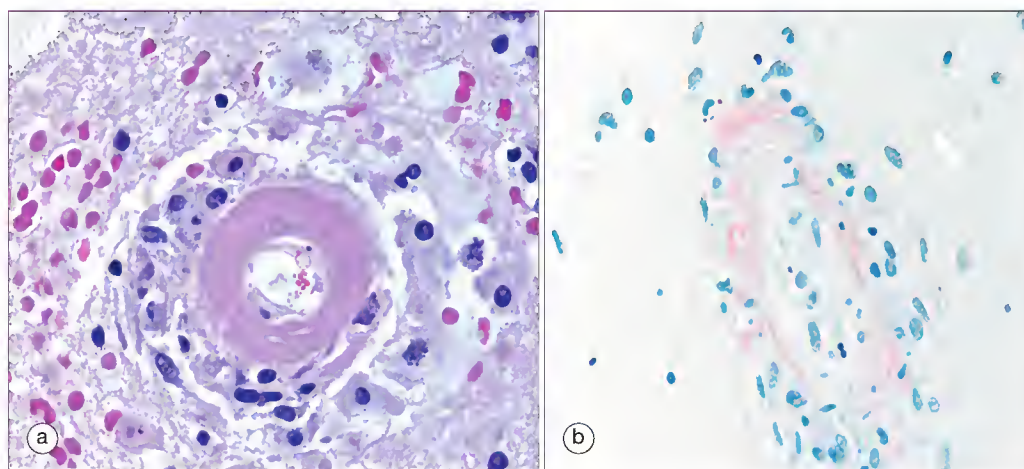


Fig. 164.5 (a) Cerebral vasculitis with amorphous eosinophilic deposits in the blood vessel wall (A β amyloid angiitis). (b) Angiodestructive inflammation with granuloma formation and meningeal lymphocytosis.

BOX 164.3 ALGORITHMIC APPROACH TO THE DIAGNOSIS OF PACNS

1. *Is there a known systemic disease?*
 - a. Systemic vasculitis, connective tissue diseases
 - b. Infection: HIV, viral, bacterial, Lyme, syphilis, mycobacterial, fungal, protozoal
 - c. Malignant hypertension, eclampsia, infective endocarditis, atrial myxoma/thrombus, patent foramen ovale, disrupted carotid plaque
 - d. Neoplasm: intravascular lymphoma, lymphoid granulomatosis
 - e. Drug exposure and illicit drug use
 - f. Recent trauma, neurosurgery, intracranial dissection
2. *Are there abnormal findings on MRI (brain, leptomeninges)?*
 - a. Vasculitis, vascular disorders including stroke syndrome or arterial venous malformation, demyelinating syndrome, sarcoidosis, infection, neoplasm
3. *Is there abnormal cerebrospinal fluid (pleocytosis)?*
 - a. Acute, recurrent, and chronic meningitis; partially treated bacterial (pyogenic), HIV, viral, syphilitic, Lyme, mycobacterial, fungal, protozoal infection
 - b. Noninfectious: PML, sarcoidosis, Behçet disease, neoplasm
4. *Are there abnormal findings on conventional cerebral angiography?*
 - a. True vasculitis: PACNS, systemic vasculitis
 - b. Infection
 - c. Reversible cerebral vasoconstriction syndromes
 - d. Neoplasm
 - e. Subarachnoid hemorrhage
 - f. Trauma
5. *Are there abnormal biopsy findings with inflammation?*
 - a. True vasculitis: PACNS, secondary vasculitis
 - b. Perivascular inflammation: demyelinating syndrome, undersampled vasculitis, infection (PML, SSPE, VZV), lymphoma
 - c. Neoplasm: lymphoma, metastatic malignancy

Small-vessel PACNS may have normal findings on cerebral angiography. However, PACNS is unlikely in the context of normal findings on brain MRI and normal spinal fluid studies. HIV, human immunodeficiency virus; MRI, brain magnetic resonance imaging; PACNS, primary angiitis of the central nervous system; PML, progressive multifocal leukoencephalopathy; SSPE, subacute sclerosing panencephalitis; VZV, varicella-zoster virus.

absence of CSF abnormalities and normal findings on MRI of the brain are associated with a high negative predictive value for the development of PACNS, which may obviate the need to perform cerebral angiography or blind brain biopsy. This assumption is based on the observation of different case series in which the majority of patients with PACNS had abnormal CSF findings and from patients with PACNS confirmed by histopathology who continue to have never completely normal CSF studies on repeated examination.^{32,33}

Even though neuroimaging plays a crucial role in the differential diagnosis of PACNS, such studies remain nonspecific or insufficient for the diagnosis of PACNS. With its good safety profile, cerebral angiography is generally required for confirmation of cerebral vasculitis before initiating immunosuppressive therapy and when brain MRI findings are suspicious for angiitis in conjunction with the clinical history. Repeated angiography is indicated before brain biopsy if the angiographic findings are suggestive of RCVS.

Brain biopsy is recommended when patients have chronic meningitis and an infectious process or malignancy is suspected. Brain biopsy is necessary when a focal inflammatory lesion or mass effect is seen on neuroimaging studies. Confirmation of the diagnosis by brain biopsy is crucial before the use of aggressive immunosuppressive therapy.

Treatment

No evidence-based treatment recommendations are available for primary CNS vasculitis. Initial reports described the clinical course of PACNS as being progressive, associated with serious morbidity, and in most cases, fatal. Treatment with glucocorticoids and cyclophosphamide achieves remission and disease control in many patients; however, some patients respond to prednisone alone. Given the aggressive course based on historical cases in the literature, the currently recommended therapy should follow the general treatment of systemic vasculitis.³⁴

In documented cases of PACNS, a combination of oral glucocorticoids and oral cyclophosphamide is suggested for at least 6 months. Intravenous methylprednisolone and cyclophosphamide should be initiated in patients with a rapidly progressive course, large-vessel involvement, and recurrent cerebral infarctions. This group of patients is known to have a poor response to treatment and may have a fatal outcome.

BOX 164.4 LABORATORY EVALUATION FOR SUSPECTED PACNS**General studies**

Complete blood count
Complete metabolic panel and hepatic function test
Erythrocyte sedimentation rate
C-reactive protein
Lipid panel
Urinalysis and urine microalbumin
Urine toxicology screen
Prothrombin and thromboplastin time
Proteins S and C
Serum and urine protein electrophoresis and serum immunoglobulin electrophoresis
Quantitative immunoglobulin
Acute hepatitis panel, B and C virus
HIV

Serology panel

Rheumatoid factor
Antinuclear antibody
Antibodies to Ro/SSA, La/SSB, Sm, and RNP antigens
Anticardiolipin antibody and lupus anticoagulant
Serum complement level: C2, C3, C4, and CH₅₀
Antibody to double-stranded DNA
Antineutrophil cytoplasmic antibody
Angiotensin-converting enzyme
Lyme titer (ELISA and Western blot)
Serum cryoglobulins
Treponema pallidum, rapid plasma antigen, and fluorescent treponemal antigen

Cerebrospinal fluid studies

Protein
Glucose
Cell count
IgG level and index
Oligoclonal bands
Venereal Disease Research Laboratory (VDRL)
Viral antibodies and antigens and polymerase chain reaction for West Nile virus, cytomegalovirus, herpes simplex and herpes zoster, and HIV
Lyme titer
ANCA titer
ACE level
India ink, Gram stain, and routine cultures, including acid-fast bacillus stain

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; CH₅₀, 50% hemolyzing dose of complement; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; PACNS, primary angiitis of the central nervous system; RNP, ribonucleoprotein.

The initial dose of prednisone recommended to achieve disease control is 1 mg/kg/day. Intravenous methylprednisolone at 15 mg/kg/day for 3 to 5 days may be used, and daily prednisone is then initiated. Cyclophosphamide induction therapy is recommended, either oral daily intake at a starting dose of 1.5 to 2.0 mg/kg/day or intermittent monthly intravenous doses of 600 to 750 mg/m² for a 6-month period. Strict patient-specific monitoring of treatment-related toxicity and infection remains essential. Thus, the cyclophosphamide dose should be adjusted to the serum creatinine level to avoid severe leukopenia. The white blood cell count should be kept above 3500/μL.

In the event of clinical remission, treatment should be switched to anti-metabolite therapy, such as azathioprine or mycophenolate mofetil, for the duration of therapy. Methotrexate may be used, but its efficacy in treating CNS disease is limited by poor penetration through the blood-brain barrier. Similarly, oral glucocorticoids should be tapered to a smaller daily dose at 4 to 6 weeks after initiation of treatment.

No optimal treatment duration has been recommended, and management of relapse is not well studied. The role of antiplatelet therapy, vasodilators, calcium channel blockers, plasma exchange, intravenous immunoglobulin therapy, or other immunomodulatory therapy, including anti-tumor necrosis factor-α therapy or rituximab, awaits prospective multicenter clinical studies in patients with biopsy-proven PACNS.

No clinical response endpoints have been established for PACNS. Frequent neurologic evaluation for clinical response is recommended on a monthly basis during the early course of treatment. Clinically meaningful improvement may be suggested by improved headache and mental status,

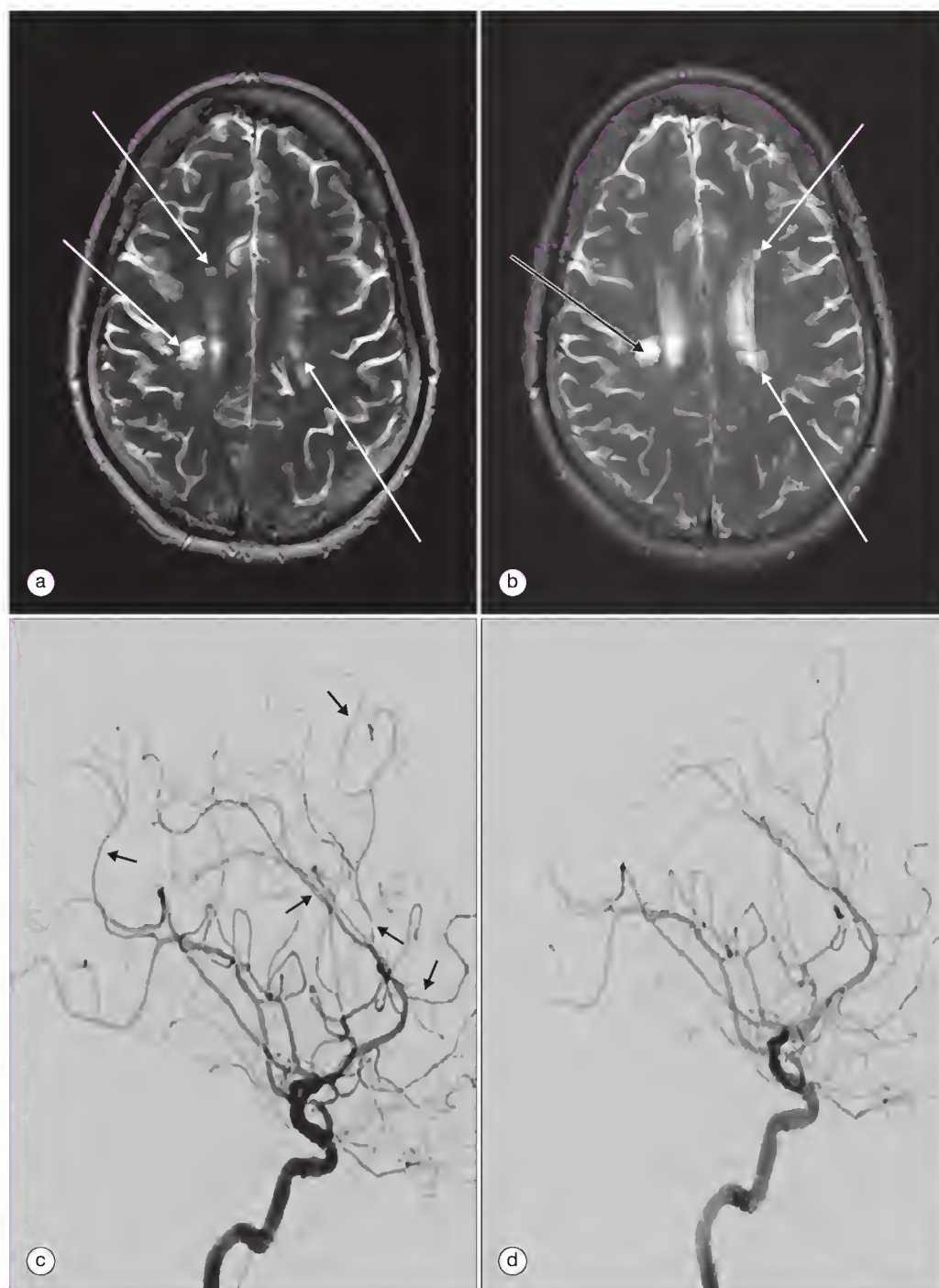


Fig. 164.6 Brain magnetic resonance images (a and b) and cerebral angiograms (c and d) of cerebral vasculitis before (a and c) and after (b and d) immunosuppressive treatment. (a) Brain magnetic resonance imaging with stable multiple remote prior lacunar infarcts (arrows) with no new diffusion weighted or enhancing lesion. (c) Cerebral angiography shows mild improvement (arrows) in the areas of vascular abnormality involving cortical vessels from all intracranial circulatory territories. A 2-mm sidewall left cavernous internal carotid artery aneurysm and a 2-mm right posterior communicating artery aneurysm were unchanged.

a fall in acute-phase response, lack of new lesions on repeated MRI, or resolution of previous inflammatory lesions (Fig. 164.6).

CSF abnormalities serve as a useful indicator of decreased disease activity and should be evaluated after 12 weeks of therapy. Disease activity and damage can also be monitored with serial brain MRI or MRA every 3 months during the first year and every 6 months during the second year to assess for resolution of infarcts, as well as to detect silent new ischemic lesions during the tapering period of immunosuppressive treatment. Repeated cerebral angiography may be indicated if the diagnosis is not clear, response to treatment is poor, a relapse of symptoms occurs, or a suspicious scar tissue lesion or mass lesion is found on MRI.³⁵

Routine vaccination against influenza and pneumonia is suggested, in addition to antimicrobial prophylaxis with trimethoprim-sulfamethoxazole to prevent *Pneumocystis jiroveci* pneumonia. Close monitoring of treatment-related adverse events, including infection, osteoporosis, and other complications such as epileptic seizures, depression, cognitive dysfunction, cardiac arrhythmias, thrombosis, and respiratory and urinary tract infections is essential; early diagnosis and adequate treatment are required to prevent serious morbidity and mortality. Efforts to limit accelerated atherosclerosis through aggressive control of diabetes mellitus, hypertension, and dyslipidemia, as well as smoking cessation, are emphasized.

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OTHER SYSTEMIC ILLNESSES

165

Monogenic autoinflammatory diseases

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■ DANIEL L. KASTNER

- Monogenic autoinflammatory diseases are a group of illnesses that typically manifest in childhood and are caused by single-gene defects in innate immune regulatory pathways. These illnesses can mimic infections clinically, but the inflammatory lesions are aseptic.
- The prototypic autoinflammatory diseases are characterized by episodes of fever flares associated with localized inflammation, with periods of remission. Another group of autoinflammatory syndromes is caused by single-gene mutations in loci regulating interleukin-1 (IL-1) processing, secretion, and signaling.
- A number of rare autoinflammatory diseases of Mendelian inheritance show variable responses to IL-1 inhibition and an inflammatory phenotype that is not well understood.
- Recently, novel autoinflammatory conditions unresponsive to IL-1-blocking therapy have been identified; these include the proteasome-associated autoinflammatory syndromes as well as early-onset inflammatory bowel disease caused by mutations in the IL-10 signaling pathway.
- Systemic AA amyloidosis can occur in any of these illnesses.
- Early diagnosis of these syndromes is important because effective therapies are available.

INTRODUCTION

The era of monogenic autoinflammatory diseases started in 1997 with the discovery that autosomal recessive mutations in the then-novel gene *MEFV* cause the periodic fever syndrome known as *familial Mediterranean fever*^{1,2} and the subsequent description of autosomal dominant mutations in *TNFRSF1A*, encoding the 55-kDa tumor necrosis factor (TNF) receptor, as the cause of another periodic fever syndrome, now termed *TNF receptor-associated periodic syndrome*, in 1999.³ The term *autoinflammatory diseases* was proposed because the genetics suggested that these periodic fever syndromes are caused by dysregulation of innate immune pathways.

Demographic, genetic, and clinical features of the Mendelian autoinflammatory diseases described in this chapter are summarized in Table 165.1a and b. In many instances, a clinical diagnosis can be made on the basis of clinical features, and the diagnosis is then confirmed by genetic testing.

THE “CLASSIC” PERIODIC FEVER SYNDROMES

Familial Mediterranean fever

Background

Familial Mediterranean fever (FMF) (OMIM #249100) is most prevalent in individuals of Ashkenazi Jewish, non-Ashkenazi Jewish, Armenian, Arab,

Turkish, and Italian ancestry. DNA analysis has also confirmed the presence of FMF in individuals with no known Mediterranean or Middle Eastern ancestry. In the past, two *MEFV* mutations were thought to be necessary for genetic diagnosis of FMF, consistent with an autosomal recessive mode of inheritance. However, there has been a growing realization that many patients with clinical FMF have only a single demonstrable *MEFV* mutation even with complete gene sequencing.^{4,5} DNA studies have raised the possibility that, at least for certain rare *MEFV* mutations, dominant inheritance is possible.^{6,7}

Approximately 90% of patients with FMF exhibit their first symptoms by the age of 20.^{8,9} Increasingly, however, genetic testing has allowed the recognition of mild disease in adults, who often give a history of symptoms dating back to childhood. There is an excess of male cases over female (usually with a male-female ratio of about 1.5:1 to 2.0:1), and despite the possibility of underdiagnosis, the incidence of clinically diagnosed FMF has been found to be as high as 1 in 248 individuals in the Libyan Jewish population,^{5,10} which implies a carrier frequency of at least 1 in 8 individuals, assuming a simple recessive model of inheritance. Environmental factors are increasingly implicated in disease severity, with milder phenotypes seen in Eastern Mediterranean patients with FMF who migrate to Europe.¹¹

Genetics and pathophysiology

The FMF gene *MEFV* was identified by positional cloning by two independent groups in 1997.^{1,2} It encodes a 781-amino-acid protein product that has been named *pyrin* and *marenostrin* by the two teams.^{1,2} Four missense mutations in exon 10, M680I (isoleucine for methionine at codon 680), M694V (valine for methionine at codon 694), M694I (isoleucine for methionine at codon 694), and V726A (alanine for valine at codon 726), were found in absolute association with disease in two large panels of families.^{1,2}

Pyrin is expressed in neutrophils, eosinophils, monocytes, dendritic cells, and synovial fibroblasts but not at significant levels in lymphocytes.^{12,13} Recognition of pyrin's N-terminal homotypic interaction domain, PYD, is the basis for two working hypotheses on pyrin function (Fig. 165.1a). Pyrin binds an adaptor protein called ASC (apoptosis-associated speck-like protein with a caspase recruitment domain)¹⁴ that consists of an N-terminal PYD and a C-terminal caspase activation and recruitment domain (CARD).¹⁵ The PYD of pyrin binds the PYD of ASC, whereas the CARD of ASC binds certain other CARD proteins, which regulate cytokine production, apoptosis, and nuclear factor- κ B (NF- κ B) activation. By one hypothesis, the pyrin-ASC interaction may inhibit the assembly of the inflammasome, a macromolecular complex that includes ASC and cryopyrin and is known to activate interleukin-1 (IL-1 β) and IL-18 (see Fig. 165.1a).¹⁶⁻¹⁸ Mice expressing a truncated pyrin are more sensitive to endotoxin, with increased caspase-1 activation, increased IL-1 β maturation, and a defect in macrophage apoptosis¹⁹; and macrophages from pyrin knockout mice produce increased amounts of IL-1 β when stimulated in culture. Moreover, pyrin has an additional inhibitory effect on IL-1 β production through its C-terminal B30.2 (SPRY) domain¹⁹ and, consistent with an antiinflammatory role for pyrin, the use of small interfering RNA to knock down pyrin in a human

TABLE 165.1A
Demographic, genetic, and clinical features of the monogenic autoinflammatory diseases

	FMF	TRAPS	HIDS	CAPS-FCAS	CAPS-MWS	CAPS-NOMID	DIRA	PGA
OMIM No.	249100	142680	260920	120100	191900	607115	612852	186580
Inheritance	AR*	AD	AR	AD	AD	AD, sporadic	AR	AD, sporadic
Ethnic distribution	Jewish, Arab, Armenian, Turkish, Italian	Broad ethnic distribution; originally Irish-Scottish	Dutch, northern European	Primarily European	Northern European	Any ethnicity	Newfoundland, Puerto Rican, Brazilian, Dutch, Palestinian	Originally whites, but other races also seen
Gene (chromosome region)	MEFV (16p13.3)	TNFRSF1A (12p13)	MVK (12q24)	NLRP3 (1q44)	NLRP3 (1q44)	NLRP3 (1q44)	IL1RN (2q14.2)	NOD2/CARD15 (16q12.1-13)
Protein	Pyrin	55-kDa TNF receptor	Mevalonate kinase	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)	IL-1Ra	NOD2
Pathogenesis	Predominantly IL-1 mediated + unknown pathway	Partially IL-1 mediated + TNF + ROS	Partially IL-1 mediated + unknown pathway	IL-1 β mediated	IL-1 β mediated	IL-1 β mediated	IL-1 mediated	NF- κ B activation + unknown pathway
Typical attack length	1-3 days	>7 days	3-7 days	30 min-72 hr	1-2 days	Continuous with exacerbations	Variable	Variable
Clinical manifestations								
Fever	Present	Present	Present	Present	Present	Present	Observed in some patients	Uncommon
Serosal	Aseptic peritonitis, pleuritis, asymptomatic pericardial involvement, acute scrotum	Peritonitis, pleuritis, pericarditis, scrotal pain	Peritonitis is uncommon and pleuritis is rare	Absent	Rarely pericarditis; peritonitis and pleuritis are rare	Rarely pericarditis; peritonitis and pleuritis are rare	Uncommon	Uncommon
Musculoskeletal	Exercise-induced myalgia, protracted febrile myalgia (rare), large-joint episodic arthritis, chronic arthritis of hip, sacroiliitis	Migratory myalgia, arthralgia, nonerosive arthritis	Arthralgia, nonerosive acute polyarthritis; myalgia is uncommon	Myalgia, arthralgia	Myalgia, arthralgia, oligoarticular arthritis	Epiphyseal overgrowth, contractures, intermittent or chronic arthritis	Recurrent multifocal aseptic osteomyelitis, perostitis, vertebral destruction, odontoid destruction	Polyarthritis, hypertrophic tenosynovitis
Mucocutaneous	ELE	Migratory erythema often accompanying myalgia; ELE	Maculopapular or purpuric exanthema, aphthous oral ulcers	Cold-induced neutrophilic urticaria	Neutrophilic urticaria	Neutrophilic urticaria	Pustular dermatitis	Scaly, erythematous, maculopapular eruption, noncaseating granulomata
Neurologic	Aseptic meningitis (rare)	Headache; aseptic meningitis (rare)	Uncommon	Headache	Sensorineural hearing loss	Delayed mental development, chronic aseptic meningitis, headache, sensorineural hearing loss	Rare CNS vasculitis	Rare (stroke, cranial neuropathy and hearing loss)
Ocular	Uncommon	Periorbital edema, conjunctivitis, uveitis	Uncommon	Conjunctivitis	Conjunctivitis, episcleritis, optic disk edema	Conjunctivitis, uveitis, papilledema, progressive amaurosis	Conjunctivitis rare	Chronic uveitis, conjunctivitis, synechiae, cataract, glaucoma, vision loss
Gastrointestinal	Mild to severe abdominal pain due to peritonitis	Abdominal pain, peritonitis, diarrhea, constipation	Abdominal pain, vomiting, diarrhea, hepatosplenomegaly	Nausea	Abdominal pain	Hepatosplenomegaly during exacerbations	Uncommon	Uncommon
Lymphadenopathy	Uncommon	Occasionally observed	Cervical bilateral adenopathy frequently observed during attacks	Absent	Occasionally observed	Occasionally observed	Uncommon	Uncommon
Amyloidosis risk	Varies according to genotype and environment	~14% of cases	Rare	Uncommon (~2%)	~25% of cases	Occasionally observed in adulthood	Not known	Not observed to date
Treatment	Daily oral colchicine, anti-IL-1 agents (anakinra, rilonacept, canakinumab)	Etanercept, anti-IL-1 agents (anakinra)	NSAIDs, CS, simvastatin, anti-IL-1 agents (anakinra, canakinumab)	Anti-IL-1 agents (anakinra, canakinumab, rilonacept)	Anti-IL-1 agents (anakinra, canakinumab, rilonacept)	Anti-IL-1 agents (anakinra, canakinumab)	Anti-IL-1 agents (anakinra)	CS, methotrexate, azathioprine, cyclosporine, anti-TNF agents

*FMF has also been described as an autosomal dominant disease.
 AD, autosomal dominant; AR, autosomal recessive; CAPS, cryopyrin associated periodic syndrome; CNS, central nervous system; CS, corticosteroids; DIRA, deficiency of interleukin 1 receptor antagonist; ELE, erysipelas-like erythema; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome with periodic fever; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NOD2, nucleotide-binding oligomerization domain 2; NSAIDs, nonsteroidal antiinflammatory drugs; OMIM, Online Mendelian Inheritance in Man; PGA, pediatric granulomatous arthritis; ROS, reactive oxygen species; NF- κ B, nuclear factor- κ B; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

TABLE 165.1B

Demographic, genetic, and clinical features of the monogenic autoinflammatory diseases

	PAPA syndrome	Majeed syndrome	FCAS2	PRAAS	DITRA	CAMPS	EO-IBD
OMIM No.	604416	146462	611762	256040	614204	602723	613148; 612567; 612381
Inheritance	AD	AR	AD	AR	AR	AD, <i>de novo</i>	AR
Ethnic distribution	Originally whites; any ethnicity	Originally Jordanian	Caribbean, white	Japanese, Hispanic, Spanish, Portuguese, white	Tunisian, Japanese	European, Taiwanese, Haitian	Originally Lebanese and Turkish
Gene (chromosome region)	<i>PSTPIP1</i> (12q24-q25.1)	<i>LPIN2</i> (18p11.31)	<i>NLRP12</i> (19q13.42)	<i>PSMB8</i> (6p21.3)	<i>IL36RN</i> (2q14)	<i>CARD14</i> (1725)	<i>IL10</i> (1q31-q32); <i>IL10RA</i> (11q23); <i>IL10RB</i> (21q22.11)
Protein	PSTPIP1	Lipin-2	NLRP12	PSMB8	IL-36Ra	CARD14	IL-10; IL-10RA; IL-10RB
Pathogenesis	Arthritis: IL-1 mediated Skin features: unknown pathways	IL-1 mediated (?)	IL-1 and IL-6 mediated (?)	IFN mediated + MAPK activation + unknown	IL-36 + IL-17/IL-23 (?)	IL-17/IL-23 + unknown pathway	IL-10 deficiency + TNF + unknown pathway
Typical attack length	Variable	Variable	2-15 days	Variable, continuous with exacerbations	Variable	Variable, continuous with exacerbations	Variable, continuous with exacerbations
Clinical manifestations							
Fever	Uncommon	Uncommon	Present	Present	Present	Uncommon	Present
Serosal	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	None	Uncommon
Musculoskeletal	Deforming aseptic pyogenic arthritis	Recurrent multifocal aseptic osteomyelitis	Myalgia, arthralgia	Myositis, arthralgia, arthritis	Uncommon	Arthritis in 30% of patients	Arthritis
Mucocutaneous	Pyoderma gangrenosum, pathergy, skin abscesses, cystic acne, hidradenitis	Pustular dermatoses	Urticarial exanthema, oral ulcers	Nodular exanthema, panniculitis, lipodystrophy	Generalized pustular psoriasis, oral mucosal involvement occasionally observed	Plaque or pustular psoriasis	Folliculitis
Neurologic	Uncommon	Uncommon	Uncommon	Basal ganglia calcifications	Uncommon	Uncommon	Uncommon
Ocular	Uncommon	Uncommon	Uncommon	Eyelid edema and erythema	Uncommon	Uncommon	Uncommon
Gastrointestinal	Uncommon	Uncommon	Abdominal pain and vomiting	Increased abdominal volume and hepatosplenomegaly	Uncommon	Uncommon	Severe colitis: bloody diarrhea, abscesses, perianal fistula, oral aphthous lesions
Lymphadenopathy	Uncommon	Uncommon	Occasionally observed	Present	Uncommon	Uncommon	Uncommon
Any/diagnosis risk	Not observed to date	Not observed to date	Not observed to date	Not known	Not known	None	Not observed to date
Treatment	CS, anti-TNF agents; anti-IL-1 agents (anakinra)	CS, anti-TNF agents; anti-IL-1 agents (anakinra, canakinumab)	CS, anti-IL-1 agents (anakinra)	CS, anti-IL-6 agents (tocilizumab), possibly JAK inhibitors	CS, cyclosporine, retinoids, anti-TNF agents	MTX, CsA, anti-TNF agents, psoriasis medications	CsA, AZA, mesalamine, mercaptopurine, MTX, TAC, anti-TNF agents, allogeneic HSCT

AD, autosomal dominant; AR, autosomal recessive; AZA, azathioprine; CAMPS, CARD14-mediated psoriasis; CS, corticosteroids; CsA, cyclosporine; DITRA, deficiency of interleukin 36 receptor antagonist; EO-IBD, early-onset inflammatory bowel disease; FCAS2, familial cold autoinflammatory syndrome 2; HSCT, hematopoietic stem cell transplantation; IFN, interferon; IL, interleukin; IL-10RA, IL-10RB, IL-36-receptor antagonist; IVIG, intravenous immunoglobulin; JAK, Janus kinase; MAPK, mitogen-activated protein kinases; MTX, methotrexate; OMIM, Online Mendelian Inheritance in Man; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PRAAS, proteasome-associated autoinflammatory syndromes; TAC, tacrolimus; TNF, tumor necrosis factor.

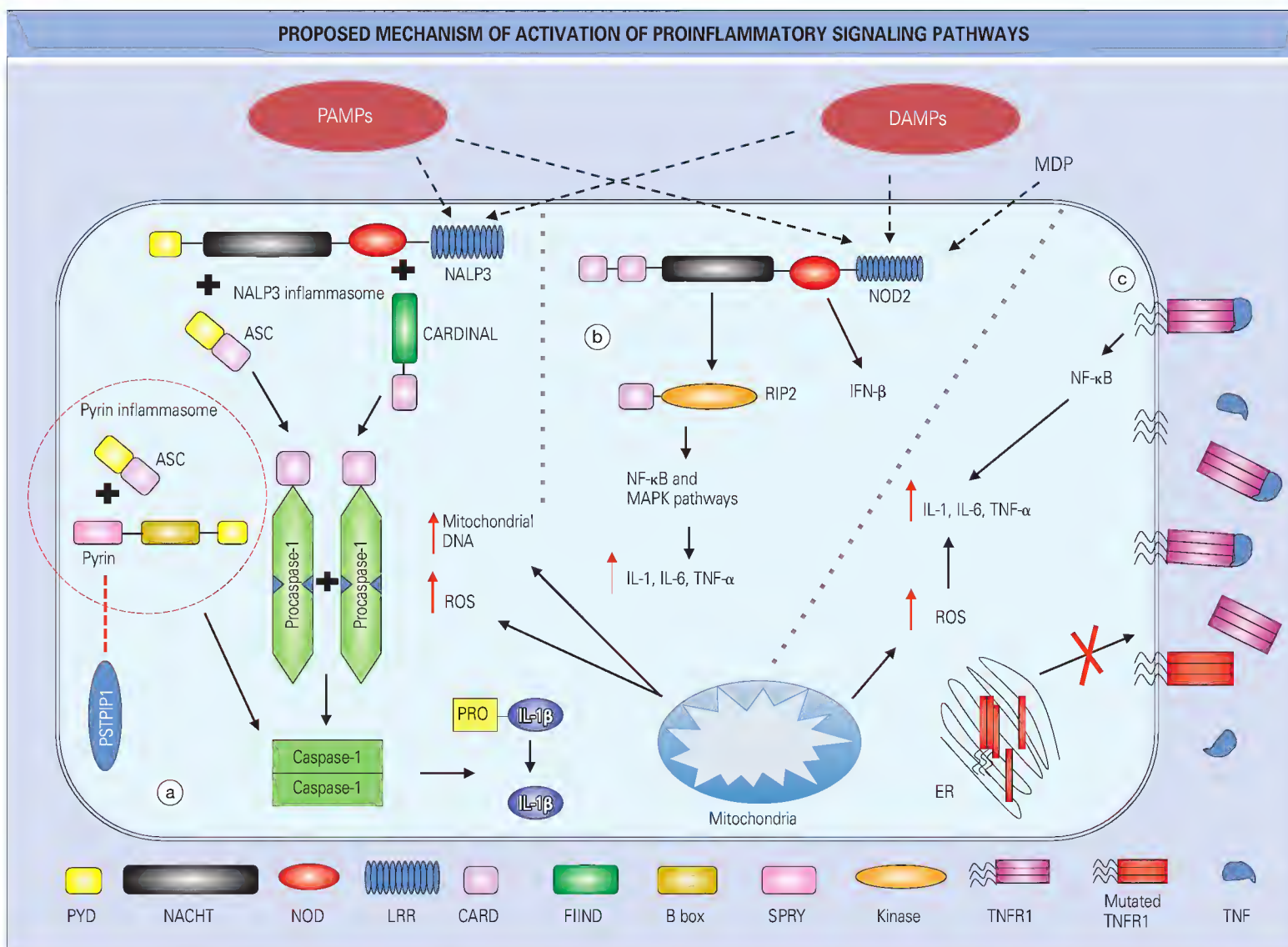


Fig. 165.1 Activation of proinflammatory signaling pathways in cryopyrin-associated periodic syndromes (CAPS); familial Mediterranean fever (FMF); pediatric granulomatous arthritis (PGA); pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS). (a) Mutated NALP3 (which causes CAPS) is constitutively activated and oligomerizes and binds to adapter molecules ASC and CARDINAL to form an active catalytic complex with two procaspase-1 molecules. Via autocatalysis, this complex generates active caspase-1, which cleaves inactive pro-interleukin-1β (pro-IL-1β) to its active form, interleukin-1β (IL-1β). Wild-type pyrin can inhibit inflammasome activation by direct binding to caspase-1. Mutated pyrin (which causes FMF) cannot exert its inhibitory effect on the inflammasome, which leads to unopposed inflammasome activation. Wild-type pyrin can also interact directly with ASC to form the "pyrin inflammasome," which is activated in the presence of FMF-causing mutations. Wild-type PSTPIP1, another regulatory molecule of the NALP3 inflammasome, binds to pyrin. Mutated PSTPIP1 (which causes PAPA syndrome) cannot dissociate from its binding to pyrin, which leads to uninhibited inflammasome and pyrin inflammasome activities. (b) Bacterial peptidoglycans stimulate the NOD2 (nucleotide-binding oligomerization domain 2) inflammasome. RIP2 is recruited, which leads to activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. Mutations in the NACHT domain (which cause PGA) lead to presumed autoactivation of NOD2 and constitutive activation of NF-κB and proinflammatory cytokines. (c) TNF receptor 1 (TNFR1) molecules are transported from endoplasmic reticulum (ER) to the Golgi complex and then to the cell surface. Wild-type TNFR1 complexes are bound to extracellular TNF, which leads to NF-κB activation. Receptor cleavage from the cell surface abrogates receptor signaling, and the soluble receptor can buffer soluble TNF. Mutated TNFR1 (which causes TRAPS) is misfolded and cannot be transported to the cell surface. Misfolded TNFR1 is sequestered in the ER and may further lead to decreased TNF-induced apoptotic signaling. TRAPS-associated TNFR1 mutations are associated with elevated baseline levels of reactive oxygen species (ROS), an enhanced oxidative capacity, and mitochondrial ROS generation. ASC, apoptosis-associated specklike protein with a caspase recruitment domain; CARD, caspase activation and recruitment domain; DAMPs, damage-associated molecular patterns; IFN-β, interferon-β; LRR, leucine-rich repeat; PAMPs, pathogen-associated molecular patterns; PYD, pyrin domain.

monocytic cell line increased IL-1β production *in vitro*.²⁰ Alternatively, pyrin and ASC may themselves form their own "inflammasome complex" with caspase-1 to activate IL-1β, as has been demonstrated *in vitro* (see Fig. 165.1b).¹⁹ A mouse model in which human pyrin mutations have been genetically introduced supports this latter view,¹⁵ as does the paucity of null mutations in FMF patients and the observation of biochemical inflammation in *MEFV* heterozygotes.²¹

Currently, over 100 FMF-associated *MEFV* mutations are listed in the Infevers online database of periodic fever mutations, although the total number of reported sequence variants exceeds 250.²² Almost half of the known mutations are in exon 10, encoding the B30.2 (SPRY) domain.

Exon 10 also includes two mutational "hot spots" (M680 and M694) that have more than one known mutation. A second major cluster of *MEFV* sequence variation is in exon 2. In contrast with the exon 10 mutations, these sequence variants, such as E148Q, are of uncertain significance and are less pathogenic mutations; they may simply be functional polymorphisms that alone are usually insufficient to cause FMF but may nonspecifically affect the overall severity of inflammation.²³ The majority of FMF-associated *MEFV* mutations represent missense single amino acid substitutions.

M694V homozygotes have an increased risk of amyloidosis,^{24,25} and some studies additionally associate this genotype with an earlier age of

onset, greater frequency of attacks, arthritis, and erysipelas-like erythema.^{24,25} M694I, M680I, and the V726A-E148Q complex allele may also confer a more severe phenotype.⁶ There is evidence that the deletion mutation at codon 694 and the M694I-E148Q complex allele as well as mutations at residue 577 are dominantly inherited.^{6,7} The E148Q substitution is usually found in FMF patients who are compound heterozygotes for E148Q and an exon 10 mutation, but it may also be seen as a complex allele in cis with an exon 10 mutation.^{26,27} Like the E148Q mutation, the P369S and R408Q substitutions, which are encoded in exon 3, are of uncertain significance.²⁸

Clinical features

The acute attacks of FMF are typically characterized by fever and serositis, synovitis, or skin rash. Attacks usually last for 24 to 72 hours, although arthritis can persist for up to 1 week. Attacks can occur weekly or as infrequently as once every few years. Physical exertion, emotional stress, and menses have been associated with attacks in some patients, but in many cases there is no obvious provocation. Some patients experience a prodromal sensation for several hours before the onset of the attack, and chills often herald the onset of fever.

Abdominal pain is the second most common manifestation of FMF and occurs in over 90% of patients. At its worst, the abdominal pain of FMF mimics an acute surgical abdomen, and many patients who seek treatment because of such pain early in their disease undergo one or more exploratory laparotomies, which usually reveal sterile peritonitis and sometimes unexplained adhesions, but no evidence of appendicitis. Pleural attacks are also common in FMF; pleurisy may be more frequent among Armenians than in other populations.⁹ Pleural attacks are usually unilateral, with sharp, stabbing chest pain on inspiration or coughing and sometimes with shoulder pain referred from the diaphragm.

Symptomatic non-uremic pericarditis is rare, even with tamponade.^{29,30} Small pericardial effusions with mild or no symptoms can sometimes be detected by echocardiography (Fig. 165.2a).

FMF arthritis often presents in childhood, most frequently manifesting as monoarticular arthritis affecting the knee or ankle, with symmetric

oligoarthritis being the next most common presentation.³¹ During the acute arthritic attacks of FMF, there may be large sterile synovial effusions with neutrophil counts of the magnitude seen in septic arthritis. Despite this, the natural history of the acute arthritis of FMF is complete resolution with no radiographic residua. In patients not treated with colchicine, chronic monoarticular arthritis can develop, and when located in the hip, this can eventually necessitate joint replacement.³² FMF patients may also be at increased risk of sacroiliitis, irrespective of HLA-B27 status or colchicine prophylaxis.³³

The most characteristic skin lesion of FMF is a tender erythematous plaque on the dorsum of the foot, ankle or lower leg, termed *erysipelas-like erythema* (see Fig. 165.2b). Histologic evaluation of biopsy specimens from skin lesions shows perivascular, primarily polymorphonuclear infiltrates³⁴; a larger, more recent study showed a more mixed cellular infiltrate³⁵ (see Fig. 165.2c), which likely indicates different stages of the rash at biopsy. Deposits of C3 can be demonstrated in vessel walls, but vasculitis is not observed.

Attacks of FMF can also manifest with exertional myalgia of the lower extremities, usually without fever, lasting from a few hours to 2 to 3 days. They occur in about 20% of patients; shorter-lasting, mild myalgia can sometimes occur without strenuous exercise.³¹ In a small percentage of patients, episodes of myalgia of the extremities can be prolonged (up to 6 weeks), severe, debilitating, and associated with fever, increased erythrocyte sedimentation rate (ESR), and a normal creatine kinase level.³⁶ This “protracted febrile myalgia” is thought to be due to vasculitis.³⁶ A small percentage of boys with FMF develop acute scrotal pain resulting from inflammation of the tunica vaginalis.³⁷ There have also been isolated reports of aseptic meningitis in FMF.³⁸

The most frequently employed clinical criteria for FMF were established at the Tel-Hashomer Medical Center in Israel and include a schema of major, minor, and supportive criteria.³⁹ These clinical criteria include frequent occurrence of symptoms such as abdominal and thoracic pain, family history, and response to treatment with colchicine.³⁹ However, it should be noted that the sensitivity and specificity of any set of diagnostic criteria vary according to the disease frequency in the population of interest.

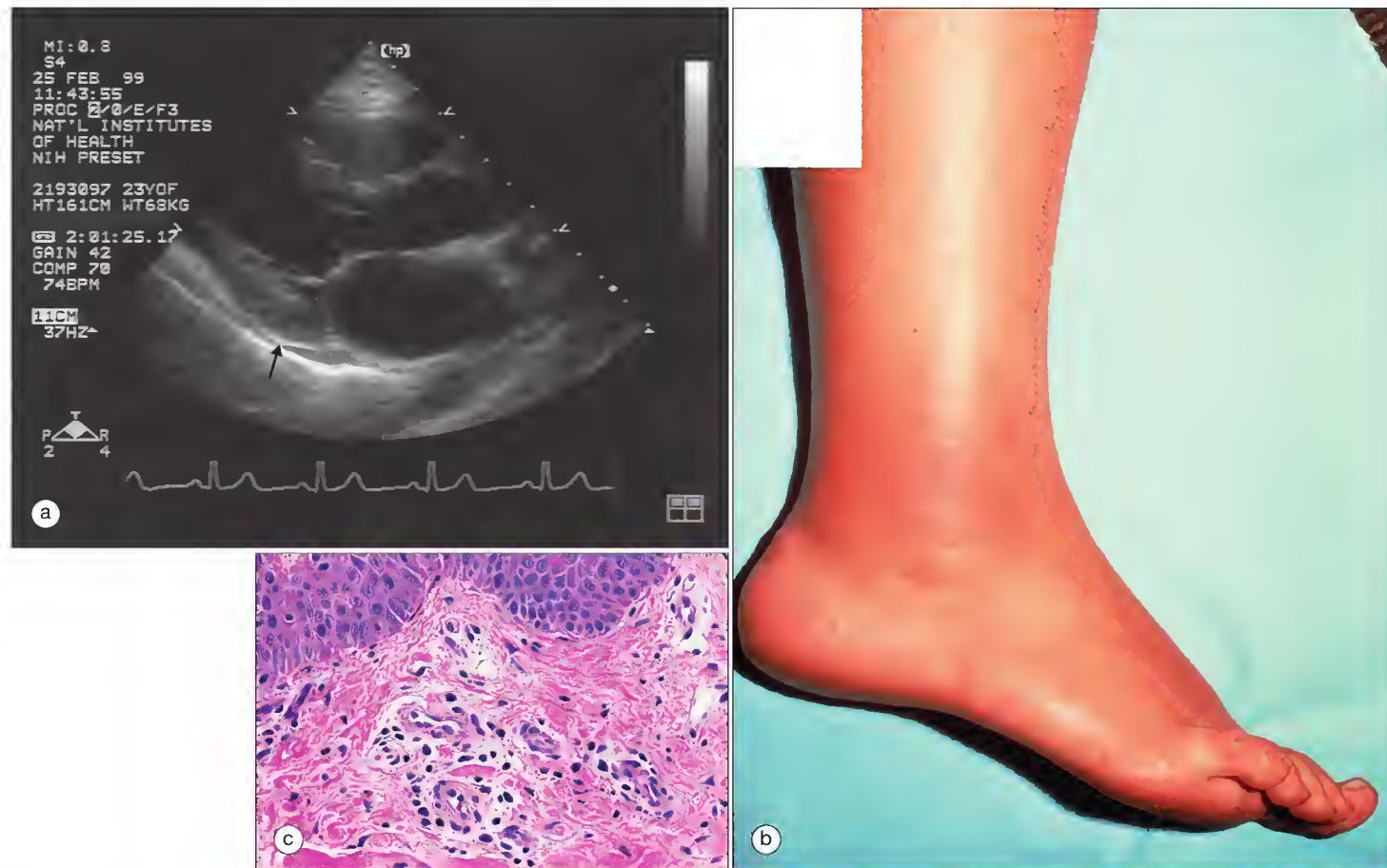


Fig. 165.2 (a) Two-dimensional echocardiogram (parasternal long-axis view) showing small posterior pericardial effusion (arrow) in a young woman with familial Mediterranean fever (FMF). (b) Erysipelas-like erythema (ELE) in a patient with FMF. (c) Skin biopsy specimen taken from the site of ELE. Note the predominantly perivascular infiltrate with mixed, predominantly mononuclear cells (hematoxylin-eosin, $\times 1000$).

For patients from high-risk populations with typical clinical manifestations of FMF, the diagnosis still can be made with confidence without the use of DNA studies. Moreover, particularly in cases in which only one mutation is found by genetic testing, clinical judgment will continue to have an important place in the diagnosis of FMF.

Laboratory findings

Laboratory studies performed during FMF attacks show a nonspecific acute-phase response, including leukocytosis, an increased ESR, and elevations in the levels of C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, and haptoglobin.⁴⁰ Patients may have moderate hypergammaglobulinemia irrespective of whether they are experiencing an attack, and serum immunoglobulin D (IgD) levels can be moderately elevated, especially in patients homozygous for the M694V mutation.⁴¹ Autoantibodies, including antinuclear antibody (ANA), rheumatoid factor (RF), anticardiolipin antibody, and antineutrophil cytoplasmic antibody (ANCA), usually are absent or present only in low titer. The cytoplasmic S100 proteins derived from monocytes and granulocytes are increasingly being used as biomarkers of autoinflammation. S100A8 (MRP-8), S100A9 (MRP-14), and S100A12 (MRP-6) are released during activation of the innate immune system.⁴² S100A12 is released in excessive amounts in FMF, compared with other autoinflammatory diseases, which suggests that neutrophil-derived S100 proteins may be involved in the pathogenesis of this disease.⁴³

Between attacks, FMF patients usually have no residual symptoms. Nevertheless, many FMF patients show persistent elevations in levels of acute-phase reactants, especially CRP and SAA, even between attacks.^{21,44} Moreover, obligate carriers of FMF mutations have increased levels of acute-phase reactants relative to noncarriers.^{21,44}

Complications of untreated disease

Systemic amyloidosis is an extremely serious manifestation of FMF.⁸ It is caused by the deposition of a degradation product of SAA, an acute-phase reactant made by the liver, in a number of different organs. The most common sites of amyloid deposition in FMF are the kidneys, liver, spleen, gastrointestinal tract, lungs, testes, thyroid, and adrenals. Before the advent of colchicine prophylaxis, amyloidosis was a frequent cause of kidney failure and death in FMF patients. Amyloid deposits in FMF seldom occur in the heart, peripheral nerves, or joints (except in the setting of long-term hemodialysis).

Type AA secondary amyloidosis occurs in 13% of Turkish patients.⁴⁵ Frequency of amyloidosis differs among countries, and in a multicenter study the country of recruitment was the most important risk factor for the occurrence of renal amyloidosis.⁴⁶ Individuals with the SAA 1.1/1.1 (α/α) genotype are also at increased risk of amyloidosis.⁴⁷ Kidneys are the most affected organs, and these patients have progressive proteinuria, nephrotic syndrome, and chronic renal failure.⁴⁵ Secondary AA amyloidosis is related to persistently elevated SAA levels. The development of AA amyloidosis is unlikely with low serum concentrations of this protein (less than 4 mg/L).⁴⁸

All FMF patients should be screened regularly for amyloidosis by urinalysis. Patients who have significant proteinuria on repeated urinalyses performed between febrile attacks may require tissue diagnosis.⁴⁹ If treatment is not initiated, the natural history of amyloidosis in FMF is progression to renal failure, usually within 3 to 5 years of diagnosis. In those patients who undergo dialysis or renal transplantation who are not adequately treated, amyloid deposition will continue in the transplanted kidney and other organs, leading to amyloid goiter, malabsorption, and diarrhea due to gastrointestinal deposition, and, occasionally, cardiac involvement.

Treatment

The mainstay of treatment for FMF is daily oral prophylactic colchicine. Dosages of 1.2 to 1.8 mg/day of colchicine prevent both the acute inflammatory attacks of FMF⁵⁰⁻⁵² and the development of systemic amyloidosis.⁵³ Intermittent dosing at the time of attacks is not nearly as effective as is daily administration, and there is no evidence that intermittent colchicine prevents amyloidosis. The major limiting toxicities of colchicine are gastrointestinal—diarrhea, cramping, and bloating—which can be minimized by starting at a low dose and gradually advancing the dose as tolerated, by dividing the daily dose, by using simethicone for flatulence, and by treating the lactose intolerance. Dosages above 1.8-2 mg/day are rarely tolerated for prolonged periods. Colchicine induces a near cessation of FMF attacks in about 70% of patients and provides at least some relief in over 90%.

Rare adverse effects of colchicine include bone marrow suppression and a myoneuropathy that is most often seen in elderly adults with renal insufficiency.⁵⁴ There are anecdotal reports of male infertility due to colchicine,⁵⁵ but most men with FMF are able to father children without discontinuing

the drug. It should also be noted that there are no controlled studies of sperm count or function before and after starting colchicine and that the amyloidosis of FMF may itself cause testicular dysfunction.⁵⁶

In patients taking colchicine regular blood counts and measurement of serum chemistry levels should be performed. Oral colchicine should be continued even in the face of an FMF attack. Patients taking daily oral colchicine should not be given intravenous colchicine in the event of an attack. The concomitant administration of oral and intravenous colchicine has been associated with fatal toxicity.⁵⁷

In patients who have an unsatisfactory response to colchicine or are unable to tolerate the drug, other immunosuppressive treatments have been tried. Corticosteroids are ineffective in either treating or preventing the acute attacks of FMF, and there are anecdotal data that they may even accelerate the amyloidosis of FMF. Interferon alfa-2b (3 million units subcutaneously) may abort FMF attacks if given at the first sensation of an attack.⁵⁸ However, a double-blind study failed to demonstrate a significant therapeutic effect,⁵⁹ and there are no data on the efficacy of interferon in preventing amyloidosis.

Given the cytokine patterns reported in FMF and the major interactions of pyrin and IL-1 β , treatments that target IL-1 have been used in patients unresponsive to or intolerant of therapeutic doses of colchicine.⁶⁰ Case reports have described improvement in FMF using IL-1 blockade with anakinra (Kineret),⁶¹⁻⁶³ and a multicenter trial of rilonacept (Arcalyst), a recombinant IL-1 receptor fusion protein, has recently suggested this anti-IL-1 agent as a treatment option for patients who show no response to colchicine or cannot tolerate it.⁶⁴ There is also anecdotal evidence supporting the use of TNF inhibitors such as etanercept⁶⁵ and infliximab in FMF.^{66,67}

Tumor necrosis factor receptor-associated periodic syndrome

Background

TNF receptor-associated periodic syndrome (TRAPS) (OMIM #142680) is an autosomal dominant, multisystemic, autoinflammatory disorder caused by mutations in *TNFRSF1A*, the gene encoding the 55-kDa receptor for TNF.³ In contrast with FMF, in which there is an evolving relationship between clinical criteria and *MEFV* mutational status, TRAPS was first proposed as a genetic diagnosis. Thus only patients with demonstrable TNF receptor mutations should be categorized as having TRAPS.

Before this terminology was proposed, there had been a number of case descriptions of dominantly inherited periodic fever in families of diverse ethnic backgrounds. Perhaps the best characterized of these was familial Hibernian (Irish) fever first described by Williamson and colleagues⁶⁸ in 1982 in a large pedigree of Irish-Scottish ancestry. The inflammatory attacks observed in this family resembled FMF in some respects, with the presence of abdominal pain, pleurisy, joint pain, an accelerated ESR, and neutrophilia. However, there were important differences,^{68,69} including a much longer duration of attacks; the presence of migratory areas of erythema, swelling and myalgia, conjunctivitis, and periorbital edema; a dominant pattern of inheritance; poor response to colchicine; and a relatively prompt response to corticosteroids.

The subsequent years have vindicated the concept of TRAPS as a distinct clinical entity with a broad ethnic distribution,⁷⁰ and mutations have been reported in patients on every continent. With these later reports, the clinical spectrum of TRAPS has broadened, but a number of common themes have endured.

Genetics and pathophysiology

There are two receptors for the proinflammatory cytokine TNF: a 55-kDa molecule (p55) encoded by *TNFRSF1A* on chromosome arm 12p, and a 75-kDa receptor (p75) encoded by *TNFRSF1B* on chromosome arm 1p. The p55 receptor is expressed on most cell types, whereas expression of the p75 receptor is restricted to leukocytes and endothelial cells. TRAPS is caused by mutations in the p55 receptor; to date there are no known periodic fever patients with mutations in the p75 receptor.

Both TNF receptors belong to a family of membrane proteins with repeating cysteine-rich extracellular motifs. By x-ray crystallography, each cysteine-rich domain (CRD) consists of a loop structure constrained by three disulfide bonds.⁷¹ The p55 receptor has four of these extracellular CRDs, a transmembrane segment, and an intracellular C-terminal death domain (similar in structure to the N-terminal PYD of pyrin) that is actually a cognate interaction motif.

There are at least 26 known mutations at cysteine residues in CRDs 1 and 2, as well as 12 other mutations not occurring at cysteines. To date no TRAPS patients have been reported with transmembrane or intracellular

TNFRSF1A mutations, truncations, null mutations (in which the protein is not expressed), or mutations in the p75 TNF receptor encoded on chromosome 1. Nearly all of the TRAPS mutations catalogued on the Infevers website are found in the first two CRDs, at the N-terminal of the protein,²² which prevents proper disulfide bond formation and protein folding. Systemic amyloidosis is seen more frequently in TRAPS in patients with cysteine substitutions than in those with the other mutations.

The R92Q (glutamine for arginine at codon 92) *TNFRSF1A* variant is seen in 1% to 4% of white control chromosomes,⁷² whereas the P46L (leucine for proline at codon 46) variant is found in approximately 2% of African American and Arab control chromosomes^{72,73} and is seen at an even higher frequency among some sub-Saharan African populations.⁷⁴ Both R92Q and P46L, therefore, meet the formal definition of polymorphisms, and their pathologic significance is controversial since they are found at similar frequencies in individuals coming to periodic fever clinics and in the general populations from which these clinics draw patients. Assuming that these two substitutions do confer susceptibility to autoinflammatory disease, their penetrance (the probability of having disease if the mutation is present) must be low, since the frequency of TRAPS does not approach 1% of the general population. Patients with R92Q have a wider spectrum of clinical manifestations than other TRAPS patients.⁷⁰ Their phenotype is milder, the age at onset is older, and there is an absence of amyloidosis.⁷⁵

The TNF receptor has a cytoplasmic death domain that signals through two pathways, one leading to NF- κ B activation and inflammation, and another leading to caspase activation and apoptosis. Alteration of these pathways provides another possible mechanism for hyperinflammation. NF- κ B activity has been measured in mononuclear cells from patients with the C73R (arginine for cysteine at codon 73) mutation and shown to be elevated.⁷⁶ TNF-induced apoptosis has been measured in neutrophils from TRAPS patients with cysteine mutations and a decrease in apoptosis was noticed,⁷⁷ which potentially interferes with a normal homeostatic mechanism.

Another possible mechanism for inflammation in TRAPS is that mutations at cysteine residues likely cause protein misfolding.¹⁹ Mutant receptors appear to be retained in the endoplasmic reticulum as abnormal disulfide-linked oligomers,¹⁹ which may trigger a ligand-independent (i.e., TNF-independent) proinflammatory state through constitutive activation of NF- κ B,¹⁹ the endoplasmic reticulum stress response, or mitogen-activated protein kinase (MAPK) (see Fig. 165.1c).¹⁹ The proinflammatory state may be further potentiated by autocrine TNF signaling through the remaining wild-type TNF receptor. More recently, additional mechanisms linking innate immune-mediated inflammation with a variety of cellular processes, including protein misfolding, diminished trafficking of mutated TNF receptor 1 to the cell surface, oxidative stress, and mitochondrial dysfunction, have been recognized to play a role in the pathogenesis of TRAPS.¹⁹ Diminished trafficking to the cell surface may further lead to decreased TNF-induced apoptotic signaling since only the p55 receptor and not the p75 receptor delivers apoptotic signals, which could lead to prolonged inflammatory responses. The latter effect may be accentuated by the reduction in ligand binding that appears to occur for certain TRAPS-associated p55 mutations. It has been difficult to document functional abnormalities *in vitro* for the R92Q substitution in trafficking or ligand-binding assays.

Clinical features

As more cases have been diagnosed and the inventory of mutations has grown to currently over 80, the usual duration of episodes in TRAPS remains substantially longer than in the other hereditary periodic fevers. However, shorter attacks lasting less than 7 days can occasionally occur in TRAPS. The interval between attacks in TRAPS, as in FMF, is highly variable among patients and over time in any given patient. Although episodes sometimes develop with no apparent provocation, physical or emotional stress, physical trauma, and menses are sometimes associated with attacks; pregnancy may be associated with an amelioration of symptoms. A small minority of patients experience waxing and waning symptoms on a nearly daily basis. Fever usually heralds the onset of inflammatory episodes and is sometimes the sole manifestation of TRAPS, especially in children. The median age of onset of TRAPS attacks is 3 years.⁷⁰

Pleuritic chest pain and severe abdominal pain, with or without peritoneal signs, occur in TRAPS, as they do in FMF. Early in their disease, patients may undergo exploratory laparotomy, and it is not unusual for patients to develop peritoneal adhesions, presumably the sequelae of recurrent peritoneal inflammation. Symptomatic pericardial involvement is much less common than peritoneal or pleural inflammation. Scrotal pain is uncommon. Arthralgia is more frequent than arthritis in TRAPS and is usually nonerosive and monoarticular, most frequently involving the hips, knees,

or ankles. The chronic arthritis seen in FMF has not been observed in TRAPS.

Features that distinguish TRAPS from FMF include a characteristic migratory myalgia and rash (Fig. 165.3a and b) that is seen at some time in nearly all TRAPS patients. Typically, this occurs as a localized area of cramping muscle pain, often with warmth and tenderness to palpation, and an overlying erythematous, blanchable rash, usually on the torso or the extremities. When it occurs on the limbs, the area of inflammation migrates centrifugally over the course of several days and is often associated with synovitis and effusion as it crosses a joint. Levels of muscle enzymes are not elevated, and magnetic resonance imaging (MRI) demonstrates edema in discrete muscular compartments and intramuscular septa (see Fig. 165.3c). Consistent with the normal muscle enzyme levels, a full-thickness biopsy specimen in one patient demonstrated predominantly panniculitis, fasciitis, and perivascular inflammation, but not involvement of the myofibrils themselves.⁷⁸ In the skin there is a superficial and deep perivascular and interstitial infiltrate of lymphocytes and monocytes.⁷⁹ It is possible that the centrifugal migration represents propagation along fascial planes.

Ocular involvement is another feature that distinguishes TRAPS from FMF.⁷⁰ Approximately 80% of patients experience conjunctivitis, periorbital edema (see Fig. 165.3d), or periorbital pain. Much less commonly, patients may develop iritis or uveitis.

Laboratory findings

The acute attacks of TRAPS are associated with neutrophilia and thrombocytosis (particularly in children) and a global acute-phase response, including an elevated ESR and increased levels of CRP, SAA, haptoglobin, and fibrinogen. Although these parameters may fluctuate with attacks, the elevations often remain even between attacks. Many patients exhibit anemia of chronic disease, polyclonal hypergammaglobulinemia, and low titers of IgM and IgG anticardiolipin antibodies. Tests for ANA, RF, and ANCA usually give negative results. When measured, soluble 55-kDa TNF receptor levels tend to be subnormal between attacks and, in contrast to other inflammatory disorders, increase only modestly during active disease.³

Complications of untreated disease

Systemic amyloidosis occurred in a subset of the families included in the initial description of TRAPS. An analysis of cases followed at the U.S. National Institutes of Health or compiled from the literature found that 14 of 100 patients with TRAPS showed evidence of systemic amyloidosis.⁷² The series was almost evenly divided between patients with nine different mutations involving cysteine residues and patients with seven noncysteine mutations, yet 13 of the 14 patients with amyloidosis had cysteine mutations.

As is the case for FMF, the amyloidosis of TRAPS is secondary to deposition of a presumed cleavage product of SAA, and the tissue distribution of amyloid deposits is similar in the two diseases. The most frequent complication of TRAPS amyloidosis is renal failure, although hepatic failure has also been observed. All TRAPS patients, but particularly those with cysteine mutations, should undergo regular urinalyses to monitor for albuminuria, an early sign of renal amyloidosis.

Treatment

Colchicine is ineffective in preventing the febrile attacks of TRAPS, and it does not prevent the development of systemic amyloidosis, either. Corticosteroids can be used to treat the attacks of TRAPS, but patients frequently require escalating dosages with time, often with diminishing efficacy and serious toxicity. Azathioprine, cyclosporine, thalidomide, cyclophosphamide, chlorambucil, intravenous immunoglobulin, dapsone, and methotrexate have all been tried empirically but have not been found effective.

There has been a growing favorable experience with etanercept, the p75-Fc fusion protein. Initial studies reported a reduction in the frequency and severity of TRAPS attacks with the drug.¹⁹ An open-label study comparing parameters between 3-month baseline, twice-weekly treatment, thrice-weekly treatment, and washout phases demonstrated a significant overall improvement in both clinical and laboratory outcomes.¹⁹ More recently, in a prospective study enrolling 15 patients, treatment with etanercept reduced the frequency and severity of the inflammatory episodes and levels of inflammatory markers, but complete normalization was not achieved.⁸⁰ Other case reports have also documented that etanercept reverses or slows the clinical progression of renal amyloidosis in TRAPS.⁸¹ One patient with the C33Y mutation and amyloidosis was found to have a marked reduction in proteinuria and regression of amyloid as demonstrated on serum amyloid P scanning.⁸² However, a different patient with the C52F mutation experienced a new onset of proteinuria, with amyloid found on renal biopsy, while taking etanercept.⁸³ In TRAPS patients at high risk of amyloidosis, it may be appropriate to use SAA levels in the serum



Fig. 165.3 (a) Erythematous dermal macules and patches in a patient with tumor necrosis factor receptor–associated periodic syndrome (TRAPS). (b) Annular patch with erythematous borders in a patient with TRAPS. (c) Bilateral thigh magnetic resonance image showing fasciitis in a patient with TRAPS and migratory myalgia. (d) Periorbital edema in a child with TRAPS.

to guide therapy. There have recently been reports of initial response to etanercept that later declines, and the drug is of limited success in other patients. Of greater concern are reports of a paradoxical inflammatory reaction in TRAPS patients receiving infliximab.⁸⁴ Reduced apoptosis with increased secretion of proinflammatory cytokines has been observed when patient mononuclear cells are treated with infliximab.¹⁹

Given recent data suggesting that there are TNF-independent pathways of cellular activation in TRAPS, it is not surprising that etanercept often does not completely normalize levels of acute-phase reactants⁸⁵ and that other cytokine inhibitors may be efficacious in at least some patients. In some centers, anti-IL-1 therapy with either the recombinant IL-1 receptor antagonist (IL-1Ra) anakinra or the longer-acting monoclonal anti-IL-1 β antibody canakinumab (Ilaris) have been used with satisfactory responses¹⁹ and have become the treatment of choice. However, failure to respond to treatment with anakinra has also been reported in individual cases.¹⁹

Treatment outcomes for over 100 TRAPS patients were recently reviewed.⁸⁶ For TRAPS patients with relatively infrequent attacks, intermittent prednisone may be a satisfactory alternative. For patients with more frequent attacks, or for whom prednisone is not advisable, intermittent anakinra therapy may be effective. For those patients with frequent attacks or a high risk of amyloidosis, maintenance therapy with etanercept or an IL-1 inhibitor may be necessary, with a preference for IL-1 inhibition

because of the well-documented possible attenuation of etanercept responses over time.

Hyperimmunoglobulinemia D with periodic fever syndrome/mevalonate kinase deficiency

Background

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) (OMIM #260920) is a recessively inherited disorder first described in six Dutch patients in 1984.⁸⁷ Although these patients manifested some findings that were consistent with FMF, their abdominal pain was less severe than that usually seen in FMF and they had much more significant lymphadenopathy. In addition, they had constant elevations in serum IgD level and large numbers of IgD+ plasma cells in the bone marrow, findings not usually seen in FMF. For these reasons, van der Meer and colleagues correctly proposed that the condition they described was different from FMF.

In the ensuing 15 years, this clinical syndrome was extensively characterized⁸⁸; it segregates in families as an autosomal recessive trait. Most of the families identified cluster in the Netherlands, France, or neighboring areas of northern Europe. Initial genetic studies ruled out linkage to *MEFV* on chromosome arm 16p.⁸⁹

HIDS is caused by mutations in *MVK*, a gene on the long arm of chromosome 12 that encodes an enzyme in the cholesterol-isoprenoid biosynthetic

pathway.^{90,91} The MVK mutations associated with HIDS leave some residual enzyme activity, whereas more severe loss-of-function mutations lead to mevalonic aciduria, a potentially fatal condition accompanied by significant developmental and cognitive abnormalities as well as recurrent fevers.

HIDS remains a relatively rare condition,^{92,93} occurring at a much lower frequency than FMF or TRAPS in the mixed population of the United States. Approximately 0.6% of the population in the Netherlands are carriers for the V377I (isoleucine for valine at codon 377) mutation, with haplotype data supporting a founder effect.^{93,94} Analysis of the MVK genotypes of HIDS patients indicates an underrepresentation of V377I homozygotes relative to the expected Hardy-Weinberg distribution, which suggests a milder phenotype or reduced penetrance for V377I homozygotes.⁹⁴

In general, elevations in serum IgD levels and mutations in MVK correlate well. However, there are occasional patients with periodic fevers and HIDS-associated MVK mutations who have normal IgD levels,^{90,95,96} and conversely there is a significant number of patients with periodic fever and elevated serum IgD levels who have no demonstrable MVK mutations.^{97,98} These observations suggest a somewhat more complicated picture than simple equivalence of the HIDS clinical phenotype with specific MVK mutations.⁹⁹ For this reason, some experts prefer the term *mevalonate kinase deficiency* to describe those patients with a recurrent fever syndrome and MVK mutations who do not have the more severe developmental manifestations of mevalonic aciduria.

Genetics and pathophysiology

HIDS is caused by recessively inherited mutations in MVK, the gene for mevalonate kinase (MK),^{90,91} an enzyme that catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid. Currently over 160 MVK variants, most of them missense substitutions, are listed on the Infevers website; more than 30 are thought to be disease causing.¹⁰ Nearly all mutation-positive HIDS patients harbor at least one copy of the substitution V377I,¹⁰⁰ and the substitution I268T (threonine for isoleucine at codon 268) is the second most common mutation.¹⁰⁰

Lymphocytes and fibroblasts from HIDS patients exhibit reduced but not absent MK enzymatic activity. In contrast, patients with the much more severe mevalonic aciduria have almost no residual enzymatic activity. These latter patients experience many of the inflammatory manifestations of HIDS but also develop dysmorphic facies, cataracts, cerebellar ataxia, cerebral atrophy, mental retardation, hypotonia, and failure to thrive.^{101,102} The MVK mutations causing HIDS are distinct from those causing mevalonic aciduria, although there is some overlap. HIDS-associated mutations are mainly missense variants distributed throughout the coding region of the gene, whereas mevalonic aciduria-associated mutations are concentrated between residues 243 and 334.¹⁰⁰

Among HIDS patients there is no correlation between MK activity and severity of disease.⁹⁸ Moreover, the biochemical connection between MK mutations and inflammation is still unclear. The crystal structure of rat MK has been determined and V377I, the most common mutation, is spatially far removed from the catalytic site of the enzyme.¹⁰³ However, this mutation may destabilize the protein and thereby lead to reduced enzyme activity.⁹⁰ Cholesterol levels in HIDS patients are usually in the low-normal range, which suggests that unavailability of cholesterol is not the mechanism of inflammatory episodes.¹⁰²

Although early studies suggested that the proinflammatory state of HIDS is induced by the accumulation of mevalonic acid,¹⁰⁴ the prevailing current hypothesis is that inflammation is caused by a shortage of isoprenoids.^{105,106} *In vitro* data obtained using leukocytes of HIDS patients suggest that farnesol or geranyl-geraniol compounds can reverse accentuated IL-1 β secretion¹⁰⁷ and that inhibitors of sterol biosynthesis, which favor nonsterol isoprenoid biosynthesis, also reduce IL-1 β secretion by HIDS leukocytes.¹⁰⁸ There is also a defect in apoptosis in the peripheral blood leukocytes of HIDS patients.¹⁰⁹

A mouse model of HIDS was generated by deleting a single MVK allele, and this resulted in increased blood levels of mevalonate and IgD.¹¹⁰ It is unlikely, however, that elevation in IgD level itself is the cause of fever and inflammation; there are a number of other conditions, including diabetes mellitus, pregnancy, and cigarette smoking, in which IgD levels are modestly increased⁸⁸ but there are no symptoms compatible with HIDS.

Clinical features

Typically, HIDS manifests very early in life, with a median age of onset of 6 months.⁸⁸ It is not unusual for childhood vaccinations to precipitate febrile episodes. Other provocative factors include infections, emotional stress, trauma, and surgery, but in many instances there is no obvious trigger. Patients frequently report some type of premonitory symptoms, and the usual attacks of HIDS last approximately 3 to 7 days. Headache is a frequent



Fig. 165.4 Diffuse erythematous and purpuric maculopapular rash in a child with hyperimmunoglobulinemia D with periodic fever syndrome.

but nonspecific concomitant of HIDS attacks. As with the other recurrent fever syndromes, the attacks are usually not truly periodic but rather episodic, and the inter-attack interval can vary greatly both among patients and over time for any given patient. With increasing age there is a tendency for the attacks to become less frequent and less severe.⁸⁸

The majority of HIDS patients have episodes of abdominal pain, sometimes severe enough to warrant exploratory laparotomy. Unexplained adhesions are sometimes found, consistent with a history of peritoneal inflammation.⁸⁸ In contrast with FMF, diarrhea is often seen with HIDS attacks, usually toward the end of the episode. Vomiting is also common. Scrotal pain has also been reported.⁹⁶ Pleurisy and pericardial involvements are rare in HIDS.

Arthralgia is very common during HIDS episodes, and arthritis was documented in nearly 70% of patients in one series.⁸⁸ Mucocutaneous lesions are common during HIDS attacks.^{88,111} Crops of erythematous macules, ranging from 0.5 to 2 cm in diameter and sometimes affecting the palms and soles, are the most frequent skin manifestation of HIDS (Fig. 165.4). Other dermatologic findings include erythematous papules and nodules, urticaria, annular erythema, and purpura. A large series of HIDS skin biopsy specimens showed swelling of endothelial cells, perivascular edema, and mixed cellular perivascular infiltrates.¹¹¹ Painful aphthous ulcers of the mouth or vagina are also sometimes seen in HIDS.⁹²

Diffuse lymphadenopathy is one of the clinical features that distinguish HIDS from other hereditary recurrent fevers.^{88,92} Swelling of the cervical nodes fluctuates with attacks; inguinal, axillary, and mesenteric adenopathy may also be present. Histologic examination shows nonspecific reactive lymphadenitis. Splenomegaly is also frequently found in children with HIDS. Results of a comprehensive overview of a large cohort of HIDS patients begun in 1994 were published by the International HIDS Study Group.¹¹² The clinical findings usually associated with HIDS actually correlate better with the presence of MVK mutations than with high IgD levels.¹¹³

Laboratory findings

During their febrile episodes, HIDS patients manifest the same vigorous but nonspecific acute-phase response seen in the other hereditary recurrent fevers. This includes increased ESR and CRP, SAA, haptoglobin, and fibrinogen levels. There is also leukocytosis with a left shift. Levels of several cytokines, including interferon- γ (IFN- γ) TNF, and IL-6, are increased in the serum during attacks.^{114,115} The urinary level of neopterin, a marker for cellular immune activation, is also increased during febrile attacks.¹¹⁵ Urinary

mevalonate levels correlate well with HIDS episodes. Autoantibodies are generally not found in HIDS.

Before the underlying gene was identified, measurement of an elevated level of serum IgD (more than 100 IU/mL or more than 10 mg/dL) on two or more occasions at least 1 month apart was required for the diagnosis of HIDS.⁸⁸ Levels do not fluctuate with attacks, nor do they correlate with overall disease severity across individuals or in a given individual over time. IgA levels (primarily of the IgA1 subclass) are also increased in over 80% of patients with HIDS.

Based on the genetics and biochemistry of MVK, new diagnostic approaches are now possible: mutational screening, quantitation of urinary mevalonic acid, and measurement of MK activity in cultured fibroblasts or leukocytes.

Mutational screening is currently the most frequent used way of confirming the diagnosis of HIDS. Since a large percentage of HIDS patients have at least one copy of either the V377I or I268T mutation, it is cost effective to screen for these mutations first before undertaking a more comprehensive sequencing effort.

Urinary mevalonate levels can be measured by routine gas chromatography/mass spectroscopy or by isotope dilution methods.^{95,102} MK enzymatic assay in cultured fibroblasts or leukocytes is probably the most technically demanding of the biochemical approaches to confirming a diagnosis of HIDS.

As noted earlier, there are a small number of patients who have recurrent fevers and MVK mutations but normal IgD levels.^{90,95} Current practice is perhaps to use the term *mevalonate kinase deficiency* in such patients. There are somewhat larger numbers of patients who have increased serum IgD levels but no MVK mutations.⁹⁷⁻⁹⁹ Such patients generally are not said to have HIDS. Further complicating matters, there can be modest elevations in the serum IgD level in a minority of patients with FMF^{41,116} and TRAPS,⁶⁹ as well as in some patients with the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA).¹¹⁷

The differential diagnosis for HIDS is broad and includes FMF, TRAPS, PFAPA, adult-onset Still disease, juvenile idiopathic arthritis, rheumatic fever, and Behçet disease.¹¹² When confronted with a patient with unexplained recurrent fever in whom FMF and TRAPS are unlikely or have been ruled out, most experts would now proceed to genetic testing, with or without measurement of serum IgD levels. For HIDS screening, patients can be evaluated for fulfillment of at least one of the following two clinical criteria: (1) age of onset of less than 5 years, and (2) joint pains during attacks and attack duration of less than 14 days.¹¹⁸ The nature of the disorder in patients with definite IgD elevations but normal results on mutational screens remain to be understood.

Complications of untreated disease

In contrast with the other hereditary periodic fevers, amyloidosis is uncommon in HIDS patients⁹² and has only recently been reported.^{119,120} It is unlikely that this difference in the frequency of amyloidosis represents a difference in the severity of inflammation integrated over time, since SAA levels are markedly elevated during attacks, and many patients exhibit subclinical inflammation even between their attacks.¹²¹ In the absence of amyloidosis, the overwhelming majority of patients with HIDS have a normal life expectancy.⁸⁸

Treatment

There is currently no consensus regarding the treatment of HIDS. Nonsteroidal antiinflammatory drugs (NSAIDs) may help to control fever and arthralgia. Corticosteroids may help to control attacks in some patients, but long-term toxicity is a major concern, especially in children. There have been mixed results with colchicine, intravenous γ -globulin, and cyclosporine.⁹² A small, double-blind, crossover trial of thalidomide demonstrated modest decreases in levels of acute-phase reactants but no effect on the attack rate.¹²²

Current therapeutic strategies in HIDS have focused on the mevalonate pathway and on cytokine inhibition.⁸⁶ Paradoxically, trials of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) have suggested a potential benefit, most notably with simvastatin.^{92,104} However, in a French survey involving 50 patients, all 8 patients who received simvastatin failed to respond to this treatment,¹²³ and in the International HIDS Study Group multicenter study, 12 of 18 patients failed to respond.¹¹² An open-label use of the TNF inhibitor etanercept produced substantial improvement in two patients with HIDS,¹²⁴ although such a response is not universal.^{125,126} The use of IL-1 inhibitors may represent yet another possible strategy.¹²⁵ Recently, the efficacy of anti-IL-1 drugs (anakinra and canakinumab) was assessed in a study that included 11 HIDS patients. Complete and partial remission were observed in 4 and 7 patients, respectively.¹²⁷

MONOGENIC SYNDROMES WITH MUTATIONS IN THE INTERLEUKIN-1 PATHWAY

The cryopyrinopathies (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease)

Background

The cryopyrinopathies, or cryopyrin-associated periodic syndromes (CAPS), comprise a clinical continuum of three historically defined diseases: familial cold autoinflammatory syndrome (FCAS; OMIM #120100), Muckle-Wells syndrome (MWS; OMIM #191900), and neonatal-onset multisystem inflammatory disease (NOMID), also known as *chronic infantile neurologic cutaneous and articular (CINCA) syndrome* (OMIM #607115).¹²⁸⁻¹³⁰ The cryopyrinopathies are all caused by mutations in *NLRP3/CIAS1*, which led to the recognition that a common pathogenic pathway must underlie these conditions and that they present as a disease severity spectrum with FCAS at the clinically milder end and NOMID at the clinically severe end of the severity spectrum. Although the inheritance pattern in FCAS and MWS is usually familial,¹³¹ the disease is sporadic in patients with the clinically severe phenotype of NOMID/CINCA.¹²⁸ The sporadic inheritance pattern in NOMID/CINCA is accounted for by the severe phenotype of untreated patients, which results in their inability to reproduce.¹²⁸ However, with the initiation of early IL-1-blocking therapy, the face of NOMID is rapidly changing, and patients who used to have severe disease can have normal or close to normal lives. The *NLRP3* gene encodes the protein cryopyrin, a component of an IL-1 β -activating complex, the NLRP3 inflammasome. This finding led to a decade of intense investigation not only into the role of IL-1 in the rare disorders CAPS and other autoinflammatory diseases, but also into its role in a large group of common disorders, including gout, diabetes mellitus, coronary artery disease, and Alzheimer disease, to name only a few.

Genetics and pathophysiology

There are few epidemiologic studies of CAPS; prevalence estimates of 1 to 2 patients per 1,000,000 people in Europe and the United States are based on the known cases treated in centers studying these patients.

FCAS, MWS, and the sporadic disease NOMID/CINCA are all caused by autosomal dominant gain-of-function mutations in *NLRP3*, which is also called *NALP3*, *CIAS1*, and *PYPAF1*. *NLRP3* encodes a protein that is expressed in monocytes, granulocytes, T cells, chondrocytes, keratinocytes, and probably other cells.¹³¹⁻¹³³ Over 100 disease-causing mutations have been reported in the Infevers database²²; 90% are located in exon 3 of the gene, which encodes the NACHT domain of the protein.^{13,131} About 50% of NOMID/CINCA patients and a much smaller percentage of recognized patients with FCAS and MWS do not have germline mutations in *NLRP3*, but recently, 70% of these presumed mutation-negative patients were found to have somatic mosaicism in *NLRP3*. In the majority of cases, the disease was milder in patients with somatic mosaicism than in patients with germline mutations.^{134,135}

The NLRP3 inflammasome and interleukin-1 β activation and secretion

As noted earlier, *NLRP3/CIAS1* encodes the protein cryopyrin, which belongs to the NOD-like receptor (NLR) family of proteins; these proteins are intracellular sensors of molecular danger signals and are characterized by the presence of a central nucleotide-binding and oligomerization (NACHT) domain, a C-terminal leucine-rich repeat domain, and either an N-terminal caspase activation and recruitment domain (CARD) or a pyrin domain (PYD); cryopyrin has a PYD. Cryopyrin forms a multimolecular complex, the NLRP3 inflammasome,^{16,17} via the recruitment of ASC, CARDINAL, and two molecules of the proinflammatory protease procaspase-1 (Fig. 165.5).¹⁷ The assembly of the NLRP3 inflammasome is mediated by self-oligomerization, permitting autocleavage and formation of active caspase-1.¹³⁶ Active caspase-1 cleaves pro-IL-1 β and pro-IL-18 into their biologically active forms. IL-1 β is a potent proinflammatory cytokine; its production, activation, and secretion are tightly regulated. The NLRP3 inflammasome provides a molecular link between the recognition of danger and the activation of the proinflammatory cytokine IL-1 β as an early "alarm/response" cytokine (see Fig. 165.5).¹³⁷

The NLRP3 inflammasome can be activated by a number of chemically and structurally diverse exogenous and endogenous or host-derived molecules. Exogenous stimuli that trigger inflammasome activation include whole pathogens; pathogen-associated molecular patterns such as

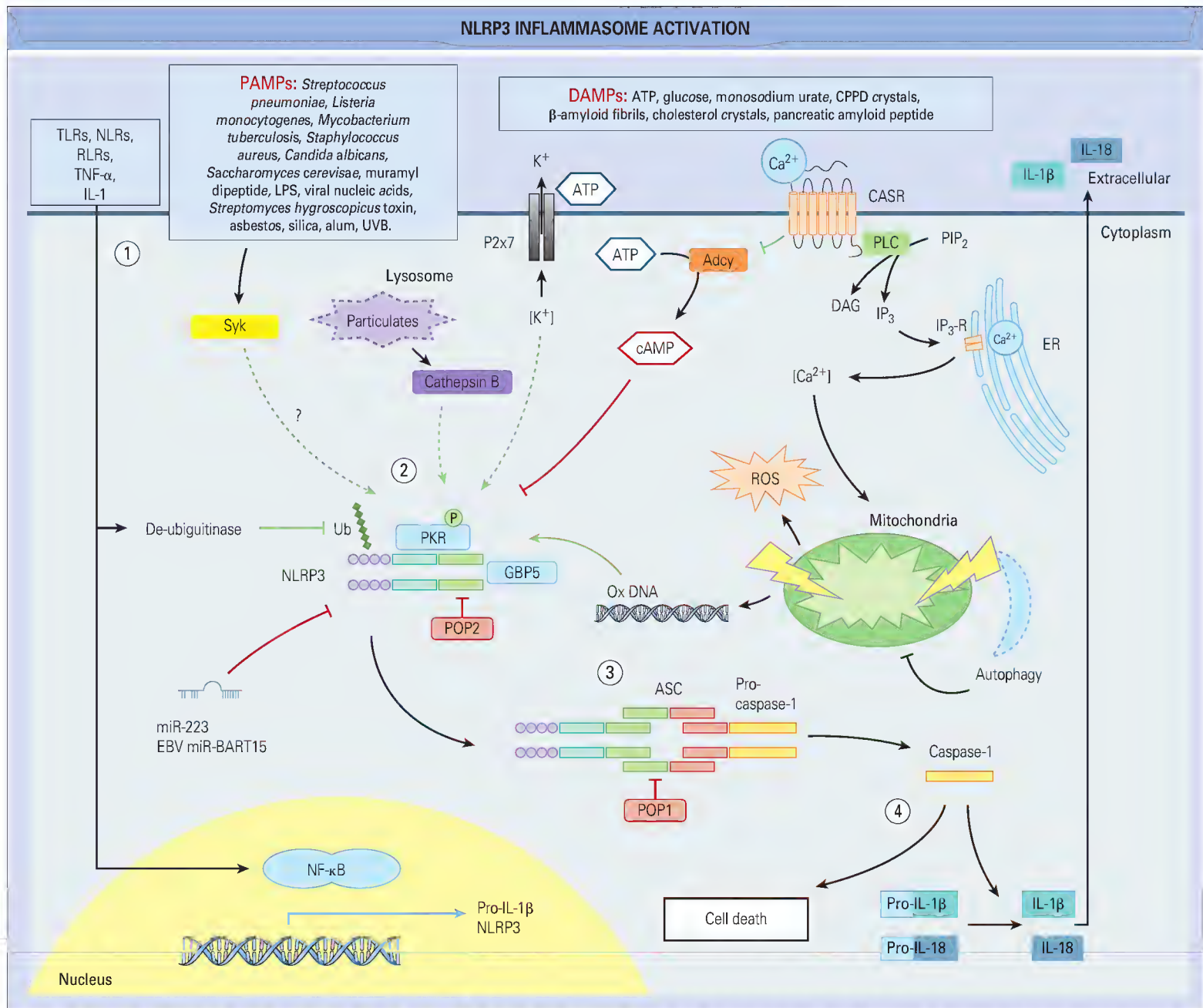


Fig. 165.5 (1) The first step in NLRP3 activation is a signal by pattern recognition receptors, most commonly Toll-like receptors (TLRs) that activate transcription of NLRP3 and pro-interleukin-1 β (pro-IL-1 β) through nuclear factor- κ B (NF- κ B). NLRP3 is also activated by de-ubiquitination. (2) The second step is NLRP3 activation per se. At least one of three events is usually required: potassium efflux, cathepsin B release from lysosomes, and production of reactive oxygen species (ROS). Two direct ROS-related NLRP3 ligands have recently been proposed: TXNIP, which is released from the redox system, and oxidized mitochondrial DNA. Mitochondria and mitochondrial ROS seem to play an important role and can be influenced by calcium signaling. Through removal of ROS-producing dysfunctional mitochondria, NLRP3 activation is downregulated by autophagy. The second messenger cyclic adenosine monophosphate (cAMP) can also bind directly to NLRP3 and inhibit its activation. Extracellular calcium decreases cAMP through CASR signaling. Kinase signaling positively regulates NLRP3 activation through PKR, which directly interacts with NLRP3, whereas Syk kinase activity is required for NLRP3 activation in response to specific ligands such as *Candida albicans*. (3) NLRP3 activation further triggers the assembly of active inflammasome complexes containing ASC (apoptosis-associated specklike protein with a caspase recruitment domain) and procaspase-1. Endogenous and viral pyrin-only proteins (POPs) can interfere with inflammasome assembly, whereas GBP5 selectively promotes NLRP3-dependent ASC oligomerization. (4) Finally, inflammasome formation leads to the processing and activation of caspase-1, which cleaves the pro forms of interleukin-1 β (IL-1 β) and IL-18; the result is the release of the mature cytokines and induction of cell death by pyroptosis. ATP, adenosine triphosphate; CPPD, calcium pyrophosphate dehydrate; DAMPs, damage-associated molecular patterns; EBV, Epstein-Barr virus; ER, endoplasmic reticulum; LPS, lipopolysaccharide; NLR, NOD-like receptor; PAMPs, pathogen-associated molecular patterns; TNF- α , tumor necrosis factor- α ; UVB, ultraviolet B light. (Adapted from Haneklaus M, O'Neill LA, Coll RC. Modulatory mechanisms controlling the NLRP3 inflammasome in inflammation: recent developments. *Curr Opin Immunol* 2013;25:40-5.)

lipopolysaccharide; (viral) nucleic acids; muramyl dipeptide; toxins; and environmental stimuli such as asbestos and silica. Endogenous triggers include indicators of cellular injury, such as extracellular adenosine triphosphate, and indicators of metabolic stress, including elevated extracellular glucose levels, monosodium urate, calcium pyrophosphate dehydrate crystals, β -amyloid fibrils, cholesterol crystals, and pancreatic amyloid peptide. Proposed pathways leading to inflammasome activation are depicted in Figure 165.5.¹³⁸

It has been recognized that the multitude of inflammasome-activating stimuli cannot possibly bind to the NLRP3 inflammasome, which raises the question of a common upstream pathway. The release of lysosomal contents during lysosomal rupture that is mediated by phagocytosed large inorganic materials, leads to the production of reactive oxygen species (ROS). It has also been suggested that mitochondrial ROS might trigger inflammasome activation and ion fluxes such as K⁺ efflux and the release of Ca²⁺ from the endoplasmic reticulum. (see Fig. 165.5).¹³⁸

Recently, oxidized mitochondrial DNA released from damaged mitochondria has been suggested to regulate NLRP3 activation through direct binding to cryopyrin; this not only further highlights the central role of the mitochondria but may be the common resulting pathway leading to inflammasome activation, which can be regulated by the mechanisms described earlier (see Fig. 165.5).¹³⁸

Hypotheses about how disease-causing gain-of-function mutations in NLRP3 can lead to inflammasome activation suggest that inflammasomes with the gain-of-function mutations release increased amounts of IL-1 β ,¹³⁹ which may be mediated through an increase in the redox state in monocytes carrying mutant cryopyrin. This, in turn, promotes more rapid caspase activation, IL-1 maturation, and secretion.¹⁴⁰ Mutations in NLRP3 cause decreased binding of cyclic adenosine monophosphate,¹⁴¹ a negative regulator of NLRP3 activation, which suggests that the mutations can modify inflammasome activation through several mechanisms (see Fig. 165.5).

Clinical features

All CAPS patients have episodes of fever, urticaria-like rash (Fig. 165.6a), conjunctivitis, arthralgia, and elevations in levels of acute-phase reactants but differ in the spectrum of multiorgan disease manifestations and in long-term morbidity and mortality.¹⁴² The skin rash is often the first noticeable disease manifestation; it is often present at birth or develops within hours of birth, but in FCAS patients it can first develop later in childhood. Other cutaneous manifestations include soft, doughy palms, soles, fingers, and toes, and clubbing of the fingernails without any evidence of pulmonary disease. Unlike in true familial and acquired cold urticaria, the ice cube test yields negative results in CAPS patients. Histologically, skin biopsy specimens show a dermal polymorphonuclear perivascular infiltrate, which is distinct from the lymphocytic and eosinophilic infiltrate found in classical allergic urticaria.¹⁴² The fever pattern in these disorders varies with the disease severity. Although in FCAS the inflammatory attacks are induced by cold exposure and subside within several hours, often to a state without residual inflammation, NOMID patients have continuous, often low-grade fever with disease exacerbations.¹⁴³ The severity

and specific disease manifestations of CAPS are discussed in the following sections.

Familial cold autoinflammatory syndrome

FCAS is at the milder end of the spectrum of CAPS.¹²⁹ FCAS flares are triggered by cold exposure and present with low-grade fever (93% of patients), polyarthralgia (96%), and urticarial rash (100%) that often start within 2 hours of cold exposure and last 12 to 48 hours.^{133,144} Other common features of FCAS include conjunctivitis (mostly with the attacks), profuse sweating, and dizziness, and headaches and nausea are also seen.¹³³ Rarely, FCAS patients have recurrent fever, mild arthralgia, inflammatory myocardiopathy, nephropathy, and thyroiditis as the only manifestation.¹⁴⁵ FCAS symptoms typically appear in early childhood, but a first presentation later in life is also seen.

Muckle-Wells syndrome

In 1962, Muckle and Wells described a familial syndrome with urticaria, hearing loss, and amyloidosis in nine individuals.¹⁴⁶ Patients with MWS have similar symptoms of fevers, urticaria-like rash, joint pain, conjunctivitis, and headaches, and recurrent arthritis and conjunctivitis episodes occur frequently.^{147,148} However, in contrast to patients with FCAS, these symptoms can be continuous and are not typically precipitated by cold exposure. During severe attacks, patients often complain of headache and have aseptic meningitis, and some MWS patients have papilledema. Episcleritis and optic disc edema can also be seen in MWS. Sensorineural hearing loss is the most typical clinical feature in MWS and is due to chronic inflammation of the inner ear, which likely leads to damage of the organ of Corti.¹⁴⁸ Significant hearing loss typically develops in the second to third decade of life in these patients.

Neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous and articular syndrome

NOMID/CINCA is at the most severe end of the CAPS spectrum and was first described in 1981.¹⁴⁹ NOMID is diagnosed clinically based on the



Fig. 165.6 (a) Urticarial rash in a patient with cryopyrin-associated periodic syndrome (CAPS)—Muckle-Wells syndrome. (b) Papilledema in a patient with CAPS—neonatal-onset multisystem inflammatory disease (NOMID). (c) Severe hydrocephalus in a patient with CAPS-NOMID. (d) Magnetic resonance image (MRI) showing cochlear enhancement in a patient with CAPS-NOMID. (e) MRI after treatment with anakinra showing resolution of the cochlear enhancement. (f) Typical patellar enlargement in a patient with CAPS-NOMID. (g) Knee MRI showing epiphyseal edema in a patient with CAPS-NOMID.

presence of characteristic features, which include neutrophilic urticaria, central nervous system (CNS) manifestations such as papilledema (see Fig. 165.6b) and aseptic meningitis with increased intracranial pressure, sensorineural hearing loss, and/or characteristic bony overgrowth. Continuous, often low-grade fevers, cutaneous rash, aseptic meningitis, and arthropathy start in the first weeks of life; exacerbations and flares are frequent.¹⁵⁰ Neutrophilic urticarial skin lesions are found in almost all patients. Neurologic involvement is a diagnostic feature of NOMID and is characterized by chronic aseptic neutrophilic meningitis that causes chronic irritability, headache, and seizures.^{150,151} Severely affected children develop hydrocephalus (see Fig. 165.6c), brain atrophy, and cognitive impairment. Patients typically develop sensorineural hearing loss within the first year of life, and cochlear enhancement is seen on MRI and suggests cochleitis as the cause of hearing loss (see Fig. 165.6d and e).

The most common inflammatory eye manifestation is conjunctivitis. Optic nerve atrophy is the primary cause of progressive vision loss, but anterior and rarely posterior uveitis can contribute.¹⁵⁰ Cognitive delay is multifactorial and due to perinatal insult and the degree of CNS inflammation.

Most NOMID patients (50% to 70%) have a deforming arthropathy that results in abnormal epiphyseal calcification, cartilage overgrowth, and joint deformities.¹⁵² Most commonly involved are the epiphyses of the distal femur and proximal tibia of the knee, which frequently leads to joint deformities and contractures. Premature patellar ossification and patellar overgrowth is a typical finding in NOMID (see Fig. 165.6f and g).¹⁵¹

Laboratory findings

Abnormal laboratory findings include marked leukocytosis with neutrophilia and thrombocytosis, anemia, and increased acute-phase reactants, such as ESR and CRP level.¹⁵⁰

Careful assessment of the CNS disease in NOMID/CINCA is often necessary, including lumbar punctures to monitor increased intracranial pressure, neutrophilic leukocytosis, and elevation of protein level in the cerebrospinal fluid. Leptomeningeal enhancement to various degrees is seen on high-resolution gadolinium-enhanced MRI, confirming the diagnosis of aseptic meningitis. The enhancement of the cochlea in the inner ear has indicated the inflammatory origin of the hearing loss in MWS and NOMID, and special cuts through the inner ear are useful in specialized clinical settings to follow inner ear inflammation and to adjust therapy. Radiographs of the long bones in patients with NOMID indicate the location of epiphyseal lesions, are used to monitor the bony overgrowth, and help to determine the need for surgical interventions such as osteotomies and stapling of the growth plates. MRI is used to rule out bone tumors and establish the presence of synovial inflammation, which is usually fairly non-impressive in most NOMID patients.

The diagnosis of CAPS is based on the clinical characteristics. The presence of *CIAS1/NLRP3* mutations is confirmatory but is not necessary to make the diagnosis and initiate appropriate therapy because mutation-positive and mutation-negative patients respond equally to IL-1-blocking therapy.¹⁵⁰ Although the majority of patients with FCAS and MWS carry germline mutations in *NLRP3*, the diagnosis of MWS can often be made on clinical grounds and should be considered in patients who have classic neutrophilic urticaria, hearing loss, and familial disease. In “mutation-negative” NOMID patients, somatic mutations were found to cause disease in about 70% of patients; somatic mutations are detected by either subcloning or deep sequencing; clinical assays to test for somatic mutations are currently not widely available, and relying on them could unnecessarily delay a therapeutic intervention.^{134,135} Given the significant benefit from IL-1-blocking therapies, a treatment challenge might help to confirm the clinical suspicion of CAPS.

Complications of untreated disease

As reported for the periodic fever syndromes, amyloidosis is also a feared complication of CAPS. In contrast to patients with FCAS, in whom secondary amyloidosis is rarely observed and is reported to occur in fewer than 2% of cases,¹⁵³ amyloidosis has frequently been described in untreated patients with MWS living in Europe, affecting 25% to 33% of patients.¹⁵⁴ Although amyloidosis in NOMID patients is not frequently reported in the literature, untreated NOMID patients with prolonged elevation of inflammatory markers are also at risk of development of amyloidosis.

Permanent organ damage related to CAPS is most prominent in NOMID and to a lesser extent in MWS and develops as a consequence of persistent inflammation in the affected organs.¹⁵⁵ Ongoing cochlear inflammation leads to sensorineural hearing loss, which develops in NOMID patients in the first decade of life and in MWS patients often in the second or third decade of life. Chronic aseptic meningitis leads to the development of increased

intracranial pressures and hydrocephalus, brain atrophy, and cognitive impairment. Chronic papilledema leads to optic nerve atrophy and progressive vision loss. Patients with hydrocephalus often have a typical facies, with frontal bossing, large cephalic perimeter, and saddle nose.^{150,151} The bony deformities were described earlier and usually do not resolve with IL-1-blocking therapies.^{132,156} In NOMID patients osseous lesions can lead to significant disability, including the development of severe limb-length discrepancies, bony overgrowth resulting in bone deformities, and joint contractures often requiring corrective surgery.

Treatment

Despite clinical heterogeneity, all patients with FCAS, MWS, and NOMID respond dramatically and invariably to IL-1 blockade. Studies have shown the efficacy and safety of anakinra (recombinant IL-1Ra) and the long-acting drugs rilonacept (IL-1 Trap, a fusion protein of the IL-1 receptor and the Fc portion of IgG) and canakinumab (an IL-1 β -blocking antibody).^{155,157,158,159} All patients show rapid improvement in clinical and laboratory parameters with treatment, which has led to the approval currently of three anti-IL-1 agents for the treatment of CAPS.

Although treatment of some patients with FCAS is aimed at improving the cold-induced symptoms by preventing cold exposure, optimal treatment with an IL-1-blocking agent (anakinra, rilonacept, or canakinumab) leads to complete resolution of symptoms in most cases and is the treatment of choice.^{160,161} In patients with MWS and NOMID, who develop organ damage from untreated disease, optimal IL-1-inhibiting therapy needs to be initiated early to prevent the development and progression of organ damage.¹⁵⁵ Recombinant IL-1Ra (anakinra) has been used for treatment of NOMID for over 10 years.¹⁵⁰ All patients show a rapid response to anakinra with dramatic improvement of inflammatory symptoms, fever, skin rash, and acute-phase reactants.¹⁵⁰ Notably, only bony overgrowth changes progress on treatment, which suggests that once the lesion is established, continuation of its growth is likely independent of IL-1.

Although dosages of IL-1-blocking drugs used to suppress disease activity in FCAS patients are typically lower than those that effectively suppress inflammation in NOMID patients, careful monitoring of the inflammatory disease lesions is often necessary to establish optimal individual treatment dosages to control organ inflammation, particularly CNS and inner ear inflammation.¹⁶² Reports of sustained responses to the IL-1-blocking therapies anakinra,^{155,163} rilonacept,^{158,164} and canakinumab¹⁶⁵ have recently been published.

The resolution of symptoms and the achievement of inflammatory remission not only in the blood but also in specific organs provided an important proof that the systemic and organ-specific inflammation seen in these disorders is IL-1 β dependent. The success of the treatment of CAPS with IL-1 blockade provided an example of how understanding the pathophysiologic processes responsible for inflammatory diseases can lead to rational targeting of the effector pathways.

Deficiency of interleukin-1 receptor antagonist

Genetics and pathophysiology

Deficiency of IL-1 receptor antagonist (DIRA; OMIM #612852) was first described in 2009. It is caused by autosomal recessive loss-of-function mutations in the *IL1RN* gene, which encodes IL-1Ra.^{166,167} Clinical descriptions of DIRA were published as early as 1993.¹⁶⁸ Nine disease-causing mutations have been reported to result in DIRA²²: three missense mutations, three nonsense mutations, two small deletions (2 and 15 base pairs), and one large genomic deletion (175 kilobases).^{6,169}

The mutations in *IL1RN* are likely founder mutations and have so far been described in Newfoundland, the Netherlands, Lebanon, Turkey, northern Puerto Rico, and Brazil. The incidence and prevalence of DIRA are unknown, with only about 40 cases reported or diagnosed worldwide so far. The allele frequency for the mutation could be estimated in the founder populations as 0.2% in Newfoundland and 1.3% in northern Puerto Rico.

IL-1Ra competes with the proinflammatory cytokines IL-1 α and IL-1 β for binding sites on the IL-1 type I receptor and prevents IL-1 signaling. The homozygous 3'-truncation mutants of *IL1RN* and the genomic deletion, including the *IL1RN* locus seen in patients with DIRA, lead to the production of a nonfunctional IL-1Ra protein or the absence of the protein, respectively, and the unopposed signaling leads to increased production of proinflammatory cytokines and chemokines, including IL-6, IL-8, MIP-1 α , and TNF.^{166,167}

Clinical features

DIRA patients have early-onset pustular dermatitis and multifocal osteomyelitis and periosteitis, associated with marked elevation in the levels of acute-phase reactants.^{166,167} Pustular skin lesions may be sparse, occur in

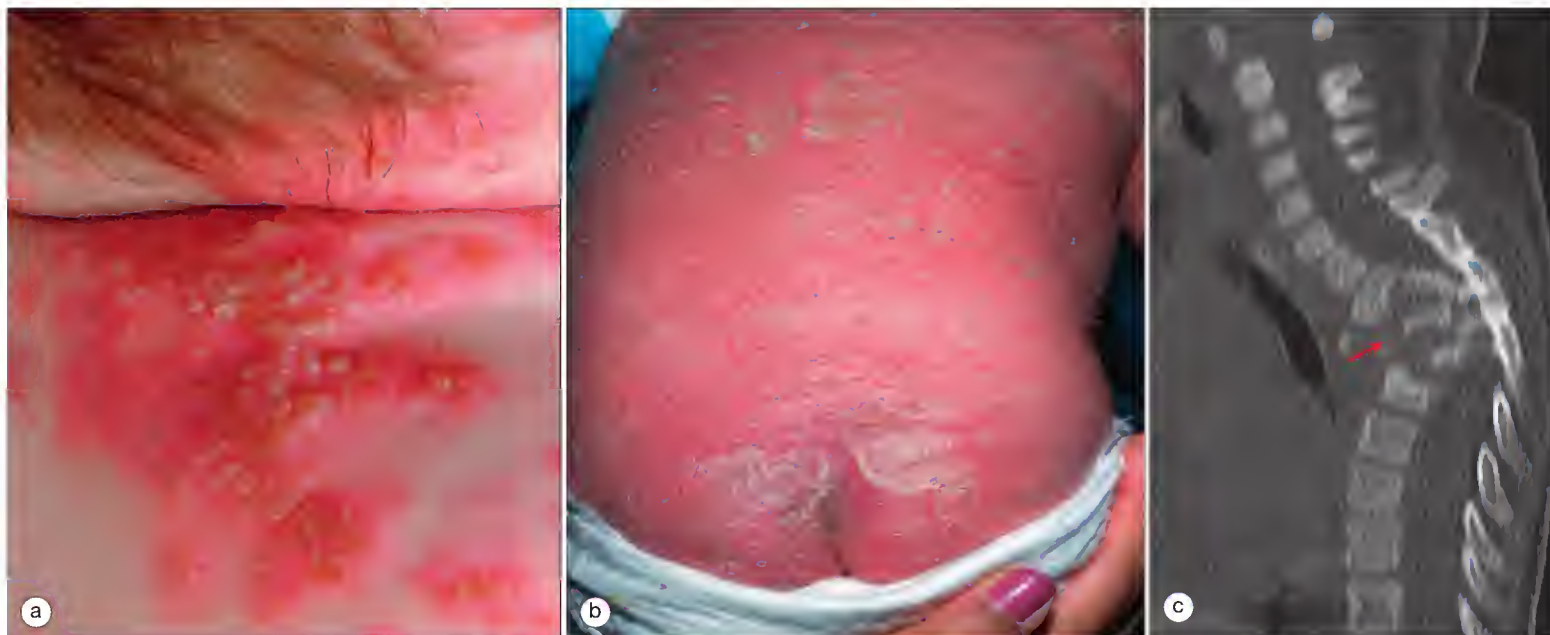


Fig. 165.7 (a) Pustular skin lesions in a patient with deficiency of interleukin-1 receptor antagonist (DIRA). (b) Erythematous and scaly skin rash in a patient with DIRA. (c) Spine magnetic resonance image showing destruction of vertebral bodies and intense kyphosis due to osteomyelitis in a patient with DIRA.

crops, or develop into a severe, generalized pustular dermatitis that at times can be ichthyosis-like (Fig. 165.7a and b).^{166,170} Histologic findings on skin biopsy include corneal pustules, acanthosis, and hyperkeratosis.^{166,170} Nail changes with onychomadesis are seen in very young untreated children.¹⁶⁶ All DIRA patients identified so far have had osteomyelitis, which is clinically characterized by pain on manipulation and periarticular swelling. Typical radiographic features are widened ribs and clavicles, as well as multifocal osteolytic lesions seen mainly in long bones.^{166,167,170} Heterotopic ossification or periosteal cloaking around the proximal femoral metaphysis is seen in very young children.

Fever is not frequent and often low grade when present and can be related to secondary skin infections in untreated patients.^{166,171} Recently, a disease-causing mutation was found to lead to intrauterine disease onset, systemic involvement resembling neonatal sepsis, and death in a premature newborn.¹⁶⁹

Laboratory findings

Patients with DIRA have persistent or recurrent increases in inflammatory markers (CRP and ESR), leukocytosis, and normocytic and normochromic anemia.

Complications of untreated disease

Untreated chronic osteomyelitis may lead to bone deformities and particularly vertebral destruction (see Fig. 165.7c); all infants should be screened for atlantoaxial subluxation due to odontoid destruction, which can lead to neck instability.¹⁷⁰ Less frequently observed manifestations in DIRA patients with untreated disease include interstitial lung disease and, rarely, CNS vasculitis.

Treatment

Recombinant IL-1Ra (anakinra) has been used in DIRA with impressive results.^{166,170} Treatment with anakinra leads to rapid resolution of symptoms and normalization of acute-phase reactants, and prevents the recurrence of both skin and bone manifestations.^{166,170}

SYNDROMES PRESENTING WITH GRANULOMATOUS SKIN LESIONS AND MINIMAL OR LOW-GRADE FEVER ATTACKS

Pediatric granulomatous arthritis (Blau syndrome/early-onset sarcoidosis)

Background

In 1985 Blau and coworkers described an autosomal dominant inherited disorder characterized by a clinical triad of chronic arthritis, granulomatous

dermatitis, and recurrent uveitis starting before the age of 4 years, which was called *Blau syndrome*. In 1996 Tromp and colleagues¹⁷² mapped the genetic cause of the disease to chromosome 16 (16q12.1-13), and in 2001 Miceli-Richard and coworkers¹⁷³ discovered that missense mutations in the *NOD2/CARD15* gene caused this clinical phenotype. In 2005 mutations in the same gene were found to cause a sporadic disease, early-onset sarcoidosis, with clinical resemblance.^{174,175} To reflect the fact that the familial and the sporadic form are the same disease, the disease spectrum is referred to as *pediatric granulomatous arthritis* (PGA).¹⁷⁶

Genetics and pathophysiology

PGA (OMIM #186580) is caused by autosomal dominant gain-of-function mutations in the NACHT domain (exon 4) of *NOD2/CARD15*.^{13,177} PGA can be inherited in an autosomal dominant manner, and familial cases have traditionally been called *Blau syndrome*. However, mutations can occur sporadically, and in these instances, the disease has been referred to as *early-onset sarcoidosis*.¹⁷⁸ So far 13 disease-causing mutations in the *NOD2* gene have been reported to result in PGA.¹³

Like *NLRP3*, *NOD2* (nucleotide-binding oligomerization domain protein 2) is a member of the NOD-like receptor family (NLR), playing an important role in innate immune defenses through detection and clearance of intracellular invasive bacteria and viruses.¹⁷⁹ It encodes a protein, *NOD2*, that has the typical three-domain protein structure of an NLR member: a caspase recruitment domain (CARD), a NACHT domain, and a leucine-rich repeat domain.¹⁸⁰ *NOD2* is present in the cytoplasm in an autoinhibited conformation, and its activation by interaction with pathogen-associated molecular patterns leads to its oligomerization via the NACHT domain and to exposure of the CARD.¹⁸¹ CARD-CARD interaction induces the recruitment of the serine-threonine kinase RICK, which results in activation of NF- κ B.^{182,183} Translocation of NF- κ B to the nucleus initiates the activation of several inflammatory genes. Gain-of-function mutations in the NACHT domain of *NOD2* might decrease the threshold for the spontaneous oligomerization of this protein, leading to a constitutive activation of NF- κ B and the inflammatory manifestations observed in PGA (see Fig. 165.1b).^{184,185}

Clinical features

PGA symptoms typically occur before the age of 4 years due to a granulomatous inflammation of eyes, joints, and skin that leads to an early-onset classic triad of disease manifestations consisting of chronic uveitis, arthritis, and dermatitis.¹⁷⁶ All patients have chronic arthritis, which almost always presents as polyarthritis (96% of cases).¹⁷⁶ A symmetric hypertrophic tenosynovitis is observed in approximately 40% of patients.¹⁷⁶ Ocular involvement is very frequent (84%) and is usually chronic and persistent (Fig. 165.8a).^{176,186} Uveitis manifests more commonly as panuveitis (50%), but 25% of the subjects may have anterior uveitis.^{176,186} Most of the patients have bilateral eye involvement, and cataract and glaucoma occur in 50% and 30%, respectively, of these individuals.^{176,179} Up to 40% of untreated patients with



Fig. 165.8 (a) Diffuse ichthyosis-like skin rash in a patient with Blau syndrome. (b) Cataract and anterior synechiae occurring as sequelae of chronic anterior uveitis in a patient with Blau syndrome.

PGA uveitis develop irreversible blindness.¹⁸⁶ Typical PGA exanthema is described as ichthyosis-like and occurs in over 85% of patients (see Fig. 165.8b).^{178,179} Less commonly observed findings include fever, camptodactyly, and central neuropathy.¹⁷⁸

Laboratory findings

Laboratory studies demonstrate persistent leukocytosis, thrombocytosis, and increased ESR and CRP levels.¹⁷⁶ Synovial, skin, and liver biopsy specimens may show noncaseating granulomas, but a definitive diagnosis is achieved only with DNA sequencing showing *NOD2/CARD15* mutations.^{13,186}

Complications of untreated disease

The most significant morbidity is eye involvement, and cataract, glaucoma, and retinal detachment are frequent complications and may lead to visual impairment and permanent vision loss.^{176,187} Untreated patients may also develop complication of chronic arthritis, such as joint deformities, ankylosis, and contractures of small joints, and decreased motion of large joints.^{188,189}

Treatment

Optimal therapy for PGA has not been well defined. NSAIDs can be used for mild clinical manifestations, whereas severe symptoms are treated with systemic corticosteroids.¹⁹⁰ Immunosuppressants (methotrexate and cyclosporine) and biologics targeting TNF and IL-1 (etanercept, infliximab, and anakinra) have been reported to result in clinical benefit, especially in patients with refractory uveitis.^{179,186}

PYOGENIC STERILE ARTHRITIS, PYODERMA GANGRENOSUM, AND ACNE (PAPA) SYNDROME

Background

In 1997 Lindor and colleagues¹⁹¹ described a kindred of 10 affected members with pyogenic arthritis, pyoderma gangrenosum and severe cystic acne. A second kindred of 11 affected patients was described by Wise and associates in 2000¹⁹²; in 2002, using genome-wide linkage, *CD2BP1/PSTPIP1* was identified, with two missense mutations, A230T and E250Q, as the disease-causing gene in both kindreds.¹⁹³

Genetics and pathophysiology

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (OMIM #604416) is a pyogenic autoinflammatory disease caused by autosomal dominant mutations in the *PSTPIP1* gene, also called *CD2BP1*.¹⁹³ Fourteen variants have been described in *PSTPIP1*, with four of them so far determined to be disease related.¹³ PAPA is exceedingly rare, and fewer than 10 families with the syndrome have been identified so far.

PSTPIP1 encodes a cytoskeletal protein, proline/serine/threonine phosphatase-interacting protein (*PSTPIP1*). *PSTPIP1* is an adaptor protein that interacts with the protein tyrosine phosphatases (PEST type), Wiskott-Aldrich syndrome protein, and pyrin, the protein encoded by *MEFV*, the gene mutated in FMF.¹⁹⁴⁻¹⁹⁶ Disease causing *PSTPIP1* mutations diminish the interactions with PEST-type protein, which results in increased phosphorylation of mutated *PSTPIP1* and increased interaction with pyrin.¹⁹⁶ It is suggested that *PSTPIP1* mutations increase activation of the pyrin (pyroptosome) associated IL-1 β activation¹⁹⁷; however, *PSTPIP1* does not seem to be an essential regulator of the Nlrp3, Aim2, or Nlrp4 IL-1 β -activating inflammasomes in a mouse model.¹⁹⁸

Clinical features

Fever is rarely observed in PAPA patients, who instead have early-onset flares of painful sterile and deforming arthritis (Fig. 165.9a), cutaneous ulcers (pyoderma gangrenosum; see Fig. 165.9b), and pathergy, cystic acne, or skin abscesses at the injections sites.^{193,199,200} PAPA syndrome symptoms usually persist into adulthood, and significant joint destruction with an impaired quality of life related to physical disability is observed.²⁰¹ A recent report describing five PAPA syndrome patients noted that three patients had an A230T mutation, one had an E250Q mutation, and one had the novel E250K mutation. All patients had sterile arthritis and pyoderma gangrenosum, three patients had sterile skin abscesses, and two had cystic acne. Other clinical findings were one osteomyelitis episode in one patient, recurrent otitis in two patients, and lymphadenopathy, splenomegaly, thrombocytopenia, hemolytic anemia, pharyngeal papillomatosis, and T-cell large granular lymphocytosis in one patient.²⁰¹ More typically around puberty, cystic acne and hidradenitis suppurativa of the axilla and groin can develop.^{191,202}

Laboratory findings

Laboratory findings are nonspecific and include leukocytosis and increased ESR and CRP levels during flares.^{193,199} Joint aspirates are aseptic and the predominant cells in the synovial fluid aspirate and in skin biopsy specimens are mature neutrophils.

Complications of untreated disease

Pyogenic arthritis results in joint destruction, with ankylosis affecting joint mobility. The pyoderma lesions heal with significant scarring of the skin.



Fig. 165.9 (a) Magnetic resonance image of the right elbow showing synovial thickening and enhancement with moderate fluid in a patient with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). (b) Extensive pyoderma gangrenosum lesion in a patient with PAPA syndrome. (c) Diffuse erythematous and scaly skin rash in a patient with *CARD14*-mediated psoriasis.

Treatment

Treatment of PAPA syndrome is challenging, and corticosteroids, thalidomide, cyclosporine, dapsone, tacrolimus, and intravenous immunoglobulin have been used with variable individual responses.^{201,203} Regarding biologics, two case reports showed that etanercept was efficacious in PAPA syndrome treatment.^{203,204} Responses were observed to infliximab in one patient, to adalimumab in two patients, and to anakinra in one patient.²⁰¹ On the other hand, two patients did not respond to anakinra, one did not respond to infliximab, and another did not respond to etanercept therapy.²⁰¹ In general, monoclonal anti-TNF antibodies (infliximab and adalimumab) were considered more effective in treating skin manifestations of PAPA syndrome.²⁰¹

MAJEED SYNDROME

Background

Majeed syndrome was first reported in 1989, and the original report described three members of a consanguineous Arab family who had chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia, and neutrophilic dermatosis.²⁰⁵ In subsequent reports the same investigators described a fourth child with the disease born into the first family and a second Arab family with two affected siblings born to consanguineous parents.^{206,207} In 2005 Ferguson and colleagues²⁰⁸ identified the genetic cause of the disease through homozygosity mapping and parametric linkage analysis of six affected members of the two previously reported families.

Genetics and pathophysiology

Majeed syndrome (OMIM #146462) is a pyogenic autoinflammatory disease caused by autosomal recessive loss-of-function mutations in the *LPIN2* gene encoding the protein lipin-2.^{6,208,209} Twelve mutations have so far been described in *LPIN2*, and four of them are disease causing.⁶ Although the pathogenesis of the disease is unclear, the recently reported clinical responses to IL-1 inhibition in two patients with Majeed syndrome suggest that the resulting mechanism may be IL-1 mediated.²¹⁰

Clinical features and laboratory findings

Majeed syndrome is clinically characterized by neonatal-onset recurrent multifocal osteomyelitis, neutrophilic dermatosis, and congenital dyserythropoietic anemia.²¹¹ Disease flares occur one to three times per month and are sometimes associated with mild fever. The patients failed to thrive with height and weight below the 5th percentile and with delayed bone age. All patients reported had significant hepatosplenomegaly and required blood transfusions on several occasions.²⁰⁵ Pustular dermatitis is the most common skin manifestation, although psoriasis-like lesions have also been reported.²¹¹ The most frequent sites of osteomyelitis are the clavicles, sternum, and long bones, whereas the mandible and vertebral bodies are rarely affected.^{206,209} Bone biopsy studies usually show a neutrophilic infiltrate.^{206,208}

Treatment

Majeed syndrome is unresponsive to treatment with antibiotics and may respond to NSAIDs, corticosteroids, IFN- γ bisphosphonates, and anti-TNF drugs.^{208,209,211} Recently the efficacy of IL-1 inhibition with either anakinra or canakinumab was demonstrated in two brothers with Majeed syndrome who showed no response to anti-TNF therapy.²¹⁰

FAMILIAL COLD AUTOINFLAMMATORY SYNDROME 2

Background

In 2008 two unrelated families from Guadeloupe who experienced episodes of fever, arthralgia, and myalgia after generalized exposure to cold were found to have autosomal dominant mutations in *NLRP12*.²¹² The disorder is referred to as an *NLRP12-associated disease* (*NLRP12AD*) and is also known as *familial cold autoinflammatory syndrome 2* (*FCAS2*) since it clinically resembles FCAS, an *NLRP3*-associated cryopyrinopathy. Several more cases and families have been described.²¹²⁻²¹⁴ The effects of the disease-causing mutations on *NLRP12* function are currently being investigated.

Genetics and pathophysiology

Autosomal dominant mutations in *NLRP12*, also known as *NALP12* and *MONARCH-1*,²¹² cause this rare disease, which can be familial but in most instances presents as sporadic disease. *NLRP12* is a member of the NLR family of intracellular sensors of molecular danger signals, but the disease pathogenesis remains unclear. Some data suggest that *NLRP12* acts as a proinflammatory protein on caspase-1 signaling and speck formation with the adaptor protein ASC.²¹⁵ Monocytes from patients with mutated *NLRP12* have increased concentrations of ROS and up regulation of antioxidant systems in the absence of stimulation by pathogen-associated molecular patterns²¹⁴ and accelerated kinetics of IL-1 β secretion.¹⁴⁰ The early secretion of IL-1 β , even in the absence of an overall increased secretion of the cytokine, may be sufficient to account for the mild inflammatory symptoms seen in this syndrome.

Clinical features and laboratory findings

In the nine patients with FCAS2 described so far, the age of onset of the clinical manifestations varied from the first days of life to 20 years of age.²¹²⁻²¹⁴ Patients with FCAS2 experience cold-induced episodes of high-grade fever and urticarial rash associated with myalgia, arthralgia, abdominal pain, and headache.²¹²⁻²¹⁴ Other manifestations observed are vomiting, oral ulcers, and lymphadenopathy.²¹²⁻²¹⁴ Two of the nine patients described, the only two monozygotic twins, had sensorineural bilateral hearing loss.²¹² In the nine patients, the length of episodes varied from several hours to 15 days.²¹²⁻²¹⁴

During flares, FCAS2 patients can have an increase in acute-phase reactants (ESR and CRP level).²¹²⁻²¹⁴ However, three of the nine patients described

did not show evidence of increased levels of inflammatory serum markers.²¹²⁻²¹⁴

Treatment

Preventing cold exposure can avoid or ameliorate FCAS2 symptoms.²¹²⁻²¹⁴ Symptoms can be partially controlled with NSAIDs and variable courses of oral steroids.²¹²⁻²¹⁴ Prophylactic administration of low-dose steroids and antihistamines during winter prevented disease manifestations in one patient.²¹⁴ Colchicine was not effective in the three patients reported to have received it.^{212,213} In the two patients who received anakinra, although an initial partial clinical response was observed, the drug was discontinued after 14 months due to a progressive clinical relapse.²¹⁵

PROTEASOME-ASSOCIATED AUTOINFLAMMATORY SYNDROMES

Background

In 1993 Tanaka and colleagues²¹⁶ reported on 2 Japanese patients with lipodystrophy, muscle atrophy, and skin eruptions; they proposed that 13 Japanese patients previously described had the same syndrome, including those in reports dating back to 1939 describing 96 patients with lipodystrophy, rashes, and systemic inflammation. In 2010 Garg and coworkers²¹⁷ reported on two Mexican siblings and a Portuguese patient with an autosomal recessive syndrome and noted the similarities with the Japanese patients; they termed the disorder *JMP syndrome*, for joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy. All patients had short stature, generalized lipodystrophy, and severe joint contractures of the elbows, hands, fingers, feet, and toes. In childhood, all patients had erythematous nodular skin lesions, and one patient had panniculitis on skin biopsy. Earlier in the same year, Torreló and colleagues²¹⁸ proposed the acronym *CANDLE* (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) for a syndrome described in four patients, including two sisters, who had recurrent fevers, annular erythematous skin lesions, lipodystrophy, and high levels of acute-phase reactants with hypochromic anemia.

Genetics and pathophysiology

In 2011 several studies showed that autosomal recessive mutations in the proteasome subunit β type 8 (*PSMB8*) gene cause JMP syndrome,²¹⁹ Nakajo-Nishimura syndrome (NNS),²²⁰ Japanese autoinflammatory syndrome with lipodystrophy,²²¹ and *CANDLE* syndrome²²² (OMIM #256040), which indicates that these disorders are disease phenotypes along the same disease spectrum.^{218,222,223} Currently, three mutations in *PSMB8* have been described (T75M, C135X, and G201V).

Proteasomes are protein degradation systems that target intracellular polyubiquitinated proteins derived from self-structures or foreign structures for proteolytic destruction.²²⁴ Proteasomes are implicated in cellular processes including apoptosis, the removal of various misfolded and immature proteins, and the production of peptides for presentation by major histocompatibility complex class I molecules (Fig. 165.10).²²⁵ In response to cytokines, the expression of three alternative catalytic subunits designated as β 1i/LMP2/*PSMB9*, β 2i/Mec11/*PSMB10*, and β 5i/LMP7/*PSMB8* is induced resulting in the formation of a proteasome isoform known as the *immuno-proteasome* (I-proteasome). I-proteasome expression is inducible in most tissues, but it is constitutively expressed in hematopoietic cells, especially lymphocytes and monocytes.²²⁶ In patients who are homozygous for *PSMB8* mutations, the assembly of the I-proteasome complex is defective,²¹⁹⁻²²¹ and polyubiquitinated proteins accumulate in tissues in these patients. Gene expression profiling using whole-blood microarray identified the IFN pathway as the most differentially regulated pathway in all six *CANDLE* syndrome patients tested,²²² and inhibition of IFN signaling with the Janus kinase (JAK) inhibitor tofacitinib decreased IFN- γ -induced IP-10 production by the patients' cells.²²² This suggested that the IFN pathway may be a target for therapeutic intervention.

Clinical features and laboratory findings

Recently, 28 patients with NNS were compared with 3 patients with JMP syndrome and 9 with *CANDLE* syndrome, and the clinical disease spectrum of the proteasome-associated autoinflammatory syndromes is summarized here. Common clinical features seen in the majority of the patients historically described as having either NNS, JMP syndrome, or *CANDLE* syndrome

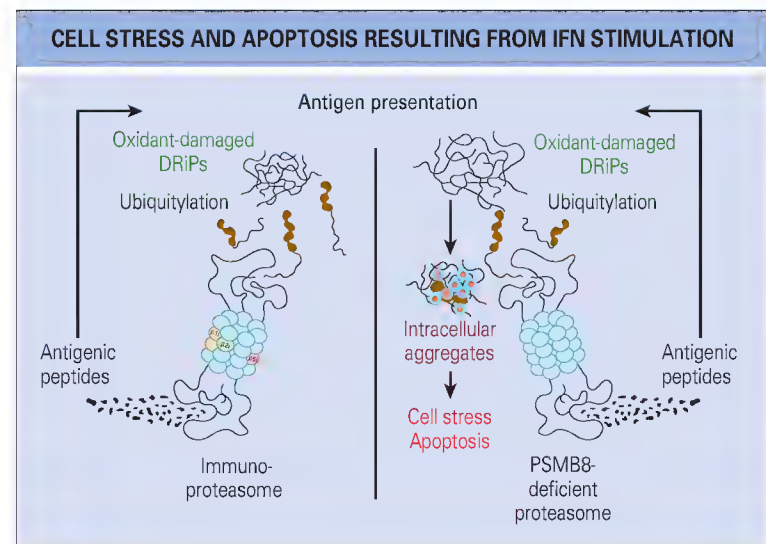


Fig. 165.10 Fibroblasts from *PSMB8* knockout mice, when stimulated with interferon (IFN), accumulate increased amounts of oxidant-damaged defective ribosomal products (DRiPs) that cannot be degraded and form aggregates leading to cell stress and apoptosis.

include high fevers; clubbed fingers; skin rashes, varying from small nodules to violaceous plaques (Fig. 165.11a), also described as “pernio-like” lesions, covering the trunk and extremities, and facial rashes leading to various degrees of edema and mimicking heliotrope rashes in some patients; arthritis with more variable joint contractures; and progressive lipodystrophy that initially affects the face and extremities but can be generalized (see Fig. 165.11b). Clubbed fingers are a result of the arthropathy and the lipoatrophy that develops early in the hands, but the elevation of the nail bed noted in hypertrophic osteoarthropathy is not typically seen in these patients. Myositis (see Fig. 165.11c), hepatosplenomegaly, basal ganglia calcification (see Fig. 165.11d), microcytic anemia, and increased acute-phase reactants (ESR and CRP level) are also observed in these patients. More variable symptoms include muscle atrophy, dyspnea, seizures, lymphadenopathy, low weight and height, hepatosplenomegaly, and metabolic abnormalities, including truncal obesity and hyperlipidemias, insulin resistance, and acanthosis nigricans.^{217,222,227} Clinical and laboratory findings less frequently observed are perioral swelling, parotitis, conjunctivitis or episcleritis, hypertrichosis, ear and nose chondritis, lymphocytic aseptic meningitis, recurrent otitis or sinusitis, epididymitis, thrombocytosis, hypergammaglobulinemia, neutropenia, and thrombocytopenia.^{220,221}

Complications of untreated disease

In childhood severe inflammatory attacks that cannot be controlled by any antiinflammatory medications including high-dose steroids can result in sudden death, likely from a triggered systemic inflammatory syndrome resulting in organ failure. Some insights into the development of organ damage from untreated disease in older patients are provided by earlier reports on adult patients^{217,227} that suggested the development of muscle atrophy and joint contracture, cardiac arrhythmias, and heart failure. Autopsy results from a patient who died of heart failure have provided further insights into the pathologic features of the disease. Extensive endothelial cell damage and calcification of multiple vessels, including cardiac and basal ganglia vessels, was observed, and it was proposed that ischemia may cause the severe skeletal muscle atrophy and myofibrillary necrosis. Other muscles affected were the tongue, extraocular muscles, and heart.²²⁸

Treatment

In the nine patients previously mentioned, most clinical symptoms partially responded to high doses of steroids (1 to 2 mg/kg/day).²²² NSAIDs, colchicine, dapsone, methotrexate, tacrolimus, and azathioprine were not effective in most patients.²²² A variable response was observed to anti-TNF, anti-IL-1, and anti-IL-6 agents, but complete disease remission was not achieved with any of the therapies described.²²² Additionally, lipodystrophy progressed in all patients despite immunosuppressive and cytokine-targeted therapy.²²² The increase in STAT1 phosphorylation and the strong IFN response suggest that IFN signaling may be a therapeutic strategy for the treatment of

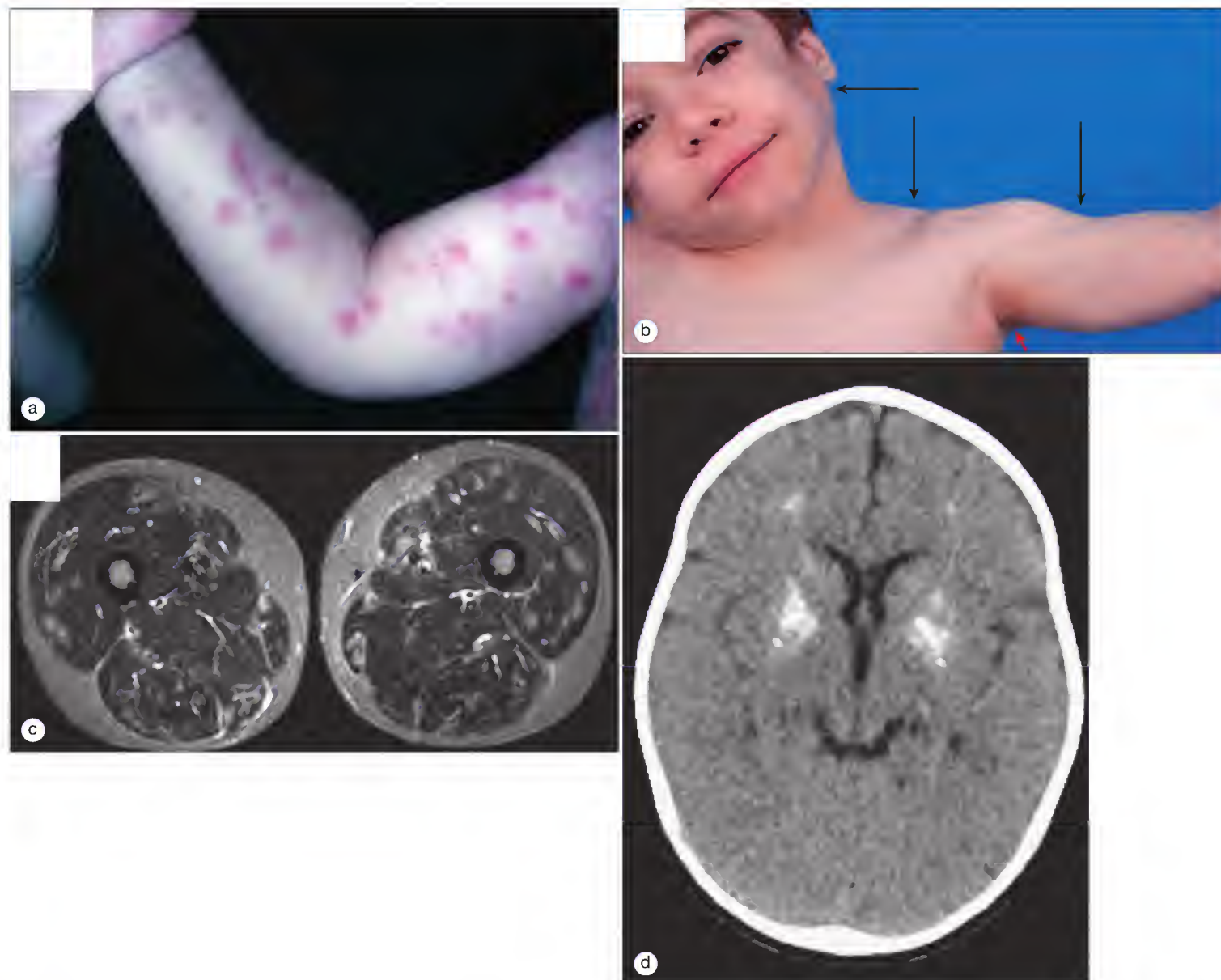


Fig. 165.11 (a) Erythematous, annular, and nodular rash in a patient with CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature). (b) Lipodystrophy (black arrows) and acanthosis nigricans (red arrow) in a patient with CANDLE syndrome. (c) Bilateral thigh magnetic resonance image (MRI) showing signs of myositis (white patches) in a patient with CANDLE syndrome. (d) Brain MRI showing basal ganglia calcifications in a patient with CANDLE syndrome.

CANDLE syndrome and other proteasome-associated autoinflammatory syndromes.

SYNDROMES PRESENTING WITH PREDOMINANTLY SKIN INVOLVEMENT

Deficiency of interleukin 36 receptor antagonist

Genetics and pathophysiology

Recently 16 family members of nine Tunisian families with generalized pustular psoriasis and fever flares were found to be homozygous for a mutation in the *IL36RN* gene, L27P, which indicates a founder mutation in Tunisia leading to this disease.²²⁹ Most of the patients described (75%) developed the disease during childhood (7 days to 11 years of age).²²⁹ Additionally, three unrelated English patients with a similar phenotype had mutations in *IL36RN*.²³⁰ More recently, 2 out of 14 Japanese patients with pustular psoriasis were found to be compound heterozygous for a splice-site mutation resulted in the skipping of exon 3; in addition, a missense mutation leading to expression of a nonfunctional protein was found in one of the patients, and a nonsense mutation leading to a stop codon R10X was found in the other.²³¹

IL36RN encodes for the IL-36 receptor antagonist (IL-36Ra), which binds to the IL-36 receptor and thus blocks binding by IL-36 α , IL-36 β , and

IL-36 γ and inhibits NF- κ B and MAPK signaling.²²⁹ IL-36Ra is highly expressed in keratinocytes and plays an important role in down regulating exacerbated inflammatory responses. Therefore the absence of IL-36Ra in patients with the described *IL36RN* mutations leads to constitutively enhanced IL-36 receptor signaling.

Clinical features and laboratory findings

Patients have recurrent and sudden onset of skin flares characterized by generalized erythematous and pustular skin rashes, associated with high fevers up to 40 to 42°C, asthenia, high levels of acute-phase reactants (e.g., CRP), and high white blood cell counts.^{229,230} Secondary skin infections and sepsis may also occur.²²⁹ In most patients, the disease flares are thought to be triggered by viral or bacterial infections (14 of 16 patients), but withdrawal of retinoid therapy, menstruation (6 patients), and pregnancy have also been triggers.^{229,230} Skin biopsy specimens demonstrate spongiform pustules, acanthosis and parakeratosis in the stratum corneum, and infiltration of the skin by CD8+ and CD3+ T cells and macrophages.²²⁹ Because the *IL36RN* mutations described result in a decrease or absence of IL-36Ra, the resulting disease was proposed to be called *deficiency of IL-36 receptor antagonist* (DITRA; OMIM #614204).²²⁹

Treatment

The definitive treatment for DITRA has not yet been established. Acitretin was used as treatment for 12 of the 19 patients described so far.^{229,230} Other

therapeutic regimens tried with variable individual responses were oral steroids in four patients, methotrexate in three patients, cyclosporine in three patients, adalimumab in two patients, infliximab in two, and etanercept in one.^{229,230} Topical steroids were used in three patients.²²⁹

CARD14-mediated psoriasis

Background

In 1994 Tomfohrde and colleagues²³² identified a psoriasis susceptibility locus, PSORS2, in a single large family of European ancestry that mapped to human chromosomal region 17q25-qter. Affected members had plaque psoriasis, and approximately 30% had psoriatic arthritis. A five-generation psoriasis pedigree from Taiwan exhibited significant linkage to the same locus.²³³ Recently, targeted and exome capture followed by next-generation sequencing of DNA obtained from members of the family identified a splice-site mutation in the caspase recruitment domain-containing protein 14 gene (*CARD14*) encoding a protein that carries a CARD mediating the assembly of CARD-containing proteins into apoptosis- and NF- κ B-signaling complexes.²³⁴

Genetics and pathophysiology

Autosomal dominant gain-of-function mutations in the *CARD14* gene caused plaque psoriasis in two families and severe generalized pustular psoriasis in an unrelated child who had a sporadic *de novo* mutation in *CARD14*.²³⁵ Mutations in *CARD14* were also shown to cause familial pityriasis rubra pilaris in 15 family members of three kindreds.²³⁶ In addition to the three mutations associated with familial disease, additional rare variants were found in several probands from large psoriasis cohorts. Although the contribution of those variants to psoriasis is not fully understood, some of these mutations were NF- κ B activating and likely constitute rare variants with a large effect size, which suggests the possibility of development of sporadic disease such as that seen in the child with a *de novo* mutation mentioned earlier.^{235,237} The fact that *CARD14* mutations cause familial psoriasis as well as pityriasis rubra pilaris indicates that these disorders fall along the same disease spectrum.

Clinical features and laboratory findings

Patients with *CARD14* mutations can have typical plaque psoriasis of variable severity that can be mostly limited to certain areas of the skin or can be generalized and involve 100% of the body surface area (see Fig. 165.9c).^{235,236} Fever and other systemic manifestations are generally not present but can occur with superinfection of the skin in patients with *CARD14*-mediated psoriasis (CAMPS; OMIM #602723).^{235,237}

Treatment

The therapeutic approach in CAMPS includes drugs used for the treatment of moderate to severe psoriasis, such as methotrexate, cyclosporine, anti-TNF agents, and, more recently, biologics targeting IL-17 and IL-23.²³⁸⁻²⁴⁰ Familial pityriasis rubra pilaris is considered refractory to the standard therapies, and a partial response to retinoids, cyclosporine, and etanercept has been described.^{236,241}

SYNDROMES PRESENTING WITH INFLAMMATORY BOWEL DISEASE

Background

In 2009 Glocker and colleagues²⁴² mapped chromosome arms 11q and 21q as the regions of interest in two families with early-onset severe enterocolitis. Targeted sequencing showed a homozygous missense mutation in *IL10RA* and a homozygous nonsense mutation in *IL10RB* in each of the families evaluated. In 2010, the same group found that autosomal recessive mutations in the *IL10* gene can also cause refractory early-onset inflammatory bowel disease (EO-IBD).²⁴³

Genetics and pathophysiology

Infantile IBD is caused by autosomal recessive mutations in the genes encoding the IL-10 receptor (OMIM #613148, OMIM #612567) and IL-10 (OMIM #612381).^{242,243} In total, six disease-causing mutations in each of the IL-10

receptor genes (*IL10RA* and *IL10RB*) and two mutations in the *IL10* gene have been described.

IL-10 is an antiinflammatory cytokine that is secreted by a wide variety of cells and has immunoregulatory effects on T cells, B cells, myeloid cells, and other cell types. IL-10 limits the secretion of proinflammatory cytokines such as TNF- α and IL-12. IL-10 signals through the IL-10 receptor, which consists of two receptor subunits, IL-10RA and IL-10RB. Dysfunction of IL-10 receptor and impaired signaling of IL-10 leads to increased production of proinflammatory cytokines, including TNF- α , IL-1 α , IL-1 β , IL-2, and IL-6, and chemokines, including RANTES, MIP-1 α , and MIP-1 β . Mice deficient in either IL-10RA or IL-10RB also have severe enterocolitis.^{242,243}

Clinical features and laboratory findings

Patients with EO-IBD have severe enterocolitis characterized by bloody diarrhea, colonic abscesses, perianal fistula, and oral ulcers.^{242,244} Symptoms usually start in the first year of life, before 3 months of age.²⁴⁴ Additionally, they have impaired weight and height development and recurrent fever.²⁴⁴ Musculoskeletal manifestations include acute recurrent arthritis of large joints, especially the knees.²⁴⁴ Remarkably, recurrent folliculitis has been observed in 75% of patients.²⁴⁴ Recurrent infections, such as otitis media, bronchitis, pneumonia, septic arthritis, and renal abscesses, may indicate a defect in the immune responses in patients with EO-IBD.^{242,244}

Treatment

Because EO-IBD is a severe disease and is frequently refractory to standard immunosuppressant therapy, hematopoietic stem cell transplantation (HSCT) has been proposed as a curative treatment.²⁴⁵ HSCT was performed in 9 of the 29 patients with IL-10 deficiency described, and complete clinical remission was achieved in all but one of these patients.²⁴⁴⁻²⁴⁶

SYNDROMES PRESENTING WITH AUTOINFLAMMATION AND IMMUNODEFICIENCY

The description of additional monogenic diseases has led to the identification of conditions that present with autoinflammatory phenotypes but also with features of immunodeficiencies. The mixed phenotype is determined by the impact the mutation can have in different immune cells. Immunodeficiencies have also been suggested to be present in patients with HIDS and EO-IBD. Two conditions have been described recently that are caused by autosomal dominant mutations in *PLCG2*: PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID) and autoinflammation and PLC γ 2-associated antibody deficiency and immune dysregulation (APLAID).^{247,248} Another condition is caused by autosomal recessive mutations in *HOIL*, a component of the linear ubiquitin chain assembly complex (LUBAC).²⁴⁹ These mutations result in impairment of LUBAC stability, which leads to reduced NF- κ B activation in response to IL-1 β in fibroblasts but hyperresponsiveness to IL-1 in mononuclear leukocytes, particularly monocytes.²⁴⁹ PLAID is characterized by cold-induced urticaria, autoimmune manifestations, and susceptibility to infections, whereas APLAID leads to early-onset recurrent erythematous plaques and vesicopustular skin lesions associated with arthralgia, corneal erosions, and interstitial pneumonia.²⁴⁸ The two patients identified with APLAID so far have developed recurrent sinopulmonary infections, presumably due to a lack of class-switched memory B cells.²⁴⁸ Both patients described showed partial responses to anakinra and to high-dose corticosteroids.²⁴⁸

Of the three patients with *HOIL* deficiency who have been described, two were siblings born to non-consanguineous parents.²⁴⁹ All three patients had early-onset recurrent fevers, hepatosplenomegaly, and increased levels of acute-phase reactants.²⁴⁹ Two patients had chronic bloody diarrhea and two had eczema and diffuse erythroderma. These patients experienced severe recurrent pyogenic, fungal, and viral infections, and all three patients had a fatal outcome.²⁴⁹ In addition, all three patients had cardiomyopathy, and two patients had amylopectinosis in cardiomyocytes.²⁴⁹ The autoinflammatory manifestations in two of the three patients were partially responsive to corticosteroids but refractory to colchicine, anti-TNF agents, and anti-IL-1 agents. The third patient underwent allogeneic HSCT at the age of 13 months but died 3 years after transplantation.²⁴⁹

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166

Sarcoidosis

■ STERLING G. WEST

- Sarcoidosis is a systemic inflammatory disorder of unknown cause characterized by noncaseating, granulomatous inflammation that can affect virtually any organ.
- Acute and chronic forms of inflammatory arthritis particularly involve the ankles and knees.
- Cystic bone lesions may produce dactylitis or rarely involve the skull, vertebrae, ribs, or pelvis.
- Muscle involvement is usually asymptomatic but may cause acute or chronic myopathies or nodular masses.
- Nonmusculoskeletal features are common and include bilateral hilar adenopathy, pulmonary infiltrates, uveitis, cardiac and neurologic involvement, and skin lesions such as erythema nodosum and lupus pernio.

HISTORY

Sarcoidosis derives from the Greek *sarco*, meaning “flesh,” *eidos*, meaning “like,” and *osis*, meaning “condition.”¹ In 1877, Jonathan Hutchinson described the first case at King’s College Hospital in London. Later, Caesar Boeck advanced the description of sarcoidosis by emphasizing the granulomatous inflammation characteristic of this disease. He was the first to use the term *sarkoid* (sarcoid) because he thought the lesions resembled sarcoma but were benign. In 1953, Sven Löfgren described the acute sarcoidosis syndrome of bilateral hilar adenopathy and erythema nodosum, frequently associated with arthritis, fever, and uveitis. Over the past century, sarcoidosis has become recognized as a multisystem granulomatous disorder with protean manifestations that may affect any organ.^{2,3}

EPIDEMIOLOGY

Sarcoidosis occurs worldwide.⁴ It has been reported in all races and ethnic groups, but with marked variations. Prevalence estimates using mass chest radiographic screening range from 0.2 in 100,000 (Portugal) to 64 in 100,000 (Sweden). In the United States the age-adjusted annual incidence rates are three times higher for blacks (35.5 in 100,000) than for whites (10.9 in 100,000) with a lifetime risk of sarcoidosis for U.S. blacks of 2.4% and for U.S. whites of 0.85%. In most series sarcoidosis affects females slightly more than males (57% to 64% females). People of all ages can be affected, but it particularly occurs in young adults 20 to 40 years of age (over 70% of cases) with possibly a second peak in women in the seventh decade.

Clinical evidence indicates that the presentation and severity of sarcoidosis vary according to race and ethnicity. Whites are more likely to have erythema nodosum, have less extrapulmonary involvement, and have lower age-adjusted mortality than other racial groups. The Japanese have more cardiac and ocular involvement, and blacks have the most severe disease with higher mortality rates.

CLINICAL FEATURES

Sarcoidosis is a systemic inflammatory disorder. The clinical manifestations are diverse, ranging from abnormal chest radiographic findings in an asymptomatic individual (up to 50% of patients) to severe multiorgan

involvement.^{2,3} Because there is no specific test for sarcoidosis, the diagnosis is established when well-recognized clinical and radiographic findings are supported by histologic evidence of widespread noncaseating epithelioid granulomas in more than one organ system.⁵ Other granulomatous diseases must be excluded. The presenting manifestations and cumulative organ involvement in sarcoidosis patients are shown in Table 166.1. Recently the ACCESS (A Case Control Etiologic Study of Sarcoidosis) trial evaluating 736 sarcoidosis patients confirmed that 95% of patients had thoracic involvement, 50% had extrathoracic involvement, and only 2% had isolated extrathoracic sarcoidosis. Notably, there were significant differences in clinical findings and prognosis among groups on the basis of race, sex, and age.⁶

Respiratory tract involvement

Respiratory tract involvement is the most common visceral manifestation (95% of cases), and any part from sinuses (2% to 18%) to lungs can be involved.^{3,7} The clinical spectrum ranges from asymptomatic hilar adenopathy (50% to 60%) to an interstitial lung disease with alveolitis. Pleural effusions are rare (fewer than 5% of cases). Endobronchial involvement is found on biopsy in 50% and may lead to airway stenosis (10%) and wheezing. Symptoms of lung disease include dry cough (30%), dyspnea (28%), and chest pain (15%). Hemoptysis is rare and occurs primarily in patients with fibrosis and cavitation filled with aspergillomas. Lung crackles are heard in only 20%, and clubbing is rare. Pulmonary hypertension occurs in 5% to 15% of all patients and in 50% of patients with dyspnea.

Chest radiographs show abnormal findings in 90% of patients and are classified using the modified Scadding staging system: stage 0, normal; stage I, bilateral hilar adenopathy; stage II, adenopathy with pulmonary infiltrates; stage III, pulmonary infiltrates only; and stage IV end-stage pulmonary fibrosis (Fig. 166.1). Notably, the stages are not chronologic and do not indicate disease chronicity or correlate with changes in pulmonary function. Hilar adenopathy is noted in 50% to 85% of patients. In the majority of patients hilar node enlargement is bilateral, but unilateral hilar (usually right-sided) and/or unilateral paratracheal adenopathy is present in up to 4% of patients. Parenchymal changes occur in 25% to 60% of cases, have a mid- to upper-zone predominance, and typically are located along the bronchovascular bundle. High-resolution computed tomography (HRCT) is more sensitive than the chest radiography and may show mediastinal node involvement and/or unexpected parenchymal disease in patients with normal chest radiographic findings. Up to 70% of patients with abnormal findings on chest radiographs have airflow abnormalities at presentation. Pulmonary function tests (PFTs) typically show a restrictive pattern, with a reduction in vital capacity, residual volume, and total lung capacity.^{3,7} The loss of diffusing capacity is the most common abnormality. Obstructive airway disease also occurs in 50% of patients due to obstruction of large and small airways from endobronchial granulomas or bronchiolitis and is a poor prognostic sign, suggesting extensive and progressive disease.

The characteristic bronchoalveolar lavage fluid cell differential shows greater than 30% to 60% lymphocytes. A CD4/CD8 T-cell ratio greater than 3.5 (94% specific, 52% sensitive) is supportive of a diagnosis of sarcoidosis. The CD4+ T cells are activated with an effector memory phenotype (CD45RO). Notably, the number of cells exhibiting cytotoxic activity (CD8+ T cells, natural killer [NK] cells, and NK T cells) increases progressively between Scadding stages I and IV. An adequate transbronchial biopsy consists of six specimens from the upper and lower lobes. With abnormal chest radiographic findings the diagnostic yield is over 90%. Endobronchial ultrasonography with transbronchial needle aspiration of hilar/mediastinal adenopathic lesions has a diagnostic yield of 83%.

Patients with good prognostic signs (Scadding stage 0 and I; Löfgren syndrome; asymptomatic stage II and III disease) should be observed for 3

TABLE 166.1
Clinical features of sarcoidosis

Manifestation	Presenting (%)	Cumulative (%)
Respiratory tract	25-50	95
Constitutional	25	33-70
Adenopathy	10-20	40
Joint disease	1-14	4-38
Uveitis	5	10-20
Hepatosplenomegaly	4	5-20*
Cutaneous	3	15-30
Other	4	
Heart	<1	5-10*
Neurologic	<1	5-10
Muscle	<1	1-5*
Bone	<1	1-13

*At autopsy, 20%-67% have heart involvement; on biopsy, 50%-80% have muscle and liver involvement.



Fig. 166.1 Pulmonary sarcoidosis. Chest radiograph demonstrating bilateral hilar adenopathy.

to 6 months before starting therapy. During the first 2 to 3 years, repeat chest radiographs and pulmonary function tests should be performed every 3 to 6 months in patients with symptoms and/or radiographic abnormalities to monitor for progression. For the 10% to 30% of patients who develop symptomatic and progressive stage II and III lung disease (a decrease in total lung capacity of 10% or more, a decrease in forced vital capacity of 15% or more, a 20% or greater decrease in lung diffusion of carbon monoxide, or progressive radiographic changes) current guidelines suggest the use of 40 to 60 mg (1 mg/kg/day) of prednisone daily for 8 to 12 weeks, with a gradual tapering of the dose to 30 mg every other day by 6 months, 20 mg every other day by 9 months, and 10 mg every other day by 12 months. Corticosteroid therapy often lasts for 2 years or longer. More than 70% of patients respond favorably, but relapses occur in 25% to 50% after tapering or discontinuation of corticosteroids, so patients need to be monitored closely. Some patients need 10 to 20 mg every other day indefinitely to prevent relapses. Steroid-sparing agents include methotrexate (15 mg/wk), mycophenolate mofetil (1 to 1.5 g twice daily), azathioprine (2 mg/kg/day), leflunomide (10 to 20 mg/day), and/or anti-tumor necrosis factor (anti-TNF) biologics (infliximab 3 to 5 mg/kg every 1 to 2 months intravenously). Pulmonary hypertension may respond to sildenafil, bosentan, or epoprostenol. In patients in whom therapy fails and who develop end-stage pulmonary fibrotic disease, lung transplantation offers a potential cure, although



Fig. 166.2 Lupus pernio. Violaceous nodular and plaquelike eruptions on the nose, cheeks, and forehead in a patient with chronic sarcoidosis.

asymptomatic recurrence of sarcoidosis in the allograft has been observed in 50%.

Ophthalmologic involvement

Eye involvement occurs in 25% to 50% of patients and can be the major clinical manifestation.⁸ It can be the initial manifestation (5% of cases) or occur at any time during the disease course. Because the disease may be asymptomatic (33%), all patients with sarcoidosis should have a baseline slit-lamp and fundusoscopic eye examination with repeat examinations annually or with development of symptoms. Any area of the eye may be involved. Acute anterior uveitis is the most common presentation, manifested by blurred vision, eye redness, photophobia, pain, and “mutton fat” keratic precipitates on slit-lamp examination. Involvement is usually bilateral, which distinguishes it from the unilateral uveitis seen in HLA-B27-associated spondyloarthritis. Other ophthalmologic manifestations include interstitial keratitis, posterior uveitis, pars planitis (“snowballing” on slit-lamp examination), scleral plaques, lacrimal gland enlargement (15% to 28%), optic neuropathy, and corneal/conjunctival nodules. Approximately 20% of patients with uveitis experience some visual loss. Eye manifestations are treated with topical, injectable, and systemic corticosteroids. Topical corticosteroids and cycloplegics are usually sufficient for anterior uveitis, although granulomatous involvement of ocular structures and posterior segment inflammation require oral corticosteroid or periocular steroid injections. Azathioprine, mycophenolate mofetil, methotrexate, leflunomide, infliximab, and rituximab have all been effective for treatment of corticosteroid-refractory disease.

Cutaneous involvement

Skin involvement occurs in up to 30% of cases and can be divided into specific and nonspecific categories.⁹ Specific lesions demonstrate granulomatous inflammation on biopsy. The most common specific skin manifestation is hyperpigmented maculopapular lesions (2 to 5 mm) commonly located on the face, nape of the neck, and upper back. Other specific lesions include skin plaques and annular lesions, which are associated with chronic disease and a poor prognosis when they occur on the head and neck. Scars and tattoos can become infiltrated with sarcoidosis. Subcutaneous Darier-Roussy sarcoidosis presents as nodules deep in the dermis and subcutaneous tissue and can remit spontaneously. Lupus pernio has a predilection for black and Puerto Rican women and is the most characteristic specific skin manifestation of sarcoidosis (Fig. 166.2). Lesions are indurated and violaceous, occurring primarily on the nose, cheeks, ears, lips, and fingers. They tend to be slowly progressive and can be disfiguring. Lupus pernio has a

significant association with chronic upper respiratory tract involvement, pulmonary fibrosis, and bony lesions of the phalanges. Conversely, nonspecific skin lesions are inflammatory but do not demonstrate granulomas on histologic examination. Erythema nodosum is the most common nonspecific skin manifestation, occurring in 10% of patients with sarcoidosis. It is seen more commonly in young white females and usually is associated with an acute presentation and benign course. A variety of atypical lesions also may be seen. In general, chronic sarcoid skin lesions do not ulcerate, itch, or cause pain. Topical corticosteroids and monthly intralesional injections of triamcinolone are often effective therapy for small sarcoid papules or plaques. Larger, disfiguring skin lesions require systemic corticosteroid therapy, antimalarials (chloroquine and hydroxychloroquine; overall response rate of 35%), methotrexate, and/or infliximab. Thalidomide, pentoxifylline, apremilast, minocycline, psoralens and ultraviolet A phototherapy, and retinoids have been anecdotally successful in a few patients with refractory sarcoid skin lesions.⁹

Cardiac involvement

Symptomatic cardiac involvement occurs in 5% of patients with sarcoidosis, but cardiac lesions are considerably more common at autopsy (20% [United States] to 67% [Japan]).¹⁰ It is more common in patients with severe disease and frequently coexists with neurosarcoidosis. Sarcoidosis may affect any part of the heart except the valves. Manifestations include sudden death, conduction disturbances, papillary muscle dysfunction, infiltrative cardiomyopathy with congestive heart failure, cor pulmonale due to severe restrictive lung disease, and pericarditis. All sarcoidosis patients should have a baseline electrocardiogram, which should be repeated annually or with development of symptoms. Electrocardiographic abnormalities occur in over 50% of patients with cardiac involvement, manifesting as various dysrhythmias, conduction disturbances, and nonspecific ST- and T-wave changes. Twenty-four-hour Holter monitoring and exercise electrocardiography should be performed in all patients with arrhythmias, conduction disturbances, or palpitations. In those with conduction blocks or arrhythmias, electrophysiologic studies are needed in performing the risk assessment for sudden cardiac death. Two-dimensional and M-mode echocardiography in patients with cardiac sarcoidosis can show granulomatous inflammation in the myocardium (hyperechogenicity of the ventricular septum), left ventricular hypertrophy and dyskinesis, restrictive cardiomyopathy, valvular incompetence due to papillary muscle dysfunction, and asymptomatic pericardial effusions (20% of patients). Cardiac magnetic resonance imaging (MRI) with gadolinium enhancement and fasting cardiac positron emission tomography with fluorine-18-labeled fluorodeoxyglucose (FDG-PET) are important new modalities used in the assessment of cardiac sarcoidosis.¹¹ Endomyocardial biopsy findings are often negative (80%), because cardiac sarcoid lesions tend to be heterogeneous and have a predilection for the left ventricular free wall.

Symptomatic cardiac sarcoidosis must be treated early and aggressively. Heart failure and/or sudden cardiac death due to conduction block or ventricular arrhythmias account for 75% of deaths due to cardiac sarcoidosis. Therefore treatment with high-dose prednisone (60 mg/day or more) should be initiated in patients with ventricular arrhythmias or cardiomyopathy.^{3,10} Antiarrhythmic agents and medications for heart failure should be used as adjunctive therapies. Cardiac MRI and FDG-PET may be useful in monitoring the response to therapy. In patients with severe or refractory disease, high-dose pulse methylprednisolone, azathioprine, methotrexate, and cyclophosphamide have been used with some success. Implantable pacemakers are indicated in those at risk of sudden cardiac death, and heart transplantation has been used in patients in whom medical management has failed.

Nervous system involvement

Symptomatic involvement of the central or peripheral nervous systems occurs in approximately 5% to 10% of patients, although signs of such involvement are three times more common at autopsy.^{12,13} Up to 33% of patients who develop neurosarcoidosis have neurologic manifestations either preceding the disease or at the time sarcoidosis is first diagnosed. Neurosarcoidosis has a predilection for the base of the brain and can occur without pulmonary or systemic features of sarcoidosis. Unilateral cranial nerve palsy, most frequently of the seventh nerve, is the most common presentation (50% of cases). *Heerfordt syndrome* is the combination of fever, parotid enlargement, arthritis, uveitis, and facial nerve palsy. It occurs most commonly in males and usually has a poor prognosis. Other features of neurosarcoidosis include leptomeningeal involvement (20% to 40%), other cranial neuropathies, hypothalamic and pituitary lesions, localized mass lesion, myelopathy (fewer than 10%), seizures, psychiatric and cognitive

dysfunction, as well as other less common manifestations. Peripheral neuropathy documented by electromyography and nerve conduction studies occurs in 8.5% to 24% of patients with neurosarcoidosis. Chronic sensorimotor polyneuropathy is the most common presentation, although mononeuritis multiplex, pure sensory neuropathy, intercostal neuritis, small-fiber neuropathy, and acute Guillain-Barré syndrome may occur.

MRI with gadolinium enhancement is the best imaging technique to evaluate sarcoid involvement of brain parenchyma, meninges, or spinal cord, as well as response to therapy.¹⁴ FDG-PET may be useful to identify areas of activity to biopsy. Cerebrospinal fluid analysis can show elevated opening pressure (10%), elevated protein level of up to 250 mg/dL (70%), normal or low glucose concentration (20%), lymphocytic pleocytosis (50%), high immunoglobulin G index, and oligoclonal bands (50% or more). Although the finding is nonspecific, the cerebrospinal fluid can show an elevated level of angiotensin-converting enzyme (ACE). Brain biopsies are invasive and may not reveal definitive pathologic changes. The prognosis of neurosarcoidosis is guarded, and symptoms can be chronic or relapsing (32%). Mortality can be as high as 10% to 15%.

Neurosarcoidosis is treated with oral prednisone (60 to 80 mg/day).^{12,13} Antiseizure medications are used as adjunctive therapy in patients with seizures. Patients with severe and refractory disease have been treated with immunosuppressive therapy similar to that used in cardiac sarcoidosis. Uncontrolled reports have suggested that antimalarial agents, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide (oral and monthly pulse), cyclosporine, infliximab, and cranial irradiation may be effective.¹³ Surgical intervention is necessary for hydrocephalus and mass lesions that are expanding or causing increased intracranial pressure. Because of the possibility of devastating sequelae and the reactivation of neurosarcoidosis, most patients are maintained on low-dose prednisone and a second immunomodulatory medication for life.

Musculoskeletal involvement

Joints

Musculoskeletal manifestations, including arthritis and peri arthritis, occur in 4% to 38% of patients. Arthralgias are considerably more common (70%). Arthritic involvement is generally divided into acute and chronic types. The most common form of joint involvement is an acute polyarthropathy/peri arthritis. This type of arthritis may be migratory, resembling rheumatic fever; intermittent, resembling palindromic rheumatism; or additive, resembling rheumatoid arthritis. It can precede other manifestations of sarcoidosis by several months. More commonly, however, it is nonmigratory and accompanied by other features of acute sarcoidosis. Among patients with acute sarcoidosis who have bilateral hilar adenopathy and erythema nodosum (Löfgren syndrome), 70% have this form of polyarthropathy/peri arthritis, often associated with fever (66%) and uveitis (Fig. 166.3).^{15,16} This presentation most commonly occurs in young white and Puerto Rican women and is rare in blacks. Large joints, especially the ankles and knees, are most frequently affected, although other peripheral large and small joints may also be involved. Palpation of periarticular tissues elicits severe tenderness consistent with a peri arthritis. Joint radiography and ultrasonography show soft tissue swelling without bony changes. Arthrocentesis reveals no or only minimal synovial fluid, which is mildly inflammatory with a lymphocyte predominance. Synovial biopsy specimens show mild, nonspecific synovitis without granuloma formation.

Patients with acute polyarthropathy at presentation have or will develop erythema nodosum in 50% to 75% of cases. Bilateral hilar adenopathy is present in over 90% of these individuals at disease onset, but in some patients it does not develop for several weeks, which makes the diagnosis of sarcoidosis difficult. The acute form of joint involvement is usually associated with a benign course. Joint pain may resolve within weeks or persist for several months (average, 3 months); however, 10% to 15% of patients have several recurrences or persistently active joint disease. Patients with a normal serum ACE level at diagnosis (70% to 85% of patients) are most likely to experience complete resolution of their disease without recurrences. Acute arthritis/peri arthritis (Löfgren syndrome) usually requires no specific therapy other than analgesics or nonsteroidal antiinflammatory drugs (NSAIDs) such as indomethacin. Low-dose prednisone may be needed in patients with severe symptoms. Colchicine appears to shorten episodes in some patients.

Chronic sarcoid arthritis without involvement of adjacent bone is most likely to occur in black patients (Fig. 166.4).^{16,17} This type of joint involvement is uncommon (1% to 4%) and usually accompanies the slower-onset, more chronic and systemic form of sarcoidosis with cutaneous lesions, parenchymal pulmonary disease, and elevated ACE levels. The arthritis may be mild and transient or recurrent and protracted. Monoarthritis is relatively



Fig. 166.3 Löfgren syndrome. At presentation the patient had knee arthritis, erythema nodosum, and bilateral hilar adenopathy evident on a chest radiograph.



Fig. 166.4 Chronic polyarthritis. At presentation the patient had long-standing sarcoidosis and involvement of the interphalangeal joints and nails.

unusual so infection and crystalline arthropathies should always be considered. Oligoarthritis is typically nondestructive, involving the shoulders, wrists, knees, ankles, and/or small joints of the hands and feet. A chronic polyarthritis resembling rheumatoid arthritis and sacroiliitis mimicking spondyloarthritis or mycobacterial infection are rare presentations. Radiographs typically show soft tissue swelling, but bony destruction is uncommon. Arthrocentesis reveals a mildly inflammatory fluid (5000 cells/mm^3) with a mononuclear cell predominance. In contrast to acute sarcoid arthritis, in chronic sarcoid arthropathy synovial biopsy specimens characteristically show granulomatous inflammation. Tenosynovitis of the wrist, ankle,

patella, or Achilles tendons can also occur (5% to 13% of cases). For chronic synovitis, low-dose corticosteroids may be helpful if NSAIDs or analgesics fail. Chloroquine, hydroxychloroquine (400 mg/day), azathioprine, leflunomide, methotrexate (7.5 to 20 mg/wk), infliximab, and rituximab have been used successfully in patients with severe musculoskeletal manifestations refractory to corticosteroids.^{3,15-18}

Bone

The frequency of bone involvement ranges from 3% to 13%.¹⁶⁻¹⁸ Bone changes may be present at disease onset but are more frequently seen in patients with chronic and established disease. Women are affected more than men (2:1), and blacks are affected more than other racial groups. Bone lesions occur frequently in patients with lupus pernio and/or other granulomatous skin lesions and predict a poor prognosis with excessive mortality. There is a predilection for the phalanges of the hands and feet. Other bones can be involved, particularly the nasal bones in patients with lupus pernio and the calcaneus, which causes heel pain mimicking spondyloarthritis. The skull, vertebrae, ribs, pelvis, sternum, maxilla, and distal ends of long bones are rarely affected. Sclerotic lesions of the axial skeleton occur mainly in middle-aged black patients and may mimic metastatic disease.

Bone lesions of the phalanges can be lytic, permeative, and/or destructive and tend to be bilateral in distribution. Lytic lesions appear as rounded, “punched-out” bone defects on radiographs and are most frequently located at the ends of the proximal and middle phalanges (Fig. 166.5). Permeative lesions reflect granulomatous involvement of cortex and trabeculae of the phalangeal shafts, resulting in a reticular, lacelike appearance on radiographs. This may result in the phalangeal shafts becoming tubular. In advanced cases sclerosis or fractures may develop or joints may be affected owing to subchondral bony involvement and collapse. Notably, sarcoid bone lesions are not associated radiographically with periostitis and rarely with sequestra, which helps to separate sarcoidosis from chronic osteomyelitis. Technetium-99m diphosphonate bone scanning, MRI, and FDG-PET may detect unsuspected osseous involvement because over 50% of bony lesions are asymptomatic.

It is not known why sarcoidosis has a predilection for the phalanges. Pathologically, granulomatous infiltration into the marrow results in rarefaction of the trabeculae. In the cortical bone there is irregular resorption, with enlargement of haversian canals containing granulomas. Occasionally, granulomatous inflammation can extend into surrounding tissues, causing infiltration of tendon sheaths. MRI can distinguish soft tissue involvement from bony lesions. Granulomatous involvement of tendon sheaths can result in sarcoid dactylitis, with swelling over the affected digits associated with pain and stiffness. The overlying skin can be erythematous, and when the terminal phalanges are involved the nails may become thickened and dystrophic. Clubbing involving one or more digits has been described. Osteosarcoidosis responds poorly to therapy.¹⁶⁻¹⁸ Corticosteroids decrease swelling but do not completely normalize bony destruction. Hydroxychloroquine, chloroquine, methotrexate, and anti-TNF agents have been reported anecdotally to be helpful adjunctive therapies.¹⁹

Muscle

Asymptomatic muscle involvement is common (20% to 80% of cases), whereas symptomatic involvement occurs in fewer than 3% of patients.^{16,18,20} A random muscle biopsy in a sarcoidosis patient without myopathic symptoms will show granulomas in up to 80% of cases and can be used for tissue diagnosis. There are three forms of symptomatic muscle disease. The most common form is a chronic myopathy. This evolves slowly over several years, resulting in symmetric proximal muscle weakness and wasting, similar to muscular dystrophy. Neurogenic atrophy due to granulomatous infiltration of nerves can occur. In patients with muscle involvement, electromyography shows myopathic changes, but muscle enzyme levels are frequently normal or only minimally elevated. Concurrent cardiac muscle involvement is often seen in patients with this type of myopathy.

Acute granulomatous myositis and muscle nodules are the other two types of symptomatic muscle involvement but are unusual manifestations. Acute sarcoid myositis is rare, occurring mostly in young black females. Patients have signs and symptoms similar to those of polymyositis with myalgias, proximal muscle weakness, muscle tenderness, high levels of muscle enzymes, and muscle necrosis/granulomatous inflammation on biopsy. Many patients have fever and an elevated erythrocyte sedimentation rate at the time of presentation. Palpable granulomatous nodules and mass or tumor-like lesions may cause pain, stiffness, and cramping of the involved muscle. Muscle MRI shows a characteristic “dark star” sign on axial images.

The response of acute granulomatous myositis to treatment with corticosteroids is good, and the course is usually benign. However, in chronic

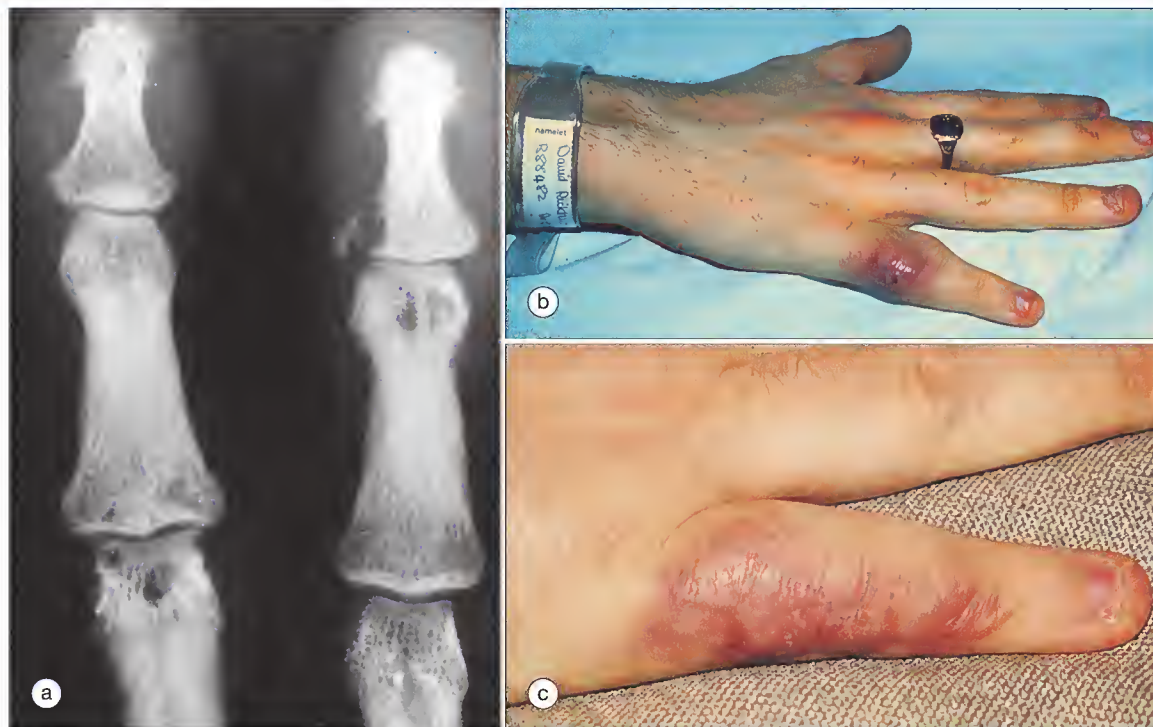


Fig. 166.5 Bone cysts and sarcoid dactylitis. (a) Radiograph of small bones of the hand showing bone cysts in an asymptomatic patient with bilateral hilar adenopathy. (b) Dactylitis with underlying bone cyst. (c) Resolution of dactylitis after treatment with oral prednisolone.

myopathy and nodular disease the response to therapy is unpredictable, with variable remissions and exacerbations requiring continued immunosuppression and adjustments of the corticosteroid dose.

Other organ system involvement

Constitutional symptoms of fever, fatigue, weight loss, and/or malaise occur in over a third of patients. Sarcoid granulomas have been reported to involve virtually any organ.³ Peripheral lymphadenopathy is common and usually nontender. Sarcoidosis of the upper respiratory tract can involve the oral, pharyngeal, and nasal mucosa, leading to obstruction, anosmia, and sometimes disfigurement.²¹ Parotid and minor salivary gland enlargement occurs in 6% and can cause sicca symptoms, mimicking Sjögren syndrome.²² The thyroid can be infiltrated, and the presence of antithyroid antibodies has been reported. The liver and spleen show granulomas on biopsy in 50% to 80% of patients.²³ The alkaline phosphatase level is frequently elevated (33%), but significant liver dysfunction is unusual. Cholestasis can result from granulomatous cholangitis or hepatic hilar adenopathy. Hepatosplenomegaly can occur and is associated with progressive fibrotic disease in other organs. Portal hypertension has been reported as a result of granulomatous phlebitis of hepatic or portal veins.

Sarcoidosis can cause granulomatous ulcers or masses in the gastrointestinal tract from the esophagus to the rectum. Pancreatic and peritoneal sarcoidosis are rare. Renal involvement is also rare. Granulomatous interstitial nephritis, glomerulonephritis, and amyloidosis may also occur. All areas of the male and female genitourinary tract have been reported to be involved in case series. Sarcoidosis has been rarely associated with vasculitis, and all sizes of blood vessels can be involved.²⁴ Black and Asian children are more likely to have large-vessel involvement that can resemble Takayasu arteritis.

Overproduction of 1,25-dihydroxyvitamin D can lead to increased intestinal absorption of calcium, causing hypercalcemia (10% to 15%), hypercalciuria (40% to 60%), nephrocalcinosis, nephrolithiasis (10%), and renal insufficiency.^{3,25} The risk of nephrolithiasis is 20% higher than in the general population. Hypercalcemia (more than 11 mg of calcium per deciliter), elevated serum creatinine concentration, and nephrolithiasis are indications for corticosteroid therapy at dosages of 20 to 40 mg/day of prednisone. Both hypercalcemia and hypercalciuria usually respond rapidly within 7 to 10 days. Antimalarials and ketoconazole (600 to 800 mg/day) act more slowly but produce a more sustained lowering of calcium level after cessation of therapy. Consumption of a low-calcium diet, avoidance of vitamin D supplements, and limited exposure to sunlight are helpful adjunctive measures. Patients should keep well hydrated to help prevent nephrolithiasis.

CHILDHOOD SARCROIDOSIS

Children of both sexes develop sarcoidosis less commonly than adults. The clinical manifestations in older children are similar to those in adults. However, in children younger than 5 years the characteristic presentation includes mild constitutional symptoms; painless, boggy, and effusive large-joint polyarthritis and tenosynovitis; skin lesions; uveitis; and lymphadenopathy and splenomegaly without typical lung disease.²⁶ This presentation must be differentiated from the rare autosomal dominant familial granulomatous disorder Blau syndrome, which is caused by a genetic mutation of the NOD2/CARD15 protein. Children with sarcoidosis usually have a spontaneous resolution of disease, but some experience residual complications. Corticosteroids with or without methotrexate are the treatment of choice for children with severely symptomatic or progressive disease.

SARCROIDOSIS ASSOCIATIONS

A variety of autoimmune disorders that may occur in association with sarcoidosis have been described in case reports.²⁷ These include rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, Sjögren syndrome, spondyloarthritis, inflammatory bowel disease, primary biliary cirrhosis and other autoimmune liver diseases, autoimmune cytopenias, autoimmune thyroiditis alone or as part of polyglandular autoimmune syndrome type III, polymyositis, inclusion body myositis, insulin-dependent diabetes mellitus, dermatitis herpetiformis, vitiligo, myasthenia gravis, and pernicious anemia. Sarcoidosis has also been associated with common variable immunodeficiency and 5q myelodysplasia, and appears as part of the immune reconstitution syndrome in patients with human immunodeficiency virus (HIV) receiving highly active antiretroviral therapy. It has been reported to occur before or simultaneously with various malignancies or after chemotherapy. Malignant lymphoma, lung cancer, testicular cancer, and lymphoproliferative disorders have been reported most often. Medication-induced sarcoidosis has been described after treatment with interferon- α (IFN- α) for hepatitis C, interleukin-2 (IL-2) for renal cell carcinoma, anti-TNF therapy for rheumatoid arthritis, and IFN- γ . Notably, each of these therapies promotes a T helper type 1 (Th1) response.

INVESTIGATIONS

The diagnosis of sarcoidosis is made by a combination of clinical, radiologic, and laboratory findings and confirmed by characteristic histologic findings.⁵

Patients with a classic presentation such as Löfgren syndrome may not need to undergo tissue biopsy. However, in all doubtful cases and in cases in which immunosuppressive treatment is likely to be needed, histologic confirmation of disease in one organ is essential. The requirement that more than one organ be involved to confirm the diagnosis of sarcoidosis does not require a second organ to be sampled. Clinical criteria for organ involvement without a biopsy have been published.²⁸ Once the diagnosis is established, the American Thoracic Society recommends the comprehensive baseline evaluation presented in [Box 166.1](#).⁵

Laboratory tests

Laboratory evaluation of patients with sarcoidosis shows many abnormalities.^{2,3} Most patients have anemia of chronic disease and lymphopenia. Some (up to 25%) may have eosinophilia. Leukocyte and platelet counts are normal (95%) unless there is significant bone marrow involvement (5%), hypersplenism, or another associated autoimmune disease. Chemistry panels are performed to rule out diabetes insipidus due to pituitary involvement or renal insufficiency due to nephrocalcinosis. Hypercalciuria occurs three times more commonly than hypercalcemia and places the patient at risk of nephrolithiasis and renal insufficiency.²⁹ Liver-associated enzyme levels are abnormal in up to one third of patients, with elevations in alkaline phosphatase and γ -glutamyl transferase occurring more often than elevations in aminotransferase levels.

Serologic abnormalities, including elevated erythrocyte sedimentation rate, increased C-reactive protein level, and hypergammaglobulinemia (30% to 80%), are common during active sarcoidosis. Low-titer rheumatoid factor is seen in up to 38% of patients, depending on the method used, and is more likely in those with chronic lung disease. A positive antinuclear antibody test result with a speckled pattern of immunofluorescence in low titer is seen in up to 34% of patients. Tests for antibodies against specific nuclear and cytoplasmic (ANCA) antigens typically yield negative results. Antiphospholipid antibodies have been reported, particularly in patients with extra-thoracic organ involvement. Tuberculin and anergy skin testing show that many patients with active disease are anergic.

ACE levels are elevated in 40% to 90% of sarcoidosis patients. Elevations correlate with active pulmonary disease and normalize with successful therapy. This enzyme is produced by epithelioid cells and alveolar macrophages at the periphery of granulomas in response to an ACE-inducing factor released by T lymphocytes. ACE may contribute to the formation of granulomas by producing angiotensin II locally, which is chemotactic for macrophages and enhances phagocytosis. Elevated ACE levels are not specific for sarcoidosis and may be caused by other diseases, such as hyperthyroidism, Gaucher disease, diabetes mellitus, leprosy, α_1 -antitrypsin deficiency, Kaposi sarcoma in HIV-infected patients, silicosis, hypersensitivity pneumonitis, cirrhosis, histoplasmosis, and asbestosis. Additionally, ACE levels are influenced by ACE gene polymorphisms (DD allele).³⁰ Therefore an elevated ACE level may be supportive, but not diagnostic, of sarcoidosis.

BOX 166.1 RECOMMENDED INITIAL EVALUATION OF PATIENTS WITH SARCOIDOSIS

1. History (occupational and environmental exposure, symptoms)
2. Physical examination
3. Posteroanterior chest radiography
4. Pulmonary function tests: spirometry and DL_{CO}
5. Peripheral blood counts: White blood cells, red blood cells, platelets
6. Serum chemistries: calcium, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), creatinine, BUN
7. Urine analysis
8. ECG
9. Routine ophthalmologic examination
10. Tuberculin skin test

BUN = blood urea nitrogen; DL_{CO} = diffusing capacity of the lung for CO; ECG = electrocardiogram.

From Statement on Sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999;160:736-755.

Imaging

The chest radiographic staging system has been described earlier (see section on [respiratory tract involvement](#)). The HRCT scan is more sensitive and correlates with histologic and pulmonary function test abnormalities more closely than the plain chest radiograph.³¹ Plain bone radiographs and technetium-99m diphosphonate scanning can detect bone lesions. MRI with gadolinium enhancement can be used to detect brain involvement, myocardial disease, muscle disease, and bone involvement.³¹ FDG-PET is a sensitive test for detecting sarcoid involvement of multiple tissues and showing organs that are candidates for diagnostic biopsy.³² Gallium-67 citrate scans are not specific and are no longer routinely used for the diagnosis of sarcoidosis.

Biopsy

Tissue biopsy is the gold standard for confirming a clinical/radiographic diagnosis of sarcoidosis. Tissue biopsy should be performed in any patient who has an atypical presentation or for whom therapy is being considered, to exclude infection or malignant disease. Transbronchial, lymph node, and skin biopsies are the most common, but a specimen can be obtained from any clinically involved organ.³³ The diagnostic yield is as follows:

- Transbronchial lung biopsy with normal findings on chest radiograph, 30% to 50%
- Transbronchial lung biopsy with abnormal findings on chest radiograph, more than 90%
- Endobronchial biopsy, 40% to 60%
- Lymph node biopsy, more than 90%
- Endobronchial ultrasound-guided transbronchial fine-needle aspiration of intrathoracic lymph nodes, 83%
- Minor salivary gland biopsy, 36%
- Parotid biopsy, 93%
- Muscle biopsy, 50% to 80%
- Liver biopsy, 50% to 80%
- Synovial biopsy in chronic arthropathy, 80%
- Biopsy of conjunctival nodules, 67%; lacrimal gland, 10% to 55%
- Skin biopsy, more than 90%
- Endomyocardial biopsy, 20%

The characteristic histologic finding is that of well-circumscribed non-caseating granulomas of the epithelioid type ([Fig. 166.6](#)). However, the presence of noncaseating granulomas is not diagnostic of sarcoidosis until other granulomatous diseases are excluded (see section on [differential diagnosis](#)). Notably, a few sarcoidosis patients may have granulomas with some minor necrosis on biopsy. Use of the Kveim-Siltzbach skin test is no longer recommended.

Additional tests

Three tests that should be done as a baseline assessment in all patients are (1) an electrocardiogram, (2) an ophthalmologic examination with a slit lamp to rule out asymptomatic abnormalities, and (3) a 24-hour urine collection for calcium to rule out hypercalciuria. Fluorescein angiography is helpful to document posterior uveitis. Pulmonary function tests, bronchoalveolar lavage fluid cell analysis,³⁴ Holter monitoring, and echocardiography are described in the sections discussing respiratory tract and cardiac involvement, respectively.

DIFFERENTIAL DIAGNOSIS

Several diseases can result in clinical presentations and granulomas on biopsy specimens that resemble those of sarcoidosis.^{2,3} Acute histoplasmosis can simulate Löfgren syndrome and must be excluded by serologic studies and cultures. Acute arthritis with erythema nodosum, but without hilar adenopathy, can occur in inflammatory bowel disease, coccidioidomycosis, histoplasmosis, psittacosis, and reactions to various medications. The pattern of arthritis in these patients is also similar to that seen in sarcoidosis.

In patients with more insidious presentations other diseases need to be considered, depending on the organ involved. In patients with pulmonary disease chronic berylliosis should be excluded by lack of a clinical history of exposure and a beryllium lymphocyte proliferation test. Hypersensitivity pneumonitis is ruled out by lack of a history of occupational and environmental exposure and results of serologic tests for precipitins. Reactions to drugs (methotrexate, IFN- α , IFN- γ , anti-TNF agents, IL-2) and other inorganic agents, such as metals (titanium, aluminum, zirconium), silica, and talc, are excluded by good history taking. Fungal serologic studies or stains

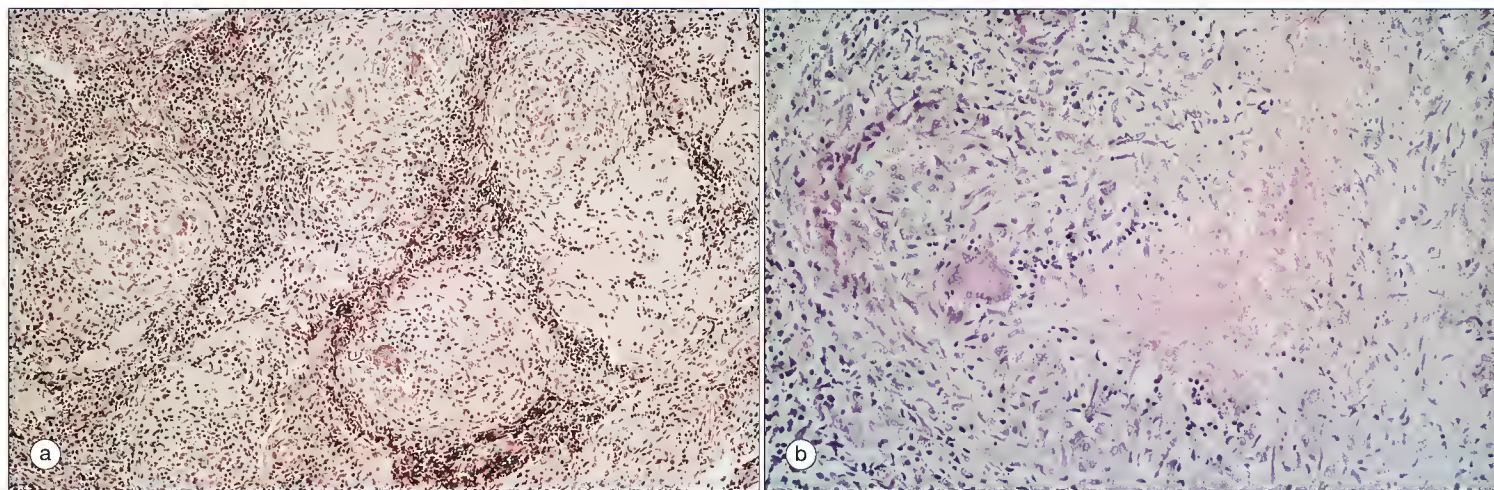


Fig. 166.6 Sarcoid granulomas. (a) Histologic section of lymph node showing noncaseating epithelioid and giant cell granulomas. (b) Histologic section from a patient with acute sarcoidosis showing noncaseating granulomas with central eosinophilic necrosis of collagen. There was subsequent natural resolution without treatment in this case.

or cultures for organisms rule out fungal and mycobacterial disease. Granulomatosis with polyangiitis (Wegener granulomatosis) is excluded by the absence of a positive result on the ANCA test and the absence of vasculitis on biopsy. Patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) have a history of asthma and prominent eosinophilia. Tissue biopsy results exclude lymphoma and eosinophilic granuloma. In patients with cutaneous granulomatous lesions treponemal infections, leprosy, tularemia, and leishmaniasis should be excluded by serologic studies and/or cultures. Granuloma annulare and granulomatous rosacea are ruled out clinically by lack of systemic involvement. Lupus vulgaris due to mycobacterial infection may mimic cutaneous plaques of sarcoidosis. Primary biliary cirrhosis can cause liver granulomas but is associated with antimitochondrial antibodies. Fungal or mycobacterial infections and brucellosis should be considered in patients with monoarticular, axial, or peripheral arthritis. Fungal and mycobacterial infections, leprosy, brucellosis, syphilis, granulomatosis with polyangiitis, eosinophilic granuloma, multiple myeloma, and lymphoma can cause bony lesions similar to those caused by sarcoidosis. Toxoplasmosis can mimic acute and chronic sarcoid myopathy, and various neoplasms and infections need to be excluded in patients with a muscle mass. Finally, granulomas in a single organ (e.g., idiopathic granulomatous hepatitis or panuveitis) without evidence of other organ involvement should not be diagnosed as sarcoidosis.

ETIOLOGY

The cause of sarcoidosis is unknown. Multiple environmental agents and genetic associations have been reported.

Environmental risk factors

Because the lung is most commonly involved, exposure to an airborne antigen is postulated. The ACCESS trial reported an increased risk of sarcoidosis in people with exposure to (1) water sources that serve as reservoirs for aerosolized microbial antigens (agriculture and water-damaged areas rich in molds); (2) metal industry (heavy metals and mycobacteria-contaminated metalworking fluids); (3) inorganic particulate matter (silicates); (4) insecticides.³⁵ Notably, chronic beryllium disease causes lesions in the lung (but not in other organs) that are histologically identical to those in sarcoidosis. Interestingly, multiple studies have shown that cigarette smoking decreases the probability of developing sarcoidosis. It is postulated that the acrolein (breakdown product of cyclophosphamide) in cigarette smoke is cytotoxic to lymphocytes trying to enter the lungs, which could account for the decreased prevalence of sarcoidosis in cigarette smokers.

Infectious agents have been associated with sarcoidosis.³⁶ Mycobacterial and propionibacterial nucleic acid have been recovered from sarcoid granulomas. Recently *Mycobacterium tuberculosis* DNA coding for a catalase-peroxidase protein (mKatG) has been found in sarcoid biopsy specimens (38%). Additionally, peripheral blood and lung T-cell responses as well as circulating immunoglobulin G against mKatG are increased in half of sarcoid patients. Other infectious agents have been proposed. However, the inability of any of these agents to cause sarcoidosis in animal models, the diversity of tissues involved in sarcoidosis that are not typically affected by some of

these organisms, the lack of response to antibiotics but improvement with immunosuppressive agents, and the failure of the prevalence of sarcoidosis to decrease in countries where bacille Calmette-Guérin vaccination is used are all evidence against a single infectious agent causing sarcoidosis.

Genetic risk factors

Genetic factors also play a role in the racial and ethnic variations in prevalence, clinical presentations, and severity of sarcoidosis.³⁷ Reports of several hundred families with two or more affected members are considered the strongest evidence for a genetic component to this disease. The ACCESS study showed that first-degree relatives of sarcoidosis patients had over a five times increased relative risk of developing sarcoidosis.³⁸ In addition, the concordance rate is reported to be two to four times higher in monozygotic than in dizygotic twins. Overall, the absolute risk that a sibling or parent of a sarcoidosis patient will develop sarcoidosis is approximately 1%. Despite this increased risk of sarcoidosis within families, affected sibling pairs show minimal concordance in clinical manifestations and outcomes.

The intraracial heterogeneity of clinical manifestations and prognoses makes it unlikely that a single gene is responsible for sarcoidosis.³⁷ HLA genes confer the most important genetic risk of susceptibility. HLA-DRB1*0301, HLA-DRB1*1101, HLA-DRB1*1201, and HLA-DRB1*1501 alleles have the strongest association with sarcoidosis risk. HLA-DRB1*0301/DQB1*0201 haplotype and CC chemokine receptor 2 (CCR2) haplotype 2 are highly associated with Löfgren syndrome and a benign course, whereas HLA-DRB1*1501/DQB1*0602 haplotype is associated with a severe, chronically progressive course. Non-HLA candidate genes associated with disease in specific ethnic groups of sarcoidosis patients include certain alleles of TNF- α , CC chemokine receptors (CCR2, CCR5), butyrophilin-like 2 (BTNL2), and annexin 11. Genomewide association studies are likely to yield other candidate genes in other ethnic groups.

In summary, because of the multiple reported associations, sarcoidosis most likely represents the end result of an immune response to various ubiquitous environmental agents in a genetically predisposed host.

IMMUNOPATHOGENESIS

The noncaseating epithelioid granuloma is the histologic hallmark of sarcoidosis and is formed by a stepwise series of events.³⁹⁻⁴¹ Granuloma formation is a protective response to isolate poorly degraded antigens to prevent dissemination and/or further local tissue damage. Candidate antigens in sarcoidosis include environmental substances, microbial remnants, and misfolded serum amyloid A.

Step 1: Lymphocytic alveolitis

The initial event in sarcoidosis is thought to be the uptake and processing of a triggering antigen by antigen-presenting cells (type II alveolar epithelial cells, alveolar macrophages, and dendritic cells) bearing HLA class II molecules in the lower respiratory tract. The recognition of antigen by CD4+ T cells is considered to be a critical event in the development of disease. Alveolar macrophage secretion of chemoattractant cytokines (IL-8, IL-15,

IL-16) and chemokines (MIP-1/CCL3-4, RANTES/CCL5, IP-10/CXCL10) coupled with the cytokine-mediated (TNF- α , IFN- γ , IL-1, IL-15) upregulation of cell adhesion molecules (ICAM-1/CD54, ICAM-2/CD102, VCAM-1/CD106, α_1 integrin/CD49a) is central to the marked accumulation of inflammatory cells and recruitment of lymphocytes (CD4+ T cells) from the peripheral blood into the lung alveoli. Studies indicate that inflammatory alveolitis precedes granuloma formation and is associated primarily with the infiltration of CD4+ T lymphocytes and mononuclear phagocytes. In patients with established disease, there is a selective oligoclonal expansion of $\alpha\beta$ T cells in the lung, which exhibits a restricted T-cell receptor repertoire. This strongly suggests an antigen-specific immune response.

Step 2: Granuloma formation

The accumulation and activation of antigen-specific Th1 lymphocytes and the reciprocal suppression of the Th2 subset are the initial events in the development of granulomatous inflammation. Alveolar macrophage/dendritic cell-derived IL-12 with the help of IL-18 and IL-27 are critical to the differentiation of naive CD4+ T lymphocytes into Th1 cells. The polarized Th1 cells secrete the Th1 cytokines IL-2 and IFN- γ . IL-2 acts synergistically with IL-15 and TNF- α from macrophages to stimulate further T-lymphocyte proliferation and differentiation. Other T-lymphocyte cytokines stimulate macrophage recruitment, activation, and proliferation (granulocyte-macrophage colony-stimulating factor, MCP-1/CCL2, MIP-1/CCL3-4). The macrophage-derived cytokines, IL-12 and IL-18, coupled with IL-2, are potent stimulators of further IFN- γ production; this amplifies the immune response through its effects on multiple target cells including macrophages, which differentiate into secretory epithelioid cells at the center of the granuloma. Both IL-1 β and IFN- γ as well as several chemokines are important in the early recruitment stage of granuloma formation, whereas TNF- α may be particularly important in the later maintenance of granuloma formation and perpetuation of inflammation.

The sarcoid granuloma is well circumscribed, round or oval, noncaseating, and made up of compact, radially arranged epithelioid cells with pale nuclei (see Fig. 166.6). Some of the epithelioid cells fuse to form giant cells, typically of the Langhans type, in which the nuclei are arranged in an arc or circular pattern around a central granular zone. Stellate asteroids (entrapped collagen) and blue Schaumann inclusion bodies (altered lysosomes in giant cells) are occasionally observed. The center of the granuloma is composed of macrophage-derived epithelioid cells and CD4+ Th1 lymphocytes, whereas the outer zone contains many CD4+ and CD8+ T lymphocytes, fibroblasts, and interdigitating antigen-presenting cells entwined in bands of collagen.

Step 3: Granuloma resolution

The immunologic factors that determine the ultimate fate of sarcoid granulomas are poorly understood. Most granulomas resolve spontaneously or with therapy, whereas others are converted into a fibrotic scar. In the 25% of patients who develop progressive fibrosis there appears to be a shift from a Th1 to a Th2 cytokine (IL-10, IL-13) predominance at the local tissue level. Alveolar macrophages, mast cells, and neutrophils contribute to this fibrotic process by releasing superoxide radicals and proteases that cause local tissue injury. This is reflected clinically by the association of progressive lung fibrosis and a worse prognosis with neutrophilia in bronchoalveolar lavage fluid. Alveolar macrophages also secrete transforming growth factor- β (TGF- β) and CC motif ligand 18 (CCL18) among others. TGF- β induces local epithelial cells to transform into collagen matrix-producing fibroblasts. CCL18 attracts bone marrow-derived fibrocytes and regulatory T (Treg) cells from the peripheral blood. The fibrocytes differentiate and contribute to the fibroblast pool. Treg cells produce IL-10 in conjunction with other cells producing IL-13. These Th2 cytokines contribute to the transformation of alveolar macrophages into macrophages of the M2 phenotype, which secrete fibroproliferative cytokines (platelet-derived growth factor). This adds to the fibrogenic cytokines (fibroblast growth factor 2, insulin-like growth factor 1, fibronectin) produced by fibroblasts, causing more proliferation and collagen matrix production. The collagen matrix produced stimulates alveolar macrophages to make more CCL18, which results in a positive feedback loop.

NATURAL HISTORY AND PROGNOSIS

The natural history of untreated sarcoidosis is difficult to predict in an individual patient.⁴² The ACCESS study showed that the extent of organ involvement in most cases is defined at presentation, with fewer than 25% of patients developing new organ involvement within 2 years of follow-up.⁴³

Therefore, during the first 2 to 3 years after disease onset, certain tests (chest radiography, pulmonary function tests, calcium levels, any test that gives abnormal results initially) should be repeated every 3 to 6 months and others (eye examination, electrocardiography) every 12 months, or sooner if symptoms develop. Most patients (60%) undergo spontaneous remission within the first 3 years, with an additional 10% to 20% experiencing resolution with corticosteroid therapy. However, in 10% to 30% the course is chronic. Of those having a chronic course, half will have progressive pulmonary disease and half will display involvement of critical extrapulmonary organs, such as the eye, brain, and heart.

The probability of a spontaneous remission can be predicted by the patient's clinical and radiologic presentation. Up to 80% of patients who have hilar adenopathy alone (radiographic stage I disease) at presentation experience spontaneous resolution, and patients with Löfgren syndrome have the best overall prognosis for full remission within 2 years. Some 50% to 60% of patients with radiographic stage II disease experience remission, in contrast to fewer than 30% of those with stage III disease. The mortality rate of patients with pulmonary fibrosis (radiographic stage IV with vital capacity of less than 1.5 L) is 25% to 40%. Although the overall prognosis for sarcoidosis is good, at least 50% of patients have some degree of permanent organ dysfunction. In addition, there is a 5% mortality rate, with progressive pulmonary disease accounting for half and cardiac and neurologic disease causing the other half of all deaths from sarcoidosis. Of patients with cardiac or neurologic manifestations, up to 10% will die of organ failure. In Japan patients die of cardiac complications, whereas in the United States pulmonary disease causes most of the deaths.

In general, the more severe the involvement and the more organ systems involved at the time of diagnosis (three or more), the worse the prognosis. Extrapulmonary involvement (cardiac or neurologic involvement, lupus pernio, hypercalcemia, bone involvement) and pulmonary hypertension are poor prognostic signs, as are black race, disease onset after 40 years of age, and symptom duration of longer than 6 months.^{2,44}

MANAGEMENT

Because the cause of sarcoidosis is unknown, therapy is empiric.⁴⁴⁻⁴⁶ Whenever possible, patients with good prognostic signs should be observed for the first 3 to 6 months without immunosuppressive therapy because of the potential for spontaneous resolution. In patients with progressive disease, the recommended dosages of corticosteroids and adjunctive therapies vary, depending on the organ system involved (see individual organ system sections for specific therapies). There have been few controlled, randomized trials to establish the appropriate dose and duration of any therapy for sarcoidosis. Despite a lack of well-controlled clinical trials proving that corticosteroids improve long-term outcome, oral corticosteroids are used as first-line treatment for symptomatic and progressive stage II and III lung disease, malignant hypercalcemia, and severe ocular, neurologic, cardiac, skin, and musculoskeletal involvement.^{46,47} In patients who have an inadequate response to or unable to taper their corticosteroids, steroid-sparing agents alone or in combination are used.⁴⁸ Recently the monoclonal anti-TNF- α agents, particularly infliximab, have been found to be effective for various disease manifestations refractory to standard immunosuppressive therapy.⁴⁹⁻⁵¹ In case studies, rituximab has been used successfully for refractory disease, particularly when granulomatous mass lesions are present.^{52,53} Solid organ transplantation can be life-saving in patients for whom all medical therapies have failed.⁵⁴

Patients must be monitored for adverse effects and prophylactic measures used to prevent toxicities. Patients receiving high-dose corticosteroids should be given prophylaxis against *Pneumocystis jiroveci*. Osteopenia and osteoporosis due to dysregulated calcium metabolism and medications used in therapy can occur in up to two thirds of patients.⁵⁵ All sarcoidosis patients who are receiving corticosteroids or who are postmenopausal should have bone density testing, and bisphosphonate therapy should be started in those at risk of fractures. Vaccinations should be kept up to date. Depression is common (46% to 66%) and should be screened for and treated. Fatigue also is common (50% to 70%), can be disabling, and may respond to armodafinil or dexamethylphenidate.⁵⁶ Hypothyroidism, hypoxemia, depression, and sleep apnea are potential and correctable causes of fatigue.

MONITORING OF THERAPY

Many tests have been used to evaluate disease activity and response to therapy. However, no serologic test, including ACE level, has proved to be a reliable marker. The best assessment is through longitudinal observation

of symptoms and signs every 3 to 6 months. Testing, including chest radiography, HRCT, and measurement of pulmonary function and other parameters reflecting internal organ involvement, should be tailored to the patient. A response to therapy is defined as a decrease in symptoms, a reduction in radiographic abnormalities, and physiologic improvement (10% to 15% increase in forced vital capacity/total lung capacity, 20% increase in carbon dioxide diffusing capacity, or an improvement in gas exchange). MRI with gadolinium enhancement and FDG-PET may be useful in assessing activity in some organs that are difficult to access, such as heart, brain, and bone.

As therapy is tapered or discontinued, the physician must remain vigilant, given the tendency of sarcoidosis to relapse (50%) and/or affect new organs. Patients with previously poor prognostic signs and/or major organ involvement need lifelong follow-up.

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Relapsing polychondritis

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- Relapsing polychondritis is a rare autoimmune disease of unknown etiology with episodic but potentially progressive inflammatory manifestations.
- Clinical features include inflammation of the auricular, nasal, laryngotracheal, costal, and articular cartilage and ocular and inner ear inflammation.
- Relapsing polychondritis may be associated with other autoimmune diseases and myelodysplastic syndrome and varies in its manifestations, course, and response to therapy.
- Involvement of the laryngotracheobronchial tree can lead to life-threatening airway compromise, and an associated systemic vasculitis may contribute significantly to morbidity and premature mortality.

HISTORY

Relapsing polychondritis (RP) is a rare disease of unknown etiology. The first clinical description of it is attributed to Jaksch-Wartenhorst, who in 1923 reported the case of a 32-year-old brewer with fever, asymmetric polyarthritis, and pain and swelling of his external ears.¹ This patient went on to develop external auditory canal stenosis, diminished hearing, and a saddle-nose deformity. A biopsy of the nasal septum showed a hyperplastic mucous membrane and the absence of cartilage. Jaksch-Wartenhorst called it *polychondropathia* and considered it to be a degenerative disorder. In 1960 Pearson and colleagues coined its currently accepted name, *relapsing polychondritis*, in a description of four cases and review of 12 previous reports.² They correctly identified RP as an intense inflammatory condition of both cartilaginous and noncartilaginous structures and recognized the severe pulmonary complications that can accompany this disease.

EPIDEMIOLOGY

RP is a rare disease, as demonstrated by the estimated annual incidence rate of 3.5 per million in Rochester, Minnesota.³ The peak age at onset is between 40 and 50 years, but cases have been observed in children and in the elderly (older than 80 years). It occurs with equal frequency in both sexes and all racial groups. Over the years, cases have been described in which RP is a primary disorder and in which RP is a secondary manifestation that occurs after the onset of the associated condition. In adults, over 30% of cases are associated with an existing autoimmune or hematologic disease (Box 167.1). In pediatric RP there is less likely to be an associated autoimmune disease, but there is often a strong family history of autoimmunity.⁴ The life expectancy of RP patients is reduced, with an estimated 5-year survival of 74% in one large series. In the subgroup of patients with systemic vasculitis the estimated survival is similar to that of patients with polyarteritis: 45% at 5 years. Infection and respiratory involvement are frequent and contribute to reduced survival.⁵

CLINICAL FEATURES

Otorhinolaryngeal disease

The classic clinical manifestation of RP is an acute unilateral or bilateral auricular chondritis. The onset is characteristic: warmth, swelling, and a red or violaceous discoloration of the cartilaginous portion of the pinna, sparing the earlobe (Fig. 167.1a). The episode lasts days to weeks and resolves with or without treatment. Over time, and with repeated attacks, the pinna loses its firmness and becomes soft and flops over (see Fig. 167.1b) or assumes a knobby, cauliflower-like appearance. In a series of 112 patients at the Mayo Medical School, auricular chondritis was the presenting feature in 39% and ultimately developed in 85% of patients.³ Inflammation of the nasal cartilage causes saddle-nose deformity (Fig. 167.2) and can also result in septal perforation. Similarly, inflammation in the larynx can result in hoarseness, dysphonia, and stridor, and “bamboo nodules” have been described.⁶ These bamboo nodules are white-yellow bilateral transverse lesions at the midportion of the vocal cords and have been seen in association with other autoimmune diseases. Hearing abnormalities occur in up to 30% of patients and can be caused by swelling of the external auditory canal, which leads to conductive deafness or vasculitis of the internal auditory artery resulting in neurosensory hearing loss (Table 167.1).⁷ Involvement of the inner ear structures can also result in vertigo.

Respiratory disease

Respiratory symptoms in RP are common and can be lethal. At onset, only 25% of patients have such symptoms, although 50% ultimately develop them. A recent large, retrospective chart review performed at an RP referral center found the prevalence of airway involvement to be 21%.⁸ Tenderness of the thyroid cartilage and the anterior trachea, hoarseness, persistent cough, choking spells, wheezing, and dyspnea on exertion can occur. Inflammation of the tracheobronchial tree leads to varying degrees of localized (Fig. 167.3) or diffuse obstruction, and damage to the cartilaginous rings can cause a dynamic obstruction leading to respiratory difficulty. Strictures usually form in the subglottic region, causing increased susceptibility to secondary infections. The reported mortality from respiratory complications varies from 10% to 50%, but the lower figure is probably more realistic.^{5,7,9-12} The influence of newer immunomodulatory agents, including biologic therapies, on the progression of respiratory disease in RP is promising but still unclear.¹³

Musculoskeletal symptoms

The arthritis of RP is episodic, seronegative, asymmetric, and oligoarticular or polyarticular. It can occur before, during, or after the diagnosis is established. It is a presenting feature in 30% of cases and ultimately develops in 75%. The episodes may last weeks to months, but the arthritis is nondeforming and nonerosive and may not correlate with the extraarticular disease manifestations. The joints most commonly involved are the ankles, followed by the wrists, proximal interphalangeal and metacarpophalangeal joints, elbows, and metatarsophalangeal joints. Inflammation of the costochondral cartilages may lead to a pectus deformity. Because RP may accompany another connective tissue disease, the patient may have the musculoskeletal manifestations of the associated disease as well.^{2,5,7,9,14} Interestingly, unlike juvenile inflammatory arthritis, the arthritis in pediatric RP does not appear to affect growth.⁴

Cardiovascular disease

The cardiovascular system is involved in fewer than 10% of RP cases. The spectrum of vasculitis associated with RP is broad, with small-vessel disease

BOX 167.1 CONDITIONS ASSOCIATED WITH RELAPSING POLYCHONDritis

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Scleroderma
- Sjögren syndrome
- Overlap connective tissue disease
- Ankylosing spondylitis and sacroiliitis
- Psoriatic arthritis
- Reactive arthritis
- Antineutrophil cytoplasmic antibody-associated granulomatous vasculitis
- Polyarteritis nodosa
- Churg-Strauss vasculitis
- Behçet syndrome
- Myelodysplastic syndromes
- Lymphoma
- Inflammatory bowel disease
- Primary biliary cirrhosis

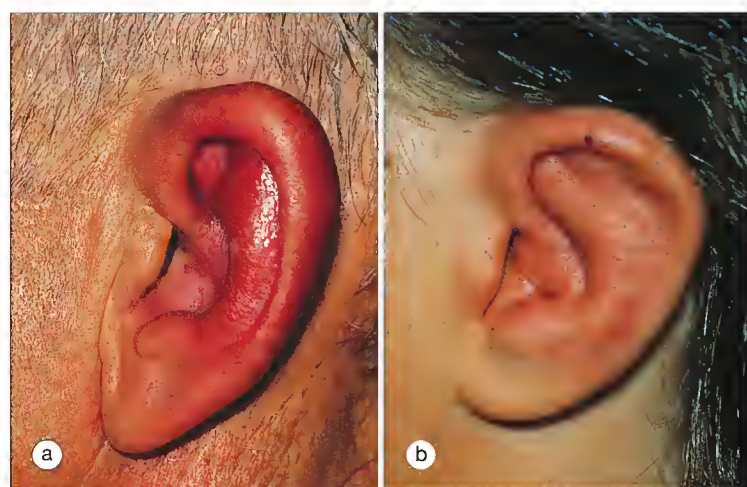


Fig. 167.1 Otorhinolaryngeal disease in relapsing polychondritis. (a) The pinna of the ear becomes inflamed: note the sparing of the noncartilaginous portion of the ear. (b) Recurrent attacks cause loss of cartilage, with the ear flopping over.

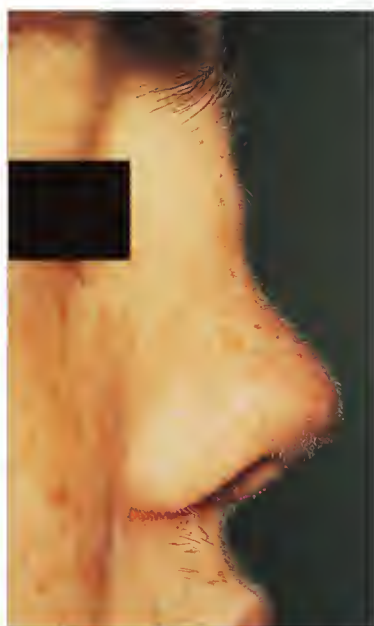


Fig. 167.2 Otorhinolaryngeal disease in relapsing polychondritis. The saddle-nose deformity is caused by damage to the nasal bridge.

TABLE 167.1**Clinical manifestations of relapsing polychondritis**

Finding	Frequency (%)	
	Initial	Total
Auricular chondritis	39	85
Saddle-nose deformity	18	29
Hearing loss	9	30
Arthritis	36	52
Costochondral cartilage inflammation	2	2
Nasal cartilage inflammation	24	54
Ocular inflammation	19	51
Scleritis/episcleritis	19	47
Laryngotracheal-bronchial disease	26	48
Laryngotracheal stricture	15	23
Systemic vasculitis	3	10
Valvular dysfunction	0	6
Cutaneous features	7	28

Adapted from Isaak BL, Liesegang TJ, Michet CJ Jr. Ocular and systemic findings in relapsing polychondritis. *Ophthalmology* 1986;93:681-9.

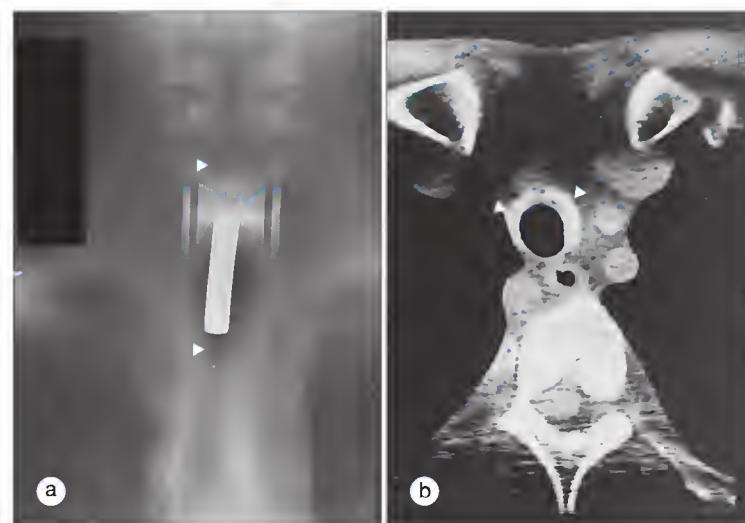


Fig. 167.3 Localized tracheobronchial obstruction due to relapsing polychondritis. (a) The radiograph shows both narrowing in the larynx above the tracheostomy tube and tracheal stenosis below (arrowheads). (b) Computed tomographic scan of the trachea shows the thickening of the tracheal wall due to inflammatory changes (arrowheads). Note how the posterior, noncartilaginous portion of the trachea is spared.

presenting as cutaneous leukocytoclastic vasculitis and large-vessel disease, similar to Takayasu arteritis, occurring. A systemic polyarteritis nodosa in medium-sized vessels has also been observed in 9% of patients. In some cases, the vasculitis may present before the diagnosis of RP can be made. Aneurysms of the thoracic and abdominal aorta can occur. Aortitis causes thinning of the media and leads to dilatation of the root of the aorta and leakage of the aortic valve. The aortic and mitral valves can be sites of inflammation as well, with incompetence of the valve developing because of aortic root dilation, valvulitis, or papillary muscle dysfunction. Recurrent aneurysms and valvular dysfunction can occur despite treatment.¹⁵ Arrhythmias, heart block, and supraventricular tachycardia, caused by myocarditis and involvement of the conduction system occur in rare cases. Frank myocarditis and pericarditis are infrequent.

Ocular symptoms

The eye is a frequent site of involvement. Initially, 19% of patients have eye symptoms, but eventually about 50% are affected. Episcleritis and scleritis can occur at onset or during the course of this disease. Keratitis, thinning

of the cornea, and corneal melt have been reported but are rare. Iridocyclitis, chorioretinitis, retinal hemorrhages, and retinal vasculitis have been observed.⁷ Periocular involvement also occurs and includes periorbital edema, tarsitis, chemosis, proptosis, and palsies of the extraocular muscles.

Renal disease

Although up to 26% of RP patients have abnormal results on urinalysis, the creatinine concentration is elevated in only 10%.¹⁶ In a few patients renal biopsy specimens have shown segmental proliferative glomerulonephritis with crescent formation. Immunoglobulin (IgG or IgM) and the C3 component of complement deposited in a granular pattern, or appearing as subendothelial and mesangial deposits, have been observed on electron microscopy. Renal involvement by an associated autoimmune disease—for example, systemic vasculitis, granulomatosis with polyangiitis (GPA), or systemic lupus erythematosus—has also been observed.

Dermatologic disease

The skin manifestations of RP are variable. They occur as an initial manifestation in 15% of patients, although up to 35% ultimately develop skin involvement. The presence of skin changes does not have any prognostic significance, although such changes appears to occur more commonly in patients who develop RP in association with myelodysplastic syndrome.^{7,17} The presence of palpable purpura, subcutaneous nodules, sterile pustules, urticaria, and angioedema has been observed. Livedo reticularis, migratory superficial thrombophlebitis, erythema nodosum, erythema multiforme, and panniculitis are rare but known. Of course, patients who develop RP in association with another connective tissue disease may manifest skin changes of the underlying illness.

Neurologic disease

Vasculitis involving the central and peripheral nervous system is seen in some patients, who develop cranial neuropathies, headaches, encephalopathy, encephalitis, aseptic meningitis, hemiplegia, and ataxia. Transverse myelitis, mononeuritis multiplex, and temporal artery nongranulomatous vasculitis have been observed.^{18,19}

Miscellaneous features

Fever has been observed in 22% of RP patients at presentation and in up to 44% during the course of the illness. The pattern is variable, and a few patients have had fever of unknown origin. Cases of the coexistence of RP with Behcet syndrome (mouth and genital ulcers with inflamed cartilage [MAGIC] syndrome) have been reported. This interesting presentation of two rare diseases occurring together suggests a shared pathogenic mechanism. Elastin was suggested as a common antigen.²⁰ However, whether this is indeed a bona fide syndrome or simply Behcet syndrome complicated by RP manifestations has been debated in the literature.²¹

DIAGNOSIS AND INVESTIGATIONS

Although the diagnosis of RP is relatively easy, many conditions can mimic the initial changes and an associated disease may confuse the clinical picture. The most commonly used criteria for diagnosis were developed by McAdam and associates²² and require the presence of three or more of the following clinical features to confirm the diagnosis:

- Bilateral auricular chondritis
- Nonerosive seronegative inflammatory polyarthritis
- Nasal chondritis
- Ocular inflammation (conjunctivitis, keratitis, scleritis and/or episcleritis, uveitis)
- Respiratory tract chondritis (laryngeal and/or tracheal cartilages)
- Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, and/or vertigo)
- Cartilage biopsy confirmation of a compatible histologic picture

Ear biopsy in auricular chondritis is performed to confirm the diagnosis of relapsing polychondritis (Fig. 167.4). In patients in whom the presentation is characteristic, such as simultaneous chondritis in both auricles or chondritis in multiple sites, a biopsy may not be necessary. If there is early disease, or if another disease ranks high in the differential diagnosis, it may be required.

All patients should be evaluated for laryngotracheal disease because of the potential for serious, life-threatening airway involvement (see Fig.

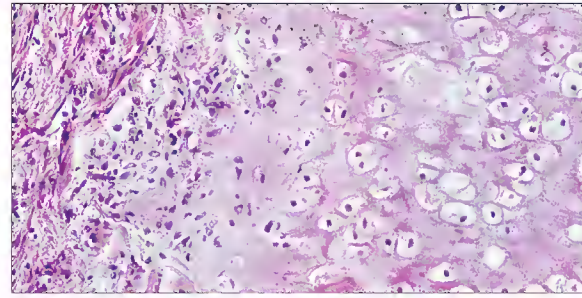


Fig. 167.4 Biopsy specimen from the ear shows perichondritis with the presence of mononuclear cells and occasional polymorphonuclear leukocytes at the fibrochondral junction (hematoxylin-eosin, $\times 200$). (Courtesy Dr. Lester E. Wold.)

167.3a). Pulmonary function tests, including inspiratory and expiratory flow-volume loops, as well as a radiologic assessment by computed tomography (CT) are both necessary, because either test alone may not reveal the full functional impact of airway disease.¹⁰⁻¹² Laryngotracheal biopsy should be considered with caution because it may lead to acute respiratory distress in patients with stenotic or collapsing airways.

The usual findings on CT of the trachea include wall thickening or luminal collapse caused by edema or granulation tissue (see Fig. 167.3b), fibrosis, and calcification of the tracheal wall. A thickened anterior and lateral tracheal wall with sparing of the posterior noncartilaginous membrane is considered pathognomonic for RP.²³ CT of the chest may also demonstrate flaccidity and dynamic collapse of the airway with expiration (tracheomalacia), as well as bronchial strictures, which lead to air trapping within the lung parenchyma itself. The radiologist should be specifically instructed to obtain CT images during expiration, because over half of RP patients referred for airway imaging have abnormalities only during this phase of the respiratory cycle.²³

In general, there is a good correlation between CT findings and direct visualization of the tracheobronchial tree by bronchoscopy. However, the latter, more invasive procedure should be considered in the evaluation of patients with RP and pulmonary symptoms, because nearly 25% of patients may have additional important findings identified by bronchoscopy. Moreover, in experienced hands, interventional procedures can be performed during bronchoscopy to alleviate airway obstruction.⁸

Renal status should be investigated to exclude the possibility of an accompanying glomerulonephritis.¹⁶ Electrocardiography should be performed to evaluate the cardiac system. In addition, echocardiography may be indicated to evaluate the valves, and CT/magnetic resonance angiography is useful to assess large-vessel involvement. Nonspecific indicators of inflammation are often observed, including an elevated erythrocyte sedimentation rate, anemia of chronic disease, leukocytosis, thrombocytosis, and hypergammaglobulinemia. If a macrocytic anemia is present, the possibility of early myelodysplastic syndrome should be considered.

If RP is observed in the setting of other autoimmune diseases, such as rheumatoid arthritis or other connective tissue diseases, then positive results may be seen on serologic tests such as those for rheumatoid factor and antinuclear antibodies. Complement levels are usually normal in RP but may be low if RP develops in a patient with lupus. The arthritis of RP is usually nonerosive and characterized by juxtaarticular osteopenia and uniform joint space narrowing. However, if RP occurs in a patient with rheumatoid arthritis, the joint damage pattern may mimic that of the latter condition. The presence of antineutrophil cytoplasmic antibodies (ANCA) has been reported in RP. However, because GPA and microscopic polyangiitis are occasionally accompanied by RP, it is possible that this reflects this disease association. Currently, there are no clinically available laboratory markers for ongoing cartilage damage.

DIFFERENTIAL DIAGNOSIS

Although the clinical manifestations of this disease are characteristic, there are circumstances in which the diagnosis may be difficult. The pinna of the ear is exposed and readily injured by trauma, chemicals, or frostbite. The trachea is similarly vulnerable to injury during prolonged endotracheal intubation. Acute streptococcal infection, fungal infection, syphilis, and leprosy all may lead to perichondritis that may be mistaken for RP. Although sparing of the earlobe is characteristic in these cases, sometimes the only

way to make a definite diagnosis is to perform a biopsy. Nasal damage can occur as a result of several different conditions, including drug abuse (e.g., cocaine use), local fungal infections, tuberculosis, syphilis, and leprosy as well as granulomatous lesions such as GPA, lymphomatoid granulomatosis, and lethal midline granuloma. Eye involvement by RP can be difficult to separate from eye involvement by the associated disease. Necrotizing scleritis and keratitis can occur with rheumatoid arthritis, GPA, polyarteritis nodosa, Behçet syndrome, and Cogan syndrome. Other features of these associated diseases may aid in the differential diagnosis. Systemic vasculitis with pulmonary, renal, central nervous system, and other organ involvement can occur. Involvement of the root of the aorta by other diseases should be considered, especially Ehlers-Danlos syndrome, Marfan syndrome, idiopathic medial cystic necrosis, or ankylosing spondylitis.

PATHOGENESIS

Cartilage is an avascular structure made up of chondrocytes, type II collagen, proteoglycan aggregates, and noncollagenous matrix proteins. It is an immunologically privileged site, and thus tolerance does not develop to these antigens. For this reason it is a target of autoimmune responses. RP should be classified as an inflammatory, autoimmune disorder for the following reasons:

1. RP is associated with other well-established autoimmune diseases.
2. RP is associated with the HLA-DR4 allele.²⁴
3. Pathologically, RP lesions show collections of lymphocytes and plasma cells, as well as deposition of immunoglobulin and complement at the fibrocartilaginous junction.²⁵
4. Elevated levels of chemokines, such as monocyte chemotactic protein-1, macrophage inflammatory protein-1 β , and interleukin-8 (IL-8), can be identified in the sera of RP patients and suggest a state of macrophage activation.²⁶
5. Indicators of humoral immune responses to cartilage antigens such as type II collagen and matrilin-1 can be identified in clinical samples from patients with RP.²⁷
6. Immunization of rodents with these same cartilage-derived antigens reproduces the disease.

Research in animal models of this disease has suggested a direct role for an autoimmune response to cartilage components in the pathogenesis of RP. Chondritis can be induced in rats by immunization with native type II collagen.^{28,29} In addition, mice transgenic for either human HLA-DQ8 or both human HLA-DQ6 and HLA-DQ8 develop chondritis and arthritis after type II collagen immunization.^{30,31} Interestingly, the double-transgenic mice develop spontaneous polychondritis, with a relapsing-remitting course, starting at 6 months of age, the mouse equivalent of middle age.³² Chondritis can also be induced in mice by injection of the cartilage matrix protein matrilin-1.³³ This model depends on particular major histocompatibility complex haplotypes, immunoglobulin, and the C5 component of complement connecting adaptive and innate immune responses with disease pathogenesis.^{34,35} Moreover, mice deficient in the antiinflammatory cytokine IL-10 develop more severe matrilin-1-induced chondritis, which implicates this molecule as a suppressor of cartilage inflammation.³⁵ Taken together, these results in rodent models suggest that RP develops when immunologic tolerance to cartilage antigens is broken. The role of enzymatic cartilage destruction is probably just as important, and local release of proteinases and oxygen metabolites may contribute to tissue damage. Whether the immune system initiates a process that is perpetuated by enzymatic damage or whether enzymatic damage exposes privileged antigens that activate the immune system, which thus allows the disease to develop and progress, is not known. Case series reporting that patients with RP and a history of cartilage trauma have more systemic and autoimmune manifestations of their disease suggest that loss of tolerance may be driven by autologous cartilage antigens.³⁶

MANAGEMENT

The initial management of acute RP has been established empirically. In situations of mild auricular and/or nasal chondritis or arthritis, many clinicians initially employ nonsteroidal antiinflammatory drugs or low-dose prednisone. In patients with serious manifestations, such as laryngotracheal

or ocular symptoms, inner ear inflammation, severe auricular or nasal chondritis, systemic vasculitis, aortitis, or glomerulonephritis, prednisone at a dose of 1 mg/kg or higher may be indicated. Our clinical experience suggests that the acute inflammation often responds well, and the corticosteroid dosage can be gradually tapered. However, if relapses occur with dose reduction, patients may require maintenance doses of prednisone and/or a corticosteroid-sparing agent to control their disease.

Strategies for refractory disease or frequent relapses during tapering of the corticosteroid dose are less certain. Because RP is so rare, controlled therapeutic trials have not been performed. The literature is replete with anecdotes of successful therapies ranging from dapsone and colchicine to immunosuppressants and biologic agents. The former two may be useful in milder disease as corticosteroid-sparing agents, whereas immunosuppressants are reserved for those with corticosteroid-refractory or corticosteroid-dependent disease. Azathioprine, cyclophosphamide, chlorambucil, leflunomide, mycophenolate mofetil, and cyclosporine, as well as plasmapheresis and intravenous immunoglobulins, have all been reported to be beneficial.³²⁻³⁴ In cases of recalcitrant RP complicated by tracheal stenosis and malacia, chondritis, and scleritis, successful treatment with biologic agents, including IL-1, IL-6, and tumor necrosis factor antagonists, has recently been described, as reviewed by Kemta Lekpa and colleagues.¹³ This review suggests that most biologics have some efficacy in RP with the exception of rituximab, to which few patients responded. Taken together, these case reports suggest that the therapeutic armamentarium available to the modern rheumatologist can be employed to treat RP. However, the efficacy of these agents in relation to one another and for specific manifestations of RP is unknown. Interestingly, high-dose chemotherapy with autologous stem cell transplantation induced complete remission in one RP patient with chondritis, scleritis, and aortitis for whom treatment with multiple biologic and cytotoxic agents had previously failed.³⁷

Treatment of RP is usually monitored by clinical response. A recent attempt was made to develop a disease activity score for RP that takes into account the various manifestations of RP, but this is still under development and is not widely used.³⁸ Some clinicians recommend annual screening electrocardiograms and pulmonary function tests with flow-volume loops to follow disease over time.³⁹ The erythrocyte sedimentation rate and C-reactive protein level may be useful in some cases if these markers portend a patient's disease activity. Multiple other biomarkers for disease activity have been proposed; however, the role of assays of these biomarkers in monitoring RP in individual patients has not been satisfactorily established.

Laryngotracheal involvement presents special management issues in following the activity of the disease and dealing with the consequences of a structurally impaired airway. Direct laryngoscopy and serial CT of the trachea can be used to monitor disease activity.^{8,23} Bronchoscopic ultrasonographic evaluation has also been described.⁴⁰ Early intervention is recommended for patients with severe focal stenosis or diffuse tracheobronchomalacia.⁴¹ Once flow-limiting airway damage has occurred, tracheostomy is necessary to treat symptomatic subglottic stenosis. Findings from a retrospective case series suggest that tracheal stents may be useful in the management of some patients.⁸ Laser therapy has been described for treatment of laryngeal and endobronchial disease.^{6,41} Nasal continuous positive airway pressure can be tried at night to assist the patient in keeping the airway open while recumbent and asleep. Surgical correction of subglottic stenosis and collapsed nasal cartilage can be performed once the disease is quiescent. Recurrent postobstructive pulmonary infections obviously require antibiotic treatment and respiratory care.

Heart valve replacement and aortic graft surgery have been successful. Surgical failure also has been observed, although such failures likely were due to continued annular inflammation leading to perivalvular leaks as well as recurrent aortitis adjacent to grafts. In a recent large surgical series, postoperative corticosteroid use was associated with valvular complications.⁴² Whether this represents the effect of corticosteroids on wound healing or reflects more severe underlying disease requiring corticosteroid use is not clear. Regardless, immunosuppressive medications should be considered after surgical intervention for the valvular complications of RP in an attempt to limit corticosteroid use and decrease inflammation.⁴²

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168 Amyloidosis

■ PHILIP N. HAWKINS

- Amyloidosis is a protein conformational disorder.
- Extracellular accumulation of amyloid fibrils disrupts the structure and function of tissues and organs.
- Amyloidosis can be systemic, affecting tissues throughout the body, or localized to one site or tissue type.
- About 5% of cases of systemic amyloidosis are hereditary.
- Clinical types of amyloidosis are classified according to the amyloid fibril protein.
- A multidisciplinary approach is required for diagnosis and treatment, including genetic and proteomic analysis in many cases.
- Developments in serum biomarkers and imaging, including cardiac magnetic imaging, provide important information for staging disease.
- A number of novel therapies are in development, including specific inhibitors of amyloid formation and immunotherapeutic approaches.

INTRODUCTION

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited in the extracellular space as insoluble fibrils that progressively disrupt tissue structure and function. The term *amyloid* is erroneously derived from the Greek word for “starchlike,” and some 30 different unrelated proteins that can form amyloid *in vivo* have now been identified, with clinical amyloidosis classified according to the fibril protein type (Table 168.1). Protein misfolding and aggregation have increasingly been recognized in the pathogenesis of various other diseases, but *amyloidosis*—the disease directly caused by extracellular amyloid deposition—is a precise term for a specific group of disorders.

Amyloid deposition is remarkable in its diversity; it can be systemic or localized, acquired or hereditary, life-threatening or merely an incidental finding. Clinical consequences occur when accumulation of amyloid is substantial enough to disrupt the structure of tissues or organs, leading to impairment of function. The pattern of organ involvement varies within and between types of amyloidosis, but clinical phenotypes overlap greatly. In systemic amyloidosis, virtually any tissue may be involved, and the disease is often fatal, although prognosis has improved as a result of increasingly effective treatments for many of the conditions that underlie it. Greater understanding of the pathogenesis of the disease has also favorably influenced the prognosis by allowing improved diagnosis and clinical characterization, along with the development of rational therapies and better supportive care including hemodialysis and solid organ transplantation. Localized amyloid deposits are confined to a particular organ or tissue and range from being clinically silent through to having serious consequences such as hemorrhage in the respiratory or urogenital tracts, or space-occupying effects. In addition to characterizing the disorders classified as types of amyloidosis, localized amyloid deposition is a hallmark pathologic feature of uncertain significance in various other important diseases including Alzheimer disease, the prion disorders, and type 2 diabetes mellitus, which are beyond the scope of this chapter.

PATHOGENESIS OF AMYLOID

Amyloidosis defies the dogma that the tertiary structure of proteins is determined solely by their amino acid sequence. Amyloid-forming proteins can

adopt two completely different stable structures, with the transformation involving massive refolding of the normal form into one that predominantly comprises a β sheet that can autoaggregate in a highly ordered manner to produce characteristic rigid, nonbranching amyloid fibrils of 10 to 15 nm in diameter and indeterminate length.^{1,2} All amyloid fibrils acquire new biophysical properties including insolubility in physiologic solutions, enhanced resistance to proteolysis, and ability to bind Congo red dye in a spatially ordered manner that produces diagnostic green birefringence under cross-polarized light (Fig. 168.1).

Amyloid deposition occurs in several circumstances:

1. As a consequence of a sustained abnormally high concentration of certain proteins, such as serum amyloid A protein in inflammation and β_2 -microglobulin in renal failure, which underlie susceptibility to AA and $A\beta_2M$ amyloidosis, respectively.
2. In the face of exposure to a normal concentration of a normal but to some extent inherently amyloidogenic protein over a very prolonged period, such as transthyretin in senile amyloidosis.
3. In the presence of an acquired or inherited variant protein with an abnormal and markedly amyloidogenic structure, such as certain monoclonal immunoglobulin light chains in AL amyloidosis and some genetic variants of transthyretin, lysozyme, apolipoprotein AI, and fibrinogen A α chain in hereditary amyloidosis.

The genetic and/or environmental factors that influence individual susceptibility to and the timing of amyloid deposition remain unclear, but once the process has begun, further accumulation of amyloid is unremitting as long as the supply of the respective precursor protein continues. A unifying characteristic of proteins that can form amyloid is that they are relatively unstable. Even under physiologic conditions they can exist in partly unfolded states involving loss of tertiary structure but retention of β -sheet secondary structure, which enables them to autoaggregate into protofilaments and thence into mature amyloid fibrils. Seeding may play a facilitating role, consistent with observations that accumulation of experimentally induced and clinical amyloid can be remarkably rapid following their start.

Composition of amyloid

Amyloid deposits comprise mainly the protein fibrils, but they also contain some common minor constituents, including certain glycosaminoglycans and the normal circulating plasma protein serum amyloid P component (SAP), as well as various other trace proteins such as apolipoprotein E.³ SAP binds in a specific calcium-dependent manner to a ligand expressed by all amyloid fibrils but not their precursor proteins.⁴ This phenomenon is the basis for the use of SAP scintigraphy in some centers for diagnostic imaging and quantitative monitoring of amyloid deposits.⁵ Studies in knockout mice indicate that SAP contributes to amyloidogenesis.

Amyloid fibril-associated glycosaminoglycans mainly consist of heparan and dermatan sulfates. Their universal presence, restricted heterogeneity, and intimate relationship with the fibrils suggest that they may also contribute to the development or stability of amyloid deposits, a possibility supported lately by the inhibitory effect of low-molecular-weight glycosaminoglycan analogues on the experimental induction of AA amyloidosis in mice and disease progression in patients.⁶

Pathologic effects

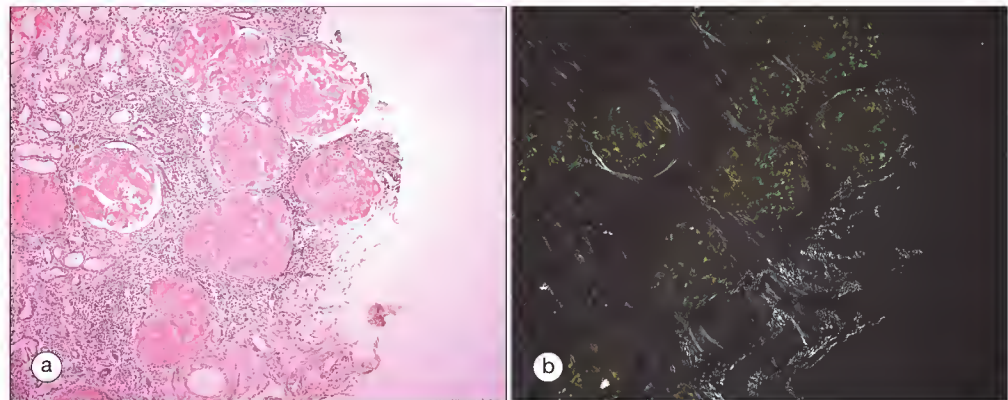
The pathologic effects of amyloid can largely be attributed to its physical presence. Extensive deposits, which may amount to kilograms, are structurally disruptive and incompatible with normal function, as are strategically

TABLE 168.1
Classification of amyloidosis*

Type	Fibril precursor protein	Clinical syndrome
AA	Serum amyloid A protein	Systemic amyloidosis usually with predominantly renal involvement associated with acquired or hereditary chronic inflammatory diseases. Formerly known as <i>secondary</i> or <i>reactive amyloidosis</i> .
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis potentially involving many organ systems associated with myeloma, monoclonal gammopathy, and occult B-cell dyscrasias. Formerly known as <i>primary amyloidosis</i> .
ATTR	Normal plasma transthyretin	Senile systemic amyloidosis with predominantly cardiac involvement (senile cardiac amyloidosis).
ATTR	Genetic variants of transthyretin (e.g., ATTR Met30, Ala60, Ile122)	Familial amyloid polyneuropathy (FAP), often with prominent amyloid cardiomyopathy. Predominantly cardiac involvement without neuropathy with certain mutations (e.g., TTR Ile122).
A β_2 M	β_2 -Microglobulin	Dialysis-related amyloidosis (DRA) associated with renal failure and long-term dialysis. Predominantly articular and periarticular involvement.
A β	β -Protein precursor (and rare genetic variants)	Cerebrovascular and intracerebral plaque amyloid in Alzheimer disease. Occasionally familial.
AApoAI	Genetic variants of apolipoprotein AI (e.g., AApoAI Arg26, Arg60)	Autosomal dominant systemic amyloidosis. Predominantly nonneuropathic with prominent visceral involvement, especially nephropathy. Minor wild-type apolipoprotein AI amyloid deposits may occur in the aorta in aging individuals.
AApoAII	Genetic variants of apolipoprotein AII	Autosomal dominant systemic amyloidosis with predominantly renal involvement.
AFib	Genetic variants of fibrinogen A α chain (e.g., AFib Val526)	Autosomal dominant systemic amyloidosis. Nonneuropathic with predominant nephropathy.
ALys	Genetic variants of lysozyme (e.g., ALys His67)	Autosomal dominant systemic amyloidosis. Nonneuropathic with predominantly renal and gastrointestinal involvement. Rarely presents with hepatic rupture.
ACys	Genetic variant of cystatin C (ACys Gln68)	Hereditary cerebral hemorrhage with cerebral and systemic amyloidosis in Icelandic individuals.
AGel	Genetic variants of gelsolin (e.g., AGel Asn187)	Autosomal dominant systemic amyloidosis. Predominantly cranial nerve involvement plus lattice corneal dystrophy. Described and most common in Finland.

*Not exhaustive and amyloid composed of peptide hormones, prion protein, and unknown proteins not included.

Fig. 168.1 Appearance of amyloid in a renal biopsy specimen. (a) Congo red stain revealing amorphous pink material restricted to the glomeruli of a patient with hereditary fibrinogen A α -chain amyloidosis. (b) Same section under high-intensity cross-polarized light showing pathognomonic apple green birefringence.



located smaller deposits, for example, in glomeruli or nerves. It remains possible that amyloid fibrils or prefibrillar aggregates may also be directly cytotoxic in some circumstances, but curiously, amyloid deposits appear to evoke little or no local reaction in the tissues. The relationship between the quantity of amyloid and the degree of associated organ dysfunction differs greatly among individuals and among different organs, and there is a strong impression that the rate of new amyloid deposition may be as important a determinant of progressive organ failure as absolute amyloid load.

Treatments that substantially reduce the supply of amyloidogenic precursor proteins frequently result in the gradual regression of existing amyloid deposits, which is often associated with preservation of or improvement in the function of amyloidotic organs. The natural clearance of amyloid is thought to be mediated by an inefficient macrophage response, which it has lately proved possible to intensify through passive antibody therapies.⁷

ACQUIRED AMYLOIDOSIS

Acquired systemic amyloidosis is known to be the cause of death in about 1 in 1000 people in the United Kingdom, and it may be much underdiagnosed among elderly individuals. The key characteristics of the main subtypes are shown in Table 168.1.

Systemic AL amyloidosis is the most serious and commonly diagnosed type, and referrals of AL amyloidosis to the UK National Amyloidosis Centre

presently outnumber referrals of AA amyloidosis by a factor of 10:1. Although less serious, dialysis related- β_2 M amyloidosis affects about 1 million patients receiving long-term renal replacement therapy worldwide and causes much suffering. Senile ATTR amyloid deposition, predominantly in the heart, occurs in about one quarter of individuals older than age 80 years, but its wider clinical significance is not yet known.

Reactive systemic amyloidosis, AA amyloidosis

AA amyloidosis is a complication of chronic inflammatory disorders, or indeed any condition that gives rise to overproduction of the acute-phase reactant serum amyloid A protein (SAA). The amyloid fibrils are composed of AA protein, an N-terminal fragment of SAA. AA amyloidosis occurs in up to 1% to 5% of patients with rheumatoid arthritis, juvenile idiopathic arthritis, and Crohn disease, and more frequently among those with lifelong autoinflammatory diseases such as familial Mediterranean fever. Most patients have proteinuric renal disease at presentation; liver and gastrointestinal involvement may occur at a later stage, but clinically significant involvement of the heart and nerves is rare.⁸

Pathologic features

The AA fibril protein is a single nonglycosylated polypeptide chain, usually of mass 8000 Da, comprising the 76-residue N-terminal portion of the 104-residue SAA, which is an apolipoprotein of high-density lipoprotein

particles. Most SAA in plasma is produced by hepatocytes under transcriptional regulation by cytokines, especially interleukin-1 (IL-1), IL-6, and tumor necrosis factor. Its circulating concentration can rise from healthy levels of up to 5 mg/L to over 2000 mg/L within 24 to 48 hours of the occurrence of an acute stimulus and can remain persistently high in chronic inflammation.

The AA protein is derived from circulating SAA by proteolytic cleavage, and sustained overproduction of SAA is a prerequisite for AA amyloid formation, but it is not known why it occurs in only some individuals or what initiates its production. In mice, only one of the three major isoforms of murine SAA is a precursor of AA amyloid fibrils. Human SAA isoforms are more complex, but homozygosity for particular types seems to favor susceptibility, although there may also be ethnic influences.

The functions of SAA are not clear, but it serves as an exquisitely sensitive and dynamic acute-phase marker with enormous range. Frequent and long-term monitoring of SAA is vital in the management of all patients with AA amyloidosis, because control of the underlying inflammatory process to substantially reduce SAA production is essential if amyloidosis is to be halted or reversed. Automated immunoassay systems for SAA are available standardized on a World Health Organization international reference standard.

Disease associations

AA amyloidosis occurs in association with chronic inflammatory disorders, chronic local or systemic microbial infections, and occasionally neoplasms, all of remarkable variety. In Western Europe and the United States the most frequent predisposing conditions are idiopathic rheumatic diseases. The lifetime incidence of AA amyloidosis in patients with rheumatoid arthritis and juvenile idiopathic arthritis in Europe is between 1% and 5%, is rather lower in the United States for reasons that are not clear, and is probably decreasing, generally due to improved treatments. Tuberculosis and leprosy are important causes of AA amyloidosis in some areas. Chronic osteomyelitis, bronchiectasis, chronically infected burns and decubitus ulcers, and the chronic pyelonephritis of paraplegia are other well-recognized associations. Hodgkin disease and renal carcinoma, which often cause a major acute-phase response, are the malignancies most commonly associated with systemic AA amyloid. Perhaps surprisingly, up to 10% of patients with AA amyloidosis do not have a clinically obvious chronic inflammatory disease, and these patients are often erroneously assumed to have AL amyloidosis. Although it may remain impossible to identify the of the precipitating acute-phase response in many such patients, the most common identifiable pathologic conditions in such cases in series at the author's own institution have been hitherto undiagnosed inherited periodic fever syndromes⁹ and cytokine-secreting Castleman disease tumors of the solitary plasma cell type, located in either the mediastinum or gut mesentery.¹⁰

Clinical features

The clinical features of AA amyloidosis are dominated by renal involvement, although histologically AA amyloid deposits are distributed widely. More than 90% of patients have nonselective proteinuria due to glomerular deposition at presentation, and nephrotic syndrome may develop before progression to end-stage renal failure.⁸ Hematuria, tubular defects, nephrogenic diabetes insipidus, and diffuse renal calcification occur rarely. Kidney size is usually normal but may be enlarged or, in advanced cases, reduced. End-stage chronic renal failure is the cause of death in 40% to 60% of cases, but acute renal failure may be precipitated by hypotension and/or salt and water depletion following surgery, excessive use of diuretics, or intercurrent infection, and may be associated with renal vein thrombosis. The second most common presentation is with organomegaly, such as hepatosplenomegaly or occasionally thyroid goiter, with or without overt renal abnormality; but in all cases amyloid deposits are widespread at presentation, which is the basis for diagnosis through rectal and other screening biopsies. Histologic involvement of the heart is frequent but rarely results in cardiac failure. Gastrointestinal dysfunction is common in advanced disease, presenting predominantly with diarrhea and occasional bleeding.

AA amyloidosis may present early in the course of an inflammatory disease, but incidence increases over time. The median duration of inflammation before diagnosis of amyloidosis is about 20 years, although it can be as little as 1 year. Prognosis is closely related to the degree of renal dysfunction and the effectiveness of treatment for the underlying inflammatory disorder. In the presence of persistent, uncontrolled inflammation, 50% of patients with AA amyloidosis die within 10 years, whereas if the causative acute-phase response can be persistently suppressed proteinuria can resolve, renal function may be retained, and the prognosis is much better (see treatment section later). Availability of hemodialysis and renal transplantation prevents early death from uremia per se, and despite amyloid deposition in

extrarenal tissues the prognosis is quite similar to that of other causes of end-stage renal failure.¹¹

Amyloidosis associated with immunocyte dyscrasia, AL amyloidosis

Systemic AL amyloidosis, formerly known as *primary amyloidosis*, develops in about 2% of individuals with monoclonal gammopathies.¹² AL fibrils are derived from monoclonal immunoglobulin light chains, which are unique in each patient; this explains the substantial heterogeneity of AL amyloidosis in terms of organ involvement and overall clinical course. Virtually any organ, other than the brain, may be directly affected, but deposition in the kidneys, heart, liver, or peripheral nervous system is most often associated with clinical consequences. Early symptoms are often nonspecific, including marked fatigue. The underlying monoclonal gammopathy is often missed on routine electrophoretic screening with the potential to further delay the diagnosis, which even under favorable circumstances tends to be made at an advanced stage. This emphasizes the need to consider AL amyloidosis as a potential diagnosis in a range of vague clinical presentations and the need for prompt appropriate investigations, such as biopsy of affected organs and sensitive serum free light-chain analysis to identify associated subtle B-cell dyscrasias.¹³

Pathologic features

AL amyloid fibrils are derived from the N-terminal region of monoclonal immunoglobulin light chains and consist of the whole or part of the variable (V_L) domain. The molecular weight of the fibril subunit protein therefore varies between about 8000 and 30,000 Da. Monoclonal light chains are unique to each individual, and the propensity for some to form amyloid fibrils is inherent to their particular structure. Fortunately, only a small proportion of monoclonal light chains are amyloidogenic, but it is not possible to identify these with any certainty from their class or abundance.

The associated B-cell dyscrasias in systemic AL amyloidosis are heterogeneous and include almost any clonal proliferation of differentiated B lymphocytes, including multiple myeloma, Waldenström macroglobulinemia, and occasionally other malignant lymphomas or leukemias. However, well over 80% of cases are associated with low-grade and otherwise "benign" monoclonal gammopathies that are often very subtle.¹⁴ Histologic studies indicate that minor, clinically insignificant amyloid deposits may occur in about 10% of patients with myeloma and in a smaller proportion of patients with monoclonal gammopathy of undetermined significance (MGUS). The cytogenetic abnormalities that commonly occur in multiple myeloma and MGUS, such as 14q translocations and 13q deletion, have also been observed in AL amyloidosis, but their prognostic significance has not been fully elucidated.¹⁵

Systemic AL amyloidosis accounts for about 1 in 1500 deaths in Britain and occurs equally in men and women. The age-adjusted incidence of AL amyloidosis in the United States is estimated to be between 5.1 and 12.8 per million persons per year, which is equivalent to approximately 3000 new cases per year. The median age at presentation is 65 years, but it can sometimes occur in young adults and is probably underdiagnosed in the elderly, in whom monoclonal gammopathies have the highest prevalence.

Clinical features

The clinical features of AL amyloidosis are protean.¹⁴ The heart is affected in 90% of AL patients, in 30% of whom restrictive cardiomyopathy is the presenting feature and in up to 50% of whom it is ultimately fatal. Other cardiac presentations include arrhythmias and angina. Renal AL amyloid has the same manifestations as renal AA amyloid, but the prognosis is worse. Gut involvement may cause motility disturbances (often secondary to autonomic neuropathy), malabsorption, perforation, hemorrhage, or obstruction. Macroglossia occurs rarely but is almost pathognomonic of the AL type (Fig. 168.2). Hypospasmodism sometimes occurs in both AA and AL amyloidosis. Painful sensory polyneuropathy with early loss of pain and temperature sensation followed later by motor deficits is seen in 10% to 20% of cases and carpal tunnel syndrome in 20%. Autonomic neuropathy leading to orthostatic hypotension, impotence, and gastrointestinal disturbances may occur alone or together with the peripheral neuropathy and has a very poor prognosis. Skin involvement takes the form of papules, nodules, and plaques, usually on the face and upper trunk; involvement of dermal blood vessels results in purpura occurring either spontaneously or after minimal trauma and is quite common. Articular amyloid is rare but may superficially mimic acute polyarticular rheumatoid arthritis, or it may present as asymmetrical arthritis affecting the hip or shoulder. Infiltration of the glenohumeral joint and surrounding soft tissues occasionally produces the characteristic "shoulder pad" sign. A rare but serious manifestation of AL



Fig. 168.2 Macroglossia in a patient with AL amyloidosis, with peripheral ridging due to teeth indentation.

amyloid is an acquired bleeding diathesis that may be associated with deficiency of factor X and sometimes also factor IX, or with increased fibrinolysis. It does not occur in AA amyloidosis, although in all types of systemic amyloidosis there may be serious bleeding in the absence of any identifiable factor deficiency due to widespread vascular deposits.

Dialysis-related amyloidosis, β_2 -microglobulin amyloidosis

β_2 -Microglobulin amyloid deposition occurs in patients with dialysis-dependent chronic renal failure and predominantly involves articular and periarticular structures.¹⁶ The amyloid fibril precursor protein is β_2 -microglobulin, which is the invariant chain of the major histocompatibility class I molecule; it is expressed by all nucleated cells and is normally filtered freely at the glomerulus and then reabsorbed and catabolized by the proximal tubular cells. Decreasing renal function causes a proportionate rise in concentration. β_2 -Microglobulin amyloidosis was first described in 1980 and occurs in patients who have been receiving dialysis for several years or, very occasionally, those with longstanding severe chronic renal impairment. Dialysis-related amyloidosis has been recognized mostly in the hemodialysis population, but it also occurs in patients receiving continuous ambulatory peritoneal dialysis. Relatively few patients are maintained on peritoneal dialysis for the 5 to 10 years required for the development of symptomatic β_2 -microglobulin amyloid, but histologic studies of early subclinical deposits suggest that the incidence of dialysis-related amyloidosis is similar among patients treated with the two dialysis modalities.¹⁷ Indeed, β_2 -microglobulin amyloid deposits are present in 20% to 30% of patients within 3 years of commencing dialysis for end-stage renal failure.

Clinical features

The clinical features are largely confined to the locomotor system. Carpal tunnel syndrome is usually the first clinical manifestation of β_2 -microglobulin amyloidosis. Some individuals develop symptoms within 3 to 5 years, and by 20 years the prevalence is almost 100%. Older patients appear to be more susceptible to the disease and tend to exhibit symptoms more rapidly. Amyloid arthropathy tends to occur a little later but eventually affects most patients on dialysis. The arthralgia of β_2 -microglobulin amyloidosis affects the shoulders, knees, wrists, and small joints of the hand and is associated with joint swelling, chronic tenosynovitis, and occasionally hemarthroses. Spondyloarthritis is also recognized, as is cervical cord compression. Deposition of β_2 -microglobulin amyloid within the periarticular bone produces the typical appearances of subchondral erosions and cysts, which can contribute to pathologic fractures, particularly of the femoral neck, cervical vertebrae, and scaphoid.

A hereditary form of β_2 -microglobulin amyloidosis has recently been identified in association with a genetic variant of the protein; it is unrelated to renal failure, and autonomic neuropathy is the predominant clinical manifestation.¹⁸

BOX 168.1 PROTEINS WITH GENETIC MUTATIONS ASSOCIATED WITH AMYLOID DEPOSITION

- | | |
|-----------------|--|
| ■ Transthyretin | ■ Fibrinogen A α chain |
| ■ Cystatin C | ■ Apolipoprotein AI |
| ■ Gelsolin | ■ Apolipoprotein AII (very rare) |
| ■ Lysozyme | ■ β_2 -Microglobulin (very rare) |

Senile transthyretin (ATTR) amyloidosis

Microscopic, clinically silent systemic deposits of wild-type senile transthyretin (TTR) amyloid are common in the elderly and involve the heart and blood vessel walls, smooth and striated muscle, fat tissue, renal papillae, and alveolar walls. In contrast to most other forms of systemic amyloidosis, including hereditary TTR amyloidosis caused by mutations in the TTR gene, the spleen and renal glomeruli are rarely affected. The brain is not involved. Clinically, the dominant feature of ATTR amyloidosis is restrictive cardiomyopathy¹⁹; the condition is also often known as *senile systemic* and *senile cardiac amyloidosis*. Deposits in other tissues rarely attain clinical significance besides causing carpal tunnel syndrome in about one fifth of cases, often before cardiac symptoms have developed. About one quarter of patients can be demonstrated to have gastrointestinal amyloid deposits on rectal biopsy. ATTR amyloidosis is rare before age 60, and most patients are at least 70 years of age, with a male preponderance.

A polymorphic variant, TTR Ile122, which occurs in 4% of African Americans, is associated with a syndrome that cannot be distinguished clinically from wild-type ATTR amyloidosis. The penetrance of this variant is not known, but susceptibility to the disease appears to be increased.

Localized AL amyloidosis

Localized deposits of AL amyloid can occur almost anywhere in the body and are consequent on the presence of a focal monoclonal B-cell dyscrasia within the affected tissue, which is itself often hard to demonstrate. Characteristic sites include the skin, airways, conjunctiva, and urogenital tract. The deposits may be nodular or confluent and are associated with a usually inconspicuous focal infiltrate of clonal B-cells producing amyloidogenic light chains. Progression of localized AL amyloid into a truly systemic disease is exceedingly rare, and conservative management is usually appropriate. It is also rare for the focal B-cell dyscrasia to become systemic and to require treatment in its own right.

Localized orbital AL amyloid presents as mass lesions that can disrupt eye movement and the structure of the orbit. Localized laryngeal AL amyloidosis is a well-recognized syndrome that is often amenable to direct or laser excision, but hereditary systemic apolipoprotein AI amyloidosis can also present in this manner. Amyloidosis presenting in the bronchial tree is virtually always localized AL type, as are solitary or multiple amyloid nodules within the lung tissue. If stenotic lesions are accessible, bronchoscopic laser excision can relieve symptoms. In contrast, diffuse alveolar-septal parenchymal deposition is commonly a manifestation of systemic AL amyloidosis. There are anecdotal reports that inhaled steroids may benefit pulmonary symptoms. Breast amyloidosis is associated with Sjögren syndrome in some cases, and MALT lymphoma should be excluded. Lichenoid and macular forms of cutaneous amyloid are distinct and are thought to be derived from keratin or related proteins, whereas nodular cutaneous amyloidosis deposits are generally localized AL type, although the latter can sometimes be a manifestation of systemic AL amyloidosis. Localized urogenital AL deposits are often incidental findings but may present with hematuria or, less commonly, obstruction. They can occur anywhere from the renal collecting system to the urethra, although they are most usually identified within the bladder. Management is conservative or with transurethral laser resection when symptoms occur; cystectomy is rarely required.

HEREDITARY SYSTEMIC AMYLOIDOSIS

Hereditary systemic amyloidosis is caused by deposition of amyloid fibrils derived from genetically variant proteins and is associated with mutations in a number of genes (Box 168.1)

These diseases are all inherited in an autosomal dominant pattern with variable penetrance and present clinically at various times from the teenage years to old age, although usually in mid-adult life. By far the most common hereditary amyloidosis is caused by TTR variants and usually presents as the syndrome of familial amyloid polyneuropathy with peripheral and

autonomic neuropathy. Cystatin C amyloidosis manifests with cerebral amyloid angiopathy with recurrent cerebral hemorrhage and clinically silent systemic deposits, and has been reported only in Icelandic families. Gelsolin amyloidosis presents with cranial neuropathy and is extremely rare. Apolipoprotein AI, lysozyme, and fibrinogen A α -chain amyloidosis present as nonneuropathic systemic amyloidosis that variously affect the major viscera, with renal involvement usually being prominent. Because a family history is quite often absent, these latter conditions are readily misdiagnosed as acquired primary AL amyloidosis and are less rare than previously thought. Indeed, recent routine use of DNA analysis suggests that 5% to 10% of patients with systemic amyloidosis of the non-AA type have hereditary forms of the disease.²⁰ It is imperative that hereditary amyloidosis be identified correctly, because prognosis, treatment, and implications for family members differ substantially from those for acquired amyloidosis.

Familial amyloidotic polyneuropathy, variant transthyretin (ATTR) amyloidosis

Familial amyloidotic polyneuropathy (FAP) is associated with heterozygosity for point mutations in the gene for TTR.²¹ It is an autosomal dominant syndrome with peak onset between the third and seventh decades. More than 100 variant forms of TTR are associated with FAP, and the amyloid fibrils are derived from a mixture of variant and wild-type TTR protein. There are probably several thousand patients with FAP in the world. The disease is characterized by progressive and disabling peripheral and autonomic neuropathy and varying degrees of visceral amyloid involvement, prominently including cardiac amyloidosis, which can be the sole clinical feature in some cases. Deposits within the vitreous of the eye are well recognized and are pathognomonic, whereas deposits in the kidneys, thyroid, spleen, and adrenals are usually asymptomatic. There are well-characterized foci of FAP associated with the most common variant, substitution of methionine for valine at residue 30 (TTR Met30), in Portugal, Japan, and Sweden, but FAP has been reported in most ethnic groups around the world. FAP is most commonly associated with TTR Ala60 in the United Kingdom.²² There is considerable phenotypic variation in the age of onset, rate of progression, involvement of different systems, and disease penetrance generally, even sometimes within a given family. Typically the disease progresses inexorably, causing death within 5 to 15 years.

Some sequence variants of TTR are not associated with amyloidosis, for example TTR Ser6, whereas others, most notably TTR Ile122, are associated with isolated cardiac amyloidosis.

Familial amyloid polyneuropathy with predominant cranial neuropathy

Familial amyloid polyneuropathy with predominant cranial neuropathy is a very rare dominant form of hereditary amyloidosis that presents in mid to late adult life with cranial neuropathy, lattice corneal dystrophy, and a mild distal peripheral neuropathy.²³ It was originally described in Finland but has since been reported in other ethnic groups. There may be skin, renal, and cardiac manifestations, but these are usually covert and life expectancy approaches normal. There is no specific treatment, and the disorder is progressively disfiguring and very distressing in its late stages. The mutant gene responsible encodes a variant form of gelsolin, which is an actin-modulating protein. The functional role of circulating gelsolin is unknown but may be related to clearance of actin filaments released by apoptotic cells.

Nonneuropathic hereditary systemic amyloidosis

Nonneuropathic hereditary systemic amyloidosis is caused by mutations in the genes for lysozyme, apolipoprotein AI and AII, and fibrinogen A α chain. Hitherto thought to be exceedingly rare, it has lately been demonstrated that many affected patients do not have a family history, and up to 5% of patients with systemic amyloidosis have a hereditary nonneuropathic type.²⁰ This has led to routine use of DNA screening at specialist amyloidosis centers.

Hereditary lysozyme systemic amyloidosis has been described in association with seven lysozyme variants, all of which are extremely rare.²⁴ In most patients the disorder manifests in middle age with proteinuria and very slowly progressive renal impairment. There are usually substantial amyloid deposits in the liver, spleen, and upper gastrointestinal tract; dry eyes due to lacrimal gland involvement is an early diagnostic clue. Curiously, in some patients with the least rare His67 variant, the disorder presents in young adulthood with hepatic rupture, whereas in most it presents later on with renal dysfunction. Cutaneous petechial hemorrhage beginning at a young age is a peculiar feature in patients with the Thr56 variant. Many patients experience few symptoms despite having substantial amyloid deposits, but

acute gastrointestinal hemorrhage or perforation is a frequent cause of death.

Apolipoprotein AI is a major constituent of high-density lipoprotein. Twenty amyloidogenic variants are known; of these, 14 are single amino acid substitutions, 4 are deletions, and 2 are deletions-insertions. The resulting clinical syndromes vary but are often associated with substantial amyloid deposits in the liver, spleen, and kidneys. Some mutations are associated with predominant cardiomyopathy and, in the case of the Arg26 variant, an FAP-like syndrome. Several C-terminal variants are associated with hoarseness due to laryngeal amyloid deposits. Other clinical consequences associated with particular mutations include male infertility and skin lesions. The majority of patients eventually develop renal failure, but liver function usually remains well preserved despite extensive hepatic amyloid deposition. Normal wild-type apolipoprotein AI is itself weakly amyloidogenic and is the precursor of small amyloid deposits that occur quite frequently in aortic atherosclerotic plaques.

Hereditary fibrinogen A α -chain amyloid was first identified in a family in 1993; since then, nine further amyloidogenic mutations have been described. These include six single amino acid substitutions, three frameshifting deletion mutations, and a deletion-insertion mutation. By far the most common mutation results in the substitution of valine for glutamic acid at position 526. This type most often presents in the absence of a family history due to low penetrance. Indeed, nearly 5% of patients referred to the UK National Amyloidosis Centre with a presumed diagnosis of acquired AL amyloidosis have hereditary fibrinogen A α -chain amyloidosis. In most patients the disorder presents in late middle age with proteinuria or hypertension and progresses to end-stage renal failure during the following 5 years or so. Amyloid deposition occurs in the kidneys, spleen, and sometimes the liver but is usually asymptomatic in the latter two sites. The majority of patients have an excellent outcome with renal replacement therapy.²⁵

DIAGNOSIS AND INVESTIGATION OF AMYLOIDOSIS

The diagnosis of amyloidosis generally requires histologic confirmation, although the mere demonstration of amyloid deposition does not by itself establish that it is clinically significant. Although amyloidosis does not occur in the absence of amyloid deposits, the latter may be an incidental histologic finding, especially in older individuals. The pathognomonic tinctorial property of amyloid deposits in tissue is apple green-red birefringence when stained with Congo red dye and viewed in intense light through cross-polarized filters. Immunohistochemical staining of amyloidotic tissue sections is the most accessible method for characterizing amyloid fibril protein type (Fig. 168.3), but it does not always produce definitive results, especially in AL type amyloidosis. Amyloid deposits can be quite patchy, and histologic analysis can never provide information about the overall whole-body load or distribution of amyloid deposits, nor does it permit monitoring of the natural history of amyloidosis or its response to treatment. To overcome these problems the author developed radiolabeled human SAP as a specific, noninvasive, quantitative *in-vivo* tracer for amyloid deposits and has used it as a routine tool in clinical practice for 20 years.²⁶ Studies of over 15,000 individuals using scintigraphy and metabolic turnover studies with labeled SAP have contributed greatly to the knowledge of amyloidosis and especially its diagnosis, monitoring, and response to treatment.

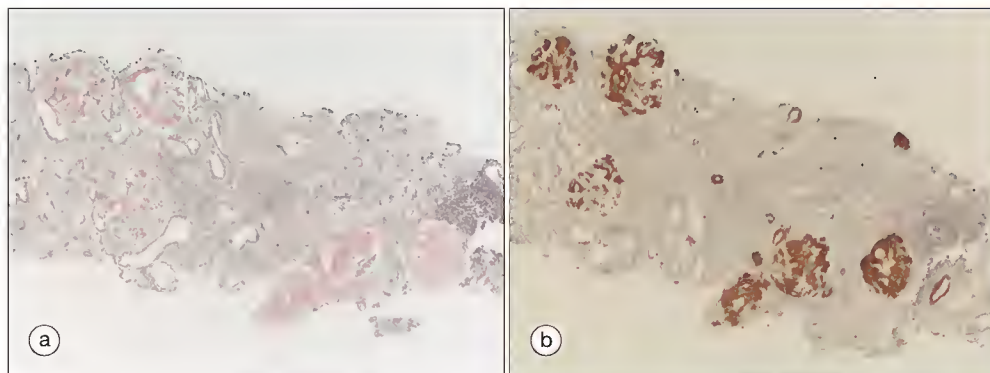
Histologic diagnosis of amyloid

The diagnosis of amyloid is most frequently made following biopsy of the kidneys, liver, heart, gut, peripheral nerve, lymph node, skin, thyroid, or bone marrow. When a possible diagnosis of amyloidosis is already being considered, biopsy of subcutaneous fat or rectum is less invasive and results are positive in about 50% to 80% of patients with systemic AA or AL types. Biopsies of affected organs have a higher yield but a greater risk of hemorrhage and other complications.

Congo red stain²⁷ with its resultant green birefringence when viewed with high-intensity polarized light is the pathognomonic histochemical test for amyloidosis,^{27,28} although other fluorochromes and metachromatic stains continue to be used quite widely. Congo red is unstable and must be freshly prepared every 2 months or less. Use of thick sections of 5 to 10 μ m and inclusion in every staining run of a positive control tissue containing modest amounts of amyloid are critical.

Immunohistochemistry is the most accessible method for characterizing the type of amyloidosis, although its success varies with fibril type and it depends on availability of a suitable tissue sample that contains neither too little nor too much amyloid. Antibodies to SAA protein are commercially

Fig. 168.3 Immunohistochemical typing of amyloid deposits. (a) Congo red stain of a renal biopsy specimen showing amyloid deposits in the glomeruli and blood vessels in a patient with rheumatoid arthritis. (b) Immunospesific staining of the amyloid deposits with a monoclonal anti-serum amyloid A protein antibody demonstrating that the amyloid deposits are of AA type.



available and virtually always stain AA deposits, as is the case with antibodies to β_2 -microglobulin in hemodialysis-associated amyloid. In AL amyloid, the deposits in fixed specimens are stained convincingly with antibodies to κ or λ immunoglobulin light chains in only about two thirds of cases, because the technique is hampered by an abundant polyclonal immunoglobulin background and the fact that the light-chain fragments in AL fibrils are chiefly variable domain and unique for each monoclonal protein. Immunohistochemical staining of TTR and other hereditary amyloid fibril proteins may require pretreatment of sections with formic acid, with alkaline guanidine, or by deglycosylation and even then does not always yield definitive results.

Electron microscopy identifies amyloid as straight, rigid, nonbranching fibrils of indeterminate length and 10 to 15 nm in diameter. A diagnosis of amyloidosis made through electron microscopy alone should be regarded with caution because other fibrillar deposition diseases occur. Immunogold staining of amyloidotic biopsy specimens can sometimes be diagnostic of fibril protein type when standard immunohistochemical staining under light microscopy has not produced definitive results.

Problems of histologic diagnosis include inadequacy of tissue samples—for example, the failure to obtain submucosal vessels in a rectal biopsy specimen—and indeed the failure to identify any amyloid in a target organ biopsy specimen never completely excludes the diagnosis. The unavoidable sampling problem means that biopsy cannot reveal the extent or distribution of amyloid generally. Experience with Congo red staining is required if clinically important false-negative and false-positive results are to be avoided. Immunohistochemical staining requires the use of positive and negative controls, including demonstration of specificity of staining by absorption of antisera with the respective antigens.

Nonhistologic investigations

Cardiac amyloid

Myocardial amyloid deposits cause a restrictive type of cardiomyopathy.²⁸ Two-dimensional echocardiography showing small, concentrically thickened ventricles; diastolic dysfunction with or without various degrees of global systolic impairment; dilated atria; homogeneously echogenic valves; and “sparkling” echodensity of ventricular walls is virtually diagnostic of cardiac amyloidosis. However, clinically significant diastolic impairment may be difficult to detect even by comprehensive Doppler ultrasonography and other functional studies, and can sometimes occur in the absence of left ventricular wall thickening. Newer echocardiographic techniques such as strain and strain rate measurements are helpful in demonstrating the typically more pronounced impairment of longitudinal compared with axial contraction. Cardiac magnetic resonance imaging, which reveals various characteristic patterns of late gadolinium enhancement, is emerging as an investigation of great value. Electrocardiography characteristically shows reduced voltages, presumably reflecting replacement of myocardium by amyloid, although this occurs less often in cardiac amyloid of the TTR type than the AL type.²⁹

Localization of certain technetium-labeled bone tracers to amyloidotic hearts has long been described in anecdotal reports, but this phenomenon has lately been revisited and its potential investigated in a systematic fashion. For reasons that remain unclear, technetium-99m diphosphonate and pyrophosphate scintigraphy appear to localize cardiac ATTR amyloid deposits reproducibly and with considerable sensitivity.³⁰

Elevation of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin concentrations occur in many types of cardiac dysfunction and in chronic kidney disease. However, significant cardiac AL amyloidosis is excluded by normal values of NT-proBNP.³¹ Cardiac troponin and

NT-proBNP concentrations appear to be powerful predictors of prognosis and survival after chemotherapy in AL amyloidosis. Staging of disease at diagnosis using measurements of these two analytes (the Mayo Clinic staging system) is now in widespread use both in the clinic and in clinical trials.³²

Genomic and proteomic studies

In cases of known or suspected hereditary amyloidosis the gene defect must be characterized. If amyloidotic tissue is available the fibril protein may be identified immunohistochemically and the corresponding gene can then be studied, but when no tissue is available, screening of the genes for known amyloidogenic proteins must be undertaken.

Biochemical and immunochemical analyses for the presence in the plasma of genetically variant amyloidogenic variant proteins also are available, but DNA analysis is the most direct approach. However, it remains essential to corroborate DNA findings by confirming one way or another that the respective protein is indeed the main constituent of the amyloid.

Proteomic analyses of amyloidotic material are increasingly being used in specialist centers, which allows amyloid deposits in ever smaller samples to be characterized.³³

Radiolabeled serum amyloid P component scintigraphy

The universal presence in amyloid deposits of SAP, derived from circulating SAP, is the basis for the use of radioiodine-labeled SAP as a diagnostic tracer in amyloidosis.³ No localization or retention of labeled SAP occurs in healthy subjects or in patients with diseases other than amyloidosis. Radioiodinated SAP has a short 24-hour half-life in the plasma and is rapidly catabolized with complete excretion of the iodinated breakdown products in the urine. However, in patients with amyloidosis, the tracer rapidly and specifically localizes to the deposits in proportion to the quantity of amyloid present and persists there without breakdown or modification. Most experience has been gained with SAP labeled with the pure gamma emitter iodine 123. The associated dose of radioactivity is less than 4 mSv and well within accepted safety limits for diagnostic nuclear medicine imaging. The uptake of tracer into various organs can be precisely and repeatedly quantified.

Important observations regarding amyloid, which have been made for the first time *in vivo* using radiolabeled SAP scintigraphy, include the following: the different distribution of amyloid in different forms of the disease; the presence of amyloid in anatomic sites not available for biopsy (adrenals, spleen); major systemic deposits of forms of amyloid previously thought to be organ limited; a poor correlation between the quantity of amyloid present in a given organ and the level of organ dysfunction; a nonhomogeneous distribution of amyloid within individual organs; and evidence for surprisingly rapid progression and regression of amyloid deposits at different rates in different organs (Fig. 168.4). The long-held belief that amyloid deposition is irreversible and inexorably progressive is evidently incorrect and simply reflects the persistent nature of the conditions that underlie it. Many case reports have described improvement in amyloidotic organ function when underlying conditions have been controlled, which suggests regression of amyloid, and serial SAP scintigraphy provided the means to show that this is indeed the case. Regression of amyloid has been observed when the supply of amyloid fibril precursor proteins has been reduced in AA amyloidosis by vigorous control of rheumatic inflammation, in AL amyloidosis by suppression of the clonal plasma cell disease by cytotoxic drugs, in hemodialysis-associated amyloidosis after renal transplantation, and in hereditary TTR and fibrinogen A α -chain amyloidosis following liver transplantation. It is

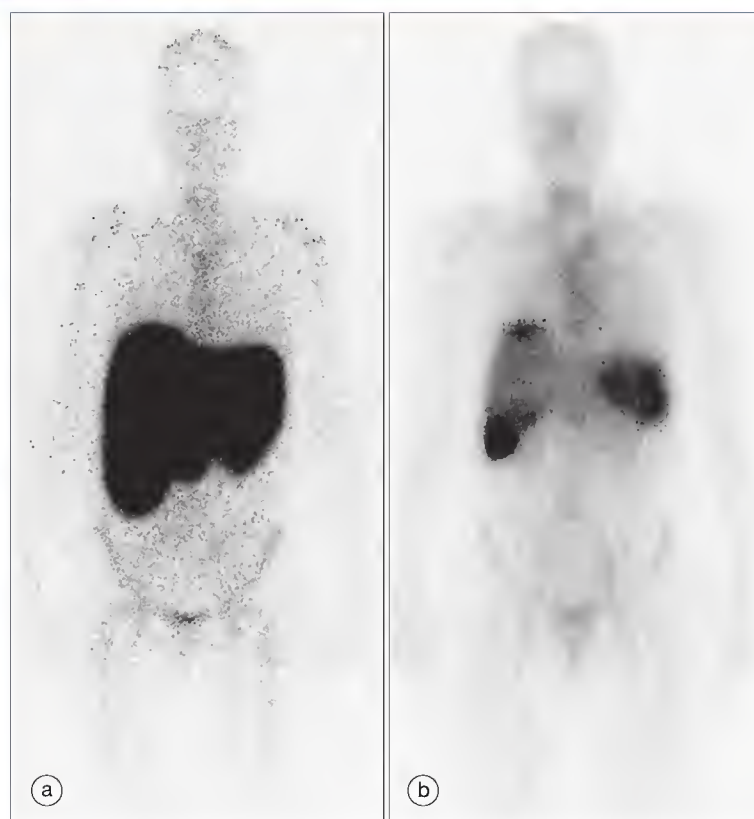


Fig. 168.4 Anterior whole-body radiolabeled serum amyloid P component (SAP) scintigraphs demonstrating regression of AL amyloid deposits following chemotherapy. (a) At diagnosis the SAP tracer localized to AL amyloid deposits in the liver, spleen, and bones of this patient, who had hepatomegaly at presentation. (b) A follow-up scan 5 years later following successful chemotherapy shows that there has been regression of amyloid in all sites, most marked in the liver, which has returned to a normal size.

now clear that amyloid deposits exist generally in a state of dynamic turnover, which has encouraging implications for patient management. Labeled SAP studies thus make a valuable contribution to the diagnosis and management of systemic amyloidosis and are performed routinely at the National Health Service National Amyloidosis Centre at the Royal Free Hospital, London.

ASSESSMENT OF ORGAN INVOLVEMENT BY AMYLOID

International consensus criteria for defining organ involvement in systemic amyloidosis were published in 2005 (Table 168.2).³⁴ Organ involvement by amyloid is variously defined clinically, histologically, and according to organ function and through other specialized investigations. Electrocardiography and two-dimensional Doppler echocardiography are the mainstays for assessing cardiac involvement, as are estimates of glomerular filtration and proteinuria for renal involvement. Liver size and serum alkaline phosphatase levels provide simple and accessible, but not overly sensitive, measures of liver involvement. In contrast, amyloid involvement of the gastrointestinal tract, lungs, soft tissues, and nervous system are much less amenable to precise definitions and are even more challenging to monitor quantitatively over time.

NATURAL HISTORY AND PROGNOSTIC FACTORS

Systemic amyloidosis is almost always a progressive disease that, without successful treatment, usually results in death within months to several years. Median survival of patients with AA amyloidosis whose underlying inflammatory disease is not well suppressed is on the order of 5 to 10 years. The prognosis is similar in familial amyloid polyneuropathy but is usually much better in nonneuropathic hereditary types, that is, those associated with mutations in apolipoprotein AI, fibrinogen A α chain, and lysozyme. The prognosis of systemic AL amyloidosis is generally worse than that of AA

TABLE 168.2

Diagnostic criteria for organ involvement by amyloid

Organ	Consensus criteria reported by Gertz and colleagues ³⁴
Heart	Echocardiogram demonstrates a mean wall thickness of >12 mm, no other cardiac cause found
Kidney	Proteinuria of >0.5 g protein per 24 hr, predominantly albumin
Liver	Total liver span of >15 cm in the absence of heart failure, or alkaline phosphatase level of >1.5 times the institutional upper limit of normal
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms Interstitial radiographic pattern
Soft tissue	Tongue enlargement, clinical Arthropathy Claudication, presumed vascular amyloid Skin Myopathy by biopsy or pseudohypertrophy Lymph node (may be localized) Carpal tunnel syndrome

From Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. Am J Hematol 2005;79:319-28.

and hereditary types, and median survival in some quite recent series was only 12 to 15 months.³⁵ Important factors that influence prognosis are the extent and severity of organ involvement, the availability of supportive measures including renal dialysis and organ transplantation, and the potential for and effectiveness of reducing the supply of the respective amyloid fibril precursor protein through intervention.

Systemic AL amyloidosis not only is the most common type but also is the most heterogeneous in its organ involvement, presentation, and clinical course. Half of deaths are due to cardiac involvement, and in patients in whom heart failure is evident at presentation, median survival is 6 months. There has been much recent effort to define prognostic factors in AL amyloidosis, and staging systems are in development. Symptomatic or substantial echocardiographic evidence of cardiac amyloid is associated with an expected survival of only 6 to 12 months. Patients with liver involvement and hyperbilirubinemia with bilirubin levels above 35 μ mol/L rarely survive longer than 4 months. Significant autonomic neuropathy, progressive clonal disease unresponsive to chemotherapy, and a bone marrow plasmacytosis of over 20% are also associated with poor outcomes. A large whole-body amyloid load as determined by SAP scintigraphy and evidence of accumulation of amyloid on follow-up SAP scans are further poor prognostic features. Prognosis is better when proteinuria or peripheral neuropathy is the dominant clinical feature or there is substantial suppression of underlying clonal disease by chemotherapy and regression of amyloid deposits on serial SAP scintigraphy. Elevated serum concentrations at diagnosis of the cardiac biomarkers troponin and BNP or its more stable precursor, NT-proBNP, are associated with a poor outcome, as is the absence of an early fall in their concentrations following chemotherapy.³⁶

TREATMENT OF AMYLOIDOSIS

The twin aims of management in systemic amyloidosis are reduction of the supply of amyloid fibril precursor proteins so that amyloid deposition diminishes and gradual regression of existing deposits may occur, and scrupulous general care, including dialysis and organ transplantation if necessary, to keep patients alive long enough for this to occur. Awareness of the compromised functional reserve of amyloidotic organs and extreme care to protect renal function are critically important. Rational management has been greatly facilitated by the recent availability of routine assays for circulating SAA in AA amyloidosis and serum free light chains in the AL type, and outcomes are much better in centers with specialist expertise.

Treatment of AA amyloidosis

Treatment of the chronic inflammatory conditions underlying AA amyloidosis, ideally to reduce serum SAA concentration to normal healthy levels, inhibits amyloid deposition, frequently leads to regression of deposits, and dramatically improves survival. Plainly, treatment varies depending on the nature of the inflammatory disorder, and successful pharmacologic approaches have ranged from nonspecific immunosuppression in inflammatory arthritis³⁷ to highly specific inhibition of IL-1 in patients with periodic fever syndromes.³⁸ Inflammatory arthritis underlies AA amyloidosis in two thirds of cases, and biologic agents targeting the key cytokine mediators of inflammation—tumor necrosis factor- α , IL-1, and IL-6—potently suppress the acute-phase response in many patients with rheumatoid arthritis, juvenile idiopathic arthritis, and seronegative spondyloarthritis. These drugs can also be effective in some patients with Crohn disease. Regular prophylactic treatment with colchicine is highly effective in suppressing familial Mediterranean fever and almost completely prevents the development of AA amyloidosis.

Localized amyloid masses can only be treated surgically. Surgical treatments include excision of solitary cytokine-secreting Castleman tumors and amputation of osteomyelitic limbs, and rarely excision of other inflammatory lesions.

A surprising finding among patients with AA amyloidosis is that of clinically covert inflammatory disease, which cannot be characterized, in up to 10% of patients. Many such patients are presumed to have primary AL amyloidosis at presentation, which emphasizes the need to perform confirmatory immunohistochemical testing in all cases. Antiinflammatory treatment must be empiric in such cases but, as is the case in all patients with AA amyloidosis, should be guided by frequent SAA measurements.⁸

Treatment of AL amyloidosis

The objective of treatment in AL amyloidosis is to suppress production of amyloidogenic monoclonal light chains in the hope that progression of the disease will be slowed down, halted, or reversed.³⁹ However, many patients have advanced multisystem disease at diagnosis and tolerate chemotherapy poorly. Quantitative measurements of serum free light chains using the robust, sensitive Freelite immunoassay are usually the most effective means of evaluating the early effects of chemotherapy and the need for ongoing treatment.⁴⁰ Chemotherapy must be tailored to the individual patient to achieve a balance between the ideal of complete remission of the underlying clonal disease and the need to minimize treatment-related toxicity and mortality. Certain organs affected by amyloid tend to fare better than others following treatment. Proteinuria and liver function often gradually improve when the clonal disease is adequately suppressed, whereas macroglossia and peripheral nerve function tend to improve extremely slowly if at all.

Many different chemotherapy regimens are in current use, ranging from oral cyclic combinations to high-dose chemotherapy with autologous peripheral stem cell rescue.⁴¹ The new agents bortezomib^{42,43} and lenalidomide,⁴⁴⁻⁴⁶ recently introduced for treatment of myeloma, are also showing great promise in AL.

Treatment of hereditary amyloidosis and organ transplantation

At present, other than transplantation to replace failed organs and, in certain cases, liver transplantation to remove the source of amyloidogenic proteins of hepatic origin, treatment of hereditary systemic amyloidosis is limited to management of symptoms. The liver is the source of plasma TTR, and over 2000 liver transplantations have been performed for treatment of hereditary ATTR amyloidosis since this “surgical gene therapy” approach was introduced in 1991. In younger patients carrying the common TTR Met30 amyloidogenic mutation the outcome is relatively good, with arrest or slowing

of progression of neuropathy and regression of visceral amyloid, but vitreous amyloid deposition may subsequently progress because some TTR is also produced within the eye. Cardiac amyloidosis present at the time of liver transplantation also usually progresses due to accumulation of wild-type TTR on the existing myocardial deposits, which excludes its applicability to the majority of patients with non-Met30 mutations. The livers of patients with hereditary TTR amyloidosis contain only microscopic amyloid deposits in the blood vessels and interstitial tissues, and normal liver function is retained. A large number of domino liver transplantations have therefore been conducted in recipients with various terminal liver diseases for whom normal livers were not available. This has certainly prolonged the lives of these patients, but several recipients have developed iatrogenic symptomatic systemic ATTR amyloidosis less than 10 years after transplantation.

Kidney and very occasionally liver transplantation is the mainstay of treatment in patients with fibrinogen A α -chain and apolipoprotein AI amyloidosis.

Supportive treatment

Supportive therapies remain a critical component of the management of amyloidosis. For cardiac amyloidosis, the mainstay of treatment is diuretics coupled with fluid restriction, daily weighing, and a low-salt diet, whereas the role of vasodilating drugs and β -blockers is unclear. Refractory edema may respond well to the addition of spironolactone and intermittent doses of metolazone. Salt-poor albumin infusions can also occasionally be helpful. Dysrhythmias may respond to drugs or to device implantation. In renal amyloidosis, rigorous control of hypertension is vital, and angiotensin-converting enzyme inhibition and/or angiotensin II blockade is often recommended when proteinuria is present. Renal dialysis may be necessary and is usually both feasible and acceptably tolerated. In autonomic neuropathy, fludrocortisone 100 to 200 μ g/day can be helpful in some patients but may simply exacerbate fluid retention. Midodrine is an effective pressor agent, starting at a dose of 2.5 mg and building up to 15 mg thrice daily. Midodrine exerts its actions via activation of the α -adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure. Gastroparesis causing symptoms of early satiety and nausea can be managed with prokinetic agents such as metoclopramide, along with advice to consume small, frequent meals of soft foods. Diarrhea due to amyloid gut involvement or autonomic neuropathy may respond to loperamide and codeine phosphate. Malnutrition is common and is often underestimated.⁴⁷ Significant weight loss should be treated with protein and vitamin supplementation, and the patient should be evaluated by an experienced dietitian. Feeding via gastrostomy may occasionally be required. Amyloid and chemotherapy-related peripheral neuropathy can be disabling and difficult to treat. For analgesia, opioids and nonsteroidal antiinflammatory drugs, amitriptyline, venlafaxine, anti-epileptics, transcutaneous electrical nerve stimulation, and/or gabapentin/pregabalin have all been used, although anecdotal reports suggest variable and limited efficacy. Withdrawal or dose reduction of any neurotoxic chemotherapeutic agents such as thalidomide or bortezomib often needs to be considered.

New treatments and future directions

Elucidation of aspects of the molecular pathogenesis of amyloid and amyloidosis has led to the development of various novel approaches to therapy. These include agents that stabilize and maintain circulating amyloid precursor proteins in their normal conformation,⁴⁸ agents that inhibit the interaction between amyloid fibrils and glycosaminoglycans, immunotherapy approaches,⁴⁹ depletion of SAP,⁵⁰ and silencing RNA and antisense oligonucleotide therapies. All of these potential new therapies have entered clinical testing, which offers real promise that specific anti-amyloid therapies may become available within the next few years.

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Digital clubbing and hypertrophic osteoarthropathy

■ MANUEL MARTÍNEZ-LAVÍN ■ CARLOS PINEDA

- Hypertrophic osteoarthropathy is a syndrome characterized by abnormal proliferation of the skin and osseous tissues at the distal parts of the extremities.
- Three features are typically present: a peculiar bulbous deformity of the tips of the digits conventionally described as *clubbing*, periostosis of the tubular bones, and synovial effusions.

HISTORY

Digital clubbing is one of the oldest clinical signs in medicine. Its original recognition has been attributed to Hippocrates (circa 450 BC).¹ Marie, in 1890,² and Bamberger, in 1891,³ described the fully developed syndrome. Marie distinguished it from acromegaly and suggested the term *pulmonary hypertrophic osteoarthropathy*. Because the site of primary disease may be in areas other than the lungs, this designation fell into disuse. The term used today is *hypertrophic osteoarthropathy* (HOA). Paleopathologic studies have demonstrated changes consistent with HOA in human skeletal remains from pre-Hispanic Mesoamerica.¹

EPIDEMIOLOGY

There are no systematic studies of the prevalence of digital clubbing in either the general population or hospital inpatients. The deformity is associated with a variety of internal illnesses, so that most clinicians, regardless of their specialty, have frequent encounters with patients who display this abnormality.

The veterinary literature contains reports of this illness in different species of mammals, in which the syndrome appears in response to the same illnesses as those reported for humans. HOA has been artificially produced in dogs by surgically caused right-to-left shunts of blood or by chemically induced lung cancer. Nevertheless, a stable animal model of the syndrome, accessible for systematic studies, has not been developed.

CLASSIFICATION

The classification of HOA is outlined in Figure 169.1. There is now evidence to support the contention that clubbing and HOA represent different stages of the same disease process.⁴ In the overwhelming majority of cases, the finger deformity is the first manifestation, and as the syndrome progresses, periostosis becomes evident. The degree of association of clubbing with the diverse illnesses varies, with clubbing ranging from being a constant finding, as in cases of cyanotic heart diseases, to being a rare manifestation, as in patients with cancer of the lung, liver cirrhosis, or Graves disease.

Synonyms for the deformity besides clubbing include *drumstick*, *pendulum*, and *hippocratic fingers*. Primary HOA is also known as *pachydermoperiostosis*. The term *acropachy* is etymologically the most appropriate and has been used to describe either clubbing or the fully developed syndrome.

CLINICAL FEATURES

In HOA there is a spectrum of symptoms. At one extreme, patients may be asymptomatic and unaware of the deformity of their digits. Other patients, in particular those with malignant lung tumors, may notice a burning sensation of the fingertips and may also experience incapacitating bone pain.

Characteristically, this pain is deep-seated, more prominent in the lower extremities, and aggravated by dependency of the limbs.

Physical examination is of foremost importance in diagnosis, because the bulbous deformity of the fingertips is unique (Fig. 169.2). The nail becomes convex (watch-crystal nail), and the skin overlying its base becomes thin and shiny, with disappearance of the normal creases. The edema and increased soft tissue produce rocking of the nail bed on palpation. Toes are also affected, but early changes are more difficult to discern here because of the splaying of the normal toe tip.

The Digital Index provides a practical method to measure clubbing (Fig. 169.3). With the use of a nonelastic string, the perimeter of each finger is measured at the distal interphalangeal joint and at the nail bed. If the sum of the 10 ratios of nail bed to distal interphalangeal joint is more than 10, clubbing is probably present. There is variation in the prominence of clubbing, and the Digital Index serves to assess the severity of the deformity or to compare groups of patients or responses to treatment.⁵ The most advanced stages, with a Digital Index greater than 11, are seen predominantly in patients with cyanotic heart diseases or primary HOA.

It is worth noting that, in the majority of cases, clubbing is the only manifestation of the syndrome. When all features of HOA are present, however, skin hypertrophy may be evident at other levels, with coarsening of the facial features or nonpitting cylindrical soft tissue swelling at the ankles ("elephant legs"). Thickening of the tubular bones may be evident in areas of the extremities not covered by muscles, such as the ankles and wrists.

Periostosis may be accompanied by tenderness on palpation of the involved area but in some instances is asymptomatic. Effusions into the large joints are frequently observed and are more easily detected in the knees and wrists. At the ankle they are more difficult to detect because of the surrounding soft tissue swelling. On palpation there is no hypertrophy of the synovial membrane. The range of motion of the joints may be slightly decreased. Arthrocentesis yields a very thick fluid with a tendency to spontaneous clotting. There is little inflammatory cell exudation, and the white blood cell count is usually less than 500/mm³ in the synovial fluid.⁶ All these features reflect the fact that HOA is not a proliferative synovial disease. Effusions are most likely a sympathetic reaction to the nearby periostosis.

There are other clinical findings associated with particular types of HOA that echo the involvement of an internal organ. Cyanosis is prominent in heart malformations associated with right-to-left shunts of blood. These patients present the prototype of HOA, because almost all have lifelong presence of clubbing and more than 33% display the fully developed syndrome.⁷ No other internal illness is so closely associated with HOA. A lesser degree of cyanosis is seen when the acropachy is associated with cystic fibrosis, pulmonary fibrosis, or chronic infections. Jaundice, ascites, and palmar erythema are common findings when the syndrome is secondary to liver cirrhosis. Chronic diarrhea is a constant finding in intestinal HOA.

Thyroid acropachy is a rare manifestation of Graves disease and is independent of the state of thyroid function. Clubbing usually coexists with exophthalmos and pretibial myxedema. The myxedema bears a resemblance to the elephant legs described in other types of HOA. Thyroid acropachy is characterized by an exuberant periosteal proliferation, located mostly at the small tubular bones of the hands and feet.⁸ Patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes) often display features of HOA, such as digital clubbing, skin thickening, and hyperhidrosis.⁹

Forms of HOA localized to one or two limbs may be seen. Most of these occur as a result of a prominent endothelial injury of that particular limb, such as in cases of arterial aneurysms or endothelial infections. A growing number of cases of localized HOA secondary to infection of an arterial graft have been reported. These are characterized by painful swelling of the

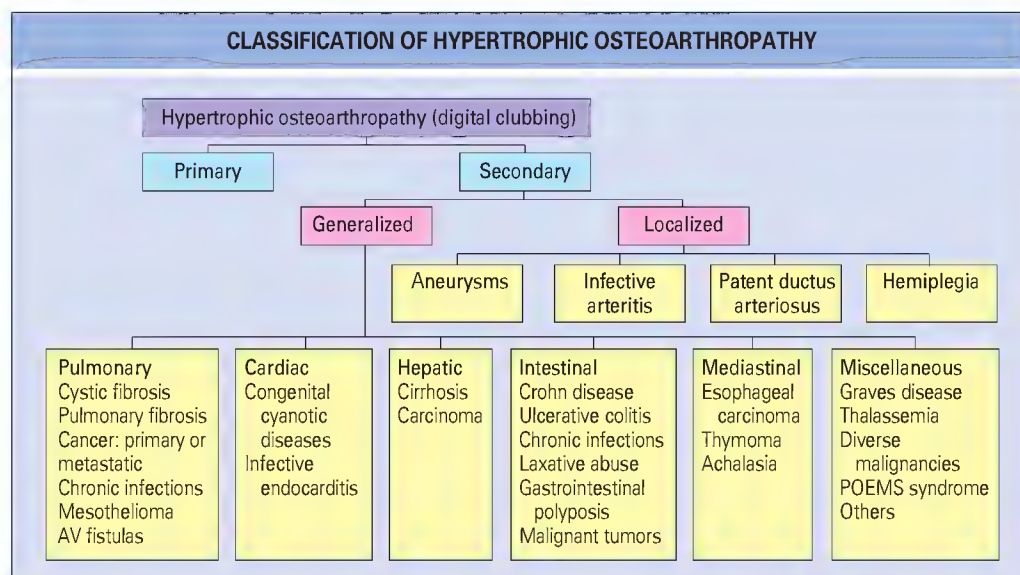


Fig. 169.1 Various forms of hypertrophic osteoarthropathy. AV, arteriovenous; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes.



Fig. 169.2 Clubbing deformity. The finger on the right is clubbed compared with the normal-shaped finger on the left.

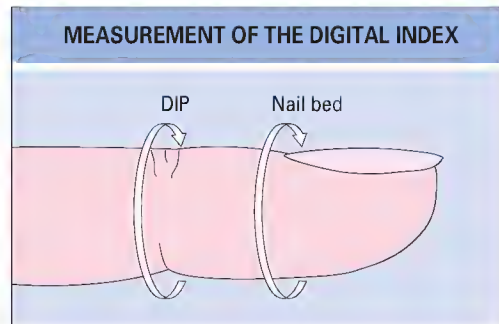


Fig. 169.3 Method of determining the Digital Index. The perimeter of each of the 10 fingers is measured at the nail bed (NB) and at the distal interphalangeal joint (DIP). If the sum of the 10 NB-DIP ratios is more than 10, clubbing is probably present.



Fig. 169.4 Hypertrophic osteoarthropathy. Wrist radiograph shows periostitis at the distal ends of the radius and ulna. The coarse, layered appearance is most evident along the diaphyses. The relative sparing of the radial epiphyses is characteristic.

affected limb associated with radiographic periostitis; clubbing has been reported in a minority of such cases.¹⁰ Another form of localized HOA is secondary to patent ductus arteriosus complicated by pulmonary hypertension. In these instances, clubbing and sometimes periostitis are limited to the cyanotic limbs.¹¹

Primary HOA is characterized by a clear-cut hereditary predisposition, with 33% of patients having a close relative with the same illness. The male-female ratio is 9:1. Primary cases are prone to display a more disseminated skin hypertrophy, hence the term *pachydermoperiostosis*.¹² This overgrowth roughens the facial features and can reach the extreme of cutis verticis gyrata, the most advanced stage of cutaneous hypertrophy. In such cases, the scalp takes on a cerebroid appearance. Another cutaneous alteration more frequently seen in idiopathic cases is glandular dysfunction, manifested as hyperhidrosis, seborrhea, or acne, or combinations thereof. A variety of associated abnormalities have been described in primary HOA: cranial suture defects, males with female escutcheon, and hypertrophic gastropathy.¹³ In primary HOA, the activity of the illness is usually limited to the growth period, with adults becoming asymptomatic. There are cases

of primary HOA that show an enigmatic clinical palindrome. Such cases display, as late manifestations, diseases that in other circumstances are known causes of HOA. In this palindrome, persistent ductus arteriosus, Crohn disease, or myelofibrosis can be the cause or the effect of HOA.¹⁴

INVESTIGATIONS

At the present time there are no useful serologic tests for HOA. An array of biochemical abnormalities may be found, however, reflecting the underlying illness.

Of utmost importance for the correct assessment of HOA are plain radiographs of the extremities, which may reveal abnormalities in an asymptomatic patient: long-standing clubbing is characterized by a bone-remodeling process that usually takes the form of acro-osteolysis (Fig. 169.4) and, more rarely, tuftal overgrowth (Fig. 169.5). Characteristically, the bone changes of clubbing are observed first at the toes; fingers are affected in more advanced cases.¹⁵ Periostitis is an orderly, evolutionary process that depends



Fig. 169.5 Clubbing and hypertrophic changes. Anteroposterior view of the foot of a 34-year-old man with primary hypertrophic osteoarthropathy demonstrates marked clubbing and hypertrophic changes, with "mushrooming" of the tufts.



Fig. 169.6 Monolayer periostosis. Typical location of the early periosteal changes of hypertrophic osteoarthropathy. A monolayer type of periostosis is seen in this anteroposterior view of the ankle of a 20-year-old woman with tetralogy of Fallot.

on the chronicity of the illness and the intensity of the underlying stimuli. It progresses in three dimensions: in the number of affected bones, in the site of involvement of a given bone, and in the shape of the periosteal apposition. In mild cases, few bones are affected (usually tibiae and fibulae); periostosis is limited to the diaphysis and has a monolayer configuration (Fig. 169.6). In advanced cases, all tubular bones are affected; in addition to the diaphysis, the metaphysis and epiphysis are also involved, and the periostosis takes on an irregular configuration (see Fig. 169.4).

Periostosis has a symmetric distribution and evolves in a centripetal fashion. It is independent of the underlying illness; primary and secondary cases feature similar changes.¹⁵ Typical of HOA is preservation of joint space and the absence of erosions or para-articular osteopenia.

Radionuclide bone scanning is a sensitive method for demonstrating periosteal involvement. There is hyperconcentration of the bone-seeking tracer at the periosteum. When this technique is used, the diagnosis of HOA is sometimes made serendipitously in patients with known malignant disease who have developed bone pain, with the study being requested for the evaluation of metastatic cancer.

DIFFERENTIAL DIAGNOSIS

When HOA is fully expressed, the drumstick fingers are so unique that its recognition poses no dilemma. Nonetheless, there are borderline cases in which neither a careful examination nor the Digital Index clarifies the situation. The most appropriate approach for such cases is to assume the presence of clubbing and to search for an underlying illness.

Diagnostic criteria for HOA are the combined presence of clubbing and radiographic evidence of periostosis of the tubular bones. The presence of synovial effusion is not essential for the diagnosis.¹⁶ Nevertheless, it should be emphasized that in some patients, particularly those with malignant lung tumors, painful arthropathy may be the presenting manifestation of the syndrome, in advance of clubbing. Such patients could be misdiagnosed as having an inflammatory type of arthritis.¹⁷ Here, important clinical features in the differential diagnosis are the location of pain (in HOA not only the joint but also the adjacent bone is involved) plus the fact that rheumatoid factor is usually absent and synovial fluid is noninflammatory.

Some patients with HOA have an exuberant skin hypertrophy that may resemble acromegaly. The presence of clubbing and periostosis plus the absence of prognathism, enlarged sella turcica, or abnormal circulating concentrations of growth hormone should lead to the correct diagnosis. A patient should be classified as having the primary form of the syndrome only after careful scrutiny fails to reveal an underlying illness.

Several cases of painful multifocal nodular periostitis have been described recently in transplant recipients taking voriconazole. Voriconazole is a new fluoride-containing antifungal medication. Fluorosis appears to be the underlying pathogenetic factor. Symptoms subsided after medication withdrawal.¹⁸

The importance of recognizing HOA cannot be overstated. If, in a previously healthy individual, any of the manifestations of the syndrome become evident, a thorough search for an underlying illness should be undertaken. Special attention must be directed to the chest, because nowadays the most frequent cause of an acute onset of HOA in adults is malignant lung tumor, either primary or metastatic. Conversely, if a patient previously diagnosed with any of the chronic illnesses outlined in Figure 169.1 develops clubbing, this alone is an unfavorable prognostic sign, indicating that the disease has reached an advanced stage.

In some clinical situations, the presence of acropachy signals a serious but treatable complication. If clubbing appears in a patient with known rheumatic heart disease, infective endocarditis should be strongly suspected. A similar consideration applies to patients with a history of prosthetic vascular surgery who develop periostosis of a limb.

STRUCTURE

The bulbous deformity of the digits is secondary to excessive laying down of collagen fibers and interstitial edema. There is also vascular hyperplasia and thickening of the vessel walls, with a perivascular infiltrate of lymphocytes.

Electron microscopic studies have confirmed the structural vessel damage by demonstrating the presence of Weibel-Palade bodies and the prominence of Golgi complexes.¹⁹ Similar changes have been observed in the bones. At this level, excessive connective tissue elevates the periosteum and new osteoid matrix is deposited beneath.

Histologic studies of the joints have found minimal synovial cell proliferation but a prominent artery wall thickening, with intravascular deposition of electron-dense material.⁷

ETIOLOGY AND PATHOGENESIS

Significant advances in the understanding of HOA have been made in recent decades.¹⁸ Any valid theory attempting to unravel its pathogenesis must explain the peculiarities of the syndrome, namely, how such different illnesses can induce so unique a deformity. It must also explain the reason for the acropachy—why the syndrome begins at the most distal parts of the extremities, evolving in a centripetal fashion. Lastly, it must also account for the pathologic features of edema, localized endothelial hyperplasia, and excessive collagen deposition. Several hypotheses that have been proposed to explain these peculiarities are now supported by experimental data.^{5,20,21}

The majority of illnesses associated with HOA have, in common, alteration of lung function. Such an alteration may be the result of exclusion of this organ from part of the circulation, a phenomenon evident in cyanotic heart diseases but also present to a lesser degree in some cases of cancer of

the lung, intestinal polyposis, or the hepatopulmonary syndrome of liver cirrhosis. In the last condition there is an “intrapulmonary” shunting of blood.²² A particularly strong argument in favor of the key role of lung bypass in the development of HOA is the existence of patients with patent ductus arteriosus complicated by pulmonary hypertension in whom the acropachy is limited to the cyanotic limbs.¹¹ Another form of alteration of lung function results from a direct injury to the lung parenchyma from an assortment of diffuse interstitial illnesses listed in Figure 169.1.

The lack of inflammatory and autoimmune phenomena by conventional serologic testing, in addition to the excessive collagen deposition evident in histologic studies, led to a proposal that a fibroblast growth factor could be at the epicenter of the syndrome.⁴ This factor would normally be present in the central venous circulation and removed in the lung. A platelet-derived growth factor was chosen on the basis of a mathematical model, which suggested that, in normal circumstances, large platelets are fragmented in the pulmonary circulation. It was suggested that, in patients with right-to-left shunts of blood, large thrombocytes that escaped fragmentation in the lung enter the systemic circulation and reach its most distal parts on axial streams, there releasing growth factors and inducing acropachy.²¹

Studies of patients with HOA associated with cyanotic heart diseases have yielded data consistent with these explanations. It has been found that these patients have a bizarre platelet population, characterized by the presence of macrothrombocytes with aberrant volume-distribution curves.²³ Such cyanotic patients also display alterations in another distal part of the circulation—the renal glomeruli. Histologic studies have disclosed glomerular enlargement, with trapped megakaryocyte nuclei inside.²⁴ These features are consistent with the theory of platelet fragmentation in the lung. Furthermore, it has also been demonstrated that these cyanotic patients, and patients with primary HOA, have increased circulating concentrations of von Willebrand factor antigen, an abnormality that reflects activation of the platelet/endothelial cell.²⁵ There are theoretical grounds to suggest that similar mechanisms may be operative in other illnesses associated with acropachy. Endothelial cell activation is a prominent feature of endarteritis and endocarditis of infective origin.

These data suggest that localized activation of the platelet/endothelial cells, with the subsequent release of growth factor(s), has a key role in the development of HOA (Fig. 169.7). Recent evidence suggests that vascular endothelial growth factor (VEGF) may play a key role in the pathogenesis of HOA. VEGF is one of the platelet-derived growth factors released during platelet/endothelial cell activation. It is also produced by malignant tumors as a mechanism of cancer growth. Furthermore, VEGF is a hypoxia-induced agent. These peculiarities may explain how different hypoxic and malignant illnesses may induce VEGF overexpression. Moreover, VEGF induces vascular hyperplasia, new bone formation, and edema, which are precisely HOA histologic abnormalities. These theoretical considerations are now supported by experimental data. Plasma and serum concentrations of VEGF are significantly higher in patients with primary HOA and with HOA associated with lung cancer than in normal control subjects.²⁶ Histologic analysis has shown that VEGF is overexpressed in the stroma of clubbed digits.²⁷

Recent genomic evidence proposes that prostaglandins may play a key role in the pathogenesis of HOA. Study of several families with primary HOA disclosed a mutation in the 15-hydroxyprostaglandin dehydrogenase gene. Affected individuals had chronically elevated prostaglandin E₂ levels.²⁸ It seems unlikely, however, that prostaglandins could play a direct final role in the pathogenesis of HOA. No evidence exists that the skeletal syndrome regresses with the use of nonsteroidal antiinflammatory drugs. These drugs are potent prostaglandin inhibitors. Rather, prostaglandin E₂ may act as facilitator of VEGF action on osteoblasts. It has been shown that the action

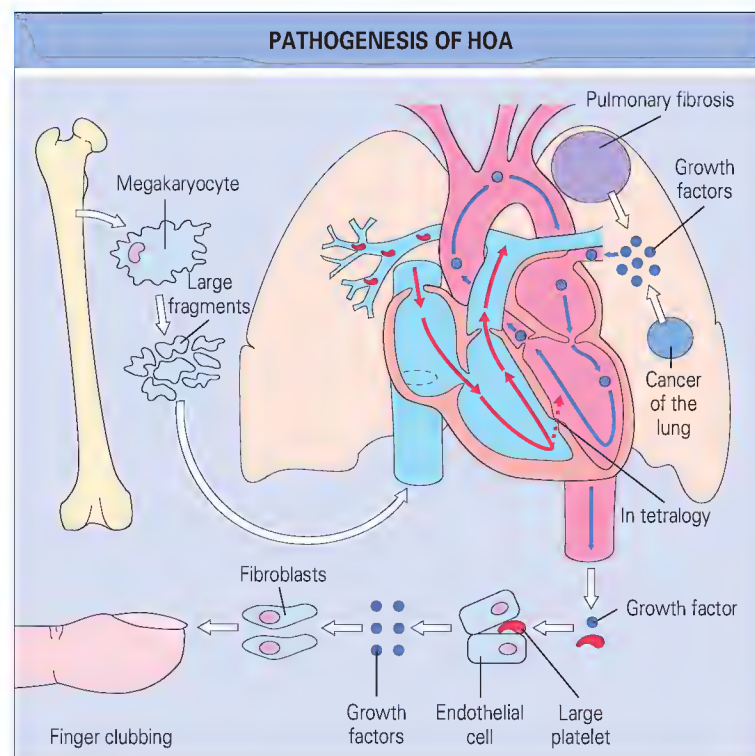


Fig. 169.7 Theoretic explanation for the development of hypertrophic osteoarthropathy (HOA). Megakaryocytes emerge from the bone marrow and, in normal circumstances, are fragmented in the lung microvasculature. In individuals with cyanotic heart disease (in this case, tetralogy of Fallot), the large fragments would not enter the pulmonary circulation; instead, they would directly enter the systemic circulation, reach its most distal sites, release growth factors, activate endothelial cells, and thus induce finger clubbing. In individuals with lung cancer, a growth factor derived from abnormal tissue would enter the systemic circulation and induce clubbing.

of prostaglandins on bones is mediated precisely through VEGF expression.²⁰ It is clear that more research is needed to elucidate the pathogenesis of HOA.

MANAGEMENT

Apart from its unsightliness, clubbing is usually asymptomatic and does not require treatment. For patients with painful osteoarthropathy, nonsteroidal antiinflammatory drugs are effective in alleviating pain in most cases. There are isolated case reports from different parts of the world stating that intravenous infusions of bisphosphonates are effective in HOA patients with refractory bone pain.²⁹ Bisphosphonates are not only osteoclastic bone resorption antagonists but also VEGF inhibitors.

Removal of a lung tumor, correction of a heart malformation, or successful treatment of infective endocarditis is followed by a dramatic regression of all features of the syndrome.

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Miscellaneous arthropathies

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- Localized arthritis can be caused by metastatic disease, cartilaginous tumors, foreign body synovitis, synovial osteochondromatosis, pigmented villonodular synovitis, synovial sarcomas, and palindromic rheumatism.
- Polyarthritis can be caused by carcinomatous polyarthritis, bypass arthritis, hypertrophic osteoarthropathy, intermittent hydrarthrosis, multicentric reticulohistiocytosis, SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), and Whipple disease.
- Systemic syndromes can be associated with angioimmunoblastic T-cell lymphoma, Castleman disease, and leukemia.
- Musculoskeletal complications of chronic kidney disease are frequently faced by clinicians caring for these patients; apatite (basic calcium phosphate) disease is the most common.
- Nephrogenic systemic fibrosis is a debilitating fibrosing condition affecting patients with chronic kidney disease after exposure to gadolinium-containing contrast agents during magnetic resonance imaging.
- Medications used to manage musculoskeletal conditions, such as colchicine and allopurinol, require significant scrutiny and dose adjustment in the context of dialysis and renal transplantation.

CANCER-RELATED MUSCULOSKELETAL SYNDROMES

When the relationship between cancer and musculoskeletal disease is reviewed, it is helpful to consider three major aspects: (1) the association of several rheumatologic disorders with an increased risk of malignancy; (2) musculoskeletal manifestations of cancer, including metastatic disease; and (3) malignancies that may present with clinical features mimicking those of a rheumatologic disease. Each of these aspects is considered separately in what follows.

Associations of rheumatologic diseases with cancer

An association between malignancy and autoimmune disease has been demonstrated for several rheumatologic disorders and has been hypothesized for others. The strongest association is that between adult-onset polymyositis or adult-onset dermatomyositis and malignancy. A full description of the details of this association is beyond the scope of this chapter; however, among patients with either polymyositis or dermatomyositis, the incidence of malignancy is increased, particularly the incidence of solid tumors. Polymyositis and dermatomyositis are associated with a significantly increased risk of developing lung cancer among men; in men, dermatomyositis is associated with a significantly increased risk of developing pancreatic carcinoma, and in women it is an associated risk for colon, breast, and ovarian carcinomas.¹ In addition, cases have been reported in which the inflammatory myopathy resolved after curative resection of the malignancy. Thus adults with polymyositis or dermatomyositis should be evaluated for evidence of an underlying malignancy; however, beyond age-appropriate screening tests, the extent of such an evaluation has not been clarified.

Another definite association is between rheumatoid arthritis (RA) or Sjögren syndrome (primary and secondary) and non-Hodgkin lymphoma.

Among patients with RA, the incidence of non-Hodgkin lymphoma (primarily B-cell lymphomas) is twofold to threefold that in the general population.² In patients with Sjögren syndrome, lymphocyte proliferation becomes more oligoclonal over time, and the incidence of non-Hodgkin lymphoma is fourfold to sixfold that of the general population. These associations are confounded by the possible increased risk of lymphoma conferred by some of the drugs used to treat these diseases, such as methotrexate, azathioprine, cyclosporine, cyclophosphamide, and tumor necrosis factor (TNF) antagonists. However, insufficient data exist to establish a causal relationship between treatments for RA and the development of lymphoma.²

Small observational studies suggest an association between systemic lupus erythematosus and malignancy, with an increased risk of developing breast, lung, and cervical carcinomas and lymphoid malignancies such as non-Hodgkin lymphoma that is unrelated to the use of cytotoxic agents. Although a retrospective study suggested an increased risk of lung carcinoma among patients with scleroderma and interstitial pulmonary fibrosis, this observation was not confirmed in a population-based cohort study.

Vasculitides, especially those associated with antineutrophil cytoplasmic antibodies (ANCA), may develop in association with myelodysplasia, hematologic and lymphoid malignancies, and solid tumors.³ Cutaneous leukocytoclastic vasculitis is associated more with the presence of hematologic malignancies than with solid tumors. Some patients with hairy cell leukemia, a rare B-cell lymphoproliferative disorder that usually presents as massive splenomegaly and pancytopenia, develop a cutaneous small-vessel vasculitis. Antiphospholipid antibodies, with or without vasculitis, may be present in patients with malignancy.

Other conditions seen by the rheumatologist may also be associated with malignancy. Both relapsing polychondritis and Sweet syndrome are associated with myeloproliferative disorders, especially myelodysplasia. Patients with multicentric reticulohistiocytosis may develop solid tumors. Patients with Paget disease of bone have an increased risk of developing osteogenic sarcomas, primarily in involved bones. Additionally, gouty arthritis can complicate chronic myeloproliferative disorders, and the aggressive treatment of leukemia and other malignancies can cause tumor lysis syndrome.

Musculoskeletal manifestations of cancer

Synovial sarcoma

Synovial sarcoma is an uncommon tumor that is misnamed because it arises from tissue adjacent to the joint and rarely, if ever, from the synovium.⁴ Although this tumor occurs most commonly between the third and fifth decades of life, it also may develop in children and adolescents. It generally presents as a mildly to moderately painful mass on a limb, more often on the leg, but it can be painless. These tumors adhere to adjacent structures, and symptoms are a consequence of local invasion. The average time from onset to diagnosis ranges from months to years, and these lesions are often misdiagnosed as benign growths before histologic analysis demonstrates them to be synovial sarcomas.

Radiographs may reveal a well-circumscribed soft tissue mass that frequently contains calcifications; however, in about half of synovial sarcomas, plain radiographs yield normal findings. Occasionally, periosteal reaction and even bone invasion is evident. Bone scans and computed tomography demonstrate the extent of the lesion and associated bony reaction. Angiograms reveal typical neovascularization and tumor blush. However, magnetic resonance imaging (MRI) with gadolinium-based contrast enhancement is the imaging procedure of choice because it shows the full extent of the lesion and the degree to which adjacent soft tissue structures, such as vessels and nerves, are involved. Additionally, MRI can help to localize the optimal

Fig. 170.1 (a) Radiograph of the digit of a patient with metastatic lung cancer shows destructive changes. (b) Inflammatory appearance of the same finger.



site for fine-needle aspiration biopsy to make a cytologic diagnosis. Surgical excision should include the tumor and its margin, if possible.

Grossly, the tumor is a circumscribed mass that adheres to the underlying tissue and to adjacent tissue structures. It is usually solid, but occasionally cystic changes may be noted. Because histologic evaluation of synovial sarcomas is difficult, expertise should be sought, and diagnoses are not infrequently changed on re-review of the tissue. Other tumors that may be confused with synovial sarcoma include epithelioid sarcomas, clear cell sarcomas, and fibrosarcoma.

The typical histologic pattern of synovial sarcomas is biphasic with two distinct cell types: fibrosarcoma-like spindle-shaped cells and epithelial cells. Spindle cells usually are the predominant cell type and have a characteristic swirling appearance with large nuclei and scant cytoplasm. These swirls appear to make clefts, at the border of which epithelial cells are often arranged. The more frequently mitotic figures are seen, the more de-differentiated the tumor, with a greater likelihood of vascular invasion and poorer prognosis. The epithelial cell component is occasionally sparse but can be visualized by silver stains that identify reticulin within the cytoplasm. The spindle cells have keratin, which can be identified by immunohistochemical analysis. Occasionally, only a single cell type (most often spindle cells) is seen, which creates difficulties in diagnosis.

Overall, the prognosis of synovial sarcomas is very poor. At the time of presentation, the tumor frequently has metastasized—often widely by hematogenous spread, most often to the lungs, and less frequently by local lymphatic spread. The 5-year overall survival is about 70%, with the prognosis being better for younger patients and for those with localized disease and tumors less than 5 cm in diameter.⁵

Treatment consists primarily of surgical resection, which usually achieves good results for small localized tumors with favorable histologic features. Radical resection, with or without amputation, is performed for larger, less well-differentiated tumors. Unfortunately, distant metastases are often discovered subsequently. Radiation therapy (40 to 75 Gy) is often administered after surgical resection, resulting in fewer relapses and better survival than among those treated with surgery alone. Combination chemotherapy with ifosfamide and doxorubicin (with or without vincristine) may be given before surgery and irradiation to improve survival and lengthen the disease-free interval.

Cartilaginous tumors

Cartilaginous tumors are discussed in Chapter 212.

Metastatic disease

Metastasis of lung or breast carcinoma and, infrequently, of kidney or prostate cancer to the proximal or distal end of long bones can present as joint

or periarticular swelling (Fig. 170.1). This typically occurs around the knee but may occur elsewhere, even in the small joints of the hands. Very infrequently, multiple metastatic lesions result from disseminated carcinoma. Cancer metastatic to the synovium has been reported infrequently.

Carcinomatous polyarthritis

Solid tumors, particularly of the breast and lung, are occasionally accompanied by an asymmetric inflammatory polyarthritis involving large and small joints. This nonerosive seronegative arthritis, which can present as RS3PE syndrome (remitting seronegative symmetrical synovitis with pitting edema) when associated with edema, may remit upon treatment of the underlying malignancy; otherwise, it can be treated with nonsteroidal antiinflammatory drugs (NSAIDs) or corticosteroids.⁶ Very infrequently, it can be an early clue to the presence of an occult malignancy.

Patients with pancreatitis, and occasionally those with pancreatic carcinoma,⁷ may develop a large joint arthritis, often involving the ankles, accompanied by intensely inflamed subcutaneous nodules that resemble erythema nodosum. These nodules, which are often several centimeters in diameter, may ulcerate and drain. Biopsy of the nodule reveals septal panniculitis similar to that seen in erythema nodosum but accompanied by fat necrosis that presumably results from release of pancreatic lipase. Synovial or bursal fluid obtained from these patients can appear milky because of the large numbers of fat droplets that result from necrosis of the fatty synovium.

Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy is discussed in Chapter 169.

Palmar fasciitis syndrome

Two publications in 1982^{8,9} reported the novel association of palmar fasciitis (Fig. 170.2) and ovarian carcinoma. These reports and subsequent case series described a syndrome that occurs in patients with a variety of neoplastic diseases: primarily ovarian but also breast, lung, pancreatic, and gastric carcinomas; Hodgkin disease; and chronic myelogenous leukemia.¹⁰ This syndrome may be difficult to distinguish from the complex regional pain syndrome (CRPS), but it generally spares the shoulders and, unlike CRPS, may be associated with synovitis. Biopsy of the palmar fascia reveals nodules or whorls of fibroblasts surrounded by dense connective tissue with fibrous septa. Some have suggested an autoimmune etiology, based on the presence of immunoglobulin deposits in biopsy specimens. However, because of its resemblance to CRPS, others consider it to be a variant of CRPS. Palmar fasciitis may improve with chemotherapy or surgery to treat the underlying malignancy, but many patients have widespread metastatic disease at the time of initial presentation.

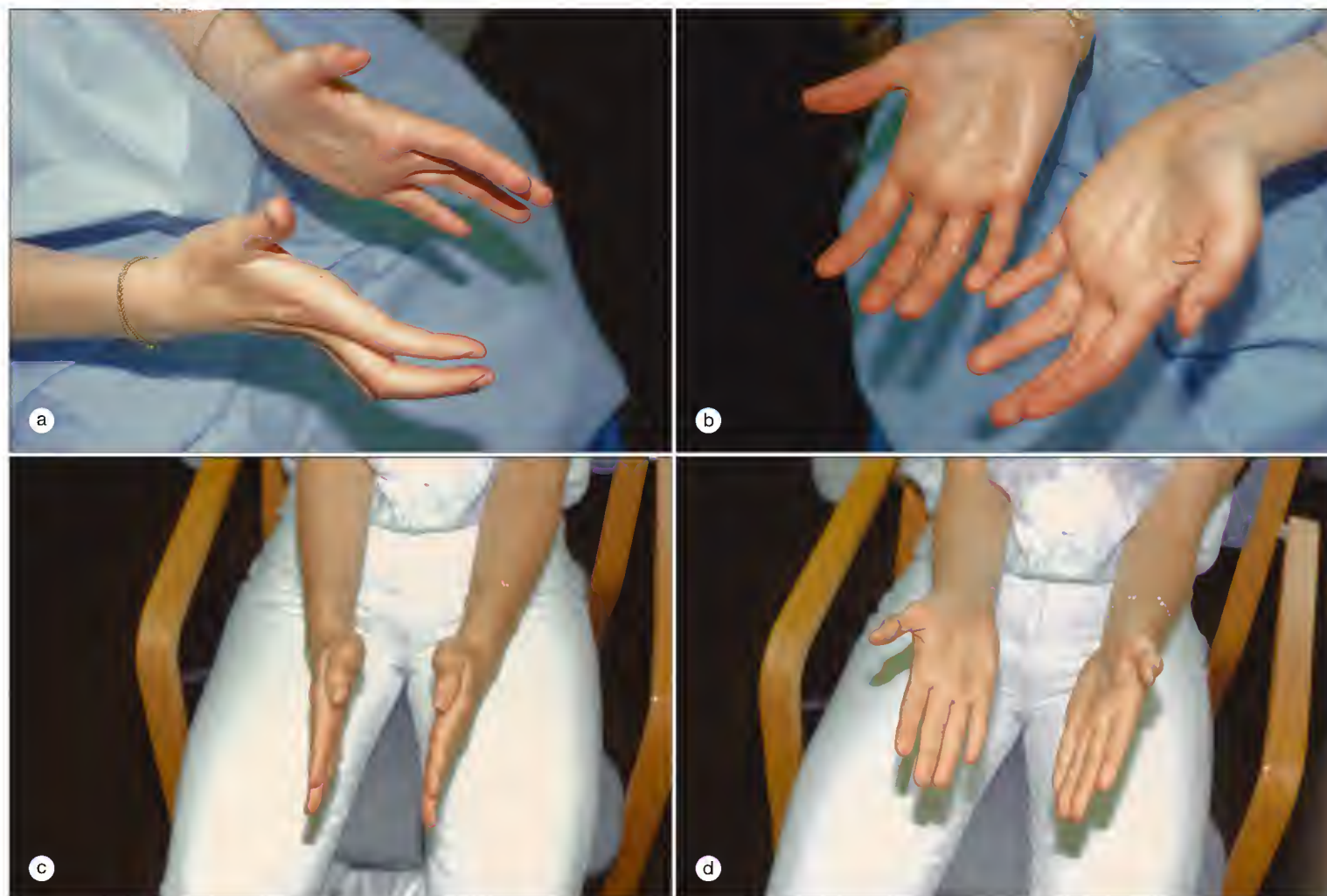


Fig. 170.2 Palmar fasciitis. (a and b) Two views of the hands of a patient with palmar fasciitis secondary to a nonmalignant ovarian cyst. (c and d) Two views of the hands of the same patient after removal of the ovarian cyst demonstrating resolution of the findings.

Neoplastic conditions that mimic rheumatologic disease

Acute lymphoblastic leukemia

Childhood acute lymphoblastic leukemia (ALL) is the malignancy that is most difficult to distinguish from a rheumatologic disease and can be misdiagnosed as systemic-onset juvenile inflammatory arthritis.¹¹ Bone pain, often in a distribution that suggests juvenile RA, can be difficult to distinguish from joint pain. Fever, constitutional symptoms, rash, and anemia may occur both in childhood ALL and in systemic-onset juvenile inflammatory arthritis. Clinical features that prompt consideration of ALL include severe night pain, tenderness to palpation over long bones, lack of improvement with NSAID therapy, and the presence of leukopenia rather than leukocytosis. On plain radiographs, radiolucent lines near the epiphyses suggest the diagnosis of ALL. If there is any indication of ALL, examination of bone marrow is mandatory. In adults, both leukemia and lymphoma can mimic adult-onset Still disease; the presence of bone pain and lytic lesions should prompt consideration of a hematologic malignancy.

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma (AITL), formerly called *angioimmunoblastic lymphadenopathy with dysproteinemia*, is a lymphoproliferative disorder that can be mistaken for an autoimmune disease because of its presentation with generalized lymphadenopathy, hepatosplenomegaly, fever, a maculopapular or urticarial rash, and constitutional symptoms. Occasionally, patients may develop a seronegative symmetric peripheral polyarthritis that usually does not respond to NSAIDs.¹² Polyclonal hypergammaglobulinemia, Coombs-positive hemolytic anemia, and other autoantibodies may be present. The diagnosis of AITL is based on its characteristic histologic appearance in which the lymph node architecture is partially to completely effaced by an infiltrate of lymphocytes, immunoblasts, and plasma cells that occupy predominantly the paracortical areas. Neoplastic T cells display clonal T-cell receptor gene rearrangements and express CXCL13, a

chemokine involved in migration of B cells into germinal centers, and CD10, a cell surface metalloproteinase. Cytogenetic studies reveal abnormalities of trisomy 3, trisomy 5, or gain of an X chromosome in approximately 70% of patients with AITL. Marked proliferation of small vessels, often with arborization, occurs within lymph nodes in AITL. The prognosis of AITL is poor compared with that of other forms of non-Hodgkin lymphoma, with a 5-year overall survival of 33% and a 5-year treatment failure-free survival of only 18%, even with combination chemotherapy.¹³

Multiple myeloma

Multiple myeloma may present as a variety of musculoskeletal problems, including carpal tunnel syndrome, destructive arthritis, or scleroderma-like skin changes caused by AL amyloidosis; bone pain; and pathologic fractures, primarily in elderly individuals. Other features of myeloma that suggest rheumatologic disease include elevation of the erythrocyte sedimentation rate (ESR), cryoglobulinemia with crystalline arthropathy, and polyneuropathy. Demonstration of lytic lesions on skeletal plain radiographs and of an increased number of plasma cells on bone marrow examination usually is sufficient to make the diagnosis of multiple myeloma.

Paraneoplastic syndromes

When a patient with an underlying malignancy has polyarthralgia and constitutional symptoms in the setting of circulating antinuclear antibodies or rheumatoid factor, the presentation occasionally can be confused with that of a systemic rheumatologic disease. Generalized aching, constitutional symptoms, and an elevated ESR, mimicking polymyalgia rheumatica, can occur in a variety of cancers; however, the subacute onset of these paraneoplastic symptoms helps to differentiate between these conditions. Infrequently, neoplasms that present as an asymmetric neuromyopathy may mimic dermatomyositis or polymyositis. However, these conditions usually can be distinguished by electromyography and muscle biopsy. Cavitory pulmonary nodules in patients with lung cancer can be mistaken for those of ANCA-associated granulomatous vasculitis.

Fig. 170.3 Multicentric reticulohistiocytosis. (a) Finger with glistening pearly-white nodules (string of pearls sign). (b) Radiographic appearance of digits showing destructive arthropathy.



OTHER SERIOUS SYSTEMIC SYNDROMES WITH RHEUMATOLOGIC FEATURES

Multicentric reticulohistiocytosis

Multicentric reticulohistiocytosis (Fig. 170.3) is a rare disorder characterized by the insidious onset of polyarthritis, which often evolves into a severe erosive deforming arthritis, and distinctive small, firm cutaneous papules and nodules on the skin. Skin lesions are pleomorphic, may be pruritic, and often occur around the joints. The most typical lesions are arranged in a string of pearls or coral bead pattern at the base of the nails. Joint involvement is symmetric and similar in distribution to that in RA except that distal interphalangeal joints are frequently involved. If left untreated, this arthritis is very destructive. Multicentric reticulohistiocytosis occurs predominantly, but not exclusively, in adults and three times as often in women as in men.

There are no characteristic laboratory findings, although most patients have a mild anemia, 30% to 60% have hyperlipidemia, and up to 50% display reactivity to purified protein derivative. The diagnosis is confirmed by biopsy of skin lesions or synovium, which reveals lipid-laden histiocytes and multinucleated giant cells that express the osteoclast markers tartrate-resistant acid phosphatase and cathepsin K. Interestingly, some patients also have a coexisting autoimmune disease or malignancy. The mechanism of disease is unknown, but increased synovial macrophage and endothelial cell staining for TNF- α , interleukin-1 β (IL-1 β), IL-6, and IL-12 has been described.¹⁴

Although no treatment is consistently effective for multicentric reticulohistiocytosis, methotrexate, cyclophosphamide, alendronate, and zoledronate have been used with success. TNF antagonist therapy has resulted in improvement in both skin and joint involvement.¹⁵

Castleman disease

Castleman disease, also known as *giant lymph node hyperplasia*, was first described in 1956 in 13 patients with mediastinal lymphadenopathy characterized by germinal-center formation and marked capillary proliferation. Pathologically it can be divided into two groups: a hyaline vascular type (90%) and a plasma cell type (10%). Patients frequently are asymptomatic, but some patients with the plasma cell variant may have diffuse extrathoracic lymphadenopathy with a variety of systemic symptoms. This multicentric form of Castleman disease is often accompanied by anemia, an elevated ESR, and polyclonal hypergammaglobulinemia. When autoimmune serologic features are present, it may mimic a systemic autoimmune disease such as systemic lupus erythematosus or Sjögren syndrome. About half of patients with multicentric Castleman disease die, most commonly of sepsis or malignant transformation of the lymph node hyperplasia into lymphoma; median survival is 26 months. When multicentric Castleman disease occurs

in the setting of human immunodeficiency virus (HIV) infection, usually accompanied by human herpesvirus 8 (HHV-8) coinfection, median survival is reduced to 14 months.

B cells in the germinal centers of affected lymph nodes in patients with the plasma cell variant of multicentric Castleman disease produce increased amounts of IL-6, and these patients have elevated serum IL-6 levels. Treatment of patients with multicentric Castleman disease with rituximab, which depletes B cells, improves clinical outcome and overall survival both among those coinfecting with HIV and HHV-8 and among those not infected with either virus. Administration of tocilizumab, a monoclonal antibody to the IL-6 receptor, effectively reverses the signs and symptoms of multicentric Castleman disease.¹⁶

POEMS syndrome

Patients with the rare POEMS syndrome present with a slowly progressive demyelinating polyneuropathy, organomegaly, a variety of endocrinologic features including diabetes and hypogonadism, monoclonal gammopathy, skin changes, and sclerotic bone lesions.¹⁷ Some patients with clinical features of the POEMS syndrome may have histologic features of Castleman disease. Proinflammatory cytokines such as IL-1 β , TNF- α , and IL-6 and growth factors such as vascular endothelial growth factor mediate this syndrome, which may mimic systemic rheumatologic disease. Although controlled trials of therapy have not been conducted, successful treatments have included irradiation of osteosclerotic lesions, corticosteroids, alkylating agents such as melphalan, thalidomide, lenalidomide, bortezomib, and high-dose chemotherapy with autologous peripheral blood stem cell transplantation.¹⁸

Whipple disease

In 1907, Dr. George Hoyt Whipple, Nobel laureate in medicine and physiology, described a 36-year-old physician who had been working as a medical missionary in Constantinople and developed cough, shortness of breath, and periodic arthritis. The patient experienced episodes of joint inflammation that lasted for 6 to 8 hours. Many different joints were affected, and he gradually lost weight and developed chronic diarrhea with fat malabsorption. Later, he developed dark skin and abdominal swelling, with probable ascites. Joint radiographs revealed only soft tissue swelling. In spite of being force-fed a diet that included four raw eggs a day, the patient lost weight and died. On autopsy a peculiar "intestinal lipodystrophy" was observed. These findings characterize a rare disease that was named *Whipple disease*.

In 1961, the cause of Whipple disease was identified by electron and light microscopy as a periodic acid-Schiff (PAS)-staining organism; this fastidious bacterium was subsequently named *Tropheryma whippeli* and grown in culture. *T. whippeli* has been detected in synovial fluid and tissue

of affected individuals by polymerase chain reaction (PCR) testing,¹⁹ even in those in which characteristic PAS staining of tissue is absent.

Whipple disease is uncommon, with an annual incidence of less than 1 per 1,000,000 population, and occurs primarily in middle-aged white males.²⁰ Individuals who work on farms, are receiving treatment with biologic agents, or have immunodeficiency syndromes or chronic kidney disease may be more susceptible. A migratory arthritis affecting predominantly large joints occurs in about 75% of patients with Whipple disease and often is the initial clinical manifestation. Some patients may develop spondyloarthritis and are found to be positive for HLA-B27. Other clinical features include uveitis, cardiac involvement, and a pathognomonic central nervous system manifestation known as *oculofacioskeletal* (or *oculomastatory*) *myorhythmia*. Late manifestations include dementia and cerebellar dysfunction. Most patients with Whipple disease demonstrate evidence of an acute-phase response, with anemia, thrombocytosis, and elevation of ESR and C-reactive protein level.

The diagnosis is confirmed by endoscopic biopsy of thickened duodenal mucosal folds demonstrating PAS-positive inclusions within macrophages of the lamina propria.²⁰ *T. whipplei* can be detected by PCR testing of body fluids, including saliva, or tissue if the diagnosis is equivocal. Celiac disease and tuberculosis, which enter into the differential diagnosis of Whipple disease, should be excluded.

Most patients do well with antibiotic therapy, although the time to response is variable and the optimal antibiotic regimen and treatment duration are unknown. Recommended treatment is oral trimethoprim/sulfamethoxazole or sulfamethoxazole given for 12 months, often preceded by 2 weeks of parenteral meropenem or ceftriaxone.²¹ Alternatively, hydroxychloroquine, which reduces the acidity of the intracellular vacuole in which the bacterium is located, can be added to doxycycline to increase the bactericidal activity of the antibiotic against *T. whipplei*.

SYNDROMES WITH PREDOMINANTLY MUSCULOSKELETAL INVOLVEMENT

Bypass arthritis

Patients who underwent jejunoileal (but not gastric) bypass surgery for weight reduction frequently experienced an intermittent polyarthritis with constitutional symptoms.²² This procedure now is rarely performed because of these complications. Occasionally, papular skin lesions with leukocytoclastic vasculitis and immune complexes evident on skin biopsy would accompany attacks of joint inflammation. These were thought to result from blood-borne dissemination of bacterial debris or immune complexes from the blind loop created by the surgery. The arthritis and skin lesions both were exquisitely painful, similar to those of the gonococcal arthritis/dermatitis syndrome. Patients also could develop other symptoms of immune complex disease, such as polyserositis and mild glomerulonephritis. Synovial fluid typically was inflammatory, but no specific abnormalities were evident on laboratory testing. Antibiotic treatment of blind loop syndrome often led to improvement of symptoms. Notwithstanding, some patients needed to have the jejunoileal bypass reversed because of persistent articular and cutaneous inflammation.

Foreign body synovitis

Foreign body synovitis is an unusual form of arthropathy that has been described primarily as monoarticular arthritis occurring after a penetrating injury from a foreign object.²³ These foreign objects can be categorized as either organic material (usually plant thorns, sea urchin spines, and seashell fragments) or inorganic material (natural or manufactured) (Box 170.1). The typical patient who develops synovitis from an organic foreign body is a young man engaged in an endeavor such as an agricultural or marine activity that puts him at risk of penetrating injury. Involved joints include those that are most susceptible to penetrating injuries, predominantly the hands and knees. Fragments of inorganic material resulting from wear of prosthetic joints (predominantly polyethylene, metallic particles, and acrylic cement) may cause synovitis around a prosthetic joint.²⁴

Foreign body synovitis generally presents as acute or subacute monoarticular arthritis, but inflammation may be episodic. Synovial fluid is inflammatory, typically revealing between 5000 and 50,000 white blood cells/mm³ and a predominance of polymorphonuclear neutrophils. Cultures are usually sterile, although, on rare occasions, the foreign material may introduce infection and cause a coexisting septic arthritis. Radiographs are sometimes helpful in diagnosing foreign body synovitis. Radiopaque foreign material can be identified by plain radiography; however, the vast majority of

BOX 170.1 REPORTED ASSOCIATIONS OF FOREIGN BODY SYNOVITIS

Organic	Inorganic
Plant	Natural
Date palm	Stone
Sentinel palm	Gravel
Blackthorn	
Rose	Synthetic
Cactus	Glass
Citrus	Rubber
Mesquite	Fiberglass
Toxic	Plastic
Wood splints	
Animal	Iatrogenic
Sea urchin spine	Starch
Fish bone	Talc
Seashell	Methylmethacrylate
Bee stinger	Silicone
	Teflon
	Metal

vegetable material is radiolucent. Standard radiographs usually show only soft tissue swelling, but erosive changes have been observed.

The inflammatory reaction to a sterile foreign body typically produces a nonspecific granulomatous synovitis that can be demonstrated on synovial biopsy, performed by either a closed or open technique. This histologic appearance can be mistaken for that of a variety of other granulomatous diseases, such as sarcoidosis. Thus, when a foreign body is suspected as the cause of synovitis, the pathologic specimen should be examined using polarizing microscopy, which often reveals a birefringent structure suggestive of plant material. Appropriate treatment requires excision of the foreign body and involved synovium.

Silicone synovitis

Silicone-containing joint prostheses may fracture and generate wear particles, which are ingested by macrophages and generate an inflammatory response. This reaction can lead to destructive synovitis, particularly in the wrist; consequently, most surgeons have abandoned silicone-containing carpal implants. However, silicone-containing implants are still used to replace the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints, in which silicone-induced synovitis occurs much less frequently and, when present, is more limited in its extent. Treatment of this inflammatory condition is directed toward control of symptoms, which may require removal of the prosthesis and synovectomy.²⁵

Intermittent hydrarthrosis

Intermittent hydrarthrosis is an uncommon syndrome affecting women that is characterized by symmetric joint effusions, predominantly involving the knees, and that does not result in joint destruction. These effusions occur periodically, often monthly at or around the menses. Patients with intermittent hydrarthrosis experience mild to moderate joint pain and stiffness when the disease is active. Aspirated synovial fluid is either bland or reflects mild inflammation. Low-dose colchicine has prevented recurrent attacks of intermittent hydrarthrosis.²⁶ Heterozygous disease-associated mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein, have been identified in patients with intermittent hydrarthrosis but without other features of familial Mediterranean fever.²⁷ This suggests that intermittent hydrarthrosis might be a mild, localized inflammatory disease that is part of the spectrum of periodic fever syndromes.

Palindromic rheumatism

A palindrome is a word or phrase that is arranged symmetrically about an axis. The most famous palindrome is the sentence attributed to Napoleon, "Able was I ere I saw Elba." Palindromic rheumatism is an intermittent inflammatory condition that affects one or, at most, a few joints in an unpredictable pattern that lasts for hours to several days. Affected joints are swollen, warm, and tender; may exhibit overlying erythema; and yield inflammatory joint fluid when aspirated.²⁸ Palindromic rheumatism may affect the same or different joints in repeated attacks. Levels of acute-phase reactants may be elevated during attacks but not in the intercurrent period.

Between attacks, affected joints are normal and joint damage usually does not develop.

Attacks of palindromic rheumatism may persist or resolve spontaneously, but approximately one third of patients (especially those with circulating rheumatoid factor or anti-citrullinated protein antibodies) develop conventional RA. Patients may be treated with NSAIDs or glucocorticoids during attacks, but these medications do not shorten the duration of joint inflammation. Hydroxychloroquine and other disease-modifying antirheumatic drugs have been used to prevent attacks but have not been evaluated systematically.

Crystal arthropathies and other intermittent disorders, such as familial Mediterranean fever, should be considered in the differential diagnosis. As in several patients with intermittent hydrarthrosis, disease-associated mutations in the *MEFV* gene were identified in 8 (12.3%) of 65 patients with palindromic rheumatism.²⁹

Fibroblastic rheumatism

Fibroblastic rheumatism is a rare syndrome characterized by multiple firm skin nodules and a symmetric polyarthritis with a distribution similar to that of RA, but also involving the distal interphalangeal joints, that often results in sclerodactyly and joint contractures.³⁰ The arthritis has been described as inflammatory and may be erosive, even mimicking that of multicentric reticulohistiocytosis. Biopsy specimens from skin nodules

demonstrate increased dermal fibroblasts and myofibroblasts and thickened collagen fibers, with loss of elastic fibers and no mucin deposition. Some have described lymphocytic infiltrates in the early lesions. Occasional synovial biopsy specimens have shown similar findings. Fibroblastic rheumatism may remit spontaneously, but subsequent exacerbations often occur. Various antiinflammatory and antirheumatic drugs have been used, including corticosteroids, methotrexate, and TNF antagonists, but there is no known effective therapy. The differential diagnosis includes scleroderma, palmar fasciitis with contractures that occurs in the setting of various carcinomas, and pachydermodactyly, which is benign localized fibrosis around the proximal interphalangeal finger joints.

Pigmented villonodular synovitis

Pigmented villonodular synovitis (PVNS) (Fig. 170.4) is a benign proliferation of synovial tissue that usually presents as an indolent, progressive monoarticular arthritis or tenosynovitis. Clinically it is divided into three forms: (1) an isolated tenosynovitis that often involves the hand, also known as *tenosynovial giant cell tumor*; (2) a diffuse form commonly found in the knee; and (3) a localized form that moves freely in the joint.

Pigmented villonodular tenosynovitis typically presents as an enlarging mass adherent to a tendon; it usually occurs in adults and is more common in women than in men. Its appearance is similar to that of a ganglion, and it never becomes malignant. Tendon and adjacent bone can be damaged if

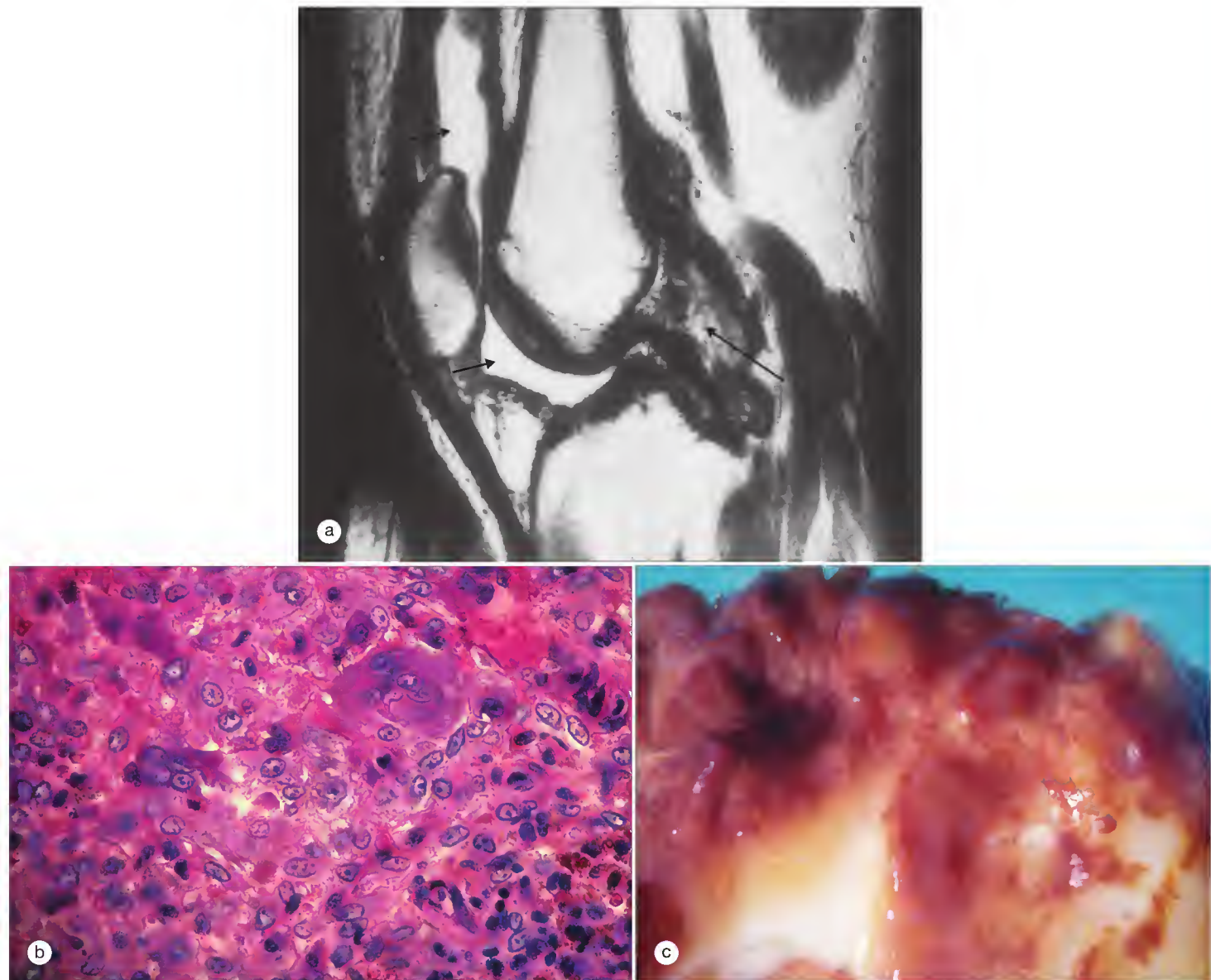


Fig. 170.4 Pigmented villonodular synovitis. (a) Magnetic resonance image of the knee. Short wide arrows indicate joint effusion in the suprapatellar pouch, and there is a lobulated mass with a typical dark image on T2-weighted scans in the popliteal fossa just below the long arrow. (b) Photomicrograph showing clusters of cells with large pale nuclei and foamy cytoplasm, giant cells, and hemosiderin in the right lower corner. (c) Gross appearance of synovium with pigmented nodules.

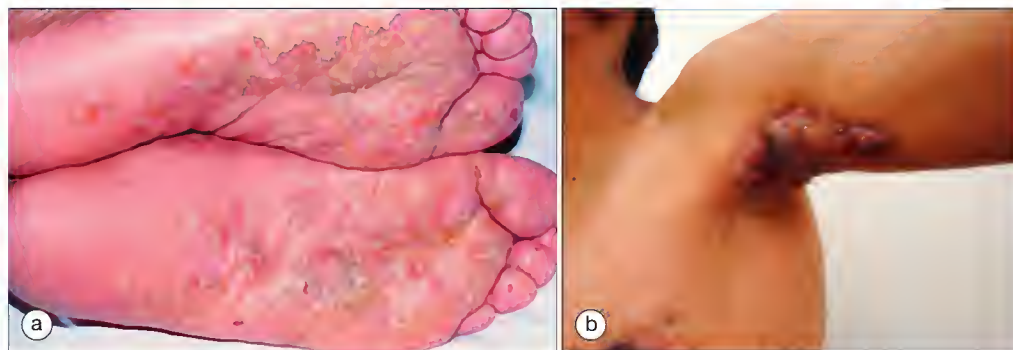


Fig. 170.5 SAPHO syndrome. (a) Palmoplantar pustulosis. (b) Hidradenitis suppurativa. (From Carneiro S, Sampaio-Barros PD. SAPHO syndrome. *Rheum Dis Clin North Am* 2013;39:401-18.)

the disease remains untreated. Treatment consists of complete surgical removal of the pathologic synovium. Recurrences can occur, especially if excision has been incomplete.

The diffuse form of PVNS presents as slowly progressive, painful swelling of a single joint.³¹ The knee is the joint most commonly affected, with the hip and ankle being the next most often involved. Rarely, it can occur in other appendicular joints or in the spine. This form of PVNS damages joints with a tight capsule, such as the hip or zygapophyseal (facet) joints of the spine. It often generates the characteristic radiographic appearance of scalloped erosions, usually with a sclerotic margin at the site of synovial insertion or reflection, which is thought to result from pressure on or direct invasion of bone by the synovial mass. Associated joint effusions can be brown or hemorrhagic.

Localized PVNS is the least frequently occurring form. It projects as a pedunculated nodule into the synovial cavity, often of the knee, where it can cause signs and symptoms of a loose body. Patients with the localized form of PVNS typically experience mild pain and locking of the affected joint.

PVNS is not visible on plain radiographs.³¹ However, on MRI it is seen as a dark soft tissue mass with intermediate to low signal intensity on T1-weighted images and low signal intensity on T2-weighted images because of hemosiderin deposition.

The cause of PVNS is unknown, but the histologic appearance of all three types is identical and all are thought to share a common pathogenesis. Microscopically, there is a proliferation of sheets of pale-staining synovial cells, foam cells that contain lipid and hemosiderin, and multinucleated giant cells, which results in a hypertrophic red-brown and occasionally yellow-hued tissue.³² Hemophilia, hemosiderosis from recurrent hemarthroses, and hemochromatosis can also produce iron-pigmented tissue. Thus not all brown-stained proliferative synovitis is PVNS. PVNS might be thought of as analogous to pannus in RA. Some investigators propose that hemorrhage into the joint plays a role in the pathogenesis of the lesion. However, attempts to reproduce the lesion by injecting blood into the joint cavities of animals have resulted in an inflammatory synovitis that most closely resembles the arthropathy that accompanies hemophilia rather than PVNS.

Several patients with PVNS have responded to either systemic or intra-articular administration of a TNF antagonist or oral administration of imatinib mesylate.³³ However, PVNS is usually treated by thorough surgical excision. This usually cures pigmented villonodular tenosynovitis and the localized pedunculated form of PVNS, but surgery is substantially less effective and less satisfactory in treating the diffuse form. Arthroscopic resection alone is inadequate therapy for diffuse PVNS. It is quite difficult to achieve an adequate resection of diffuse PVNS in the knee or hip; thus recurrences are frequent. In diffuse disease in which bony destruction has been caused by the lesion, synovectomy combined with total joint arthroplasty remains the most successful approach.³⁴

It is particularly difficult to perform a curative resection of PVNS in the vertebral column. Radiotherapy long has been attempted to treat nonresectable and recurrent disease. Both yttrium-90 silicate and dysprosium-65 ferric hydroxide macroaggregate have been used with some success, often in combination with extensive surgical débridement. External irradiation is not commonly used to treat PVNS.

SAPHO syndrome

SAPHO is an acronym designating a syndrome that contains some or all of the following clinical features: synovitis, acne, pustulosis, hyperostosis, and osteitis. This uncommon disorder usually affects young adults but has been observed in patients of all ages, including children and the elderly, and has

been known by a variety of names, including *recurrent multifocal osteomyelitis* and *acne-induced arthritis*. The term SAPHO was coined in 1987 and refers to a heterogeneous disorder, the hallmarks of which include osteosclerotic bone lesions with sterile osteomyelitis and a variety of skin lesions. Approximately half of patients with SAPHO syndrome have palmoplantar pustulosis; the others may have a variety of skin manifestations that include psoriasis, hidradenitis suppurativa, severe acne, and, infrequently, Sweet syndrome (Fig. 170.5).

The bone lesion typical of SAPHO syndrome is osteosclerotic hyperostosis, which often involves the acromioclavicular and sternoclavicular joints. Other sites where these bone lesions typically develop include the anterior chest wall, sternum, clavicle, symphysis pubis, thoracic and cervical spine, and mandible. These sclerotic bone lesions demonstrate increased radionuclide uptake on technetium-99m bone scanning; cultures of bone biopsy specimens usually are sterile but occasionally grow *Propionibacterium acnes*. A sterile, but erosive, inflammatory synovitis can develop in joints adjacent to bone lesions. SAPHO syndrome can be considered to be spondyloarthritis: approximately 13% of patients have the HLA-B27 gene, and about one third of patients have sacroiliitis or spondylitis. Around 10% of patients with SAPHO syndrome also have inflammatory bowel disease, with a predominance of Crohn disease.³⁵

Patients are likely to remain symptomatic; however, SAPHO syndrome does not appear to be overwhelmingly disabling. This disorder is typically characterized by sporadic outbreaks or attacks during which new osteosclerotic bone lesions develop. Skin lesions tend to be more persistent and less responsive to therapy than osteoarticular manifestations. It is not known if aggressive treatment of the skin disease ameliorates the bone disorder.³⁵

NSAIDs and intra-articular corticosteroid injections provide effective treatment for the majority of patients with SAPHO syndrome.³⁵ Most of those in whom NSAID therapy fails show a response to systemic corticosteroids. Nevertheless, some patients require methotrexate to treat progressive disease. Several patients have been given prolonged courses of doxycycline empirically to treat a presumed infectious agent, even when biopsy shows no evidence of infection; this has been associated with improvement in a few cases. TNF antagonist treatment has improved both skin and osteoarticular disease.³⁶ Several patients with SAPHO syndrome also have been treated successfully with bisphosphonates, including pamidronate, zoledronic acid, and alendronate.

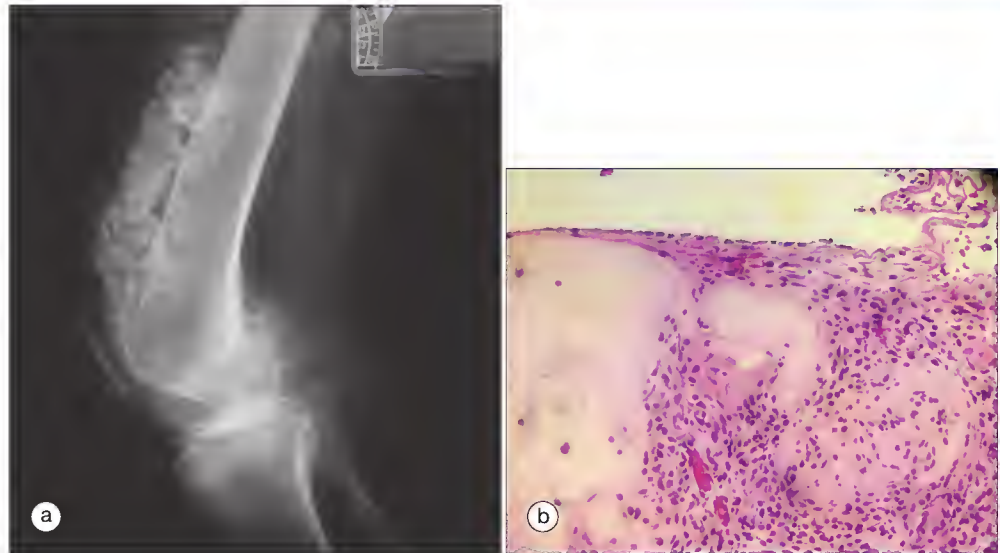
Synovial osteochondromatosis

Synovial osteochondromatosis (Fig. 170.6) is an uncommon condition that results from metaplasia of synovial tissue into cartilage, which can subsequently calcify or ossify.³⁷ However, the factors that precipitate the development of synovial osteochondromas are incompletely understood. Patients have joint pain, swelling, and tenderness, usually in a monoarticular distribution, and may experience locking of the affected joint. Over half of cases occur in the knee; the hip and elbow are also commonly affected, but involvement of many other joints or bursae also has been described. Although the disorder occurs in children, most patients with synovial osteochondromatosis are older, with an average age between 30 and 50 years. Men are affected slightly more often than women.

The pathogenesis of synovial osteochondromatosis is unknown, but the synovium is strikingly hypertrophied with numerous villi. Cartilaginous nodules are present both within the synovium and free within the synovial cavity. Malignant transformation has been reported very infrequently.

Plain radiographs show the characteristic appearance of “popcorn” within the joint cavity if the lesions are calcified. Uncalcified lesions can be visualized by MRI. The differential diagnosis includes loose bodies from trauma and tumoral calcinosis. No detailed analyses of synovial fluid have

Fig. 170.6 Synovial osteochondromatosis. (a) Radiograph of knee with typical “popcorn”-shaped calcification. (b) Synovial biopsy specimen showing osteochondrometaplasia on the left (hematoxylin-eosin).



been reported, but calcium pyrophosphate dihydrate (CPPD) crystals have been described in association with synovial osteochondromatosis.

NSAIDs are typically administered for pain control. Operative management involves removal of loose bodies and synovectomy, either by open arthrotomy or by arthroscopy.

Diabetic muscle infarction

Diabetic muscle infarction is an infrequent complication of long-standing diabetes mellitus that also has been called *aseptic myonecrosis* and *ischemic myonecrosis*. It presents as the acute onset of muscle pain and swelling, most commonly in the thigh, and may be accompanied by mild constitutional symptoms. Patients with type 1 and type 2 diabetes mellitus are affected, usually after more than 10 years of disease; most also have diabetic microvascular complications, such as nephropathy, neuropathy, and retinopathy.³⁸ Diabetic muscle infarction probably occurs as the result of an initial small thromboembolic event that causes ischemia because of impaired collateral circulation in the setting of diabetic microvascular disease, with resulting edema and compartment syndrome that causes further muscle ischemia; however, the hypoxic muscle damage results in a significant inflammatory response, hyperemia, and reperfusion with generation of reactive oxygen species that cause additional edema and compartment syndrome with further muscle damage.³⁹

Laboratory testing may reveal elevation of creatine phosphokinase levels or ESR. Electromyography demonstrates nonspecific abnormalities. MRI is the imaging technique of choice to evaluate diabetic muscle infarction and demonstrates hyperintense signal of infarcted muscle, muscle enlargement, and subcutaneous and subfascial edema on T2-weighted images.⁴⁰ Biopsy usually is not necessary and, because of potential infectious and wound healing complications, should be reserved for cases in which the diagnosis is uncertain or pyomyositis is suspected.

Patients should rest and take analgesic medications. Treatment with antiplatelet agents and antiinflammatory medications may hasten recovery.⁴⁰ Conversely, surgical resection may delay recovery and increase the risk of recurrence and mortality from complications of diabetic macrovascular disease compared with medical or conservative therapy.

Retroperitoneal fibrosis

Idiopathic retroperitoneal fibrosis typically presents as a periaortic mass with associated back or abdominal pain, often with obstructive nephropathy due to encasement of the ureters. This rare disease, with an annual incidence of 1.3 per 100,000 population, occurs more commonly in older males.⁴¹ In most cases, the fibrosis occurs between the renal artery and the bifurcation of the aortic aorta, but it may extend superiorly or inferiorly. Extraperitoneal fibrosis, such as Riedel thyroiditis, mediastinal fibrosis, sclerosing cholangitis with autoimmune pancreatitis, and orbital pseudotumor, occurs in some patients with retroperitoneal fibrosis. The finding of increased numbers of immunoglobulin G4 (IgG4)-positive plasma cells in biopsy samples from patients with idiopathic retroperitoneal fibrosis as well as from those with extraperitoneal fibrosing syndromes has prompted grouping of these conditions as “IgG4-related disease.”⁴²

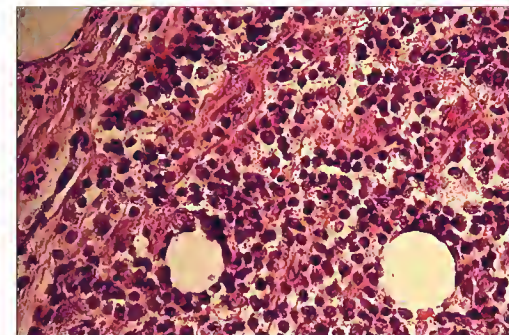


Fig. 170.7 Retroperitoneal fibrosis. Biopsy specimen from the affected area demonstrates extensive fibrosis and lymphocytic inflammatory infiltrate.

Retroperitoneal fibrosis has been described in association with a number of rheumatologic diseases, including ankylosing spondylitis, systemic lupus erythematosus, polyarteritis nodosa, and ANCA-associated granulomatous vasculitis. Its occurrence in the setting of treatment with certain medications, such as methysergide and other ergot derivatives, has suggested a causative role for these drugs. Atherosclerotic plaque extruded from the aorta, in which the immunogenic material appears to be ceroid and oxidized low-density lipoproteins, also has been proposed as a potential cause. Most patients with retroperitoneal fibrosis have increased levels of acute-phase reactants, and many have circulating antinuclear antibodies.⁴¹

Biopsy of retroperitoneal fibrotic lesions is appropriate to assess the degree of inflammation and to exclude the diagnosis of sarcoma or lymphoma (Fig. 170.7). Computed tomographic scanning is the imaging procedure of choice to diagnose the disease (Fig. 170.8a) and follow the response of retroperitoneal fibrosis to treatment (Fig. 170.8b).

Initial treatment usually involves stenting or surgery to relieve ureteral obstruction. Medical therapy consists of high-dose corticosteroids, often with the addition of steroid-sparing immunosuppressive drugs. Both azathioprine and cyclophosphamide have been used with success.⁴³ Treatment with either the estrogen receptor antagonist tamoxifen or mycophenolate mofetil,⁴⁴ in combination with corticosteroids, has resulted in regression of retroperitoneal fibrosis in some patients.

MUSCULOSKELETAL SYNDROMES ASSOCIATED WITH CHRONIC KIDNEY DISEASE

Musculoskeletal complications are reported to occur in more than one half of patients receiving long-term hemodialysis, but the studies investigating the prevalence of these conditions are limited by the relatively small number of patients examined.⁴⁵ As of December 31, 2011, 430,273 people in the United States were treated with dialysis for stage 5 chronic kidney disease. (According to the 2013 U.S. Renal Data System Annual Data Report and the U.S. Census Bureau, the U.S. population at that time was 312,780,968.)

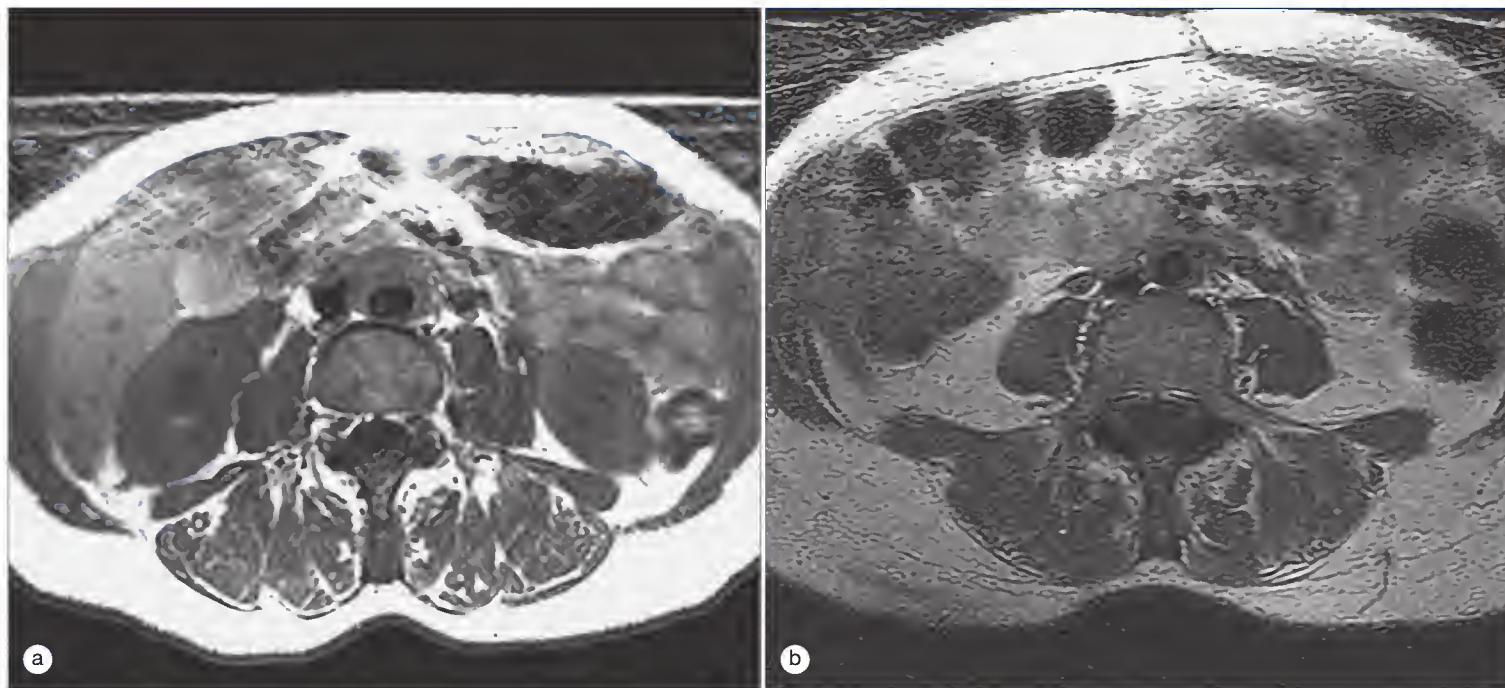


Fig. 170.8 Retroperitoneal fibrosis. (a) At the time of presentation for back pain, the patient had extensive fibrosis in the retroperitoneum, as seen in this computed tomographic image. The fibrosis encases the paravertebral muscles. (b) After several months of corticosteroid therapy (1 mg/kg/day of prednisone), the patient's fibrosis had improved significantly.

If only half of those patients who receive long-term hemodialysis in the United States have musculoskeletal symptoms, then a conservative estimate of the prevalence of musculoskeletal conditions among patients with stage 5 chronic kidney disease is comparable to the prevalence of systemic lupus erythematosus in the general population.

Arthritis and periartthritis

Arthritis, tendinitis, and enthesitis among patients receiving long-term dialysis frequently prompt the request for rheumatologic consultation. Although common in patients with chronic kidney disease before the initiation of dialysis treatment, acute attacks of gouty arthritis are uncommon in hyperuricemic individuals with uremia. The inflammatory response to monosodium urate crystals is diminished in patients receiving long-term hemodialysis, with decreased monocyte release of IL-1 β , IL-6, and TNF- α compared with individuals with normal renal function. Moreover, dialysis modalities remove urate efficiently and thus facilitate the dissolution of urate deposits in patients with gout.

Joint and periarticular inflammation caused by apatite (basic calcium phosphate) crystals occur more commonly than acute gouty arthritis in these patients, especially when the serum calcium-phosphorus product exceeds 75 mg²/dL². Other calcium-containing crystals may deposit in and around articular tissue; CPPD crystals may cause either an acute, robust inflammatory arthritis, similar to that of acute gout, or a chronic, smoldering synovitis. Calcium-containing crystals most commonly deposit around the shoulder, but deposits also may occur around the small joints of the hand, the hip, the wrist, the ankle, and the elbow. These deposits, which appear on radiographs of the shoulder as "multiloculated," nodular, periarticular calcifications, may enlarge to become palpable and visible masses (called *tumoral calcinosis*). Limited calcification in tendons, ligaments, and the joint capsule may be associated with acute attacks of painful periarticular inflammation (Fig. 170.9). Partial or complete tendon ruptures may also occur, often without antecedent symptoms, especially in the setting of uncontrolled secondary hyperparathyroidism. However, with better control of hyperphosphatemia and hyperparathyroidism in recent years, calcific periartthritis is no longer as prevalent as it was earlier.

Calcium oxalate crystals can cause acute and chronic synovitis. Although small joints of the distal extremities are more commonly affected, large joints may also become inflamed. Chondrocalcinosis may be evident on radiographs of involved joints. Calcium oxalate crystals may also deposit in vascular smooth muscle, resulting in acrocyanosis and livedo reticularis. Because ascorbic acid (vitamin C) is metabolized to oxalate, caution should be observed in prescribing vitamin C supplementation for these patients.⁴⁶



Fig. 170.9 Periarticular calcium hydroxyapatite deposition in the hands of a patient receiving long-term hemodialysis.

Monosodium urate, CPPD, and calcium oxalate crystals can be identified without difficulty by compensated polarizing light microscopy; however, the identification of apatite and basic calcium phosphate crystals is more difficult because of their small size. Alizarin red S (0.1% weight per volume in water, titrated to pH 6.4 with 0.1 N formic acid, prepared freshly every few months) will stain apatite and other calcium-containing crystals in synovial fluid. A small drop of the stain should be placed on the edge of the wet-mount coverslip should an initial examination of the preparation fail to reveal birefringent crystals. The dye will diffuse across the slide within several seconds and stain calcium-containing crystals bright red, whereas the background will remain reasonably clear.

Bacterial infections of bursae and joints occur in individuals undergoing hemodialysis in whom percutaneous vascular access is established several times each week. The most common pathogenic organism is *Staphylococcus aureus*. Diagnosis (by joint aspiration with examination and culture of synovial fluid) and treatment are as for nonuremic patients.

Initial clinical laboratory evaluation of the patient with chronic kidney disease and articular or periarticular inflammation should include assessment of serum calcium, phosphate, albumin, uric acid, and intact parathyroid hormone levels. Phosphatonins, such as fibroblast growth factor 23 and

matrix extracellular phosphoglycoprotein, are phosphaturic factors that mediate forms of hypophosphatemic rickets and oncogenic osteomalacia. Fibroblast growth factor 23, levels of which are elevated in patients with chronic kidney disease, is an important inhibitor of renal 1α -hydroxylation of 25-hydroxyvitamin D and thus of phosphate absorption from the gastrointestinal tract. Although measurement of phosphatonins remains investigational, understanding how to modulate these factors should allow for more effective control of calcium and phosphate levels in patients with stage 5 chronic kidney disease.

β_2 -Microglobulin amyloidosis

β_2 -Microglobulin amyloidosis is a systemic infiltrative disease that affects patients with severe chronic kidney disease, predominantly those who have received long-term hemodialysis. β_2 -Microglobulin is an 11.8-kDa protein that is required for expression of HLA class I molecules, to which it is non-covalently bound, on the surface of nucleated cells. Usually cleared by renal filtration, β_2 -microglobulin was inadequately cleared by traditional dialysis modalities, especially hemodialysis using low-flux bioincompatible cellulose-derived membranes that are poorly permeable to “middle molecules” of 0.3 to 5 kDa and to low-molecular-mass proteins. Synthesis and secretion of proinflammatory cytokines by peripheral blood leukocytes coming in contact with bioincompatible dialysis membranes and with bacteria in the dialysate solution also increased β_2 -microglobulin synthesis. Since the early 1990s, coincident with the widespread use of biocompatible synthetic dialysis membranes such as polysulfone and polyacrylonitrile and of purified dialysate solutions, the occurrence of β_2 -microglobulin amyloidosis has decreased markedly.

Although β_2 -microglobulin amyloid deposits have been detected in joint tissue in patients with long-standing stage 5 chronic kidney disease before the initiation of dialysis treatment, this disease usually does not become clinically evident until a patient has undergone regular dialysis for several years. The prevalence of β_2 -microglobulin amyloidosis increases with longer

duration of survival on long-term dialysis treatment and with older patient age. However, in developed countries, this disease now is seen only in patients who have received hemodialysis or peritoneal dialysis for longer than 20 years.

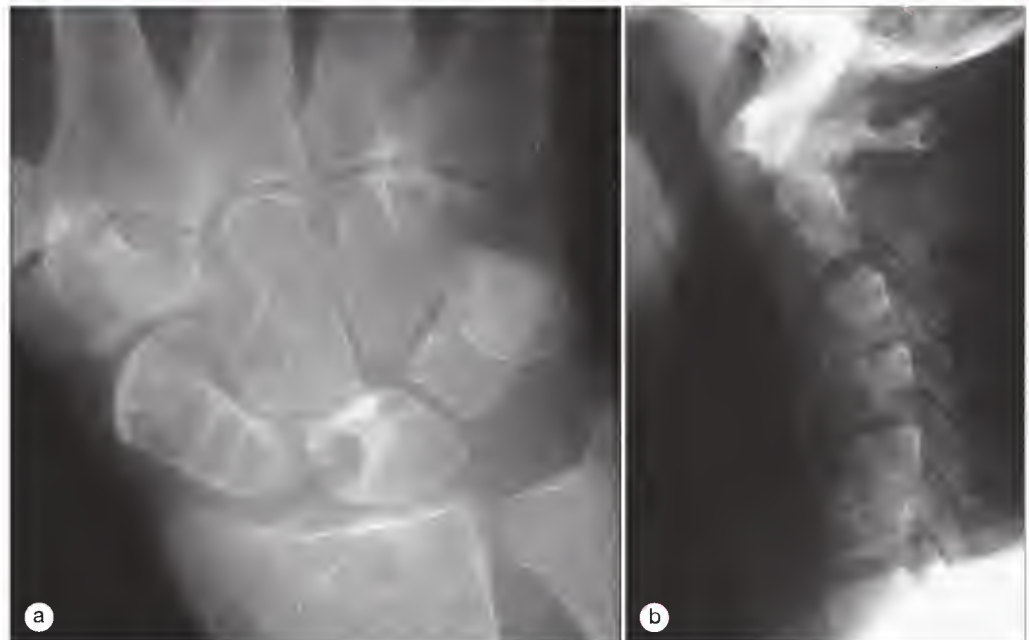
The characteristic triad of shoulder periartthritis, carpal tunnel syndrome, and flexor tenosynovitis is highly suggestive of β_2 -microglobulin amyloidosis in a patient receiving long-term dialysis treatment (Fig. 170.10).⁴⁵ Other skeletal manifestations include rapidly enlarging cystic erosions of bone by β_2 -microglobulin amyloid-containing synovium, which most often occur in the carpal bones and in the femoral neck, and destructive spondyloarthritis with a radiographic appearance resembling that of diskitis, which is observed predominantly in the lower cervical spine (Fig. 170.11). In some patients receiving long-term dialysis treatment, β_2 -microglobulin amyloid is deposited in the extradural space, sometimes causing spinal cord or nerve root compression, and around the odontoid process of C2, forming a cervicocapital pseudotumor. However, this polyarticular destructive change now is rarely seen. Systemic deposition of β_2 -microglobulin amyloid has been described in the skin, the heart, and the gastrointestinal tract, where it can cause malabsorption and colonic ulceration in patients who have undergone hemodialysis for many years.

Serum β_2 -microglobulin levels decrease rapidly and joint pain and stiffness improve after renal transplantation. Bone cysts no longer enlarge in patients with functioning renal allografts; however, the destructive spondyloarthritis may progress. Short of renal transplantation, hemodialysis using a biocompatible synthetic membrane and purified dialysate should be performed to prevent β_2 -microglobulin accumulation. Because no medical treatment has altered the course of this disease, individual manifestations should be managed separately. The greater risk of infection associated with intraarticular corticosteroid injections in dialysis patients should be weighed carefully against the brief duration of symptomatic improvement that this therapy may provide. The risk of NSAID toxicity, especially gastrointestinal effects, is greater among patients with stage 5 chronic kidney disease, and their use should be limited. Analgesics and low-dose oral corticosteroids are

Fig. 170.10 β_2 -Microglobulin amyloidosis. (a) Shoulder periartthritis with typical “shoulder pad” sign. (b) Flexor tenosynovitis with irreducible flexion contractures of the fingers and a subcutaneous soft tissue mass in the palm. (From Kay J. *Beta 2-microglobulin amyloidosis*. *Rheumatol Rev* 1993;2:211-8.)



Fig. 170.11 β_2 -Microglobulin amyloidosis. (a) Radiograph of wrist showing multiple subchondral cysts in the carpal bones, at the bases of the metacarpal bones, and in the distal radius. (b) Lateral cervical spine radiograph showing changes characteristic of destructive spondyloarthritis. The intervertebral disk spaces between the third and fourth cervical vertebrae and between the fifth and sixth cervical vertebrae are narrowed and the vertebral endplates are eroded without appreciable formation of osteophyte. (From Kay J. *Beta 2-microglobulin amyloidosis*. *Amyloid* 1997;4:187-211.)



better options to treat patients with β_2 -microglobulin amyloidosis who experience persistent pain. Rehabilitation modalities should be used to treat the frequent symptoms of impingement syndrome that develop because of amyloid infiltration of the supraspinatus tendon and to prevent finger flexion contractures caused by chronic palmar flexor tenosynovitis. Neutral resting wrist splints may be worn to improve symptoms of carpal tunnel syndrome. When necessary, carpal tunnel release and hand flexor tenosynovectomy surgery may be performed. At the time of surgery, tissue should be obtained for confirmation of the diagnosis by Congo red staining and by immunohistochemical techniques using antibodies to β_2 -microglobulin.

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF), originally called *nephrogenic fibrosing dermopathy*, was first observed in 1997 among renal transplant recipients and first described in 2000 as a condition that resembled scleromyxedema in 14 patients with stage 5 chronic kidney disease who were receiving hemodialysis.⁴⁷ However, unlike scleromyxedema, NSF spares the face and is not associated with circulating paraproteins. When significant visceral involvement was recognized, its name was changed to NSF. Subsequently, many additional cases of NSF have been identified.

All patients identified to date with NSF have had underlying renal dysfunction. Most have had stage 5 chronic kidney disease (glomerular filtration rate < 15 mL/min/1.73 m² or requirement for dialysis) and had been receiving hemodialysis. However, cases of NSF have developed in patients after successful renal transplantation, in several individuals after recovery from acute renal failure, and even in patients with lesser degrees of chronic kidney disease. Thus, although underlying kidney disease appears to be a feature common to most patients with this disease, NSF is not a complication of renal replacement therapy alone.

In 2006, after observing that five of nine patients with stage 5 chronic kidney disease who were undergoing long-term hemodialysis developed skin changes of NSF within days to weeks after receiving a gadodiamide contrast agent during MRI, Grobner proposed that NSF might result from exposure to gadolinium.⁴⁸ Subsequently, exposure to gadolinium-containing contrast agents has been demonstrated to be very strongly associated with the subsequent development of NSF among individuals with stage 5 chronic kidney disease.⁴⁹

Cutaneous features of NSF typically first involve the distal lower extremities and subsequently extend proximally.⁵⁰ Initially, patients typically report itching or burning and may notice cutaneous erythema. Some patients may have superficial skin changes in which hypopigmented, pink or flesh-colored macules or papules coalesce into patches or thin plaques, usually on the upper extremities. As the disease progresses, red to violaceous or hypopigmented fixed plaques may develop in a reticular pattern on the extremities or trunk. Dimpling of skin around hair follicles may create a peau d'orange appearance. Deep induration may develop over the upper arms, back, or thighs, creating a cobblestone-like uneven texture.

As in scleroderma, the skin on the legs and arms becomes markedly indurated so that it cannot be pinched between the thumb and forefinger, and often associated hyperpigmentation is present (Fig. 170.12). However,



Fig. 170.12 Nephrogenic systemic fibrosis.

facial involvement has not been observed in patients with NSF, and Raynaud phenomenon does not usually occur. Decreased mobility of periarticular skin typically results in fixed flexion deformities, with limited finger, elbow, and knee extension. These joint contractures may progress to compromise performance of activities of daily living and make it impossible for the patient to walk.

As more cases of NSF have appeared, prominent systemic involvement has become evident. Many patients with NSF have yellow plaques on the sclera of their eyes, nasal and temporal to the iris. Visceral fibrosis involving the heart, lungs, pleura, skeletal muscle, diaphragm, esophagus, liver, genitourinary tract, thyroid, lymph nodes, and dura mater has been identified in patients with NSF. Although often asymptomatic, visceral fibrosis may contribute to the development of cardiomyopathy, pulmonary hypertension, and skeletal muscle weakness, among other clinical manifestations.

NSF is diagnosed when characteristic clinical features are present; the diagnosis is confirmed by histologic examination of a deep skin biopsy specimen. Increased number of dermal fibroblasts is the most characteristic histologic feature of NSF. Collagen deposition is increased in the dermis, and interlobular septa and collagen bundles are surrounded by clefts. In the dermis, mucin deposition is increased and CD34+ fibrocytes, presumably originating from the circulation, are arranged in a reticular pattern or with their dendritic processes flanking intact elastic fibers. Cells of monocyte-macrophage lineage, which stain for factor XIIIa and CD68, also may be present in the dermis. Demonstration of gadolinium in tissue by inductively coupled plasma mass spectrometry provides further support for the diagnosis of NSF.

No laboratory test is diagnostic of NSF. Circulating antinuclear antibodies and antibodies to Scl-70, which are detected in many patients with scleroderma, typically are not present in patients with NSF. Circulating paraproteins, which often are present in patients with scleromyxedema, are not associated with NSF.

NSF almost always progresses relentlessly and does not usually regress spontaneously. Among patients with stage 5 chronic kidney disease, those with cutaneous changes of NSF have a threefold increased risk of dying within 2 years of the diagnosis of NSF.⁴⁹

No therapy has been demonstrated to be universally effective for the treatment of NSF. Anecdotal reports have been published of variable subjective improvement in signs and symptoms of NSF with several treatments, including sirolimus, intravenous sodium thiosulfate, plasmapheresis, ultraviolet A phototherapy, and extracorporeal photopheresis with ultraviolet A light. Treatment of several NSF patients with oral imatinib mesylate, 400 mg daily, has resulted in objective improvement in clinical measures of skin tethering and joint mobility and in the histologic appearance of fibrosis.⁵¹

Because essentially all cases of NSF have developed after exposure to a gadolinium-containing contrast agent, prevention of this devastating condition involves the careful avoidance of administration of these agents to individuals at risk. Patients with stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m²) should not be given a gadolinium-containing contrast agent. For individuals with lesser degrees of renal dysfunction the diagnostic benefit of using a gadolinium-containing contrast agent in an imaging study must be weighed very carefully against the potential risk of the patient's developing NSF.

Use of antirheumatic drugs in patients receiving dialysis

All NSAIDs inhibit renal prostaglandin production and thus have the potential to cause reduced glomerular filtration, salt retention, and hyperkalemia, all of which may be important in dialysis patients with residual renal function. Because they are highly bound to proteins, NSAIDs are removed poorly by dialysis; postdialysis supplemental doses are unnecessary. NSAIDs are metabolized primarily by the liver; however, 40% to 95% of NSAID metabolites are excreted in the urine as glucuronide conjugates or other compounds. Because few data are available regarding the bioactivity and toxicity of these metabolites, manufacturer product labeling suggests that NSAIDs be used with caution and at reduced dosages in patients with renal failure. Patients undergoing long-term dialysis are especially susceptible to gastrointestinal bleeding, and consideration should be given to the concurrent use of a proton pump inhibitor or a prostaglandin analogue such as misoprostol when treating with NSAIDs.

The dosages of drugs used to treat gout must be adjusted in patients with chronic kidney disease. Both allopurinol and its active metabolite oxypurinol, as well as uric acid, are cleared by dialysis. Because the risk of allopurinol hypersensitivity syndrome is greater when higher doses are administered to patients with chronic kidney disease, allopurinol should be initiated at

lower doses; however, the dose should be increased cautiously to that which is adequate to achieve a lowering of serum urate level to less than 6 mg/dL.⁵² The half-life of colchicine is prolonged, and toxicity occurs more frequently in individuals with compromised renal function. Because its bioavailability is extremely variable in patients with stage 5 chronic kidney

disease and it is not cleared by dialysis, use of colchicine should be avoided. Prolonged administration of colchicine to patients with chronic kidney disease has caused a severe lysosomal, vacuolar myopathy with marked elevation of serum creatine kinase levels and, occasionally, severe heart failure.

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OSTEOARTHRITIS AND
RELATED DISORDERS

171

Osteoarthritis: epidemiology
and classification

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- Osteoarthritis is the most common form of arthritis. It is strongly associated with aging and typically affects the knee, hip, spine, great toe, and hands.
- Racial and ethnic differences in frequency of osteoarthritis have been observed, with blacks more likely to have knee osteoarthritis but less likely to have hand osteoarthritis compared with whites. Hip and hand osteoarthritis are relatively rare in Chinese compared with white populations.
- Osteoarthritis can be defined by radiographs, clinical examination, or symptoms. Symptoms are more common with more severe radiographic osteoarthritis, but the association between radiographic changes and symptoms is not absolute.
- Mortality is increased in individuals with osteoarthritis compared with the general population.
- As more sensitive measures of osteoarthritis such as magnetic resonance imaging and biomarkers are developed and validated, definitions of osteoarthritis may change.

INTRODUCTION

Osteoarthritis (OA) is a condition found worldwide, is strongly associated with aging, and is the most common type of arthritis, affecting 27 million adults in the United States in 2005.¹ According to the Healthcare Cost and Utilization Project website (www.hcup-us.ahrq.gov), OA was the most common principal diagnosis for inpatient hospital stays in adults 45 to 64 years of age in 2009, with an increase of 151% in the rate of stays per 10,000 population.² Because of its effect on ambulation and mobility, OA of the knee and hip has significant functional impact and is associated with considerable medical costs, accounting for the vast majority of the 686,000 total inpatient stays for knee replacements and 438,000 total inpatient stays for hip replacements in the United States in 2009—dramatic increases from the 329,000 knee and 291,000 hip replacement inpatient stays in 1997.² Because of the aging of our society and the obesity epidemic, the burden of OA will continue to increase over the next 20 years.^{3,4}

The joint degradation in OA affects all structures in the joint and should be considered a failure of the total joint. It is characterized by thinning and fibrillation of the cartilage with loss of joint space, osteophyte formation, subchondral bony sclerosis, subchondral cysts, and deformity. The pathophysiology of OA involves not only cartilage degradation, but also changes in the subchondral bone, synovium, ligaments, tendons, meniscus, muscle, and nerve tissues. Clinically, this can be accompanied by pain on use of the

joint; stiffness, particularly after inactivity; bony enlargement and tenderness; synovial hypertrophy and effusion; limited range of motion; and decreased joint function. End-stage OA likely represents a final common pathway of a variety of conditions (e.g., inflammation, trauma, metabolic disorders) that, despite differences in etiology, lead to the same pathologic and clinical result.

OA typically affects the knees, hips, hands, spine, and feet. Classifications can differentiate between OA that is localized and OA that is “generalized,” affecting multiple joint groups. OA can also be classified as hypertrophic or atrophic, based on radiographic features of joint space narrowing or osteophytosis, and as primary or secondary to other conditions, such as metabolic disorders (e.g., ochronosis or hemochromatosis), anatomic abnormalities (e.g., slipped capital femoral epiphysis or chondrodysplasias), trauma or joint surgery, or previous inflammatory arthritis. This type of classification can be useful in clinical care and in development of inclusion and exclusion criteria for epidemiologic studies and clinical trials, but the distinctions can be artificial and ignore the more common situation of overlapping causes. The American College of Rheumatology (ACR) classification of OA is shown in [Box 171.1](#).⁵

This chapter discusses the following:

- Definitions of OA: radiographic, clinical, or symptomatic
- Prevalence of radiographic OA
- Incidence and progression of radiographic OA
- Symptomatic OA
- Mortality in OA

DEFINITIONS OF OSTEOARTHRITIS

OA can be defined pathologically, radiographically, or clinically, and the choice of definition can substantially affect prevalence estimates.⁶ The ACR criteria for the classification of OA of the hand, hip, and knee are shown in [Table 171.1](#).^{5,7,8} OA definitions for epidemiologic investigation are evolving in recognition of imperfect congruence between radiographic and clinical definitions,⁹ the variation in frequencies of and risk factors for OA in different joint sites, and new and more sensitive metrics to identify pathologic features such as magnetic resonance imaging (MRI) and biochemical markers. The presence of radiographic OA usually requires identification of a definite osteophyte with or without joint space narrowing on plain radiograph. Clinical OA is usually defined by abnormalities on physical examination consistent with OA, such as Heberden or Bouchard nodes in the hand, or limited and painful range of motion on internal rotation of the hip. Symptomatic OA is usually defined as pain, aching, or stiffness in a joint with radiographic OA. Definitions can vary according to joint site, frequency or intensity of pain, and time span over which symptoms are assessed. Definitions of incident OA and progression of OA may also vary according to joint site, individual radiographic features assessed, and the original metric used to define OA.

BOX 171.1 AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR CLASSIFICATION OF OSTEOARTHRITIS

- I. Idiopathic
 - A. Localized
 1. Hands (e.g., Heberden and Bouchard nodes [nodal], erosive interphalangeal arthritis [nonnodal]): scaphometacarpal, scaphotrapezial
 2. Feet (e.g., hallux valgus, hallux rigidus, contracted toes [hammer/cock-up toes]): talonavicular
 3. Knee
 - a. Medial compartment
 - b. Lateral compartment
 - c. Patellofemoral compartment (e.g., chondromalacia)
 4. Hip
 - a. Eccentric (superior)
 - b. Concentric (axial, medial)
 - c. Diffuse (coxae senilis)
 5. Spine (particularly cervical and lumbar)
 - a. Apophyseal
 - b. Intervertebral (disk)
 - c. Spondylosis (osteophytes)
 - d. Ligamentous (hyperostosis [Forestier disease or DISH])
 6. Other single sites (e.g., shoulder, temporomandibular, sacroiliac, ankle, wrist, acromioclavicular)
 - B. Generalized: includes three or more areas listed above (Kellgren-Moore)
 1. Small (peripheral) and spine
 2. Large (central) and spine
 3. Mixed (peripheral and central) and spine
- II. Secondary
 - A. Posttraumatic
 - B. Congenital or developmental diseases
 1. Localized
 - a. Hip diseases (e.g., Legg-Calvé-Perthes, congenital hip dislocation, slipped capital femoral epiphysis, shallow acetabulum)
 - b. Mechanical and local factors (e.g., obesity [?], unequal lower extremity length, extreme valgus/varus deformity, hypermobility syndromes, scoliosis)
 2. Generalized
 - a. Bone dysplasias (e.g., epiphyseal dysplasia, spondyloapophyseal dysplasia)
 - b. Metabolic diseases (e.g., hemochromatosis, ochronosis, Gaucher disease, hemoglobinopathy, Ehlers-Danlos syndrome)
 - C. Calcium deposition disease
 1. Calcium pyrophosphate deposition disease
 2. Apatite arthropathy
 3. Destructive arthropathy (shoulder, knee)
 - D. Other bone and joint disorders (e.g., avascular necrosis, rheumatoid arthritis, gouty arthritis, septic arthritis, Paget disease, osteopetrosis, osteochondritis)
 - E. Other diseases
 1. Endocrine diseases (e.g., diabetes mellitus, acromegaly, hypothyroidism, hyperparathyroidism)
 2. Neuropathic arthropathy (Charcot joints)
 3. Miscellaneous (e.g., frostbite, Kashin-Beck disease, caisson disease)

DISH, diffuse idiopathic skeletal hyperostosis.

From Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039-49.

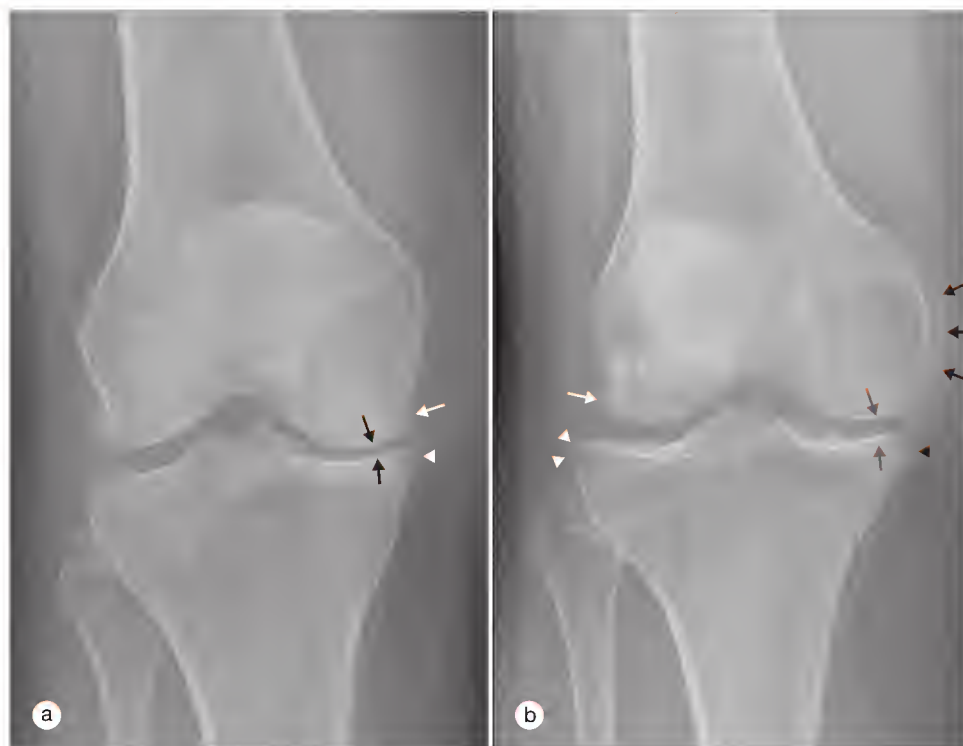


Fig. 171.1 Examples of semiquantitative radiographic assessment with use of the Kellgren-Lawrence and Osteoarthritis Research Society International (OARSI) grading schemes. (a) Kellgren-Lawrence grade 3. No lateral femoral and tibial osteophytes are seen (OARSI grade 0). A medial femoral osteophyte OARSI grade 1 (white arrow), a medial tibial osteophyte OARSI grade 2 (white arrowhead), lateral tibiofemoral joint space width OARSI grade 0, and medial tibiofemoral joint space narrowing OARSI grade 2 (black arrows) are depicted. (b) Kellgren-Lawrence grade 2. A lateral femoral osteophyte OARSI grade 2 (white arrow), a lateral tibial osteophyte OARSI grade 2 (white arrowheads), a medial femoral osteophyte OARSI grade 3 (black arrows), a medial tibial osteophyte OARSI grade 2 (black arrowhead), a normal lateral tibiofemoral joint space width OARSI grade 0, and medial tibiofemoral joint space width OARSI grade 1 (gray arrows) are shown. (From Guermazi A, Hunter DJ, Roemer FW. Plain radiography and magnetic resonance imaging diagnostics in osteoarthritis: validated staging and scoring. *J Bone Joint Surg Am* 2009;91[Suppl 1]:54-62.)

Radiographic osteoarthritis: definitions

Radiographic determination of OA has long been considered the gold standard, and multiple ways to define radiographic disease have been devised. The Kellgren-Lawrence (KL) radiographic grading scale and atlas have been in use for more than five decades. This overall joint scoring system grades OA in five levels from 0 to 4, defining OA by the presence of a definite osteophyte and more severe grades by the presumed successive appearance of joint space narrowing, sclerosis, cysts, and deformity (Table 171.2, Fig. 171.1).¹⁰ The KL scoring system has been used extensively but has been

criticized by some because of its reliance on the presence of a definite osteophyte to define a case, as well as inconsistencies in interpretation across studies.¹¹ Additionally, although individuals categorized as KL grade 1 are often classified as unaffected, these individuals likely have early OA, based on their more likely progression to higher radiographic grades over time compared to those categorized as KL grade 0.^{12,13}

Semiquantitative evaluation of individual radiographic features such as osteophytes, joint space narrowing, sclerosis, and cysts at individual joint sites can also be used.¹⁴ Direct measurement of the interbone distance as an indicator of the joint space width in the knees and hips has been proposed

TABLE 171.1
American College of Rheumatology criteria for osteoarthritis (OA) of the hand, hip, and knee

	Items required for presence of OA
Hand	
Clinical	
1. Hand pain, aching, or stiffness for most days of prior month	1, 2, 3, 4 or 1, 2, 3, 5
2. Hard tissue enlargement of ≥ 2 of 10 selected hand joints*	
3. MCP swelling in ≤ 2 joints	
4. Hard tissue enlargement of ≥ 2 DIP joints	
5. Deformity of ≥ 1 of 10 selected hand joints*	
Hip	
Clinical and radiographic	
1. Hip pain for most days of the prior month	1, 2, 3 or 1, 2, 4 or 1, 3, 4
2. ESR ≤ 20 mm/hr (laboratory)	
3. Radiographic femoral and/or acetabular osteophytes	
4. Radiographic hip joint space narrowing	
Knee	
Clinical	
1. Knee pain for most days of prior month	1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5
2. Crepitus on active joint motion	
3. Morning stiffness ≤ 30 min in duration	
4. Age ≥ 38 yr	
5. Bony enlargement of the knee on examination	
Clinical and radiographic	
1. Knee pain for most days of prior month	1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6
2. Osteophytes at joint margins (radiograph)	
3. Synovial fluid typical of OA (laboratory)	
4. Age ≥ 40 yr	
5. Morning stiffness ≤ 30 min in duration	
6. Crepitus on active joint motion	

*Ten selected hand joints include bilateral second and third proximal interphalangeal joints, second and third distal interphalangeal joints, and first carpometacarpal joints. DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal. From Altman R, Asch E, Blach D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum* 1986;29:1039-49; Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991;34:505-14; and Altman R, Alarcón G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601-10.

TABLE 171.2
Kellgren-Lawrence radiographic grading system for osteoarthritis

Grade	Classification	Description
0	Normal	No features of osteoarthritis
1	Doubtful	Minute osteophyte, doubtful significance
2	Minimal	Definite osteophyte, unimpaired joint space
3	Moderate	Moderate diminution of joint space
4	Severe	Joint space greatly impaired with sclerosis of subchondral bone

Adapted from Kellgren JH, Lawrence JS, editors. *The epidemiology of chronic rheumatism, atlas of standard radiographs*. Oxford: Blackwell Scientific; 1963.

as a more powerful tool to define OA and to investigate progression in epidemiologic studies and clinical trials of disease-modifying therapies.^{15,16} Standardized protocols for radiographic image acquisition and methods for scoring have been devised that show good reliability, and use of digitized images and computer scoring can decrease error.¹⁷ However, the sensitivity of these metrics in demonstrating change over time and effect of therapeutic interventions is limited, and more functional and dynamic imaging metrics are under evaluation. These issues are discussed further in Chapters 177 and 180.

Studies have compared several of these scoring systems in measuring prevalence of radiographic OA and its association with symptoms and other OA outcomes. Composite definitions accounting for both osteophytes and joint space narrowing are most strongly associated with hip pain and later total hip replacement.^{18,19} A recent study of hand OA found independent associations between osteophytes and joint space narrowing and hand joint pain.²⁰ Neogi and colleagues,²¹ after controlling for confounding by examining knee pain and radiographic OA features *within individuals* with knees discordant for pain, found strong correlations between radiographic measures (KL grade, osteophytes, or joint space narrowing) and pain.

Prevalence of radiographic osteoarthritis

Although OA affects individuals worldwide, some geographic variation in disease does exist and can inform investigations into etiology and pathogenesis. The following discussion includes data on radiographic OA of the hip, knee, and hand, with a mention of other sites that have been less well characterized.

Prevalence of radiographic hip osteoarthritis

The overall prevalence of radiographic hip OA varies widely, from less than 1% to 27%, depending on the population being studied.²² Although early studies reported low rates of hip OA in African and Caribbean blacks²³ and lower rates of hip replacement in blacks than in whites,²⁴ more recent evidence from population-based studies shows that blacks and whites in the United States have a similar prevalence of hip OA.^{25,26} The first National Health and Nutrition Examination Survey (NHANES I), conducted from 1971 to 1975, reported no difference in the prevalence of hip OA, defined by KL grade, between blacks and whites.²⁵ The Johnston County Osteoarthritis Project reported a similar prevalence of radiographic hip OA (defined as a KL grade of 2 or higher) among whites (27%) and blacks (32%); frequencies of severe radiographic hip OA (KL grade 3 or 4) were also similar (2.4% in whites and 3.1% in blacks).²⁶ Hip OA was 80% to 90% less frequent in Chinese individuals than in whites in a study using standardized methods and the same readers for all radiographs.²⁷ The prevalence of radiographic hip OA, defined as a minimal joint space of 2.5 mm or less, is higher in Iceland, present in about 8% of those aged 35 years or older, compared with 1.2% in South Sweden; a strong genetic component is felt to be responsible for this difference.²⁸

Prevalence of radiographic knee osteoarthritis

A subset of individuals aged 60 years and older participating in NHANES III (1991 to 1994) had an overall prevalence of radiographic knee OA of 37%, higher than estimates from NHANES I, and higher in blacks (52%) than in Mexican Americans (40%) or non-Hispanic whites (36%).²⁹ Other U.S. studies have examined the prevalence of radiographic knee OA with some variation in results, perhaps based on cohort effects and differences in study design, radiographic reading protocols, and population studied. Radiographic knee OA was present in 33% of men and 42% of women in the original cohort of the Framingham Osteoarthritis Study (1983 to 1985), without substantial change at follow-up (1992 to 1995; Fig. 171.2).³⁰ Twenty-eight percent of participants in the Johnston County Osteoarthritis Project aged 45 years and older had radiographic knee OA, with slightly more blacks affected than whites.³¹

In the Beijing Osteoarthritis Study, radiographic knee OA was more common in Chinese women than in white women from Framingham, despite a lower body mass index (BMI) among the Chinese women.³² The Copenhagen Osteoarthritis Study (1992 to 1994) found a relatively low prevalence of radiographic knee OA of 12% for men and 14% for women, which was partially explained by a low BMI (mean, 26 kg/m²) in that group.³³

Many studies of radiographic knee OA are limited to the tibiofemoral joint and therefore underestimate the prevalence of radiographic knee OA and symptomatic knee OA by omitting the patellofemoral joint. Much of patellofemoral joint OA coexists with tibiofemoral OA, but it can exist as an isolated phenomenon in up to about 13% of individuals, particularly in younger populations,³⁴ has been associated with significant pain and disability, and may have unique biomechanical or other risk factors.³⁵

INCREASING PREVALENCE OF KNEE PAIN AND SYMPTOMATIC KNEE OSTEOARTHRITIS: SURVEY AND COHORT DATA

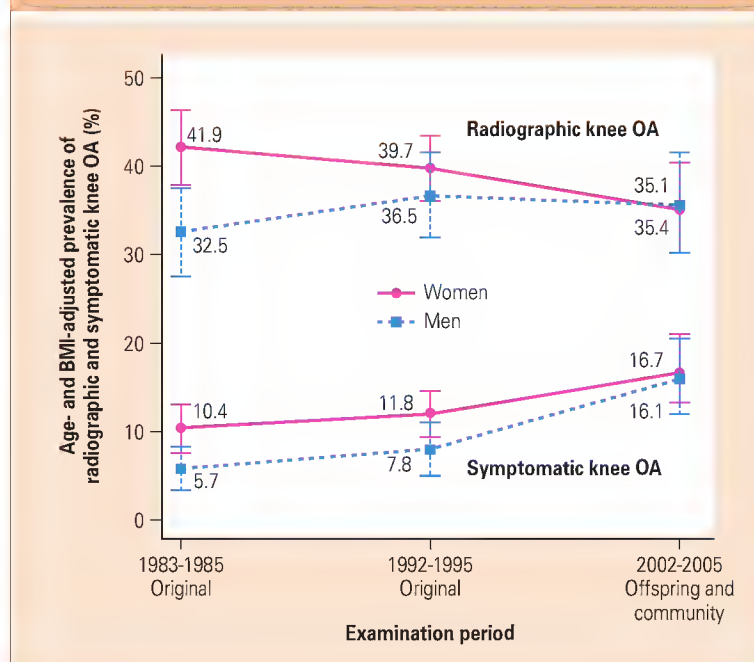


Fig. 171.2 Age- and body mass index (BMI)-adjusted prevalence of radiographic and symptomatic knee osteoarthritis (OA) in participants in the Framingham Osteoarthritis Study across three examination periods. Error bars represent 95% confidence intervals. For radiographic knee OA (Kellgren-Lawrence grade of 2 or higher), test for trend from 1983 to 2005: $P = .82$ (men) and $P = .04$ (women). For symptomatic knee OA (knee pain in the knee with radiographic OA), test for trend from 1983 to 2005: $P < .001$ (men) and $P = .006$ (women). (From Nguyen UDT, Zhang Y, Zhu Y, et al. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann Intern Med* 2011;155:725-32.)

Prevalence of radiographic hand osteoarthritis

Radiographic hand OA is usually defined as a KL grade of 2 or higher in specific joints, namely, the distal interphalangeal (DIP) joints, the proximal interphalangeal (PIP) joints, and the carpometacarpal (CMC) joints or thumb base. Involvement of the metacarpophalangeal (MCP) joints has received less study. Criteria for case definitions may include the presence of radiographic hand OA in any hand joint or in a selected subset of hand joint sites, usually including the DIPs, PIPs, and CMCs.⁷ Radiographic hand OA is extraordinarily common, particularly in older age groups. The Framingham Osteoarthritis Study observed radiographic OA in 22.1% of hand joints of older men and in 32.7% of hand joints of older women.³⁶

Radiographic hand OA involving any hand joint was present in 25.5% of black women and 19.2% of white women in the Southeast Michigan cohort of perimenopausal women.³⁷ The Rotterdam study reported that 67% of women and 55% of men aged 55 years and older had radiographic hand OA in at least one joint and 28% had radiographic hand OA in at least two of three hand joint sites (DIP, PIP, CMC).³⁸ The age-specific frequency of involvement of hand joint groups in this study is displayed in Figure 171.3. Radiographic hand OA is relatively uncommon in Chinese and Japanese adults.^{39,40}

Prevalence of radiographic osteoarthritis in other sites

OA in other common sites such as the spine and first metatarsophalangeal joints is less well studied. The Framingham Heart Study showed a high prevalence of facet joint OA (60% in men and 67% in women) by computed tomographic imaging, although no association with pain was identified.⁴¹ Degenerative disk disease of the lumbosacral spine is also extremely common, with anterior osteophytes and disk space narrowing present in 91% and 68%, respectively, in one population-based study of women,⁴² and in 88% and 58% in a cross-sectional study including African American and white men and women⁴³; whether degenerative disk disease represents spinal OA remains controversial. OA of the joints of the feet is also common but understudied; one estimate reported a prevalence of 42% in the first metatarsophalangeal joint in an elderly population with a high prevalence of OA at other joints.⁴⁴

AGE-SPECIFIC FREQUENCY OF INVOLVEMENT OF HAND JOINT GROUPS WITH RADIOGRAPHIC OA

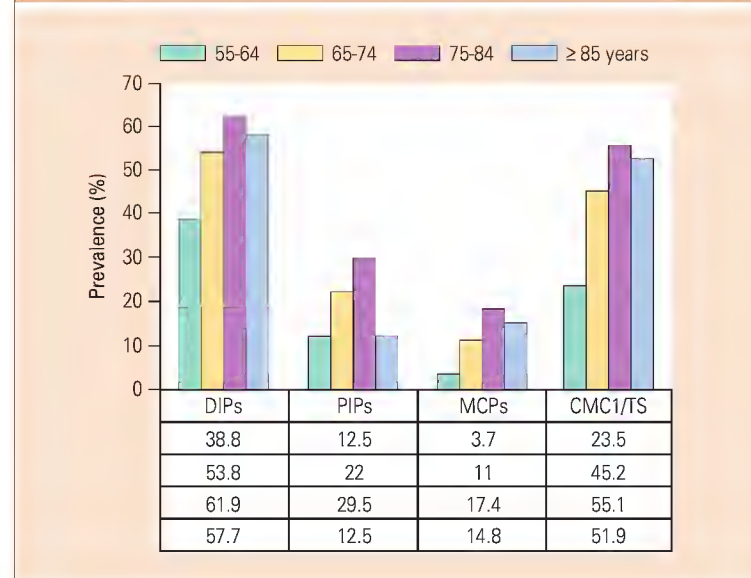


Fig. 171.3 Prevalence (in percent) of radiographic osteoarthritis (OA) (Kellgren-Lawrence grade of 2 or higher) affecting various hand joint groups in different ages cohorts in the Rotterdam study. CMC1, first carpometacarpal joint; DIPs, distal interphalangeal joints; MCPs, metacarpal phalangeal joints; PIPs, proximal interphalangeal joints; TS, trapezioscapoid joint. (From Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability [the Rotterdam study]. *Ann Rheum Dis* 2005;64:682-7.)

Incidence and progression of radiographic osteoarthritis: definitions

Incidence and progression of radiographic OA are defined separately for individual joint groups and, increasingly, for the individual radiographic features of osteophytes and joint space narrowing or their combination.

Development of KL grade 2 or higher from a baseline of 0 or 1 can be used to define incident hip OA; other definitions using algorithms such as the Croft scale or the development of a minimum joint space of 2.5 mm or less consider the presence of specific radiographic features. In the Rotterdam study, after a mean follow-up of 6.6 years, incident hip OA was identified in 3.9% of 5481 hips with KL grade 1 or less at baseline.⁴⁵ Beattie and colleagues,⁴⁶ in a study of statin use and hip OA using data from the Study of Osteoporotic Fractures, reported development of incident OA in 566 of 4933 older white women who did not have OA at the baseline evaluation 8 years earlier (11% incidence) based on a composite definition. Arden and colleagues¹⁸ have reported that composite definitions based on the presence of more than one individual radiographic feature had the strongest associations with pain and future need for hip replacement and recommended the use of such composites to define incident hip OA in epidemiologic studies.

Progression of hip OA in the Study of Osteoporotic Fractures over 8 years was defined by an increase in the summary radiographic grade, increase in total osteophyte score, decrease in minimal joint space of at least 0.5 mm, total hip replacement, or increase in lower-extremity disability score.⁴⁷ Sixty-five percent of hips with radiographic OA at baseline demonstrated radiographic progression by these criteria, with risk of progression higher in those with hip symptoms at baseline. In contrast, a study of individuals undergoing colon radiography in Iceland found that fewer than 3% of normal hips later required hip replacement, compared with 17% of hips with baseline hip OA, defined as a minimum joint space of 2.5 mm; these data suggest a lower rate of progression, although differences in methods and population make direct comparisons difficult.⁴⁸

For radiographic knee OA, incidence is commonly defined as the development of KL grade 2 or higher from a baseline grade of 0 or 1, or alternatively by the development of a definite osteophyte. Felson and colleagues⁴⁹ reported that 15.6% of elderly Framingham study participants developed incident radiographic knee OA over an 8-year follow-up period, with women at higher risk than men. More recently, the Chingford study of older white women reported an annual cumulative incidence of radiographic knee OA of 2.3% over 14 years, or a total incidence of 39.5%.¹³

Progression of radiographic knee OA can be defined as an increase in KL grade in those with prevalent radiographic knee OA at baseline. In such analyses, those with KL grade 4 cannot progress, except to joint replacement. Alternatively, progression could also include an increase in the grade of semiquantitatively defined osteophytes or joint space narrowing. LaValley and colleagues⁵⁰ found that definitions incorporating both osteophytes and joint space narrowing, rather than ordinal assessment of joint space narrowing alone, yielded the most precise estimates of radiographic knee OA worsening in relationship to known risk factors. Quantitative determination of changes in minimum joint space width is the only U.S. Food and Drug Administration–accepted structural outcome measure for clinical trials of disease-modifying OA drugs and is the most frequently used measure in the clinical trial setting.⁵¹

New MRI measures are being developed and validated and will require updated definitions of OA incidence and progression.⁵² MRI technology allows assessment of not only bone but also articular cartilage, menisci, osteophytes, subchondral bone, and ligamentous and synovial structures using both qualitative and quantitative methods. Semiquantitative scoring systems encompassing many of these features have been developed for the knee, although issues such as optimal sequence and image quality, time for scoring, and necessary reader expertise and training have yet to be fully addressed.⁵³ It also remains unclear what constitutes a pathologic lesion versus an incidental finding because of the high sensitivity of MRI.⁵⁴ MRI is attractive as a new standard measure in knee OA, but barriers such as high cost to obtain and operate the equipment, length of time required for acquiring and interpreting the images, and contraindications to the procedure have limited its use in most large longitudinal cohort studies, although that has begun to change with the Osteoarthritis Initiative.⁵⁵ However, MRI may well be the modality of choice in future clinical trials of structure-modifying drugs and epidemiologic studies, provided its reach can be extended beyond tertiary research centers (see Chapter 177).

Symptomatic osteoarthritis: definitions

Although the likelihood of symptoms, variously defined as pain, aching, and stiffness, is higher with more severe radiographic grades of OA, it has long been recognized that there is a lack of perfect congruence between radiographic findings of OA and clinical symptoms.⁹ Up to 60% of individuals with radiographic knee OA may not complain of pain. However, recent studies using novel methods to control for confounding have suggested a closer relationship between radiographic findings and symptoms.²¹ Additionally, individuals with radiographic knee OA but without frequent pain may still have quadriceps weakness^{55,56} and have a higher likelihood of disability or dependence on others to perform tasks of daily living.⁵⁷ This suggests that individuals may curtail symptom-inducing activities and that even “asymptomatic” radiographic OA is not without consequence.

Nonetheless, in recognition that OA associated with symptoms and disability is more significant in determining the need for medical care and services than asymptomatic OA, epidemiologic definitions of OA that incorporate symptoms and impact are of increasing importance. Symptomatic OA is usually defined as the presence of symptoms in a joint with radiographic OA. Incidence of symptomatic OA would be defined as the development of radiographic OA in someone with symptoms, the development of symptoms in someone with radiographic OA, or the development of both symptoms and radiographic OA in someone without either at baseline. Progression of symptomatic OA would involve progression of either radiographic OA or symptom severity or both.

Another potential definition of symptomatic knee and hip OA progression not captured in these definitions is joint failure leading to total joint replacement. Because many factors such as country of residence, health care system factors, demographic factors, comorbidities, willingness to undergo surgery, and psychological factors influence the receipt of a joint replacement, perhaps a more appropriate metric in this regard would be progression leading to the need for total joint replacement; how this would be defined for research and policy purposes is currently the subject of considerable attention in the epidemiologic research community.⁵⁸ A summary of prevalence estimates for symptomatic OA in the hands, knees, and hips is presented in Table 171.3.

Prevalence of symptomatic hip osteoarthritis

Exact figures for the prevalence of symptomatic hip OA in the population are difficult to derive from studies in the literature to date. In the Rotterdam study, OA of KL grade 2 or higher in the hip was present in 7.8% of men and 6.4% of women. Among those with a radiographic KL grade of 2 or higher, 2.1% of men younger than the median of 65.2 years reported hip pain, and 17% of older men, 36% of younger women, and 32% of older

TABLE 171.3

Prevalence of symptomatic osteoarthritis (OA) in the hands, knees, and hips from population-based studies*

Anatomic site, age (yr)	Study	% with symptomatic OA		
		Male	Female	Total
Hands, ≥26	Framingham OA study	3.8	9.2	6.8
Knees				
≥26	Framingham OA study	4.6	4.9	4.9
≥45	Framingham OA study	5.9	7.2	6.7
≥45	Johnston County OA project	13.5	18.7	16.7
≥60	NHANES III	10.0	13.6	12.1
Hips, ≥45	Johnston County OA project	8.7	9.3	9.2

*Adjusted to the projected 2000 population age ≥8 yr except for NHANES III estimates, which were adjusted to the 1980 census population.

NHANES III, National Health and Nutrition Examination Survey III; OA, osteoarthritis.

From Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26-35.

women reported hip pain.⁵⁹ A French study of individuals aged 40 to 75 years conducted from 2007 to 2009 reported an overall prevalence of symptomatic hip OA of 1.9% among men and 2.5% among women, with higher frequencies in older age groups.⁶⁰ The Johnston County Osteoarthritis Project identified hip symptoms in 36% of the nearly 3000 individuals studied, with 10% meeting criteria for symptomatic hip OA (defined as the presence of symptoms in a hip with KL grade 2 or higher).²⁶ The frequency of symptomatic hip OA was higher in women and blacks and increased with age.²⁶ As was found in studies of radiographic hip OA, symptomatic hip OA is infrequent in Chinese individuals, with frequencies ranging from 0.03% to 2% in five different studies.⁶¹

Prevalence of symptomatic knee osteoarthritis

The prevalence of symptoms in those with radiographic knee OA varies depending on definitions of radiographic OA, definitions of pain and symptoms, and population studied. Based on data from NHANES III, the prevalence of symptomatic knee OA is estimated to be 12% in adults 60 years old and older.²⁹ The Framingham Osteoarthritis Study found that 9.5% of persons aged 63 to 93 had symptomatic knee OA; prevalence was higher in women (11.4%) than in men (6.8%).⁶² A more recent estimate of the prevalence of symptomatic knee OA in adults aged 45 years and older, reported by the Johnston County Osteoarthritis Project, was 16%.³¹ Nguyen and colleagues³⁰, examining Framingham data for 1983 to 2005, reported a substantial increase in both age- and BMI-adjusted knee symptoms (in women, from 16% to 33%; in men, from 9% to 28%) and symptomatic knee OA (in women, from 10% to 17%; in men, from 6% to 16%) over 20 years despite the lack of any significant change in radiographic OA prevalence (see Fig. 171.2).

Whereas reduced joint space width in the hip has been associated with hip pain,¹⁹ osteophytes may have a larger role in knee pain. Lanyon and colleagues⁶³ reported that the presence of osteophytes was more strongly associated with pain than was joint space narrowing. Stronger associations between knee pain and osteophytes have been shown in individuals with both tibiofemoral and patellofemoral osteophytes than in those with osteophytes in either compartment alone.⁶⁴ However, a study using a within-person knee-matched design reported that although both joint space narrowing and osteophytes were associated with pain, the magnitude of the association was higher for joint space narrowing.²¹ Multiple features on MRI have also been associated with knee pain. Bone marrow lesions, particularly when large, are strongly related to knee pain, whereas synovitis and effusion are moderately associated. Weak relationships have been seen between pain and cartilage volume or thickness, and no consistent association exists between meniscal tears and pain.⁶⁵

Prevalence of symptomatic hand osteoarthritis

Radiographic OA in at least one hand joint is almost universally present in older age groups, but not all is symptomatic. Symptoms may be in the hand in general or in any joint of a specific hand joint group; the CMC joint may contribute more strongly to hand symptoms than other hand joints.⁶⁶ Symptomatic hand OA, with pain in a specific hand joint on most days and radiographic OA in that same joint, was present in 16% of older women in the Framingham cohort and 8% of men (age-standardized estimates were 14% for women and 7% for men), the thumb base and DIP joints were most

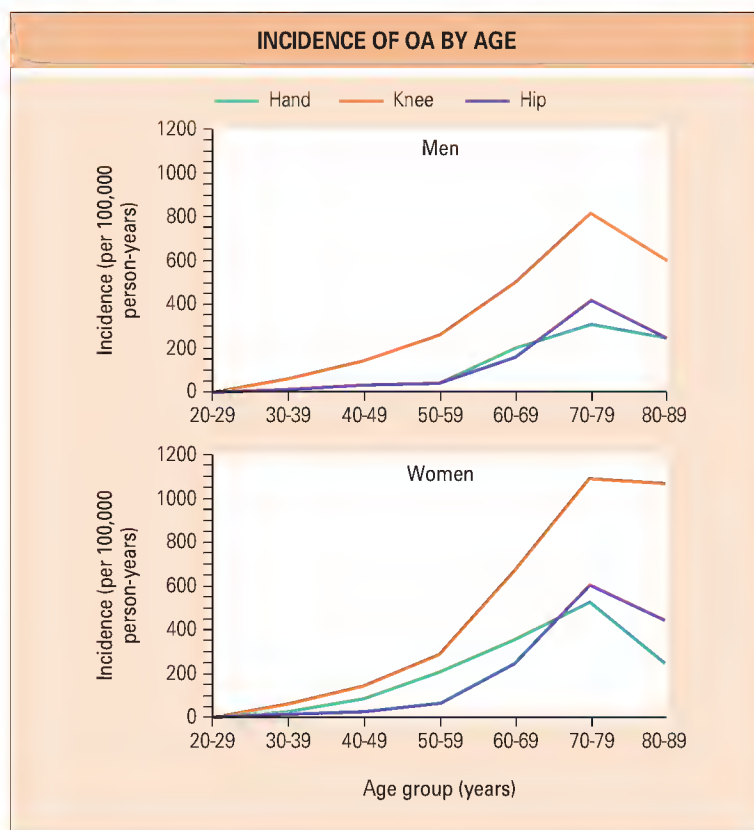


Fig. 171.4 Incidence of symptomatic osteoarthritis (OA) of the hand, knee, and hip as a function of age. (Data from Fallon Community Health Plan; Oliveria SA, Felson DT, Reed JL, et al. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum* 1995;38:1134-41.)

frequently involved.⁶⁷ In the Rotterdam study, in which the frequency of radiographic hand OA was more than 60%, the frequency of hand pain was 14%, with slightly stronger associations with the most severe radiographic grades and with the number of joints affected with OA.³⁸ Dillon and colleagues,⁶⁸ using data from NHANES III, reported a prevalence of 8% for symptomatic hand OA, defined according to ACR clinical criteria; they estimated that 1 in 12 older adults in the United States may be affected by symptomatic hand OA.

Incidence and progression of symptomatic osteoarthritis

Longitudinal studies of incident symptomatic OA in the community are few and are often done using large administrative databases, which have inherent limitations including diagnostic and coding errors. Oliveria and colleagues⁶⁹ reported age- and sex-standardized incidence rates of symptomatic hip, knee, and hand OA of 88, 240, and 100 per 100,000 person-years, respectively, in participants in a Massachusetts health maintenance organization (Fig. 171.4). Kopec and colleagues,⁷⁰ using an administrative database in British Columbia, Canada, reported trends in standardized incidence rates for OA in any joint site over an 8-year period (Fig. 171.5). A study using a military database to assess incident hip OA found an overall incidence rate of 35 cases per 100,000 person-years, with higher rates among women and blacks (54 cases per 100,000 person-years for women, and 51 cases per 100,000 person-years for blacks).⁷¹

Progression of symptomatic OA is also understudied, despite its significant impact. In the Study of Osteoporotic Fractures, of approximately 6000 women followed over 8 years, 12.6% had radiographic hip OA at baseline, with almost half of cases symptomatic. At follow-up, almost a quarter of hips with symptomatic OA at baseline had progressed to total joint replacement.⁴⁷ A different way of assessing the burden of symptomatic OA is by considering the lifetime risk, which represents the probability of developing the condition over the course of a lifetime. Using data from the Johnston County Osteoarthritis Project, Murphy and colleagues⁷² reported a lifetime risk of symptomatic knee OA of 45%, with higher risk in those with prior injury and in obese individuals. The lifetime risk of symptomatic hip OA was 27% and was higher in women than in men (31% and 20%, respectively).⁷³ A UK study estimated the lifetime risk of total joint replacement

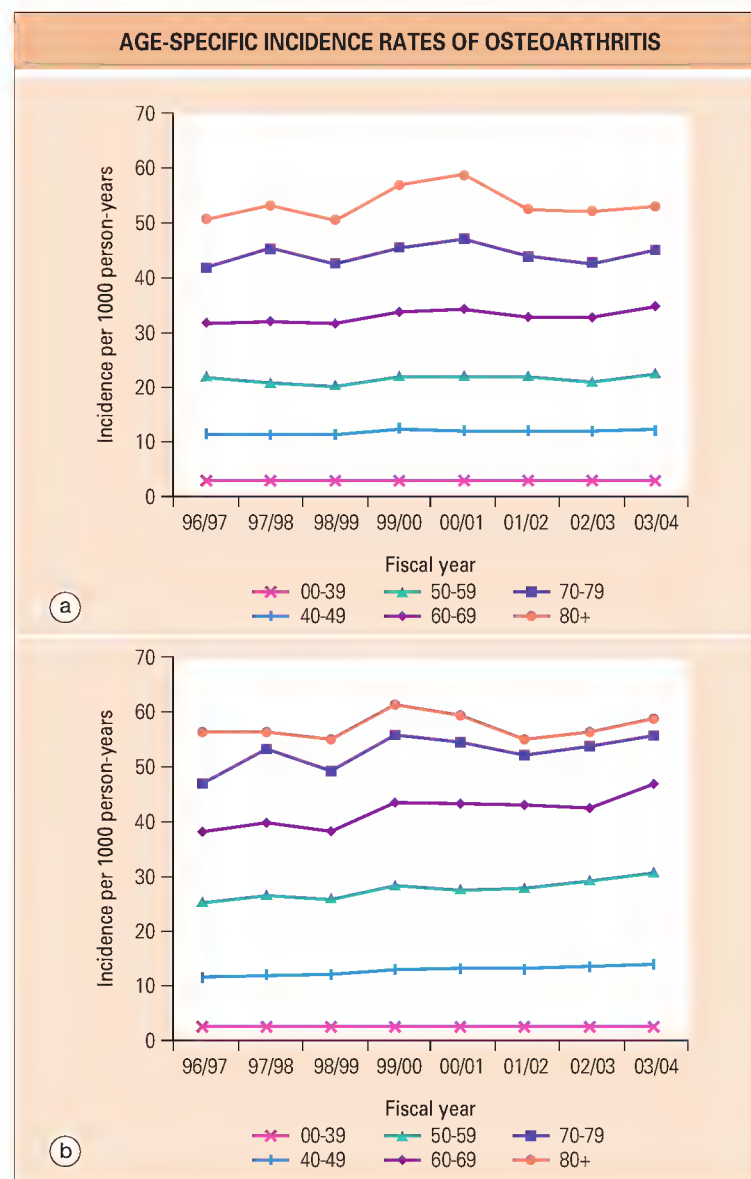


Fig. 171.5 Incidence rates of osteoarthritis in British Columbia, Canada, from 1996-1997 to 2003-2004 for men (a) and women (b) of various ages. (From Kopec JA, Rahman MM, Sayre EC, et al. Trends in physician-diagnosed osteoarthritis incidence in an administrative database in British Columbia, Canada, 1996-1997 through 2003-2004. *Arthritis Rheum* 2008;59:929-34. Reprinted with permission of John Wiley & Sons.)

at the knee (11% for women and 8% for men) and hip (12% for women and 7% for men),⁷⁴ revealing a substantial difference between estimates for symptomatic OA and for “end-stage” OA, although comparisons are complicated by the impact of numerous factors that affect the decision to undergo joint replacement. Assessment of incidence and progression of symptomatic OA is another area that will likely benefit from the increasing use of MRI, because this modality provides a greater sensitivity to change compared with conventional radiography.⁵²

MORTALITY IN OSTEOARTHRITIS

Hochberg⁷⁵ published a systematic review that revealed moderate evidence of increased mortality in individuals with OA compared with the general population. One study showed an increased mortality risk with increasing numbers of joint groups affected by OA, as well as reduced survival in individuals with hand, bilateral knee, or cervical spine involvement, but not in those with hip, foot, or lumbar spine involvement.⁷⁶ This modestly increased mortality risk, determined through a review of nine studies, appeared to be due primarily to cardiovascular and gastrointestinal causes.⁷⁵ A study published since that review confirms excess all-cause mortality in OA patients (defined as those having a KL grade of at least 1 in at least one knee or hip) compared with the general population (standardized mortality

ratio [SMR], 1.55; 95% confidence interval, 1.41 to 1.70); the excess risk was particularly notable for cardiovascular mortality (SMR, 1.71) and dementia-related mortality (SMR, 1.99).⁷⁷ Higher mortality was associated with increasing age, male sex, walking disability, and self-reported comorbidities (diabetes, cancer, cardiovascular disease) but not with joint affected, previous joint replacement, obesity, nonsteroidal antiinflammatory drug use, depression, or baseline hip or knee pain. The authors hypothesize that reduced physical activity and a chronic inflammatory state in OA patients may contribute and should be aggressively managed.⁷⁷

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172

Local and systemic risk factors for incidence and progression of osteoarthritis

■ DAVID T. FELSON ■ YUQING ZHANG

- Osteoarthritis is caused by a combination of systemic factors and factors in the local joint environment. The systemic factors such as aging cause joints to be vulnerable to acute or repetitive injury.
- Osteoarthritis is mechanically driven, and factors that increase focal loading (stress) across the joint increase the risk of disease incidence and progression. For knees, this is varus/valgus malalignment, and for hips, the most common cause is abnormal joint shape, which often develops in childhood.
- In the knee, obesity and previous major joint injuries such as a meniscal tear are powerful risk factors for disease, but the etiologic roles of physical activity and muscle weakness across the knee are less clear.
- Because knees and hips with osteoarthritis all have risk factors for disease, they also all have risk factors for disease progression. Therefore identifying risk factors for progression is very difficult, whereas risk factors for new-onset (incident) disease can be identified readily.

INTRODUCTION

An appreciation of risk factors that lead to osteoarthritis (OA) may provide insights not only into disease pathogenesis but also into opportunities for disease prevention and treatment. This chapter focuses on risk factors for OA of the knee, hip, and hand, the structures most commonly affected by symptomatic disease. Since most studies have focused on OA of the knee, the joint whose involvement is most commonly disabling, the majority of this review covers knee studies. Furthermore, the chapter focuses primarily on risk factors for incidence on the assumption that they also affect risk of progression. The one exception is malalignment, which is a stronger risk factor for progression than incidence. When there are specific relevant risk factors for hip or hand OA, these are discussed.

THE CHALLENGE OF STUDYING INCIDENCE VERSUS PROGRESSION IN OSTEOARTHRITIS

Epidemiologists generally distinguish between the new onset of disease (incidence) and worsening of disease in persons who already have it (progression). In OA this distinction is generally applied to radiographic disease, in which incident disease is defined in persons who initially have no radiographic disease and then develop it. Individuals who already have radiographic disease are followed for disease progression. Natural history studies and clinical trials focus almost solely on disease progression because subjects with clinical symptoms usually have radiographic OA.

Although the distinction between incidence and progression has been useful for OA research, any distinction is artificial, because there is no clearcut time when disease suddenly occurs. OA is an evolving disease of insidious onset. Structural changes and symptoms often do not occur suddenly but rather develop gradually, from mild and occasional to worse and persistent. Any threshold beyond which a person is labeled as having disease divides a continuum of both structural change and pain evolution into categories that are, to some extent, artificial. Further, depending on the

particular radiographic feature and the definition of pain that constitutes the threshold, OA may be defined differently by different investigators in different studies.

THE DISCORDANCE BETWEEN RADIOGRAPHIC OSTEOARTHRITIS AND JOINT PAIN

Many persons with radiographic disease have little if any joint pain, and many persons with joint pain do not have radiographic OA. Further, the radiographic changes of OA occur fairly late in the development of disease. What is most important from a clinical and public health perspective is joint pain, which causes suffering and disability. Even though there is a discordance between radiographic disease and joint pain, radiographic knee OA is a very strong risk factor for knee pain (e.g., those with Kellgren-Lawrence grade III OA in the knee have a ninefold risk of knee pain compared with those who have grade 0 OA).¹

Because the literature on risk factors for OA contains a mixture of studies of radiographic disease (most studies) and studies of symptomatic disease, this chapter mixes them also. There is no evidence yet that specific risk factors affect pain and not structural disease represented by radiographs, although for some risk factors such as muscle weakness, there appears to be a much stronger relation with symptoms than with structure.

A FRAMEWORK FOR UNDERSTANDING SYSTEMIC AND LOCAL RISK FACTORS FOR OSTEOARTHRITIS

As shown in Fig. 172.1, OA is caused by a combination of systemic factors and factors in the local joint environment. Many systemic factors may cause disease by affecting the vulnerability of the joint within the local environment (e.g., muscle weakness, neurologic response times). Because they operate on all joints that might be vulnerable to OA, systemic factors are conceived as having systemic effects, but the mechanisms underlying their effects on specific joints are in fact local.

Systemic risk factors

As reviewed in the previous chapter, OA occurs primarily as people get older. Changes in the joint environment with aging have a combined effect on the joint, making it vulnerable to the development of OA. Cartilage gets thinner with age. This may increase the laxity of the joint, making it more vulnerable to injury and it increases cartilage susceptibility to shear stress at the basal levels where cartilage attaches to bone. Early lesions of cartilage damage² show clefts at this basal level suggesting shear-stress damage. With age, chondrocytes, which do not replicate throughout life, become senescent and become less responsive to regulatory growth factors in the cartilage matrix environment,³ and the cartilage matrix itself changes in ways that make it more vulnerable to injury.

The local joint environment also changes with age in ways that make the joint susceptible to damage. With age, muscles become weaker and less well conditioned. Reaction times slow so that incipient injury to a joint from an oncoming weight-bearing load may not be buffered or shock absorbed as competently in an older joint as in a younger one. Aging assumes such a major place as a risk factor for OA because, in aging, more than one of these factors operates at the same time to increase disease risk.

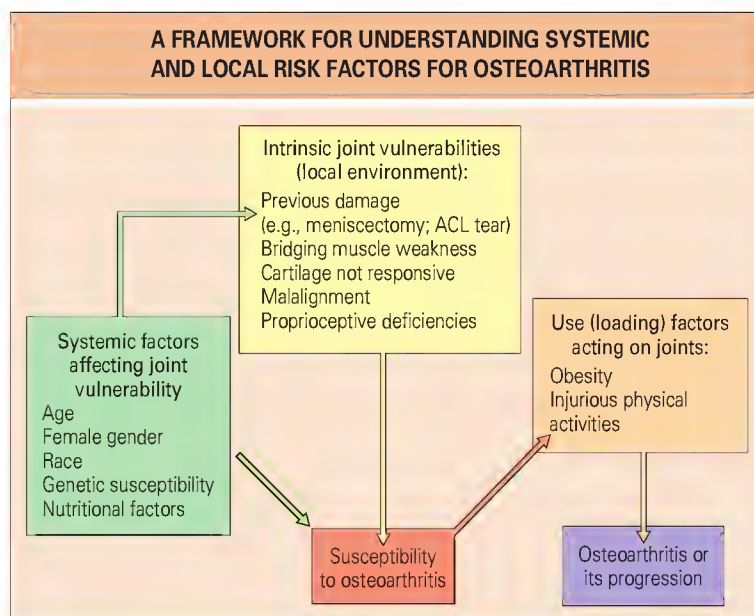


Fig. 172.1 Systemic risk factors can act both systemically and, more often, by affecting elements of the local joint environment that increase susceptibility of the joint to osteoarthritis. ACL, anterior cruciate ligament.

Much less well understood is the increase in OA risk that occurs in women compared with men, especially in women after menopause. Some of the changes in local joint environment may be more prominent in women (e.g., loss in strength and conditioning), and hormone-related changes that occur in postmenopausal women may increase disease risk, although the data on estrogen loss and its relation to the development of OA are mixed.⁴

The relation of systemic factors such as genetic and ethnic predisposition are covered elsewhere in this section, but like other systemic factors, it is likely that these operate by making the local joint environment more vulnerable to disease.

Another set of systemic factors that may influence the risk of disease are nutritional deficiencies. For a number of vitamin and other micronutrient deficiencies, there is now conflicting evidence on their association with disease. For example, vitamin D deficiency was tied to progressive knee OA in one study⁵ and incident hip OA in another,⁶ but subsequent studies of knee OA have shown no association of vitamin D deficiency with disease risk.⁷ Despite one report suggesting that vitamin E deficiency may be related to OA progression risk,⁸ trials testing vitamin E supplementation showed no effect on OA.⁹

Even if it does not have direct effects on joint structure, vitamin D deficiency may have indirect effects on joint health by lowering the threshold for joint pain. Vitamin D deficiency has been linked with generalized pain, and vitamin D deficiency may impair muscle function so that rehabilitation is difficult and conditioning impeded in those affected, which could in turn affect the course of knee OA in that person.

Vitamin K deficiency due to inadequate intake of cruciferous vegetables is common in older people. Vitamin K is a critical cofactor involved in enzymes that are active metabolically in both cartilage and bone, and its deficiency may impair the actions of these enzymes, making cartilage and underlying bone vulnerable. In one large study, vitamin K deficiency was associated with hand and to a lesser extent knee OA,¹⁰ and results of a limited clinical trial in hand OA,¹¹ although not formally positive, suggested in subgroups in whom vitamin K deficiency was corrected by supplementation that joint space loss was prevented. A more definitive study of the effect of vitamin K on OA is needed.

That systemic predilection is an important element of OA risk stems from studies showing that a person with OA in one joint is at high risk of getting it in others, even other joints distant from the first. For example, those with hand OA have a high risk of getting knee or hip OA,¹² and persons with meniscal tears, already at high risk of knee OA, are at even higher risk if they have hand OA.

Factors in the local joint environment

The physiologic distribution of load across a joint conforms with normal joint anatomy when the joint is healthy. For example, the medial

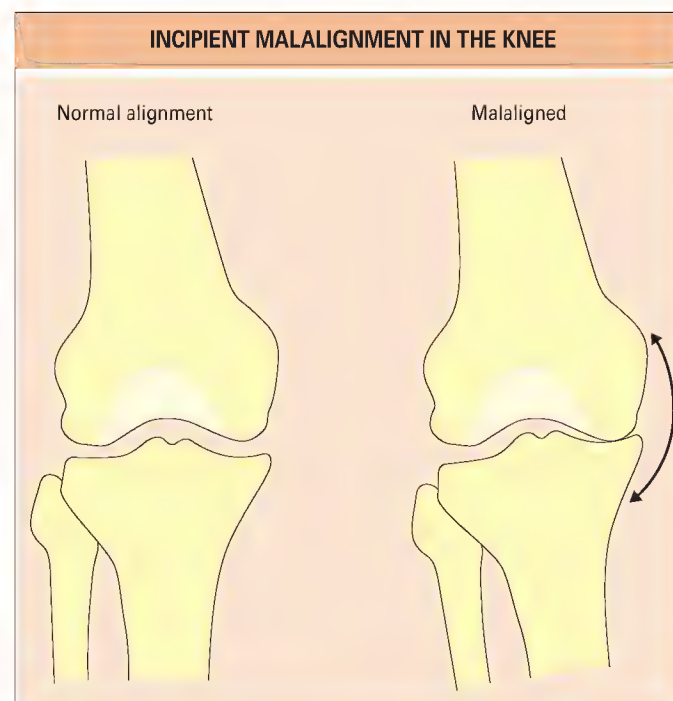


Fig. 172.2 With normal alignment (left), loading occurs physiologically. With early medial disease (right), there is a tilting of the joint so that focal load (stress) increases medially (curved line with two arrowheads), which leads to further focal medial load. A vicious cycle of increased medial joint damage, more tilting, and further increased medial stress develops.

compartment of the knee is designed to carry more load than the lateral compartment based on its larger size and concave-convex tibiofemoral condylar shape. In all joints, cartilage and other structures in the joint are designed to bear a certain amount of stress (force per unit area) during loading and joint use. When the direction of the transarticular load changes or when the joint becomes misshapen, altering loading patterns inside the joint, focal loads within the joint transcend physiologic parameters and joint damage can occur. This damage usually occurs focally at the site of excess load. For example, when the knee becomes varus malaligned (bowlegged), excess load is transmitted through the medial compartment of the knee, and areas within the medial compartment experience a heightened risk of cartilage loss and bony change. Such changes can be induced in rabbits just by putting a spring across the proximal and distal medial knee compartment, which increases load medially.

In the hip, abnormal joint shapes may develop during childhood but may not be clinically manifest until adult years because the excess loads conferred by these abnormal joint shapes are tolerated until adult years when compensatory joint-protective mechanisms do not work as well. Any combination of different directions of load or abnormal focal stresses because of abnormal joint shape accelerates the development and progression of OA and can constitute one of the strongest risk factors for disease.

OA is a mechanically driven disease, and one of the key contributors to loading in the knees is malalignment in the frontal plane (varus or valgus). In nonosteoarthritic knees, there is usually at most a trivial degree of malalignment, since malalignment develops as a consequence of disease.¹³ As disease develops, focal involvement within the joint (e.g., focal cartilage loss or meniscal extrusion) leads the knee to tilt and bony remodeling occurs, with the knee becoming increasingly malaligned (Fig. 172.2); with a little bit of varus malalignment comes increasing medial loading and more damage to the medial side of the knee, which leads to yet more tilting of the joint and more malalignment. The same is true of valgus malalignment.¹⁴ In this way, malalignment may contribute to a vicious cycle of focal joint damage leading to increased focal stress and further joint damage.

The direction of loading across the knee is determined by the origin and direction of pull of the muscles that move the joint; for the knee, the proximal origin is around the hip joint and the distal origin, the ankle. Thus the mechanical axis around the knee is determined by a line from the femoral head to the knee (the femoral mechanical axis) and the angle it forms with a line drawn from the ankle to the knee (the tibial mechanical axis). Full-limb radiographs that assess the mechanical axis from the hip to the knee and from the knee to the ankle are the ideal measure of standing

malalignment. The knee radiographs contain images of only the distal femoral and proximal tibial shafts and where they intersect in the knee, and a measure of this angle (the anatomic axis), despite its being correlated with the mechanical axis, is an imperfect substitute for measurement of the mechanical axis.¹⁵ Although it is easy to assess malalignment on a radiograph, the radiograph measures malalignment only in one static position. The optimal way to assess medial-lateral alignment across the knee is during walking, so-called dynamic alignment. A key measure of medial load is the adduction moment, an estimate of the load across the medial compartment of the knee during walking.¹⁶ High adduction moments are a feature of medial knee OA and markedly increase the risk of further medial disease progression.¹⁷ Limbs with varus mechanical axes are at high risk of progression of medial knee OA,^{18,19} either measured as later medial joint space loss on radiography or medial cartilage loss on magnetic resonance imaging (MRI).²⁰ and valgus limbs have an increased risk of lateral joint space loss and commensurate cartilage loss. In knees without OA, malalignment is also a risk factor for disease incidence.^{14,21}

Because varus malalignment is extremely common in advanced OA, it is sometimes not clear conceptually whether it simply represents one element of disease occurrence or should be regarded as a risk factor. The truth is that it is both, but its presence in severe disease makes it difficult to disentangle whether severe disease propels progression by itself or whether it does so only in the face of malalignment. Regardless, malalignment, when present, is such a potent risk factor for disease progression in knee OA that other known risk factors assume less prominence when compared to it. For example, obesity is a potent risk factor for the new onset of knee OA, but in knees with established disease, obesity's effect on progression varies depending on the limb's alignment.¹³ Only in neutrally aligned knees is there an effect of obesity on disease progression.²² In knees with disease and varus malalignment, obesity has no effect on the risk of progression, which suggests that the effects of malalignment are dominant. This potent effect of malalignment constitutes one major reason why risk factors for progression of knee OA have been hard to identify.

Previous joint injury

In some joints such as the ankle and the wrist, which are only rarely affected by OA, most disease is caused by major joint injury.²³ For example, a plafond fracture of the ankle causes inevitable OA. In joints more commonly affected by OA such as the knee and hip, major joint injuries, perhaps even unrecognized ones, also are likely to be major causes of disease. Even though such injuries originate outside the joint, they are placed in the category of local joint environmental factors because they ultimately alter the joint environment in ways that dictate what happens to the joint. In the knees, the common joint injuries with important effects on subsequent joint function and disease are anterior cruciate ligament (ACL) tears and meniscal tears.

ACL tear is increasingly common in young athletes, especially girls. Jumping and landing with an internally rotated femur is a major precipitant of tearing of the ACL, an injury that is often accompanied by other internal derangements such as meniscal and medial collateral ligament tears. The risk of knee OA after an ACL tear differs greatly depending on whether the meniscus or other structures in the knee were damaged at the time of the injury. Isolated ACL tears may pose only a modest risk of later knee OA (0% to 13% at a longer than 10-year follow-up).²⁴ Graft surgeries to repair the ACL or reconstitute the ACL do not decrease the risk of later knee OA, in part because the grafts probably do not reestablish normal knee biomechanics.

Menisci, fibrocartilaginous structures sitting between the femur and tibia in the medial and lateral knee compartments, distribute weight-bearing load widely throughout the knee; they also serve as spacers between the femur and the tibia so that ligaments do not become lax. Meniscal tears are a major cause of knee OA. Tears occur either acutely or chronically. Young and middle-aged persons can sustain acute tears during sports and other activities, sometimes during twisting injuries. These tears are often operated on and repaired with the meniscus partially resected. Knees that have undergone these partial meniscectomies are at high risk of later knee OA,^{25,26} and this high rate of OA has led to concerns that perhaps menisci should not be even partially removed because of the important biomechanical functions they serve. However, in a longitudinal study of persons with and without incidental meniscal tears, none of whom had undergone surgery, those with meniscal tears had a much higher risk of later knee OA²⁷ than those without such tears. Thus when the meniscus is torn (symptomatically or not), whether operated on or not, this tear markedly increases the risk of later knee OA. Chronic meniscal tears²⁸ occur in from 20% to 40% of middle-aged and older men and women and are not strongly associated with knee pain.

Thus not only are meniscal tears, even incidental ones, potent risk factors for later OA of the knee, but they are common findings. This suggests that much of the knee OA that occurs in middle-aged and older people may be a consequence of a meniscal tear. In middle-aged persons, incidental tears may occur in already degenerating meniscal tissue, and such degenerative changes may precede changes in hyaline cartilage; these changes make the meniscus highly susceptible to tears with minor injury, which then cause disease elsewhere in the joint.

Those with OA who have concurrent meniscal tears are also at high risk of experiencing disease progression.²⁹ Menisci are tethered to a variety of other structures within the joint, and when these connections get torn, menisci are extruded outside the joint margin, and the joint is essentially without a functioning meniscus. This extrusion, which can be partial or complete, is itself a major risk factor for disease progression.²⁹

Neuromuscular factors and osteoarthritis

The local joint environment includes structures outside the articular surface, including muscles and the nervous system that controls those muscles. Healthy muscles and their coordinated movements during loading, weight bearing, and joint excursion are critical to joint protection. To the extent that joints move beyond physiologic range of motion because of a tear in a ligament, joints can be put in positions in which protective mechanisms do not work optimally, and that can lead to joint injury. This could be one reason why women with hyperlaxity of the joints may be at increased risk of OA, although the effect of hyperlaxity on OA is by no means clear.³⁰ Perhaps more importantly, muscle conditioning and the spinal reflex system that coordinates muscular movement smoothly through joint excursion must function normally for the joint to be protected during use. Muscles move in a coordinated fashion thanks to nervous system organs inside periarticular muscle, ligament, and skin, which provide instantaneous spinal cord-based feedback on the position and movement of muscles across the joint and constitute the system of proprioception across the joint. Studies³¹ suggest that those with knee OA have impaired proprioception compared to those of a similar age without knee OA. Proprioception can be measured in a number of ways, which do not all provide the same physiologic information. One method is to assess a person's ability to detect trivial passive movement of the joint, and another is to evaluate a person's ability to reproduce a particular knee flexion angle after they have used their muscles to generate that flexion angle. If they cannot reproduce that flexion angle, then their proprioceptive acuity is poor. In a study of over 2000 individuals with and without knee OA,³² those who showed poor accuracy in reproducing knee flexion angle had a slightly greater functional decline and slightly worse pain than those who showed better accuracy but did not have an increased risk of incident or progressive radiographic knee OA. Measuring proprioceptive acuity is fraught with problems of poor reproducibility, and different ways of measurement can sample different physiologic phenomena only some of which may be relevant to knee OA. Thus further data are needed on the impacts on OA of different neurosensory inputs that are part of proprioceptive pathways.

In addition to coordination of muscle activity across the joint, optimal neuromuscular function should include adequate muscle strength so that muscles can stabilize the joints during activity, preventing them from moving beyond physiologic excursion limits, and contract in such a way that load is distributed broadly across the joint. In theory, a person whose muscles bridging the joint are strong should have less risk of developing knee OA and a lower risk of progression if disease is present.

Despite the conceptual appeal of invoking muscle strength as an important factor related to the development of knee OA, the results of longitudinal studies examining the relation between muscle strength and the development of knee OA have been mixed. Two large well-done studies suggest that weak quadriceps strength increases the risk of both radiographic OA³³ and joint space loss³⁴ in women but not men. Importantly, in one of these studies,³⁵ quadriceps weakness increased the risk of developing symptomatic knee OA in both sexes. The ratio of quadriceps to hamstring strength has shown no relation to the development of knee OA.³⁵ In longitudinal studies of individuals with knee OA, quadriceps weakness does not appear to predispose to radiographic progression nor to cartilage loss on MRI.^{36,37} Even prolonged strength training programs have had only a borderline effect on disease progression.³⁸ Quadriceps weakness may predispose to structural disease in the patellofemoral joint more than it does in the tibiofemoral articulation.^{39,40} Although studies examining quadriceps weakness and structural disease have generated inconsistent findings, persons who are weaker have worse pain and function in the diseased joint than those who are stronger.^{33,41} This relationship is present even when those who have pain during the muscle strength examinations are excluded.⁴²

Muscle strength or function may contribute to disease in the knee in other ways. Strong hip external rotators and abductors can alter the position of the knee during walking and thereby affect knee mechanics and influence the development or progression of knee OA. In fact, weakness of muscles surrounding the hip exists in persons with knee OA,⁴³ but it is not clear if this weakness is causal. Also, obese persons at high risk of knee OA often have higher muscle mass and strength than thinner persons at lower risk of OA. However, these obese persons may have weakness relative to the amount of muscle mass (so-called muscle-specific torque) and that may predispose them to OA.⁴⁴

Ironically, in hand joints high levels of grip strength may act like a vise to excessively increase joint loading and thereby increase the risk of OA in proximal hand joints. Thus metacarpophalangeal joints of the hands and the joints at the base of the thumb are at high risk of OA when grip strength is increased.⁴⁵ It is not clear whether this same relationship exists for other joints.

Hip osteoarthritis and abnormalities of joint shape

When the proximal and distal sides of a joint fit together normally, load is distributed physiologically. When one of the bones is misshapen, either due to a developmental abnormality or as a result of injury, this can introduce increased levels of focal load (stress) across the joint. The increase may be modest and the effects may not be immediate; it may take many years for the increased loading to generate the joint injury that represents OA. Abnormal bone shape likely accounts for a large percentage of hip OA in the community. A variety of shape abnormalities can occur. One is hip dysplasia in which there is an underdevelopment of the acetabulum leading to undercoverage of the femur and excess focal stress where the edge of the acetabulum contacts the femur. Others include a nonspherical femoral head or an acetabulum that extends too far around the femoral head; both of these latter problems can cause femoroacetabular impingement (FAI).⁴⁶ Longitudinal studies suggest that FAI is an important cause of later hip OA.⁴⁷⁻⁵⁰ The consequences of any of these abnormalities is that the person with the abnormality is at high risk of developing hip OA; the age at which the disease develops is related to the severity of these abnormalities and may be a consequence of use-related factors (particular sports other activities).

Although FAI is slightly more common in men than in women, the presence of hip dysplasia in early childhood is far more common in girls than in boys and can sometimes be identified and corrected at birth. Milder forms of dysplasia of the acetabulum are likely not identified at birth and survive into adolescence and adulthood, causing later hip OA.

Chinese persons, both in China and in the United States,⁵¹ have a much lower risk of hip OA than whites in the United States.⁵² Morphometric analyses of nondiseased hips in Chinese and white women⁵³ showed that FAI changes were far more common in whites, which suggests that this anatomic abnormality is the likely source of racial differences in hip OA prevalence.

Risk factors relating to loading of the joint

OA develops as a consequence of impaired joint physiology on which is superimposed excess loading. In the context of a physiologically normal joint without a previous injury, normal levels of human physical activity are unlikely to cause disease. For example, marathon runners who do not run professionally do not appear to be at any increased risk of knee OA.⁵⁴ OA occurs when that loading occurs in an environment in which the joint is already injured or impaired or in which the loading is so excessive or injurious that even a normal, well-functioning joint cannot tolerate it without injury. For example, marathon runners who have sustained previous meniscal tears are at extremely high risk of later OA of the knee. Also, Olympic team marathoners and professional runners, who probably subject their knees and hips to a quantity of loading that may be beyond normal physiologic adaptation, are at high risk of later hip and knee OA.⁵⁴⁻⁵⁶

Loading is not a simple construct. There is the quantity of a given load during a step or use of a joint, a quantity that might be affected by the strength of muscle contraction; the load borne by a weight-bearing joint would be increased in an obese person, for example. Then the joint might be at risk based on the speed with which that load was applied (e.g., a runner would apply more load to the knee than a walker). Understanding the effect of loading on the development of OA will necessitate disentangling different types of load and their relative effects on joint function, especially in an environment in which joint-protective mechanisms might be impaired.

Obesity

Being overweight increases a person's risk of developing knee OA. For women the risk of disease increases monotonically with weight. This may or may not be true for men because studies conflict on this matter, but among men it is clear that being obese or very overweight increases the risk of knee OA.^{13,57} In general, the relation of obesity with knee OA is stronger in women than in men.

For hip OA the relation of obesity is less strong and less clear. The development of new-onset symptomatic OA is increased in persons who are obese, as is the risk of developing bilateral radiographic disease, although there is no significant or consistent relationship between obesity and the development of unilateral OA of the hip.^{57,58} The weaker relationship of obesity with hip OA than with knee OA may be because hip OA is often caused by hip shape abnormalities (see earlier), and weight therefore may play a lesser role in hip disease.

Obese persons have more severe pain than nonobese persons with the same level of radiographic disease, and they also tend to be more functionally limited. Weight loss studies suggest a modest effect on improvement of symptoms for those with knee OA, although the amount of weight loss achieved in these trials has been relatively small (5 to 10 kg). Studies of persons undergoing bariatric surgery, which produces massive weight loss, have shown a dramatic improvement in knee OA symptoms, which suggests that if weight loss were sufficient, patients' symptoms would improve.⁵⁹ Indeed, recent randomized trials in which those assigned to calorie restriction achieved sustained weight loss suggest that a major improvement in knee pain can be achieved, especially if the weight loss is accompanied by an increase in physical activities such as walking.⁶⁰

Obesity could cause disease through two different mechanisms. First and most obviously, it could produce excessive load that then leads to joint deterioration. In fact, each pound of increased weight increases loading across the knee by 3 to 6 pounds.⁵⁷ However, studies also suggest that obese persons are at a higher risk of hand OA than persons who are not obese.⁶¹ In all likelihood, there is no increase in load across hand joints in persons who are obese. Therefore another explanation for obesity's effect on OA is that obesity may have metabolic effects on joints, which in turn produce some joint degeneration including cartilage loss. Obesity has a far greater effect on knee OA than it has been shown to have on hand OA, which suggests that most of the effect of obesity can be explained by its effect in producing excess load. Studies so far have failed to identify a metabolic factor that affects OA occurrence.⁵⁷

Physical activity: injurious or protective?

Physical activity is greatly varied and so are its effects on the joint. Furthermore, at different stages of disease the effects of physical activity may differ, so that in a normal joint, activity and loading across the knee might have trophic effects on joint cartilage and other structures, whereas in joints that are damaged, particular types of physical activity might be injurious. Given the various types of physical activity and their likely different effects at different stages of joint diseases, it is not surprising that the results of studies evaluating effects of physical activity on OA vary tremendously. Some studies suggest that physical activity might actually protect against the occurrence of disease, whereas others point to a heightened risk of disease or its progression in those who engage in particular types of physical activity or who already have diseased joints. These conflicting data suggest that there is no single answer to the whether physical activity causes or protects against OA. The relation of physical activity to disease may depend on the specific activity and stage of disease.

Epidemiologic studies that have incorporated such MRI findings of OA as cartilage defects and bone marrow lesions have been a bit more consistent in suggesting that physical activity increases the risk of joint damage. For example, in a cross-sectional study, those with no knee pain but with high physical activity scores had more evidence of cartilage loss, meniscal damage, and other findings of OA than those with lower activity scores.⁶² Further, in persons who had MRI evidence of knee joint damage at baseline, damage to the joint worsened over time more often if the individuals walked more than 10,000 steps a day than if they walked less than this amount.⁶³ Even so, studies including MRI assessments have not been consistent in their findings.⁶⁴

In nondiseased joints in middle-aged women, physical activity has been associated with increased joint space, and in one study of persons who had experienced injury but did not have OA, physical activity actually led to an improved biochemical profile within cartilage as documented by biochemical imaging of cartilage.⁶⁵ Further, in recreational runners, running marathons (at least occasionally) does not increase the risk of getting knee OA. Moreover, in older persons, self-reported heavy levels of activity and walking

several miles a week did not increase joint space loss or MRI findings of cartilage loss. This was true even in a group of persons with knee OA, which suggests that walking may be an exercise that, even in vulnerable knees, is not risky.⁶⁶

If physical activity does not consistently increase the risk of OA in the knee and other joints, when and in whom might it pose a risk? First, as noted earlier, elite marathon runners—those on Olympic teams and who run professionally—are at a high risk of developing knee and hip OA at a relatively early adult age (in their 30s or 40s).⁵⁶ Second, those whose jobs require manual labor with repetitive activities that load a specific joint excessively and repeatedly tend to get OA in the overused joint (e.g., cotton pickers in hand joints; miners in backs and knees), which suggests that even normal joints can develop OA if these joints are forced to do the same laboring task for hours every day and many weeks each year over many years. Lastly, marathon runners who have already had meniscal tears are at high risk of advanced OA if they continue to run.⁶⁷ Studies of physical activity and OA have been greatly limited by the challenge in accurately assessing physical activity patterns in people. Surveys of self-reported physical activity are highly imprecise and may not identify those who are especially active in ways that might be dangerous to their knees or hips. In the meantime,

those with disease are at heightened risk of disease progression if they continue to engage in impact-loading activities that might have led to the joint injury in the first place; thus football players with knee injuries will get worse disease if they continue to play.

The peculiar case of bone mineral density: is it systemic or local?

High bone mineral density increases the risk of knee and hip OA independently of other factors such as obesity and strength. The relation of high bone mineral density to hand OA is less consistently reported, and bone mineral density probably has no effect on the risk of progressive OA.⁶⁸

One explanation for the relation of high bone mineral density with knee and hip OA could be that high bone mineral density in the lumbar spine and proximal femur reflects long-standing high levels of physical activity and obesity, both of which load these bones. The same factors may be tied to increased risk of knee and hip OA. However, that would not explain any relation of high bone mineral density with hand OA, which has been shown in some studies.⁶⁹ This well-known association of high bone mineral density with OA risk remains a mystery.

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173

Clinical features of osteoarthritis

■ ROY D. ALTMAN

- Osteoarthritis (OA) is the most common articular disease.
- About 50% of persons with radiographically evident OA have symptoms.
- Pain is the most common reason why a patient with OA consults a physician.
- Pain in OA has many potential sources. There is no direct pain from cartilage, synovial fluid, or the inner two thirds of menisci. Pain fibers are present in the remaining tissues surrounding the joint.
- A variety of other symptoms can result from OA that affect function and quality of life.
- Signs of OA can be absent, subtle, or severe.
- Although OA can involve virtually any joint in the body, the most commonly affected joints are hands and feet, hips, and knees.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, accounting for 30% of physician visits.¹ It may be defined as a “heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins.”² More specifically, OA is “usually a progressive disease of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial joint tissues, including articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, peripheral nerves, or synovium. This ultimately results in the breakdown of cartilage and bone, leading to symptoms of pain, stiffness and functional disability. Abnormal intra-articular stress and failure of repair may arise as a result of biomechanical, biochemical and/or genetic factors. This process may be localized to a single joint, a few joints, or generalized, and the factors that initiate OA likely vary depending on the joint site.”³ OA is usually classified as either primary (idiopathic) or secondary (i.e., associated with a known condition). Although OA is present by histologic or radiographic criteria in nearly 80% of people by the age of 80 years, at any age only half have symptoms.⁴ Symptoms are often variable and intermittent. OA affects as many as 12% of the U.S. population between the ages of 25 and 74 years.⁵ There is a modest correlation between the presence of symptoms and the severity of anatomic or radiographic changes.

Although variable in its presentation and course, OA often carries significant morbidity. In addition to the effects on the individual, the cost of OA to society is also significant,¹ related to its high prevalence, the reduced ability of those affected to perform both occupational and nonoccupational activities, the occasional loss of a patient's ability to undertake self-care, and the related drain on health care resources.⁶

OA is no longer considered a “degenerative” or “wear and tear” arthritis but rather involves dynamic biomechanical, biochemical, and cellular processes.⁷ OA is currently viewed as a disease of the entire joint and, therefore, the failure of the joint as an organ.⁸

Although the lesions of OA are almost always bilateral, there is a tendency for one side to be more symptomatic than the other. The symptomatic side may alternate over time. The presence of unilateral disease may suggest OA secondary to trauma. In contrast to systemic inflammatory arthritides, OA lacks constitutional symptoms (e.g., fever, weight loss, malaise).

When OA is symptomatic, the most prominent complaint is pain. It remains unclear why fewer than 50% of persons with severe radiographic

OA (Kellgren and Lawrence⁹ grade III and IV) report pain.¹⁰ Most often, symptoms of OA are insidious in onset, but flares can occur. Symptoms and signs of OA are listed in [Box 173.1](#).

SYMPTOMS

Pain

Pain is the most common reason why a patient with OA seeks the help of a physician.¹¹ The pain of OA changes during the day and has been demonstrated to vary by 20% within a given week and from week to week.¹² Pain in OA is also influenced by pain at other sites and by patient adaptation and avoidance strategies, and it is inextricable from function.¹³ The pain of OA is associated with poor sleep, fatigue, changes in mood, and impaired quality of life. When pain is present, determining the cause is difficult ([Table 173.1](#)).¹⁴ In knee OA, patients may localize their pain to a compartment of the knee or to the front of the knee but will most often describe their pain as poorly localized. Joint pain is often referred distally; for example, hip pain may be referred into the thigh or knee. Anterior knee pain may represent patellofemoral (anterior compartment) OA. Patients often ascribe increasing pain and stiffness to changes in weather, particularly changes in barometric pressure and ambient temperature.¹⁵ Patients with unilateral knee pain commonly develop bilateral disease (80% by 12 years).¹⁶

The severity of pain should be noted and ideally measured at each visit. The three most commonly used pain scales are the five-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe), the 100-mm visual analogue scale (from 0 mm = no pain to 100 mm = the most pain possible), and the 11-point numerical rating scale (from 0 = no pain to 10 = the most pain possible).

Pain can also be measured through standardized testing. For the hip or knee, the Western Ontario McMaster Universities (WOMAC) Osteoarthritis Index quantifies pain, stiffness, and function in separate subscales. The algofunctional index of Lequesne measures hip or knee pain and function in a single scale. The WOMAC index has been incorporated into the Hip Dysfunction and Osteoarthritis Outcome Score (HOOS) and the Knee Dysfunction and Osteoarthritis Outcome Score (KOOS). Because of the often cyclic nature of OA, an 11-item tool, the Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP), has been developed.¹⁷ For the hand, validated scales include the Australian-Canadian Hand Osteoarthritis Index (AUSCAN) and the Functional Index for Hand Osteoarthritis (FIHOA).¹⁸

The quality of the pain may hint at its pathologic origin. Pain that occurs after exercise is often caused by subchondral ischemia—so-called bone angina. This pain is often aching and deep seated. Pain along the joint margin, with tenderness at the site, may indicate periosteal pain from stretching of the capsule or ligaments or overgrowing osteophytes. The sudden onset of pain with a catching sensation of the knee may be associated with a torn meniscus or a loose body inside the joint. Knee pain accentuated by sitting on a low chair or couch is often patellofemoral in origin. Among individuals 50 years of age or older, 57% with knee pain had pain in at least two other joint areas.¹⁹

There has been considerable progress in the understanding of pain mechanisms (see Chapter 24).²⁰ Identifying the source of pain may help direct therapy. Contributions of the different articular tissues to pain are discussed next.

Damage to articular cartilage

Damage to articular cartilage is a hallmark of OA; yet articular cartilage normally lacks nerve endings and is not a direct source of pain.^{21,22} Menisci similarly do not contain nerves in their weight-bearing surfaces (i.e., the

BOX 173.1 SYMPTOMS AND SIGNS OF OSTEOARTHRITIS

Symptoms	Signs
■ Pain	■ Altered gait
■ Discomfort	■ Tenderness
■ Depression	■ Hard tissue enlargement
■ Stiffness	■ Swelling with/without effusion
■ Reduced function	■ Crepitus
■ Weakness	■ Limitation of motion
■ Grinding or clicking	■ Deformity
■ Instability/buckling	■ Ligamentous instability

TABLE 173.1
Relationship between anatomic site and possible physiologic mechanism for pain in osteoarthritis

Anatomic site	Mechanism
Cartilage (defective or lost)	<i>Synovial:</i> inflammation induced by cartilage “char” fragments, cartilage crystal shedding, cartilage release of cytokines (e.g., interleukin-1), enzymes (e.g., metalloproteinases) <i>Subchondral bone:</i> mechanical stress (see below) <i>Instability:</i> stress on capsule
Menisci	Tear or degeneration: stretch at insertion to the joint capsule, catch between surfaces
Synovial cavity	Stretch of joint capsule, transport of inflammatory mediators between synovium and cartilage
Synovium	Inflammation, hypertrophy
Subchondral bone	Ischemia with increased subchondral pressure, decreased oxygen tension, and increased pH Avascular necrosis Regeneration or repair of infarcted bone
Osteophytes	Periosteal elevation Neural impingement
Joint capsule	Stretch from joint distention Stress at insertion to periosteum and bone
Ligaments	Stress at insertion to periosteum and bone
Bursae	Inflammation, with or without calcification
Muscle	Spasm, contracture Nocturnal myoclonus
Central nervous system	Depression, anxiety, fibromyalgia, nonrestorative sleep
General	Ethnic and cultural factors, coping skills, prior pain experience, abuse Altered function placing stress on other areas of the musculoskeletal system

inner two thirds) and cannot directly account for pain. Nevertheless, abnormalities in articular cartilage, menisci, and even synovial fluid can indirectly cause pain in OA.

Damaged articular cartilage indirectly causes pain due to loss of its structural integrity, alteration in biomechanics, cartilage debris, and release of inflammatory mediators. Structural damage to cartilage causes uneven surfaces, which results in a grinding sensation felt by the patient and crepitus on examination, often accompanied by pain.

When damaged cartilage “char” fragments are released into the synovial cavity, the synovium attempts to clear them, precipitating an inflammatory synovial response. Other microscopic and submicroscopic particulate material released from damaged articular cartilage, such as collagen, proteoglycans, and crystals as well as proteolytic enzymes and cytokines, triggers a synovial inflammatory response. Although synovial inflammation is most often less severe than in the traditional “inflammatory” arthritides (e.g., rheumatoid arthritis), activation of inflammatory responses always occurs in OA joints, at both the synoviocyte and chondrocyte level (which justifies the term *osteoarthritis*).²³

Abnormal cartilage may contain a variety of calcium crystals, including calcium pyrophosphate dihydrate, hydroxyapatite, and basic calcium phosphate. Surface disruption may allow crystal shedding into the joint cavity, which stimulates varying degrees of inflammation.²⁴ In cases in which cartilage is fissured and the subchondral bone is exposed, hydroxyapatite crystals from bone or cartilage may leach or be sheared into the synovial cavity. In addition, the absence of articular cartilage allows loosening and instability of the joint and exposure to subchondral bone.

Other loose bodies in the joint, such as “joint mice” or osteochondromatosis, are potential indirect causes of pain. The disrupted portion of torn menisci can be displaced, stretching the joint capsule. Meniscal horizontal fissures do not usually cause symptoms, but fragments of the degenerated menisci may elicit an inflammatory response or act as loose bodies in the joint cavity.

Role of synovial fluid

Synovial fluid can indirectly cause pain by serving as a transport medium, distending the joint capsule, and/or limiting joint function. In OA the synovial fluid may act as a reservoir for inflammatory cytokines, cells, and crystals. In addition, excess synovial fluid distends the joint, which potentially compresses synovial blood vessels and stimulates pressure receptors in the capsule.²⁵ A distended joint compromises the normal transport of nutrition and gases by synovial fluid between cartilage and synovium. The residual waste products linger in the synovial space and perpetuate inflammation.

The synovium contains nerve fibers. These include A β (large myelinated mechanoreceptor), A δ (large myelinated mechanoreceptor/nociceptor), and C (small nonmyelinated nociceptor) fibers.²⁰ The latter can release both substance P and calcitonin gene-related peptide (CGRP). Substance P stimulates both the pain response and inflammation.²⁶

Role of subchondral bone

Subchondral bone is directly related to pain in OA.²⁷ When subchondral ischemia or increased venous pressure occurs, peptides such as substance P and CGRP are released from the nerve endings in bone.²⁸ The pain of ischemic bone is aching and deep seated. In OA, subchondral cysts and sclerosis are radiographic evidence that localized osteonecrosis has taken place. Bone marrow lesions adjacent to the knee, which may represent areas of trabecular remodeling and can be detected by magnetic resonance imaging, are associated with knee pain and compartment-specific structural deterioration.^{29,30}

Osteophytes are the most consistent pathologic and radiographic finding associated with the presence of pain.³¹ Osteophytes may cause pain directly by distending the periosteum; pain can sometimes be elicited by applying pressure over an osteophyte about the knee or interphalangeal joint of the hand.

Damage to meniscus, capsule, and related tissues

Damaged menisci of the knee change the biomechanics of gait, alter the normal joint congruity, catch between joint surfaces, and stretch the joint capsule. Indeed, an abnormal meniscus is an important predictor of OA disease progression.³²

The joint capsule and periarticular ligaments are stretched by synovial effusions, abnormal menisci, or instability and may cause pain through mechanoreceptors and nociceptors. Stress at the ligamentous insertion on the periosteum stimulates nociceptors. When the periarticular tissues are distorted, the ligaments may be abnormally stressed, which induces contractures that result in decreasing function and increasing pain from stress at ligamentous insertions and periarticular muscle spasm.

Periarticular bursae may become inflamed and hence be a source of pain (e.g., anserine bursitis medial and inferior to the knee). Bursal inflammation is sometimes associated with calcium formation (e.g., calcific bursitis).

Muscle spasm is probably a common source of pain in OA. Muscle spasm may occur in the form of nocturnal myoclonus, altering sleep patterns and resulting in fibromyalgia-like symptoms.³³ Muscle spasm of the lower extremities must be differentiated from pain related to vascular causes (e.g., night cramps) or restless leg syndrome and pain of spinal radicular origin. Joint contractures in OA can cause pain on stretching of the periarticular ligaments and muscles.

Psychological factors and pain

The severity of joint pain is modulated by the individual's perception of pain and unique ethnic, cultural, and personal circumstances. It tends to be more severe in the evenings, on weekends, and early in the work week.³⁴ Pain is complicated by the presence of coexistent or induced psychological distress, such as depression. Pain is also influenced by anxiety and secondary gains.

There is altered central pain processing in OA, characterized by a generalized greater sensitivity to pain in response to experimental stimuli.³⁵

Stiffness

Stiffness may be defined as a sensation of a gelling or tightening of the involved joint that usually occurs after inactivity, such as in the morning or when rising after sitting for a prolonged period. The stiffness in OA usually lasts only a few minutes and almost always less than 30 minutes, in contrast to the diffuse stiffness of rheumatoid arthritis. Also, the stiffness in OA is usually confined to the symptomatic joints.

Other symptoms

The patient may have a sensation of fullness and swelling about the joint. There may be associated warmth. Inflammation and/or contraction of weight-bearing joints is associated with gait disturbance, increased muscle spasm, and reduced quality of life. A contracted knee or hip can produce a prominent limp (see later). Aids to ambulation may reduce the severity of alterations in function.

Impaired function of a weight-bearing joint places stress on the contralateral weight-bearing joints. It is not uncommon for the patient with impaired right knee function (perhaps with pain) to have difficulty with the left hip and vice versa.

Hypertrophic bone formation in interphalangeal joint OA may contribute to reduced dexterity and difficulty performing fine motor movements, such as knitting, sewing, or playing a musical instrument. OA of the first carpometacarpal (CMC) joint may make it difficult to perform many activities of daily living, such as holding a pen.

Inactivity secondary to pain may lead to significant weakness and can be compounded by periarticular muscle atrophy.

Patients may complain of enlargement of the joints of the hand or knee. They may also complain of increasing deformity of the knees, such as knocked (valgus) or bowed (varus) knees. There may be a click or grinding sensation with joint motion, and this grinding may be associated with pain. In the knee, instability is often associated with a feeling that the knee is “giving out.”

SIGNS

Gait

OA of weight-bearing joints leads to altered gait patterns, mostly caused by a conscious or subconscious attempt to protect the joint. Hip, knee, ankle, and foot arthritis give rise to distinctive gait patterns. Obesity compounds the effects of OA in weight-bearing joints by increasing pressures across joint surfaces and altering gait patterns. Increasing body mass index alters knee adduction, knee flexion, and knee rotation moments during gait, with additional changes in knee flexion moment and flexion angle.¹⁶ Alterations in gait aggravate pain in other weight-bearing joints and the low back.

OA of the hip or knee frequently is associated with significant changes in the periarticular muscles, often with atrophy and weakness. Reduced muscle strength is compounded by reduced proprioception.³⁶

Tenderness

There may be tenderness of soft tissues (e.g., synovium, capsule, bursae, and periarticular muscles) or periosteum at the insertion of capsule or ligaments.

Joint swelling

There may be enlargement of the joint from synovitis, synovial effusion, or bony enlargement. Effusions are usually cool or slightly warm to palpation. Effusion of the distal interphalangeal (DIP) joint may present as a cystic herniation (Fig. 173.1); aspiration often reveals a jellylike material reminiscent of a ganglion cyst. Swelling of the joint from an effusion frequently leads to loss of extension.

Crepitus

Grinding, crunching, or cracking may be heard over a joint with OA. Crepitus is caused by movement of uneven surfaces across each other and is best demonstrated with active motion of the joint. This contrasts with the benign “cracking” of the proximal interphalangeal (PIP) joints that occurs when



Fig. 173.1 Interphalangeal osteoarthritis of the hand, with cystic herniation of the fifth proximal interphalangeal joint.

smooth cartilage surfaces are separated, which creates a vacuum sound with release of nitrogen gas.

Limitation of motion

There may be loss of function with reduced motion as a result of pain, synovitis/effusion, or periarticular soft tissue contractures. When motion of a weight-bearing joint is limited, additional stress is placed on ipsilateral and contralateral weight-bearing joints.

Deformity

Deformity may be present in any of the peripheral joints with OA. However, it is most notable in the interphalangeal joints of the hands with enlargement and subluxation, in the first CMC joint, in the knees (varus/valgus deformity), or in the hips (shortened extremity). Deformity may be associated with joint fusion or instability.

Instability

Range-of-motion examination may reveal instability in various planes of motion. For example, instability of the knee may be demonstrated in the anteroposterior planes (cruciate ligament laxity or deficiency) or in the mediolateral planes (loss of meniscus, collateral ligament laxity, loss of medial compartment bony stock).

CLINICAL PRESENTATIONS

OA may involve virtually any joint in the body. Because there is usually an insidious onset of symptoms, an acute presentation suggests a concomitant inflammatory component (e.g., microcrystalline synovitis). OA is most often monarticular in presentation, slowly evolving to the contralateral side.

There are patterns to joint involvement. In general, OA of the knees and hips occurs in a monarticular or oligoarticular distribution. OA of the hands and OA of the feet are generally present in the same individual to varying degrees. There is a subgroup of patients who have OA in three or more joint groups, which is known as *generalized OA*.³⁷ The characteristics of OA at some individual sites are discussed next.

Shoulder

Shoulder pain is sometimes related to glenohumeral OA. Pain is typically aching and is associated with extremes of motion or occurs after activity of the shoulder. OA of the shoulder usually coexists with, and is difficult to



Fig. 173.2 Destructive arthropathy (Milwaukee) of the shoulder. A large synovial effusion is apparent over the lateral aspect of the humerus (a) or anteriorly in front of the glenohumeral joint (b).



Fig. 173.3 Interphalangeal osteoarthritis of the hands. Knobby, hard tissue changes of the distal interproximal joints as well as hard and soft tissue changes of the proximal interphalangeal joints with deformity are seen. The metacarpophalangeal joints and wrists are spared. There is knobby deformity at the base of the left thumb, reflecting radial subluxation of the first proximal metacarpal at the first carpometacarpal joint.

differentiate from, other abnormalities of the shoulder (e.g., rotator cuff abnormalities, adhesive capsulitis, labrum, and bursitis). Symptomatic shoulder OA appears to be more common than previously recognized.

A peculiar destructive arthropathy (Milwaukee shoulder) is associated with persistent shoulder pain, large synovial effusions, and demonstration of a variety of synovial fluid calcium crystals (Fig. 173.2) (see Chapter 191).

Acromioclavicular joint OA can produce pain that can be aggravated by weight bearing or other stressful activities. Painless enlargement of the acromioclavicular and sternoclavicular joints is commonly associated with reduced shoulder motion.

Hands

Patients often have unsightly enlargement of digits that may or may not be painful, or pain at the base of the thumb. Examination demonstrates hard tissue (bony) enlargement and deformities of the interphalangeal joints. There may be tenderness and occasionally other signs of inflammation. There is often a partial loss of range of motion and subluxation. The European League Against Rheumatism has developed diagnostic criteria for hand OA.³⁸

DIP joints are typically involved, with slow bony enlargement over a period of years (Heberden nodes) (Fig. 173.3). Heberden nodes are more commonly symptomatic in women than in men and often are present in more

than one family member. In women they frequently appear around the time of the menopause, but a clear relation to reduced estrogen concentrations has not been established. The enlargement is not confined to any one aspect of the joint, although there is a predilection for the radiodorsal and ulnodorsal aspects of the joints. Involvement of the second and third DIPs is particularly common. Enlargements are often more severe in the dominant hand. There is frequently associated deformity, with radial, ulnar, or palmar deviations; these are most often unsightly rather than painful. A predominantly palmar subluxation may give the appearance of a mallet finger. There is often some loss of dexterity. There may be an acute swelling of the DIP joint, with cystic herniation of the capsule (see Fig. 173.1). Aspiration of these cysts yields a jellylike material. Microscopic examination reveals large polymorphonuclear leukocytes, with many refractile inclusion cysts that stain for fat (reminiscent of the fluid extracted from a wrist ganglion).

There are often associated hard and/or soft tissue changes in the PIP joints (Bouchard nodes) and central bony erosive changes radiographically. Deformities of the PIP joints are particularly common (see Fig. 173.3). The second and third PIP joints are most commonly involved. Involvement of the MCP joints occurs but is decidedly less common except in instances of secondary OA (e.g., associated with acromegaly, hemochromatosis).

OA of the first CMC joints (trapeziometacarpal and trapezioscapoid) is common. There is a tendency for osteophytes to develop on the distal ulnar surface of the trapezoid, associated with radial subluxation of the proximal head of the first metacarpal. This gives the base of the thumb a “squared” or “knobby” clinical appearance (see Fig. 173.3). In contrast to PIP and DIP involvement, this deviation is commonly associated with pain and disability. The severity of hand OA is associated with reduced grip and pinch strength.³⁹ Pain at the base of the thumb may be on the radial side of the joint or on the palmar aspect of the joint at the proximal insertion of the thenar muscles.

Although the course of hand OA is usually insidious, in a subset of these patients the disease may have an aggressive and destructive course. This has suggested a classification of hand OA into nodal (noninflammatory) OA and erosive interphalangeal (inflammatory) OA. Debate continues as to whether nodal and erosive interphalangeal arthritis are separate entities or part of the spectrum of the same condition. On occasion, the evolution of interphalangeal OA may be indistinguishable from early-onset rheumatoid arthritis or psoriatic arthritis.

Hips

Patients with hip OA most often have groin or anterior hip pain that radiates into the thigh. Pain is associated with early ambulation and weight bearing and is lessened or relieved by rest. Examination most often reveals difficulty rising from a seated position, altered gait favoring the arthritic hip, and reduced range of motion on examination, with pain on motion, particularly internal rotation.

Hip OA is most commonly associated with an insidious onset of pain (malum coxae senilis, coxarthropathy). Pain is noted on weight-bearing activity and must be distinguished from referred lumbar pain. Both lumbar

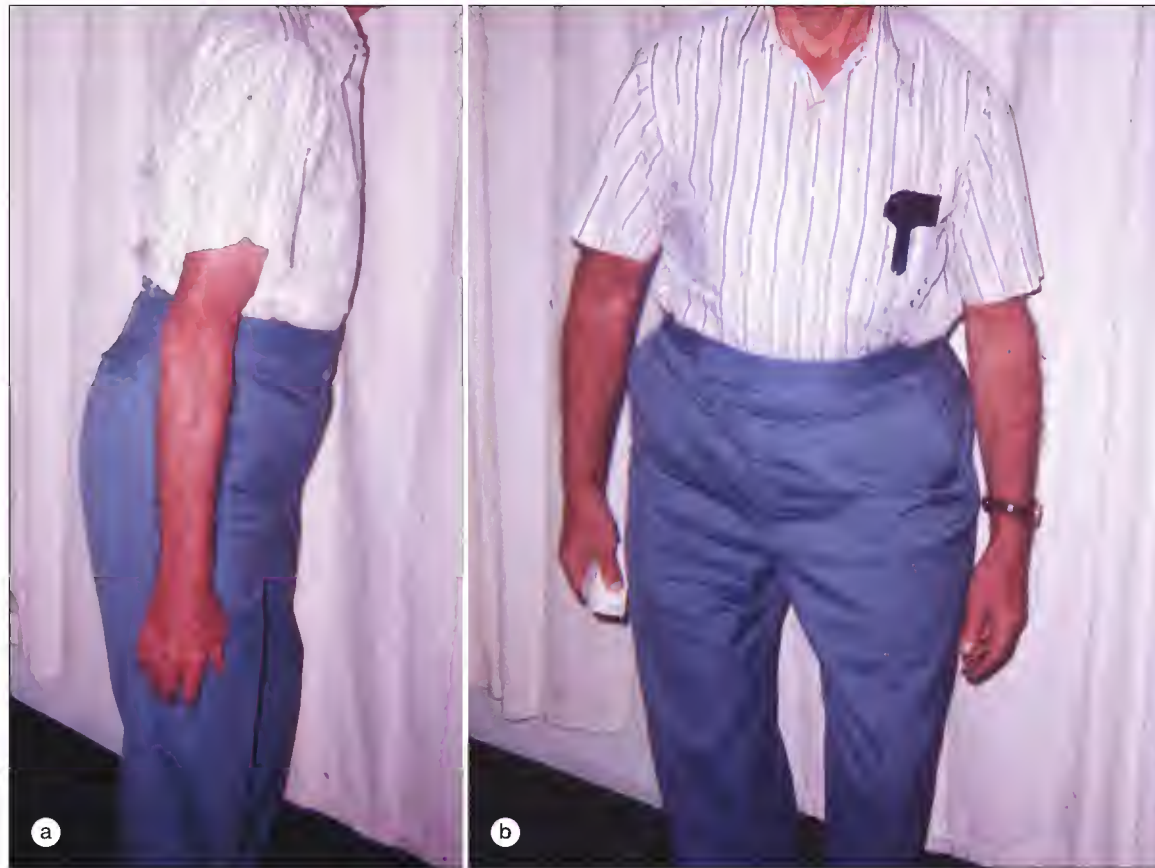


Fig. 173.4 Osteoarthritis of the hips. Severe osteoarthritis secondary to pelvic Paget disease causes medial and axial migration of the femoral heads into the acetabuli, resulting in hip flexion contractures. The patient stands with a bent-forward posture that is apparent from a lateral (a) or anterior (b) view.

spine and hip OA may be painful when the patient rises from a seated or reclined position and during early ambulation. Pain from lumbar stenosis often has its onset after ambulation for a distance and, because of radiation to the thighs, is more suggestive of claudication (pseudoclaudication). More severe hip OA may be painful at all times, even at rest. Pain is usually localized to the groin or medial thigh but may be lateral, suggesting (and associated with) trochanteric bursitis and/or meralgia paresthetica. Hip OA is associated with an antalgic gait, one in which the patient overshifts the weight while walking to reduce the pain. There is loss of extension that often goes unnoticed. Loss of hip flexion and rotation is noticed by the patient because of difficulty when attempting to put on socks or shoes. When severe, a flexion contracture is associated with a prominent limp (Fig. 173.4). Severe OA of the hip is associated with a loss of internal rotation (less than 15 degrees) on examination.⁴⁰ The involved hip is flexed, externally rotated, and adducted. The Trendelenburg sign may be present: standing on the involved extremity leads to a drop in the contralateral hip from weakening of the ipsilateral hip abductors. Another late sign is shortening of the extremity as the femoral head migrates superiorly and axially into the acetabulum, in association with a flexion contracture of the hip.

Most hip OA is slowly progressive. However, there is a subset of patients, estimated at 10%, with a rapidly progressive form of hip OA that evolves over a few months. Unfortunately, at this time, there is no particular clinical characteristic or set of characteristics that at onset can separate those with rapidly progressive OA from those with the less aggressive forms.

Hip pain must be distinguished from referred lumbar spine pain, trochanteric bursitis, meralgia paresthetica, avascular necrosis, transient osteoporosis of the hip, femoral/acetabular impingement, torn labrum, and nondisplaced hip fractures, which can be difficult to detect on routine radiography.

Knee

Patients often experience an insidious onset of pain about the knee, particularly with weight bearing and stair climbing (gonarthrosis). The patient may have noticed knee swelling and/or varus/valgus deformity. Examination sometimes reveals swelling with loss of the usual crease in the skin and soft tissues over the inner (null) facet between the patella and the



Fig. 173.5 Osteoarthritis of the knee. This morbidly obese woman has an enlarged knee with a flexion contracture. Lack of mobility is reflected by her use of a wheelchair. Synovial effusion of the knee is difficult to detect by inspection or palpation in a knee distal to a thigh of this size.

femoral condyle, in addition to a bulging suprapatellar sac. When present, the effusions are usually cool to palpation. There may be warmth and tenderness, but redness is uncommon. Reduced function may be due to a flexion contracture (also known as *extension lag*, the inability to extend to 0 degrees) and sometimes an extension contracture (loss of flexion with inability to flex to 115 degrees) (Fig. 173.5). The flexion contracture is noticeable due to a prominent limp. The extension contracture causes difficulty rising from a seated position. There is often tenderness of the anserine bursa and crepitus on active motion of the knee.

Crepitus on motion is best detected on active joint motion. Occasionally distention of the popliteal semitendinosus bursa (popliteal or Baker cyst) may be present. There may also be herniation or rupture of the bursa

into the thigh or leg (herniated or ruptured popliteal cyst) suggestive of thrombophlebitis (pseudothrombophlebitis syndrome). Marginal osteophytes, intrasynovial loose bodies (joint mice), or moveable bodies (osteochondromas) may be palpable. Medial narrowing of the joint space (radiographic interbone distance) may lead to or aggravate a varus deformity, whereas lateral joint space narrowing may lead to a valgus deformity. Varus deformity with valgus deformity of the contralateral knee gives the patient a “wind-swept” appearance. There is often associated quadriceps weakness and atrophy.

Knee OA may be associated with pain at the distal medial joint margin (anserine bursitis at the insertion on the pes anserinus of the tibia). This is particularly common in the elderly with significant varus deformity. Both varus malalignment and standing balance correlate with the severity of knee OA.⁴¹ Knee OA also has been associated with quadriceps weakness, reduced knee proprioception, and increased postural sway.⁴² When present, reduced proprioception occurred in the contralateral knee.⁴³ It was thought that both pain and muscle weakness influence postural sway. Although quadriceps strength was significantly lower in patients with OA of the medial compartment of the knee, the hip adductor muscles were actually stronger, perhaps in compensation for the varus deformity.⁴⁴

Meniscal tears may be difficult to determine on physical examination of patients with knee OA. A positive McMurray test is the only true predictor of an unstable meniscal tear.⁴⁵ Cruciate ligament deficiency can be detected by an anterior or posterior drawer sign. In presentations with acute hemarthrosis, cruciate ligament injury should be suspected.

Adult patellofemoral OA is not commonly symptomatic. Anterior knee pain is aggravated by sitting in low chairs (e.g., at movie theaters) and can be precipitated by pressure with mediolateral movement of the patella in the intercondylar groove (patellar apprehension or grind test). There is a variant of patellofemoral OA in young women (chondromalacia patellae) that produces anterior knee pain. Symptoms from patellofemoral OA are usually self-limiting, resolving in a period of several months; some patients experience improvement after a course of patellar taping by a physiotherapist. However, there is a small subset of adults with patellofemoral OA who have significant and persistent pain with disability.⁴⁶

OA of the knee may be associated with varying degrees of subchondral spontaneous osteonecrosis of the knee. This is suspected in patients with a rather abrupt onset of particularly severe pain refractory to the usual therapy and is usually due to a subchondral insufficiency fracture. In early phases, it is best detected by magnetic resonance imaging. Uncommonly, there is a destructive arthropathy associated with a variety of calcium crystals.

Ankle

Talonavicular and subtalar joint OA is usually secondary to trauma with or without ligamentous damage or to an old ankle fracture. Patients complain of ankle pain on weight bearing. Examination reveals swelling of the ankle that must be distinguished from a variety of conditions, such as Achilles bursitis, plantar fasciitis, talocalcaneal coalition, painful os trigonum, posterior tibial tendinitis, and pedal edema.

Feet

Patients with OA of the feet most often present with pain of the first metatarsophalangeal (MTP) joint, particularly with walking. Examination commonly reveals an enlarged joint, with medial subluxation and lateral deviation of the big toe (bunion deformity). There are sometimes signs of inflammation over the involved joint, with tenderness and loss of dorsiflexion. Abnormalities of additional toes are common.

The typical pattern of involvement of the feet includes the first MTP joint, commonly called the *bunion joint* (hallux valgus) (Fig. 173.6). The joint enlarges medially, with a lateral drift of the first toe, which often overlaps with the second toe.

There may be loss of function of the first MTP (hallux rigidus), usually occurring without drifting of the great toe but limiting toe-off with ambulation. In this condition, the enlargement is usually dorsal.

There is often painful and tender swelling of foot joints. Associated contractures of additional toes (cock-up deformity) with loss of plantar fat pads are often seen. Disabling pain on ambulation may ensue. Pes planus, with relaxation of the transtarsal ligament and a pronator forefoot deformity, aggravates the symptoms. The patient may find it difficult to wear certain types of shoes, particularly those with high heels.

The talonavicular joint is at the pinnacle of the arch of the foot and is particularly prone to OA in the dorsal portion of the joint. This form of OA is aggravated by pes planus. Midfoot OA is associated with a short first metatarsal and/or a long second metatarsal bone.⁴⁷



Fig. 173.6 Metatarsophalangeal (MTP) and interphalangeal osteoarthritis of the feet. There is bilateral enlargement of the first MTP joint, with medial subluxation of the phalanx. Flexion contraction of toes (particularly of the right second digit), with subluxation of the MTP, has caused an associated callus over the dorsum of the proximal interphalangeal joint. The right third digit is subluxed under the second digit. There is relaxation of the transtarsal ligament, with medial subluxation of the MTP and bony enlargement of the fifth MTP joints (tailor bunion, bunionette).

EVALUATION

Laboratory tests

There are no laboratory tests that are diagnostic for OA. Low-grade inflammation in OA can be detected by measurement of serum acute-phase reactants, such as C-reactive protein. Synovial fluid and serum markers of OA are being investigated as tools to detect the presence of OA or to predict or detect disease progression.^{48,49} To date, however, no individual marker has accomplished either of these goals, and a combination of markers may be needed.

Synovial fluid from patients with OA is usually clear and colorless or with a slight yellow tinge. The polymorphonuclear leukocyte content is usually less than 2000 cells/mL. Inflammatory synovial effusions may occur in the presence of calcium crystals. Synovial fluid from a DIP cyst is often jellylike and contains large polymorphonuclear leukocytes with several refractile inclusion cysts. Synovial fluid from a joint with osteochondromatosis is often very viscous and relatively acellular. It should be pointed out that normal synovial fluid contains fewer than 100 cells/mL; hence the modest increase in synovial fluid leukocytes in OA is reflective of low-grade inflammation.

Crystals may be present in as many as 70% of synovial fluid specimens from patients with OA.⁵⁰ Although all calcium crystals have been shown to precipitate inflammation, the relationship of hydroxyapatite and several forms of basic calcium phosphate to the synovitis that is present in patients is not well established.

Imaging

A detailed description of the imaging characteristics of OA is given in Chapter 177.

CONCLUSION

Symptomatic OA is common and affects a large segment of the population, particularly women older than 50 years of age. Although OA can affect nearly any joint in the body, OA of the weight-bearing joints leads to the most disabling symptoms. Hand, hip, and knee OA can cause significant morbidity, impairment of physical activity, physical disability, and increased all-cause mortality. Pain is the most common complaint that causes the patient to seek a physician's assistance. Examination often reveals loss of function and may uncover some of the signs of inflammation. The findings on careful history taking and physical examination should lead to the formulation of an individualized program of therapy.

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Animal models of osteoarthritis

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EXPERIMENTAL ANIMAL MODELS THAT REPRODUCE THE CHANGES OBSERVED IN NATURALLY OCCURRING OSTEOARTHRITIS ARE EXTREMELY VALUABLE FOR THE FOLLOWING REASONS:

- They allow the study of alterations in a timewise fashion and permit sequential evaluation of the disease lesions.
- They facilitate the understanding of osteoarthritis pain mechanisms and the discovery of novel therapeutic approaches.
- They permit the evaluation of disease-modifying osteoarthritis drug treatment effects, using noninvasive joint imaging such as magnetic resonance imaging.

LARGER ANIMAL MODELS OF OSTEOARTHRITIS PROVIDE THE FOLLOWING:

- Larger tissue samples allowing extensive exploration of the biochemical and molecular mechanisms of the disease
- A more global exploration of the effects of drugs on different osteoarthritis pathways, which includes clinical evaluation, quantification of the disease changes by imaging, and morphologic examination
- Translational data for treatment dosages and route of administration because they better mimic human clinical conditions

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis. The joint tissues are the sites of abnormal pathophysiologic pathways responsible for the development and progression of OA; further details are provided in Chapter 175 and elsewhere in this book. The evolution of structural changes in OA occurs over an extended period, which makes it very difficult to study the etiopathogenesis of the disease in humans. Experimental models capable of reproducing the changes that occur in OA can be valuable, especially for studying these alterations in a timewise fashion with the possibility of sequential evaluation of the disease lesions. In recent years efforts have been under way to standardize the outcomes of OA animal models.¹ Another dimension of OA is the pain, which is the most prominent clinical symptom of this disease. An unresolved issue in OA pain research is the lack of understanding of the mechanisms responsible for its induction and maintenance. There is therefore an urgent need to improve the characterization of animal models to facilitate the discovery of novel approaches to pain relief for OA patients.

This chapter concentrates on the experimental OA models that have been most commonly used for the identification and study of therapeutic targets, the development of disease-modifying osteoarthritis drugs and agents (DMOADs), and the treatment of pain. These models are reviewed and their similarities to the natural disease in humans are examined. This review is arbitrarily divided according to the size of the animals used: large, medium, and small. Not all experimental animal models used and studies done to date can be reviewed due to chapter size limitations.

LARGE ANIMAL MODELS

Among the large animal models of OA, one of the most studied models of induced OA is the canine anterior cruciate ligament transection (ACLT).

This model has been extensively studied morphologically and pathophysiologically and has demonstrated interesting similarities to the human disease. It is the model most commonly used to test the efficacy of DMOADs. Another canine surgical model is the groove model, which is more sensitive for therapy aimed at cartilage defects and more appropriate for studies examining cartilage protection and repair. Another large animal model of interest is the sheep meniscectomy model, which has been used in clinical investigations of a number of DMOADs. Large animal models of spontaneous disease include the monkey and dog models; however, the former is not widely used.

Induced osteoarthritis models**Dog****Anterior cruciate ligament transection model**

The traumatic rupture of the anterior cruciate ligament (ACL) is a frequent musculoskeletal disorder, both in dogs and in humans, which has been demonstrated to be a significant risk factor for the development of knee OA. In the first dog model to be introduced, OA was induced by experimentally transecting the ACL in normal mongrels using a closed surgical procedure (stab incision).² A variant of this model involves use of an open surgical procedure.³ This latter model was further modified by performing a dorsal root ganglionectomy before the surgery to accelerate the development of structural lesions by creating a neuropathic arthropathy.⁴

In the dog ACLT model, the cartilage biology and morphologic, histologic, and matrix biochemical changes were reported to be analogous to those observed in the naturally occurring disease. In-depth analyses have been done of the metabolic and structural changes in the articular cartilage, the synovial membrane, and the subchondral bone. The macroscopic changes in the cartilage are first seen as a yellowish discoloration of the surfaces, particularly in the weight-bearing areas of the condyles and plateaus, with some cartilage swelling seen in the adjacent area in the early phase of the disease. These early lesions lead to fibrillation and a progressive erosion of the cartilage down to the subchondral bone over the months following the surgery. Several factors can influence the rate of progression of these lesions in this dog model, such as weight and amount and type of exercise. From a histologic point of view, additional changes include loss of proteoglycan content in the cartilage and hypertrophy and cloning of chondrocytes, which eventually progresses to hypocellularity of the tissue in the more severe stages. Also observed in the later stages is a thinning of the calcified cartilage layer and invasion of the tidemark by blood vessels.

The OA cartilage lesions are associated with an increased level of proteoglycan and type II collagen synthesis with a breakdown of the collagen network and reduced aggrecan size. An increase in the level of proteases was also found, including matrix metalloproteinase-1 (MMP-1), MMP-3, and MMP-13, as well as cathepsin K, ADAMTS4, and ADAMTS5.⁵ The upregulation of MMP synthesis was mediated by activation of several key intracellular signaling pathways in which the mitogen-activated protein kinases (MAPKs) play an important role. The increased level of the inducible form of nitric oxide synthase (iNOS) induces the production of nitric oxide, which in turn mediates chondrocyte apoptosis, cartilage degradation, and synovial inflammation. There is also an increase in local production of leukotrienes. More specifically, leukotriene B₄ has been found to be among the factors that mediate the increased levels of MMPs, ADAMTS, and iNOS in cartilage and interleukin-1 β (IL-1 β) in the synovium.⁶

In the dog ACLT model, synovitis is present at all times following surgery and is of significant severity. In the early stages, it is likely to originate from the postsurgical reaction and intraarticular bleeding, whereas in the long term it would seem to be part of the global disease process. Histologically, the main changes are hyperplasia and hypertrophy of the lining cells with

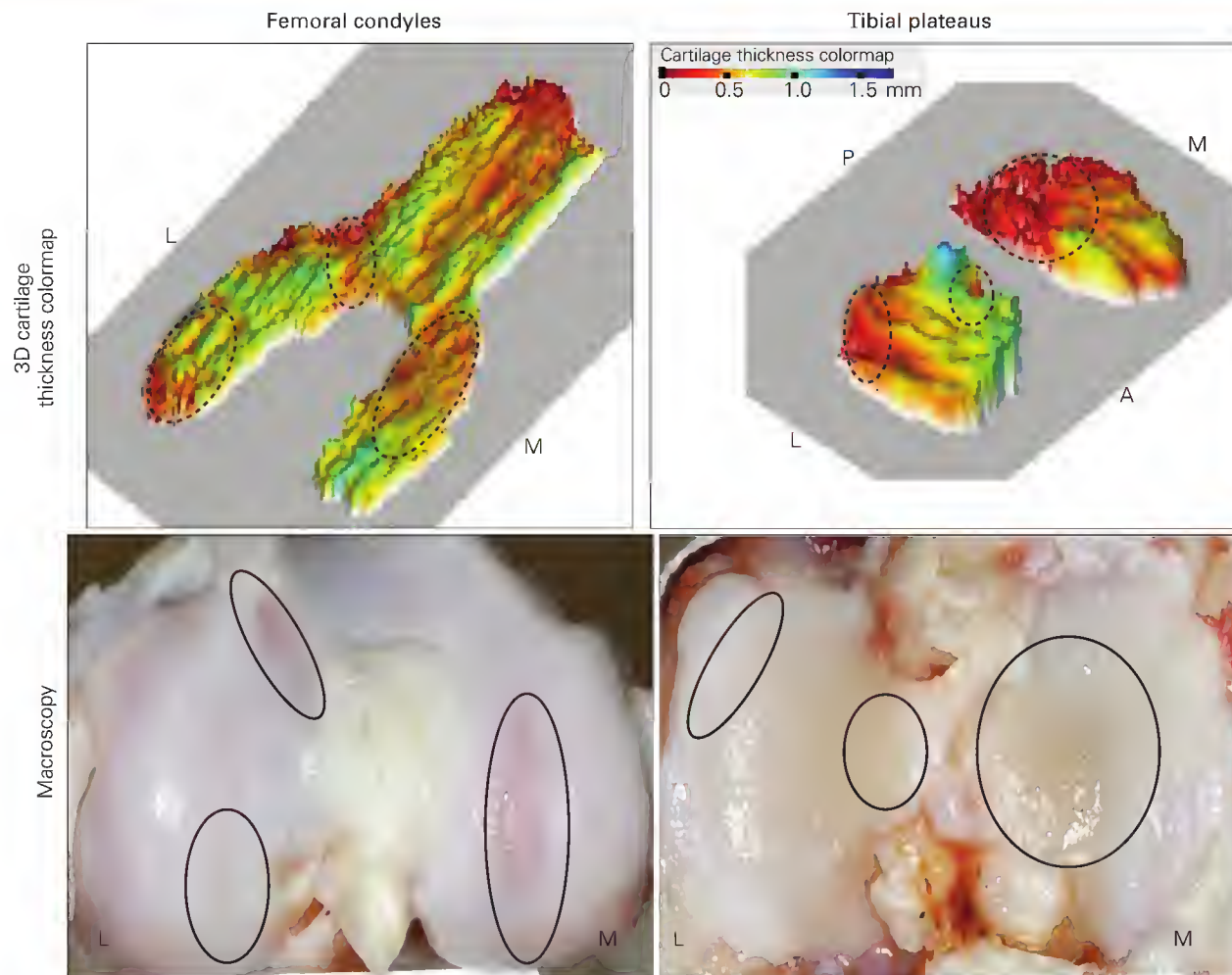


Fig. 174.1 Comparative assessment of cartilage lesions by magnetic resonance imaging (MRI) and macroscopic grading in an osteoarthritic (OA) dog knee. The technology of this three-dimensional (3D) reconstruction of femoral condyle and tibial plateau cartilage thickness from MRI data acquisition can precisely detect and quantify the severity of the macroscopic cartilage lesions, as shown in this OA knee 26 weeks after anterior cruciate ligament transection. A, anterior; L, lateral; M, medial; P, posterior. Circles indicate areas of cartilage lesions corresponding to the macroscopic findings. (Modified from Boileau C, Martel-Pelletier J, Abram F, et al. Magnetic resonance imaging can accurately assess the long-term progression of knee structural changes in experimental dog OA. *Ann Rheum Dis* 2008;67:926-32.)

mononuclear cell infiltrate of the sublining tissue. This diseased tissue is also the site of the production of cytokines, inflammatory mediators, and proteases that contribute to cartilage degradation.

In the first few months following ACLT, the subchondral bone is the site of intense remodeling, predominantly resorptive in nature, with thinning of the subchondral plate and an increase in the trabecular space. There is an abundance of bone resorption units associated with an increase in the local production of bone resorption biomarkers such as MMP-13, cathepsin K, and urokinase.

The cartilage changes were shown to evolve over a long period, and a progression up to 4 years after surgery was reported.⁷ A recent study using quantitative magnetic resonance imaging (MRI), which documented cartilage changes up to 26 weeks following the surgery, supports the previous findings (Fig. 174.1).⁸ Moreover, the bone marrow lesions were found to increase in size over time and to be topographically associated with cartilage lesions.⁸ These findings have raised the possibility that the bone changes may play a role in the genesis of cartilage lesions.

One of the typical behavioral features of this dog model is a variable lameness of the affected limb. The fact that the lameness correlates with a reduction in the subchondral bone volume in early OA is strongly suggestive of a relationship between subchondral bone changes and pathologic articular cartilage. It also was shown that the functional impairment correlated with structural changes in ACLT dogs and that bone marrow lesions, cartilage defects, osteophytes, and joint effusion size impair the limb remission, but that cartilage volume loss and meniscal alterations are related more to excessive mechanical stress.

In this model, lameness is interpreted and referred to as a behavioral correlate of pain in the joint. For the assessment of a given treatment, it is suggested that gait analysis be used concomitantly with other functional methods such as functional activity and limitation-of-activities measures.

Indeed, at short intervals after surgery the force platform analysis alone is most likely confounded by structural effects. However, at longer intervals after surgery the force platform analysis appears to be more accurate because the relative contributions of structural effects versus direct pain effects may be different as the joint damage progresses over time.

Groove model

The groove model, a canine model of joint degeneration with much less severe joint damage,⁹ results from surgically applied damage to the weight-bearing cartilage of the condyles combined with forced loading. Recently, a bilateral version (damage of the lateral and medial condyles) of this model was developed and characterized, in which the features appeared to be slightly more severe than those in the unilateral model.¹⁰ It is suggested that these models be created via arthroscopy to limit the confounding effects of arthrotomy. In the unilateral model, histologic and histochemical examinations revealed pathologic cartilage predominantly in the medial compartment (femur and tibia), which was often mild. Although this model showed osteophyte formation and cartilage damage in which there was an increased synthesis of proteoglycans, decreased retention of the newly formed proteoglycans, and increased release of proteoglycans resulting in decreased proteoglycan content, these are much less pronounced than in the ACLT model. Interestingly, in this model the degenerative cartilage changes are progressive, whereas synovial inflammation diminishes over time.⁹ There is a discrepancy in the literature with regard to whether or not there is thinning of the subchondral bone in the groove model. These contradictory findings could be attributed to the difference in the groove models used.

Sheep and goats

Sheep and, to a lesser extent, goats have been used to study the pathogenesis of OA and the effect of treatment with potential DMOADs. These species

offer the advantage of being large animals with biomechanics closer to that of humans. As with the dog, the size of the sheep's joints allows outcomes to be measured in numerous ways, including routine arthrocentesis and synovial fluid collection; imaging such as radiography, computed tomography, and MRI; as well as gait analysis, arthroscopic joint examination, topographic evaluation of lesions, and histologic, biochemical, and molecular analyses.

The main OA models in sheep involve surgical induction of OA, with the most common involving partial or total meniscectomy. The sheep ACLT model has been reported as an OA model but is not commonly used, and the surgery alone appears to induce very limited or mild cartilage damage in this species.¹¹ Some investigators have used ACLT combined with medial meniscectomy.

The most frequently used sheep model is the total unilateral medial and/or lateral meniscectomy model. The lesions in the lateral meniscectomy model are generally more severe than those in the medial meniscectomy model. The development of cartilage lesions is progressive over time following surgery. Mild lesions are observed at 3 months after surgery and significant changes are seen between 6 and 9 months, which progress to full-cartilage-thickness erosion by 24 months. Cartilage lesions are associated with other joint structural changes, such as osteophytes and subchondral bone remodeling. The histologic cartilage changes are similar to those reported in the OA dog models. There is also a thickening of the subchondral cancellous bone with an increase in bone mineral density. Exercise involving weight bearing accelerates the rate of progression of lesions. The biochemical cartilage changes, including a reduction in the level of matrix macromolecules such as aggrecan, are associated with a preferential increase in the synthesis of dermatan sulfate proteoglycans (decorin), particularly in zones of cartilage subjected to high mechanical stress. The release of aggrecan fragments from the cartilage correlates with increased levels of active MMPs found in the tissue. The synovial membrane also undergoes histologic changes characterized by hyperplasia but without evidence of subsynovial tissue inflammation. The characterization of pain responses in this model is largely lacking.

Spontaneous osteoarthritis models

Monkey

Characterization of spontaneous OA has been performed in two nonhuman primates: rhesus¹² and cynomolgus¹³ macaques. In the former model, the prevalence and severity of OA increased with age and, in females, with parity. Both models exhibit OA lesions morphologically similar to those seen in humans. In the rhesus, features included a decrease in the levels of glycosaminoglycans in old animals with OA compared with age-matched normal animals and decrease in collagen with severity of OA. In the cynomolgus, lesions are most severe in the medial tibia and are characterized by fibrillation, clefting, and loss of articular cartilage, with concomitant marked thickening of the underlying subchondral bone. Interestingly, bone changes were more common and severe than cartilage changes and morphologically appeared to precede the cartilage changes.¹³ Compositional analysis of the mineralized plate beneath the articular cartilage in OA showed thickened and overmineralized calcified cartilage and subchondral bone. To the authors' knowledge, no reports on the effects of drugs on OA progression in these models have been published.

With regard to OA pain, although some of the older animals affected with OA walked with an altered gait similar to limping, which indicates that they experienced symptomatic disease, there have been no reports to objectively quantify the OA-associated pain.

Dog

Both the clinical expression and pathogenesis of naturally occurring canine hip dysplasia and OA are considered analogous to those of the human diseases. Progressive and degenerative canine OA causes notable signs of pain, such as lameness and physical disability. Pain and lameness may be acute or chronic, and OA may occur in any joint in dogs.¹⁴

Certain breeds may be predisposed to primary idiopathic OA. For the most part, canine OA is considered secondary to acquired or congenital musculoskeletal disorders. Concomitant factors such as aging and obesity likely accelerate progression. However, mechanical factors appear to predominate in the etiopathogenesis of canine spontaneous OA. Surveys in the United States suggested that approximately 20% to 30% of the canine population over 1 year of age suffers from OA.¹⁵ In certain breeds, the prevalence of hip dysplasia ranged from 41% to 73%.¹⁶

A diagnosis of OA is based on clinical signs, physical examinations, radiographs, and synovial fluid analyses. Some subjective (client-based) tools for the measurement of OA-related pain outcome in dogs have been

validated, and as an objective evaluation, gait analysis using a force platform provides a noninvasive assessment of lameness. The trotting gait was more sensitive than the walking gait for differentiation of dogs with low-grade hind limb lameness. Also used to decouple gait mechanics from pain originating in other organs, such as the muscles or skeleton, is intraarticular anesthetic injection. Gait analysis successfully served to detect acute pain in these animals, but other standardized pain assessment instruments for dogs have been developed and validated.¹⁷⁻²⁰ An advantage of these assessments is that they report the owner's evaluation of the dog's pain over a period of time, which increases the sensitivity of functional outcome measures.

Sheep

Spontaneous OA, although rare in sheep, may occur in the unprotected region of the tibias, but this sheep model has not been reported as a viable model.

Large animal model limitations

The OA morphologic, biochemical, and structural changes in the dog ACLT and the sheep meniscectomy models reveal several similarities to the natural disease. The dog groove model creates immediate cartilage injury and loss with resultant incongruity and changes in load-bearing articulation of the joint that can be a potential model for knee injuries by a traumatic force. This model might be valuable for studies looking specifically at OA secondary to previous articular cartilage defects. However, the pain is also milder, which may make demonstrating effects of drugs on behavior difficult.

The dog and sheep models allow evaluation of the progression of structural changes through several types of imaging technologies, and the joint size can be used for a large number of analyses to study the effect of DMOAD interventions on joint structure as well as disease pathways. However, because sheep are ruminants rather than monogastrics, the bioavailability of oral therapies may require additional validation. These models also permit the possibility of performing gait analyses as a surrogate marker of pain and functional ability.

The nonhuman primate models of spontaneous OA are interesting because of the availability of age-matched controls, tissue with early OA, joints large enough for radiologic and other imaging technologies, and morphologic and biochemical studies. The drawbacks are their relatively long life spans, uncontrolled environmental factors, and, most importantly, ethical concerns.

In conclusion, interesting information about the OA disease process has been generated by studies using large animal models. The striking similarities in the disease pathways between these surgically induced OA models and the human natural disease, the parameters that can be evaluated in these models, and their use in DMOAD studies (Table 174.1) makes these models—especially the canine ACLT model—quite attractive. In idiopathic OA, various etiologic factors join forces to bring about the structural and molecular changes typical of the disease, although it is likely that some factors that contribute to the natural human disease may not have an effect in these models.

With regard to the disease-modifying effects of certain OA drugs and agents in these models and in clinical trials in humans, a good correlation has been shown, in general, for both positive and negative findings. Obvious limitations of the preclinical studies arise from the variability in experimental protocols from one study to another. Moreover, the level of effectiveness of treatment is rather difficult to compare between human and animal model studies due to the methodologic differences. Most preclinical studies have been of short duration, which is an obvious additional limitation.

With regard to pain evaluation, the major limitation is the predictive value of the drug efficacy assessment, because there is a need to further develop and validate pain assessment techniques and improve the predictive validity of the evaluation instruments.

MEDIUM-SIZED ANIMAL MODELS

Among the intermediate-sized animals used in OA research, the rabbit has been the most popular. Rabbit models of OA include those in which OA is created chemically, by repetitive trauma, by patellar impact, and after surgical alteration of joint mechanics. The two most studied rabbit models are the ACLT and partial meniscectomy models. With regard to the feline models, the most employed induced model is the ACLT model. Spontaneous OA models have also been reported in these two species, with the cat being the most studied.

TABLE 174.1

Summary of drugs/agents evaluated *in vivo* in some of the large animal models of osteoarthritis (OA) for disease-modifying effects

Model	Tested drug	Effect of treatment
Dog ACLT	Corticosteroids	Reduced OA cartilage degradation and osteophyte formation
	NSAIDs	Protected against (licofelone, tenidap) or accelerated (indomethacin) OA cartilage degradation
	iNOS inhibitor	Reduced OA cartilage degradation and synovial inflammation
	IL-1Ra	Reduced OA cartilage degradation
	Diacerein	Reduced OA progression
	Doxycycline	Reduced OA development and progression
	Bisphosphonate (NE-10035)	Reduced subchondral bone turnover; no effect on osteophytes or cartilage degradation
	Bisphosphonate (tiludronate)	Reduced OA development and progression and subchondral bone changes
	Calcitonin	Reduced cartilage damage, protected against cartilage degradation and subchondral bone changes
	PPAR- γ agonist (pioglitazone)	Protected against development of OA lesions
	Hyaluronan	No effects on OA progression
	Avocado and soya unsaponifiables	Reduced OA cartilage lesion development and subchondral bone remodeling
	<i>Brachytemma calycinum</i> D. Don	Reduced OA cartilage lesion development
	Strontium ranelate	Reduced OA cartilage lesion progression, improved subchondral bone remodeling
Sheep	Hyaluronan	Reduced OA progression, improved subchondral bone remodeling
	Avocado and soya unsaponifiables	Reduced OA progression, prevented subchondral bone remodeling
	Diacerein	Improved OA cartilage lesions and subchondral bone parameters in lesional areas
	Chondrogenic-induced bone marrow stem cells	Retarded progression of OA

ACLT, anterior cruciate ligament transection; IL-1Ra, interleukin-1 receptor antagonist; iNOS, induced nitric oxide synthase; NSAIDs, nonsteroidal antiinflammatory drugs; PPAR- γ , peroxisome proliferator-activated receptor- γ .

Induced osteoarthritis models

Rabbit

New Zealand white rabbits are frequently used medium-sized models of OA, which include the hemi meniscectomy or partial meniscectomy model. Following an incisional exposure to the medial compartment of the stifle (knee), the anterior horn of the meniscus is freed from its lateral attachment on the tibia. A small portion is removed from the lateral part of the anterior horn of the freed meniscus. There is relatively little bleeding in contrast with the ACLT technique. Once the wound is closed, the freed meniscus appears to act similarly to a torn meniscus in humans, altering joint mechanics and inducing a traumatic model of OA.

The ACLT model requires open surgery, and bleeding is common. The procedure is similar to that in the dog ACLT model (open surgery). After the procedure, OA develops insidiously over a period of 6 to 12 weeks; 8 weeks is suggested for early OA and 16 weeks for late OA.²¹ To characterize changes, the operated joint is often compared with the contralateral stifle or with a joint undergoing sham surgery. A few studies have employed models in which both stifles were operated on, with one used as the control for the treated contralateral joint.

Studies of the stifle joints have included examination of gross and microscopic anatomy, as well as synovial fluid and synovium assessment. The cartilage lesion depth and size can be measured and osteophytes assessed. Microscopic examination can evaluate proteoglycan content and cartilage changes. As in the large models of induced OA, abnormalities have been demonstrated in the synovium and cartilage. The cartilage and the joint can be studied using gait analysis,²² biochemical methods, and MRI.²³ Data showed that the ACLT procedure tended to induce lesions on the postero-medial aspects of the joint, particularly on the covered areas of the tibia. This suggests that these cartilage areas are the most prone to change and hence are the specific areas of the joint to be studied.²⁴ Findings from 4 and 8 weeks after ACLT surgery revealed that the expression of MMP-1 in synovium lagged behind its expression in cartilage, which suggests that the pathologic process was initiated in the cartilage. The rabbit meniscectomy model was also used to measure pain and demonstrated decreased weight bearing by the ipsilateral limb over time.²²

Cat

There exists an ACLT model for the cat. Unlike in the canine model, the ground reaction forces and the hind limb kinematics revert to near-presurgical patterns within 5 months after surgery. Early adaptive responses following ACLT appear to be associated with a reduction in the mechanical loading, but a continued progression toward OA occurs despite almost normal knee mechanics at 1 year following surgery. At 12 to 16 weeks after ACLT, there is an increase in the articular cartilage,²⁵ and long-term experiments revealed cartilage degradation and formation of osteophytes at the

joint margins consistent with the development of OA. Specifically, there was focal loss of articular cartilage on the medial tibia, the condyles, and the retropatellar surface. The areas where the cartilage was not completely eroded away showed hypertrophic cartilage with surface lesions, and loss of proteoglycan in the superficial zone. The menisci appeared fibrillated and exhibited tears, particularly in the medial plateau. The synovial inflammation associated with ACLT returned to normal approximately 1 month after surgery.²⁶ Concurrent with the articular cartilage degeneration, there was a decrease in cancellous bone mass and subchondral plate thickness in both medial and lateral compartments as early as 16 weeks after surgery, and these changes became more pronounced in the development of the disease 5 years after surgery.²⁷

Spontaneous osteoarthritis models

Rabbit

Naturally occurring OA in the rabbit has been reported recently.²⁸ Data showed that the presence and severity of OA were significantly influenced by both age and body weight but not by gender. Hind limb joints, including the knee and hip, were most commonly affected. OA was detected in radiographs from about 40% of the studied domestic rabbits. Of the affected rabbits, 37% had two or more pairs of joints involved, and 13% had three or more pairs affected. There was a significant association between rabbit breed and the presence of OA, with dwarf rabbit breeds having a lower incidence than the 12 nondwarf breeds. No differences in OA prevalence were found among the nondwarf breeds.

Cat

Until this decade, little attention was paid to spontaneous OA in cats. Spontaneous OA has been shown to occur in cats, with the prevalence increasing dramatically with age.^{29,30} In cats older than 6 years, OA was found in at least one joint in 61% of animals and in more than one joint in 48%; in cats older than 14 years, OA was found in at least one joint in 82%.³¹ Advancing age, but not obesity, appears to be the main risk factor for both increasing prevalence and increasing severity of feline OA, which is most frequently seen in the elbow, hip, and stifle joints. Older cats exhibit difficulties with mobility, and it is common to observe radiographic evidence of OA in multiple joints of aged cats.

Although OA is very common in older cats, it is poorly diagnosed in clinical practices. This may be due to the poor correlation between orthopedic evaluation and severity of OA structural changes and/or the lack of validated chronic pain assessment tools for cats.³⁰ In cats, the disease seems to be constitutional rather than the end stage of a variety of developmental diseases, as seen in dogs. The diagnosis can be based on radiography and a combination of history, owner observations, lameness, and orthopedic examination findings. A recent study using MRI demonstrated a good

correlation between functional and structural evaluations of OA lesions in cats.³² More work is being done to develop validated owner questionnaires that rely on client-specific outcome measures, using items such as walking, running, jumping up and down, climbing stairs, playing with toys, and so on. For pain evaluation, gait analysis, accelerometry techniques, the von Frey withdrawal threshold (assessing allodynia/hyperalgesia), and collar-mounted accelerometers to measure activity levels were shown to be capable of characterizing OA-associated pain outcomes in cats.³²

Medium-sized animal model limitations

Advantages of the rabbit models include facility of handling, inexpensive purchase and maintenance costs, ease of surgery, relatively small cage requirements, and rapid development of OA. Disadvantages are the small volume of cartilage that is removed from the joint, which often requires pooling of specimens; the anatomic differences between rabbit and human cartilage and subchondral bone; the difficulty in mobilizing rabbits; and the number of animals needed for any given experiment. In contrast with the human joint, rabbit cartilage is normally thinner and more cellular, the subchondral bone is stiffer, and the epiphyses are not closed unless older rabbits are selected for study. This is also important for the spontaneous OA rabbit model, of which a downside is the wide variability in the age at which bone maturity is achieved, because even 9- to 10-month-old rabbits can have open physes or growth plates in the distal femur and proximal tibia.

The rabbit has proven to be an easy model in which to explore potential DMOAD therapies for OA. However, several agents that were promising in the rabbit models have been disappointing in humans. The discrepancies in the findings of the therapeutic effects of these agents between the rabbit models and human disease are not fully explained. It could be that the therapeutic agent is not effective in humans or there may be problems with dosing. It could also be that this medium-sized model reflects only subsets of human OA, not the full spectrum of the human disease. Despite these drawbacks, until an effective therapy is available, the rabbit models of OA will continue to be useful in preclinical studies.

Cat models of both induced and spontaneous OA may offer advantages similar to those of the rabbit. However, although some histologic features were reported in the induced OA model, biochemical knowledge of OA articular tissues is lacking for both the induced and spontaneous OA models. Furthermore, in the spontaneous OA model, the recognition of chronic arthritic pain is a major challenge compared with other species because, instead of developing lameness, cats use behavioral strategies to disguise pain. A lack of familiarity with feline joint radiographs means that radiographic identification of OA in cats can also be problematic. At present, this model serves mainly for pain assessment and documentation of response to analgesic treatment. However, although gait analysis appears to have potential and accelerometry could be used as a complementary approach providing objective assessment of motor activity, validated, precise, and sensitive techniques to measure clinical outcomes in this OA model are still in their infancy. In addition, species-specific differences in pharmacology in cats further complicate translational research.

SMALL ANIMAL MODELS

Many small animal models of OA have been developed, which generally involve the mouse, the rat, or the guinea pig. Some are models of spontaneous OA, whereas in others OA is induced through various interventions. In contrast to the large and medium-sized animal models in which induction is almost always performed by mechanical means, in small animals it can also be induced by biochemical joint alterations. Small animal models, which can reproduce important features of human OA including cartilage destruction, osteophyte formation, and synovial inflammation, have been valuable research tools for exploring the pathophysiology and treatment of OA. They allow for the evaluation of various catabolic and anabolic pathways that are highly relevant to the disease process. For example, some models such as the STR/ort mouse have helped to demonstrate the cleavage site of aggrecan by proteases. Small animal models are most useful for gaining insight into many aspects of the pathophysiology of OA because they provide the unique possibility of performing studies in a large number of animals aimed at a comprehensive evaluation of the disease process. Some imaging technologies for small animals have also been developed that can be used to assess disease progression and quantify structural changes.^{33,34}

This section summarizes some of the different possibilities that these small animal models of OA offer in exploring the disease process.

Induced osteoarthritis models

In small animals, OA can be induced, particularly in the knee joint, following different types of interventions that produce metabolic and/or mechanical changes in the joint and create OA-like modifications in the cartilage, synovium, and subchondral bone. The most common induced models are produced by intraarticular injections of chemicals or proteases, by surgery, or by genetic modification.

Intraarticular injections

In one of the intraarticular knee injection models OA is induced by monoiodoacetate (MIA), an inhibitor of glycosyltransferases.³⁵ MIA injection induces alterations in chondrocyte biology in contrast to the mechanical models, in which joint instability is created. This model has been induced mainly in the rat, mouse, and guinea pig. The severity of joint alterations from MIA injection is dose dependent, and MIA generates pain and structural and biochemical alterations associated with OA. There is considerable variation in the dose and volume used in preclinical studies to induce OA in the MIA model (1 to 4.8 mg). In cartilage, the changes are characterized by proteoglycan depletion and degradation in which aggrecanase- and MMP-generated catabolic epitopes have been detected. The cartilage lesions develop rapidly following MIA injection. The classic duration for this model is 28 to 30 days, but it has been studied for up to 56 days.³⁵ Cartilage surface irregularities are present 7 days after injection, and the lesions reach maximal intensity between 14 and 21 days depending on the dose injected. Changes in chondrocyte morphology are observed as early as 1 day after MIA injection and loss of chondrocytes starting at day 7. MIA injection also resulted in subchondral bone remodeling 5 to 7 days after injection, evolving into bone sclerosis.³⁵ The eburnation of subchondral bone is usually found at day 28. Synovial membrane hyperplasia and fibrosis are also seen, but only with the high doses. The highest doses of MIA (up to 3 mg per knee in rats) led to total loss of cartilage in 15 days.³⁶ This model also induced osteophyte formation. The inflammatory early phase in this model also features joint swelling and immune cell infiltration of the patellar fat pad, and resolves fully by day 7.

The hyperalgesia induced by MIA injection makes this model attractive for studying OA pain. Data showed the existence of two phases of pain following MIA injection. The first manifests within a day, lasts up to a week after the injection, and appears mediated primarily by inflammation. The second manifests later and is thought to be the result of joint destruction. Hence, in parallel with the degenerative changes, a pain phenotype rapidly develops in the hind limb ipsilateral to the injected knee, suggesting the presence of central sensitization. It was recently shown that at later time points, OA pain in this model is associated with a neuropathic component. However, there is considerable variation in the OA pain level and different pathophysiologic sequelae according to the dose used. An MIA dose higher than 1 mg was suggested to be associated with a much greater degree of neuronal injury and/or central sensitization that includes afferents innervating territories outside of the knee joint, and is suggested to be used to investigate clinical OA pain with neuropathic features or descriptors. This is in line with the finding of a recent study using a very high MIA dose (4.8 mg), which showed that the induction of the ongoing pain originating from the site of injury was dependent on afferent fiber activity.³⁷ Obviously, more studies are needed to better understand the mechanisms of pain induced by this model.

Subjective and objective assays to measure the behavioral endpoints have been used in this model. The pain responses are typically measured by assessing mechanical and/or thermal hypersensitivity of a hind paw as well as by applying calibrated pressure and torque to the knee. Other methods include assessment of hind limb weight bearing, primary mechanical hyperalgesia, hind limb grip strength, and sleep disruption. Recently, two weight-bearing tests that evaluate nonreflexive and nonreferred OA-induced nociception, the Knee-Bend and CatWalk tests, were found to be reliable methods for assessing movement-induced nociception in the MIA rat model.^{38,39} The use of electrophysiologic recordings of nerve fibers provides direct insight into the underlying nociceptive processes.

Other attempts have been made to create mouse and rat OA models through intraarticular knee injection of different proteolytic enzymes such as papain, trypsin, hyaluronidase and collagenase. Convincing results were obtained with the collagenase injection, which induced not only cartilage damage but also joint instability, synovial membrane inflammation, subchondral bone remodeling, and osteophyte formation.⁴⁰ This model was also demonstrated to be associated with an excess production of prostaglandin E₂, an important feature of human OA. However, no correlation was found between the amount of collagenase injected and the level of cartilage damage.

Surgical procedures

A significant number of models have been developed using different surgical procedures. The most common are those induced by joint instability, including ACLT with or without partial or complete ablation of the meniscus, or by artificial induction of metabolic and/or hormonal changes.

Meniscectomy and/or anterior cruciate ligament transection

OA can be surgically induced by meniscectomy or ACLT in guinea pigs and in rats. Models have also been developed in mice that use different combinations of meniscectomy and ligament transection.^{41,42} The latter produced various degrees of OA severity depending on the extent of joint instability. Another model, produced by a surgical tear in the medial meniscus in rats, was demonstrated to induce consistent and reproducible lesions mimicking many of the human OA features.⁴³ In these models, the surgery is most frequently carried out on the medial side of the joint.

These models generally offer the advantage of faster development of OA lesions than in large and medium-sized animals, and structural changes including cartilage lesions and osteophyte formation have been documented up to 12 weeks after surgery. The interventions induce cartilage changes that are typical of OA: histologic changes in cartilage and depletion of cartilage matrix components, which can progress to a total loss of articular cartilage. Moreover, in the rat ACLT model, the early lesions are also characterized by subchondral bone resorption followed by increased formation of this tissue, which is associated with the development of osteophytes in the periarticular zones.⁴⁴

Pain behaviors have been examined extensively in some of the murine surgically induced OA models. Pain assessments included weight bearing, mechanical hyperalgesia, cold allodynia, mechanical allodynia, and vocalization in response to knee compression. Recently developed tools to assess rodent gait characteristics, including spatiotemporal evaluations of gait patterns and dynamic assessments of reaction forces, have been found to be useful.

Weight-bearing assessment of male C57BL/6 mice following destabilization of the medial meniscus (DMM) showed that the pain was biphasic: early pain due to surgery and, from week 12 onward, significant OA pain.⁴⁵ Another study using this model in male and female DC-1 mice demonstrated tactile allodynia in the ipsilateral hind paws starting at 2 and 4 weeks after surgery, respectively.⁴⁶ Assessment of pain by measurement of hind paw weight distribution in rats subjected to medial meniscal tear revealed changes in weight distribution that appeared as early as 3 days after surgery and remained consistent for at least 3 weeks after surgery.⁴⁷ An earlier study reported alterations in weight bearing at later time points following surgery. The difference between these studies was suggested to be due to the procedures and/or rat strains. Although tactile allodynia was observed in only a proportion of the animals,⁴⁷ this subset of animals had histologic changes similar to those in animals that did not exhibit tactile allodynia, which reveals a lack of correlation between pain assessment and joint damage. Moreover, there were no differences in thermal or mechanical hyperalgesia between the two groups.

Studies in the rat ACLT model reported increased paw elevation time for up to 14 days after surgery.⁴⁸ In the rat model combining ACLT and resection of the medial menisci, decreased walking duration on a treadmill was found to be associated with an increase in the number of neurons positive for calcitonin gene-related peptide in the dorsal root ganglion innervating the joint.⁴⁹ In addition to altered sensory function, this model also showed a late onset of electrophysiologic changes, with a pattern consistent with peripheral neuropathy but not peripheral inflammation.⁵⁰

Ovariectomy

Another surgically induced OA model is ovariectomy in the Sprague-Dawley rat. The hypothesis supporting this model is that estrogen deficiency in postmenopausal women is thought to be a risk factor for disease progression. The model is "postmenopausal-like" induced by estrogen deficiency⁵¹ and is characterized by mild erosion of knee cartilage starting at 9 weeks after surgery. This model is influenced by the age of the animal at the time of surgery; rats 5 to 7 months old should be used. Moreover, the joint lesions are compartment specific, with lesions preferentially in the femur. The cartilage lesions are similar to those seen in the early stages of OA in other models, with changes in cellularity and loss of cartilage matrix integrity, including alterations in collagen fibers and structure. Subchondral bone resorption is also observed and is thought to contribute to the disease process. At present, OA pain has not been studied in this model.

Spontaneous osteoarthritis models

Mouse

It is well known that OA can occur naturally in a number of mouse strains, such as the STR/ort, BALB/c, DBA/1, and C57BL/6 mice. These models show many of the features of human OA, including the occurrence of joint space narrowing, cartilage lesions, alterations in cartilage matrix molecules, and osteophyte formation. In contrast to humans, in which OA is more prevalent in females, in STR/ort and DBA/1 mice a higher prevalence is found in males. Although it is well known that the development of OA structural changes is age related, these models have helped to identify other factors that influence disease development. For example, they have revealed the effects of loss of innervation and anatomic abnormalities, as well as the roles played by many important catabolic factors, cytokines, and proteases and, importantly, the role of genetics.

Guinea pig

Spontaneous OA changes have also been shown in Hartley guinea pigs⁵² and develop preferentially in the medial compartment. As is the case with some mouse strains, the male guinea pig is more prone to the development of rapidly progressive OA. Changes can be seen as early as 3 months of age, with lesions of mild to moderate severity found on the medial tibias of most of the animals by 6 months, and severe lesions in the medial compartment at 1 year. The morphologic changes include cartilage fibrillation, subchondral bone remodeling, synovial membrane hyperplasia, and osteophyte formation as well as an increase in collagen turnover and proteoglycan loss.

Recent studies using this model of spontaneous OA have yielded interesting findings. Inhibition of cathepsin K was associated with a reduction in levels of cross-linked C-telopeptides of type II collagen and joint pain.⁵³ Long-term oral administration of glucosamine and chondroitin sulfate inhibited OA progression by downregulating MMP-3 expression.⁵⁴ The importance of an ω -3 polyunsaturated fatty acid diet in maintaining cartilage integrity is supported by a study in which such a diet reduced spontaneous OA in Hartley guinea pigs in association with a decrease in OA disease markers.⁵⁵

Very few studies of OA pain have been conducted using this model. However, one study in which joint nociception was evaluated using electrophysiologic recordings from knee joint afferents revealed increased spontaneous activity and noxious movement-evoked nerve firing in aged animals.⁵⁶

Genetic models

Genetically modified mice are valuable tools for studying the roles of different molecular processes and key mediators involved in the pathophysiology of OA. Genetic modification can consist of gene shutdown by mutation or deletion or of gene overexpression. Some of the genetic modifications have been particularly useful in identification of the roles played by the matrix components in the development of OA cartilage changes and can serve as useful tools for understanding the complex pathophysiology of the disease. For example, collagen type II (COL2A1)-deficient transgenic mice exhibit degeneration of articular cartilage that resembles OA. Knock-out mice lacking α_1 integrin exhibit an aging-dependent OA phenotype. Mice overexpressing MMP-13 in articular cartilage display OA-like characteristics, and tissue inhibitor of metalloproteinase-3 (TIMP-3)-deficient mice exhibit increased aggrecan loss associated with a mild degree of cartilage degradation. Transforming growth factor- β -deficient mice exhibit an OA-like phenotype. Targeted disruption of Mig-6 leads to early-onset degenerative joint disease.

The combination of genetic modification with surgical induction of OA has been especially useful for delineating the *in vivo* roles of a variety of genes involved in cartilage biology and the pathophysiology of OA. Notably, the DMM model in mice has been very informative. For example, the aggrecanases ADAMTS4 and ADAMTS5 have drawn considerable interest as potential therapeutic targets for the treatment of OA. ADAMTS5-deficient but not ADAMTS4-deficient mice subjected to DMM-induced OA showed a protection against cartilage erosion, the occurrence of OA, and subchondral bone changes.^{41,57,58} However, such a finding is in contrast to the results of studies using human chondrocytes and cartilage explants, in which both ADAMTS4 and ADAMTS5 were shown to be involved in the depletion of aggrecan. In addition, when the DMM model was used in mice deficient in syndecan-4 (a member of the transmembrane heparin sulfate proteoglycans), regulation of ADAMTS5 activation and cartilage breakdown during OA was shown to occur via direct interaction with the protease and regulation of MAPK-dependent synthesis of MMP-3.⁵⁹ A recent study in which the receptor EphB4 (a specific receptor of ephrin-B2) was conditionally overexpressed in bone and the mice subjected to DMM surgery identified a

protective role in OA joint tissues.⁶⁰ In another study using the DMM model, TIMP-2-deficient mice developed accelerated OA via promotion of angiogenesis, which suggests that TIMP-2 is essential for maintenance of normal articular cartilage homeostasis.⁶¹

Small animal model limitations

Small animal models are particularly helpful for exploring very specific pathways involved in the pathophysiology of OA and for testing specific DMOAD strategies. They offer several advantages, including low cost and ability to perform a wide variety of studies. However, to date, there have been a limited number of studies in small animal OA models from which results have successfully been extrapolated directly to humans. This being said, the variety of OA models available in small animals presents many opportunities to study the wide range of disease features and also offers the great advantage of rapid disease development compared with the human disease. These models also provide the opportunity to study structural changes in the different joint tissues at the same time. Genetically modified models can be used to validate specific therapeutic targets. Small animal models also allow the comparison of results obtained from spontaneous versus induced OA models to study key phenomena of OA development. In addition, the emergence of tissue-specific genetic modification in mice, such as Cre-lox technology, has enabled the generation of tissue-specific gene-deficient and overexpressing mice, which can facilitate the understanding of the *in vivo* role of each targeted gene in OA pathobiology. These models can also be used to identify the interdependence of the separate joint tissues.

Although they are useful tools for research, it is important to understand the limitations imposed by small animal models. For instance, the sample material available from the articulation and, more precisely, from each tissue, is very limited. Moreover, differences exist among certain models in the severity of structural changes based on gender and body weight, as in the spontaneous OA guinea pig model, as well as in the degree of joint stability. There are some particularities of certain species that must be kept in mind. For example, mice do not express or produce MMP-1, and ADAMTS5 was shown to be of pivotal importance in this model, whereas in humans this is not clear. It was also recently shown that the deleterious effect of activation of the Wnt/ β -catenin pathway in OA cartilage that is seen in small animal models should be revisited because the data indicate that in humans this system inhibits the IL-1 β activation of some MMPs as part of a negative feedback loop counteracting nuclear factor- κ B.⁶² Additionally, the finding that the surgically induced OA rat model better approximates the human condition than the spontaneous OA guinea pig model highlights the need for experimentation in multiple animal models. Although rodent behaviors can be used to describe some of the symptomatic consequences (pain) of OA and behavioral assays have been developed, certain tests may not be

adequate because they rely on stimuli that are not applied to the affected joint; they thus evaluate referred nociception and/or fail to evaluate movement-related nociception, the latter of which is a hallmark of OA-induced pain. With regard to the MIA model, the divergent sequelae following different doses of MIA must be taken into account, especially when indirect outcome measures of joint pain have been employed and when higher doses are used.

CONCLUSION

Animal models of OA have been shown quite convincingly to be useful in the study of the evolution of joint structural changes that occur during OA and in the exploration of the different pathophysiologic mechanisms responsible for those changes. Obviously, there are a number of limitations of OA models. For instance, the advantages of spontaneous versus induced OA models and large versus small animal models are still under debate, and the mechanisms leading to the structural changes observed in spontaneous OA models remain largely unknown. Each offers advantages and disadvantages. Spontaneous OA models are useful in the study of the primary onset of OA and can be applied to investigate prevention and treatment. However, use of these models can be time-consuming, and differences exist in the onset, incidence, and severity of the disease among animal species. Surgically induced OA models develop damage rapidly and reproducibly. Nonetheless, they are mainly posttraumatic models, and the disease at first involves biomechanical instability. Intraarticular administration of agents generates OA in a short time, and these models can mimic the final stage of OA, at least in cartilage. These models are valuable mainly for investigating pathologic processes in cartilage and the therapeutic effects of drugs in this tissue. This could be a concern because, although articular cartilage degradation was once considered the hallmark of OA, the concept of the joint as an organ is now recognized as fundamental to basic and clinical research in OA, and at present the theory put forward is that a DMOAD has to modulate more than one tissue of the joint to be effective. Genetically modified mice are used for mechanistic studies aimed at understanding the functional role of specific molecules in OA pathologic processes. Reservations include their frequent lack of physiologic relevance to the human disease and their use as drug-screening tools; in addition, these studies are time-consuming and expensive.

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175

Pathogenesis and pathology of osteoarthritis

■ THOMAS AIGNER ■ NICOLE SCHMITZ ■ DONALD M. SALTER

- Osteoarthritis (OA) is characterized primarily by focal cartilage damage, bone sclerosis, and synovioathy.
- Changes within the articular cartilage can be categorized by typing, staging, and grading of the lesions.
- OA is strongly associated with age, but bone and cartilage changes in OA are different from those of normal aging.
- There are many different hypotheses that try to explain cartilage and joint degeneration, including chronic mechanical (over)load, matrix proteolysis, age-induced changes in the cartilage matrix and the chondrocytes, and increasing damage to the genomic DNA of the chondrocytes leading to a deranged cellular phenotype.
- The production of proinflammatory cytokines as well as the activation of cellular inflammatory signaling pathways, including interleukin-1 and the MAP kinases, likely play an important role in OA pathogenesis.
- Biomechanical factors are essential in the pathogenesis of OA. Altered joint biomechanics are generated by joint incongruity, laxity, muscle weakness, and impaired proprioception in addition to trauma and heavy physical load.
- Despite the fact that presumably a great variety of different phenomena contribute to the pathogenesis of OA, premature aging of the chondrocytes and the matrix probably plays a crucial role in its initiation and progression; thus OA might be in analogy the “morbus Alzheimer” of the joint.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and the leading source of physical disability with severely impaired quality of life in people in industrialized nations. Although derived from the Greek words *osteon* for bone, *arthron* for joint, and the suffix *-itis* for inflammation, the site of the most pronounced structural alterations is not the bone but the joint cartilage, and severe inflammation is seen in only a few patients. OA is generally considered a disease of the elderly, progressively causing loss of joint function, but although it is true that OA prevalence increases sharply with age it is not part of normal aging. Very little is known about the underlying causes of OA, and many hypotheses regarding its pathogenesis have been proposed. Genetic defects causing malfunction of structural genes give rise to premature and often severe OA in certain families, but in the majority of OA cases no such defects have been identified. Risk factors other than age include obesity, metabolic diseases, joint malalignment, and joint trauma. Each can contribute to the initiation and progression of the disease in different compartments of the joint. Biochemical processes involving cartilage, bone, and synovium eventually intertwine and collectively damage all three joint compartments. This results in articular cartilage breakdown, osteophyte formation, subchondral bone sclerosis, bone marrow lesions, and changes in the synovium that manifest as episodic synovitis (Fig. 175.1). Advances in molecular biology raise hopes that new therapeutic targets will be identified that will allow more than just symptomatic therapy. Joint replacement is still the unsurpassed therapy for advanced and incapacitating OA. However, with increasing appreciation of the contribution of all three joint compartments to disease progression, research in OA pathogenesis, biomarkers, and treatment has broadened immensely, and many new potential therapeutic targets have emerged over the past years.

THE NORMAL JOINT: ANATOMY, PHYSIOLOGY, AND FUNCTION

Understanding joint dysfunction requires some knowledge of the normal joint and comparison of the diseased state with the physiologic situation (Fig. 175.2). The most important requirements for normal joint function are the freedom of the opposed articular surfaces to move pain free and largely friction free within the required range of motion as well as to distribute load correctly across joint tissues. Thus a pathologic condition in many cases might be caused by acute or chronic mechanical overloading, systematic mal-loading, or habitual underloading leading to disuse atrophy.

Correct functioning of the joint is largely dependent on its design. Joints are highly specialized organs whose properties are provided by the articular cartilage, which, under physiologic conditions, is capable of sustaining high cyclic loading. Articular cartilage covers the joint surfaces and is mainly responsible for the unique biomechanical properties of the joints. Joints are complex composites of different types of connective tissue, including subchondral bone, cartilage surfaces, ligaments, and the joint capsule. The bone defines the shape of the joint, and the articulating surfaces—in combination with the articular cartilage—determine the absorption properties during movement. The synovial capsule and, in particular, the synovial membrane (i.e., the synovial lining cell layer) also contribute to the physiologic functioning of the articulating joints. The synovial capsule, together with the ligaments, provides the mechanical stability of joints and ultimately determines their flexibility and range of motion. The synovial membrane, containing highly metabolically active surface cells, or synoviocytes, plays a crucial role in nourishing the chondrocytes as well as maintaining the normal metabolic milieu within the joint by removing metabolites and matrix degradation products from the synovial space. Synoviocytes also produce large amounts of important mediators (cytokines and growth factors), matrix-degrading enzymes, as well as hyaluronic acid and other factors such as lubricin/superficial zone protein that aid joint lubrication and free movement. For this reason, all tissues and cells within the joint act to maintain the local milieu of the synovioarticular joint organ and work in concert to allow optimal function and integrity of joints.

PATHOLOGY

The progressive macroscopic and histologic changes in articular cartilage in OA are well recognized (Figs. 175.3 and 175.4). Macroscopically, normal hyaline articular cartilage is smooth and pale cream to yellowish in color. In OA the cartilage appears more discolored, soft, and roughened with the underlying subchondral bone exposed in later stages (see Fig. 175.3f and g). These changes can be seen and graded radiographically (see Chapter 177) and can be visualized in more detail histologically (see Fig. 175.4). In early OA cartilage volume is increased due to increased water content and proteoglycan swelling, which occurs secondary to physical or proteolytic disruption of the type II collagen network. Subsequently, cartilage proteoglycan content decreases, a result of increased expression and activity of matrix-degrading enzymes (see Fig. 175.4b). As OA progresses direct physical forces on the weakened cartilage cause surface matrix fibrillations, cracks in the superficial layer of the articular cartilage that run parallel to the surface. These cracks extend, following the tangential and vertical orientation of the collagen fibers in the mid and deep cartilage zones. Fissures branch and propagate as a result of ongoing mechanical trauma, and this, in conjunction with continuing proteolytic activity, leads to progressive cartilage loss (see Fig. 175.4e). In contrast to the reduction in the volume of noncalcified articular cartilage, the thickness of the calcified cartilage zone increases and is associated with duplication/multiplication

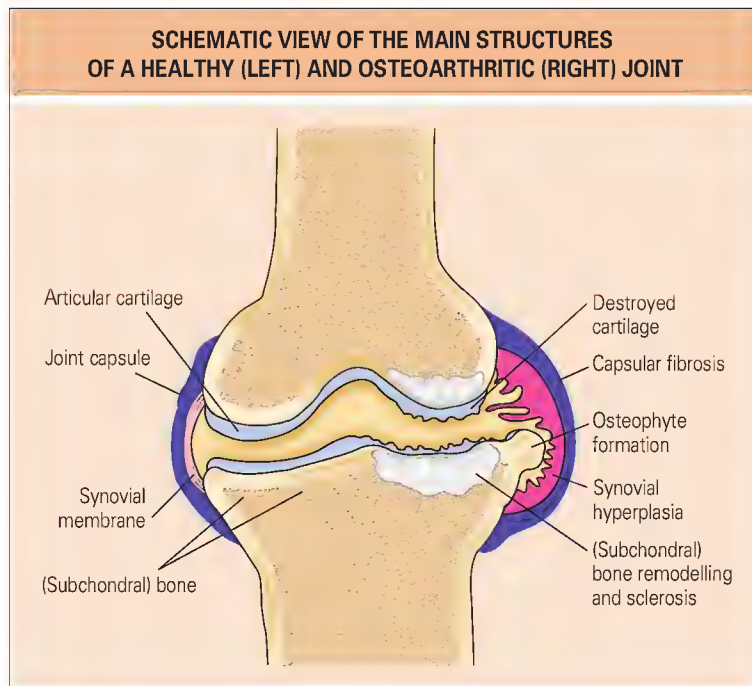


Fig. 175.1 In osteoarthritis (OA) the articular cartilage is lost or severely thinned, the (subchondral) bone is sclerotic, the joint capsule is thickened, and the synovial membrane is activated. (Courtesy E. Bartnik, Frankfurt.)

and vascular invasion and innervation through the tidemark that separates calcified from noncalcified cartilage. Microcracks also appear in the calcified cartilage and may initiate bone remodeling. The duplication/multiplication of the tidemark reflects episodes of tidemark advance, which also contribute to cartilage thinning. The subchondral bone becomes thickened, giving rise to radiologic subchondral sclerosis, and areas of failed efforts to repair subchondral bone fractures develop into radiolucent cysts containing myxoid and fibrocartilaginous tissue. Osteophytes arise at the periphery of the joint from perichondral/periosteal stem cells that are induced to proliferate and undergo chondrogenic differentiation under the influence of growth factors such as transforming growth factor- β (TGF- β). A similar but less structured process is observed in the areas of the eburnated bone, in which the articular cartilage is absent. Here, metaplastic cartilage in the form of nodules or tufts is found either within the bone marrow or at the naked bone surface.

TYPING, STAGING, AND GRADING OF JOINT CARTILAGE ALTERATIONS IN OSTEOARTHRITIS

The classification of OA cartilage degeneration is complex because patients have a variety of histories, symptoms, and morphologic changes. Common to all, however, are symptoms of pain or limitation in joint movement associated with structural joint (cartilage) damage. Although other joint tissues are involved in OA, cartilage has traditionally been used to score OA severity. In general, the process of joint destruction can be evaluated with regard to the pathogenesis ("typing"), the extent ("staging"), and the degree of the most extensive focal damage ("grading").¹

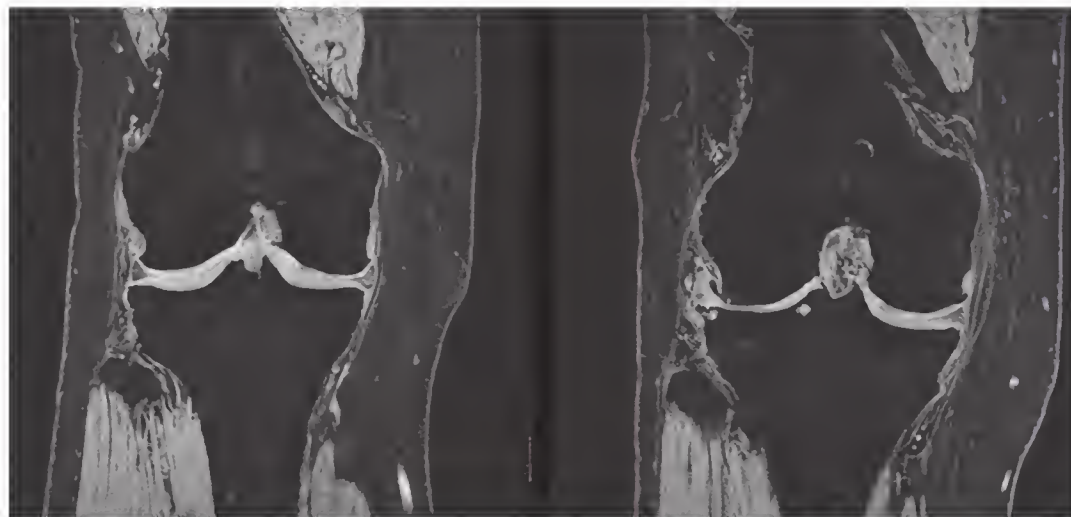


Fig. 175.2 Coronal magnetic resonance imaging data sets of the knee acquired using a fast low-angle shot (FLASH) or spoiled gradient echo (SPGR) sequence. This imaging sequence has been extensively validated for detecting cartilage lesions and for performing quantitative measures of cartilage volume and thickness. The left image shows a healthy knee with normal cartilage thickness, the right image a knee with osteoarthritis. Note the osteophytes and the extensive cartilage loss in the lateral femorotibial compartment. (Courtesy Felix Eckstein, Salzburg, Austria.)



Fig. 175.3 (a) Macroscopic appearance of the femoral condyles of a normal knee. (b) Femoral condyles of a severely damaged knee. (c) Arthroscopic image of a cartilage defect of the femoral condyle within the knee joint. (c, Courtesy Dr. W. Eger, Rummelsberg, Germany.)

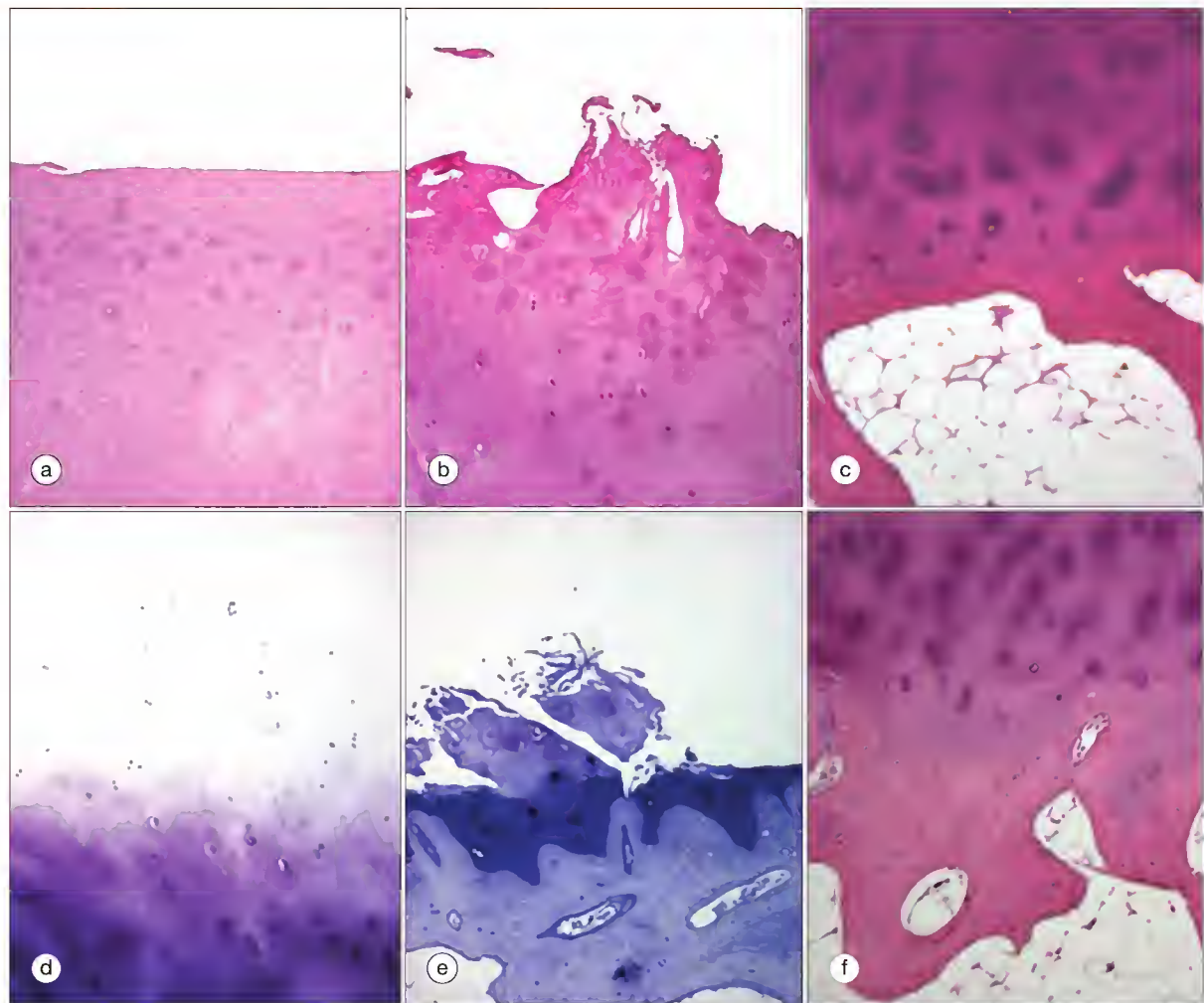


Fig. 175.4 Conventional histologic preparations show fibrillation and matrix loss in osteoarthritic (OA) cartilage (b) compared with normal cartilage (a). In severely damaged areas nearly all articular cartilage is destroyed (e). Also a moderate (d) to severe (e) loss of proteoglycans is found, as visualized by toluidine blue staining. Besides changes in articular cartilage, changes in the subchondral bone are prominent in OA as well; namely, thickening of the subchondral bone plate (f) compared with normal (c).

BOX 175.1 TYPING OF JOINT DESTRUCTION

Primary

No (major) causative reason known

Secondary

- Articular gout
- Bone infarction
- Endocrine disorders (e.g., hyperparathyroidism, hypothyroidism)
- Hemophilia
- Intraarticular infections
- Joint instability (e.g., ligament and meniscus lesions)
- Neuropathic arthritis (e.g., Charcot joint)
- Overload causing excessive wear (work, sports, varus or valgus deformity)
- Paget disease
- Trauma

Typing relates mostly to classification as primary (idiopathic) OA or secondary OA (caused by another disorder). Primary OA is most frequently observed. Although the designation “primary” implies that there is no obvious cause, minor preexisting conditions (i.e., preconditions or risk factors) still may exist in this type of OA. The major causes leading to secondary OA are listed in [Box 175.1](#).

Grading and staging are more debated. *Grading* should refer to evaluation of histologic changes at one (arguably the worst) site of joint destruction, whereas *staging* should refer to assessment of how far the overall disease has progressed toward an end stage (in analogy to grading and staging of tumors). Both represent an attempt to score processes relevant to the disease.

The grading system most commonly used (partly with minor modifications) is the histochemical-histologic grading system of Mankin and coworkers ([Table 175.1](#); [Fig. 175.5](#)).² Criticisms of the Mankin system

TABLE 175.1

Grading of osteoarthritis according to Mankin and colleagues (1971)

Feature	Score	Histologic feature
Cartilage structure	0	Normal
	1	Superficial fibrillation
	2	Pannus and superficial fibrillation*
	3	Fissures to the middle zone
	4	Fissures to the deep zone
Chondrocytes	5	Fissures to the calcified zone
	0	Normal
	1	Diffuse hypercellularity
	2	Cell clusters
	3	Hypocellularity
Safranin O staining	0	Normal
	1	Slight reduction
	2	Moderate reduction
	3	Severe reduction
	4	No staining
Tidemark	5	Total disorganization*
	0	Intact
	1	Tidemark penetrated by vessels†

*Might best be removed (relates to osteophyte formation).

†Might best be supplemented with “or duplicated tidemark.”

From Mankin HJ, Dorfman H, Lippiella L, et al. Biochemical and metabolic abnormalities in articular cartilage from osteoarthritic human hips. *J Bone Joint Surg Am* 1971;53:523-37.

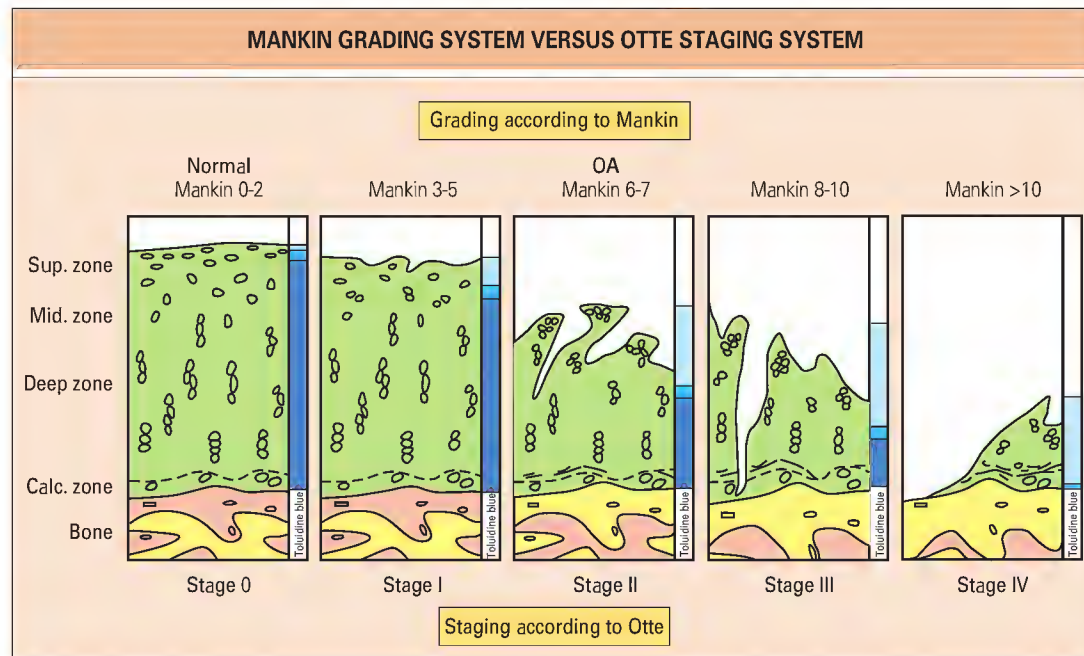


Fig. 175.5 The grading system for osteoarthritis (OA) proposed by Mankin and colleagues (1971)² compared with the staging system proposed by Otte (1969).⁴⁶ Calc., calcified; Mid., middle; Sup., superior.

TABLE 175.2

Grading scheme originally suggested by Outerbridge (1961) for macroscopic changes seen on the patella

Grade I	Softening and swelling of the cartilage
Grade II	Fragmentation and fissuring in an area ≤ 0.5 inch in diameter
Grade III	Area more than half an inch in diameter is involved
Grade IV	Erosion of cartilage down to bone

From Outerbridge RE. The etiology of chondromalacia patellae. J Bone Joint Surg Br 1961;43:752-7.

include the fact that there can be high interindividual variability that might be related to the experience of the users. Additionally some of the subcategories of the Mankin score do not assess primary cartilage degeneration but describe features observed in secondary cartilage formation (e.g., osteophyte formation) and should be excluded in future scoring attempts. Whereas the Mankin system addresses the part of the joint cartilage that is viewed under the microscope, scoring systems that look at the whole joint surface macroscopically—but also, if needed, the worst lesion histologically—provide additional information. The Outerbridge system (Table 175.2) was described primarily for the patella but later was successfully applied to other joints. At the site of the greatest cartilage damage, grading and staging are closely correlated. A purely macroscopic staging system is too imprecise for scientific purposes, and a new scoring system has been proposed by Pritzker and colleagues³ (Table 175.3) that combines histopathologic grading parameters with the extent of the lesions. With new scientific insights and more extensive and specific medical therapeutic options it is likely that more elaborate and validated grading and scoring systems will need to be developed. Of crucial importance will be the use of defined and unified nomenclature to make studies, descriptions, and results comparable. Currently, similar-sounding terms are used for partly different phenomena and different-sounding words are used for the same entity (e.g., fissuring, clefting, flaking). Therefore a consensus nomenclature has been proposed by the Osteoarthritis Research Society International (OARSI)⁴ (Table 175.4).

TYPING AND GRADING OF SYNOVIAL MEMBRANE ALTERATIONS IN OSTEOARTHRITIS

Clinically relevant OA is invariably associated with some sort of pathologic synovial changes. This reflects the notion of a direct relation between clinical symptoms and the synovial reaction in OA. Most likely these changes

TABLE 175.3

Scoring of osteoarthritis according to Pritzker and colleagues (2006)

Grade	Histologic properties
0	Matrix: surface intact (normal architecture) Cells: intact, appropriate orientation
1	Matrix: superficial zone intact, edema and/or superficial fibrillation (abrasion), focal superficial matrix condensation Cells: cell death, proliferation (cluster formation), hypertrophy
2	As above: Matrix: discontinuity at superficial zone (deep fibrillation) ± Loss of proteoglycan staining in upper third of cartilage ± Focal perichondral increased proteoglycan staining in middle zone ± Disorientation of chondron columns
3	As above: Matrix: vertical fissures into middle zone and branched fissures ± Loss of proteoglycan staining into lower two thirds of cartilage ± New collagen formation cells: cell death, regeneration, hypertrophy in cartilage domains adjacent to fissures
4	As above: Cartilage matrix loss with delamination of superficial zone Excavation with matrix loss from superficial to middle zone ± Formation of cysts in the middle layer
5	Complete matrix loss with denudation of the sclerotic subchondral bone or fibrocartilage ± Microfracture with repair limited to bone surface
6	Bone remodeling (more than osteophyte formation only) with microfracture, fibrocartilage, and osseous repair above the previous surface

Data from Pritzker KP, Gay S, Jimenez SA, et al. Osteoarthritis cartilage histopathology: grading and staging. Osteoarthritis Cartilage 2006;14:13-29.

are at least partly involved in the progression of the disease. In OA four different types of OA synoviopathies are identified: hyperplastic, inflammatory, fibrotic, and detritus rich (Table 175.5).⁵

Detritus-rich synovitis, which is found in end-stage OA disease, is due to abundant macromolecular cartilage and bone detritus (i.e., bone and cartilage fragments attached to or incorporated into the synovial membrane; Fig. 175.6h and i) in addition to molecular debris that is not visible microscopically. A significant amount of fibrinous exudate is also found at the synovial membrane surface. This exudate may be combined with incorporated fibrin, which reflects longer ongoing fibrinous exudation being

■ TABLE 175.4

OARSI terminology for osteoarthritic joint pathology—a proposal for a consensus

Preferred term	Definition	Synonym
Superficial zone	Includes the surface and upper zones.	
Surface zone	Cartilage zone immediately subjacent to the joint surface. Collagen fibers are aligned parallel to surface (without cells). This zone might be not be present in normal cartilage samples or in some species.	Lamina splendens
Upper zone	Collagen fibers are aligned parallel to surface. Chondrocytes, elongated and flattened, are aligned parallel to collagen fibers and to joint surface.	Horizontal zone/layer Tangential zone/layer Superficial zone/layer
Middle zone	Zone subjacent to upper zone. Collagen fibers are aligned intermediately between upper and deep zone alignments. Chondrocytes are in groups (chondrons) aligned parallel to collagen fibers.	Transitional zone/layer Intermediate zone/layer
Deep zone	Zone subjacent to middle zone and above calcified cartilage.	Radial zone/layer
Upper deep	Collagen fibers are aligned predominantly perpendicular to joint surface.	
Lower deep	Chondrocytes within chondrons are aligned parallel to collagen fibers and perpendicular to joint surface.	
Tidemark	Zone of increased calcification at border of uncalcified and calcified cartilage.	Calcification front
Penetration		Ligne bordant (increased basophilic stain)
Advancement		
Duplication/multiplication		
Calcified cartilage	Zone between tidemark and subarticular bone plate.	Calcified zone
Surface undulations	Surface irregularities that do not involve discontinuity of the articular surface.	Roughening Unevenness
Fissure	Vertical cracks, irregularities, or discontinuities of cartilage matrix.	Cleft Crack
Superficial	Restricted to surface and superficial zone.	Flaking Fraying
Middle	Restricted down to middle zone.	Fibrillation
Deep	Restricted down to deep zone.	Fissuring
Simple	Unbranched fissure.	
Complex	Branched fissure.	
Split/splitting	Horizontal (0 to 60 degrees to cartilage surface) matrix cleft/separation.	
Erosion	Loss of articular cartilage tissue including superficial and at least portions of deeper cartilage layers.	Loss
Surface		Ulceration
Into the superficial zone		Abrasion
Into the middle zone		Delamination
Into the deep zone		Flaking
Full depth		Spallation Excavation
Eburnation	Smooth shiny bone surface indicative of exposed bone at articular surface.	Denudation

OARSI, Osteoarthritis Research Society International.

From Pritzker KP, Aigner T. Terminology of osteoarthritis cartilage and bone histopathology—a proposal for a consensus. *Osteoarthr Cartil* 2010;Suppl 3:S7-S9.

■ TABLE 175.5

Major histopathologic features of the four patterns of osteoarthritis-associated synoviopathy in comparison to each other and to normal synovial membrane

	Normal	Hyperplastic synoviopathy	Inflammatory synoviopathy	Fibrotic synoviopathy	Detritus-rich synoviopathy
Villous hyperplasia	—	++(+)	++(+)	++(+)	++(+)
Synovial lining—proliferation	—	+	++	++	++(+)
Synovial lining—activation	—	+	++	+	+
Fibrinous exudate	—	—	(+)	+	++(+)
Capsular fibrosis	—	—	(+)	+++	+++
(Macromolecular) cartilage and bone debris	—	—	(+)	—	+++
Granulocytic infiltrate	—	—	—	—	+
Lymphoplasmocellular infiltrate—diffuse	—	—	++	(+)	++(+)
Lymphoplasmocellular infiltrate—aggregates/follicles	—	—	++	(+)	(+)

From Oehler S, Neureiter D, Meyer-Scholten C, et al. Subtyping of osteoarthritic synoviopathy. *Clin Exp Rheumatol* 2002;20:633-40.

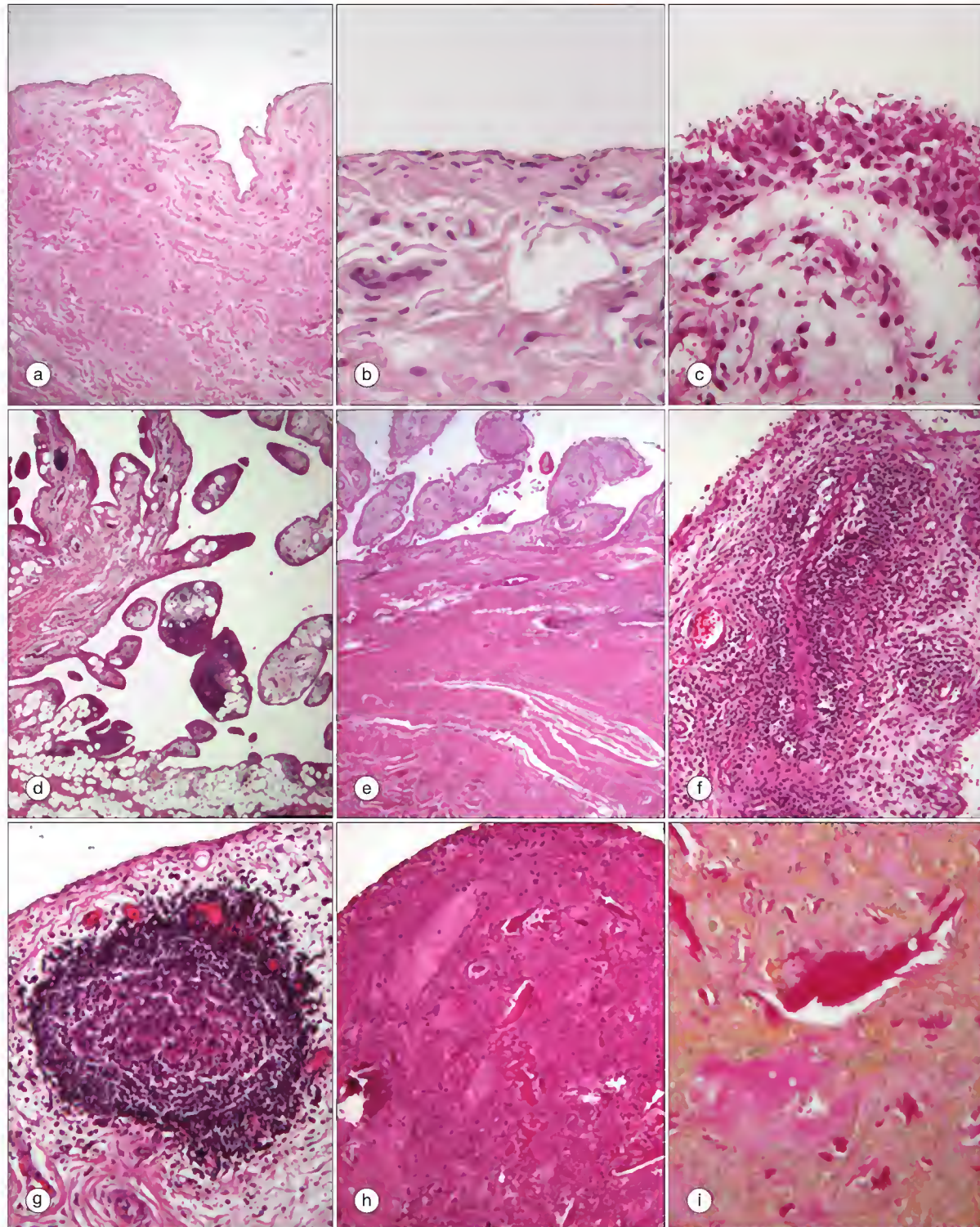


Fig. 175.6 Normal synovial membrane (a and b) shows a rather flat surface with a flat layer of inactive, nonproliferated layer of synoviocytes. In contrast, in osteoarthritis (OA), at least in some cases, synoviocytes are severely activated and proliferated (c) similar to the situation found in rheumatoid arthritis. In late-stage OA most synovial specimens show a moderate to abundant synovial hyperplasia (d and e) and often some sort of capsule thickening (e). In a minority of cases OA synovial membranes show mild to moderate inflammatory infiltrates (f and g) usually lying in aggregates around blood vessels (f). In some cases lymphoid follicles also are found (g). End-stage rapid progressive cartilage destruction leads to detritus-rich synovitis with cartilage and bone fragments incorporated into fibrinous exudate (i, van Gieson stain) or the synovial stroma (h). (Reprinted with permission from Aigner T, van der Kraan P, van den Berg W. Osteoarthritis and inflammation— inflammatory changes in osteoarthritic synoviopathy. In: Buckwalter JA, Lotz M, Stoltz JF, editors. *Osteoarthritis, inflammation and degradation: a continuum*. Amsterdam: IOS Press; 2007, p. 219-30.)

organized. Detritus-rich synovioarthritic lesions usually contain a minor inflammatory cell infiltrate consisting of lymphocytes and granulocytes as well as some foreign body giant cells. Another form of OA synoviopathy found in late-stage disease, fibrotic OA synoviopathy (capsular fibrosis) (see Fig. 175.6e),⁵ is characterized mainly by shortening and thickening of the joint capsule. This may be partly responsible for some symptoms such as joint stiffness in OA patients.

The most interesting of the OA synoviopathies, in terms of pathogenesis, is inflammatory OA synoviopathy, which is characterized by moderately

extensive lymphocytic infiltrates (see Fig. 175.6f and g). It is intriguing to speculate whether this condition reflects an autoimmune process that may be occurring, at least in this subset of OA patients. The lymphocytic infiltrate in the subsynovial stroma appears to correlate directly with interleukin-1 β (IL-1 β) in the synovial fluid as well as matrix metalloproteinase-1 expression by synoviocytes, which suggests a direct stimulatory role of the inflammatory cells on the activity of the synovial lining cells. The presence of inflammation in a significant portion of OA patients points to the option of antiinflammatory therapy for some subsets of OA patients.

In early OA, a mostly hyperplastic OA synoviopathy is found (see Fig. 175.6d). This pattern shows only moderate synovial hyperplasia, with or without cellular activation but without significant capsular fibrosis or significant inflammatory cell infiltration or detritus. Overall, three forms of alterations to the synovial surface are seen:

1. Cytoplasmic volume of the usually flat synovial lining cells (hyper-trophy) increases. These cells may become cuboidal or even cylindrical, which suggests that they have been activated in some way (see Fig. 175.6c).
2. The normal single (flat) cell layer of synovial lining cells (see Fig. 175.6a and b) proliferates to form as many as five cell layers (hyperplasia)
3. The whole synovial surface, including the underlying stroma, can become hyperplastic and form the classic synovial villi.

Synovial hyperplasia per se can be found in all forms of OA synoviopathy and in chronic synovitis. Thus villous hyperplasia is largely a nonspecific feature of chronic synovial alteration and activation.

A well-established scoring system is not yet available for human OA synoviopathy. A simple scoring system proposed by Krenn and colleagues⁶ to separate inflammatory and noninflammatory synovial alterations is based mainly on the intensity of inflammatory infiltrates and synovial and stromal activation. In 2002 a scoring system specifically for OA synoviopathy was developed that divided the OA-associated synoviopathies into the four categories noted earlier (see Table 175.5)—hyperplastic, fibrotic, inflammatory, and detritus rich—which are subdividable into mild, moderate, and strong

depending on the intensity of changes present.⁵ This system aims to reflect the different roles of OA synoviopathy and their implications for the clinical disease. Regardless of the scoring system used, it is important that changes present in the overall joint be averaged because synovial changes are notoriously heterogeneous within affected joints and a single assessment may give erroneous results.

EVALUATION OF REGENERATIVE CARTILAGE FORMATION IN OSTEOARTHRITIC JOINTS (CHONDRO-OSTEOPHYTE FORMATION)

Central for a basic understanding of osteophytic tissue is an analysis of the developmental steps during osteophyte formation. Although it is clear that osteophyte development is a continuous process and many osteophytes show various portions in different stages at the same time, basic steps can be defined based on the cellular phenotype and the matrix composition of the predominating tissue (Fig. 175.7).⁷ To date, the molecular mechanisms in the development of osteophytes are largely unknown. Mechanical or biochemical stimuli could play a central role. However, most osteophytes do not take part in the articulating process and are subsequently not exposed to major mechanical load. Thus it is more likely that growth factors play a dominant role in the induction and promotion of osteophyte formation. For example, the exogenous application of TGF- β and bone morphogenetic protein type 2 into knee joints of adult mice leads to significant osteophyte formation.

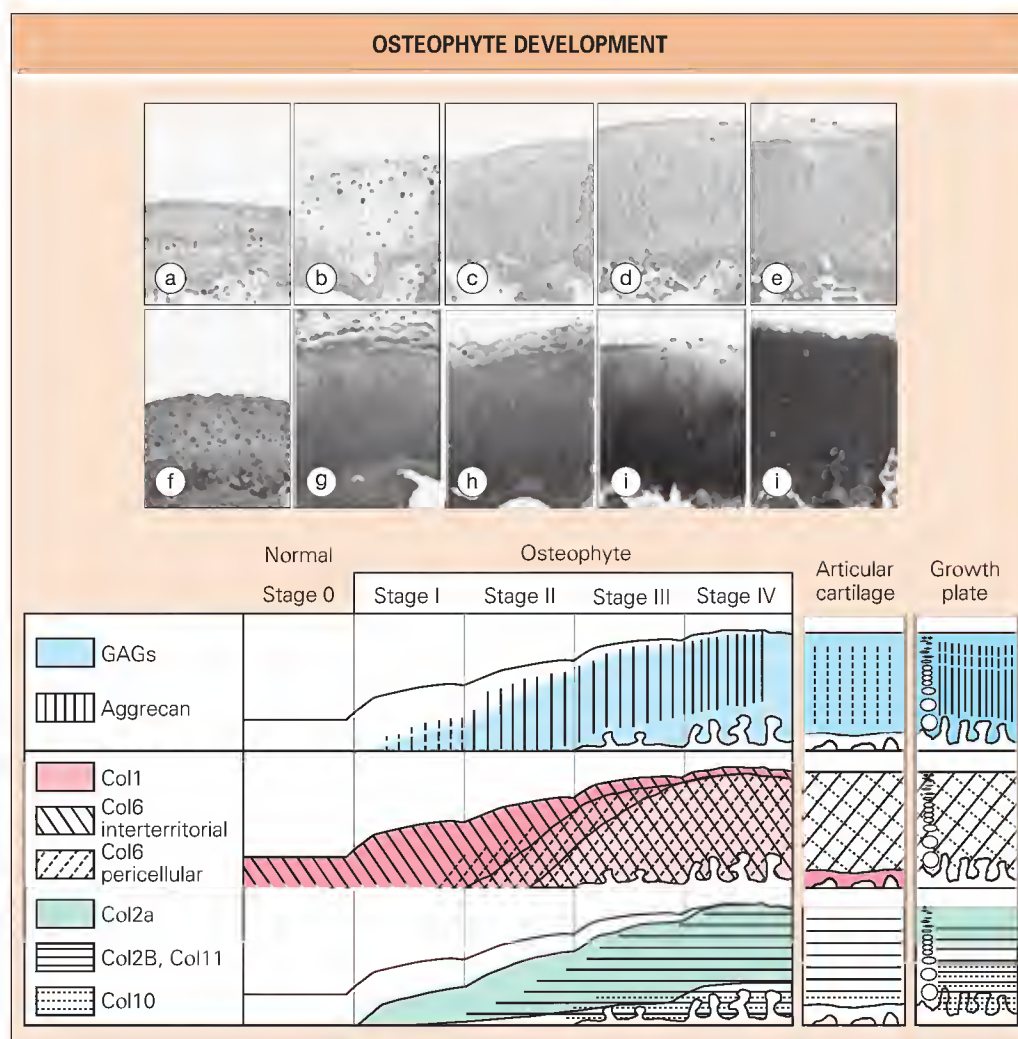
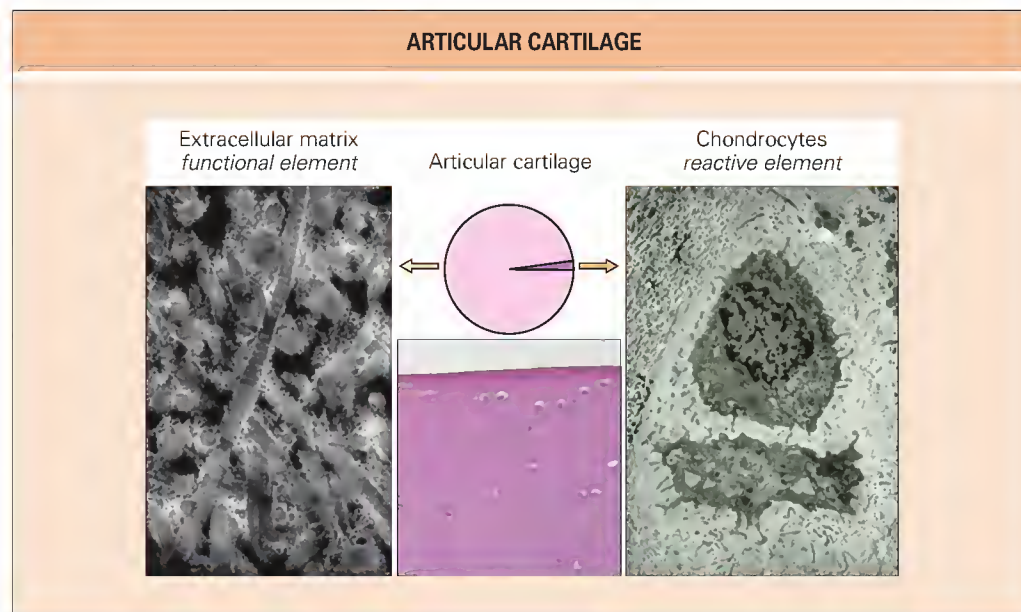


Fig. 175.7 Osteophyte development can be subdivided into four stages with different structural organization, although at a given time many osteophytes show different areas that are at different stages. Stage I (early chondrocytes) is characterized by the first chondrocytic differentiation of previously undifferentiated mesenchymal precursor cells (b, g, k). In stage II (chondrocytes) there are extensive areas of newly formed cartilage, but no (endochondral) bone formation is observed (c, h, k). Stage III (early osteophytes) is characterized by an arrangement similar to that of the fetal growth plate cartilage with hyperplastic differentiation in the deepest cartilage layers and active bone formation underneath (d, i, k). In stage IV (mature osteophytes) a structure most resembling hyaline articular cartilage physiologically covers the joint surfaces (e, j, k). Normal periosteum is shown in a and f (a to e, hematoxylin-eosin; f to j, toluidine blue). Col, collagen; GAGs, glycosaminoglycans. (Reprinted with permission from Gelse K, Söder S, Eger W, et al. Osteophyte development—molecular characterization of differentiation stages. *Osteoarthritis Cartilage* 2003;11:141-8.)

Fig. 175.8 Articular cartilage consists mainly of extracellular matrix (more than 95% of tissue volume), its functional element. Interspersed in between the abundant matrix are the cells, the chondrocytes, which are the living (i.e., reacting) element of the articular cartilage tissue. (Reprinted with permission from Aigner T, Sachse A, Gebhard PM, et al. *Osteoarthritis: pathobiology—targets and ways for therapeutic intervention. Adv Drug Deliv Rev* 2006;58:128-49.)



Osteophytes could be considered as attempts at endogenous repair in degenerating joints; an increase in the articulating joint surface might represent a response to mechanical overloading and thus have a supportive function. However, osteophytes are found mainly in non-weight-bearing areas, and their mechanical stability and biologic benefit are questionable. Understanding osteophyte formation and classifying its maturation stage is interesting in itself to understand changes going on in the chondro-osseous department in OA joints, but in addition osteophyte formation represents an interesting *in-vivo* model system for understanding and evaluating processes occurring after many modern cartilage repair strategies (e.g., transplantation of mesenchymal precursor cells to fill up cartilage defects).

ANIMAL MODELS OF OSTEOARTHRITIS

Animal model systems represent an important adjunct and substitute for studies of OA in humans. They provide means to study OA pathophysiology as well as assist in the development of disease-modifying therapeutic agents and biologic markers for diagnosing and determining a prognosis for the disease. Not surprisingly, identification of an optimal model system for the human disease is difficult or impossible, and a number of models involving various species are currently in use. These include models of spontaneous OA as well as models in which OA is induced (surgically, enzymatically/chemically, mechanically, or genetically) (see Chapter 174). Unfortunately, all the models differ somehow, and no gold standard has yet been identified. Given this heterogeneity of the OA disease process, identification of an appropriate disease mechanism-oriented model may be a more realistic goal and better suited to a particular investigation than the “universal model” that has not yet been identified. Rather, as a consequence of the heterogeneity of this disease in humans, a plethora of models is required.

PATHOGENETIC CONCEPTS IN OSTEOARTHRITIS

OA is a heterogeneous condition, and most likely there are many different causes that initiate or promote the disease process. An overview of the relevant pathogenetic concepts for OA is provided here.

Articular cartilage and the extracellular matrix

Articular cartilage is a highly specialized and uniquely designed biomaterial (see Chapter 5). It is largely an avascular, aneural, and alymphatic matrix that is synthesized by the sparsely distributed resident cells—the chondrocytes. The cartilage matrix can be subdivided into different cartilage zones—superficial, radial, deep, and calcified—based on the arrangement of the cells and the matrix fibrils; it can also be separated into different compartments depending on its relationship to the cells: the pericellular matrix is immediate to the cells, the interterritorial matrix compartment represents the major portion of the cartilage matrix at a distance from the cells, and the territorial matrix is the cell-associated compartment in between, which

has not really been well defined and characterized (Fig. 175.8). In terms of physical properties, tensile strength comes from the collagen network, which hinders expansion of the viscoelastic aggrecan component. The aggrecan-hyaluronan aggregates bind high amounts of water owing to their extensive fixed charges and are responsible for the resistance to compression of the tissue. Thus, under compression, the cartilage matrix is compliant but rapidly regains its elasticity as water molecules are drawn back into the matrix on unloading by the strongly hydrophilic aggrecan aggregates.

Most of the cartilage matrix is formed during fetal development and the phase of skeletal growth until the closure of the growth plates at the end of adolescence. Indeed, the collagen backbone appears to show virtually no turnover during life, at least in the (inter)territorial matrix compartments. However, other matrix components—namely, the large aggregating proteoglycan aggrecan and the small proteoglycans as well as some collagen types (e.g., types VI and IX)—show a significant turnover throughout life. This physiologic turnover is highly relevant for the maintenance of the cartilage matrix integrity on the molecular and particularly the macromolecular level.

Pathologic matrix degradation

One major threat to the cartilage matrix⁸ and thus to the integrity of articular cartilage are matrix-degrading enzymes that destroy the collagen network and proteoglycans (Fig. 175.9). Besides direct degradation of molecular components, destabilization of the supramolecular structures also takes place and plays an important role in the loosening of the overall matrix architecture.

The destruction of articular cartilage and the loss of its biomechanical function is largely due to the destruction and loss of the (inter)territorial cartilage matrix. So far, our knowledge focuses on degradation processes of the two major components of the interterritorial cartilage matrix: the collagen network and the interwoven proteoglycan aggregates. Loss of aggrecan and its fixed negative charges is characteristic of the early stages of cartilage degeneration, whereas the overall content of collagen remains rather constant nearly throughout the disease process. Still, loosening of the collagen network is also a major feature in early cartilage degeneration. As yet it is unknown which is primary—the loss of proteoglycan or loosening of the collagen network—because each eventually influences the other. Loosening of the collagen network leads to a loss of proteoglycans, and a loss of proteoglycans leads to a mechanical overload and thus damage to and loosening of the collagen network. In particular, the latter appears to be responsible for the hyperhydration of articular cartilage in the early phases of the disease process, which is macroscopically visible as softening and swelling. Degradation processes appear to be prominent specifically in the surface zone and around the chondrocytes. Enhanced levels of many metalloproteinases including matrix metalloproteinases (MMPs), as well as members of the ADAM (a disintegrin and metalloproteinase) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motif) families are the most likely candidate enzymes responsible for the increased matrix degradation in OA cartilage.⁹ So far it is rather enigmatic which proteases are really crucial for the degradation of the various cartilage matrix components,

THE HALLMARK OF OA CARTILAGE DEGENERATION IS A LOSS OF CARTILAGE MATRIX HOMEOSTASIS

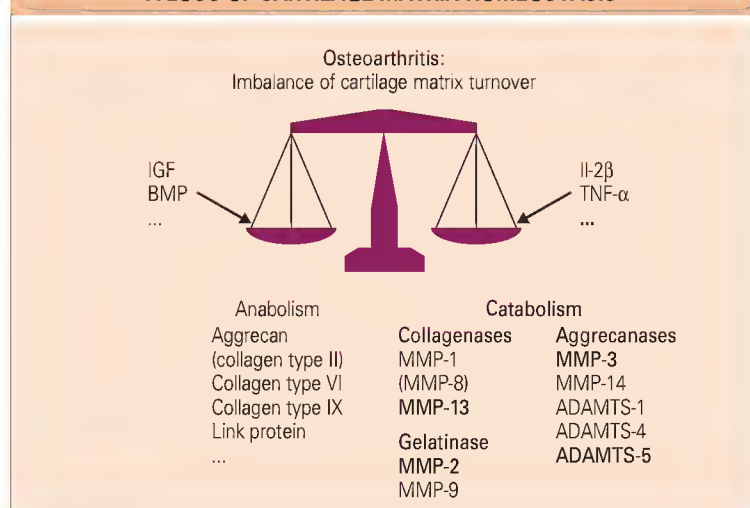


Fig. 175.9 In osteoarthritic (OA) cartilage, the insufficiency of anabolic factors such as insulin-like growth factor 1 (IGF-1) and bone morphogenetic proteins (BMPs) in combination with an increased influence of catabolic factors such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) result in an overexpression of matrix-degrading proteases (collagenases, aggrecanases, and gelatinases). The catabolic activity of these enzymes cannot be counterbalanced by the concurrent increase in anabolic activity (i.e., expression of aggrecan and collagen types II, VI, and others). ADAMTS, a disintegrin and metalloproteinase with thrombospondin type 1 motif; MMP, matrix metalloproteinase.

although MMP-13 is certainly a top candidate for primary collagen type II fibril degradation, MMP-2 (gelatinase A) is a good candidate for subsequent cleavage of denatured collagen fibrils (gelatins), and ADAMTS-4 and ADAMTS-5 are favored to be the major aggrecanases responsible for the proteoglycan breakdown.

Age-induced degenerative changes in the cartilage matrix

The extracellular matrix changes with age. There is accumulation over time of physically damaged and proteolytically cleaved matrix molecules that are not sufficiently removed and replaced as part of a permanent physiologic turnover of cartilage. These damaged components threaten the functional integrity of the cartilage matrix under physiologic or excess mechanical stress. In addition, molecular modifications of the matrix occur that influence the functional integrity. The collagen network stiffens due to increased covalent, cross-linking of the single collagen chains, which makes the fibrillar network more rigid and less flexible for physiologic deformation occurring during joint loading and movement. In consequence, the collagen network is prone to microfracturing during compression and undergoes molecular disintegration. Aggrecan molecules also change with age. Aggrecan monomers and polymers get smaller and have fewer sugar side chains. Interestingly, not only is this related to accumulating molecular degradation but also newly synthesized aggrecan aggregates appear to be smaller in aged tissue and thus carry lower fixed charges. Although the molecular mechanisms driving this decline are so far unclear, severely reduced sugar side chains significantly limit the ability of aggrecan to bind water and thus to maintain the elasticity of the articular cartilage matrix.

The time-dependent formation of advanced glycation end products is another interesting phenomenon involving posttranslational, nonenzymatic protein and lipid modifications that contribute to changes in matrix biochemistry and chondrocyte biology in aging cartilage. The accumulation of advanced glycation end products has been shown to increase the stiffness of the collagen network and can downregulate the anabolic activity of chondrocytes, further unbalancing cartilage tissue homeostasis.

Crystal deposition disease

Inorganic crystals are not infrequently observed within the articular tissues of degenerate joints. In general three major forms of crystals are seen in synovial joints: monosodium urate crystals (gout; see Chapter 187), basic

calcium phosphate, and calcium pyrophosphate dihydrate (pyrophosphate arthropathy or chondrocalcinosis articularis; see Chapters 190 and 191). Calcium pyrophosphate dihydrate crystals are strongly associated with OA cartilage degeneration and can be detected on routine radiography and by conventional polarizing microscopy. Overall, the cause and relevance of chondrocalcinosis continue to be ambiguous; clearly, it is well correlated with the degeneration of the articular cartilage and it is thought to be related to a metabolic imbalance within the cells and the tissue, most likely the articular cartilage and the chondrocytes. However, so far it remains unclear which comes first—the cell and matrix degradation or the crystal formation. Most likely they promote each other, with metabolic disturbance leading to cellular degeneration and vice versa.¹⁰

Role of biochemical differences

An interesting feature of OA is that not all joints are affected equally. Knee and hip joints are most often involved, whereas ankles are generally spared in symptomatic OA. Although it is obvious that there are anatomic differences between the ankle and knee joint, this alone does not explain why the knee is more susceptible to OA. Studies comparing knee and ankle cartilage have identified several biochemical differences that might be of additional relevance (Table 175.6): (1) differences in biochemical composition and biomechanical properties of the matrix resulting in higher dynamic stiffness of the ankle cartilage, (2) decreased response to catabolic factors such as IL-1, and (3) more efficient matrix repair with an increase in collagen type II synthesis and aggrecan turnover seen in ankle lesions.¹¹ Thus there seem to be differences not only in the anatomy and morphology of the joints and their cartilage but also in the cellular phenotype of the chondrocytes themselves, which may explain why some joints are less prone to develop OA than others.

The articular cartilage and chondrocytes

The articular cartilage consists mostly of extracellular matrix. This matrix is the functional element of the cartilage tissue; that is, the matrix provides the mechanical properties of the cartilage tissue. However, the cells (i.e., the chondrocytes) represent the only vital element of the cartilage tissue, although they represent only about 2 to 3 volume percent of the articular cartilage in the adult. Thus, besides changes in the extracellular matrix, changes within the cells also are obviously potential causes of the OA disease process, and the study of the chondrocyte cell phenotype and behavior (Fig. 175.10) can provide substantial scientific insights into the disease mechanisms of OA.

Developmental history as a model of chondrocyte reactivity in the adult

A very important and interesting aspect of cellular behavior in the adult organism is the recapitulation of molecular mechanisms that occurred during fetal development (Fig. 175.11). This phenomenon is also true for OA chondrocytes. In fact, many of the biologic changes that occur in OA cells mimic a differentiation pattern characteristic of fetal skeletogenesis. This includes changes not only in cellular phenotypes and in anabolic and catabolic events but also in other basic mechanisms such as matrix calcification, apoptosis, and proliferation. Thus these evolutionary and developmental comparisons are attractive for explaining chondrocyte behavior and disease pathways in the adult, but uncoordinated degenerative events should not be mistaken for tightly regulated developmental processes (Fig. 175.12). Both scenarios presumably involve similar molecular and regulatory events, but just as in a jigsaw puzzle, the assembly is the challenge.

The osteoarthritis chondrocyte phenotype

Chondrocytes in normal adult articular cartilage are stable, postmitotic, differentiated cells that maintain tissue homeostasis by synthesizing very low levels of extracellular matrix components to replace damaged molecules, thus preserving the structural integrity of the cartilage matrix. The cells are the major regulators of the matrix anabolism and catabolism of articular cartilage. One well-documented change in OA cartilage is the induction of an activated cellular phenotype within the chondrocytes whereby matrix anabolism is strongly stimulated. Nevertheless, the chondrocytes fail to compensate for matrix damage induced externally (e.g., by mechanical stress or enzymatic degradation through synovial proteases). Additionally, the chondrocytes do play an active role in the degradative process themselves, a phenomenon termed *chondrocytic chondrolysis*.¹² During chondrocytic chondrolysis, OA chondrocytes activate or upregulate

TABLE 175.6

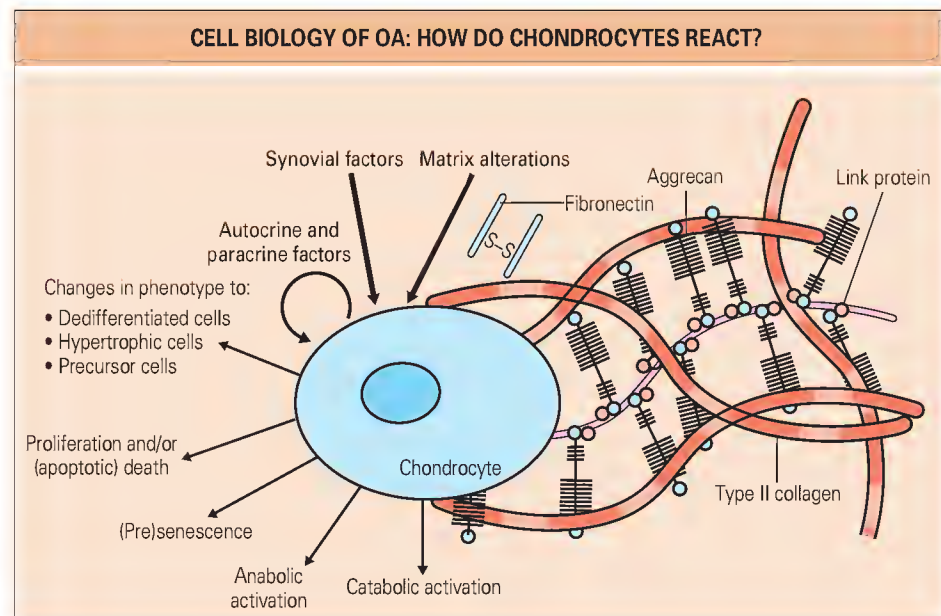
Differences between knee and ankle joint stability, motion, and cartilage

Feature	Knee	Ankle
Joint stability	Relatively unstable Noncongruent	Highly stable Highly congruent
Joint motion	Flexion/extension Rotation	Flexion/extension
Cartilage		
Cellularity	Same	Same
Cartilage thickness	2-6 mm	1-1.5 mm
Superficial chondrons	Single cells	Clusters of 2-4 cells
Sulfated glycosaminoglycan content	Lower	Higher
Water content	Higher	Lower
Collagen content	Same	Same
Dynamic stiffness	Lower	Higher
Hydraulic permeability	Higher	Lower
Peak stress with 65% final strain	11 MPa	16 MPa
Glycosaminoglycan synthesis		
In explants	Higher	Lower
In alginate	Same	Same
Proteoglycan half-life	22.68 days	16.58 days
Protein synthesis	Lower	Higher
IC ₃₀ for IL-1 reduction of proteoglycan synthesis		
In alginate	11 pg/mL	56 pg/mL
In explants	6 pg/mL	35 pg/mL
Influence of Fn-fs on		
Proteoglycan synthesis (antianabolic)	Low dose (1 nmol/L)	High dose (100 nmol/L)
Proteoglycan loss (catabolic)	Significant at 7 days	Not significant after 28 days
Attempted repair	No significant rebound	Significant rebound
Response to degeneration	Upregulation of collagen degradation	Upregulation of matrix synthesis

IC₃₀, concentration that inhibits 30%; IL-1, interleukin-1; MPa, megaPascals.

From Eger W, Schumacher BL, Mallenhauer J, et al. Human knee and ankle cartilage explants: catabolic differences. *J Orthop Res* 2002;20:526-34.

Fig. 175.10 In osteoarthritis (OA) chondrocytes are exposed to severely abnormal extracellular stimuli, including autocrine and paracrine factors, synovial factors, and altered matrix constituents, that induce a plethora of abnormal cellular responses made apparent by the changes in anabolism, catabolism, and phenotype that have been demonstrated in these cells. Also, chondrocyte numbers are modified by proliferation or apoptosis. In this schematic, an OA chondrocyte is embedded in a cartilaginous extracellular matrix of type II collagen, aggrecan, and fibronectin, for simplicity. Other collagens, proteoglycans, and noncollagenous proteins are also present at varying levels. (Reprinted with permission from Aigner T, Söder S, Gebhard PM, et al. *Mechanisms of disease: role of chondrocytes in the pathogenesis of osteoarthritis—structure, chaos and senescence*. *Nat Clin Pract Rheumatol* 2007;3:391-9.)



the expression of many matrix-degrading proteases such as the MMPs that are largely responsible for the breakdown of the collagenous and noncollagenous cartilage matrix components. This elevated proteolytic activity is not sufficiently counterbalanced by an increase in the chondrocyte anabolic activity. This is particularly true for the upper zones of damaged cartilage (the progression zone), in which the anabolic activity even drops again severely.¹³

Inflammatory signaling, reactive oxygen species, and reactive nitrogen species

Activation of proinflammatory (signaling) pathways and production of reactive oxygen and nitrogen species by chondrocytes appear to play a crucial role in OA disease progression. These occur independent of direct inflammatory cell infiltration within cartilage, with the chondrocyte acting as an

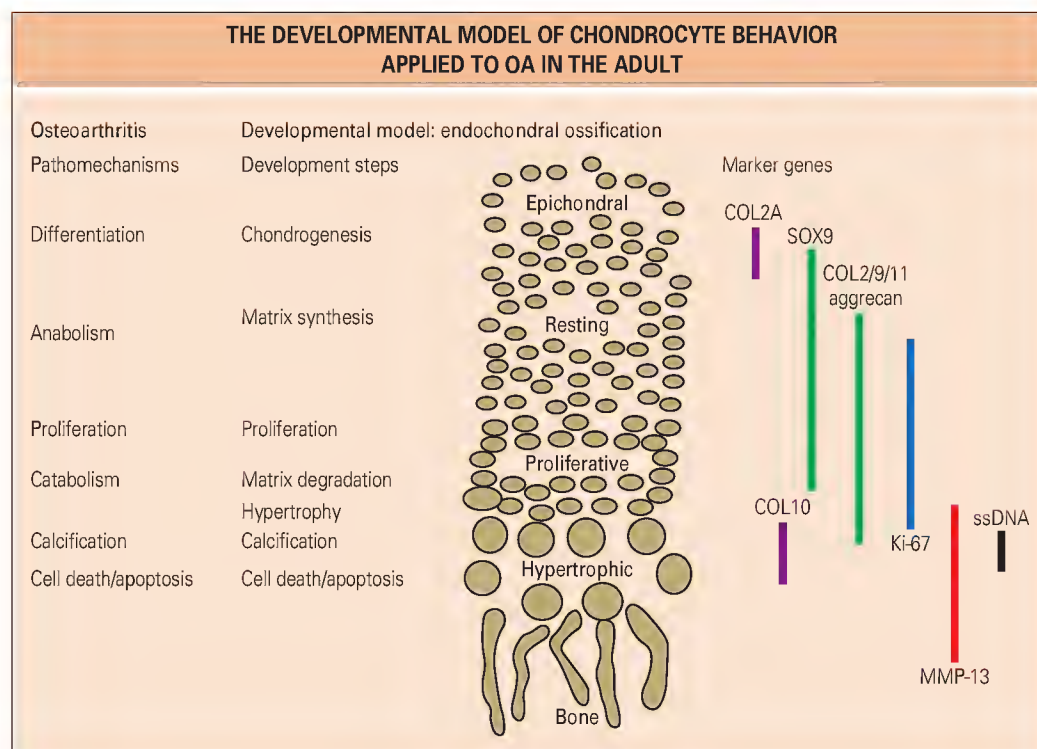


Fig. 175.11 One way to interpret cellular behavior in adult osteoarthritis (OA) is to investigate whether it shows similarities to developmental or evolutionary processes. Several processes that occur in OA are also known to have occurred during fetal chondrogenesis, including changes in the chondrocytic phenotype (differentiation), matrix anabolism and catabolism, (apoptotic) cell death, proliferation, and matrix calcification. The analysis of events during fetal development allows us to identify marker genes that can assist in the determination of the molecular context of a gene in the adult chondrocyte. For example, expression of SOX9 indicates differentiation to the chondrocyte phenotype, type IIA collagen (COL2A) is a chondroprogenitor cell marker, and type X collagen (COL10) is a marker of hyperplastic chondrocytes. Ki-67 indicates cell proliferation, whereas the onset of matrix metalloproteinase-13 (MMP-13) expression suggests increased matrix catabolism potentially linked to hyperplastic differentiation. Single-stranded DNA (ssDNA) indicates apoptotic DNA fragmentation, whereas aggrecan, COL2, COL9, and COL11 indicate anabolic cell activity (the synthesis of new cartilage matrix). Despite the appeal of a comparative approach, one should be cautious not to mistake uncoordinated degenerative processes for highly structured developmental processes. (Reprinted with permission from Aigner T, Söder S, Gebhard PM, et al. Mechanisms of disease: role of chondrocytes in the pathogenesis of osteoarthritis—structure, chaos and senescence. *Nat Clin Pract Rheumatol* 2007;3:391-9.)

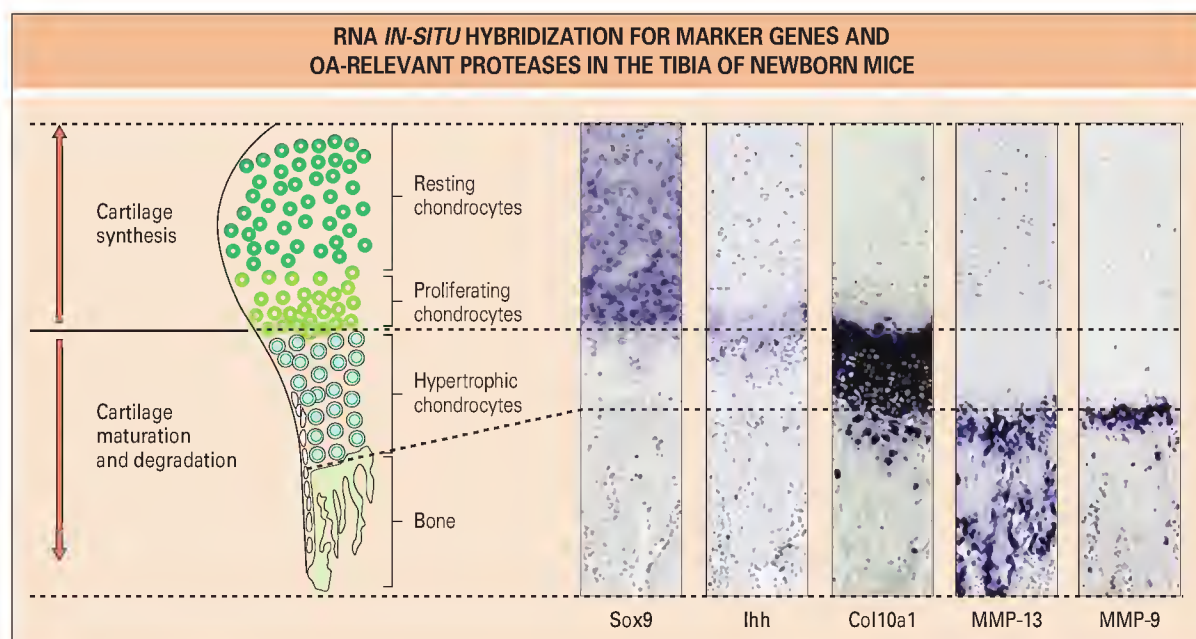


Fig. 175.12 Anabolic and catabolic events in the growth plate of the primary ossifying skeleton are at least in part separated. Sox9 messenger RNA expression marks the zone of proliferation, which differs from the region of terminal chondrocyte maturation characterized by the expression of Ihh as a marker for the prehyperplastic chondrocyte and Col10A1 as a specific marker for the entire hyperplastic cartilage. MMP, matrix metalloproteinase. (Reprinted with permission from Aigner T, Gerwin N. Growth plate cartilage as developmental model in osteoarthritis research—potentials and limitations. *Curr Drug Targets* 2007;8:377-85.)

“inflammatory” cell. Proinflammatory signaling cascades are activated by diverse pathways, including Toll-like receptors, matrix degradation products, adverse mechanical loads, and action of classic inflammatory cytokines such as IL-1 and IL-6. Activated inflammatory pathways induce catabolic responses in chondrocytes with production of matrix-degrading proteases such as MMP-1, MMP-3, MMP-13, and ADAMTS aggrecanases and down-regulation of expression of the cartilage matrix components aggrecan and collagen type II. IL-1 affects gene expression patterns within articular chondrocytes via multiple intracellular pathways including the MAP kinases and nuclear factor- κ B pathways.^{14,15}

Because it is an avascular tissue, the partial pressure of oxygen is very low in cartilage, and chondrocytes live in a relatively hypoxic environment with an oxygen tension of around 6% at the joint surface to 1% in the deep layers of the articular cartilage. A major factor in chondrocyte adaption to hypoxia is the transcription factor hypoxia-inducible factor-1 α (HIF-1 α), which has key functions in controlling energy generation and cell survival, and even influences matrix synthesis.¹⁶ During normal oxidative metabolism reactive oxygen species (ROS) are formed as natural byproducts.¹⁷ They are involved in the control of a number of biologic processes including cell activation, proliferation, apoptotic cell death, and regulation of a wide variety of gene products, including cytokines, MMPs, adhesion molecules, and matrix components. In OA elevated production of ROS in combination with depletion of antioxidants leads to cellular or tissue oxidative stress. ROS may directly oxidize nucleic acids, transcriptional factors, membrane phospholipids, and intracellular and extracellular components, which leads to impaired biologic activity, cell death, and breakdown of matrix components. Significantly, ROS are a major cause of DNA damage within the genome. In addition to ROS, reactive nitrogen species (RNS) also are thought to be important in the pathogenesis of OA.¹⁸ RNS are derived from nitric oxide (NO), are produced in small amounts by nitric oxide synthase (NOS), and perform important functions in many physiologic processes. Increased expression of induced NOS as part of a proinflammatory responses results in increased production of NO and RNS. The mechanisms by which NO and RNS contribute to OA pathogenesis are being defined. NO has multiple effects on chondrocytes including inhibition of ATP production and matrix synthesis and promotion of cell death by caspase-3 and tyrosine kinase activation.

Obesity and adipokines

Being overweight is a strong risk factor for the development of OA in both weight-bearing and non-weight-bearing joints, which suggests roles for both biomechanical and systemic/metabolic factors.

The biomechanical hypothesis proposes that in obese patients increased weight results in excessive loading through weight-bearing joints that is over and above the physiologic range. Furthermore, abnormal gait and joint malalignment may affect stresses within and across joints in obese individuals, compounding the biomechanical problem. Although loading within a physiologic range is necessary for cartilage to remain healthy, excessive mechanical stress disrupts the homeostasis of the cartilage matrix. This occurs as a direct physical insult to the cartilage matrix, but in addition chondrocytes are able to sense mechanical loads through mechanoreceptors such as integrins that initiate intracellular signaling cascades, triggering a variety of cellular responses including the release of paracrine or autocrine factors. Within a physiologic range these mechanoreceptors induce anabolic activity, but with excessive loads proinflammatory and catabolic pathways are activated.

The association of obesity with hand OA, however, indicates an effect through mechanisms other than excessive or abnormal loading of joints. Therefore the systemic/metabolic hypothesis proposes that metabolic factors related to obesity act directly or indirectly on chondrocytes leading to the increased risk of developing OA.¹⁹ Several studies suggest that adipokines, proteins synthesized and secreted mostly by white fat adipocytes, are the major factors linking obesity to OA. Leptin, the prototypic adipokine, is present in OA cartilage and shows biologic activity on chondrocytes. It acts as a proinflammatory cytokine and a catabolic factor in cartilage metabolism via induction of MMPs.

A third (indirect) effect of obesity is certainly also the induction of a (latent) diabetic metabolic state in obese patients over time, which, for example, enhances formation of advanced glycation end products within the cartilage matrix with all their detrimental effects on matrix mechanical properties and cell behavior as discussed earlier.

The concept of progressive (apoptotic) cell loss

One of the simplest explanations for OA cartilage degeneration would be loss of viable chondrocytes due to cell death during the disease process.

Because chondrocytes are the only source of new matrix synthesis any significant cell loss would immediately result in a distortion of cartilage matrix homeostasis. Articular chondrocytes cannot self-renew, and cell loss would therefore be permanent and detrimental. Many studies have therefore addressed whether cell death plays a role in the pathologic process of OA.²⁰ Cell death can, in principle, be divided into apoptosis and necrosis. Apoptosis has evolved as a mechanism to eliminate surplus, abnormal, or dysfunctional cells whose survival and proliferation would be detrimental. Apoptosis is thus normally a beneficial process, although aberrant apoptosis can occur in pathologic states and apoptosis is clearly disadvantageous when it leads to the elimination of healthy cells. The presence of empty chondrocyte lacunae within cartilage matrix is a seemingly obvious histologic feature of OA cartilage.²¹ However, opinions on the prevalence and importance of chondrocyte death in OA pathologic changes differ widely,²² and most likely apoptotic cell death is a rather rare event.^{23,24} Also, lacunar emptying appears to be largely a technical artifact, mainly due to cell shrinkage except in late-stage disease where there is enhanced cell loss.²³

Apoptosis is a complex cellular process, and the factors responsible for apoptotic cell death in articular cartilage are largely unknown.²⁵ Because β_1 integrin-mediated cell matrix interactions provide survival signals for chondrocytes, reduction in extracellular matrix integrity due to degradation may be partly responsible for chondrocyte death *in vivo*. In cultured chondrocytes, treatment with Fas ligand (or anti-Fas), NO donors, tumor necrosis factor- α (TNF- α) or IL-1, taurosporin, ceramide, or retinoic acid has been shown to induce apoptosis, but it is uncertain which of these factors articular chondrocytes are sufficiently exposed to in the body. Certainly, chondrocytes become somewhat fragile if the pericellular matrix is removed or deranged²⁶ as in OA cartilage.^{27,28} In fact, degradation products of pericellular matrix components such as fibronectin might directly induce cellular death programs in chondrocytes.

Overall, the experimental evidence clearly suggests that apoptosis occurs in OA cartilage but at a very low rate, at least in the earlier stages. The relative contribution of apoptotic cell death to the pathogenesis of OA is difficult to assess because of the chronic nature of the disease process. Also, it is difficult to establish whether apoptosis is primary or secondary to cartilage matrix destruction. There is a good likelihood that, at least in later-stage disease, chondrocyte death and matrix loss form a vicious cycle, with the progression of one having promoting effects on the other.

The aging chondrocyte: genomic integrity and the chaotic phenotype

It has been known for a very long time that age is the most prominent risk factor for OA, but the explanations for this clear and strong association have changed over time.²⁹ In addition to continuing wear and tear, as cited in the classic hypothesis, the aging of matrix (see earlier) and cells are presumably very important etiopathogenetic factors for explaining this relationship.

The senescence theory of OA postulates that chondrocytes become senescent due to cellular stress and/or (focal) proliferation, which finally leads to a failure of the cells to fulfill their essential functions of maintaining proper matrix turnover. In general, cellular aging is associated with changes that undermine the ability of cells to maintain tissue homeostasis and culminate in cellular senescence. Replicative senescence occurs in cultures of continuously dividing somatic cell populations, including chondrocytes, after a limited number of population doublings and is due to telomere erosion. In postmitotic cells such as chondrocytes *in vivo*, progressive cellular senescence rather than replicative senescence appears to be important. Progressive cellular senescence is precipitated by steadily increasing damage to the genomic DNA, mostly secondary to oxidative stress. Oxidatively damaged molecules (DNA, proteins, lipids) accumulate with aging and gradually derange cellular functions.³⁰ Such molecules are normally removed and replaced during replication; however, this constant molecular renewal is not possible in postmitotic cells, and the oxidatively damaged molecules accumulate with time.

Substantial DNA damage and other cellular degenerative alterations are seen in OA chondrocytes.³¹ These effects would be expected to lead to apoptotic cell death in most cell types. Apoptosis appears to occur rather rarely in OA cartilage, however. Instead, the chondrocytes remain in a pre-apoptotic or para-apoptotic state with an uncoordinated pattern of gene expression, as shown in many *in-vivo* studies of chondrocyte behavior (Fig. 175.13). In this respect, the downregulation of molecules that are usually responsible for regulating cell integrity and/or removal after nonacceptable cell damage may be an important permissive factor at this stage. For example, the expression of the small guanosine triphosphatase RhoB, a molecule that is constitutively expressed by normal articular chondrocytes, is significantly downregulated in OA cartilage.³² RhoB is involved in cytoskeletal

organization, cell transformation, and survival but, most importantly, appears to be required for the apoptotic response, at least in some cell types. One intriguing speculation is that the downregulation of RhoB in OA chondrocytes might be a prerequisite for the sustained preapoptotic or paraapoptotic phenotype of OA chondrocytes despite the substantial DNA damage that in normal cells would lead to apoptotic cell death.

Aging does not inevitably lead to OA, and not all aged chondrocytes show loss of function. Nevertheless, even in the “normal” joints of elderly people the cartilage no longer looks juvenile. The major difference between normal aged cartilage and OA cartilage is that, in the former, lesions do not progress and do not result in symptomatic disease. Although all individuals are susceptible to the same age-related changes, these appear to progress faster in some individuals (e.g., patients with primary OA) than others. Thus OA shows “premature” or accelerated degeneration of articular cartilage due to a premature senescence of the chondrocytes that maintain its structural integrity. By analogy to neurodegenerative disorders one could call OA the “morbus Alzheimer” of articular cartilage and chondrocytes.²⁹ This analogy is particularly intriguing because OA chondrocytes, and to a lesser extent aged chondrocytes, show discoordinate reaction patterns (see Fig. 175.13),³⁰ which are most likely related to a disturbance of the “cellular brain,” the gene regulation machinery. Also, cartilage and brain share an important similarity: both have “(very) old,” largely postmitotic cells (i.e., basically no cell supply and proliferation after puberty) and thus show hardly any

regeneration capacity. However, cartilage has an additional problem in that it lacks the plasticity of the neuronal network. A functionally intact chondrocyte cannot adequately replace a dysfunctional chondrocyte located at a distance from it. Additional research is needed to determine whether accelerated cell aging processes account for the phenotype of the disease or, as is the case in Alzheimer disease, there are additional features that would allow one to take new therapeutic approaches. Even if cell aging is an inevitable feature of OA (e.g., for limiting tumorigenic capacity), these processes can be used to identify and manipulate the causes of premature chondrocyte degeneration.

The synovial membrane

The two main clinical symptoms of OA, pain and stiffness, are both significantly related to synovial inflammation and capsular fibrosis. Although its clinical importance is clear, however, the role of synovial inflammation in the pathogenetic process of cartilage destruction remains largely unknown (Fig. 175.14).³³ The synovial (inflammatory) reaction observed in OA joint disease has been considered primarily to be a secondary effect resulting from the release of cartilage debris from the damaged articular cartilage. This is in contrast to the situation found, for example, in rheumatoid arthritis, which is considered to originate from a synovial inflammatory autoimmune reaction with secondary cartilage destruction. However, inflammatory

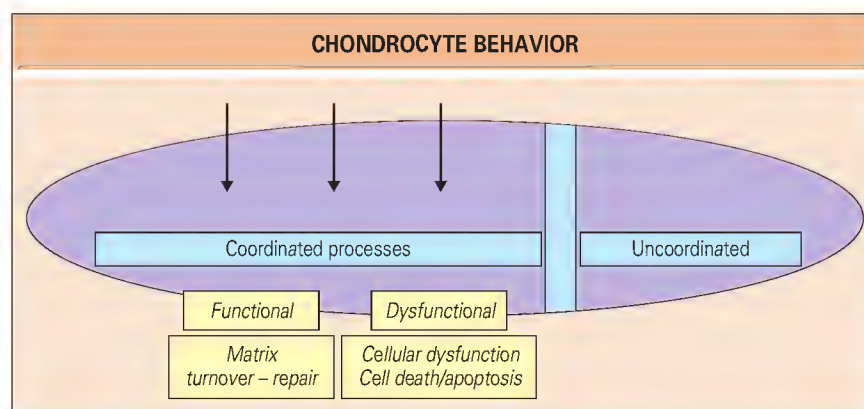


Fig. 175.13 Articular chondrocytes in the normal joint behave in a very structured manner: they react to extracellular stimuli (e.g., joint loading, matrix changes, and exposure to cytokines and growth factors) according to their internal, predetermined program. In cartilage degeneration in osteoarthritis (OA), chondrocytes are exposed to abnormal stimuli such as nonphysiologic loading conditions, byproducts of matrix destruction (e.g., fibronectin and collagen fragments), and cytokines and growth factors that are not normally expressed in cartilage. This exposure leads to structured/deterministic cellular reactions, some of which are functionally positive for the tissue (e.g., anabolism) and others of which are dysfunctional or detrimental (e.g., increased matrix catabolism and cell death). Potentially even more problematic for preserving tissue homeostasis are the unstructured/stochastic reaction patterns typically seen in OA chondrocytes, which lead to a significant microheterogeneity of cellular reaction patterns.

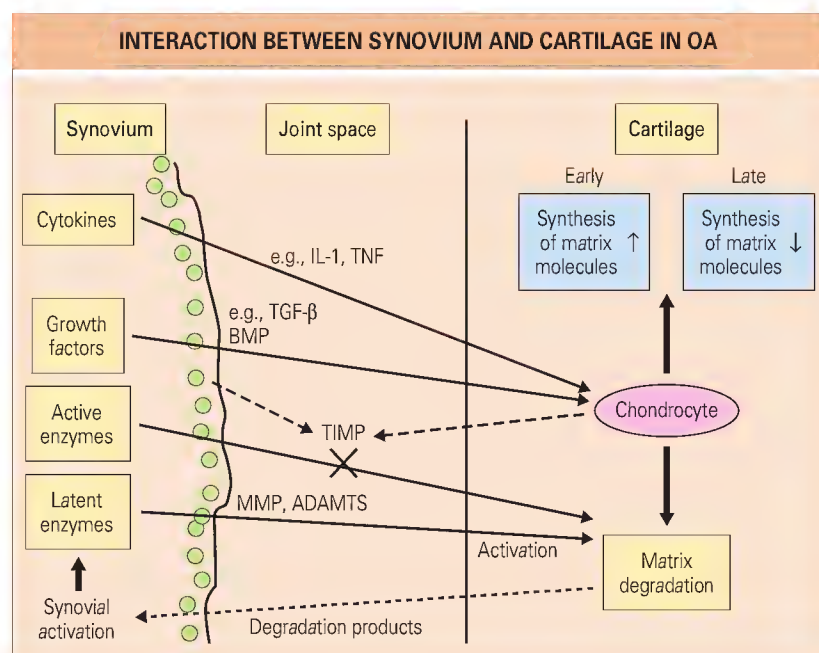


Fig. 175.14 In osteoarthritis (OA), molecular detritus from the cartilage activates the synovial lining cells. The synovial lining cells produce cytokines, growth factors, and (latent) enzymes. Synovial cell-derived cytokines and growth factors further activate the chondrocytes. Enzymes produced by the synovial lining cells can directly degrade matrix molecules if not inactivated by inhibitors in the synovial fluid. Latent enzymes can be activated in the milieu of the OA cartilage. ADAMTS, a disintegrin and metalloproteinase with thrombospondin type 1 motif; BMP, bone morphogenetic protein; IL-1, interleukin-1; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor. (Reprinted with permission from Aigner T, van der Kraan P, van den Berg W. Osteoarthritis and inflammation—inflammatory changes in osteoarthritic synoviotherapy. In: Buckwalter JA, Lotz M, Stoltz JF, editors. Osteoarthritis, inflammation and degradation: a continuum. Amsterdam: IOS Press; 2007, p. 219-30.)

reactions in the synovial membrane do occur to some degree in all OA joints. Also, the fact that most OA patients display a minor elevation of serum C-reactive protein level suggests that the inflammatory component plays some role in the disease process.

Synoviocyte activation and proliferation as well as synovial hyperplasia presumably all represent reactive changes in response to increased demands for clearance of molecular debris in the synovial fluid of the joint. Although a cellular inflammatory component is missing in particular cases of early OA, synovial hyperplasia and activation is likely to generate significant problems for articular cartilage homeostasis. Synoviocytes are able to secrete not only matrix-degrading proteases (e.g., MMPs) but also catabolic cytokines and growth factors (e.g., IL-1, TNF- α) as well as ROS/NOS-inducing inflammatory and catabolic signaling pathways within chondrocytes.

The subchondral bone

A debate continues as to whether the changes in subchondral bone are a cause or a consequence of changes in the overlying cartilage. It is likely that both are true. In some instances altered structure of the subchondral bone will lead to secondary changes in the cartilage, whereas in other situations changes in subchondral bone will be adaptive in response to altered mechanical loads as cartilage deteriorates. In established OA increased thickening of the subchondral bone plate (compare Fig. 175.4f with normal bone shown in Fig. 175.4c) and changes in the architecture of subchondral bone trabeculae result in radiologically distinctive osteosclerosis. Subchondral bone sclerosis occurs as a modeling/remodeling response to the increased mechanical loads that are transmitted to the bone as a consequence of altered biomechanics within the joint and cartilage loss. The trabecular bone volume increases by around 20% due to an increase in the number of bone trabeculae and reduced separation between trabeculae, rather than through thickening of the trabeculae. Because the new bone formed is less mineralized than normal bone, although there is an increase in apparent density, the material density of the bone is significantly reduced.

Subchondral bone cysts usually occur deep to areas in which the overlying cartilage has been completely lost. Subchondral bone cysts are histologically diverse, consisting of pools of mucoid material or reparative mesenchymal tissue showing variable degrees of fibrous and fibrocartilaginous differentiation. There is usually evidence of new bone formation and remodelling at the periphery of the cysts, but the cysts themselves do not normally contain bone—hence their radiolucency. Bone marrow lesions are areas of ill-defined bone marrow hyperintensities seen on T2-weighted magnetic resonance images in patients with OA. Histologic studies indicate that these are areas of localized bone and marrow necrosis with fibrosis and reparative changes. Some may progress to bone cysts. Bone marrow lesions are associated with pain in OA patients, and at least in moderate to advanced lesions, the changes in the subchondral bone represent an interesting target tissue for symptomatic treatment in these patients.

Influence of mechanical load

Mechanical loading within a physiologic range maintains joint tissues and cartilage in a healthy state. Mechanical loading that is either below or in excess of the physiologic range causes cartilage degeneration. For this reason, abnormalities of mechanical loading are central to the development of OA. OA arises when there is an imbalance between the mechanical forces within a joint and the ability of the cartilage to withstand these forces. This arises in two situations. In the first, normal articular cartilage is exposed to abnormal mechanical loads, whereas in the other, the articular cartilage is fundamentally defective with biomaterial properties that are insufficient to withstand normal load bearing.

The mechanisms by which mechanical loads influence cartilage structure are beginning to be understood (see Chapter 8). Chondrocytes sense and respond to mechanical stimuli transmitted through the matrix. The mechanical forces are recognized by mechanoreceptors such as integrins and stretch-activated ion channels. Activation of these transmembrane molecules by physiologic mechanical loads results in stimulation of a series of regulatory molecules and intracellular signal cascades including FAK, PKC, JAK/STAT and MAP kinases that ultimately leads to changes in gene expression and protein production. Thus an anabolic response is produced that maintains, and in some circumstances improves, cartilage structure and function. The particular cascade stimulated depends on the mechanoreceptor activated and the involvement of downstream autocrine and paracrine activity. Anabolic responses resulting in increased expression of aggrecan and inhibition of protease production involve $\alpha_5\alpha_1$ integrin and release of locally acting mediators that include interleukin-4 and substance P.³⁴ In contrast, overloading induces a stress response with molecular and biome-

chanical changes that shift the balance of tissue remodeling in favor of catabolic over anabolic activity. Although these events also appear to be integrin mediated, the molecules involved and pathways activated are different from those seen when cartilage is physiologically loaded. Stimulation of stress-induced intracellular pathways leads to the production of proinflammatory cytokines such as IL-1 and TNF- α and increased production of MMPs and aggrecanases. Interestingly, chondrocytes from OA cartilage show an altered responsiveness to mechanical loads because they fail to show an anabolic response to physiologic loading but instead demonstrate a proinflammatory IL-1 β -dependent response. This may further accelerate disease progression and attenuate cartilage repair.

Neuromuscular function and proprioception—roles in joint homeostasis

Joint stability depends on several neuromuscular factors, including the strength and coordination of the joint-related muscles as well as proprioception (the ability to sense the position and movement of the limb).³⁵ The association of weak quadriceps femoris with radiographic and symptomatic knee OA is most likely due to loss of joint stability and abnormal loading on movement. Thus muscle strengthening seems to have a preventive effect for OA. Whether the knee joint benefits from quadriceps strengthening after the onset of OA is unclear. Proprioception is also important for joint stability. Proprioception relies on specialized nerve endings, mechanoreceptors, which are located in the muscles and the ligaments and are essential for fine tuning of muscular movement. Proprioception declines with age, and a further decrease is seen in patients with OA. However, it is unclear whether impaired proprioception in OA contributes to or results from the disease.

GENETICS, FUNCTIONAL GENOMICS, AND EPIGENETICS

Genetics

OA, like nearly all other diseases, is initiated and progresses dependent on the genetic background of the individual. Therefore the potential of genetics for elucidating the pathogenesis of OA has been the subject of intensive investigation for years (see Chapter 176). However, overall pathogenetic concepts based on genetic data are missing, and the overall ability of the genetic information to explain OA development is rather limited. One major difficulty is to separate genes that influence the development of the joints (thus resulting, e.g., in abnormal joint shape and biomechanical weakness) from genes that lead to an insufficiency of the cells to maintain adequate repair and joint homeostasis later in life, which are relevant for preventing and treating OA.^{36,37} Another reason for the complexity of the interpretation of genetic data is that many of the genes detected are likely to be linked to processes in other organ systems such as neuronal cross-linking, muscle strength, and mental perception. All these have roles in OA development and disease manifestation without being related to cartilage physiology and pathobiology.

It has been known for some time that OA “runs in families,” but to what extent this is due to shared genetic influences or shared family environment is still uncertain. The disease is clearly multifactorial and polygenetic; that is, it results from the interaction of several, possibly many, genes. Overall, the relevance of the genetic aspects of OA joint disease is still under debate, presumably also because of the considerable heterogeneity of the genetics of OA. Also, it seems that different combinations of different susceptibility genes may apply to different forms of OA,³⁸ and in fact different classes of mutated genes lead to different types of early- and late-onset OA.³⁶

Functional genomics and proteomics

One major change in OA research in recent years has been the shift from investigating primarily biochemical aspects of articular cartilage matrix destruction to studying the molecular aspects of the disease process. It is the molecular phenotype of the resident chondrocytes that determines the homeostasis of the cartilage matrix. The cellular reaction pattern of the chondrocytes in OA cartilage degeneration is poorly understood, however, mainly because many of the involved genes have not yet been identified and characterized. Such gene profiling is precisely one of the strengths of gene expression chip technology.³⁹ In fact, many studies have been performed during the past decade using the array-chip technology, and quite a few interesting genes and gene clusters have been found; these included, in addition to known candidate gene groups such as anabolic and catabolic

genes, new gene networks such as a cluster of oxidative defense genes (e.g., the gene for superoxide dismutase-2 [SOD2], the major mitochondrial ROS scavenger) and others. Further studies must validate the relevance of these findings for understanding and manipulating these molecular networks in the context of OA. These attempts will be supplemented by proteomics, which will reveal an even more complex pattern.⁴⁰

Epigenetics

Clearly, one major issue during disease progression is a severe alteration of the gene expression phenotype of the articular chondrocytes. Besides gene regulation by ordinary transcription factors, epigenetic gene regulation may play an important role in determining gene expression levels; namely, methylation of genes coding for cytokines, growth factors, and so on.^{41,42} First experimental data indicate that differences in the methylation status within disease-relevant promoters are likely to induce or repress respective gene expression.⁴³ This is not true for all genes, however. Thus, for example, no changes were found in the methylation levels of the aggrecan gene in aged and diseased chondrocytes.⁴⁴ The overall genomewide methylation level remains unchanged in normal and in diseased and aged chondrocytes,

although this does not exclude differences in methylation levels for selected promoter regions. Altogether, the data are sparse so far. The implications of epigenetic dysregulation in OA chondrocytes remain open for future investigations. Also, the effects of alterations in micro-RNA expression in OA chondrocytes represent a new and exciting but still unresolved issue.^{42,45}

CONCLUSION

OA is a disease of the diarthrodial joint, with the gross and microscopic pathologic changes being seen in all joint tissues, although changes in articular cartilage are still thought to be paramount in the disease. The risk factors that predispose to the development of OA, such as increasing age, obesity, mechanical loading, and genetics, have been known for some time, and we are now beginning to understand how these may influence normal joint structure and function and predispose to OA. New insights into the cellular, biochemical, and molecular changes in the tissues of the synovial joint with the onset and progression of OA as it arises under different clinical scenarios may at last indicate novel routes by which this debilitating disease can be treated or prevented.

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176

Genetics of osteoarthritis

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- Osteoarthritis (OA) has an important genetic component, which has been explored in humans both in monogenic syndromes and in its complex common form.
- Monogenic studies have identified mostly extracellular matrix-related genes, whereas genomewide association and candidate gene studies have revealed the complexity of OA, with many genes contributing modestly to overall disease risk.
- The contribution of genetics to the common OA form has now been estimated to be on the order of 39% to 65%, and first-degree relatives of individuals with OA have a twofold to threefold increased risk of disease.
- Several of the genes identified appear to relate to skeletal development mediated by bone morphogenetic proteins (*ASPN*, *SMAD3*, *GDF5*) and Wnt signaling (*DOT1L*); other genes are known to be related to cartilage metabolism (*CHST11*).
- The functional role of many of the genes identified still remains to be elucidated.

INTRODUCTION

The multifactorial nature of osteoarthritis (OA) is well recognized, and a number of environmental risk factors such as obesity, previous injury, and meniscectomy are strongly associated with its development.¹ The role of genetic factors in the development of OA has received considerable attention, aided by our rapidly expanding knowledge of molecular biology. This chapter reviews the data that support the role of genetic variation in the common, as well as rare, forms of OA.

EVIDENCE FOR INHERITANCE OF OSTEOARTHRITIS

A strong genetic component to certain forms of OA has been recognized for more than 60 years. In 1941 Stecher² demonstrated that Heberden nodes of the fingers were three times more common in the sisters of 64 affected individuals than in the general population. Subsequently, in 1944 Stecher and Hersch^{2a} concluded that these lesions were inherited as a single autosomal dominant gene with a strong female predominance.

The most common form of inherited OA is primary generalized OA, which was first described as a clinical entity by Kellgren and Moore in 1952.³ This form is characterized by the presence of Heberden and Bouchard nodes and premature degeneration of articular cartilage, often in a concentric pattern in many joints. Subsequent studies provided additional evidence for the familial occurrence of Heberden and Bouchard nodes and of OA involving multiple joints. In a study of 391 cases of OA, 120 mostly middle-aged women were identified as having a polyarthritis characterized by signs of inflammation and acute onset of symptoms. Of these patients, 20% gave a family history of similar joint disease.³ This and other studies suggested a polygenic form of inheritance rather than a single gene defect in primary generalized OA.³

TRAITS AND OUTCOMES STUDIED IN THE GENETICS OF OSTEOARTHRITIS

In both epidemiologic and genetic studies the definition of OA that is used most often is a radiographic one, usually based on the Kellgren and Lawrence grade.⁴ In addition, several studies have focused on “clinical OA” defined as radiographic OA plus the presence of pain, some have used the American College of Rheumatology classification criteria for OA, and some studies have used total joint replacement with a primary indication of OA as a surrogate for severe clinical OA.⁵ It is worth noting that OA represents a group of disorders with distinct risk factor profiles and disease courses.^{4,6,7} To separate and define these subphenotypes, it is therefore desirable to investigate the components that define different forms of OA, such as radiographic severity, extent of cartilage loss, presence or absence of synovitis, pain and functional severity of the disease, and generalized versus non-generalized disease, among others. The genetic contribution to some of these factors is only beginning to be addressed.

TWIN AND FAMILY STUDIES

Twin studies

Comparing the resemblance of identical twins with regard to a trait or disease with the resemblance of nonidentical twins offers the first estimate of the extent to which genetic variation determines variation in that trait, or heritability. The heritability of OA has been calculated in twin sets after adjustment of the data for other known risk factors such as age, sex, and body mass index. Such findings show that the influence of genetic factors in radiographic OA of the hand, hip, and knee in women is between 39% and 65%, independent of known environmental or demographic confounding factors. Classical twin studies and familial aggregation studies have also investigated the genetic contribution to cartilage volume and progression of disease (e.g., research by Zhai and colleagues^{8,9}). A comparison of the similarities in identical and nonidentical twins allows one to estimate the extent to which genetic factors determine variation in the measures of OA. Examples of OA traits whose heritability has been assessed using a twin study design are presented in Table 176.1.

Familial aggregation studies

Analysis of familial aggregation is the sine qua non for continuing the genetic analysis of a disorder, and several studies have reported the risk ratio for a relative of an affected individual compared with the population prevalence (λ s). A study in Nottingham¹⁰ assessed the prevalence of hip OA in siblings of individuals undergoing total hip replacement (THR) compared with the prevalence of radiographic hip OA in individuals undergoing intra-venous urograms for investigation of a renal problem (i.e., control subjects). This study reported a λ s of 4.99 for Kellgren and Lawrence grade III or higher, a λ s of 5.01 for a minimum joint space width, and a λ s of 8.53 for THR. A similar study by the same group was carried out using total knee replacement (TKR) as the selection criterion¹¹ and reported a λ s of 2.13 for tibiofemoral OA and 2.08 for any radiographic knee OA. Use of self-reported total joint replacement in a smaller data set¹² resulted in a λ s of 1.87 for THR and a λ s of 4.81 for TKR. More recently a U.S. study carried out a similar analysis and reported λ s values of 2.85 for THR and 2.92 for TKR, although the familial aggregation for TKR did not remain statistically significant after adjusting for age and sex.¹³ Familial aggregation of specific knee OA phenotypes such as anteromedial OA that correspond to lesions

in the tibial plateau and preservation of cartilage of other compartments of the knee have also been reported in UK populations.¹⁴ Unlike other patterns of OA, cartilage degeneration in anteromedial OA is consistent with increased loading and thus might be assumed to be due mostly to mechanical causes, rather than genetic factors. Yet the λ s of 3.21 reported for this form of OA suggests a substantial genetic contribution for this particular type of OA as well.

FAMILIAL DISORDERS ASSOCIATED WITH OSTEOARTHRITIS

Some characteristics of OA resemble chondrocyte differentiation processes during skeletal development by endochondral ossification.¹⁵ Based on this observation, it has been proposed that signaling molecules regulating chondrocyte activity in growth cartilage may also be involved in OA pathogenesis.¹⁵ Endochondral ossification is initiated by the formation of cartilage templates of future bones, built by mesenchymal progenitor cells, which differentiate into chondrocytes. The differentiated cartilage cells undergo a cascade of late differentiation events culminating in chondrocyte hypertrophy. After invasion of blood vessels from the subchondral bone, the majority of hypertrophic cells undergo apoptosis, and the cartilage template is remodeled into trabecular bone.¹⁵ Similarly, proliferation of chondrocytes, hypertrophic differentiation of chondrocytes, remodeling and mineralization of the extracellular matrix, invasion of blood vessels, and apoptotic death of chondrocytes occur during OA.

The similarities in the pathologic progression of the disease, even when the initiating events are different, suggest that there may be a common

molecular sequence of events underlying OA progression. Therefore it has been a major emphasis to understand rare monogenic skeletal disorders that resemble OA to understand the molecular basis of OA.¹⁶

Premature OA is in fact part of the pathologic processes associated with many mutations affecting cartilage extracellular assembly or stability, such as Stickler syndrome type I, multiple epiphyseal dysplasia, and osteochondritis dissecans.

A large number of other disorders influencing skeletal development exist but are not discussed here because they are not OA-like and do not result in early-onset OA. The following is only a brief summary, and for more detailed information the reader is referred to other chapters in this book dealing with monogenic disorders of skeletal development and to the review by Warman and coworkers.¹⁷ A partial list of monogenic disorders that display OA or OA-like syndromes is presented in (Table 176.2).

NATURE OF THE GENETIC INFLUENCE IN OSTEOARTHRITIS

Linkage studies

Genetic linkage is observed when the genetic markers and the disease locus map relatively close to each other on the same chromosome. If family data are available, genetic markers can be used as tools to dissect the inheritance pattern of a gene involved in a specific trait or disease. For example, pairs of siblings who both are affected with OA have been used to identify chromosomal regions harboring OA genes. The higher the proportion of alleles identical by descent that sibs concordant for OA share at a given marker, the closer that marker is to an OA-related gene. Several genome-wide linkage studies have been conducted in humans to identify quantitative trait loci (QTLs) for OA. Hunter and colleagues¹⁸ reported four significant linkage regions for the hand (logarithm of odds of linkage [LOD] score, 3 or higher) when the individual joints were treated separately, which suggests that a splitting rather than a lumping approach may be more successful.

Livshits and colleagues,¹⁹ using twin sib pairs, have shown a replication of QTLs on chromosome 2 (LOD score, 2.9) and chromosome 19 (LOD score, 4.26) for hand OA. A genome-wide linkage scan was done to identify susceptibility loci for total hip replacement, using DNA from a large Icelandic family with a high prevalence of primary hip OA; a locus with an LOD score of 2.58 was identified on chromosome arm 16p.²⁰ A similar locus mapping to chromosome 16 was reported in a study from the United Kingdom.²¹ This is the first instance in which what may be the same susceptibility locus for OA has been independently described in two different populations with hip OA. Linkage studies, although of use for investigation of monogenic conditions, are of limited value for common OA because the genomic regions identified are very large and depend on subsequent fine mapping, which is done by genetic association methods.

TABLE 176.1
Heritability of various osteoarthritis-associated traits derived from twin studies

Trait	Heritability (h^2)	Study
Radiographic knee osteoarthritis	39%	Spector et al ⁴⁴
Radiographic hip osteoarthritis	60%	MacGregor et al ⁴⁵
Femoral cartilage volume	61%	Hunter et al ¹⁸
Tibial cartilage volume	76%	Hunter et al ¹⁸
Patellar cartilage volume	66%	Hunter et al ¹⁸
Change in knee joint space narrowing grade	74%	Zhai et al ⁹

TABLE 176.2
Selected monogenic disorders that display early-onset osteoarthritis or osteoarthritis-like symptoms

Chromosome region	Gene	Name of disorder
12q13.1	<i>COL2A1</i>	Achondrogenesis type 2 (Langer-Saldino achondrogenesis); platyspondylic dysplasia, Torrance type; hypochondrogenesis; spondyloepiphyseal dysplasia (SED), congenital; spondyloepimetaphyseal dysplasia (SEMD), Strudwick type; Kniest dysplasia; spondyloperipheral dysplasia; mild spondyloepiphyseal dysplasia with premature-onset arthrosis; Stickler syndrome type I
1p21	<i>COL11A1</i>	Stickler syndrome type II, Marshall syndrome
6p21.3	<i>COL11A2</i>	Otospondylomegaliphyseal dysplasia (OSMED), recessive type; OSMED, dominant type (Weissenbacher-Zweymüller syndrome, Stickler syndrome type III)
19p12-13.1	<i>COMP</i>	Pseudoachondroplasia, multiple epiphyseal dysplasia (MED) type 1 (EDM1)
6q13	<i>COL9A1</i>	MED type 6 (EDM6)
1p32.2-33	<i>COL9A2</i>	MED type 2 (EDM2)
20q13.3	<i>COL9A3</i>	MED type 3 (EDM3)
2p23-24	<i>MATN3</i>	MED type 5 (EDM5), SEMD matrilin type
18q12-21.1	<i>DYM</i>	Dyggve-Melchior-Clausen dysplasia
6q22-23	<i>WISP3</i>	Progressive pseudorheumatoid dysplasia
15q26.1	<i>AGC1</i>	SED Kimberley type, SEMD aggrecan type, familial osteochondritis dissecans
10q23-q24	<i>PAPSS2</i>	SEMD PAPSS2 type
11q22.3	<i>MMP13</i>	SEMD Missouri type
Xp22	<i>SEDL</i>	SED tarda, X-linked

TABLE 176.3

Selected genetic associations with osteoarthritis (OA) derived from candidate gene studies (maximum P value = 5×10^{-4})*

SNP ID	Gene	Ethnic group	Trait	P value	Putative or known function	Study
rs143383	<i>GDF5</i>	Asians	Hip OA	2×10^{-13}	Bone morphogenetic protein, joint development	Miyamoto et al ²³
rs143383	<i>GDF5</i>	Whites	Knee OA	8×10^{-9}	Bone morphogenetic protein, joint development	Valdes et al ²⁴
D14 allele in VNTR [†]	<i>ASPN</i>	Asians	Knee OA	1×10^{-6}	TGF- β signalling	Nakamura et al ⁴⁶
rs12901499	<i>SMAD3</i>	Whites	Knee OA	7×10^{-6}	TGF- β signalling	Valdes et al ²⁵
rs10980705	<i>EDG2</i>	Asians	Knee OA	3×10^{-5}	Lysophosphatidic acid receptor	Mototani et al ⁴⁷
Haplotype rs225014-rs12885300 [‡]	<i>DIO2</i>	Whites	Hip OA	2×10^{-55}	Thyroid metabolism	Meulenbelt et al ²⁶
rs12901499	<i>SMAD3</i>	Whites	Hip OA	3×10^{-4}	TGF- β signalling	Valdes et al ²⁵
rs8065080	<i>TRPV1</i>	Whites	Symptomatic knee OA	4×10^{-4}	Nociception	Valdes et al ⁴⁸

*Only variants for which replication studies were carried out and with an overall sample size of >1000 are included.

[†]Allele unless otherwise indicated, can be haplotype or genotype.[‡]Refers to a specific haplotype in a recessive mode.[§]Only women.

SNP, single nucleotide polymorphism; TGF, transforming growth factor.

Candidate genes

Candidate gene association studies rely on a-priori understanding of the cause of OA and allow only very small regions of the genome to be targeted for investigation. Consequently many important genes have probably been overlooked using this method. Notwithstanding, candidate gene studies have identified a number of important genes such as *ASPN*, *FRZB*, and *PTGS2* that continue to be compelling targets for functional studies and further genetic replication in independent populations.

The candidate gene association method identified the polymorphism rs143383 within the 5' untranslated region [UTR] of the gene *GDF5*. This is still the most robustly replicated polymorphism to be associated with OA and the only locus to replicate successfully across diverse Asian and European populations. Although very few genes meet the strict criteria of replication, even fewer have also demonstrated functional significance. Among these, some of the most compelling are the asporin gene *ASPN*,²² the *GDF5* gene encoding growth differentiation factor 5,^{23,24} and the *SMAD3* gene.²⁵ These three genes have in common being part of the bone morphogenetic protein (BMP) signaling pathway (Table 176.3). Another interesting gene identified first by linkage analysis and later by association is the deiodinase iodothyronine type II gene (*DIO2*).²⁶ *DIO2* encodes an intracellular enzyme in the thyroid hormone pathway responsible for the local bioavailability of thyroid hormone in specific tissues, including the growth plate. The active thyroid hormone triiodothyronine plays an essential role in the control of chondrocyte proliferation and differentiation, inhibiting BMP-2-induced growth of mouse rib. More recently it has been shown that carrier status at one of the *DIO2* markers identified initially, rs12885300, is significantly associated with a specific hip shape.²⁷ Because nonoptimal joint geometry is a risk factor for the development of OA, this result suggests that the role of *DIO2* in hip OA is mediated, at least in part, by an effect on joint geometry.

Selected candidate genes associated with OA are shown in Table 176.3. The selection criteria for these associations were the following: they are genetic variants for which data were available from at least one replication cohort, and the P value had been adjusted for multiple testing and conferred nominal significance of at least $P < .0005$. This P value cutoff for candidate genes represents the level needed to achieve 80% Bayesian posterior credibility for a genetic association that has a prior probability of being true of 10%.²⁸

Genomewide association studies

With the advances in high-throughput single nucleotide polymorphism (SNP) genotyping technology, genomewide association studies (GWASs) have become possible in the past 5 years. These studies take advantage of linkage disequilibrium (LD), that is, the fact that in any given chromosomal region in the genome alleles at physically nearby loci are associated in the population. The markers analyzed need not be functional but may simply be in LD with the functional variant.²⁹ However, the large-scale nature of these studies introduces a multiple testing issue, which makes the need for

very large sample sizes or replication of any positive associations an absolute requirement. GWASs are nevertheless a powerful approach for unlocking the genetic basis of complex diseases such as OA. Individual studies may be hampered by sample size limitations, which result in lack of statistical power, and meta-analyses based on consortium efforts may help overcome some of these limitations.

Several GWASs for OA have been carried out (Table 176.4). Initially, small-scale studies of sparse maps of approximately 100,000 SNPs were reported that used small discovery populations and larger-scale replication populations. Such a study found DVWA (double von Willebrand factor type A domain) to be associated with OA in Asian populations.²² Later a UK GWAS using pooled DNAs from 357 cases and 285 controls reported the identification of a signal (rs4140564) between *PTGS2* and *PLA2G4A*.³⁰

In 2010 results from three GWASs for OA were published: the Rotterdam and arcOGEN (Arthritis Research Campaign Osteoarthritis Genetics) studies in the Netherlands and United Kingdom, respectively, and a third in Japan. The Japanese study used a standard approach employing 899 cases and 3396 controls. Replication increased the size to 1879 cases and 4814 controls. Two SNPs located within a small region of the HLA locus on chromosome arm 6p were identified to be associated with knee OA ($P < 7 \times 10^{-8}$).³¹ However, replication was not achieved in either of two European cohorts or, surprisingly, in a population of Han Chinese.³² A subsequent large-scale replication study encompassing 36,408 control subjects and 5749 knee OA patients of European descent found that the SNPs identified by Nakajima and coworkers were conclusively not associated with OA in European populations.³³ The same study showed that in Japanese individuals these SNPs are in strong LD ($r^2 = 0.86$) with the HLA class II haplotype DRB1*1502 DQA1*0103 DQB1*0601 (frequency in Japanese, 8%) which would be protective for knee OA. In white and Chinese samples, the SNPs identified by the Japanese GWAS are not in LD with that haplotype ($r^2 < 0.07$), and the HLA haplotype in question is also much rarer (0.8 % and 2.3% of individuals, respectively) than in Japanese. Thus, although the HLA class II region may be implicated in risk of knee OA, the results to date do not allow a generalization to European populations.³³

As for the GWASs in samples of European descent, the GWAS in Rotterdam also used a relatively small discovery cohort of 1341 cases and 3496 controls from the Netherlands. Replication involved additional European cohorts and North Americans of European descent. This produced a respectably powered study of 14,934 cases and 39,000 controls. A signal ($P < 8 \times 10^{-8}$; odds ratio [OR], 1.14) was identified in a region on chromosome band 7q22 that included a large LD block extending over 500 kilobases [kb] associated with knee and hand OA. The addition of several more cohorts to the original study increased the evidence for the veracity of this signal. However, the LD block contains six known genes, all of which are equally good candidates for association with OA. These include *PRKAR2B*, encoding cyclic adenosine monophosphate-dependent protein kinase regulatory subunit type II- β ; *GPR22*, encoding G protein-coupled receptor 22; and *COG5*, encoding component of oligomeric Golgi complex 5. Additional investigation intriguingly revealed an expression QTL within *GPR22* in high LD with the identified association signal.³⁴ A subsequent meta-analysis that

■ TABLE 176.4

Genetic associations with large joint osteoarthritis (OA) and related traits derived from genomewide association studies (with $P < 1 \times 10^{-7}$)

SNP ID	Gene	Ethnic group	Trait	P value	Putative or known function	Study
rs12982744	<i>DOT1L</i>	Whites	Minimum hip joint space width	1×10^{-11}	Wnt signaling	Castaño Betancourt et al ⁴²
rs11718863	<i>DVWA</i>	Asians	Knee OA	7×10^{-11}	Cartilage-specific tubulin binding	Miyamoto et al ⁴⁹
rs11177	<i>GLN3/GLT8D1</i>	Whites	Hip or knee OA	7×10^{-11}	Cell cycle control, tumorigenesis, and cellular senescence	arcOGEN Consortium ⁴¹
rs4836732	<i>ASTN2</i>	Whites	THR	6.1×10^{-10}	Glial neuronal migration	arcOGEN Consortium ⁴¹
rs9350591	<i>FILIP1/SENP6</i>	Whites	THR	2×10^{-9}	Specific gene product not known at this time	arcOGEN Consortium ⁴¹
rs10947262	<i>BTNL2</i>	Asians	Knee OA	5×10^{-9}	Immunomodulatory function, T-cell response	Nakajima et al ³¹
rs4730250	<i>COG5/GPR22/DUS4L/HBP1</i>	Whites	Knee OA	9×10^{-9}	Specific gene product not known at this time	Evangelou ³⁵
rs11842874	<i>MCF2L</i>	Whites	Knee or hip OA	9×10^{-9}	Cell motility	Day-Williams et al ³⁸
rs10492367	<i>PTHLH</i>	Whites	Hip OA	1.5×10^{-8}	Chondrogenic regulator	arcOGEN Consortium ⁴¹
rs835487	<i>CHST11</i>	Whites	THR	2×10^{-8}	Chondroitin sulfotransferase involved in cartilage metabolism	arcOGEN Consortium ⁴¹
rs7775228	<i>HLA-DQB1</i>	Asians	Knee OA	2×10^{-8}	Immune response (antigen presentation)	Nakajima et al ³¹
rs12107036	<i>TP63</i>	Whites	TKR in women	7×10^{-8}	Member of the p53 family of transcription factors	arcOGEN Consortium ⁴¹
rs8044769	<i>FTO</i>	Whites	TKR in women	7×10^{-8}	Control of energy homeostasis	arcOGEN Consortium ⁴¹
rs10948172	<i>SUPT3H/RUNX2</i>	Whites	Hip or knee OA in men	8×10^{-8}	Probable transcriptional activator	arcOGEN Consortium ⁴¹

arcOGEN, Arthritis Research Campaign Osteoarthritis Genetics; SNP, single nucleotide polymorphism; THR, total hip replacement; TKR, total knee replacement.

encompassed 6709 cases of knee OA cases and 44,439 controls showed conclusively that this signal is associated with genomewide significance in samples of European descent (OR, 1.17; 95% confidence interval [CI], 1.11 to 1.24; $P = 9.2 \times 10^{-9}$) but not in Asian populations (OR, 1.03; 95% CI, 0.85 to 1.25; not significant).³⁵

Finally, the arcOGEN study was conducted by a UK-based consortium involving seven collection centers. The discovery cohort consisted of 3177 cases and 4894 controls, and replication of signals involved additional European cohorts as well as white North Americans, resulting in an overall meta-analysis sample of 13,768 cases and 53,286 controls. This GWAS was unable to identify a signal of genomewide significance. This disappointing result highlights the difficulty in finding OA genes even when a study is adequately powered. It points to the fact that there are probably many genes contributing to OA, all of which individually have very modest genetic effect.³⁶ Using these same GWAS data UK scientists have generated 1000 Genomes Project–based imputation³⁷ on the same data from the arcOGEN consortium as earlier (3177 knee and hip OA cases and 4894 population controls). The resulting imputed genotypes were then used to detect previously unidentified risk loci. Through large-scale replication it was possible to establish robust association with SNPs in the MCF2 cell line–derived transforming sequence-like gene (*MCF2L*).³⁸ The top signal, rs11842874, reached a combined OR of 1.17 (95% CI, 1.11 to 1.23; $P = 2.1 \times 10^{-8}$) across a total of 19,041 OA cases and 24,504 controls of European descent.

MCF2L is a rho-specific guanine nucleotide exchange factor. In human cells MCF2L regulates neurotrophin-3–induced cell migration in Schwann cells.³⁹ Although this might potentially supports the relevance of nociceptive molecular pathways in genetic susceptibility to OA, Valdes and coworkers⁴⁰ have reported an association between the MCF2L gene variant and radiographic severity at the patellofemoral knee compartment. Thus further research into the role of this gene in OA pathogenesis is necessary.

In the arcOGEN study a second GWAS was conducted in 7410 patients with severe OA, 80% of whom had undergone total joint replacement, and 11,009 unrelated controls from the United Kingdom.³⁷ The most promising signals were replicated in an independent set of up to 7473 cases and 42,938 controls from studies in Iceland, Estonia, the Netherlands, and the United Kingdom. This study has identified several new genetic loci associated with large joint OA (see Table 176.4) which are discussed here.

The most significant association signal resided on chromosome 3 and was followed up by two SNPs in perfect LD with each other: rs11177, a missense polymorphism within exon 3 of *GNL3*, coding for nucleostemin

(OR, 1.12; 95% CI, 1.08 to 1.16; $P = 1.25 \times 10^{-10}$); and rs6976, situated in the 3' UTR of the *GLT8D1* gene. Interestingly, the authors also reported that whereas nucleostemin was barely detectable in cultured chondrocytes from control subjects it was clearly detectable in cultured chondrocytes from OA patients and was significantly upregulated in OA compared with control chondrocytes.

All of the remaining four signals with genomewide significance emanated from cases with hip OA: rs4836732, located within intron 18 of the *ASTN2* gene (OR, 1.18; 95% CI, 1.12 to 1.25; $P = 2.42 \times 10^{-9}$); rs9350591, located 38 kb upstream of *FILIP1* and 70 kb upstream of *SENP6*; rs10492367 (OR, 1.14; 95% CI, 1.09 to 1.20; $P = 1.48 \times 10^{-8}$), 59 kb downstream of *KLHDC5* and 96 kb downstream of *PTHLH*; and rs835487 (OR, 1.13; 95% CI, 1.09 to 1.18; $P = 1.64 \times 10^{-8}$), located within intron 2 of *CHST11*. Three additional signals approached genomewide significance: rs12107036 was associated with OA in females who had undergone TKR and resides within intron 12 of *TP63*; rs8044769 was strongest in the female OA stratum (allele C OR, 1.11; 95% CI, 1.07 to 1.15; $P = 6.85 \times 10^{-8}$) within intron 1 of *FTO*; and, in the male OA stratum, rs10948172 (OR, 1.14; 95% CI, 1.09 to 1.20; $P = 7.92 \times 10^{-8}$), situated in the vicinity of the *SUPT3H* gene.⁴¹ For the most part the role of these molecules in OA pathogenesis remains to be elucidated.

A different approach was used by Castaño Betancourt and colleagues,⁴² who, rather than concentrating on OA phenotype itself, carried out a GWAS on cartilage thickness in the Rotterdam study and identified a SNP in the *DOT1L* gene that was strongly associated with minimum hip joint space width on radiographs.⁴² This result was replicated in independent cohorts in the United Kingdom and overall achieved a genetic effect size (expressed as the regression coefficient β) of 0.09 mm per allele ($P = 1.1 \times 10^{-11}$). The allele associated with larger minimum hip joint space width was found also to be strongly associated with decreased risk of hip OA (OR, 0.88; 95% CI, 0.82 to 0.94; $P = 1.1 \times 10^{-4}$). Experimental work by the same authors showed that this gene plays a role in chondrogenic bone development via regulation of Wnt signaling.⁴²

Although GWASs have proved to be a great success in investigating some traits and have overcome many of the reliability problems encountered in earlier analytic methods, they have attracted criticism. Not least among the complaints is the vast resources required to undertake such a study. Moreover, the analysis of hundreds of thousands of SNPs dictates that the level of significance needs to be lowered to reflect the multiple testing inherent in such analysis. The genomewide significance threshold required to

consider a genetic variant as “true” is $P < 5 \times 10^{-8}$, which places a considerable burden on investigators because it necessitates using very large sample sizes or detecting only variants with a relatively large effect size (which is not seen in common diseases such as OA). This means that many true signals are potentially being overlooked. This α level, combined with the knowledge that many signals have very modest genetic effects of between 1.1 and 1.2, has required that the sample sizes of these studies be increased substantially to tens of thousands of cases to identify the associated signals successfully.

It should be noted, however, that the existence of low effect sizes is not limited to genetic studies of OA or other common traits. At the same time, GWASs, by setting strict rules on the selection of cases and controls and on the significance threshold, which is put at the level of $P < 5 \times 10^{-8}$, have considerably raised the quality of genetic studies and drastically diminished the rate of false-positive reporting. GWASs have strongly highlighted the need for replication of findings, supporting the requirement for collaborative efforts. Large genetic consortia in Europe and the United States are already facilitating these kinds of collaborations in OA.

Finally, criticisms of GWASs have grown with their very success. With the ever-increasing numbers of identified signals for each of the common traits under investigation, it has been noted that the combined effect of these loci have been unable to account for a significant proportion of the genetic risk associated with the given disease. This is known as the “missing heritability” problem, and many explanations have been proposed to account for it.⁴³

Popular ideas include the lack of identification of tens, hundreds, or even thousands of genes because they are either rare (minor allele frequencies of less than 1%), have a very small genetic effect (OR of around 1.1 or less), or are not captured by the common arrays employed. Moreover, these rare variants, even if they have large genetic effects (ORs of more than 2.0), still are not detected by the current GWAS arrays, which are based on variants screened by the HapMap Project. As shown by the 1000 Genomes imputation OA GWAS discussed earlier,³⁸ some important variation indeed is missed by these arrays. Depending on the platform and ethnicity, most GWASs will capture only 85% to 96% of the genome and will completely overlook rare variants and copy-number variations. If the first two factors

are considered together, it is apparent that the size of cohorts required to capture these variants is beyond the scope of most investigators. Thus a combined analysis of increasingly large numbers of studies is called for, which necessitates international collaborations to achieve the hundreds of thousands of cases required for detection of such signals.

CONCLUSIONS

The recent rapid improvement in genetic techniques has enabled us to identify a number of genes predisposing to OA. Tremendous efforts have been directed to finding genes that confer risk of both rare and common forms of OA. Although the study of monogenic syndromes that resemble OA or result in early-onset OA has greatly increased our understanding of cartilage biology, it has not helped us understand the molecular genetic etiology of the complex, common form of OA. There are some points in common between. The common complex form of OA seems to be strongly influenced by bone morphogenetic proteins and Wnt signaling, which are central to skeletal development.

On the other hand, genetic studies of OA and other complex diseases have highlighted the need for replication of findings; this would reduce the false-positive signals and points up the need for collaborative efforts. GWASs have revealed a considerable amount of information about the genetic architecture of the disease. OA is a polygenic complex disorder, and many risk alleles, each with a small effect, are important in OA. The GWASs and large candidate studies of OA have so far indicated molecules involved in skeletal development as an etiologic pathway in the late onset of OA as it occurs in the general population. During the coming few years, additional genetic and functional studies will offer a more complete picture of the contribution of genetic factors to OA and the underlying molecular pathways.

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Imaging of osteoarthritis

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- Plain radiography is the most feasible method of imaging of osteoarthritis (OA) in clinical practice, although it is often not required because both diagnosis and progression of OA are usually adequately assessed clinically.
- Magnetic resonance imaging visualizes the joint as a whole organ, improving understanding of the pathologic processes, natural history, and potential sources of pain in OA. It is not used routinely for the diagnosis or clinical assessment of OA but is of increasing importance in the research environment.
- Ultrasound allows dynamic assessment of joints; it can assess inflammation (synovial hypertrophy and effusions) and damage (erosions and joint space loss); it also may allow guided therapy for OA joints.
- Other imaging modalities (radionuclide scintigraphy, computerized tomography, positron emission tomography) may be used on a case-by-case basis but do not yet have a routine role in OA investigation or management.

INTRODUCTION

Osteoarthritis (OA) is the most prevalent joint disease worldwide and is increasingly common in aging Western populations. The use of imaging should be considered in light of the particular clinical question and individual tool characteristics. Conventional radiography (CR) is usually not required for the routine clinical diagnosis of OA; because treatment is symptomatic and symptoms are not generally well correlated with the severity of radiographic features of OA, CR does not often assist in treatment decisions unless joint replacement is being considered. It is accepted that the OA disease process involves all tissues of the joint including the cartilage, subchondral bone, synovium, and periarticular tissues, and this has led to the increasing use of modern imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI) for evaluating the disease, particularly in the research environment.

It should be noted that CR has the longest history in imaging of OA and that there is a predominance of knee studies in the literature for both CR and modern imaging.

CONVENTIONAL RADIOGRAPHY

Plain radiography is inexpensive and widely available, and its images are easily understood. Although, as mentioned, its role in clinical diagnosis and management of OA is limited, it may have a place in excluding other diagnoses at the time of joint pain presentation.

Radiographic image quality is influenced by the sensitivity of the imaging system and the radiographic view. The latter is important because failure to standardize the radioanatomic positioning of the joint between examinations reduces the sensitivity of the technique to detection of changes over time (Fig. 177.1).¹

In OA, subchondral sclerosis and osteophytosis are generally the earliest radiographic features. They increase with time in both extent and size and precede radiographic joint space narrowing (Fig. 177.2), which occurs at a later stage of the disease.¹

What pathologic features can conventional radiography assess in osteoarthritis?

Osteophytes

Osteophytes form as outgrowths at articular margins, capsular insertions, and central articular regions in the unloaded region of joints (Figs. 177.3 and 177.4).

Subchondral bone changes

Increased subchondral cortical plate thickness and subjacent trabecular sclerosis are among the earliest changes in OA. Subchondral bone also demonstrates trabecular loss, which becomes marked with advancing disease (see Fig. 177.2), and increased local bone turnover results in younger, less highly mineralized bone. Radiolucencies noted in the subchondral bone may be juxtaarticular erosions or subchondral cysts, which tend to occur in more advanced OA at sites of increased mechanical load and frequently communicate with the articular surface.

Joint space narrowing

The “interbone” distance was traditionally thought to represent articular cartilage thickness in load-bearing views of the joint. However, it is now recognized from MRI studies that meniscal degeneration and extrusion in the knee joint can contribute to joint space loss.² On CR, joint space narrowing is focal and not uniform, reflecting asymmetric cartilage loss across the articular surface.¹ This feature can prove useful in distinguishing early OA from other arthritides such as rheumatoid arthritis. Marked joint space narrowing is more typical of later stages of the disease (see Figs. 177.1 and 177.2b).¹

Bone remodeling and attrition

Subchondral bone in OA patients is mechanically weaker than that in individuals with nonarthritic joints. It is detected radiographically as flattening and increased congruity between the articular surfaces (Fig. 177.5). With cartilage loss in the load-bearing compartment, tongue-and-groove corrugation may develop, and with complete loss of cartilage the subchondral bone is further flattened (see Fig. 177.5b). Ultimately, the surfaces become deformed, with the collapse of the bone leading to altered limb alignment and deformity.

Radiographic procedures

Validated procedures for the radiographic assessment of OA joints are necessary to standardize assessment of the severity and progression of OA. Standardized radiographic procedures minimize any distortion in the radiographic image of the joint by positioning the joint so that the central ray of the x-ray beam passes between the margins of the joint space (Fig. 177.6). The most reliable and reproducible method for imaging the tibiofemoral compartment of the knee is the standing semiflexed view. Fluoroscopic guidance, which ensures that the center of the x-ray beam is parallel to the tibial plateau, can be used to ensure correct positioning before the radiograph is obtained (Fig. 177.7). The patellofemoral compartment can be assessed using either a lateral or a “skyline” (axial) view (Fig. 177.8). In the axial view the detector is placed on a step and the knee is flexed to 30 degrees from the vertical. The axial view can give a false impression of the patellofemoral alignment if it is undertaken without weight bearing.

Hip radiographs are conventionally taken with the hip in 15 to 20 degrees of internal rotation. Unlike in knee examination there is no advantage to obtaining the radiograph with the patient in a standing position. A lateral oblique view may be used to detect anterior or posterior joint space loss.

The optimal view for imaging the hand is a dorsopalmar view with the fingers in line with the forearm when laid flat on the x-ray detector holder.

Radiographic grading systems

The Kellgren-Lawrence (KL) grading system remains the most widely used scale to quantify radiographic OA lesions. The KL system grades radiographic findings on a scale of 0 to 4 by assessing the presence and severity of osteophytes, joint space width, subchondral bone sclerosis, and deformity of bone contour. It has limitations based on the incorrect assumption that radiographic changes are linear over the course of the disease and that the relationship among these features is constant. In contrast, the Osteoarthritis

Research Society International (OARSI) atlas classification grades tibiofemoral joint space narrowing and osteophytes separately in each compartment of the knee.³

Scoring systems for OA of the hand include the semiquantitative Kallman scale, the Verbruggen numerical scoring system, and a global scoring system in which 32 joints in the hands are scored yes/no for features of radiographic OA. These scoring methods have been demonstrated to have similar reliability and may be used to detect radiologic change in hand OA over time.⁴

Researchers generally agree that weight-bearing views, particularly semiflexed views, are best for evaluating structural progression in the knee with OA, because supine views may not demonstrate joint space narrowing evident on weight-bearing views. Precision of measurement of joint space width (JSW) is improved with radioanatomic alignment of the medial tibial plateau.⁵

A recent OARSI Task Force concluded that measurement of JSW is still a recommended option for structure modification trials, with the understanding that JSW in the knee represents a complex construct and that a long trial duration may be needed.⁶

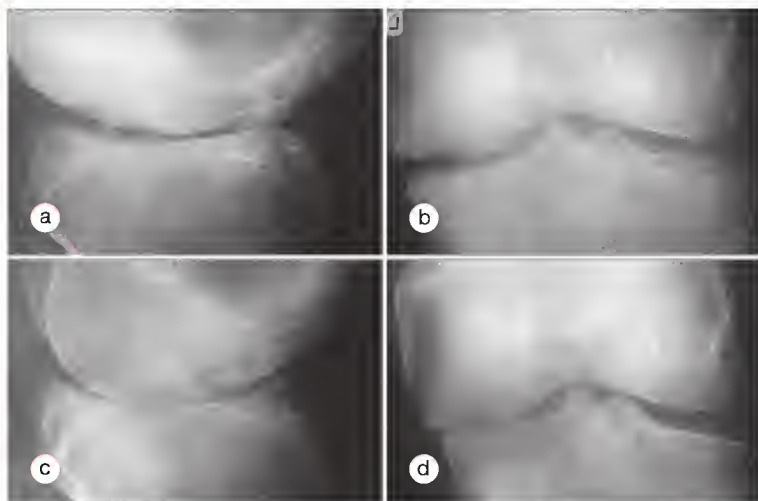


Fig. 177.1 Differences in joint position at radiography affect joint space assessment. With the knee extended (top row), radiography does not reveal joint space narrowing, but in the semiflexed position (bottom row) joint space narrowing is detected. With advanced disease, lateral radiographs in the standing extended knee view (a) show the femoral condyle resting on the anterior rim of the tibia, producing a gap visible as a joint space in the anteroposterior view (b). Conversely, in the semiflexed view of the same knee, the femoral condyle occupies the central region of the tibial plateau (c) with no cartilage present. No joint space is visible in the anteroposterior view (d).

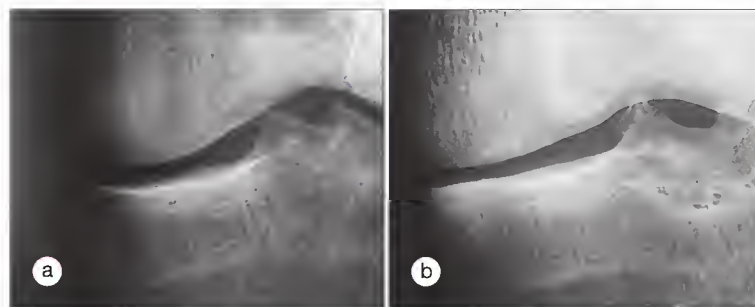


Fig. 177.2 Radiographic progression of osteoarthritis. Part of macroradiographs (reduced) showing the medial compartment in osteoarthritic knees. (a) Early disease: joint space width greater than 3 mm. (b) Definite disease: joint space width less than 3 mm. With progressive joint space loss, note the increase in subchondral cortical plate thickness and subjacent horizontal trabeculae, which results in a ladderlike appearance that is enhanced by subarticular osteoporosis. Periarticular osteopenia in (a) adjacent to the developing marginal osteophyte is not visible in (b), because osteophytic growth appears to have halted. Osteophytes at the tibial spines appear as irregular outgrowths in (a) and (b). A marginal osteophyte is visible at the posterior rim of the tibia in (b).

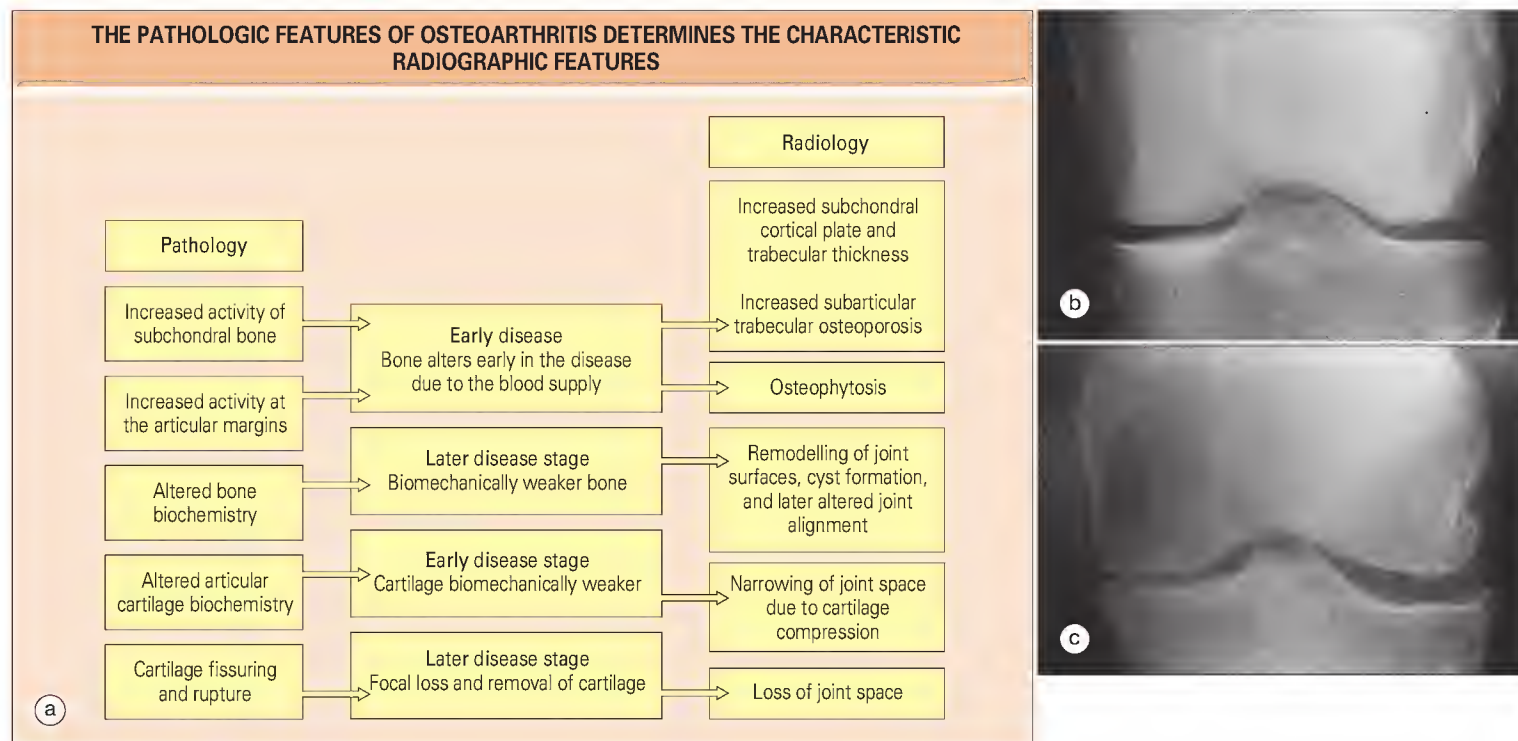


Fig. 177.3 (a) Pathologic changes in osteoarthritis and the corresponding characteristic radiographic features visualized in plain radiographs of joints with early- and late-stage disease. (b) Radiograph of a healthy knee. (c) Radiograph of a knee with late disease showing most of the features listed in (a).



Fig. 177.4 Radiographic changes in osteoarthritis (OA). (a) Hypertrophic OA of the hip, with concentric joint space narrowing and extensive osteophytosis and subchondral sclerosis characteristic of the marked bony reaction. (b) Atrophic or destructive OA of the hip, in which there is destruction of subchondral bone, with a relative paucity of osteophyte formation associated with joint space narrowing. (c) Secondary OA of the hip, here caused by a dysplastic hip. The shallow acetabulum and uncovering of the head of the femur results in OA of the upper pole of the joint, with joint space narrowing, subchondral sclerosis, cysts, and osteophytosis. (d) Erosive OA at a distal interphalangeal joint: apart from joint space narrowing, subchondral sclerosis, and osteophytosis, there is loss of the cortical margin, central erosions, and marked soft tissue swelling.

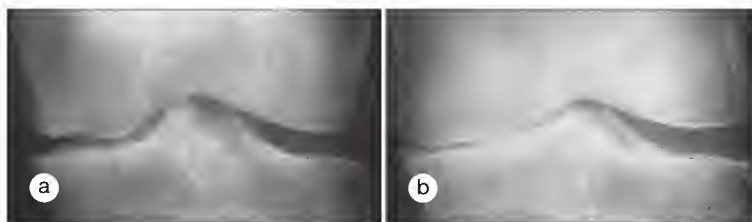


Fig. 177.5 Articular bone distortion and flattening in osteoarthritis (OA), caused by weaker bone. (a) OA knee in the standing extended view showing marked subchondral sclerosis with tongue-and-groove corrugations on the femoral and tibial articular surfaces of the medial compartment. (b) The same knee 21 months later. The corrugations visible in (a) are reduced or absent, which results in a flattened articular surface.

PLANE FOR MEASUREMENT OF MINIMUM JOINT WIDTH

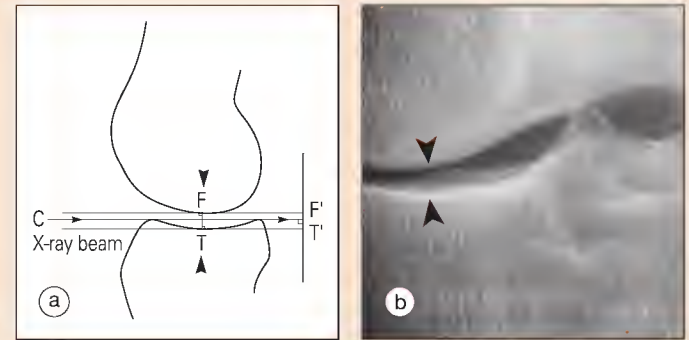


Fig. 177.6 (a) For measurement of minimum joint space width in the tibiofemoral compartment, the plane is taken in the middle of the joint, coincident with load transmission (arrows), perpendicular to the central ray (C) of the x-ray beam and parallel to the film. (b) Arrowheads identify the corresponding site in the anteroposterior radiograph of an osteoarthritic knee. F, femur; T, tibia; F' and T', their projections onto the x-ray film.

JSW can be measured manually using calipers or a graduated ruler and a micrometric eyepiece, or with semiautomated computer software, which has been developed to improve the accuracy of JSW measurement over manual methods. JSW measurements include minimum JSW, mean JSW, joint space area, and JSW at fixed locations.⁹ Software analysis of digital knee radiographs has been shown to be comparable to cartilage morphometry analysis using MRI in detection of OA progression.⁷

Relation to clinical features

There is some discordance among radiographic change, clinical symptoms, and the degree of disability experienced by patients; however, a recent large study noted a strong association between increasing KL grade and increasing frequency and severity of knee pain.⁸ In a study of more than 700 patients with knee pain, the presence of radiographic OA, as defined by the KL score, was consistently associated with the severity of pain, stiffness, and physical function.⁹ However, other studies suggest that only around half of those with radiographic knee OA report knee pain.¹⁰

Likewise, not all patients with knee pain demonstrate radiographic OA. A literature review reported that the proportion of patients with knee pain found to have radiographic OA ranged from 15% to 76%.¹⁰ This lack of consistency across the data might be due to the failure of studies to use x-ray views of all three compartments of the knee, but even when a range of radiographic views is employed, the highest proportion of people with pain who have radiographic knee OA is 76%.¹¹ Earlier radiographic studies of OA, which excluded the patellofemoral joint, may have underestimated the contribution of structural pathologic changes to pain and disability. Duncan and colleagues¹² demonstrated that a posteroanterior view alone identifies around half of the cases of radiographic OA in patients with knee pain; the proportion increased to 87% with two views and 98% with all three views (posteroanterior, supine skyline, and supine lateral).

With regard to individual radiographic pathologic features, the presence of joint space narrowing, and to a lesser extent osteophytes, has been shown to be associated with knee pain.⁸ Joint space narrowing and the presence of osteophytes have also recently been found to be associated with pain in individual hand joints.¹³

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) offers outstanding soft tissue contrast in a tomographic presentation. It provides sections in any plane prescribed by the operator. The technique allows visualization of articular cartilage, fibrocartilage (such as the menisci), synovium, bone contours, bone marrow, and ligaments. Because it is now clear that OA is a disease of the whole joint, MRI has become invaluable, allowing better analysis of both the structure-pain relationship and structural progression. MRI is able to detect pathologic changes at a much earlier stage of the disease than CR, commonly when radiographic findings are normal. An increasing number of studies are documenting the frequency of occurrence of multiple structural

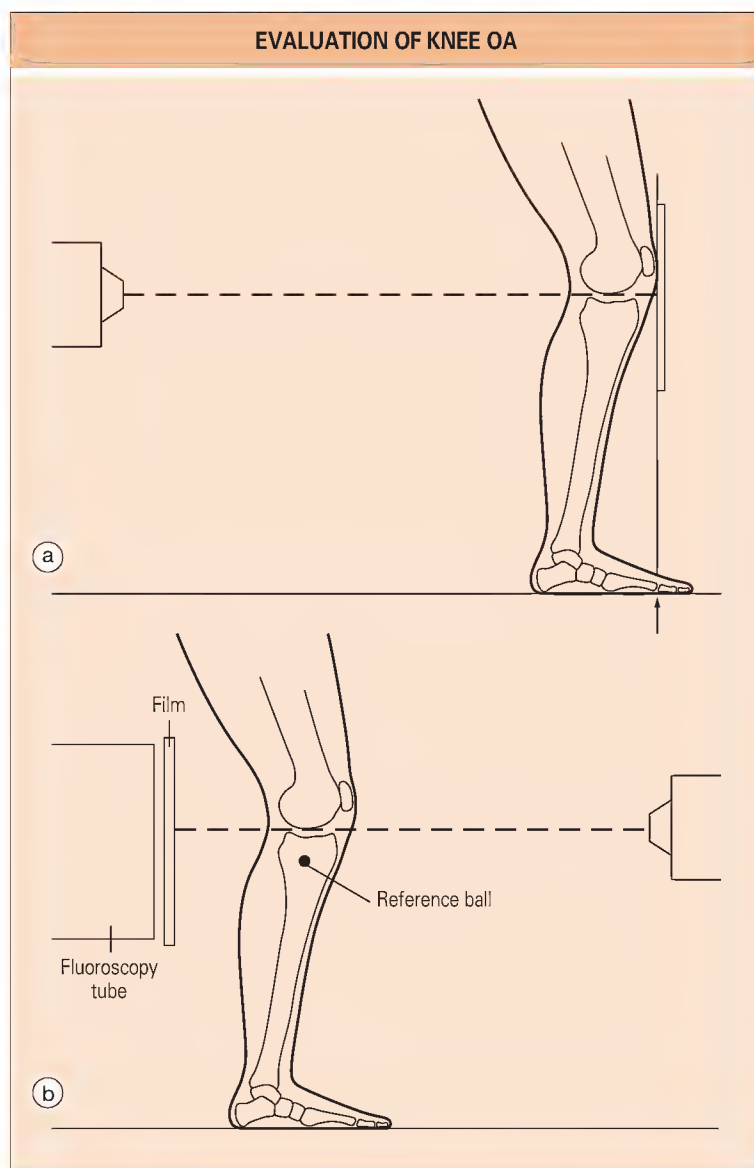


Fig. 177.7 Reproducible radiographic methods for reliable evaluation in knee osteoarthritis (OA). (a) The patient stands in the semiflexed position; both knees are bent and in contact with the film cassette, and the feet are slightly externally rotated (about 15 degrees). The first metatarsophalangeal joint of each foot (arrow) is positioned immediately below and in line with the front edge of the film cassette. The x-ray beam is directed midway between the knees, and the tube's positioning light is aligned with the horizontal plane of the joint. (b) The knee can also be positioned reproducibly in the semiflexed view by using fluoroscopy to position the tibial plateau horizontally and parallel to the x-ray beam. A metallic reference ball is used to correct for radiographic magnification.



Fig. 177.8 Axial or skyline method for imaging the patellofemoral joint. The film is placed on a step and the knee is flexed to 30 degrees from the vertical. This view provides a reliable assessment of the interbone distances at the medial and lateral compartments.

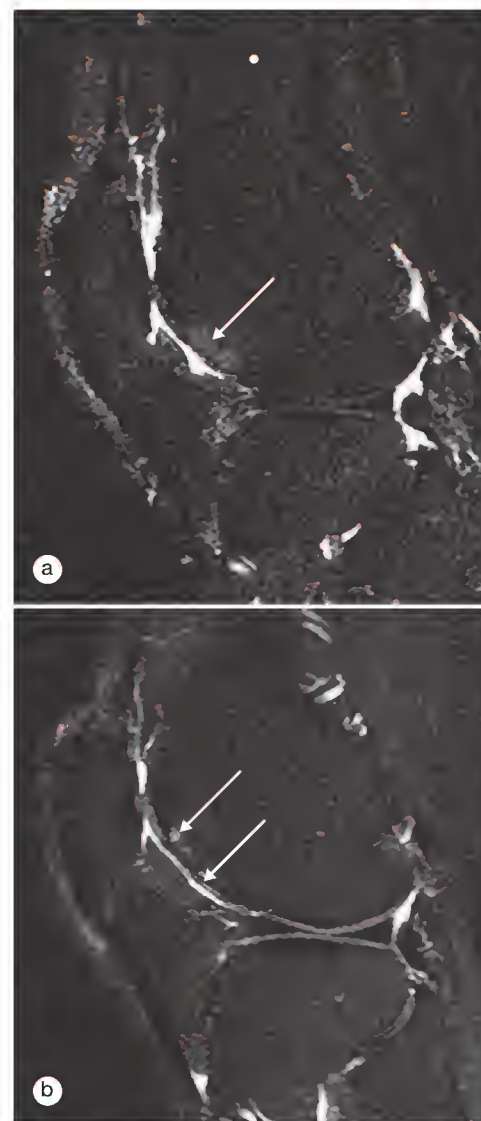


Fig. 177.9 Sagittal T2-weighted fat-suppressed magnetic resonance images of the knee. (a) Bone marrow lesions (BMLs) with an edematous pattern (arrow) are apparent on the anterior lateral trochlea. (b) Image taken 6 months later shows that these lesions have become cystic in nature (arrows). Note also articular cartilage loss overlying the BMLs.

abnormalities in OA joints. In general, MRI abnormalities are seen more frequently with increasing KL grade.

What pathologic features can magnetic resonance imaging assess in osteoarthritis?

Subchondral bone marrow changes

The most common MRI-detected subchondral bone abnormality is manifested as a high-signal area seen on fat-suppressed T2-weighted or short tau inversion recovery (STIR) sequences and has been referred to as a *bone marrow lesion* (BML). The presence of these bone marrow lesions has been associated with both pain and structural progression in the OA knee.^{14,15} Cysts are also observed in the subchondral bone and may be seen to develop with time on a background of a bone marrow lesion (Fig. 177.9).

Bone attrition

Bone attrition is thought to represent remodeling of the subchondral bone and is represented by a flattening or depression of the articular bone cortex. It is commonly seen in conjunction with BMLs. Typically seen in advanced OA, it might occur in milder OA and earlier in the disease than previously thought.¹⁶

Osteophytes

Although marginal osteophytes might be visualized better with CR than with MRI, central osteophytes are more easily detected with MRI. MRI has



Fig. 177.10 Coronal magnetic resonance image of a distal phalangeal joint demonstrating synovitis (after gadolinium contrast administration).

also demonstrated that osteophytes are common in people with no knee symptoms even in the absence of CR changes.

Erosion

Although classically considered a feature of the inflammatory arthritides, bone erosion may be demonstrated in OA. An erosive form of hand OA is recognized on CR, but MRI evidence suggests that erosions may be present even in the absence of CR evidence of erosion,¹⁷ with MRI detecting approximately twice as many joints with erosions compared with CR.¹⁸

Synovitis and joint effusion

Contrast-enhanced MRI remains the gold standard for assessing synovial hypertrophy, with studies demonstrating that the prevalence of definite synovitis in the OA knee in large cohorts is 80% to 90%.^{19,20} Studies of hand OA using contrast-enhanced MRI noted synovitis in over half of the distal interphalangeal and proximal interphalangeal joints (Fig. 177.10).²¹ Joint effusion is best detected on fat-suppressed proton density-weighted or T2-weighted fast-spin echo sequences.

Quantitative MRI markers of synovitis include synovial membrane thickness, synovial fluid volume, and the rate of synovial enhancement after intravenous injection of contrast agent (Fig. 177.11). Accurate quantification of synovitis can be achieved without using contrast agents,²² and recent concerns over the potential toxicity of gadolinium-based contrast agents in patients with severe renal impairment means that this method may warrant further development.

Fibrocartilage and ligament abnormalities

Meniscal tears and extrusion are common in OA (Fig. 177.12). The frequency of MRI-detected meniscal tears increases as the KL grade increases and meniscal damage has also been associated with the development or enlargement of BMLs over time.²³ Fibrocartilage in other joints such as the labrum of the hip and shoulder and the triangular fibrocartilage of the wrist may also show degeneration and tearing, which can be detected with MRI.

Studies have suggested that ligament abnormalities seen on MRI may be an early feature of the disease, and this has been shown in both the knee and small joints of the hand.²⁴ The association of anterior cruciate ligament (ACL) tears and subsequent development and progression of radiographic OA is well described. A high incidence of ACL changes is seen in MRI studies of OA patients, with the occurrence of complete ACL tear reported in up to 20% of one cohort.²⁵

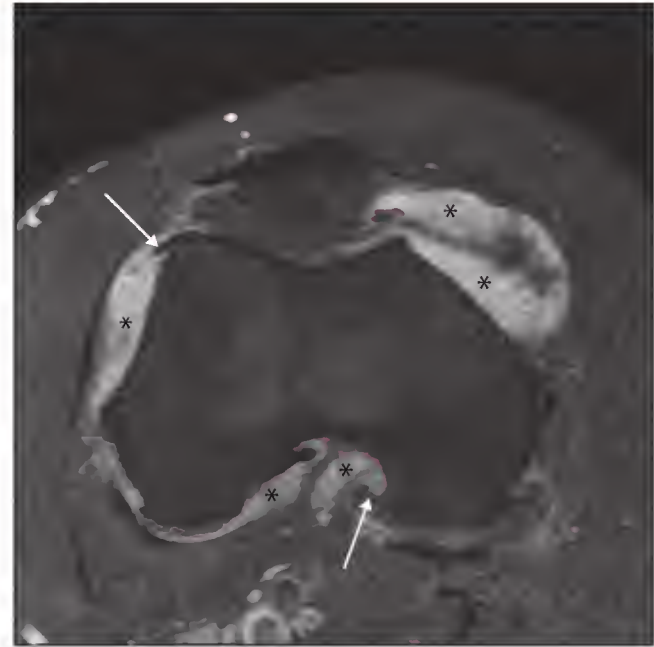


Fig. 177.11 Axial T1-weighted fat-suppressed magnetic resonance image of the knee with gadolinium contrast. The high-signal synovitis is well demonstrated in the suprapatellar pouch and intercondylar notch (asterisks). Osteophytes are also seen (arrows).

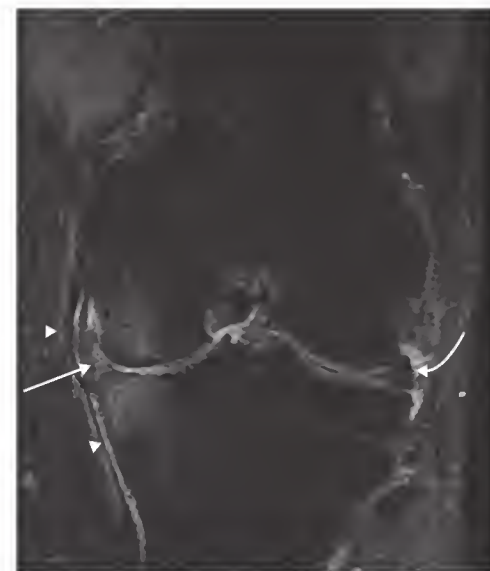


Fig. 177.12 Coronal T2-weighted fat-suppressed magnetic resonance image of the knee demonstrating bone marrow lesion and cartilage loss on both sides of the medial joint. The medial meniscus is markedly degenerate with maceration and abnormally increased signal (straight arrow) compared with the normal lateral meniscus (curved arrow). Abnormally increased signal is also seen on both sides of the medial collateral ligament (arrowheads).

Cartilage abnormalities

With the increasing sophistication of MRI sequences available and improved spatial resolution of modern scanners, MRI can demonstrate changes in the morphology of articular cartilage previously impossible to show noninvasively (Figs. 177.13 and 177.14).

In addition, modern techniques have allowed the examination of cartilage quality. A range of techniques such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T₂ and T₁ρ mapping can provide information on the composition and structure of the cartilage matrix, although these remain research tools and are often difficult to standardize (Fig. 177.15).^{26,27}

Relation to clinical features

A growing number of publications have explored the structural associations of MRI abnormalities with clinical aspects of OA. It is now clear that the

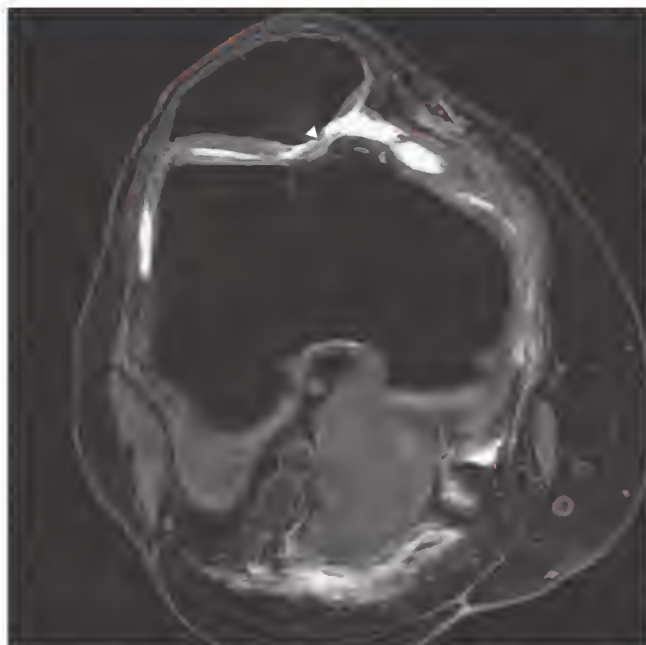


Fig. 177.13 Axial T2-weighted fat-suppressed magnetic resonance image of the knee demonstrating cartilage loss over the crista and medial facet of the patella (arrowhead).



Fig. 177.14 Coronal oblique T1-weighted fat-suppressed magnetic resonance arthrogram of the shoulder with intraarticular gadolinium demonstrating a large osteophyte (black arrow) and areas of cartilage damage to both the glenoid and humeral head (white arrows).

pain in OA is associated with subchondral BMLs²⁴ and the presence of synovitis and effusion,^{19,28,29} with extensive synovitis being strongly associated with knee pain.¹⁹ Furthermore, fluctuations in BMLs or synovitis over time have been associated with change in symptoms.^{15,28-30} The presence of bone attrition and areas of denuded bone have also been associated with knee pain.^{31,32} MRI studies to investigate the association of pain with the presence of osteophytes and meniscal tears have yielded conflicting results, but studies of ACL tears in OA have shown no association with pain.³³ It is also worth noting that MRI will demonstrate abnormalities in the tibiofemoral joint, particularly osteophytes and cartilage defects, in most middle-aged and elderly people even in the presence of normal radiographic findings, regardless of symptoms.³⁴ In hand OA, MRI-detected synovitis, bone attrition, and joint erosion have recently been demonstrated to be associated with joint tenderness.²¹

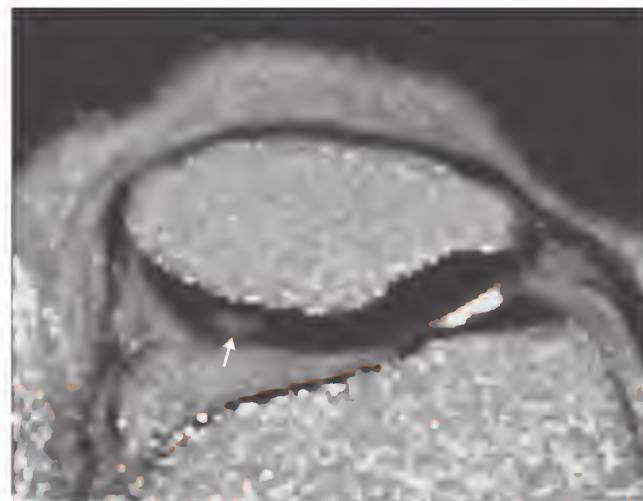


Fig. 177.15 T2-mapped magnetic resonance image of the knee demonstrating early intrasubstance degeneration of the patellar cartilage seen as prolonged T2 signal (arrow).

Quantification of magnetic resonance imaging pathologic changes

To evaluate cartilage loss in longitudinal studies, sophisticated techniques have been developed to measure cartilage, including measurements of volume and sensitive measures of cartilage thickness.³⁵ An ordered-values approach to describing change in cartilage thickness over time may improve the detection of cartilage loss in longitudinal studies of treatment with potential disease-modifying drugs.³⁶ A subset of core measures that comprehensively describes cartilage morphology and its longitudinal change has been described.³⁷

There are no well-validated quantitative measures for assessing noncartilage features; however, a number of semiquantitative scores have been designed for evaluating knee MRI—for example, the Boston Leeds Osteoarthritis Knee Score (BLOKS), the Whole-Organ MRI Score (WORMS), and the Knee Osteoarthritis Scoring System (KOSS).^{38,39} Each of these measurement tools divides the knee into various anatomical subregions and uses categorical scales to describe the extent of a number of multiple pathologic features within these subregions. The reliability of these methods is often reported, and validity has been reported for the BLOKS BML score. The BLOKS score has recently been iteratively updated to the MRI Osteoarthritis Knee Score (MOAKS), which refined the scoring of BMLs, cartilage, and meniscal pathology. This scoring system demonstrated good reliability, but data are still limited as to its validity and responsiveness.⁴⁰ Semiquantitative systems specifically for scoring synovitis, which have been validated against the more time-consuming gold standard of synovial volumetric analysis, have also been described.^{41,42}

An MRI scoring system for hand OA has been developed—the Oslo Hand Osteoarthritis MRI (OHOA-MRI) score.⁴³ Early data suggest that this may be a useful scoring system (although the metacarpophalangeal [MCP] and carpometacarpal joints are not included) and good reliability was demonstrated; further development of this system is ongoing through the Outcome Measures in Rheumatology Clinical Trials MRI group.

Clinical use of magnetic resonance imaging

At present, given the absence of structure-modifying therapies, MRI has little use in the routine clinical management of OA. MRI studies are complex and there is a range of variables including magnet strength, different acquisition sequences, and use or nonuse of contrast agent. Quantification of MRI findings is improving, and most of the improvements are related to improved accuracy and reliability in measurement of cartilage volume and thickness. Until recently, there has been no agreed MRI definition of OA, but a recent publication in this field provides the first attempt to suggest an MRI definition of tibiofemoral OA.⁴⁴ As a result of this exercise, it has been suggested that MRI OA of the knee can be defined as the presence of both full-thickness cartilage loss and definite osteophyte formation. Alternatively, either full-thickness cartilage loss or definite osteophyte formation, along with the presence of two or more of the features of partial-thickness cartilage loss, meniscal damage or extrusion, BML, or bone attrition, also can define MRI OA of the knee. The usefulness of this proposed definition is yet to be

determined, but it may enable studies of “early” OA before radiographic changes are evident.

ULTRASOUND

Ultrasound (US) is a real-time imaging modality that allows dynamic assessment of joints and provides a dimensional aspect that is not achieved with plain radiography. It is a noninvasive, widely available, and cost-effective technique, minimizing discomfort and inconvenience to the patient, and involves no radiation, which makes repeated evaluation of peripheral joints more feasible. Most work assessing the validity of US has focused on inflammatory arthritis. US has been shown to be more accurate than radiography at detecting cortical erosions in inflammatory arthritis.⁴⁵ Recent work in hand OA has demonstrated that US detected more osteophytosis (especially at the MCP joints) and joint space narrowing than CR⁴⁶ and is a reliable tool for detecting cartilage abnormalities in the MCP joints,⁴⁷ which suggests that US is a useful tool for hand OA research. Other recent work suggests that US is a valid and reliable method for assessing hand OA compared with contrast-enhanced MRI.⁴⁸

What pathologic features can ultrasound assess in osteoarthritis?

US can demonstrate a wide spectrum of structures including the bony cortex, tendons, ligaments, bursae, and peripheral aspect of the menisci. Although articular cartilage can be identified, US is handicapped by its inability to “see” through bone structures. The hardest area of cartilage to examine is that in the central load-bearing regions of a joint where the cartilage is particularly affected in the OA process. US can detect early bone changes in OA as a hyperechoic signal in the area of the attachment of the joint capsule to the bony cartilaginous margin. This corresponds with the eventual appearance of osteophytes seen on the conventional radiograph.⁴⁹ However, pathologic changes deep to the cortex such as subchondral bone changes (e.g., BMLs) cannot be visualized. US readily demonstrates joint effusion and synovitis, although this is easier in some joints than in others (Figs. 177.16 and 177.17). US has been used to assess hand OA, with studies largely in people with erosive OA; effusions and gray-scale synovitis were noted in up to half of the distal interphalangeal and proximal interphalangeal joints assessed.^{50,51} Synovitis and effusion were particularly prevalent in those with erosive OA rather than nonerosive OA.⁵²

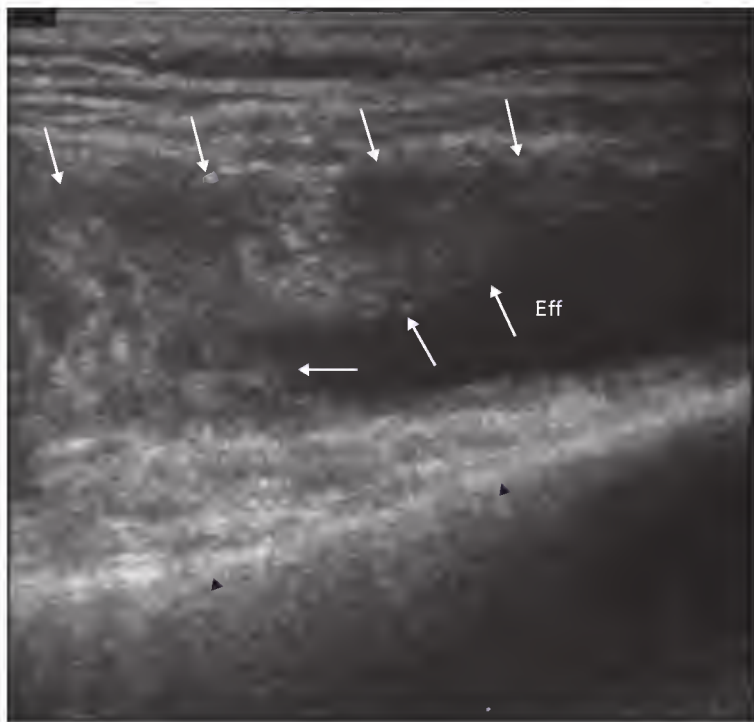


Fig. 177.16 Sonogram of the knee joint (taken longitudinally through the suprapatellar pouch). The anterior cortex of the femur is shown (black arrowheads). A knee joint effusion (Eff) and synovitis are apparent in the suprapatellar pouch (white arrows).

Relation to clinical features

Synovitis and effusion, or both, are commonly detected in patients with OA, with between 47% and 100% of patients having synovitis/effusion on US examination of a symptomatic knee.⁵³ US is more sensitive than clinical examination at detecting synovial hypertrophy and effusions, and US detection of gray-scale synovitis has been validated against arthroscopic biopsy results and MRI detection of synovitis in large-joint OA.

In general, there are more US-detected pathologic findings in symptomatic OA than in asymptomatic or control joints. Recent work has demonstrated that painful hand joints are more likely to demonstrate US pathologic changes than nonpainful joints; in particular, synovitis using gray-scale and power Doppler imaging, osteophytes, and joint space narrowing have been demonstrated.⁵⁴ The association between synovitis/effusion and hand pain has been demonstrated in other work.⁵⁰ Although the association between US-detected pathologic changes and symptoms is generally weak, US-detected synovitis or joint effusion has been shown to correlate with painful knee OA. Furthermore, US-detected effusion at baseline has been found to be a significant predictor of total joint replacement at 3 years.⁵⁵

Clinical use of ultrasound

US is highly operator dependent, and adequate training is required. Standard diagnostic criteria are evolving, and semiquantitative scoring techniques have been proposed for the assessment of US findings in hip, knee, and hand OA.⁵⁶ The current roles of US in OA may be acting as a tool for guiding intraarticular injections, helping to differentiate OA from inflammatory diseases, and confirming the presence of osteophytes to support a diagnosis of OA. Work validating US findings as a biomarker for OA is currently ongoing.

OTHER IMAGING TECHNIQUES

Scintigraphy

Bone scintigraphy is an imaging modality that reflects alterations in the metabolic activity of bone through the use of radiopharmaceutical agents, commonly technetium-99m-labeled methylene diphosphonate (MDP). This compound accumulates rapidly in bone by adsorption to the mineral phase of bone. Imaging with a gamma camera detects areas of isotope accumulation representing points of high skeletal bone turnover.

Early studies using scintigraphy in nodal hand OA demonstrated increased activity in the subchondral bone before any typical radiographic changes were seen in OA. A later study involving patients with chronic knee pain compared scintigraphy findings with MRI findings and demonstrated good correlation between MRI-detected subchondral bone lesions and isotope uptake.⁵⁷ Scintigraphy (through detection of these BMLs seen on

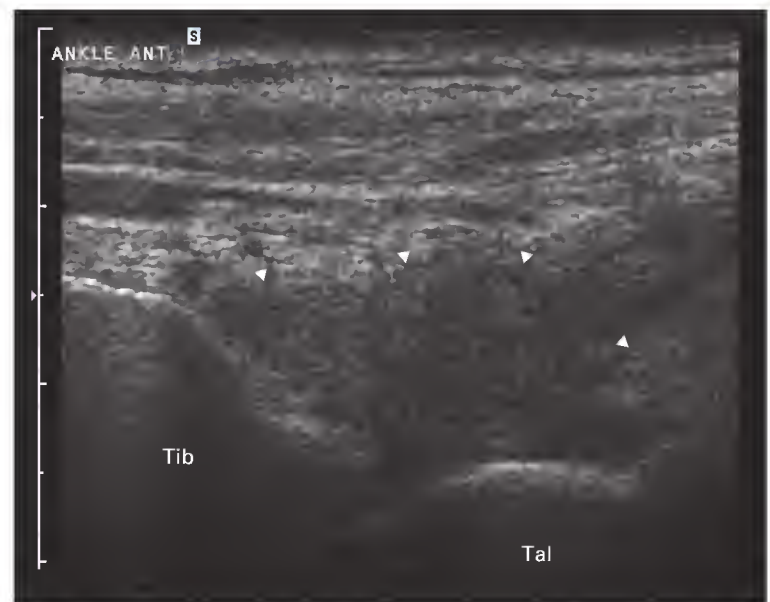


Fig. 177.17 Sonogram taken longitudinally across the anterior ankle joint. There is severe synovitis filling the anterior joint space (arrowheads). Tal, talus; Tib, tibia.

MRI) has predicted disease progression in OA. Normal bone scan findings at baseline in individuals with established OA was highly predictive of a lack of radiographic disease progression (as determined by measurement of joint space width) at 5 years.⁵⁸

Scintigraphy is inexpensive and readily clinically available; however, despite the sensitivity of the technique, it shows low specificity and is associated with a significant radiation dose. For these reasons it has limited clinical applicability in OA.

Positron emission tomography

Positron emission tomography (PET) demonstrates metabolic changes in target tissues and reflects glucose metabolism in different tissues. The role of PET in assessing OA is not yet established, and limitations include its cost and exposure to ionizing radiation.

Computed tomography and computed tomographic arthrography

Computed tomography (CT) is a cross-sectional digital imaging method based on advanced radiographic technology. It is particularly effective at depicting cortical bone and may be useful when detailed presurgical

planning is required. CT has an established role in assessing facet joint OA of the spine. CT arthrography, using a contrast medium, has the ability to clearly image the articular surface of a joint, and this technique is comparable to MRI for qualitative assessment of knee cartilage. This may be particularly useful when MRI is unavailable or contraindicated. The technique gives no information on the intrinsic structure of the cartilage and can demonstrate only defects extending to the superficial surface of the cartilage. CT does not yet have an established role in OA trials or clinical practice and has the drawbacks of low soft tissue contrast and radiation exposure.

SUMMARY

Radiography is still a useful imaging investigation for evaluating an individual with suspected OA because of its low cost and availability, and the ease of interpreting the results. The ability of MRI to evaluate the knee as a whole organ and to assess cartilage composition has made it invaluable, both for understanding the natural history of the disease and for guiding future treatments. US can play an important role in diagnosing OA and in monitoring synovitis and response to treatment. The other modalities discussed may be used on a case-by-case basis but do not have a routine role in OA investigation or management.

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Assessment of the patient with osteoarthritis and measurement of outcomes

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- In clinical practice, the need to perform quantitative assessments is driven by requirements to describe current clinical status, detect change in clinical status, and quantify response to treatment and symptom state attainment.
- Establishment of current clinical status is important, particularly when assessing new patients or those not seen for some time. It provides a quantification of an individual's disease burden and serves to describe the consequence of the disease.
- Detection of change in status provides evidence for worsening or improvement over time.
- Quantification of response to therapy facilitates decision-making as to whether the therapeutic objective has been achieved and whether further intervention is required.
- Quantification of the symptom state attained with therapy facilitates decision-making as to whether the therapeutic objective has been achieved, whether the patient has reached an acceptable level of symptom severity, and whether further intervention is required.

INTRODUCTION

Osteoarthritis (OA) can be considered an illness—that is, the clinical manifestations of a disease for which people seek care—and a disease—that is, the structural changes at the joint level that are associated with OA. The focus of this chapter is the assessment of the “illness” of OA; specifically, the assessment of clinical severity and the consequences of OA from the patient's perspective are discussed.

To address this topic appropriately, the chapter adopts a biopsychosocial model, which focuses on health as an interaction of individual, social, and environmental factors, rather than a biomedical perspective of OA, which views disease as a malfunction of the physical body or somatic pathologic process and includes the presence of the related somatic signs and symptoms. For example, when a strictly biomedical model is used, OA pain is viewed as resulting from a nociceptive transmission arising from the inflamed or damaged joint and surrounding soft tissues.¹ However, use of such a model makes it difficult to explain a number of clinical observations in OA, such as why people with similar OA severity as determined radiographically may experience very different levels of pain or other symptoms.² This imperfect correlation between disease and illness in OA is largely due to the well-documented influence on OA symptoms of not only biologic and physiologic factors but also social, cultural, and personal factors as well as individual subjectivity.³ For example, a large body of work has shown that more supportive relationships are associated with positive psychological and physical health and that the reverse is also true.^{4,5} The impact of social support on health may be direct, for example, by affecting self-esteem or health behaviors (e.g., adherence to therapy), and/or indirect (i.e., a buffering effect or reduction of stress, which positively affects health).⁶ Consistent with this thinking, better coping in OA has been linked to reduced pain and fewer symptoms of depression and anxiety,⁷ and greater self-efficacy has been shown to predict higher thresholds for and tolerance of pain.⁸ Altogether, studies performed to date in OA suggest a relationship between OA pain and mood that is mediated by factors such as self-efficacy and coping

strategies, and modified by social support, age, and gender. Using such a biopsychosocial perspective implies that the assessment of the patient with OA, whether in clinical practice or in clinical research, should ideally incorporate the evaluation of all these factors.

DIFFERENCES BETWEEN PATIENT ASSESSMENT IN CLINICAL RESEARCH AND IN ROUTINE CLINICAL PRACTICE

The requirements for assessments of health status in clinical research are similar to those in clinical practice. In both environments, health status measures are required to be ethical and their scores valid, reliable, and responsive, as is described in more detail in Chapter 2. There are, however, several important differences, the most important being that in routine clinical care the focus is on individual patients, rather than on groups of patients. This focus on the individual requires higher standards of reliability to ensure that measurement error is minimized so that clinicians can be confident in the estimates of health status measure scores and, consequently, in their ability to quantify change in status. In contrast, clinical research most often focuses on groups. For the remainder of this chapter, the focus is on evaluation of individuals with OA in the context of clinical research.

THE WORLD HEALTH ORGANIZATION'S INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY, AND HEALTH

The use of a conceptual framework to guide one's selection of measures is increasing. The International Classification of Functioning, Disability, and Health (ICF),⁹ developed by the World Health Organization, is a conceptual model that has been widely adopted in rheumatology. The ICF model espouses a biopsychosocial perspective; it proposes complex interactions between *biologic impairments* (loss or abnormality in body structure or physiologic function, including mental functions, e.g., joint pain, fatigue, and mood in OA), *activity limitations* (difficulties an individual may have in executing activities, e.g., walking in OA), *participation restriction* (problems an individual may experience in carrying out valued activities, e.g., travel or work), and *key contextual factors*, both personal (e.g., age, gender, and coping behaviors) and environmental (e.g., use of arthritis health care and social services), which may facilitate or hinder performance across ICF components (Fig. 178.1).

SELECTION OF MEASURES FOR EVALUATION OF PATIENTS WITH OSTEOARTHRITIS

Examination of physical signs of osteoarthritis

The skill, knowledge, and ability to conduct a thorough interview and physical examination are generic requirements in rheumatology (see Chapter 28). Through a combination of verbal, tactile, and visual cues, an impression is gained regarding the nature, severity, and consequence of the condition. Chapter 173 provides a detailed review of the clinical features of OA. As in the clinic, in clinical research the following features should be assessed: bony enlargement, tenderness on palpation, passive crepitus, pain on motion, presence of erythema, and effusion or soft tissue swelling. Joint

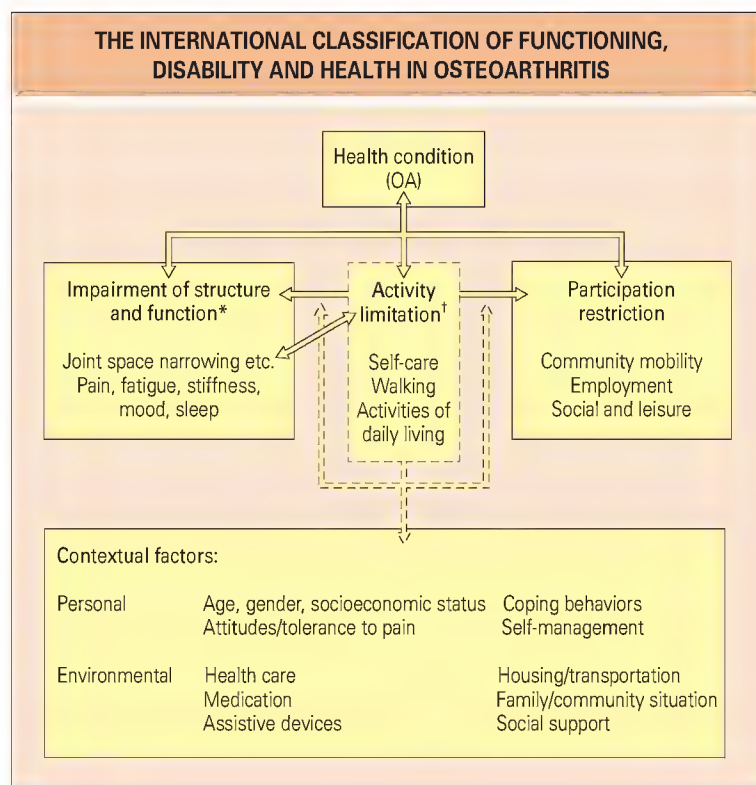


Fig. 178.1 Conceptual framework showing complex interactions between biologic impairments, activity limitations, participation restriction, and contextual factors in osteoarthritis (OA).

*Signs and symptoms of disease, both primary and secondary, include joint space narrowing and other structural features of OA, as well as pain, stiffness, fatigue, and other aspects of health, including sleep disruption.

†Activity limitation is referred to as *function or physical disability* in arthritis measures. (From World Health Organization. *International classification of functioning, disability and health*. Geneva: World Health Organization; 2001.)

instability and malalignment, indicating biomechanical abnormality, may also be assessed. However, although the specifics of the examination are unchanged, as noted already, standardization of the assessment is key in the clinical research setting.¹⁰ Training of joint assessors is therefore generally required before study initiation to ensure high agreement within and between assessors on joint findings (i.e., high intrarater and interrater reliability).

The distribution and number of involved joints in OA is often recorded on a joint homunculus, indicating, for example, involvement of the first carpometacarpal joints of the hands, first metatarsophalangeal joints of the feet, hip joints, or knee joints. Pain in the lower back is also often documented. Separate homunculi may be used to indicate tender and/or painful joints versus those that are stiff and/or swollen. This simple descriptive exercise provides a basis for tracking the disorder's evolution—for example, in longitudinal observational studies and in clinical trials in OA—to assess the number of “other painful joints” as a covariate to consider in evaluating response to a therapeutic intervention of an “index” or specifically targeted single painful joint.

Symptom reporting using standardized questionnaires

The selection of specific measures depends on the measurement objective. Measurement may be conducted at the level of an individual joint (e.g., left knee) or anatomic region (e.g., lower extremity or hands), the disease in its entirety (e.g., overall OA), or the person as a whole (e.g., health status or health-related quality of life [HRQOL]). Furthermore, one or more aspects of the condition may be the focus of assessment (e.g., pain, fatigue, and/or function). Therefore a battery of measures, used in combination, may provide a more robust evaluation. The general measures of HRQOL provide an appreciation of an individual's overall condition. However, these measures lack the necessary content and attribution to understand the specific status of the musculoskeletal condition, because health status and HRQOL scores are often influenced by comorbidities. For this reason, it is generally recommended that generic health status or HRQOL measures be used together with disease-specific measures.¹¹

In clinical research, as in practice, the use of standardized questionnaires, ideally completed by the patient, is highly recommended wherever possible. Such patient-reported outcome measures are much less labor intensive to use than those that require administration by an interviewer. The availability of electronic data capture has further facilitated the process of questionnaire completion and data entry when such measures are used, improving data quality in clinical research. Administration of these tools also needs to be standardized for optimal data quality. For example, attention must be paid to standardization of the timing and/or order of questionnaire administration and standardization of physical assessments, because variability may affect the results obtained.

Among people living with OA, pain, stiffness, fatigue, and associated changes in mood (e.g., depression and anxiety) and sleep are key concerns. Recently, increased attention has been paid to better understanding these symptoms in OA with a view to evaluating the adequacy of existing measures and, when needed, developing new measures. This work has identified some limitations to the current tools available to clinicians and researchers to evaluate these symptoms in OA. Many of these tools were not developed specifically for use in this condition but rather as generic measures and/or for use in other clinical conditions. As a result, new OA-specific measures are emerging. Although a detailed review of all measures available to evaluate pain, fatigue, stiffness, sleep, and mood in the context of OA is beyond the scope of this chapter, the most commonly used measures to date in OA clinical research are discussed here. Table 178.1 provides a summary of selected generic, arthritis-specific, and OA-specific measures; Table 178.2 shows the ICF domains that are assessed by commonly used measures. Many of these measures may also be suitable for use in clinical practice.

Assessment of pain

The instruments most often used to date to evaluate pain in OA include both generic pain measures, most notably a visual analogue scale or numeric pain rating scale,¹² the McGill Pain Questionnaire,¹³ and the SF-36 bodily pain scale,¹⁴ and arthritis-specific measures, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (specific to hip and knee OA)¹⁵ and the Australian-Canadian Hand Osteoarthritis Index (AUSCAN; specific to hand OA).¹⁶ Of the listed arthritis-specific measures, only the WOMAC and AUSCAN indexes, which are both composed of subscales evaluating pain, stiffness, and physical functioning, were developed specifically for use in OA. A number of other pain measures exist but have been less often applied to the OA population.

Recent qualitative research in hip, knee, and hand OA, which has elucidated the key elements of the OA pain experience, has raised concerns about the adequacy of these measures to evaluate pain in OA.¹⁷ Studies have found that the OA pain experience is characterized by the intensity or severity of the pain, the quality or characteristics of the pain (e.g., burning, stabbing, aching), the relation of the pain to activity and thus the impact on functioning and participation, the effect on sleep, and the psychological consequences (e.g., frustration because of the inability to do things that were valued as well as worry about the future).¹⁷ Review of the items and domains of existing pain measures, both generic and OA specific, indicates that most widely used measures do not fully capture the OA pain experience. To address this gap, the Osteoarthritis Research Society International–Outcome Measures in Rheumatology Clinical Trials (OARSI-OMERACT) Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) has been developed, which evaluates two domains of pain, including intermittent and constant pain, as well as the predictability of intermittent pain using two supplementary questions.¹⁸ It is intended for use alongside a measure of physical disability. The ICOAP has demonstrated reliability, validity, and responsiveness.¹⁷⁻¹⁹

Another recent development is the mounting evidence to suggest that central sensitization may contribute to the pain experience in a subset of people with symptomatic OA.²⁰ Central sensitization in OA may lead to an altered pain phenotype characterized by neuropathic-like symptoms and somatosensory abnormalities.²⁰⁻²² Symptom-based measures including the painDETECT questionnaire have been developed and validated to identify a neuropathic component to pain in other chronic pain populations.²³ A few knee and hip OA studies have employed neuropathic pain symptom measures.^{22,24,25} A knee-specific version of painDETECT, the modified pain-DETECT, has been developed to assess neuropathic-like symptoms in individuals with painful knee OA.²² Preliminary evidence suggests that this measure is valid and reliable; however, validation work is ongoing.²⁶

Assessment of fatigue

Research indicates that fatigue is as common a complaint in OA as in inflammatory arthritis^{27,28} and has a similar negative impact on HRQOL.²⁹ Others have acknowledged the multidimensionality of fatigue in OA—physical,

TABLE 178.1

Selected outcome measures for use in osteoarthritis clinical research

Construct	Generic	Measures to consider		
		Arthritis specific	OA specific	
			Hip/knee	Hand
Health-related quality of life (HRQOL)	SF-36 Health Utilities Index (HUI)	AIMS2 Health Assessment Questionnaire (HAQ)	OAKHQOL	
Pain	Visual analogue scale Numeric rating scale SF-36 bodily pain scale McGill Pain Questionnaire Chronic Pain Grade Scale	Joint homunculus	WOMAC pain Lequesne Indices ICOAP	AUSCAN Cochin
Fatigue	Visual analogue scale Numeric Rating Scale Profile of Mood States Fatigue Scale Functional Assessment of Chronic Illness Therapy Multidimensional Fatigue Symptom Inventory			
Subjective sleep quality	Visual analogue scale Numeric rating scale Pittsburgh Sleep Quality Index Sleep Disorders Questionnaire Chronic Pain Sleep Inventory			
Mood	SF-36 mental component score Center for Epidemiologic Studies Depression Scale (CES-D) Beck Depression Inventory Hospital Anxiety and Depression Scale (HADS)			
Activity limitation	SF-36 physical component score 50-ft walk time Timed chair stand test Timed up and go test Jebsen-Taylor Hand Function Test	AIMS2	WOMAC function Lequesne Indices HOOS/KOOS	DASH AUSCAN Cochin FIHOA

AIMS2, Arthritis Impact Measurement Scales 2; AUSCAN, Australian-Canadian Hand Osteoarthritis Index; Cochin, Cachin hand functional disability scale; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; FIHOA, Functional Index for Hand Osteoarthritis; HOOS, Hip Disability and Osteoarthritis Outcome Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; ICOAP, Measure of Intermittent and Constant Osteoarthritis Pain; OAKHQOL, Osteoarthritis Knee and Hip Quality of Life; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

emotional, and mental fatigue—and the relationship of OA fatigue to OA pain and pain medications, aging, and poor sleep.²⁸ Currently, no OA-specific fatigue measures exist. The available generic measures of fatigue that might be used to evaluate fatigue in OA clinical research include those that conceptualize fatigue as unidimensional—that is, they provide a single evaluation of overall or “general” fatigue—and those that consider fatigue as multidimensional. The former include the visual analogue scale or numeric rating scale, and two other measures, the Profile of Mood States Fatigue Scale (POMS-Fatigue)³⁰ and the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue),³¹ all of which have been used in the setting of inflammatory arthritis. In comparison, the Multidimensional Fatigue Symptom Inventory (MFSI)³² assesses the many aspects of fatigue that have been identified as important in focus groups of people with OA,^{28,33} including both mental and physical fatigue, and has good psychometric properties. A number of these measures have been used in observational OA research studies, which have found that fatigue measures relate significantly to measures of pain, depression, disability, and sleep.^{28,34}

Assessment of sleep

A number of self-completed measures are now being applied in the OA population to evaluate subjective sleep quality in people with this condition. These include the Pittsburgh Sleep Quality Index (PSQI)³⁵; the Sleep Disorders Questionnaire³⁶; the Chronic Pain Sleep Inventory,³⁷ which has been validated for assessment of sleep disturbances in individuals with chronic pain³⁸; and the use of sleep diaries. Many of these measures incorporate a cut-point score that may be used to discriminate individuals with “poor sleep” or possible underlying sleep disorders from those without. Several of these measures have now been validated for use in hip and knee OA.

Assessment of mood

Depressed and/or anxious mood is common among people living with chronic, painful OA. This has relevance for the assessment and interpretation of scale scores for OA pain and fatigue because both these outcomes

may be strongly influenced by the presence of mood disorders.³⁹ Although a number of measures are available, mood has been most often evaluated in clinical studies of OA using the Center for Epidemiologic Studies Depression Scale (CES-D),⁴⁰ the Beck Depression Inventory,⁴¹ and the widely validated anxiety or depression subscales of the Hospital Anxiety and Depression Scale (HADS).⁴² Of note, the CES-D measures depressive symptoms; age- and sex-adjusted normative values are available, and scores of 16 or higher are considered indicative of significantly depressed mood.

Assessment of activity limitations and participation restrictions in osteoarthritis

Measures of joint tenderness and/or swelling, muscle strength, and joint range of motion provide information about impairment but not about activity limitations or participation restrictions, which are the consequence to the individual of these impairments. Thus these measures generally require supplementation with specific measures of activity limitations and participation restrictions.

Measurement of activity limitations using standardized questionnaires

Standardized questionnaires, many of which are patient self-reported as opposed to interviewer administered, have also been developed to evaluate activity limitations or physical functioning. Although many of these measures have been developed with the idea that the content reflects functioning of a specific joint and hence are considered to be joint-specific measures, the items often reflect activities that involve the entire extremity or functional unit (e.g., walking). Measures that assess activity limitations due to hand OA are different from those used to evaluate hip or knee OA; however, overlap in the content of measures used for OA of joints within an extremity does occur (e.g., hip and knee).

The most commonly used generic measure for hip and knee OA is the physical function subscale of the SF-36.¹⁴ This 10-item measure does include

TABLE 178.2
International Classification of Functioning, Disability, and Health (ICF)
domains assessed by selected outcome measures*

Measure	ICF domain		
	Impairments	Activity limitations	Participation restrictions
Generic measures			
SF-36	Pain Mental health General health Vitality	Physical functioning	Social functioning
Arthritis- and osteoarthritis-specific measures			
WOMAC	Pain++ Stiffness	Pain++ Physical function	
KOOS/HOOS	Symptoms Stiffness Pain† Quality of life++	Pain† Function, daily living Function, sports and recreational activities	Quality of life+
Lequesne Indices	Pain+ Stiffness	ADL knee ADL hip++ Pain++ Walking	ADL hip+
OAKHQOL	Pain/sleep Mental health	Physical activity	Social activities

*Scales within some measures include items that assess more than one ICF domain; where this is the case, + and ++ are used to refer to the distribution of the items; ++ indicates the domain assessed by most items within the scale, whereas + indicates that some items also assess this domain.
†For the HOOS and KOOS, the pain subscale includes approximately equal numbers of items assessing impairments and activity limitations.
ADL, activities of daily living; HOOS, Hip Disability and Osteoarthritis Outcome Score; KOOS, Knee Injury and Osteoarthritis Outcome Score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

some upper extremity items, however, and represents the physical function of the person more globally. As noted previously, such generic measures should be used in conjunction with disease-specific measures.

Arthritis-specific and so-called joint-specific measures have also been used. For the hip, these include the WOMAC index,¹⁵ the Lequesne Indices of Clinical Severity—Hip,⁴³ and the Hip Disability and Osteoarthritis Outcome Score (HOOS).⁴⁴ For the knee, the WOMAC index, the Lequesne Indices of Clinical Severity—Knee, and the Knee Injury and Osteoarthritis Outcome Score (KOOS)⁴⁵ are most commonly used. The WOMAC physical function subscale includes the same 17 items for the hip and knee and a summated score is created. The measure has been extensively evaluated across the spectrum of severity of hip and knee OA.⁴⁶ However, there has been recognition that the WOMAC index may not include items of sufficient difficulty.⁴⁷ To address this limitation, the HOOS⁴⁴ and KOOS⁴⁵ were developed. These measures include the 17 physical function items of the WOMAC Likert 3.0 (referred to as the *Function, daily living subscale*) as well as a subscale of higher-demand activities, sport and recreational activities (referred to as the *Function, sports and recreational activities subscale*). The HOOS and KOOS scores have demonstrated reliability, validity, and responsiveness.^{44,45} The HOOS and KOOS physical function subscales also are available as short measures and were developed in a population with a spectrum of OA severity.^{44,48,49}

Finally, the Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) instrument has been developed to evaluate HRQOL in individuals with hip and knee OA.⁵⁰ The OAKHQOL tool has demonstrated reliability and validity and has been found to capture the ICF domains better than other measures commonly used to evaluate HRQOL in OA, including the SF-36, WOMAC, and Lequesne instruments.⁵¹

For OA of the upper extremity, generic upper extremity measures, such as the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, have been used to evaluate OA-related hand function.^{52,53} The measurement properties of the DASH questionnaire have been evaluated in hand OA,⁵³ and a shorter version, the quick DASH, has also been developed.⁵⁴

Arthritis-specific upper extremity and/or hand measures have also been developed. The Arthritis Impact Measurement Scales (AIMS) have a dexterity subscale that can be used to evaluate one aspect of hand function, but the more specific measures of hand function for OA include the Cochin hand functional disability scale,⁵⁵ the AUSCAN index,¹⁶ and the Functional

Index for Hand Osteoarthritis (FIHOA).^{56,57} The Cochin scale, originally developed for people with rheumatoid arthritis, has been evaluated in people with hand OA and found to be reliable, valid, and responsive.⁵⁵ The AUSCAN index was specifically developed to evaluate hand OA and has been evaluated for reliability, validity, and responsiveness in this condition.¹⁶ The FIHOA evaluates 10 daily activities involving the hands and was developed as a clinical tool for evaluation and symptomatic follow-up of patients with hand OA. This tool has also been evaluated for reliability, validity, and responsiveness.^{56,57} The aforementioned tools represent a sampling of the most frequently used questionnaires for evaluation of physical functioning and activity limitations in hip, knee, and hand OA.

These questionnaires rely on the patient's self-assessment of his or her functional ability or capacity and, as with any measure, scores inherently include sources of measurement error. When someone no longer engages in an activity (e.g., heavy housework), whether due to a disease, lack of necessity, or personal choice, responses to questions may not be an accurate reflection of the degree of impairment. For this reason, performance-based measurement may also be useful.

Performance-based assessment of impairments and activity limitations

Performance-based measures evaluate different components of function than those assessed by patient self-report and may augment the assessment of physical functioning in individuals with OA.⁵⁸ These performance-based measures assess performance of a standardized maneuver, such as walking or rising from a chair, in a controlled setting. Results of such assessments generally correlate only moderately with assessment of similar constructs using self-report measures.⁵⁸ Some work indicates that self-report measures tend to overestimate performance, which suggests a difference between what people perceive they can do and what they actually can do.⁵⁸

For evaluating lower extremity performance, the 50-foot (or other specific distance) walk time, the timed chair stand test, and the timed up and go (TUG) test⁵⁹ are most frequently used in clinical trials and observational studies of hip and knee OA. The timed chair stand test evaluates lower extremity body strength as an indicator of functional status and has been assessed for reliability and validity.⁵⁹ The TUG test assesses basic mobility skills and has been validated for use in hip and knee OA patients awaiting joint replacement surgery. Standardized grip strength and pinch grip measurements, in addition to more comprehensive generic hand function tests, like the Jebsen-Taylor Hand Function Test,⁶⁰ are useful assessments in hand OA. These measurements can be performed reliably by trained assessors.⁵⁹

Assessment of participation restrictions

The impact of arthritis on diverse social roles like relationships with others, occupation, leisure, and community involvement has been identified as a key area of importance in research and practice.⁶¹ However, to date, there has been little evaluation of participation restriction, and assessment of the impact of OA has focused largely on the impact of the disease in terms of impairment and activity restriction (see Table 178.2). The Jette Late-Life Function and Disability Instrument,⁶² which evaluates difficulty with and frequency of participation in a social context (e.g., leisure, social activity, travel, management of health, personal finances), has been used in a study of people undergoing joint replacement for OA.⁶³ Although detailed evaluation of the measurement properties of the tool in OA is lacking, participation was shown to change over the course of the first year of recovery following joint replacement.⁶³ Development and evaluation of measures of participation in people with OA is ongoing.^{64,65}

Evaluation of key contextual factors

As noted earlier, it should be appreciated that a number of contextual factors, including but not limited to the patient's sociodemographic characteristics, education and income, coping style, self-efficacy, social support, and access to and use of health care strategies for arthritis, influence OA impairments, activity limitations, and participation restrictions. Standardized, valid, and reliable measures exist to evaluate these constructs, and depending on the intent of the research, these factors may also warrant evaluation to aid in interpretation of research findings.

RESPONSIVENESS AND INTERPRETATION OF CHANGE IN PATIENT STATUS

Longitudinal assessment of patients, whether in the context of a clinical trial or an observational cohort study, implies the need for measures that can detect meaningful changes in clinical status (i.e., *responsiveness*) as well as

an understanding of what a measured change means for the patient (i.e., *interpretation of the measured change*). Differentiating real change from change occurring within measurement error can also be difficult. It is critical to remember that responsiveness and the interpretation of change, like reliability and validity, are a function of the measure score and context interaction. For this reason, the responsiveness metrics and interpretation for a measure are represented by a range of values based on the varying contexts (e.g., it will differ by the patient sample and type of intervention).

Responsiveness of measure scores

At the group level, responsiveness of a measure is evaluated by an estimate of the effect size. It can be calculated to reflect within-subject change, between-subject change, or both. In the case of paired observations, this effect size is called a *standardized response mean*. The calculation reflects the nature of the paired or unpaired data.

Interpretation of changes in measure scores

There are numerous approaches to interpreting change at the individual level. These include the *minimally clinically important difference* (MCID), threshold methods such as the *patient acceptable symptom state*, and *responder criteria*. The essence of the issue in interpreting change relates to whether measured change reflects *meaningful* change to patients. Thus OA researchers have sought to determine the MCID for various generic and OA-specific measures commonly employed in OA clinical research using a variety of approaches and for different clinical research settings, such as in randomized trials of rehabilitation⁶⁶ and pharmacologic treatments in OA.⁶⁷⁻⁶⁹ The MCID represents the minimum amount of improvement that patients perceive as beneficial.⁷⁰

Both distribution-based and anchor-based methods have been used to establish clinically meaningful change. With a distribution-based method, the effect size may be used to define MCID. However, the U.S. Food and Drug Administration now requires that anchor-based methods be used to determine the MCID when making claims for interventions. Anchor-based methods rely on determining the amount of change in relation to an external indicator of change, usually a patient global rating of how much better or worse he or she is from “slightly” to “a great deal” better or worse.⁷⁰ The MCID is often defined as the mean difference in the change score for patients who rated themselves as “slightly better” after treatment and those who rated themselves as “equal” to their pretreatment level. When this approach

is used, varying MCID definitions for the commonly used OA measures, such as the WOMAC pain and function subscale scores, have been recommended.^{15,71,72}

A threshold approach has also been used to interpret change in OA symptoms and functioning over time. This approach considers that small or large change may occur but that it is not important change if it has not reached a critical threshold value or “state.”⁶⁹ This threshold may be determined by various methods, such as adopting a known population value (e.g., reaching the minimal required physical activity for energy output that has a positive health effect) or a patient-determined value of a “patient-acceptable symptom state,” as has been done in hip and knee OA.^{69,71,72}

Finally, responder criteria have been developed to evaluate meaningful change in pain, function, and patient global assessment using available OA measures. The OMERACT-OARS responder criteria⁷³ have been developed for use in hip and knee OA. Use of these criteria requires that the patient have a certain minimum score before intervention; otherwise, it is impossible for the patient to improve sufficiently to be designated as a “responder,” even if improvement does occur. Comparable criteria for hand OA, including MCID, patient-acceptable symptom state, and responder criteria have not yet been developed.

Changes in patient status over time can be monitored over an extended period using a combination of responder and state attainment criteria. The relationship between responder criteria and state attainment criteria can be best exemplified by the statement, “It is good to be better, but better to be good.”⁶⁹ In addition to the OMERACT-OARS responder criteria, additional responder criteria that have been proposed for OA include minimum perceptible clinical improvement,⁶⁸ minimum clinically important improvement,⁷⁴ and the WOMAC 20-50-70 responder criteria.⁷⁵

CONCLUSION

An essential element in the evaluation of individuals with OA, whether in clinical practice or clinical research, is the need for reliable, valid, and responsive outcome measurement tools. Although many such tools exist for the rheumatologist's use, the sophistication with which these tools are used has increased substantially. This is attributable largely to increased reliance on conceptual models, like the ICF, to inform the selection and interpretation of measures and potentially their interrelationships, and an increased emphasis on identifying and measuring constructs that are important and meaningful to individuals living with OA.

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Preclinical osteoarthritis

■ VIRGINIA BYERS KRAUS

- Preclinical osteoarthritis (OA) is the early phase of the disease before abnormalities are apparent on a sensitive imaging modality such as ultrasound or magnetic resonance imaging.
- The strongest evidence for the existence of preclinical OA is provided by the sequence of changes in biomarkers and pathologic stages observed after a major joint injury; this paradigm provides hope that these observations can be translated into diagnostic algorithms for the early detection of idiopathic OA.
- Conventional OA risk factors function poorly for detection of preclinical OA.
- Early diagnosis and intervention in OA would improve the likelihood of disease modification and thereby reduce medical costs, morbidity, and disability.
- Reclassification of the disease as no longer a purely radiographic entity to a disease process that includes preclinical, preradiographic, and radiographic stages would provide a scenario amenable to the development of primary, secondary, and tertiary prevention strategies.

DEFINITION

Preclinical disease is defined as the very earliest phase of a disease process before it becomes clinically recognizable. Alternatively, it is the phase before the appearance of symptoms. For osteoarthritis (OA), clinically recognizable disease has generally been synonymous with the appearance of radiographic changes of OA, including joint space narrowing and osteophyte formation. With the advent of more sensitive imaging techniques, preradiographic stages of disease are recognizable; both magnetic resonance imaging (MRI)¹⁻³ and ultrasound^{4,5} have provided concrete evidence of structural joint abnormalities predating the quintessential radiographic changes associated with OA. These imaging techniques establish a new threshold for what constitutes definitive “clinically recognizable” disease.

It is currently difficult to define preclinical OA as the stage that predates symptoms for two reasons. For one, joint symptoms can be ascribed to multiple causes, and thus symptoms outside the context of the clinically recognizable structural changes of OA cannot currently be definitively diagnosed as being attributable to an OA disease process. Moreover, symptoms of OA wax and wane and might appear and disappear during the preclinical phase of OA, just as they do during the clinically recognizable phases of disease (see Chapter 173 for a discussion of the symptoms of OA). Until our understanding and diagnosis of the cause of early joint symptoms improve, this potentially waxing and waning symptom threshold abrogates our ability to currently define preclinical OA as a presymptomatic stage. Therefore the focus of this chapter is on preclinical OA constituting the early phase of disease before OA-related abnormalities are detectable with MRI or ultrasound (or other sensitive imaging modality) (Fig. 179.1).

Of note, the “preclinical OA” described here should be distinguished from “preclinical models of OA,” which refer to animal models of disease⁶ and are discussed in Chapter 174.

EVIDENCE FOR PRECLINICAL OSTEOARTHRITIS

The World Health Organization defines chronic diseases as being of long duration and generally slow progression (www.who.int/topics/chronic

diseases/en/). Chronic diseases are characterized by complex causality, multiple risk factors, long latency periods, a prolonged course of illness, and functional impairment or disability (www.aihw.gov.au/chronic-diseases/). Many conditions can be considered chronic diseases, including coronary heart disease, chronic obstructive pulmonary disease, and osteoporosis. These chronic diseases are viewed as being amenable to preventive measures; such perception has led to the development of public health strategies to encourage healthy environments and lifestyles. For instance, it has led to efforts to control blood pressure and serum cholesterol levels to reduce the burden of heart disease and stroke. OA fits this chronic disease paradigm well. Such recognition that OA fits this chronic disease paradigm would be expected to broaden the scope of study beyond a focus on diagnosis, monitoring, and treatment of end-stage radiographic disease to include efforts to identify and characterize the preclinical and preradiographic stages to spearhead more effective endeavors to reduce the burden of disease.

The strongest evidence for the existence of preclinical OA is provided by the sequence of pathologic stages observed after a major joint injury. Unlike primary idiopathic OA, posttraumatic OA has a known time of onset, which makes it much more tractable as a method for detecting and monitoring preclinical OA. Based on longitudinal studies, intraarticular pathogenic processes initiated at the time of injury result in radiographic OA 10 to 20 years later.⁷ Longitudinal studies of the aftermath of severe joint injury have convincingly established the existence of a prolonged preclinical molecular phase of the disease characterized by protein and microRNA biomarker abnormalities.⁸⁻¹⁷ After knee injury, cartilage degradation is favored over repair, with increased collagen cleavage taking place.¹⁸⁻²⁰ Within the first month after joint injury in humans, elevations have been documented in the synovial fluid concentrations of cartilage proteoglycan fragments,^{8,20} metalloproteinases (MMP-3/stromelysin-1),^{10,13} tenascin-C,¹⁶ and collagen fragments.²⁰ Aggrecanase cleavage of aggrecan (at 392Glu-393Ala in the interglobular domain) is one of the early key events in arthritis and joint injuries.^{14,15} Elevations of cartilage components in serum can persist over decades after joint injury.⁹⁻¹³ The sustained increased release of cartilage macromolecular fragments after joint trauma is thought to be a harbinger for the development of posttraumatic radiographic OA in patients with injuries. Many of these fragments are not only biomarkers of early disease pathology but could themselves also act to induce and prolong inflammation following joint injury^{16,21} and therefore represent biomarkers within the causal pathway of disease.

In the course of idiopathic (primary) OA devoid of a clear inciting severe acute injury, it is difficult to track the early events. Nevertheless, a few studies have identified premonitory alterations in biomarkers that herald the later appearance of idiopathic radiographic OA. In one study, patients in whom radiographic OA of the hand or knee developed 10 years later had significantly different serum concentrations of four proteins (increased MMP-7, increased interleukin-15, increased plasminogen activator inhibitor-1, and decreased soluble vascular adhesion protein-1) when compared with controls without radiographic OA in the ensuing decade.²² In another study, serum concentrations of the joint tissue components cartilage oligomeric matrix protein (COMP) and hyaluronan (HA) predicted the occurrence, 7 years later, of incident knee joint space narrowing (COMP and HA) and osteophyte formation (COMP).²³ Several studies have suggested that serum COMP predicts the development of radiographic hip OA between 6 and 8 years later.^{24,25} COMP is also increased in the absence of signs of radiographic hip OA in patients with symptoms of hip abnormality.²⁶ These biomarker abnormalities years before idiopathic radiographic OA support the existence of a preclinical phase of OA characterized by serologic abnormalities reflecting preclinical molecular alterations. The existence of preclinical OA is also suggested by the finding of macroscopically

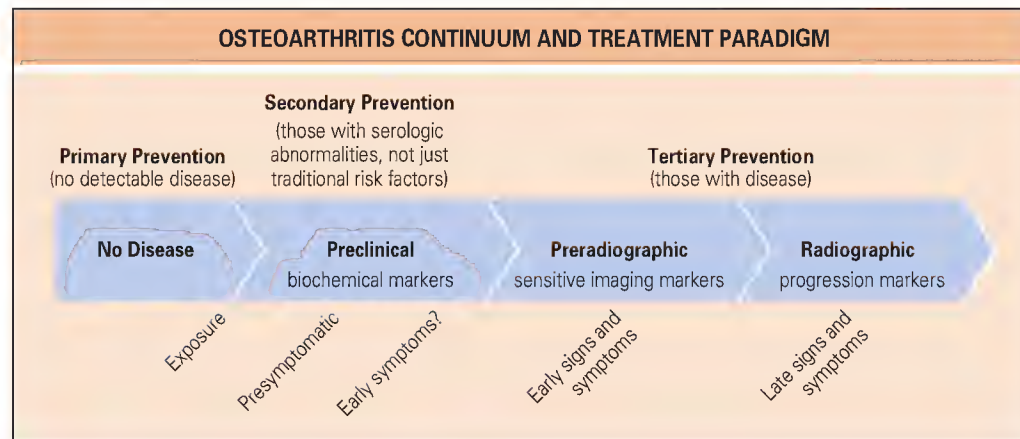


Fig. 179.1 In this schema, osteoarthritis (OA) progresses through stages. Although tools for identifying preclinical OA are limited, events ensuing from acute joint injury attest to the existence of a relatively prolonged asymptomatic preclinical phase of OA before a preradiographic and, later, a radiographic stage. Each of these phases demands a different intervention strategy: the earliest preclinical phase with no apparent illness calls for primary preventive interventions to protect the health of the joint and prevent the appearance of clinically recognizable stages of disease; the preradiographic phase of clinically recognizable but early disease requires secondary preventive measures to halt or slow progress of the disease, if possible, in its earliest stages; the radiographic phase of OA calls for tertiary preventive measures to prevent or reduce the illness of OA, namely the symptoms and disability in the face of a long-term health problem.

degenerated cartilage from cadaveric donors without a clinical history of OA.²⁷ Taken together, these studies demonstrate that metabolic alterations in articular cartilage occur long before radiologic changes are observed and support a chronic disease paradigm for OA that includes a preclinical phase as depicted in [Figure 179.1](#).

DETECTION OF PRECLINICAL OSTEOARTHRITIS

About half the people with knee pain do not have radiographic OA.³ How might those with joint symptoms attributable to preclinical OA be discerned from those with joint symptoms resulting from some other cause? Attempts to identify preclinical OA and subsequent risk for clinically recognizable OA currently rely on a combination of conventional risk factors and the presence of cardinal signs and symptoms of OA. However, baseline conventional risk factors, signs, and symptoms have limited ability to predict subsequent incident radiographic OA 3 to 12 years later.^{28,29} For instance, the use of 10 diagnostic criteria in one study (age, sex, body mass index, previous injury, pain in the entire leg, difficulty descending stairs, palpable effusion, fixed flexion deformity, restricted knee flexion range of motion, and coarse crepitus) was poorly predictive of incident radiographic knee OA 3 years later, with an area under the receiver operating characteristic curve of just 0.59.²⁹ Another long-term (12-year) study that monitored subjects with and without baseline clinical signs and symptoms of OA (crepitus, morning stiffness, knee bone enlargement, and age >38 years) but no baseline radiographic OA suggested an annual development of incident radiographic knee OA of 6.5% in the absence of clinical OA and 7.5% in the presence of clinical OA.²⁸ The limited prognostic ability of conventional risk factors is probably due in part to the fact that the progression from risk factor exposure to the development of radiographic OA depends on the variable likelihood that individuals exposed to the same risk factors will progress through the stages of preclinical OA to preradiographic OA to radiographic OA.

PROGRESSION OF OSTEOARTHRITIS

Because not all radiographic OA progresses to a severe grade of disease or results in joint replacement, by inference, probably not all preclinical or preradiographic OA progresses to more advanced stages of disease ([Fig. 179.2](#)).^{7,28,30} Several hypotheses are encompassed in the graphic in [Figure 179.2](#) in which OA is depicted as a continuum (preclinical to preradiographic to radiographic). One, the rate of progression of OA accelerates with increasing severity of disease. Two, degradation and repair occur simultaneously at all stages of disease (small turning wheels reflecting turnover rates); the greater the degradation rate, the greater the synthetic repair required to meet the demands of the catabolic events (ever larger turnover cycles as the individual progresses further along the trajectory to OA). Third, an excess of catabolism over anabolism drives the trajectory to radiographic OA. Fourth, the mechanisms of progression will probably not be uniform in all

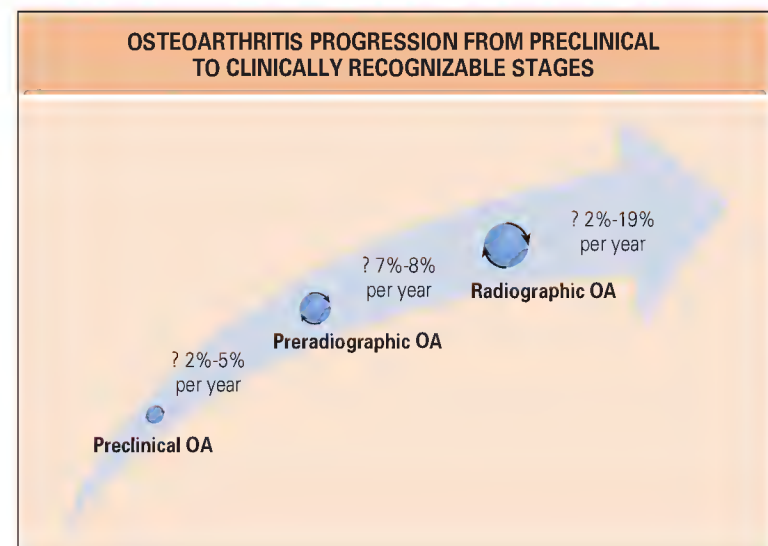


Fig. 179.2 At present, rates of evolution from preclinical to preradiographic to radiographic osteoarthritis (OA) are not precisely known. After a severe acute knee injury, the annual rate of progression in the preclinical phase of OA must be at least 2% to 5% annually to account for the overall average risk for development of radiographic OA of 50% by 10 to 20 years later⁷; under less extreme circumstances the rate is probably lower. Knowledge of rates of progression to radiographic OA from preradiographic OA are limited but may be estimated at 7% to 8% annually given the current information available.²⁸ The rate of progression of radiographic OA to more severe radiographic stages is estimated to be 2% to 19% annually based on calculations using data from the placebo arms of a number of studies (summarized by Manno and colleagues³⁰). These figures should be treated as rough estimates in need of refinement through future longitudinal studies with more comprehensive patient phenotyping of different joints and patient subtypes and sensitive imaging and biochemical markers.

OA phenotypes.³¹ Fifth, the proportion of at-risk individuals who proceed along the OA trajectory at any point in this continuum is uncertain.

Surprisingly little is known about the actual rates of progression through each stage. The rate of progression from preclinical OA to preradiographic OA is entirely unknown. In the specialized circumstance of severe acute joint injury, radiographic OA develops in 50% of individuals after an average of 10 to 20 years⁷; this equates to an estimated rate of progression during the preclinical stages of at least 2.5% to 5% annually. As described earlier, the rate of progression from the preradiographic phase to incident radiographic OA may be estimated from one study to be 6.5% to 7.5% annually in the absence or presence of symptoms.²⁸ The rate of progression from

TABLE 179.1

Summary of studies providing estimates of radiographic progression of osteoarthritis*

Study (N in placebo arm)	Study duration (wk/yr)	Subjects with radiographic progression among those with baseline symptoms N progressors/N with symptoms (% progression; % per year)	Subjects with radiographic progression among all subjects N progressors/N total (% progression; % per year)
Hip studies			
Echodiah (136)	156/3	30/52 (57.7%; 19.2%)	30/136 (22%; 7.3%)
Eradias (127)	156/3	24/46 (52.2%; 17.4%)	24/127 (19%; 6.3%)
Knee studies			
Pavelka (54)	156/3	3/14 (21.4%; 7.1%)	3/54 (6%; 2%)
Reginster (69)	156/3	12/26 (46.2%; 15.4%)	12/69 (17%; 5.7%)
Doxy (120)	120/2.31	16/37 (43.2%; 18.7%)	16/120 (13%; 5.6%)
Gait (50)	104/2	4/30 (13.3%; 6.7%)	4/50 (8%; 4%)
Kostar (625)	104/2	55/316 (17.4%; 8.7%)	55/625 (8.8%; 4.4%)
Stopp (163)	104/2	19/68 (27.9%; 14%)	19/163 (11.7%; 5.8%)

Progression is defined as change in joint space width greater than 0.5 mm by study end.

*Data from placebo-treated subjects.

Data derived from Manna RL, Bingham CO 3rd, Paternotte S, et al. OARSI-OMERACT initiative: defining thresholds for symptomatic severity and structural changes in disease modifying osteoarthritis drug (DMOAD) clinical trials. *Osteoarthritis Cartilage* 2012;20:93-101.

preradiographic to radiographic OA is estimated to be 2% to 19% annually based on calculations using data from the placebo arms of a number of studies summarized by Manno and colleagues³⁰ and shown in Table 179.1; higher rates of progression were observed in subsets of subjects with a high symptom load. Further longitudinal studies are needed to provide more precise estimates of progression for each stage of disease and to understand how these rates may differ by patient subsets, joint type, and risk factors. The paradigm of joint injury in humans would seem to be the best place to start to gain such information.

TRIGGERING MECHANISMS

As proposed for other diseases,³² the action of additional potentiating “triggering” mechanisms in the presence of preclinical disease also influences progression to events or, in the case of OA, progression to preradiographic and radiographic OA. Given the waxing and waning nature of symptoms, there is every reason to think that disease progression undergoes nonlinear or phasic progression; this has been supported by the observation that metabolic disturbances in cartilage turnover, as reflected by serum COMP concentrations, are phasic and elevated during periods of radiographic knee OA progression.³³ Molecular differences between the cartilage at different joint sites,^{34,35} and the generation of specific neopeptides from joint tissues with metabolic disturbances, suggest that biomarkers might be developed in the future that reflect disease activity of specific joint types or even of OA specifically. Taken together, biomarkers indicative of joint tissue metabolism could constitute a means of detecting the preclinical molecular stages of OA in advance of preradiographic OA and assess the impact of specific triggering events.

With the recent recognition of a definite and central role for innate immunity in OA²¹ it is now possible to develop a holistic understanding of the pathogenesis of the disease process. From its inception, OA is an active disease process, not just a process of mechanical attrition, involving mechanical insults that activate mechanosensors to induce cellular responses to altered mechanical load, including the induction and activation of specific matrix degrading enzymes³⁶; this propagates inflammation through the generation of molecular fragments that act as disease associated molecular patterns to activate the innate immune response (Fig. 179.3)—a major biologic transducer of disease progression. The cogwheel graphic in Figure 179.3, which symbolizes the ability of cogs to start and stop, portrays the penchant for OA to wax and wane. This representation shows the interaction of inciting mechanical insults and environmental factors, the potentiation by risk factors and genetics, and the resulting activation of an innate immune response and impaired wound healing³⁷ leading to the chronic disease process that we know as OA. Given this newly emerged understanding of the pathogenesis of OA, it is intriguing to speculate that a robust innate immune response would protect against infectious disease, particularly in the pre-antibiotic era, but be deleterious in potentiating age-related

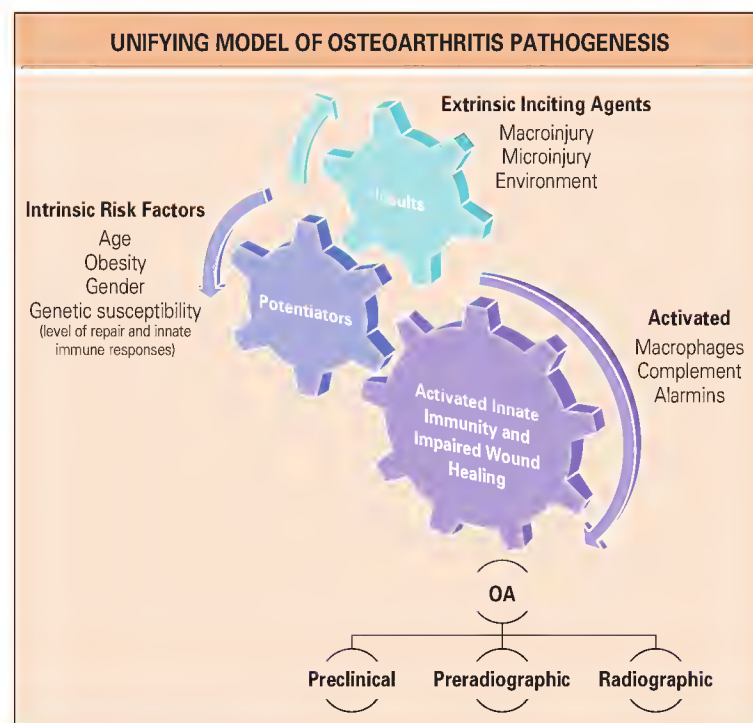


Fig. 179.3 This model depicts osteoarthritis (OA) as a condition incited by the mechanical insults of microinjury, macroinjury, and environmental factors. The interaction of extrinsic inciting insults with potentiating intrinsic factors determines the relative susceptibility to progression of disease mediated by a biologic innate immune inflammatory response analogous to a chronic wound. The resulting pathology is manifested first as a preclinical (not clinically recognizable) entity, with progression in some individuals to preradiographic stages (detected by sensitive imaging modalities) and eventually to radiographic stages. The interacting cogwheels, able to turn intermittently, depict the penchant for OA activity to wax and wane. The exact timing of the onset of the illness of OA that includes symptoms in this continuum of OA pathogenesis is unclear at present.

chronic diseases in our current postantibiotic era characterized by increasing longevity. There are in fact hints that the latter is true based on studies showing that low innate production of cytokines on *ex vivo* stimulation of blood with lipopolysaccharide is associated with a lower risk for OA and the absence of OA in old age.^{38,39} Conversely, a robust repair response would be expected to protect from OA and prevent OA progression along the stages of disease (see Fig. 179.2). The capacity for joint tissue repair differs by

joint type^{35,40} and is likely a key determinant of OA prevalence and rates of progression. Data suggest a joint type specific gradient of repair responses, with ankle>knee>hip repair capacity that would explain the rarity of severe ankle radiographic OA⁴¹ and the apparent greater rate of progression of hip versus knee OA.³⁰ A better understanding of these differences could enhance our ability to identify at risk joints early in the disease development stage.

TREATMENT PARADIGMS

OA is a slow, insidious, and debilitating process that like other prominent chronic diseases, is probably more amenable to remission early in the disease process. Maintenance of cartilage homeostasis would be expected to halt progression of the disease. A tipping of the homeostatic balance in favor of anabolism over catabolism would be expected to reverse the disease. As noted by Luyten and coauthors,⁴² inactivation of inflammation and joint destruction would be sufficient in some patients at a very early stage of the disease; however, additional therapies targeting tissue restoration through cell proliferation and differentiation might be needed to achieve the ultimate goal of complete recovery of structural joint integrity. The pattern of biomarker alterations observed after joint injury matches the pattern of cartilage components released from cartilage stimulated *in vitro* with proinflammatory cytokines.^{20,43} Many treatments exist for *in vitro* cartilage injury and suggest potential benefit. These biomarker observations provide great hope that disease-modifying therapies are within reach for early pre-clinical OA once it can be diagnosed reliably, because there are already many known pharmacologic agents with chondroprotective effects in the cartilage explant model and acute injury animal models of OA.^{20,44}

POTENTIAL BENEFITS WITH EARLY DIAGNOSIS OF OSTEOARTHRITIS

Annual medical expenditures in the United States attributable to OA are estimated to be as high as \$185.5 billion, or 19% of the aggregate medical

expenditures for the U.S. adult population.^{45,46} It is generally agreed that the prospect for early diagnosis and intervention in OA would improve the likelihood of disease modification and thereby reduce medical costs, morbidity, and disability. In this regard, OA fits the description provided by Machiavelli more than 500 years ago, "In the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."⁴⁷ A precedent for improved outcomes with early identification and treatment now exists for rheumatoid arthritis.^{48,49} This paradigm should help facilitate the approach to the diagnosis and treatment of OA.

SUMMARY

It is generally agreed that the early stages of OA would be more amenable to modification, including halting or slowing the disease process to prevent recalcitrant, disabling, and more costly late stages of the disease. Consensus, however, is needed for a new paradigm of OA that conceives of a pathologic continuum beginning with a preclinical stage; such a conception is the norm for other chronic diseases.⁵⁰ This would require reclassification of the disease from a purely radiographic entity to a disease process with a preclinical phase characterized by serologic abnormalities such as elevations of cartilage extracellular matrix components in body fluids, a preradiographic stage, and a radiographic stage. Just as not all radiographic OA progresses, it is likely that not all preclinical or preradiographic OA progress to later stages. To gain this information, more studies are needed to discern and monitor the disease process from its incipient to its end stages. The scenario of acute joint injury, with a known date of onset, provides a potential gateway to understand the preclinical stages of OA and offers the most promising context in which to elucidate the continuum of pathologic stages of this joint disorder. Ultimately, it will be important to establish the temporal relationship between changes in imaging markers and onset of symptoms and the molecular events that predate these manifestations of disease to achieve the goal of ultimately preventing and curing OA.

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Assessment of imaging outcomes in osteoarthritis

■ DAVID J. HUNTER

- In the absence of a therapeutic intervention that can irrefutably modify structural progression, the role of monitoring progression of osteoarthritis (OA) in clinical practice is limited.
- Regulatory approval of potential therapies for OA requires that structural alteration be linked to some clinical benefit either at the time when the structure was measured or at a later point in time.
- Progression of knee OA is typically assessed by measuring change in the width of the joint space between the medial femoral condyle and medial tibial plateau on plain radiographs.
- Though yet to be formally accepted by regulatory authorities, magnetic resonance imaging has several advantages in monitoring progression of OA of the knee.

INTRODUCTION

Osteoarthritis (OA) is the clinical and pathologic outcome of a range of disorders that result in structural degradation and functional failure of synovial joints.¹ The joint failure may cause pain and disability and is ranked as the leading cause of disability in elders. Current estimates suggest that OA affects an estimated 21 million Americans² and that symptomatic knee OA develops in 6% of adults older than 30 years³ and in 13% of those older than 60.⁴

Despite this prevalence, OA remains a condition that is poorly understood and for which few safe and effective therapeutic options are available. In an effort to target the disease (both symptoms and structure), modifying structural progression has become a focus of drug development in OA. However, further development of definitive structure-modifying therapies is constrained by a number of factors, including (1) the need for long-term follow-up to observe changes in structure (and potential therapeutic effects on it), (2) the heterogeneous clinical manifestations of OA, and (3) the unclear relationship between structural progression and clinical endpoints. Underpinning the capability of demonstrating structural change in clinical trials is access to responsive and highly reproducible markers that measure the rate of progression in individuals. Once we have an approved disease-modifying agent, we will also need such measures for patients in clinical practice.

Traditionally, measurement of structural change (often incorrectly paraphrased as cartilage loss⁵) in OA has been performed on plain radiographs. Standardized radiographic protocols for measuring joint space width (JSW) in the medial tibiofemoral (TF) compartment have become accepted for quantifying structural progression in knee OA. Newer methods, including magnetic resonance imaging (MRI), a noninvasive three-dimensional method for assessing joint morphology, may eventually supplant the widespread use of plain radiographs in clinical trials.⁶

This chapter focuses on the imaging assessment of OA outcomes. Most of the chapter focuses on the TF compartment of the knee and specifically on radiographic and MRI developments in measuring progression of OA. Interpretation of these measures is considered and directions for future research and development proposed.

ROLE IN RESEARCH VERSUS CLINICAL PRACTICE

In the absence of a therapeutic intervention that can irrefutably modify structural progression, the role of monitoring progression of OA (either by

plain radiography or MRI) in clinical practice is limited. Hence, there is currently no rationale for obtaining serial radiographs if the clinical state remains unchanged. Thus what follows is a description of the principal methodologies used to monitor structure in clinical research. As outlined in Chapter 177, OA radiography does play a role in defining the presence of disease, determining the compartment or compartments of the joint that are affected, and categorizing its severity. In addition, conventional radiography is commonly used in clinical practice because radiographs are easily interpreted.

REGULATORY REQUIREMENTS

Radiographic measurement of joint space narrowing (JSN) is currently recommended in the U.S. Food and Drug Administration⁷ and European Medicines Agency⁸ guidance documents as the imaging endpoint for clinical trials of disease-modifying OA drugs. At present, an alteration in structural progression would probably be determined by plain radiography, but it is possible that newer technologies may include MRI or even ultrasound once appropriately validated. Currently, approval of potential therapies for OA requires that structural alteration be linked to some clinical benefit either at the time when the structure was measured or at a later point in time. With this concept in mind, it is obviously important that improvements in OA structural features be ascertained that are more likely to be linked to the clinical symptoms experienced by patients or, alternatively, that can serve as a surrogate for a clinically meaningful outcome.⁹

PLAIN RADIOGRAPHY

Conventional radiography is the least expensive method for imaging joint structure in patients with OA. The presence and severity of disease are typically classified with the Kellgren and Lawrence (K&L) grading system,¹⁰ a system that is heavily dependent on the osteophyte for classification of disease. Because of the inherent limitations of the K&L grading system, individual grading systems for the different disease features, including osteophytes and JSN, have been developed. These site-specific ordinal scales (graded 0 to 3) categorize the feature according to its severity and are accompanied by published atlases that provide images representing the specific grades.¹¹ Observational studies show a variable relationship between individual radiographic features, pain, and function in OA.^{12,13} Progression on the ordinal JSN scale is a criterion commonly used for assessment of OA progression, and complete loss of joint space characterized by bone-on-bone contact, which corresponds to JSN grade 3, is one of the factors considered in the decision for joint replacement.¹⁴

Radiographic joint space width

Progression of knee OA is typically assessed by measuring change in the width of the space between the medial femoral condyle and medial tibial plateau on plain radiographs.¹⁵ This generates a continuous measure of JSW, and a reduction in this space is termed JSN (not to be confused with the ordinal measure described earlier). From the reduction in this space the health, integrity, and thickness of hyaline articular cartilage are inferred.^{5,15,16}

Radiographic protocols

Radiographs are a two-dimensional projection of a three-dimensional joint structure that are subject to problems caused by variability in joint repositioning. The conventional standing, fully extended anteroposterior protocol

of the knee in the weight-bearing position was the most commonly used technique and continues to be the usual approach for diagnosis. However, this protocol is not recommended for monitoring disease progression because there is no attempt to standardize the degree of knee rotation or flexion or the radiographic beam for optimizing alignment of the medial tibial plateau.¹⁷

Standardized radiographic protocols of the flexed knee for measuring JSW in the medial TF compartment have become accepted for quantifying changes in TF knee OA. Recent analyses suggest that the better the

positioning in terms of medial tibial rim alignment (or inter-rim distance) with the radiograph beam, the greater the sensitivity in detecting OA progression and the more accurate identification of the location of JSN¹⁸ (Fig. 180.1). Long-term reproducibility of knee positioning, as assessed by variability in the inter-rim distance (also termed intermargin difference), or the distance between the anterior and posterior rims of the medial tibial plateau on serial radiographs, was shown to be significantly less satisfactory on medial tibial plateau and fixed-flexion radiographs than on semiflexed anteroposterior and Lyon-Schuss radiographs.^{19,20} There remains, however, considerable controversy over the preferred method of acquiring knee radiographs¹⁵ and measuring JSW.¹⁶

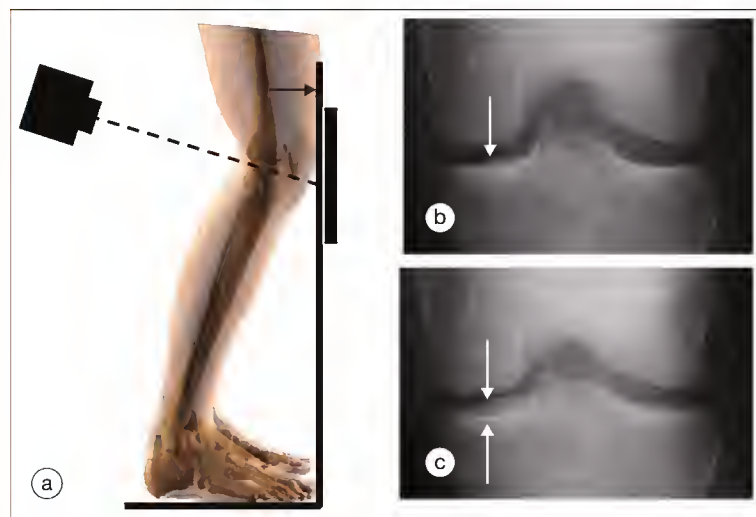


Fig. 180.1 Positioning of the subject for fixed-flexion (FF) and Lyon-Schuss (LS) radiographs and examples of good and poor alignment of the medial tibial plateau (MTP) with the radiographic beam. (a) Positioning of the subject. The FF protocol uses a fixed 10-degree caudal radiographic beam and positions the thighs, patellae, and pelvis flush with the film cassette and coplanar with the tips of the great toes, which results in a fixed knee angulation of approximately 20 degrees of flexion. In the LS protocol, positioning is identical to that for an FF view. However, the angle of the radiographic beam is not fixed but is adjusted for each examination to align the MTP with the radiographic beam. Alignment is achieved with fluoroscopy to superimpose (within 1.5 mm) the anterior and posterior margins of the plateau. (b) Good alignment, as defined by virtual superimposition of the anterior and posterior margins at the center of the plateau (arrow). (c) Radiograph with poor alignment, as depicted by the wide separation (>1.5 mm) of the anterior and posterior margins of the MTP (arrows) or so-called inter-rim distance. (Reproduced with the authors' permission from Merle-Vincent F, Vignon E, Brandt K, et al. Superiority of the Lyon Schuss view over the standing anteroposterior view for detecting joint space narrowing, especially in the lateral tibiofemoral compartment, in early knee osteoarthritis. *Ann Rheum Dis* 2007;66:747-53.)

Methods of measuring joint space width

JSW can be measured either manually with the use of callipers or a simple graduated ruler and a micrometric eyepiece or in a semiautomated fashion with computer software.²¹⁻²³ The most common metric that is generated is the minimum JSW, which constitutes the smallest distance between the medial femoral condyle and medial tibial plateau. The smallest standard deviation of the difference between test-retest measurements of minimum JSW in pairs of radiographs reaches about 0.1 mm in the most reproducible methods,^{23,24} which equates to a smallest detectable difference of at least 0.2 mm, a value that remains relatively large in view of the 0.10- to 0.15-mm expected average annual rate of JSN in knee joints with OA.²⁵ Recent analyses have suggested that measuring JSW at fixed locations along the joint (the JSW[x] coordinate system) is both more reliable and more sensitive to change than the minimum JSW is (Fig. 180.2).²²

MAGNETIC RESONANCE IMAGING

Though yet to be formally accepted by regulatory authorities, MRI has several advantages in monitoring progression of OA of the knee.²⁶ There is a significant body of supporting data on the longitudinal change in cartilage morphology (thickness, volume) as a primary endpoint reflecting OA progression/cartilage loss.²⁷ MRI of the knee can directly visualize articular cartilage and cover the entire joint three-dimensionally in one examination, which means that the cartilage, its defects, and other joint tissue involvement can be visualized directly regardless of their location.²⁸

Methods of analysis of magnetic resonance images

Broadly speaking, the features of OA can be measured semiquantitatively or quantitatively by MRI, and either morphologic or compositional measurements of articular cartilage can be obtained.

Observer-dependent semiquantitative image analysis

Semiquantitative scoring is a valuable method for assessing multiple features of the knee with conventional MRI acquisitions.²⁹⁻³² Such approaches score, in an observer-dependent semiquantitative manner, a variety of features that are currently thought to be relevant to the functional integrity of the knee or potentially involved in the pathophysiology of OA. These articular

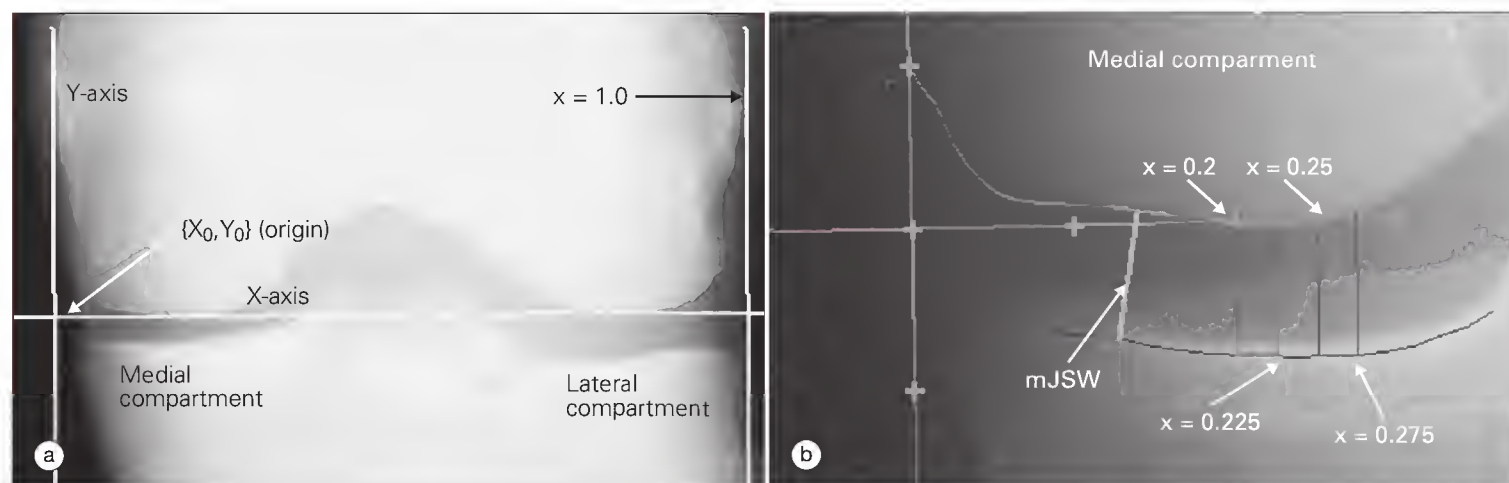


Fig. 180.2 (a) Landmarks and definition of the coordinate system.²² (b) Location-specific measurement of joint space width, JSW(x) ($x = 0.2, 0.225, 0.25$, and 0.275), in the medial compartment (minimum JSW). Measurements of JSW(x) are made at the x-locations (vertical line segments) defined by the coordinate system. (Courtesy Dr. Jeff Duryea.)

features can include articular cartilage integrity, subarticular bone marrow lesions (Fig. 180.3), subarticular cysts, subarticular bone attrition, marginal and central osteophytes, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis/effusion (Fig. 180.4), medial and lateral meniscal integrity, intraarticular loose bodies, and periarticular cysts/bursitis. These instruments for scoring OA on MRI have shown adequate reliability, specificity, and sensitivity, but their sensitivity to change is modest.²⁷

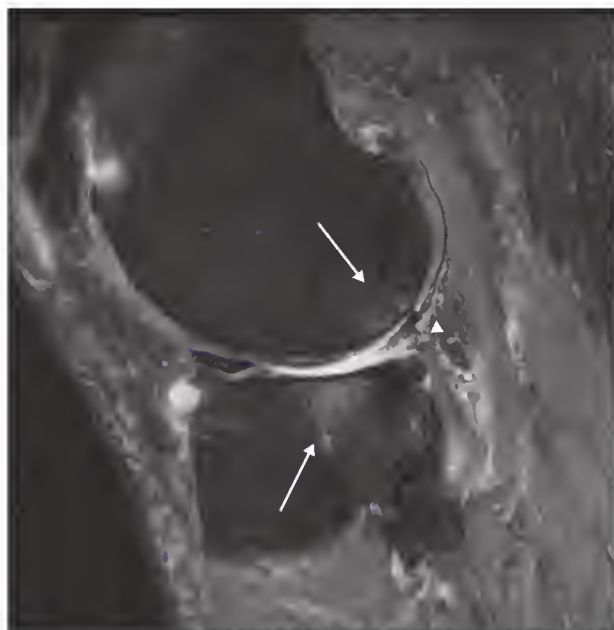


Fig. 180.3 Sagittal fat-suppressed intermediate-weighted magnetic resonance image depicting diffuse ill-defined hyperintensities (arrows) abutting the subchondral plate in the weight-bearing lateral view of the tibia and femur that are characteristic of bone marrow lesions. Also apparent are extensive osteophytosis and a cartilage defect in the lateral tibial plateau and femoral condyle and bone attrition in the tibial plateau. An oblique tear of the partially macerated posterior horn of the lateral meniscus (arrowhead) has occurred.

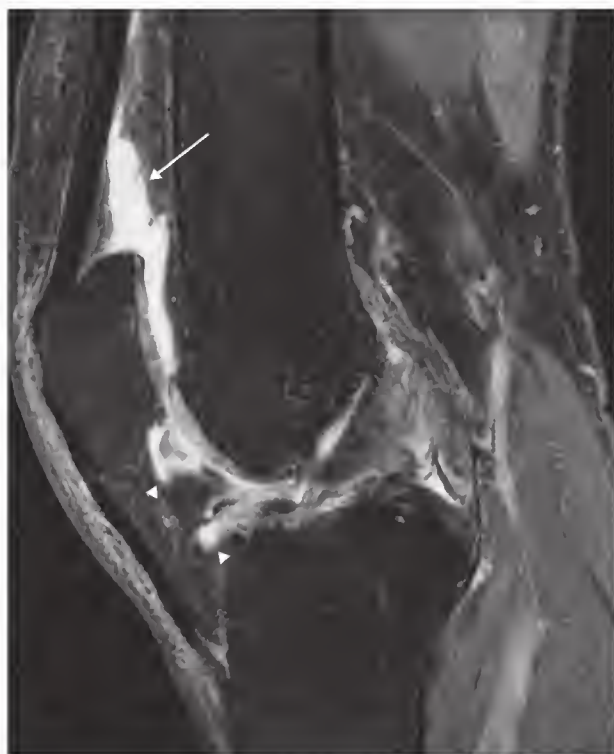


Fig. 180.4 Sagittal fat-suppressed intermediate-weighted magnetic resonance image showing knee joint effusion (arrow) and infrapatellar synovitis (arrowheads). On this non-contrast-enhanced image the magnitude of synovitis is difficult to determine.

Computer-aided image processing to quantitatively assess whole-joint morphology (cartilage, bone, synovium, etc.)

The three-dimensional coverage of an entire cartilaginous region by MRI allows direct quantification of cartilage volume, surface areas, and thickness. Quantitative analysis of cartilage morphometry is becoming widely used for the assessment of OA.²⁸ Measurements of cartilage volume with MRI have previously been shown to correlate well with *ex vivo* assessments of cartilage volume (stripped away from bone).^{33,34} Measurement of cartilage volume or thickness provides quantitative data with which to monitor the progression of OA.³⁵ The ideal segmentation strategy is one that produces accurate and precise results in a reasonable amount of time with minimal subjectivity (Fig. 180.5). These methods are described in more detail elsewhere.²⁸ In addition to cartilage volume, other features such as bone marrow lesion volume and synovial fluid volume can also be quantitatively assessed. Of the MRI measures used to date, measurement of cartilage morphometry is the most mature, with a substantive literature base demonstrating its validity, responsiveness, and reliability.^{27,36}

Compositional measures of articular cartilage

Even though quantitative measurement of morphology can be used to monitor loss of cartilage tissue, there is interest in using MRI to detect changes that precede gross tissue degradation. Applications of parametric mapping techniques sensitive to early cartilage damage, including T2 mapping, dGEMRIC, and T1rho, have been extensively reviewed elsewhere.^{37,38} Intuitively, compositional measures may have a great role to play in examining changes that occur in early disease before gross defects become apparent, whereas morphologic measures—both semiquantitative and quantitative—may have a greater role in later stages of disease. Particularly for the supposedly “early” changes of OA, however, the natural course of these changes and their relationship with clinical outcome remain to be established.

Semiquantitative progression

Some recent studies have used assessment of semiquantitative cartilage morphology on MRI as the outcome for ascertaining important risk factors for disease progression.²⁷ The menisci have many functions in the knee, including equal distribution of stress between the relatively incongruous TF joint surfaces, enhancement of stability, and lubrication. Damage to the morphology of the meniscus and alteration in its position appear to be a potent risk factor for progression of cartilage lesions measured semiquantitatively on MRI.³⁹ Bone marrow lesions have also been found to be associated with semiquantitatively measured compartment-specific progression of OA in cartilage.⁴⁰

Mechanical factors are the dominant risk factor for structural progression, and varus malalignment was shown to predict medial TF progression measured both quantitatively and semiquantitatively after adjusting for other local factors (meniscal damage and extrusion, laxity).⁴¹ Interestingly, quantitative measurement of cartilage in this cohort appeared to demonstrate greater responsiveness than did semiquantitative measurement; however, many of the subjects whose condition progressed had a late stage of disease, for which morphometric measures appear to demonstrate their greatest responsiveness.

Quantitative magnetic resonance imaging-based cartilage measurements for evaluating longitudinal change in cartilage morphometry

More extensive discussion of the technical validity, precision, and sensitivity to change of quantitative measures of cartilage morphology can be found elsewhere.⁴² Early longitudinal studies suggested that changes in cartilage volume or thickness on the order of -4% to -6% (standard deviation of $\approx 5\%$) occur per annum in OA in most knee compartments monitored for periods of up to 3 years.²⁸ The annual changes in cartilage volume/thickness exceeded the precision errors and appeared to be associated with clinical symptoms, as well as with time until total knee arthroplasty.^{28,43} One study detected loss of cartilage volume in the absence of any change in radiographic JSW, thus suggesting that MRI has greater sensitivity to change than radiography does.⁴⁴

More recent studies, however, have observed smaller rates of change than those just quoted, with rates of about -1% to -3% and standardized response means of -0.3 to -0.5 per year.^{45,46} These more conservative estimates have important implications for planning future clinical trials of disease-modifying treatments of OA with MRI techniques.

The conservative study designs based on large MRI progression series currently in the public domain require large sample sizes if quantitative cartilage morphometric measures are used as the endpoint. If one could

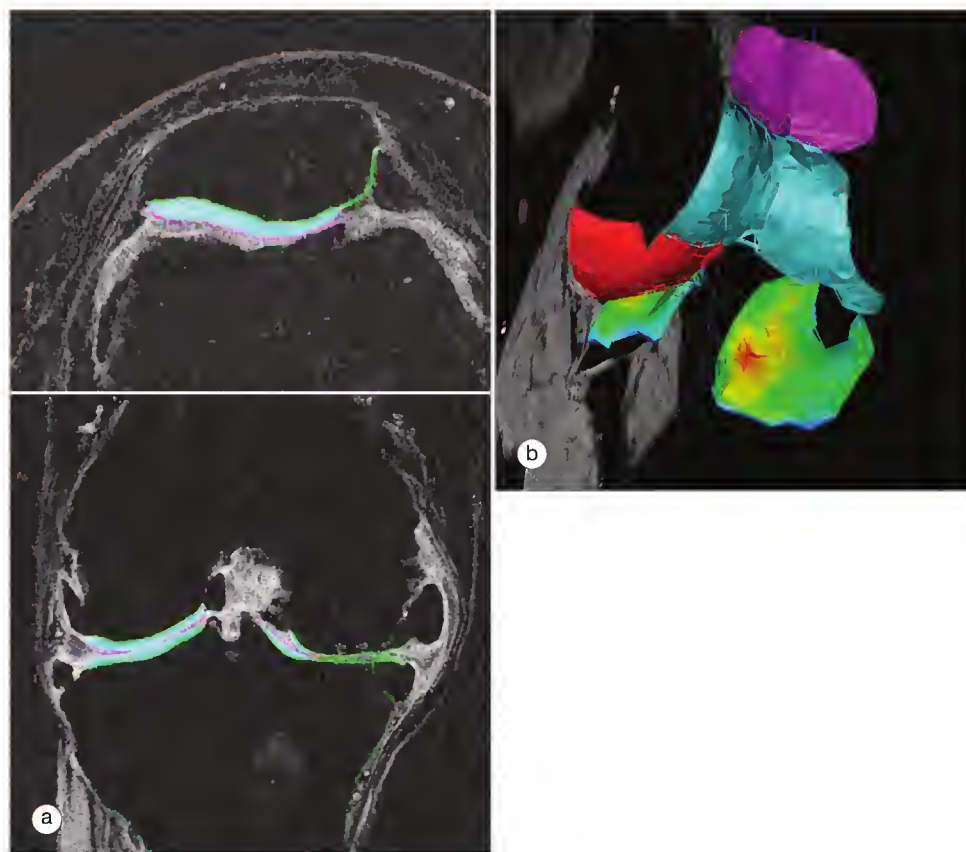


Fig. 180.5 (a) Axial (top) and coronal (bottom) images in a patient with knee osteoarthritis and segmentation of cartilage. Note that the total subchondral bone area is segmented, also in areas in which the cartilage has been lost (green line). In this way, not only cartilage volume and thickness but also the denuded area can be computed. (b) Segmented cartilage model. Patellar cartilage is purple, femoral (trochlear) cartilage is turquoise, and the lateral femoral condyle is red. The tibial cartilage displays thickness maps, with the thickest regions in red and the thinnest in blue. (a, Courtesy Institute of Anatomy and Musculoskeletal Research, Paracelsus Medical University, Austria, under the supervision of Felix Eckstein; b, Courtesy Dr. Jan Hohe, PhD, Chondrometrics GmbH, Ainning, Germany.)

confidently design studies based on smaller sample sizes or shorter study durations (or both), this would, however, greatly reduce the resource implications for MRI-based interventional studies. Several studies have suggested that baseline clinical, biomarker, and imaging features are predictive of progression of cartilage loss in the medial compartment of the knee and could be used to provide greater study power by selecting a population at greater risk for more rapid progression.⁴⁷

Issues in interpreting progression of quantitative measures

Some attempt has been made to develop nomenclature for the regions of the knee and the different measures that can be performed (from volume to thickness to denuded area and beyond), but there is probably great redundancy in many of these measures, and the field would benefit from simplifying the terminology and identifying those that are most highly correlated with clinical outcome.⁴⁸

A substantial percentage of the variability in cartilage volume is determined by joint surface area.⁴⁹ Wang and colleagues⁵⁰ demonstrated that the medial and lateral tibial plateau area increased over a 2-year period (2.2% and 1.5% per annum, respectively), with increases at the medial (but not lateral) part of the tibia being larger in men, in participants with a high body mass index, and in subjects with a higher baseline grade of medial JSN. Metaphyseal enlargement with age and OA⁵¹ might create problems for measurements of cartilage volume that do not adjust for bone size, and either adjustment for subchondral bone area or direct measurement of cartilage thickness has thus been recommended.⁴⁹

In early OA, cartilage may not be thin but rather thicker and swollen with water, which is imbibed by cartilage when the collagen network is disrupted and the charge of proteoglycans is altered.⁵² Thus, measuring cartilage volume in regions of the knee (e.g., medial tibia area) and regional mean thickness as distinct from focal measures of change (region-of-interest analysis centered around focal defects⁵³) and measures of denuded cartilage may provide very different results about the important pathologic changes

occurring in early disease. Distinguishing what measures are most discriminatory at each stage of the disease process is essential for using these measures appropriately.

If structural modification is the intent of treatment, it should be done while being mindful of attaining improvement in symptoms and not be divorced from it. This is particularly important because of the current predilection of focusing treatment targets on hyaline articular cartilage. Articular cartilage is both aneural and avascular. Consequently, cartilage is incapable of directly generating pain, inflammation, stiffness, or any of the symptoms that patients with OA typically describe.⁵⁴ Given the relative unimportance of the symptomatic manifestations of OA, it is ironic that articular cartilage has received so much attention whereas other common sources of symptoms in the joint are ignored. We need to pay greater heed to the pivotal role of other tissues in disease symptoms and etiopathogenesis, especially synovium, bone, fat, meniscus, and ligaments.

CONCLUSION

OA is the most common form of arthritis and one of the leading causes of disability in elders. With little currently available for the treatment of this disease, better understanding of responsive and valid structural endpoints is essential for identifying potential new interventions for treating this disease. The measures of progression that we are currently using are optimal for late stages of disease and not early disease, for which intervention may be more rational. Currently, a large number of epidemiologic and clinical trials of OA are under way and are collecting both plain radiographic and MRI data. Investigations to identify the most valid and responsive set of endpoints are ongoing in these studies. Before recommending the widespread use of one particular imaging construct in structure-modifying clinical trials it is essential that we have this information, as well as an established relationship with clinical endpoints such as pain, function, and need for joint replacement.

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181

Management of osteoarthritis

■ ROY D. ALTMAN ■ MARC C. HOCHBERG

- Osteoarthritis (OA) is the most common form of arthritis, and pain is its most common symptom.
- Currently, the aims of treatment are to reduce pain and improve function and health-related quality of life.
- Management of OA should be individualized and requires a combination of nonpharmacologic and pharmacologic modalities.
- Patient education, weight control, and exercise are the cornerstones of successful nonpharmacologic management of OA.
- Oral and topical pharmacologic therapies, including acetaminophen, nonsteroidal antiinflammatory drugs, and nonopioid analgesics, are often effective in relieving pain.
- Intraarticular agents, including corticosteroids and hyaluronate products, may be useful in the symptomatic treatment of hip and knee OA.
- The adverse event profile of the therapeutic plan should be minimized whenever possible and be consistent with the values and preferences of the patient.
- Pharmacologic structure-modifying interventions are currently under active investigation.
- Surgical interventions are available for patients whose disease fails to respond to nonpharmacologic interventions.

INTRODUCTION

Osteoarthritis (OA) comprises a heterogeneous group of conditions with a variety of patterns of expression.^{1,2} OA can be conceptualized as an illness with a constellation of symptoms, including pain, aching, discomfort, stiffness, fatigue, and sleep disturbance; the symptoms of OA are reviewed in Chapter 173. OA can also be described as a disease characterized by pathologic changes in articular cartilage and subchondral bone with variable degrees of local synovitis; the pathology of OA is reviewed in Chapter 175. Before initiating therapy the diagnosis of OA should be confirmed by history and physical examination, plus conventional radiographic imaging if necessary. Presently, management of patients with OA is focused on the following goals:

- Relieving symptoms, including pain
- Limiting physical dysfunction by maintaining or improving joint mobility
- Improving health-related quality of life

Management of OA comprises two aspects:

- The first is assessment of OA patients: What data should be collected to help in the therapeutic decision? How should such data be collected?
- The second is treatment of OA: What therapeutic modalities are available? What are their optimal indications? What are their potential benefits and risks?

Assessment of patients with OA in both clinical practice and clinical research is reviewed in Chapter 178. The remainder of this chapter focuses on the nonpharmacologic and pharmacologic modalities available for use in patients with symptomatic OA, with comments on surgical alternatives. The treatment modalities are presented in the context of recommendations for management published by the American College of Rheumatology

(ACR) in 2012³ and the Osteoarthritis Research Society International (OARSI) in 2008 (Fig. 181.1 and Box 181.1).⁴⁻⁶ Readers should be aware of other recommendations reviewed by the ACR in 2012, including but not limited to those published by the European League Against Rheumatism (EULAR),⁷⁻⁹ the National Institute for Clinical Excellence (NICE) in the United Kingdom, and the American Academy of Orthopaedic Surgeons (AAOS).^{10,11}

TREATMENT MODALITIES

Objectives

Treatment aims for patients with OA include (1) education about OA, (2) reduction of pain, (3) optimization and maintenance of physical function, and (4) attempts to prevent or slow the progression of structural damage (e.g., cartilage, bone, ligament, muscle). Currently available treatments include a wide range of nonpharmacologic, pharmacologic, and surgical modalities. The OARSI recommendations for the management of hip and knee OA used an evidence-based and experts' consensus opinion approach (Box 181.2).⁵ The ACR guidelines were developed by using the Grading of Recommendations Assessment, Development and Evaluation method, a process that rates existing scientific evidence with an expert panel to develop evidence-based recommendations. The ACR recommendations emphasize different nonpharmacologic and pharmacologic treatment modalities that are joint-specific and extend previously published EULAR recommendations for hand, hip, and knee OA,⁷⁻⁹ including both nonpharmacologic and pharmacologic therapies. Treatment of OA at other sites is not discussed.

Optimal management of patients involves a combination of both nonpharmacologic and pharmacologic modalities individualized to the patient's values and preferences. We first review the nonpharmacologic modalities, which serve as the basis for the patient's treatment, and then the pharmacologic modalities, which can be added as necessary for additional control of symptoms. It should be pointed out that in most patients a single therapeutic modality may not provide an adequate clinical response. Despite the lack of adequate clinical trials, multimodal therapy—a combination of at least one nonpharmacologic modality in addition to at least one pharmacologic modality—is commonly employed for treatment of individual patients. A pyramid approach to the management of patients with lower limb OA based on the ACR recommendations is shown in Figure 181.1.

Nonpharmacologic modalities

Patient education

Despite the widespread recommendation that patient education be part of the basic program for the management of patients with symptomatic OA, the supporting evidence suggests only a weak effect of patient education, including cognitive-behavioral therapy, on pain and functional limitation.^{12,13}

Exercise

A physical exercise program should have the following objectives: reduce pain, increase or maintain range of articular motion, increase or maintain muscular strength, improve mobility and physical activity, and reduce activity and functional limitations. There have been numerous systematic reviews of randomized, controlled trials of different exercise programs in patients suffering from hip or (more frequently) knee OA.¹⁴⁻¹⁹ These reviews concluded that there is high-quality evidence that programs of exercise therapy, be they aquatic (water based), aerobic (land-based), or resistance in nature, are able to decrease pain and improve functional capacity in patients with OA. The

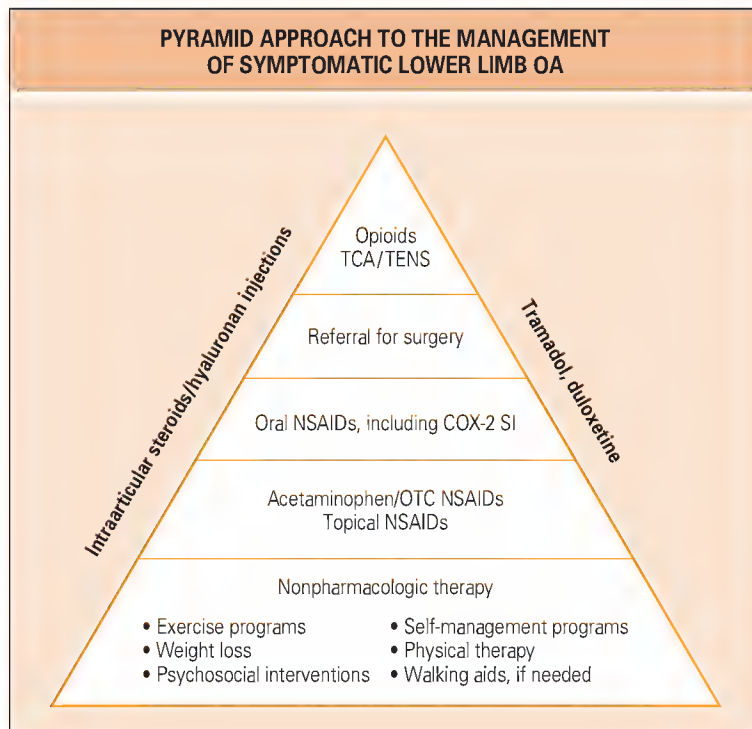


Fig. 181.1 Management of symptomatic lower limb osteoarthritis (OA) based on the 2012 American College of Rheumatology recommendations. COX-2 SI, cyclooxygenase-2-selective inhibitor; NSAIDs, nonsteroidal antiinflammatory drugs; OTC, over the counter; TCA, tricyclic antidepressant; TENS, transcutaneous electrical nerve stimulation.

BOX 181.1 OARSİ RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH HIP OR KNEE OSTEOARTHRITIS

Nonpharmacologic therapies

- Patient education
- Self-management
- Aerobic exercise
- Strengthening exercise
- Water-based exercise
- Weight loss
- Insoles
- Braces
- Patellar taping
- Cane/stick
- Telephone contact
- Massage
- Local heat/ice
- Acupuncture
- Transcutaneous electrical nerve stimulation
- Yoga
- Low-energy lasers
- Ultrasound

Pharmacologic therapies

- Acetaminophen (paracetamol)
- Nonsteroidal antiinflammatory drugs
- Cyclooxygenase-2-selective inhibitors
- Topical nonsteroidal antiinflammatory drugs
- Topical capsaicin
- Opioid analgesics
- Diacerein
- Glucosamine sulfate
- Chondroitin sulfate
- Avocado/soybean unsaponifiables
- Intraarticular corticosteroids
- Intraarticular hyaluronic acid preparations
- Herbal compounds
- Oral corticosteroids

Surgical interventions

- Joint lavage
- Arthroscopic débridement
- Osteotomy
- Total articular replacement
- Knee fusion

OARSİ, Osteoarthritis Research Society International.

treatment effects observed (i.e., improvement over the control group) are usually moderate (effect sizes ranging from 0.4 to 0.6) and typically occur after 3 to 6 months of therapy. Numbers needed to treat are in single digits. The evidence is generally stronger for knee OA than for hip OA.

Exercise programs should include manual therapy such as stretching exercises and soft tissue mobilization aimed at maintaining or improving range of motion, along with exercises aimed at improving muscle

performance in terms of dimension and strength.²⁰ Such exercises should be adapted according to the presence or absence of a painful episode of OA. During painful episodes, isometric exercises such as quadriceps contraction or exercises in a nonloading position (cycling, rowing with adapted tools) or in a partial nonloading position (aquatic exercises) should be proposed. During painless (or at least less painful) periods, the exercise program could include stretching and muscle performance exercises.

Whatever the type of exercise prescribed, they should be performed at least three to five times per week. Efficacy is better in compliant patients. Therefore, it seems that regular interventions, such as telephone calls and visits to physiotherapists, are important to ensure long-term adherence to the exercise program.

Weight loss

Weight loss is recommended for all patients with symptomatic lower limb OA who are overweight.^{21,22} Overall, evidence is strong that weight loss of at least 5% of body weight is associated with a small but significant improvement in both pain and physical function. Obviously, because of the common occurrence of comorbid cardiovascular and metabolic conditions such as hypertension, diabetes mellitus, and coronary artery disease, weight reduction is important not only for the patient's OA but also for general health and well-being.

Orthotics

Orthotics are used mainly to improve symptoms but might also help correct abnormal biomechanical forces operating across the joint. The type of orthotic used is obviously joint specific. The use of foot orthoses in patients with knee OA is controversial.²³⁻²⁶ There is no compelling evidence at this time that the use of orthotics reduces progression of structural damage in patients with knee OA.

Braces and patellar taping

As with orthotics, braces are used mainly to improve symptoms but might also help correct abnormal biomechanical forces operating across the joint. The efficacy of bracing remains controversial because few published randomized controlled trials have provided convincing evidence for the use of bracing in patients with knee OA.^{23,27} Neither the ACR nor the AAOS was able to make recommendations for or against the use of braces for symptomatic treatment of knee OA.^{3,11} Medial patellar taping, however, is efficacious in relieving pain, although it is frequently accompanied by minor skin irritation from the tape itself.²⁷ The patient should be instructed in taping by a physical therapist.

Use of assistive devices

In patients with weight-bearing joint pain, appropriate use of a cane, crutch, or walker could be a useful adjuvant therapy. A cane or single crutch should be held on the side contralateral to the affected hip or knee and be advanced with the affected limb when walking to effectively reduce load on the affected joint—the tip should be changed regularly. A useful length of cane is the distance from the floor to the patient's greater trochanter; this brings the elbow into 15 to 20 degrees of flexion. Ideally, the patient should be fitted for a cane and instructed in its use by a physical therapist. The same principles apply to a walker.

Other nonpharmacologic interventions

A number of other nonpharmacologic interventions have been conditionally recommended by the ACR for patients with knee OA, including tai chi, transcutaneous electrical nerve stimulation (TENS), and traditional Chinese acupuncture.²⁸⁻³²

The ACR suggests that both TENS and traditional Chinese acupuncture be reserved for patients who are candidates for total joint arthroplasty (see later) but are either unwilling to undergo or have medical contraindications to these procedures.³

Pharmacologic treatment modalities

Topical agents

The most widely used topical agents are preparations containing capsaicin, lidocaine, and nonsteroidal antiinflammatory drugs (NSAIDs). Capsaicin preparations have been shown to be efficacious in controlled double-blind studies of OA of the hand and knee. Some of the topical NSAIDs have demonstrated benefit in double-blind placebo-controlled trials of knee and hand OA.³³⁻³⁵ Furthermore, topical NSAIDs have been shown to be efficacious as orally administered NSAIDs and to have a lower incidence of upper gastrointestinal side effects.^{34,35} It is clear that topical agents should be considered a useful, if not first-line option in patients with symptomatic knee

BOX 181.2 OARS RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH HIP OR KNEE OSTEOARTHRITIS

- Optimal management of osteoarthritis (OA) requires a combination of nonpharmacologic and pharmacologic modalities.
- All patients with hip and knee OA should be provided access to information and education about the objectives of treatment and the importance of changes in lifestyle, exercise, pacing of activities, weight reduction, and other measures to unload the damaged joint or joints. The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health care professionals. Subsequently, emphasis should be placed on encouraging adherence to the regimen of nonpharmacologic therapy.
- The clinical status of patients with hip or knee OA can be improved if they are contacted regularly by telephone.
- Patients with symptomatic hip and knee OA may benefit from referral to a physical therapist for evaluation and instruction in appropriate exercises to reduce pain and improve functional capacity. This evaluation may result in the provision of assistive devices such as canes and walkers, as appropriate.
- Patients with hip and knee OA should be encouraged to undertake—and continue to undertake—regular aerobic, muscle-strengthening, and range-of-motion exercises. For patients with symptomatic hip OA, exercises in water can be effective.
- Patients with hip and knee OA who are overweight should be encouraged to lose weight and maintain their weight at a lower level.
- Walking aids can reduce pain in patients with hip and knee OA. Patients should be given instruction in the optimal use of a cane or crutch with the contralateral hand. Frames or wheeled walkers are often preferable for those with bilateral disease.
- In patients with knee OA and mild to moderate varus or valgus instability, a knee brace can reduce pain, improve stability, and diminish the risk of falling.
- Every patient with hip or knee OA should receive advice concerning appropriate footwear. In patients with knee OA, insoles can reduce pain and improve ambulation. Lateral-wedged insoles can be of symptomatic benefit for some patients with OA in the medial tibiofemoral compartment.
- Some thermal modalities may be effective in relieving symptoms in patients with hip and knee OA.
- Transcutaneous electrical nerve stimulation can help in short-term pain control in some patients with hip or knee OA.
- Acupuncture may be of symptomatic benefit in patients with knee OA.
- Acetaminophen (up to 4 g/day) can be an effective initial oral analgesic for the treatment of mild to moderate pain in patients with knee or hip OA. In the absence of an adequate response or in those with severe pain or inflammation, alternative pharmacologic therapy should be considered on the basis of relative efficacy and safety, as well as concomitant medications and comorbid conditions.
- In patients with symptomatic hip or knee OA, nonsteroidal antiinflammatory drugs (NSAIDs) should be used at the lowest effective dose, but long-term use of such drugs should be avoided if possible. In patients with increased gastrointestinal risk, either a cyclooxygenase-2 (COX-2)-selective agent or a nonselective NSAID with coprescription of a proton pump inhibitor or misoprostol for gastroprotection should be considered, but NSAIDs, including both nonselective and COX-2-selective agents, should be used with caution in patients with cardiovascular risk factors.
- Topical NSAIDs and capsaicin can be effective as adjunctive agents and alternatives to oral analgesic/antiinflammatory drugs for knee OA.
- Intraarticular injections of corticosteroids can be used for the treatment of hip or knee OA and should be considered particularly when patients have moderate to severe pain not responding satisfactorily to oral analgesic/antiinflammatory agents and in those with symptomatic knee OA with effusions or other physical signs of local inflammation.
- Intraarticular injection of hyaluronate may be useful in patients with knee or hip OA. They are characterized by delayed onset, but prolonged duration of symptomatic benefit when compared with intraarticular injection of corticosteroids.
- Treatment with glucosamine or chondroitin sulfate (or with both) may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months, treatment should be discontinued.
- In patients with symptomatic knee OA, glucosamine sulfate and chondroitin sulfate may have structure-modifying effects, whereas in those with symptomatic OA of the hip, diacerein may have structure-modifying effects.
- The use of weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients with hip or knee OA when other pharmacologic agents have been ineffective or are contraindicated. Stronger opioids should be used only for the management of severe pain in exceptional circumstances. Nonpharmacologic therapies should be continued in such patients and surgical treatments considered.
- Patients with hip or knee OA who are not obtaining adequate pain relief and functional improvement from a combination of nonpharmacologic and pharmacologic treatment should be considered for joint replacement surgery. Replacement arthroplasty is an effective and cost-effective intervention for patients with significant symptoms or functional limitations associated with a reduced health-related quality of life despite conservative therapy.
- Unicompartmental knee replacement is effective in patients with knee OA restricted to a single compartment.
- Osteotomy and joint-preserving surgical procedures should be considered in young adults with symptomatic hip OA, especially in those with dysplasia. For young and physically active patients with significant symptoms from unicompartmental knee OA, high tibial osteotomy may offer an alternative intervention that delays the need for joint replacement for possibly 10 years.
- The role of joint lavage and arthroscopic débridement in knee OA is controversial. Although some studies have demonstrated short-term relief of symptoms, others suggest that improvement in symptoms could be attributable to a placebo effect.
- In patients with OA of the knee, joint fusion can be considered as a salvage procedure when joint replacement has failed.

OARS, Osteoarthritis Research Society International.

OA, particularly in the elderly.³⁶ Short-term trials have suggested benefit from topical lidocaine patches. There are no published clinical trials of the many nonprescription topical agents or topical corticosteroids.

Oral analgesics

Acetaminophen (paracetamol)

Acetaminophen (paracetamol) is recommended for symptomatic treatment of patients with OA and mild to moderate pain by several societies because of its efficacy, safety, and cost. Several systematic reviews and meta-analyses of randomized placebo-controlled trials of acetaminophen for knee OA showed a small, but significant effect in relieving pain without an accompanying effect on either functional improvement or stiffness.^{6,33,34,37}

The safety profile of acetaminophen has been revisited, in particular when considering a 4000-mg daily dose. The results of a pharmacoepidemiologic study suggest that high (≥ 3000 mg) doses of acetaminophen may convey the same risk for upper gastrointestinal complications as traditional nonselective NSAIDs.³⁸ Similarly, the results of observational studies suggest that chronic use of acetaminophen may convey the same risk for hypertension as traditional NSAIDs.³⁹ Acetaminophen is a weak inhibitor of both cyclooxygenase-1 (COX-1) and COX-2, which is the reason for its apparent upper gastrointestinal and renovascular toxicity, although selection bias in study design cannot be excluded.⁴⁰ In addition, one should be cautious

when combining acetaminophen with oral NSAIDs; however, the combination of acetaminophen and topical NSAIDs can be used.

Another particular concern is the concomitant use of acetaminophen with over-the-counter combination products that also contain acetaminophen. Indeed, acetaminophen is the most common cause of drug-induced liver failure, as well as the need for hepatic transplantation, in the United States. Hence, an Advisory Committee of the U.S. Food and Drug Administration recommended that the maximal single daily dose of acetaminophen be lowered to 3000 mg and that combination products containing acetaminophen, including acetaminophen-opioid analgesics, be removed from the market. High-dose acetaminophen has also been associated with a prolonged prothrombin time in patients undergoing coumarin anticoagulation.

Nonsteroidal antiinflammatory agents

NSAIDs are used widely for the management of OA. A detailed description of their mechanism of action and the potential gastrointestinal, renal, and cardiovascular toxicity observed in clinical trials and observational studies can be found in Chapter 53. In addition, readers are referred to a “white paper” published by the ACR on the use of NSAIDs⁴¹ and the Safety of Nonsteroidal Anti-inflammatory Drugs website (www.sos-nsaids-project.org) for results from the European Union-funded pharmacoepidemiology project.

Systematic reviews of randomized placebo-controlled clinical trials that evaluated the use of NSAIDs for OA clearly demonstrate moderate short-term efficacy in comparison to placebo, although this appears to be magnified with use of the “flare” study design.^{6,33,34}

Nonsteroidal antiinflammatory drugs versus acetaminophen. A systematic review and meta-analysis found NSAIDs to be more efficacious than acetaminophen for OA-related pain, yet the risk associated with discontinuing therapy because of gastrointestinal adverse events was approximately 50% higher with traditional NSAIDs than with acetaminophen.³⁷ Furthermore, the majority of patients with OA expressed a preference for NSAIDs over acetaminophen. Hence, NSAIDs are a reasonable alternative to acetaminophen, especially in patients with OA and moderate to severe pain.

Cyclooxygenase-2-selective inhibitors versus traditional nonselective nonsteroidal antiinflammatory drugs. A systematic review of randomized trials of OA to evaluate the COX-2-selective inhibitors celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib concluded that efficacy was comparable between these agents, as well as equivalent doses of traditional nonselective NSAIDs.⁴² Only two COX-2-selective inhibitors are presently available, celecoxib and etoricoxib. They are indicated primarily in patients at increased risk for symptomatic gastrointestinal ulcers and complicated upper gastrointestinal events, including perforation and bleeding.⁴³ Their use in patients either receiving concomitant antiplatelet therapy or with cardiovascular risk factors has been the subject of several published recommendations by specialty societies.⁴⁴⁻⁴⁶ Perhaps the safest and most cost-effective approach for OA patients at risk for complicated upper gastrointestinal events is to use a COX-2-selective inhibitor in combination with a proton pump inhibitor. The same gastrointestinal ulcer protection has not been demonstrated with other antiulcer regimens.^{47,48} A comprehensive individual patient data meta-analysis of the cardiovascular and gastrointestinal safety of COX-2-selective inhibitors was published in August 2013 and demonstrated a modest increased risk for cardiovascular thrombotic events other than stroke, congestive heart failure, all-cause and cardiovascular-specific mortality and upper gastrointestinal bleeding compared to placebo.⁴⁹

Centrally acting analgesics

Duloxetine, a dual serotonin and norepinephrine reuptake inhibitor, was shown to be efficacious in relieving chronic knee pain in patients with OA.⁵⁰ It can be used either alone or in combination with NSAIDs in patients with persistent pain.⁵¹ Tramadol (a weak μ -opioid antagonist and serotonin reuptake inhibitor) is also efficacious in patients with OA either alone or in combination with acetaminophen or NSAIDs.⁵² The drug should be started at a low dose (50 mg once daily) and titrated upward slowly to minimize potential adverse events, especially in the elderly.⁵³

Opioid analgesics have been shown to be efficacious for short-term pain relief in patients with OA; however, they are rarely indicated for long-term therapy.^{54,55} Indeed, long-term use should be restricted to patients who continue to have severe pain and are either not candidates for or are unwilling to undergo total joint arthroplasty.⁴ Opioid analgesics have severe potential side effects, including falls and fractures, which is particularly of special clinical relevance in elderly patients.^{56,57} Principles underlying the use of opioid analgesics for chronic musculoskeletal pain are reviewed in Chapter 52. The American Academy of Pain Management and the American Pain Society have published recommendations for the use of opioid analgesics for chronic noncancer pain; these recommendations should be followed by all practitioners who are considering the use of opioid analgesics in their patients with OA.⁵⁸

Intraarticular therapy

Corticosteroids

Intraarticular depot corticosteroids are recommended in several guidelines for the management of patients with OA. Several systematic reviews and meta-analyses support the efficacy and safety of intraarticular steroids for hip and knee OA.⁵⁹⁻⁶¹ Onset of efficacy is rapid, with maximal efficacy reached in less than 1 week; the response lasts only 4 weeks in randomized controlled trials but often 3 months or longer in clinical practice. There is limited evidence that the presence of an effusion leads to a better response to intraarticular depot corticosteroids. However, in our opinion the presence of a knee effusion reflects an inflammatory synovitis, thus justifying the use of intraarticular depot corticosteroids.

Adverse events following intraarticular injection are uncommon.⁶² A placebo-controlled trial of repeated intraarticular steroid injections given every 3 months for 2 years demonstrated no particular detectable side effect or change in joint space width when compared with intraarticular saline.⁶³

Hyaluronate preparations

Viscosupplementation refers to the intraarticular injection of preparations of hyaluronic acid, a high-molecular-weight polysaccharide that is a major component of normal synovial fluid and cartilage, to relieve pain and improve function. Many hyaluronate preparations are currently available; there are differences in molecular weight, viscosity, origin (avian or bacterial), presence or absence of cross-linkage, and number of injections in each series. Several systematic reviews have evaluated the randomized controlled trials of intraarticular hyaluronan preparations, often with differing results.^{6,64-70} The main conclusions are that a course of intraarticular hyaluronic acid injections is associated with a small, but significant symptomatic effect lasting up to 26 weeks in comparison to intraarticular saline injections. Adverse events include the occasional injection site reaction and rare flare of pseudogout. Pseudoseptic reactions and granuloma formation have been reported mostly with cross-linked products.

Slow-acting symptomatic osteoarthritic drugs

Pharmaceutical compounds other than analgesics and NSAIDs have been licensed for the management of OA in Europe but not in the United States. The main differences between these compounds and NSAIDs follow:

- Delayed onset of action
- Carryover effect after use of the compound is discontinued
- Potential beneficial structural (disease-modifying) effect

Diaceirin

Diaceirin is an anthraquinone derivative that has been shown to inhibit the production of interleukin-1 (IL-1) and reduce cartilage breakdown and the development of cartilage lesions in preclinical models of OA. Two systematic reviews of randomized placebo-controlled trials demonstrated efficacy in comparison to placebo, with a small but significant effect size; the major adverse event was diarrhea, which was dose dependent.^{71,72}

The potential structural effect of diaceirin was investigated in a 3-year placebo-controlled trial involving 507 patients suffering from painful hip OA.⁷³ Radiographic progression (i.e., a decline in joint space width of at least 0.5 mm during the study) was significantly reduced in the diaceirin-treated group when compared with the placebo group. This reduction in radiographic progression was accompanied by a 25% reduction in the occurrence of total hip replacement; this reduction did not reach statistical significance, though, perhaps because of small numbers of events.

Glucosamine sulfate

Glucosamine is commercially derived from chitin, the specially processed exoskeleton of shrimp, lobster, and crab. Crystalline glucosamine sulfate is available commercially as a pharmaceutical drug in Europe; however, it is not registered in the United Kingdom or the United States. Evidence from systematic reviews of randomized placebo-controlled trials suggests that crystalline glucosamine sulfate, marketed as a pharmacologic agent in Europe (see earlier), is efficacious in the treatment of knee OA, whereas glucosamine preparations, including glucosamine hydrochloride, available as nutritional supplements in the United Kingdom and North America, are not.^{6,68,74-76} Reasons for this difference are unclear.

Two placebo-controlled randomized trials were conducted to assess the structure-modifying effect of crystalline glucosamine sulfate in patients with knee OA.^{77,78} Both showed a statistically significant reduction in the decline in joint space narrowing with glucosamine sulfate in comparison to placebo. A follow-up of patients who participated in these trials suggested that 3 years of glucosamine therapy might result in a reduced requirement for knee surgery.⁷⁹

Because of these findings (on one hand, positive symptomatic effect, positive structural effect, and long-term clinically relevant effect such as a reduction in the requirement for surgery and, on the other hand, potential biases of the reported studies⁷⁴⁻⁷⁶) and also because of the importance of the consequences for management of patients in daily practice, the National Institutes of Health (NIH) sponsored a large (3238 patients) multicenter U.S. study on painful knee OA (the GAIT trial).⁸⁰ This study was designed *a priori* to be split into two parts: the first 6 months for evaluation of their effect on symptoms and the following 24 months for evaluation of their effect on both symptoms and structure. The study design included five arms: placebo, celecoxib 200 mg daily (active control), glucosamine hydrochloride 500 mg three times per day, chondroitin sulfate 400 mg three times per day, and the combination of glucosamine plus chondroitin sulfate. When compared with placebo, there was a statistically significant difference in the primary outcome variable (i.e., response defined by at least 20% improvement in pain) in favor of celecoxib (70.4% vs. 60.1% responder rate), but no statistically significant difference in favor of glucosamine, chondroitin

sulfate, or the combination (percentage of responders: 64.0%, 65.4%, 66.6%, respectively). However, a predefined subgroup analysis performed in patients with severe pain at entry did demonstrate a statistically significant difference for the combination (glucosamine plus chondroitin sulfate) versus placebo (percentage of responders: 79.2% vs. 54.3%, respectively), but not for celecoxib versus placebo. Regarding long-term structural effects, no significant differences were found between groups in the rate of decline in joint space width over a period of 2 years.⁸¹ Hence, if a practitioner decides to use glucosamine for the treatment of symptoms and structure modification in patients with knee OA, the glucosamine sulfate preparation approved as a pharmaceutical agent in Europe should be used. A noninferiority trial of a fixed-dose combination of glucosamine hydrochloride and chondroitin sulfate (Droglican, Bioiberica S.A., Barcelona) versus celecoxib is in progress in several European countries; results are expected in 2014.

Chondroitin sulfate

Chondroitin sulfate is a macromolecule that provides (like hyaluronic acid) the framework for collagen formation. The rationale for use and information on the data available for symptomatic efficacy are similar to that discussed for glucosamine sulfate for relief of symptoms in patients with knee OA.^{6,68,76,82} A systematic review of randomized double-blind placebo-controlled trials did demonstrate a significant but small effect on slowing the rate of decline in joint space width in patients with knee OA.^{83,84} This result was robust to the inclusion of data from GAIT, even though the latter study did not demonstrate significance by itself.⁸¹ As with glucosamine sulfate, chondroitin sulfate seems to be very safe. The recommended dose is 800 mg once daily.

Avocado/soybean unsaponifiables

Avocado/soybean unsaponifiables (ASUs) can be considered either as a supplement or as a drug. Despite the fact that ASUs are commonly used for both hip and knee OA in France, evidence of its efficacy is only fair and the effect size is small.⁸⁵

Surgical interventions

Surgical interventions for OA can be categorized into three groups based on the rationale or the main objective of the treatment: (1) improving current symptoms (e.g., lavage and joint débridement); (2) preventing the risk for structural progression (e.g., osteotomy); and (3) improving the symptoms related to advanced disease (e.g., joint arthroplasty or replacement).

Arthroscopic or tidal lavage and joint débridement

In theory, lavage of the joint (through a large needle or by arthroscopy) removes debris, including microscopic or macroscopic fragments of cartilage or calcium pyrophosphate crystals, that may induce synovitis, a probable source of pain. Tidal irrigation is a similar procedure but uses only one entry site. Arthroscopic débridement consists of smoothing rough, fibrillated articular and meniscal surfaces, shaving tibial spine osteophytes that interfere with motion of the joint, and removing inflamed synovium. Several randomized controlled trials of arthroscopic débridement with lavage have not demonstrated efficacy in comparison to either sham surgery or usual

care in unselected patients with knee OA.^{61,86-88} The exact place of arthroscopic débridement and lavage in treating knee OA, if any, remains to be established; it may be indicated only in patients with symptoms and signs of internal derangement, including meniscal tears.

Osteotomy

Malalignment has been recognized as the most important predisposing factor to further structural progression in knee OA. Therefore, correction of this abnormality through either bracing or surgery has potential for structure modification. Observational studies suggest that osteotomy could be considered in patients with either mild to moderate medial tibiofemoral OA with varus malalignment or moderate superolateral hip OA with evident hip dysplasia.⁸⁹ However, lack of evaluation of the safety and long-term efficacy of this treatment modality precludes any formal recommendation, which explains the huge intercountry variability in use of this treatment. A randomized trial comparing high tibial osteotomy and unicompartmental knee replacement in patients with medial compartment knee OA and varus malalignment is in progress in Europe.

Total joint arthroplasty

Articular replacement is considered the “gold standard” because it is very effective in providing pain relief and restoring function in many patients with hip and knee OA. Consensus conferences sponsored by the NIH have proposed consensus criteria for total articular replacement in patients with hip and knee OA; in general, the indication for surgery is based on the severity of the patient's pain and functional limitation, the impact of OA on health-related quality of life, and the presence of moderate to severe radiographic features of OA.^{90,91} In daily practice, the decision should include consideration of the patient's comorbid medical conditions and willingness to undergo the procedure.

Recommendations for the management of hand osteoarthritis

Recommendations for the management of hand OA were published by the ACR in 2012³ and by the EULAR in 2007.⁹ Several systematic reviews of nonsurgical therapies for hand OA were used as the basis for the ACR recommendations.⁹²⁻⁹⁵ The data suggest that there is some evidence to support the efficacy of occupational therapy, including instruction in joint protection techniques and the use of assistive devices and thermal modalities; splinting of the first carpometacarpal (CMC) joint and topical therapies, including capsaicin and NSAIDs; oral NSAIDs, including COX-2-selective inhibitors; and tramadol. Hydroxychloroquine may be efficacious in patients with inflammatory interphalangeal joint OA who have not responded adequately to topical or oral NSAIDs; neither sulfasalazine nor methotrexate are recommended in this situation. Intraarticular injections of corticosteroid and hyaluronate preparations are not more efficacious than saline injections for OA of the first CMC joint. Trials of tumor necrosis factor inhibitors failed to demonstrate efficacy in patients with erosive hand OA either for symptomatic or for structural outcomes.⁹⁶ Trials of monoclonal antibodies to IL-1 for hand OA are in progress.

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Diffuse idiopathic skeletal hyperostosis

■ GEOFFREY LITTLEJOHN

- Diffuse idiopathic skeletal hyperostosis is a chronic, age-related condition characterized by new bone growth, especially at entheses.
- Radiologic findings are characteristic.
- Hyperostosis results in an increase in bone mass.
- Few symptoms are related to diagnostic changes in the thoracic spine.
- Hyperostosis carries the risk of important cervical and lumbar arthropathy, enthesopathy, and neural impingement.
- An association exists with obesity, type 2 diabetes, gout, dyslipidemia, hypertension, hyperinsulinemia, and other features of metabolic syndrome.
- Growth factors, particularly insulin, are implicated in the disorder.

HISTORY

Diffuse idiopathic skeletal hyperostosis (DISH), also known as *ankylosing hyperostosis* or *Forestier disease*, is a ubiquitous skeletal condition affecting many species and most human populations studied. Forestier and Rotes-Querol¹ first presented comprehensive anatomic, radiologic, and clinical data on the disorder, which was then termed *ankylosing hyperostosis*. The condition is seen as a well-defined syndrome with both axial and peripheral manifestations. The diffuse nature of the condition later led to use of the term *diffuse idiopathic skeletal hyperostosis*.²

EPIDEMIOLOGY

There is a 2:1 reported male predominance in DISH, with the prevalence in both sexes rising with age and weight (Fig. 182.1)^{3,4}; the condition is uncommon before the age of 45 years.⁵

Although diagnostic criteria vary, population surveys indicate that DISH is a common condition. In Scandinavia the annual cumulative incidence is estimated to be 7 per 1000 in men and 4 per 1000 in women beyond the age of 30.⁶ Prevalence rates vary in different populations but are consistent with these findings.⁷ Approximately 10% to 15% of men and 5% to 10% of women older than age 65 have DISH, although some populations have an increased predisposition for the disorder (Table 182.1).^{8,9} It is possible that the prevalence is increasing in some of these populations.¹⁰

CRITERIA AND CHARACTERISTIC DESCRIPTION

Criteria for the diagnosis of DISH rely principally on radiologic findings in the thoracic spine. These criteria typically require new bone formation to bridge four contiguous vertebral bodies in the absence of both degenerative disk disease and inflammatory sacroiliac or facet joint changes.¹¹ In routine clinical practice, however, it is more common to see significant age-related disk or facet joint degenerative changes occurring in conjunction with changes of DISH. Thus study populations of “pure” DISH may differ in clinical characteristics from those with DISH occurring in conjunction with other common degenerative spinal conditions.

The condition is characterized by widespread new bone formation, with an increase in the amount of normal new bone, heterotopic bone formation,

and specifically the presence of new bone growth into the enthesal regions (Fig. 182.2). The enthesis is that region where the tendon, ligament, joint capsule, or annulus fibrosus fibers insert into bone.¹² Although it was the prominent new bone growth in the anterolateral enthesal regions along the thoracic spine that first brought attention to this condition, it may affect any skeletal structure to differing degrees.

DISH changes are most characteristic in the thoracic spine, where uninterrupted new bone may “flow” from one vertebra to another. It is more prominent on the right side of the thoracic vertebra, which is thought to be a consequence of the pressure effect of the left-sided aorta. The presence of the anterior longitudinal ligament over the anterior two thirds of the vertebral bodies dictates the distribution of the new bone formation. There is often a gap in the new bone adjacent to the intervertebral disk or between the new bone and the intact original cortex. When disk changes are absent, the newly formed bone may be applied close to the vertebral bodies and can, at times, mimic an inflammatory spondylitis. In DISH the original cortex remains under the ossified ligament, whereas in spondylitis erosion of the cortex is characteristic, particularly at the vertebral corners, and underlying sclerosis is present when the inflammation is active. DISH may coexist with spondylitis or any other condition. In particular, because the condition is more prominent with increased age, it commonly coexists with intervertebral disk disease, and in such situations the bulging of the disk material anteriorly may give rise to dramatic anterior spinal hyperostotic change. In the more mobile cervical and lumbar spine regions, hyperostotic changes are more characteristic than simple bridging, and spinal stenosis may result.

There is a spectrum of spinal new bone formation, with increasing amounts laid down with increasing duration.⁴ The well-defined condition occurs over several years, but regression of new bone growth over a short period has been noted in the context of a pressure effect from an enlarging aortic aneurysm.¹³ The spinal new bone formation appears to be a dynamic process, with deposition and remodeling likely similar to that which occurs in other skeletal areas. Peripheral new bone formation is also more prominent in the enthesal areas, particularly around heels, knees, and elbows, among other regions. Such changes also occur on a spectrum ranging from minor to quite marked hyperostosis.¹⁴ Pronounced peripheral hyperostosis may precede spinal changes diagnostic of DISH. All of these changes appear to be part of the one condition; however, the diagnosis of DISH currently rests on characteristic findings in the spine and not in the periphery.

The “diffuse hyperostosis” of DISH includes increased bone formation as demonstrated by phalangeal tufting, increased cortical thickness of tubular bones of the hand, and an increase in the size of the sesamoid bones.¹⁵ Increased bone mineral density has been noted in the spine when dual energy x-ray absorptiometry is used, possibly due to the effects of increased enthesal ossification,¹⁶ but quantitative computerized tomographic techniques have shown no differences in peripheral bone density or geometry.¹⁷

Heterotopic new bone formation after surgical procedures, such as total hip replacement, may occur in DISH.¹⁸

DISH may coexist with inflammatory joint diseases such as rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, or gout. It has been shown to modify the radiologic reaction to rheumatoid arthritis, with less destructive bone disease and a tendency for erosions to heal more quickly.¹⁹ There is an increased prevalence of DISH in patients with gout and Paget disease.^{9,20}

CLINICAL FEATURES

The process of new bone deposition in DISH is asymptomatic.²¹ However, the consequences of new bone growth in areas described earlier may cause

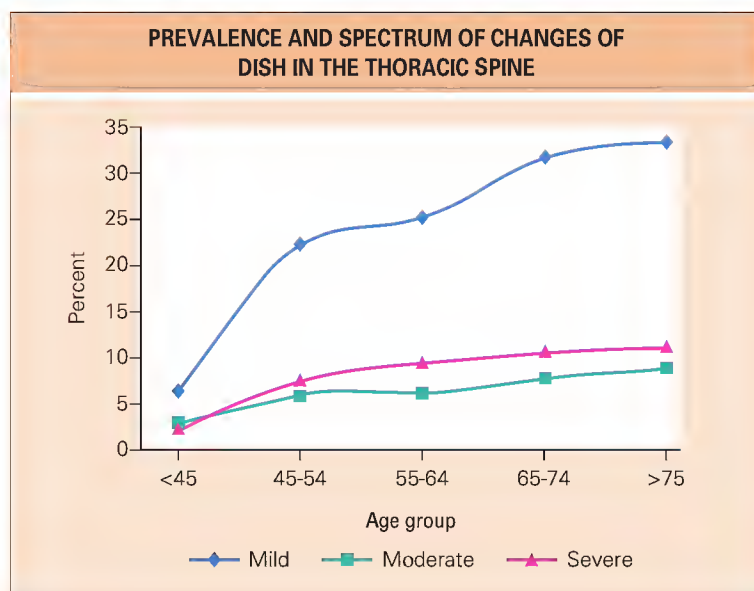


Fig. 182.1 Occurrence of diffuse idiopathic skeletal hyperostosis (DISH) in the thoracic spine in different age groups. Data are from 296 individuals at autopsy.¹³ Mild, enthesal new bone present at two or more levels; moderate, continuous new bone spanning fewer than four levels; severe, continuous new bone spanning four or more levels (typical DISH). See also Fig. 182.6.

TABLE 182.1

Prevalence of diffuse idiopathic skeletal hyperostosis

Population	Prevalence
White populations (various studies) ¹⁴⁻¹⁶	Men 10% Women 8%
Pima Indians ¹⁷	Men 54% Women 14%
Men with gout ¹⁸	58%

*Table gives the prevalence of diffuse idiopathic skeletal hyperostosis at age 65 years or older (selected studies¹⁴⁻¹⁸).
Diagnostic criteria vary slightly.*

increased stiffness in neck, back, or peripheral joints.^{22,23} Tight spinal structures may also increase regional symptoms, including tenderness.²⁴

In peripheral joints, a stiffening arthropathy due to thickening and shortening of ligaments has been described long before the characteristic spinal changes appear.²² Clinically, there may be painless reduction of internal rotation of shoulders and hips and reduced flexion of fingers and knees.

Pain may be present in some patients who have peripheral enthesopathy (e.g., from a calcaneal spur), most likely because abnormal biomechanical stress causes injury to the enthesis. However, although the majority of such extraspinal enthesal changes are asymptomatic, adequate controlled studies are lacking.

Important clinical features arise when new bone growth obstructs or impinges on other tissues. In the cervical spine DISH may give rise to dysphagia²⁵ or cervical myelopathy.²⁶ Association with ossification of the posterior longitudinal ligament²⁷ can result in myelopathy and even quadriplegia. In the lumbar spine, spinal stenosis may occur secondary to posterior osteophytic ridges and facet arthropathy with marked hyperostosis.

Uncommonly, fractures through bony bridges may occur; if so, they may be difficult to diagnose and treat.²⁸

DISH is associated with a particular type of hip disease²⁹ and increased prevalence of Heberden nodes.³⁰ The elongated tibial spines common in obesity-related knee osteoarthritis are ossifications of the enthesal attachments of the cruciate ligaments.¹⁴

INVESTIGATIONS

DISH cannot be diagnosed without radiologic evaluation. Although DISH is often first identified on a routine posteroanterior chest radiographic



Fig. 182.2 Hand of a patient with diffuse idiopathic skeletal hyperostosis demonstrates the full spectrum of bone and enthesal changes in this disorder. Note prominent phalangeal enthesopathy (second and third proximal phalanges), "arrowheading" (tufts of terminal digits), exostoses (second and fifth metacarpophalangeal heads), capsule bone (fourth proximal phalangeal joint), cortical thickening (tubular bones), and enlargement of sesamoid bones. The soft tissues and joint spaces are normal.¹⁵

projection (Fig. 182.3), the appropriate studies are posteroanterior and lateral views of the thoracic or dorsal spine.³¹ Computed tomography (CT) provides more dramatic images (Fig. 182.4) but is not necessary unless the presence of conditions such as spinal stenosis is being sought. Magnetic resonance imaging (MRI) shows the ligamentous thickening that precedes ossification. Plain radiographs of peripheral areas show variable degrees of peripheral enthesopathy (see Fig. 182.2). Bone scans show no change in the involved area but may help identify an associated process such as spinal fracture or mechanically induced inflammatory enthesal changes.

Routine biochemical findings and erythrocyte sedimentation rate are normal. There are often abnormalities associated with hyperinsulinemia, non-insulin dependent diabetes, dyslipidemia, gout, and metabolic syndrome.³²⁻³⁴

DIFFERENTIAL DIAGNOSIS

One of the most important differential diagnoses is that of ankylosing spondylitis. The new bone formation in DISH may be smooth and tightly fused to the underlying cortex, thus mimicking ankylosing spondylitis. Usually, however, exuberant and bumpy bony change within the anterior longitudinal ligament, with preservation of the original cortex, is characteristic of DISH. The diagnostic problem is occasionally compounded by anterior osteophytosis of the sacroiliac joints, which may lead to a change falsely interpreted on plain radiographs in posteroanterior view as postinflammatory fusion of the joints. In this situation, CT of the sacroiliac joints shows the anterior fusion with no inflammatory change in the joint itself, and MRI confirms lack of any inflammation-related bone edema.

Degenerative disk disease characteristically results in disk space narrowing with horizontal osteophytes, prominent anteriorly. Facet joint hypertrophic changes are commonly seen and narrow the intervertebral neural foramina as well as the spinal canal. The hyperostotic peripheral joint changes of DISH resemble primary osteoarthritis in distribution but are distinguished by early stiffening and relative preservation of joint space in the early stages.^{15,22}

Acromegaly is also characterized by new bone formation, but subcutaneous soft tissue and cartilage thickening are prominent. In early acromegaly there is hypermobility, in striking contrast to the stiffening characteristic of DISH. The bony spurs and hyperostosis of DISH may at times be identical to those seen in acromegaly, and both conditions are associated with hyperostosis frontalis interna.³⁵ There is no increase in joint space or in soft tissue thickness in DISH.¹⁵ Repetitive trauma, fluorosis, hypervitaminosis A, and

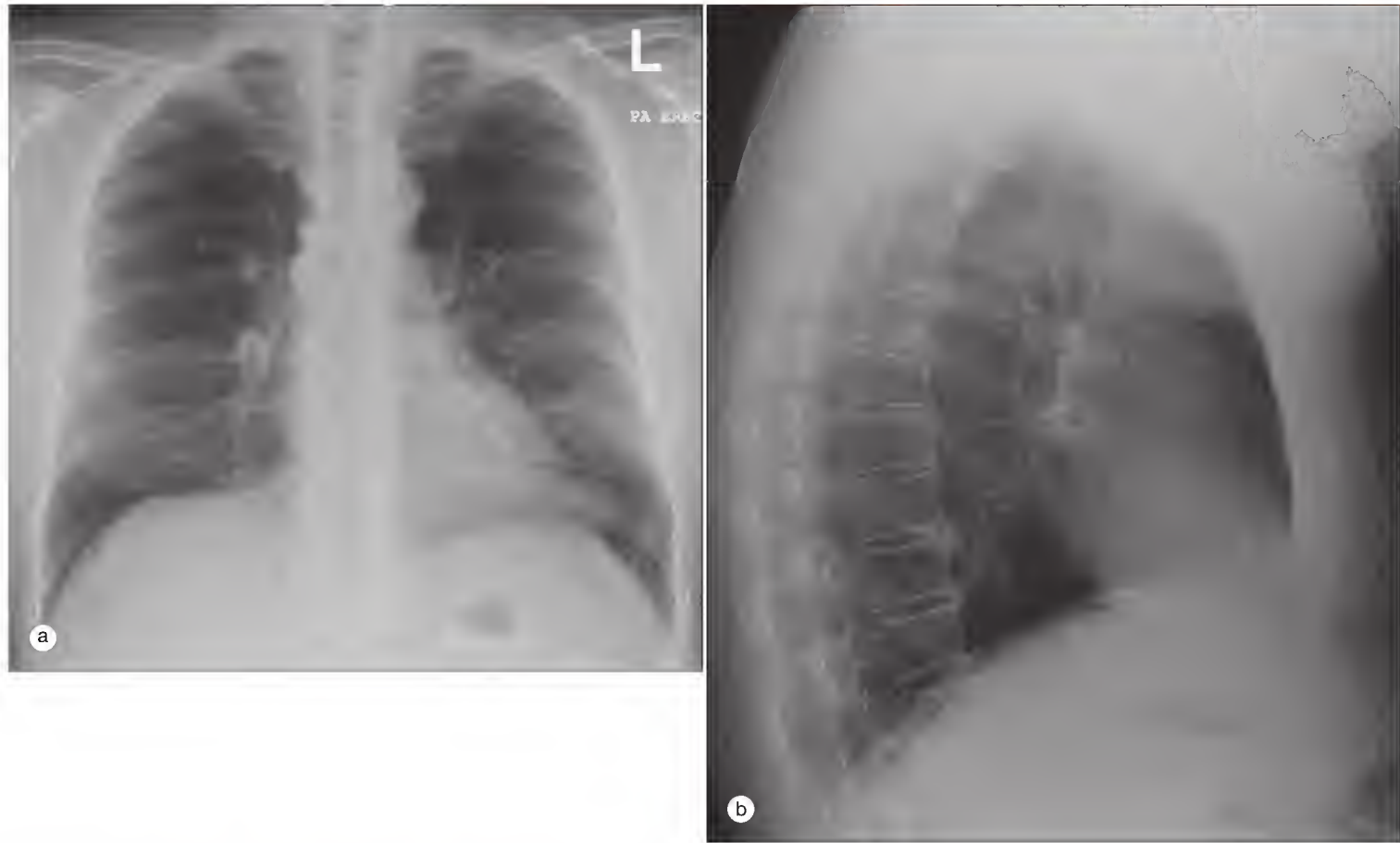


Fig. 182.3 Typical radiographic findings in the thoracic spine on routine chest radiographs in posteroanterior (a) and lateral (b) views, with “flowing” new bone formation linking four contiguous vertebrae, predominantly right-sided, in the absence of intervertebral disk change.



Fig. 182.4 Computed tomographic reconstruction of the thoracic spine of a patient with diffuse idiopathic skeletal hyperostosis. There is prominent new bone deposition on the right anterolateral thoracic spine.

retinoid therapy may all produce enthesopathy, which may require differentiation from DISH.

ETIOLOGY AND PATHOGENESIS

The principal changes in DISH occur at the enthesis. Chondrocytes lying in the enthesal region bordering the bony interface are activated and cause

changes to the surrounding matrix that favors subsequent ossification (Fig. 182.5). Later, vascular invasion occurs from the adjacent cortical haversian canals and preferential ossification occurs at, or close to, the enthesis (Fig. 182.6).^{4,36} The resultant enthesal bone deposition is further modified by local mechanical factors.

The propensity to deposit new bone has an underlying metabolic cause. Since the early reports of Forestier, an association between obesity and DISH has been noted.¹ Subsequently a link was observed with impaired glucose tolerance and related adult-onset type 2 diabetes.^{32,37} The prevalence of these abnormalities in patients with DISH ranges from 17% to 60% and thus is much higher than in the general population. Conversely, the prevalence of DISH in patients with adult-onset type 2 diabetes ranges from 13% to 50%. Glucose intolerance and obesity seem to act as independent factors in their association with DISH, although there is no relationship between the degree of hyperglycemia and the severity of the bony change. No patients with type 1 or insulin-deficient diabetes have been found to have DISH.

Levels of candidate bone growth factors such as growth hormone and somatomedin (insulin-like growth factor) are not consistently abnormal in DISH. In contrast, levels of insulin, which also has growth factor activity, have been found to be significantly higher in individuals with DISH (Fig. 182.7).^{37,38} Hyperinsulinemia is seen in Pima Indians, who have a high prevalence of DISH,⁸ and it is also associated with hyperostosis frontalis interna and ossification of the posterior ligament (OPLL) (Fig. 182.8).³⁹ Insulin promotes endochondral ossification by enthesal chondrocytes.⁴⁰ The hyperinsulinemia likely relates to the documented association among DISH, central obesity, hypertension, lipid abnormalities, and increased risk of vascular disease,⁴¹ all of which are components of metabolic syndrome.³³

OPLL, more common in Japan, shares many features with DISH but is present predominantly in the cervical spine. Patients with OPLL also have increased rates of type 2 diabetes, and in addition, involvement of bone growth factors such as bone morphogenic proteins and transforming growth factor- β has been demonstrated in various histochemical and cytochemical analyses.⁴²

Dickkopf-1 (Dkk-1) is an inhibitor of osteoblastogenesis and low levels link with new bone formation. One study found Dkk-1 levels to be low in DISH,⁴³ although another study did not confirm this observation.⁴⁴

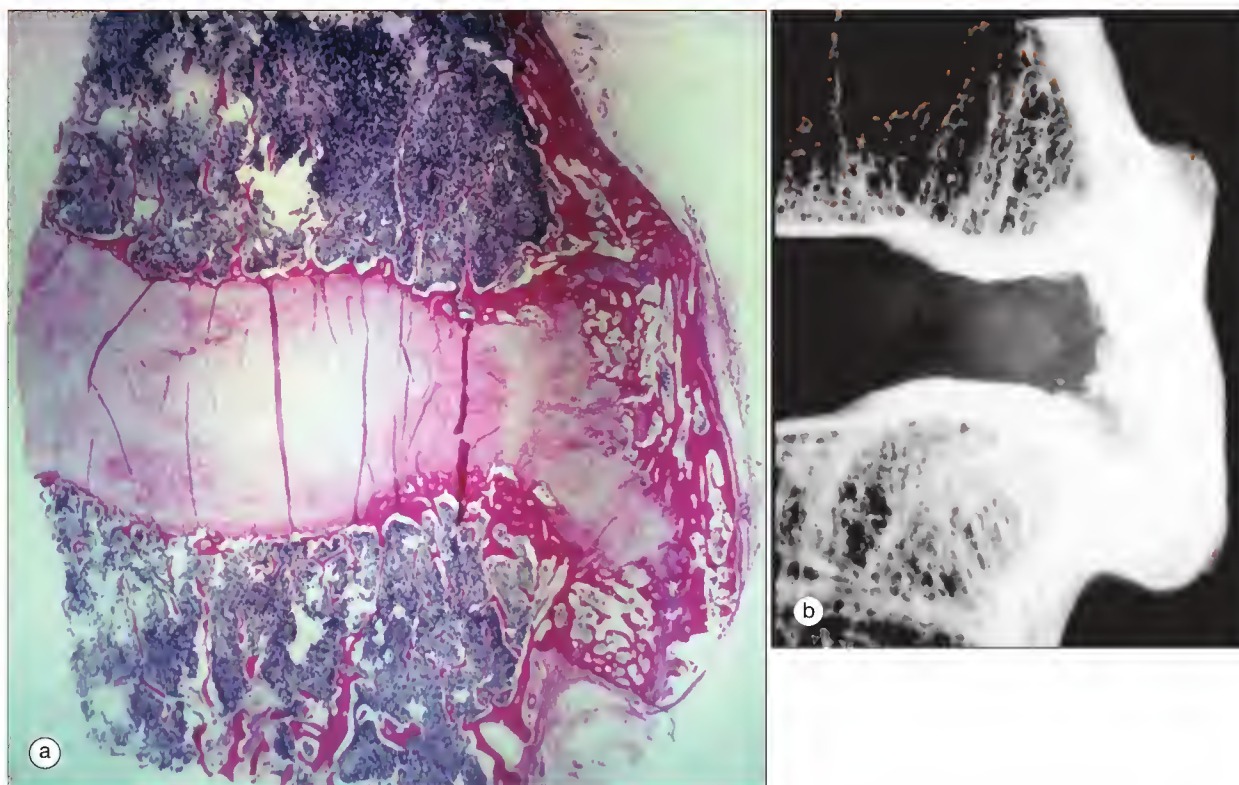


Fig. 182.5 Histopathologic (a) and radiologic (b) changes in an intervertebral disk in a patient with diffuse idiopathic skeletal hyperostosis.

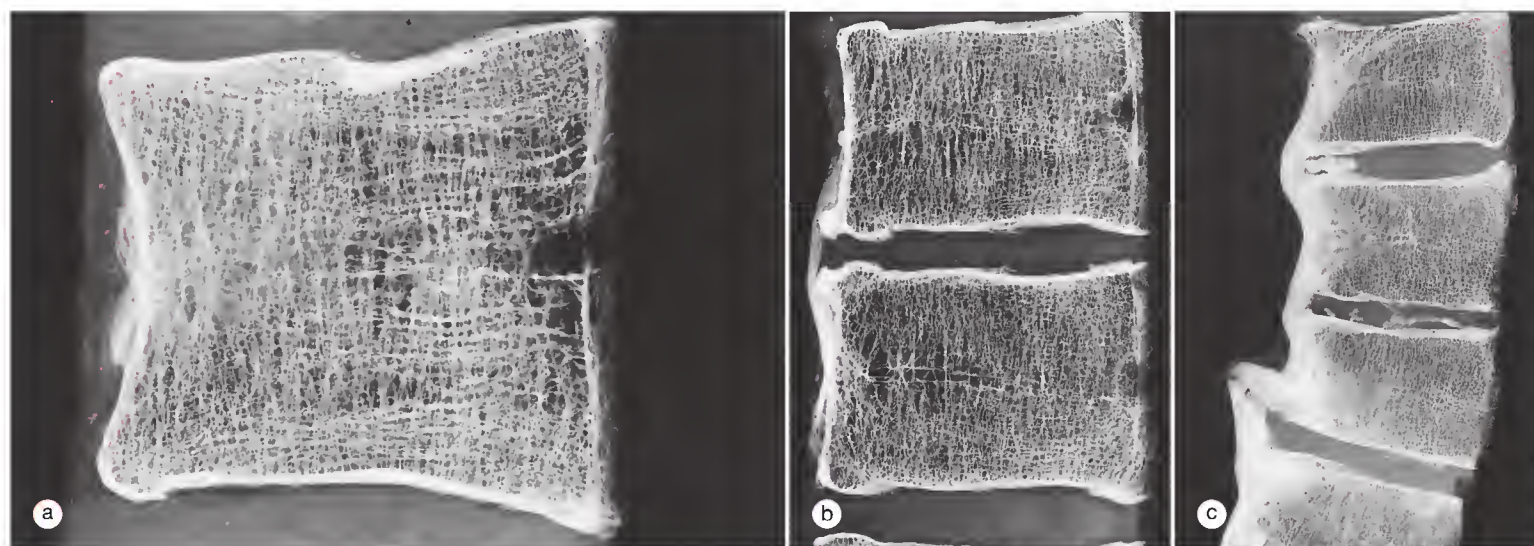


Fig. 182.6 Progressive spinal enthesal changes in diffuse idiopathic skeletal hyperostosis (DISH). The earliest change is shown in (a), with ossification at the site of attachment of the anterior longitudinal ligament to the middle of the vertebral body, well away from the annulus. Note the separation of the ossification from the intact cortex, except at the site of attachment. Moderate changes are seen in (b), with ossification bridging the disk space but still firmly attached to cortex at the middle of the vertebral body. Advanced changes, typical of established DISH, are shown in (c), with smooth attachment of the new bone to the original cortex. The ossified ligament is much thickened and interrupted at the lower level.

Chronic vitamin A toxicity in animals and humans produces DISH-like changes. Studies of vitamin A and metabolites in stimulated states indicate an increased level of these retinoids in patients with DISH,⁴⁵ but the significance of this remains speculative.

Familial clustering^{46,47} and association with the *COL6A1* gene in some populations⁴⁸ suggest that genetic factors are also likely to be involved in DISH.

MANAGEMENT

Prevention

A high risk of DISH may be anticipated in large-boned, large-muscled individuals with abdominal obesity and metabolic syndrome. Thus patients

with gout, hypertension, and peripheral enthesopathies and stiffness of the hips and shoulders or large, stiff fingers may have this disorder. Abnormal lipids characteristic of metabolic syndrome and abnormal glucose metabolism including hyperinsulinemia may be found. The best therapy at this stage is weight reduction, ideally through a fitness program (Table 182.2).

Specific interventions

There is no specific treatment available for established DISH. However, patients should be carefully assessed and treated for components of metabolic syndrome, namely, diabetes, dyslipidemia, gout, and hypertension.

Physical therapy may benefit patients with stiffened spinal regions and help relieve symptoms in peripheral joint areas, although no confirmatory published literature is available.

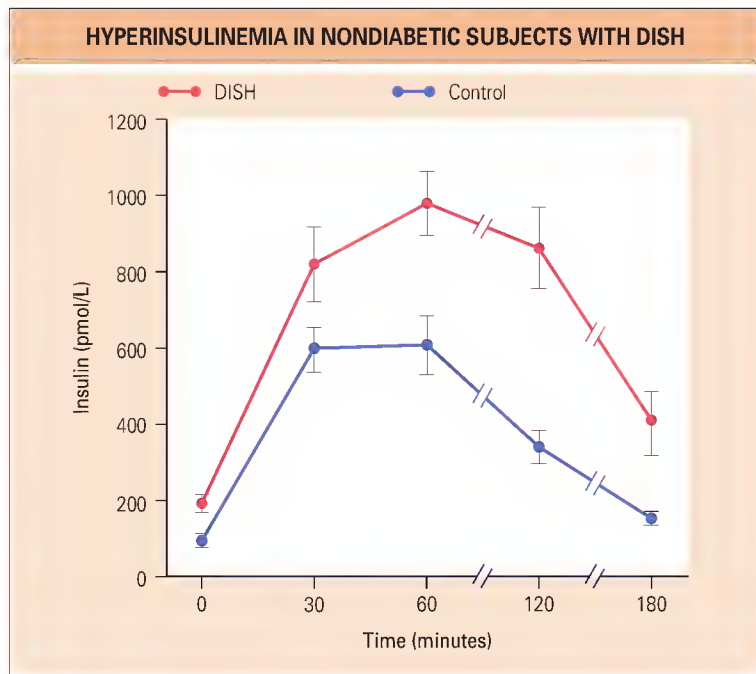


Fig. 182.7 Hyperinsulinemia during a standard glucose tolerance test in nondiabetic individuals with diffuse idiopathic skeletal hyperostosis (DISH), compared with control subjects matched for age, gender, and body mass index.⁴² Values are mean $\pm$ standard error in pmol/L.

TABLE 182.2
Management issues in diffuse idiopathic skeletal hyperostosis

Issue	Management
Spinal and peripheral enthesopathy	
Asymptomatic (usual)	Encourage exercise and ideal body weight, assess cardiovascular risk factors
Symptomatic	As above; plus physical therapy, local injection therapy, use of analgesic/antiinflammatory agents
Complications	
Facet arthritis	Physical therapy, injection
Spinal stenosis	Exercise, injection, surgery
Dysphagia	Conservative management, surgery
Osteoarthritis	Standard approaches
Associated metabolic syndrome	
Hypertension, diabetes, dyslipidemia, gout, obesity	Treat vigorously



Fig. 182.8 Magnetic resonance image of the cervical spine of a 58-year-old white male with concurrent diffuse idiopathic skeletal hyperostosis and ossification of the posterior ligament, with the latter causing symptomatic cervical cord compression.

Surgical interventions may rarely be necessary for complications such as osteophytic dysphagia or spinal stenosis.

Peripheral enthesal pain, usually induced by microtrauma, may be helped by the use of orthotics, physical therapy, or carefully placed local anesthetic and corticosteroid injections.

Peripheral osteoarthropathy may be preceded by asymmetric acceleration of capsular thickening and new bone formation around the joint, with stiffening further increasing the crushing forces through the joint. Anecdotally, local cortisone injections may improve range of motion and relieve pain.

The risk of heterotopic bone formation following hip arthroplasty may be reduced by administration of nonsteroidal antiinflammatory medications, although this complication is uncommon.⁴⁹

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183

Neuropathic arthropathy

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- Neuropathic arthropathy is a progressive, destructive joint disease associated with sensory loss.
- It is characterized by relative lack of pain resulting from sensory neuropathy, and by atrophic changes on plain radiography.
- Bony swelling and soft tissue enlargement, effusion, laxity, instability, and deformity occur.
- Common sites of joint involvement are the midfoot, ankle, and knee, and less commonly, the hip, spine, shoulder, and wrist.
- Joint destruction, subluxation, heterotopic new bone formation, and recurrent or persistent joint effusion are involved.

HISTORY

Neuropathic arthropathy is a relatively painless, progressive, destructive arthropathy caused by a neurologic deficit. The first description was probably by William Musgrave (1655-1721), a physician from the West of England, but it was the French neurologist Jean-Martin Charcot (1825-1893)¹ who gave his name to the condition. In 1868 he described “l’arthropathie des ataxiques” in a French soldier with tertiary syphilis who had been marching 25 km each day. He thought that the “bag of bones” represented spontaneous fractures as a result of nerve degeneration and bone atrophy. Sir James Paget named the condition after Charcot in 1881, but in this chapter the term *neuropathic arthropathy* is used throughout. In 1917 Eloesser assessed the role of trauma in the development of neuropathic arthropathy by cutting the posterior roots of the spinal cord in cats, which resulted in analgesia, anesthesia, and ataxia. His work was used to support the neurotraumatic theory of pathogenesis. In 1936 Jordan² gave the initial description of neuropathic arthropathy associated with diabetes. Diabetes is now the most common cause of neuropathic arthropathy, accounting for two thirds of all cases in the lower limb.³ Leprosy⁴ is a common cause in endemic areas of the disease.

Neuropathic arthropathy can complicate a variety of sensory neurologic disorders. In addition to tabes dorsalis (syphilis), diabetes, and leprosy, has been described in syringomyelia,⁵ multiple sclerosis, amyloidosis, congenital insensitivity to pain,⁶ spinal cord trauma⁷ and tumors, arachnoiditis after spinal anesthesia or meningitis, familial dysautonomia (Riley-Day syndrome), familial and other polyneuropathies,⁸ peroneal muscular atrophy, and neurofibromatosis.⁹ In childhood the most common cause is spina bifida with meningocele. Neuropathic arthropathy has been described secondary to the neuropathy of human immunodeficiency virus (HIV) infection¹⁰ (which may be exacerbated by the use of nucleoside reverse transcriptase inhibitors); the success of highly active antiretroviral therapy means that prolonged life span may result in more HIV-associated neuropathic arthropathy in the future. In up to 30% cases of neuropathic arthropathy, no apparent neurologic disorder is found.

ETIOLOGY

Diabetes mellitus

Sensory neuropathy is a complication seen in up to 60% of individuals with diabetes mellitus, especially if it is long-standing or poorly controlled. Neuropathic arthropathy occurs in 0.1% to 0.5% of diabetic patients, with an

approximately equal sex ratio.³ Typically patients have severe distal symmetric neuropathy, are 50 to 60 years old, and have at least a 10-year history of diabetes.¹¹ Neuropathic arthropathy in diabetes is frequently associated with ulcers and ischemic lesions in the feet, as well as other evidence of microangiopathy.

Syringomyelia

An estimated 20% to 25% of patients with syringomyelia develop neuropathic arthropathy.⁵ It is usually monoarticular and typically affects joints of the upper extremity, especially the glenohumeral joint¹² (Fig. 183.1), elbow, wrist (Fig. 183.2a and b), or fingers. Bilateral and symmetric involvement is less frequent in syringomyelia than in tabes dorsalis. Neurologic manifestations due to spinal cord damage include loss of pain and temperature sensation, although tactile and postural sensitivity is preserved; wasting of the intrinsic muscles of the hand (see Fig. 183.2c); and amyotrophic paralysis in the upper limb. Magnetic resonance imaging (MRI) (Fig. 183.3) can demonstrate spinal cord enlargement,¹³ especially in the cervical region.

Tabes dorsalis

Of patients with tertiary syphilis, 5% to 10% develop neuropathic arthropathy.¹⁴ It is still the classic model for neuropathic joint disease despite its decreasing incidence.¹⁵ Both sexes are affected equally. The onset is usually in adulthood. The lower limb joints are affected in 60% to 75% of cases, with involvement of knee, hip, ankle, shoulder, and elbow in descending order of frequency (Fig. 183.4). Other joints involved are the forefoot, midfoot, vertebral column, and sternoclavicular joints. Monoarticular involvement predominates but is not universal. Diagnosis requires identification of specific antitreponemal antibodies in blood and cerebrospinal fluid.

Leprosy

Leprotic patients develop peripheral neuropathy with a variety of secondary changes in the feet. Neuropathic arthropathy can result from long-standing neuropathy, with little evidence of active leprosy.⁴ The disease alters the shape of the hands and feet owing to subluxation of individual joints. In the feet the changes usually start in the medial arch and later involve the lateral arch, talus, and calcaneus. In extreme cases, dissolution of the midfoot results in separation of the forefoot and the hindfoot, and the tibia is driven downward to become weight bearing. The pathogenesis in this type seems to be mainly direct trauma to the forefoot.

Congenital indifference to pain

Another group of disorders that can lead to neuropathic arthropathy includes congenital insensitivity to pain and hereditary sensory neuropathies types I to IV. The pathogenesis appears to be the same as that in other causes of neuropathic arthropathy. Often, there is marked disproportion between the severity of the disease process and clinical symptoms.⁶

Meningomyelocele (spinal dysraphism)

Neuropathic changes in childhood raise the possibility of congenital indifference to pain or meningocele. Principally the ankle and tarsal articulations are affected. In active children changes may appear in the first 3 years of life and include osteoporosis, diaphyseal and metaphyseal fractures, injuries of the growth plate, epiphyseal separations, persistent effusions, articular destruction, and soft tissue ulcerations.

CLINICAL FEATURES

The distribution of joint involvement depends on the underlying neuropathy (Table 183.1). Monoarticular or oligoarticular involvement is most common, but polyarticular forms do occur.

Early neuropathic arthropathy is characterized by an acute inflammatory phase with erythema, warmth, swelling, and edema.¹⁶ Pain may be present despite sensory neuropathy. Pedal pulses are typically easily palpable, and a temperature gradient of 2° to 5° C between the affected and contralateral foot might be noted. There may be a history of trauma. Radiographic findings may be normal at this stage,¹⁷ but MRI scans may suggest neuropathic arthropathy.¹⁸ The differential diagnosis includes infection, sprain, and cellulitis (see also later). Correct diagnosis is vital, because delay and continued weight bearing leads to increased bone destruction and major deformities. Untreated, the disease progresses to chronic neuropathic arthropathy.

In diabetes the midtarsal joint is most commonly affected, which results in midfoot collapse and a valgus forefoot. The hindfoot may also be affected, and pathologic fracture of the fibula can occur. Tarsometatarsal joint

involvement is associated with edema of the dorsum of the foot and bony deformities, with dorsal prominence or plantar protrusion. On examination, the range of motion is usually subnormal but may even be excessive as a result of laxity and subluxation (Figs. 183.5 and 183.6). Instability becomes permanent and deteriorates with time. Downward collapse of the tarsal bones may produce abnormal convexity of the plantar surface, with the end result being a rigid rocker-bottom foot. Trophic skin lesions and ulcers frequently accompany the articular disorder on the sole of the foot.

Neuropathic arthropathy at the knee is usually of gradual onset, although it may be subacute or even acute, occurring within a few hours (pseudoinflammatory). The knee becomes warm and swollen, with signs of joint effusion. Patients may delay seeking medical opinion until the knee has become permanently swollen, with instability leading to valgus, varus, or recurvatum deformities, and enlargement of the articular bones and periarticular tissues. Despite gross abnormalities the patient may be able to walk, albeit with a limp.

A similar clinical picture is seen in other major limb joints. When the hip is affected (Fig. 183.7) there is often extensive joint destruction, shortening of the leg, severe loss of function, and a limp. The hand is rarely involved, and the manifestations in general are less severe. They include vasomotor problems, digital ulcers, thickening of the fingers, and painless subluxation of the finger joints. In the spine localization is most frequent in the lumbar region, although the cervical and dorsal spine may also be involved. Severe deformity (kyphosis, scoliosis) may result despite normal mobility and relative absence of pain. Because of this paucity of symptoms, the condition is often first discovered during routine examination. Occasionally, signs of nerve root compression are present.

The belief that neuropathic joints are painless is probably untrue. Arthralgia is well documented in up to 50% of patients, although the symptoms are usually less than expected from the degree of joint destruction.



Fig. 183.1 Syringomyelia with neuropathic disease of the shoulder. Atrophic changes and soft tissue calcification are seen. (Courtesy Dr. I. Watt.)

TABLE 183.1

Joint involvement in neuropathic arthropathy

Disease	Site of involvement
Diabetes mellitus	Midtarsal, metatarsophalangeal, tarsometatarsal
Syringomyelia	Shoulder, elbow, wrist
Amyloidosis	Knee, ankle
Congenital sensory neuropathy	Knee, ankle, intertarsal, metatarsophalangeal
Tabes dorsalis	Knee, hip, ankle
Leprosy	Tarsal, tarsometatarsal



Fig. 183.2 Syringomyelia. (a) A neuropathic wrist joint in a patient with mild syringomyelia. Note the swelling and deformity of the joint. (b) Radiograph showing the gross destruction of the proximal carpal row with attrition and simplification of the bony margins. Residual fragments of bone and considerable soft tissue swelling can also be seen. (c) Wasting of the intrinsic muscles of the hand and claw deformity.



Fig. 183.3 Magnetic resonance image of the cervical spine in a patient with syringomyelia, showing the fluid-filled syrinx in the center of the spinal cord.



Fig. 183.4 Syphilitic Charcot knee joints showing gross destructive changes.

IMAGING

Plain radiography

In the early stages, radiographs may show normal findings or reveal only soft tissue swelling. Other early features include periosteal calcification and joint effusion. The presence of an enlarging and persistent effusion, minimal subluxation, fracture, and fragmentation suggests the possibility of neuropathic arthropathy. After a few weeks the calcification becomes more dense and the bone margin less well defined.^{16,17}

Radiographs in established neuropathic arthropathy (Fig. 183.8) show a disorganized joint characterized by bone resorption and formation occurring simultaneously. Fractures may occur, and free fragments of bone may be seen in the joint cavity. The degree of sclerosis, osteophytosis, and fragmentation is greater than in other articular diseases. The bone fragments and irregular articular surfaces resulting from the osseous destruction are generally well defined and sharp; poorly margined, ill-defined bone contours, as occur in septic arthritis, are not evident unless there is additional infection (not infrequent, especially in diabetic patients). Intraarticular bony



Fig. 183.5 Diabetic neuropathy of the hindfoot. Destruction of the joint with collapse and fragmentation is seen.



Fig. 183.6 Neuropathic ankle. Marked instability of the subtalar and midtarsal joints is seen with collapse on weight bearing.



Fig. 183.7 Neuropathic hip secondary to tabes dorsalis. (Courtesy Dr. I. Watt.)

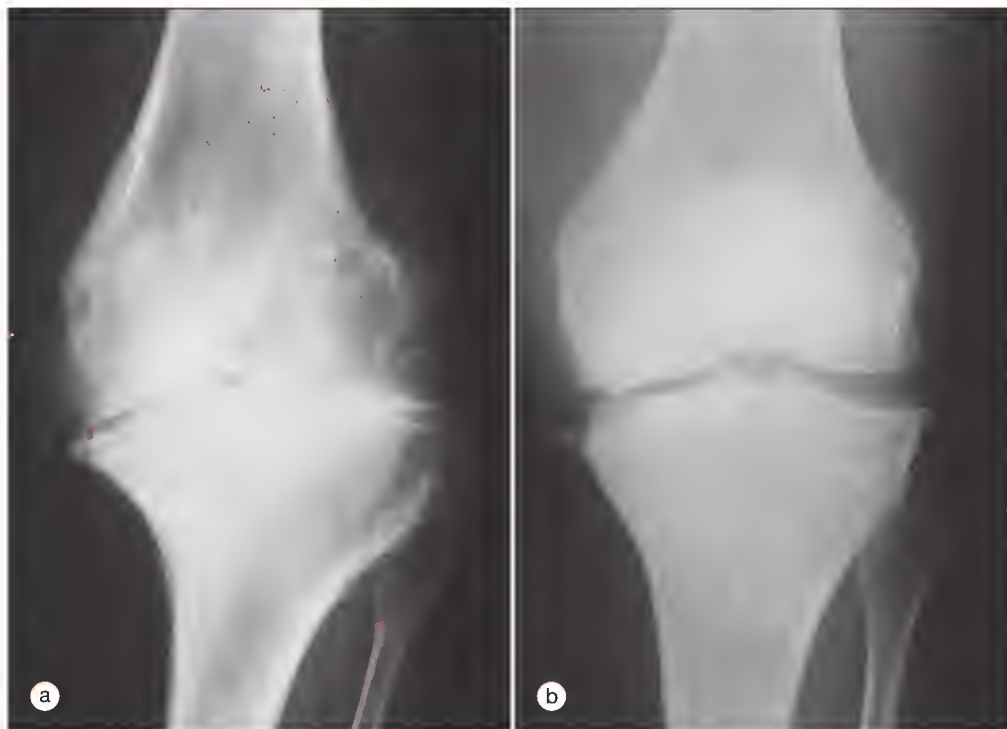


Fig. 183.8 Neuropathic disease of the left knee (tabes dorsalis). (a) Advanced form of the disease in the knee. (b) The same knee 13 years previously showing partial fracture of the tibial epiphysis.



Fig. 183.9 Neuropathic disease of the lumbar spine (tabes dorsalis). Lateral radiograph of the lumbar vertebrae showing partial destruction of L2 and diffuse exuberant osteophytes.

fusion is an uncommon manifestation of neuroarthropathy at any site, with the exception of the spine (Fig. 183.9).¹⁷

Progression from the early stage can be rapid, which suggests that microfractures evolve quickly into gross fragmentation, with complete destruction of the articulation within a few weeks.

Other imaging techniques

Bone scintigraphy (late phase) can be useful for assessment of bone turnover, evaluation of disease progression, and monitoring of activity.¹⁹ MRI is more sensitive than radiography¹⁸; the primary early abnormality is

extensive bone marrow edema. Although there are other potential causes for this, including infection, joint trauma, seronegative arthritis, complex regional pain syndrome (CRPS) and transient bone marrow edema, early neuropathic arthropathy can be differentiated from these various other conditions on the basis of the clinical history and presence of peripheral neuropathy. Given the importance of early diagnosis in preventing chronic neuropathic arthropathy, early use of MRI has a valuable role (Fig. 183.10).

MRI also allows the extent of the soft tissue lesions to be defined and may be of value in the differentiation of neuropathic arthropathy from infection, a distinction that can be difficult to make, especially when neuropathic arthropathy is complicated by adjacent loss of skin integrity. Of course both may coexist, especially in the diabetic foot.²⁰ Infection results in high signal on T2 weighting and short tau inversion recovery and low signal on T1 weighting. Acute neuropathic arthropathy is similar, but chronic neuropathic arthropathy has normal marrow signal or low signal on T1 and T2 weighting. Other features that may help differentiate neuropathic arthropathy include distribution, deformity, and soft tissue changes. Positron emission tomography–computed tomography (PET-CT), if available, may also be useful for differentiating neuropathic arthropathy from osteomyelitis. The sensitivity of PET-CT in this situation has been reported as 100% and its specificity as 93.8%.²¹ Areas of low signal intensity on MRI have been reported in the medullary cavity of the bone on both T1- and T2-weighted spin echo images in syringomyelia (see Fig. 183.3) even before the actual resorptive process occurs.²²

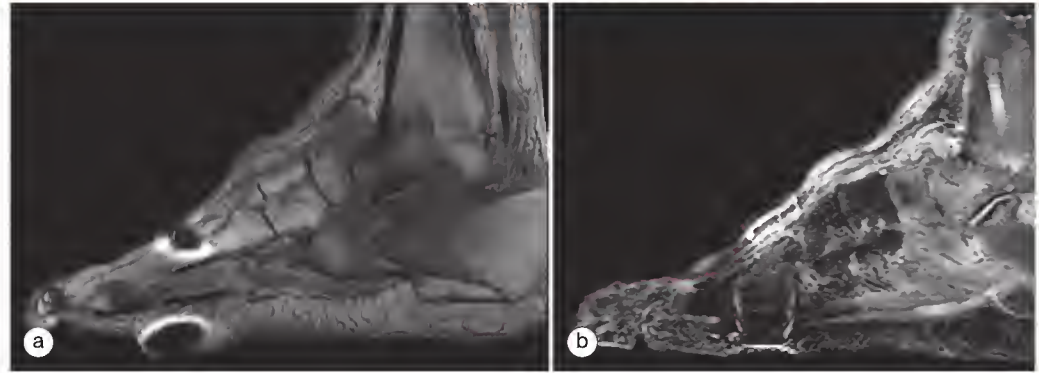
LABORATORY INVESTIGATIONS AND HISTOLOGIC ANALYSIS

The synovial fluid may be serous, serosanguineous, or frankly hemorrhagic, and lipid crystals secondary to subchondral bone lesions may be seen. Bone biopsy may sometimes be useful to exclude other diagnoses such as osteosarcoma, metastatic carcinoma, or osteomyelitis. The most common histologic findings are fibrosis with cartilaginous and bony metaplasia and embedded fragments of necrotic or viable bone (detritic synovitis). Necrotic and reactive cartilage and rice body–like articular fibrinous material have also been described in the joint. Laboratory evidence of an acute-phase response or systemic disturbance is lacking.

DIFFERENTIAL DIAGNOSIS

Typical presentation is a swollen joint with mild discomfort in a patient with known neuropathy. The combination of marked clinical manifestations in the presence of relative lack of pain and good functional capacity, together

Fig. 183.10 Magnetic resonance images of the hindfoot in a patient with neuropathic arthropathy. (a) T1-weighted sagittal image. (b) Short tau inversion recovery sagittal image. There is extensive bone marrow edema around the subtalar and calcaneocuboid joint with soft tissue edema anterosuperior to the midfoot. Erosion is seen at the anterosuperior margin of the talus with some destruction of the navicular. Note evidence of previous surgical ankle fusion.



with a typical radiographic picture, suggests the diagnosis. If a neurologic disorder is not readily apparent or if the clinical or radiographic appearances are unusual, then the diagnosis may be more difficult, especially in early disease. Differential diagnoses include infection (joint or bone); crystal disease (gout, calcium pyrophosphate deposition disease, or hydroxyapatite arthropathy); other inflammatory arthritis including rheumatoid arthritis²³; tumor; and thrombophlebitis. Bony fragmentation and collapse are also manifestations of osteonecrosis. Similar appearances have been reported in posttraumatic osteoarthritis (OA) and after repeated intraarticular corticosteroid injections.

A careful neurologic examination should be carried out because this should identify a sensory neuropathy. In practice, the most important differential diagnosis is septic arthritis, and if there is any clinical doubt one should aspirate the involved joint and send synovial fluid for microscopic analysis and culture. An algorithmic approach to distinguishing neuropathic arthropathy of the foot from osteomyelitis has been proposed.²⁴

PATHOGENESIS

The pathogenesis of neuropathic arthropathy remains controversial.²⁵ Although sensory impairment, overuse, and trauma are recognized as predisposing factors, these are neither necessary nor sufficient to account for the observed clinical and pathologic features.

Any theory of pathogenesis must take account of those features that distinguish neuropathic arthropathy from other forms of destructive arthritis. These include peripheral neuropathy, abnormal biomechanics, and marked destructive changes with fracture and loss of bone. It must also explain asymmetry, relative rarity (only a small minority of patients with sensory neuropathy develop neuropathic arthropathy), and the fact that chances of developing neuropathic arthropathy do not appear to relate to either the severity of neuropathy or the degree of physical activity.²⁶ Finally, a satisfactory theory should explain why the condition is self-limiting.

Traditionally, two theories have been proposed. The first, the “neurotraumatic” theory, suggests that somatic muscular reflexes that normally protect the joint from exceeding certain safe limits in range of movement are lost in the presence of neuropathy, which leads to repeated trauma and ultimately joint destruction. Volkmann and Virchow described the changes as resulting from “a multiplicity of subclinical traumas, which are unperceived because of the insensitivity of the affected joints.”²⁷

The second, or “neurovascular,” theory holds that neuropathic arthropathy develops as a result of increased blood flow, with the relative hyperemia resulting in active resorption of bone. There is good evidence that blood flow is increased in peripheral neuropathy, due to loss of sympathetic innervation and reduced peripheral vascular resistance.²⁶ Also, cases have been described in which neuropathic arthropathy developed in patients with diabetes only after reconstructive vascular surgery.²⁸ A potential problem with this theory is that autonomic neuropathy, suggested as a major determinant of neuropathic arthropathy, is not invariably present in conditions such as leprosy or hereditary sensory neuropathies, which nevertheless cause neuropathic arthropathy.

Both these theories presuppose that sensory nerves actively prevent development of neuropathic arthropathy in normal joints, and disruption of these nerves should lead inevitably to a neuropathic joint. In fact, it is clear that even extensive deafferentation of a joint does not necessarily lead to pathologic joint processes in the absence of trauma or infection. Attempts to create neuropathic arthropathy in cats, rabbits, and dogs have met with limited success. In the canine anterior cruciate ligament (ACL) transection model of OA, ACL transection inevitably led to OA in active dogs, but

denervation at the dorsal root ganglion alone did not lead to OA or neuropathic arthropathy even if the dogs were allowed to remain active.²⁹ However, the combination of ACL transection and denervation led to more severe OA than ACL transection alone.³⁰

These experiments refute the theory that neuropathic joints result from a peripheral sensory neuropathy in the presence of normal activity, although they would explain the development of joint destruction in the presence of neuropathy and joint instability.

Recently an attempt to link these findings has been made by suggesting a role for inflammation and, in particular, proinflammatory cytokines.²⁶ Inflammation is undoubtedly a key feature of neuropathic arthropathy and may result from microtrauma or fracture, although a role has also been suggested for ulceration, infection, and local surgery, including orthopedic procedures³¹ or revascularization.²⁸ The acute inflammatory response triggers expression of the receptor activator of nuclear factor- κ B ligand (RANKL) and, hence, activation of nuclear factor- κ B (NF- κ B). In turn, this causes activation of osteoclasts and increased bone resorption, which leads to further fracture and potentiation of the inflammatory cycle.

Stimulation of the RANKL–NF- κ B axis is part of the normal response to fracture, allowing lysis of bone fragments before new bone formation. Normally, however, the process is switched off, perhaps by pain and immobilization. Loss of the normal pain response in neuropathic arthropathy may cause the lytic process to continue. It is also possible that the RANKL system may be primed in diabetes³² because it is potentiated by free radicals and hyperglycemia. Neuropathy itself may further activate the system due to loss of neurally derived antagonists of RANKL such as calcitonin gene-related peptide. This downregulation of inhibitor nerve pathway (loss of sensory neuropeptide and cholinergic antiinflammatory pathway) may be one cause of the exaggerated inflammatory response to minor trauma.³³

Clearly such a hypothesis has implications for clinical practice. Inhibitors of inflammation such as high-dose steroids or tumor necrosis factor (TNF) antagonists may break the vicious cycle, although benefit would have to be weighed against risk—especially risk of infection.

MANAGEMENT

The treatment of the neuropathic joint depends on the joint involved and the stage of disease. Despite progress in our understanding of the disease, curative treatment of established neuropathic arthropathy remains impossible. Treatment of the neurologic disorder, such as surgical repair of syringomyelia, is indicated when possible but will not reverse established arthropathy. Management is further hampered by a paucity of randomized controlled trials and by the lack of consensus on disease definition. There is agreement that the key to successful conservative treatment is early recognition to prevent joint destruction.³⁴

Acute neuropathic arthritis

The aims of early treatment are to arrest the acute process and prevent deformity. Early early diagnosis is vital in this regard, which makes the early stages of neuropathic arthropathy a true medical emergency.

Reduction of weight bearing

Immobilization of the joint and, in cases of lower limb involvement, cessation of weight bearing are important during periods of apparent flare in activity. Joint immobilization with a plaster cast may be required for up to 6 months, with the aim of stabilizing the joint and improving the osteoarthritic lesion. Such prolonged periods of immobilization require clear

explanation to the patient, especially because the patient may be relatively asymptomatic at the time. Orthotic devices are used as required to permit limited mobilization. A balance has to be struck between restricting mobility and allowing a return to weight-bearing ambulation, and some studies suggest that, if immobilization is good, weight bearing can be permitted without detriment.³⁵ Recently pneumatic walking braces have been introduced for ankle and foot arthritis, which reduce weight bearing but are comfortable, lightweight, and removable at night.³⁶

Bisphosphonates

Because excess osteoclastic activity is thought to be responsible for the bone destruction in neuropathic joint disease, therapies that inhibit osteoclasts, such as bisphosphonates, may be helpful, especially if given early. A 12-month randomized, double-blind, placebo-controlled trial of a single intravenous infusion of pamidronate 90 mg or placebo in 39 patients with diabetic neuropathic arthropathy showed greater improvement in symptoms, markers of bone turnover, and skin temperature in treated patients at 1 year.³⁷ A retrospective study (n = 23) of neuropathic arthropathy affecting the feet compared intravenous pamidronate with traditional immobilization techniques and found a significant reduction in temperature and bone turnover as judged by alkaline phosphatase activity.³⁸ However, a recent study found no benefit of intravenous zoledronic acid on the clinical resolution of acute neuroarthropathy in terms of total immobilization time.³⁹

Other treatments that have been used in the acute stage include low-intensity ultrasound, magnetic fields, and nonsteroidal antiinflammatory drugs (NSAIDs) to control pain, but there is no evidence of an effect on progression.

Chronic neuropathic arthropathy

Once chronic neuropathic arthropathy is established in the foot, the goals of treatment are primarily to reduce the risk of foot ulceration. Reduction of plantar pressure, preservation of skin integrity, and support for the foot are important aims. Input from an expert orthotist is vital; provision of a good foot orthosis or rocker soles in adapted footwear may be all that is required.

Neuropathic arthropathy elsewhere is treated following similar principles: supports, splinting, orthosis, and preservation of skin integrity. Pain needs to be managed with analgesics or NSAIDs. Ulcers require rigorous hygiene: disinfection, sterile bandaging, and antibiotic treatment of any superimposed infection.

Surgery is best avoided if possible due to the risk of worsening of the condition, nonunion, infection, and precipitation of acute neuropathic arthropathy in the contralateral limb. Sometimes simple excision of abnormally weight-bearing bone may be all that is required,³¹ but for marked instability or a fixed deformity open reduction and arthrodesis may be indicated. Other indications for surgery include ulceration and unacceptable deformity, because these increase the risk of further bony breakdown. Surgical options vary by site. At the knee arthrodesis is the preferred option. The risk of nonunion may be reduced by use of careful technique; firm fixation of the bones with an intramedullary rod or other device; and débridement of all synovial tissue and scarred capsule. Neuropathic knees⁴⁰ and hips⁴¹ can be treated by total joint arthroplasty, although this can be challenging technically and the rate of reoperation is high.

Surgical algorithms for the treatment of neuropathic arthropathy of the foot are based almost entirely on level 4 or 5 evidence. Uncontrolled retrospective case series and case reports guide the use of exostectomy, fusion, and Achilles tendon lengthening. There is inconclusive evidence concerning timing of treatment and use of different fixation methods.⁴²

Unfortunately, the combination of marked joint destruction and, not infrequently, superimposed infection can make amputation the only viable option.

CONCLUSION

Apart from an association with diabetes, neuropathic arthropathy is a rare condition. It is important to consider, however, because early recognition and treatment may significantly alter the prognosis. It enters the differential diagnosis of monoarthritis and, in an appropriate clinical setting, should prompt a careful neurologic examination.

The mechanism by which sensory changes result in such gross destructive arthritis is unclear but may relate to production of cytokines consequent to low-grade trauma and inflammation. The disease bears a marked resemblance to certain forms of atrophic OA; this, combined with recent animal experiments, raises the intriguing possibility that neurologic factors may play a role in OA. Future targets for research might include further evaluation of the role of bisphosphonates in acute neuropathic arthropathy and the effect of targeting inflammation by the use of either nonspecific inhibitors such as steroids or specific antagonists of, for example, TNF- α or RANKL (such as denosumab). The rarity of the condition makes it an ideal subject for international collaborative research.⁴³

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184 Osteonecrosis

■ TIMOTHY McALINDON ■ ROBERT J. WARD

- Osteonecrosis is cell death in components of bone: hematopoietic fat marrow and mineralized tissue.
- Osteonecrosis is not a specific disease entity. It is the final common pathway of a number of conditions, most of which lead to impairment of the blood supply to the femoral head; this explains the frequently used terms *avascular necrosis* and *aseptic necrosis*.
- The femoral head is the site most commonly and severely affected by osteonecrosis. However, osteonecrosis may also develop in other locations (including the distal femur, humeral head, and small bones of the wrist and foot).
- Radiologic changes are typical at the late stages of the disease, but radiographic findings can be normal at early stages. Magnetic resonance imaging is especially useful in these stages.
- Predisposing factors (mainly corticosteroid use and alcohol abuse) should be carefully sought.

INTRODUCTION

Osteonecrosis refers to a clinical syndrome in which regional death of the cellular elements of bone, typically in a subchondral location, leads to trabecular and subchondral collapse with consequent pain, impairment, and long-term joint damage. Osteonecrosis can occur in a variety of clinical settings and skeletal sites, with or without apparent predisposing factors. Although a number of synonyms have historically been used to refer to this disorder (such as *aseptic necrosis* and *avascular necrosis*), the commonalities among these suggest that osteonecrosis is the endpoint of a number of conditions that impair blood supply to regions of bone. However, within the clinical spectrum of osteonecrosis, there exist distinct subsets with unique features that suggest rather specific causes (e.g., bisphosphonate-associated osteonecrosis of the jaw, transient osteoporosis of the hip in pregnancy, and spontaneous osteonecrosis of the knee). The condition is of clinical importance because there is often a lag in diagnosis, and early intervention may be necessary.

EPIDEMIOLOGY

The true incidence and prevalence of osteonecrosis are unknown. The most reliable data relate to the hip joint and are inferred from the number of hip arthroplasties performed each year for this specific indication. Recent estimates suggest that osteonecrosis accounts for up to 10% of hip arthroplasties.¹ From this it is assumed that there are approximately 10,000 to 20,000 new cases of osteonecrosis diagnosed each year in the United States.² The condition affects both genders and all age groups but with a substantially greater prevalence among males.³ Patients with osteonecrosis tend to be younger than 50 years of age³; however, the demographic characteristics of patients with osteonecrosis vary for the different subtypes.

Osteonecrosis is associated with a variety of clinical conditions such as systemic lupus erythematosus (SLE) and chemical exposures such as corticosteroid and alcohol use (Box 184.1).⁴ Indeed, recent epidemiologic studies have tended to focus on specific subsets or exposures such as

osteonecrosis associated with renal transplantation or intravenous administration of zoledronic acid.⁵ The factors that have received the most scrutiny include corticosteroid exposure, alcohol use, SLE, coagulopathies, and hemoglobinopathies, and bisphosphonate use.⁴

Corticosteroids

Accumulated data from numerous clinical reports and risk factor studies provide strong evidence for a causal relationship between corticosteroid exposure and development of osteonecrosis. The incidence (or cumulative prevalence) rates of osteonecrosis among different cohorts exposed to corticosteroids range from 0.6% to 38%, presumably because of widely varying exposures and host factors. Although there is a general trend in the more systematic analyses toward increased risk of osteonecrosis with greater dose and longer duration of use of corticosteroids,⁴ the identification of individuals at particular risk from corticosteroid exposure is clearly difficult.

Alcohol

Alcohol consumption is also considered to be an established risk factor for osteonecrosis. One case-control study demonstrated a dose-response relationship for alcohol in osteonecrosis, with risk ratios of 3, 10, and 18 for those regularly consuming less than 400, 400 to 1000, and 1000 mL/wk or more, respectively, compared with nondrinkers.⁶ One theory suggests that altered fat metabolism secondary to alcohol use may lead to adipocyte hypertrophy and subsequent microvascular compression with resulting increased intraosseous pressure.⁷ Recently it has also been determined that both alcohol and corticosteroids have adverse effects on bone cell lineage by enhancing adipogenesis and inhibiting osteocytogenesis by marrow stem cells.⁸ Other studies point toward direct cytotoxic effects of alcohol.⁹ Interestingly, there appear to be differences in the frequencies of alcohol-metabolizing enzyme gene polymorphisms among subpopulations of patients classified as having alcohol-related osteonecrosis.¹⁰

Systemic lupus erythematosus

Osteonecrosis occurs frequently in SLE, with clinically apparent disease in up to 15% of patients and even higher prevalence when asymptomatic disease is detected using magnetic resonance imaging (MRI). Much of this risk is related to corticosteroid treatment. However, attempts to determine which patient characteristics mediate this risk have produced inconsistent results.¹¹⁻¹⁴ It is likely that multiple factors in patients with SLE interact with or contribute to the development of osteonecrosis, including procoagulant factors such as anticardiolipin antibodies.¹⁵

Coagulopathies and hemoglobinopathies

Osteonecrosis appears to be associated with a range of coagulation disorders and with hemoglobinopathies, most notably sickle cell disease and sickle cell-hemoglobin C (hemoglobin SC) disease. Among patients with sickle cell disease the prevalence of symptomatic osteonecrosis is 3% to 5% and rises to 10% to 41% when asymptomatic osteonecrosis is included.^{16,17} In sickle cell disease, the risk of osteonecrosis is related to measures of the disease process including frequency of crises, hematocrit levels, and mean corpuscular volume.¹⁶ These clinical observations suggest that thrombosis and vasoocclusion participate in the development of osteonecrosis. Studies of hypofibrinolysis and thrombophilia in osteonecrosis have found increased plasminogen activator inhibitor activity and polymorphism of the plasminogen activator inhibitor-1 gene in certain patients.^{15,18-20}

BOX 184.1 EXPOSURES AND MEDICAL CONDITIONS ASSOCIATED WITH OSTEONECROSIS

Trauma	Slipped capital femoral epiphysis
Dysbaric osteonecrosis	Systemic lupus erythematosus
Radiation	Coagulopathies
Corticosteroid use	Hemophilic disorders
Alcohol use	Hemoglobinopathy
Bisphosphonate use	Pregnancy
Hyperlipidemia	Gaucher disease
Legg-Calvé-Perthes disease	Human immunodeficiency virus
Congenital dysplasia of the hip	infection

Bisphosphonate-induced osteonecrosis of the jaw

Bisphosphonates are the mainstay for treatment of osteoporosis. In 2003 the first report of osteonecrosis of the jaw associated with bisphosphonate use was published, stimulating numerous further reports and speculation on the etiology of this disorder. Most instances occurred in association with intravenous administration of bisphosphonates accompanying a chemotherapeutic regimen for multiple myeloma or breast or prostate cancer. The risk of osteonecrosis of the jaw related to *oral* bisphosphonate used for treatment of osteoporosis is estimated at 0.01% to 0.04%.²¹ The risk is higher for those with Paget disease and those being treated for malignancy, and the event is often triggered by dental work or trauma that leads to exposure of bone.²¹ In patients treated with zoledronic acid and/or pamidronate for myeloma, breast cancer, or prostate cancer the overall prevalence is about 5%.⁵ Proposed mechanisms include increased susceptibility of bone to infection and necrosis caused by decreased bone turnover²² and direct toxicity of high-potency bisphosphonates to bone cells.⁵

PATHOLOGIC FEATURES

Necrosis of all cellular components of bone, both in hematopoietic fat marrow and mineralized tissue, is the hallmark of osteonecrosis. Death of the cellular components of bone results in destruction of the osseous components of bone with structural consequences (Fig. 184.1).

In the early (prenecrotic) stage, there is interstitial edema and plasmolysis confined to the bone marrow, with occasional foam cells. The primary indication of necrosis of bone tissue is disappearance of osteocytes, the cavities of which are empty and often enlarged. As the severity progresses, the medullary spaces become filled with necrotic tissue, which is subsequently associated with trabecular necrosis and emptying of the lacunae. The bone sequestrum is composed of dead trabeculae without osteocytes but maintained architecture. The bone marrow tissue exhibits disappearance of stem cells, adipocyte nucleolysis, and membrane loss, often without persistence of recognizable cell remnants. Subchondral fracture, when present, is usually located in the dead bone, typically somewhat parallel to the edges of the epiphysis, which results in the characteristic radiologic “crescent sign.” Around the dead bone tissue is usually a zone of repair comprising fibrovascular proliferation, bone resorption, and new bone apposition on the remains of the old dead trabeculae.

At a macroscopic level, osteonecrosis is regional and highly circumscribed. It can be confined to a medullary section of bone or involve a periarticular segment such as the subcortical femoral head. The biomechanical consequences of osteonecrosis are largely contingent on its anatomic location and extent of involvement. Areas confined to a medullary location can be asymptomatic, whereas involvement of the subcortex adjacent to a joint surface leads to articular collapse and joint destruction. For individuals with polyarticular osteonecrosis, as can be seen in sickle cell disease, the condition can have devastating functional consequences.

Pathogenesis

In its simplest characterization, focal bone death results from a compromised arterial blood supply, a paradigm best exemplified by the posttraumatic form of osteonecrosis. However, in the spontaneous forms of osteonecrosis a pathologic basis for interruption of the blood supply is rarely clear. This conundrum has led to speculation about processes that could compromise the health of affected regions of bone and result from exposures known to be associated with osteonecrosis. Most of these involve a proposed vascular mechanism:



Fig. 184.1 Coronal section of a femoral head removed during total hip replacement. The cartilage above the sequestrum is of irregular height. Osteophytes of the superior and inferior aspects of the femoral head are present. There is a sclerotic border delineating the sequestrum. The trabecular architecture is otherwise preserved.

- Disturbances of fat metabolism
- Intravascular occlusion by coagulation, thrombi, fat emboli, abnormally shaped red blood cells
- Elevated intraosseous pressure
- Intramedullary hemorrhage
- Osteocytotoxicity

Other processes that might participate in the overall extent of destruction include the following:

- The reparative response itself
- Mechanical stress
- Inhibition of angiogenesis

Altered fat metabolism

Evidence indicates that increases in the amount of fat within the femoral head elevate intracortical pressure and lead to sinusoidal collapse.²³ Numerous studies have shown diverse effects of corticosteroid exposure on lipid metabolism and on differentiation of bone marrow–derived stem cells favoring adipocytogenesis.⁸ *In vivo* studies have confirmed that corticosteroids increase the fat content of the femoral head and that this increase correlates with an increase in intraosseous pressure and decreased blood supply.^{24–28} Interestingly, this effect has been abrogated by the administration of clofibrate, a lipid-lowering agent.²⁹ Steroids have also been shown to be capable of causing fat emboli in animal models.²⁴ Overall, these studies implicate an abnormality of fat metabolism and/or morphology that may compromise blood flow to the affected area through an increase in intraosseous pressure.

Although most of these studies originated in pursuit of a corticosteroid effect, it is pertinent that abnormalities of lipid metabolism have also been observed in patients with osteonecrosis attributed to alcohol use. Patients with alcohol-associated osteonecrosis frequently have elevated serum cholesterol and triglyceride levels,³⁰ and the cholesterol content of bone samples from patients with osteonecrosis has been found to be elevated.³¹ Abnormalities of trabecular fat cell size and bone marrow pressure have also been demonstrated in an alcoholic rabbit model.³² Alcohol also appears to induce differentiation of marrow stromal cells into adipocytes in a dose-dependent manner and reduces osteogenesis.³³

Intravascular coagulation

Intravascular coagulation of the intraosseous microcirculation, progressing to more generalized thrombosis, is a strong contender as a process leading

to osteonecrosis. Many of the conditions reported to be associated with osteonecrosis have attributes capable of triggering intravascular coagulation. This could occur as a primary event (as in antiphospholipid antibody syndrome¹⁵) or as a secondary reaction to some other process (such as thrombosis secondary to fat embolism).

Also, numerous gene abnormalities or polymorphisms associated with hypercoagulable states occur with increased frequency in individuals with osteonecrosis, including the mutations factor V Leiden and prothrombin 20210A, and deficiency of protein C or S. Several studies of coagulation factors have found abnormalities relating to plasminogen activator inhibitor in patients with osteonecrosis, which suggests reduced fibrinolysis as a potential risk factor.^{15,18-20} Such observations prompted a clinical trial of low-molecular-weight heparin, which slowed progression of osteonecrosis in patients with early-stage disease.³⁴

Elevated intraosseous pressure

As a nondistensible structure with a cortical shell, bone has limited capacity to accommodate an increase in space occupied within. Any such changes may elevate intracortical pressure and compromise blood flow.³⁵

Intramedullary hemorrhage

Intramedullary hemorrhage is frequently present in the vicinity of osteonecrotic lesions and is generally considered to be a secondary phenomenon. However, examination of osteonecrotic zones with recent hemorrhage has shown arteriopathy, which suggests that recurrent intramedullary hemorrhage may contribute to the pathogenesis of osteonecrosis.^{36,37}

Osteocytotoxicity

The histologic observations of absent or nonviable osteocytes in trabecular samples without osteonecrosis generate the possibility that osteocyte death may be a primary rather than secondary event in its development. Toxic accumulation of lipid droplets within the osteocytes apparently occurs with high-dose steroids and alcohol and can damage the cell membrane and lead to cell death.^{31,38} Recently it has also been determined that both alcohol and corticosteroids have adverse influences on bone cell lineage by enhancing adipogenesis and inhibiting osteocytogenesis by marrow stem cells.⁸

Other participatory processes

A number of other processes including attempts at repair may have sequelae that contribute to the progression of osteonecrosis. The presence of necrotic bone stimulates a number of cellular activities aimed at replacing necrotic bone with new bone. However, this process can be counterproductive in various situations, such as when the remodeling leads to a shift to compact bone or interrupts blood supply and attempts at revascularization.³⁹⁻⁴¹ Mechanical stress may also contribute to the progression of osteonecrosis. Two animal studies of osteonecrosis found a greater extent of osteonecrosis in the animals that were allowed to bear weight than in those that could not.^{42,43}

CLINICAL FEATURES

The clinical presentation of osteonecrosis is quite variable, with characteristics tending to reflect the anatomic region of localization. Osteonecrosis in the femoral head, for example, usually causes pain in the groin or anterior thigh. However, osteonecrosis can be asymptomatic, especially when confined to medullary bone. The pain from acute osteonecrosis can also be especially intense and may require opioid analgesics. It is differentiated from ordinary joint pain by its severity, presence at rest, lack of relationship to weight bearing, and (in early stages) preservation of joint range of motion. These clinical characteristics can be viewed as “red flags” for the possibility of osteonecrosis. With the development of articular collapse and secondary osteoarthritis, an osteoarthritic constellation of symptoms supervenes. Osteonecrosis is usually a unilateral phenomenon but can be bilateral and even multifocal.

Typical sites of involvement by osteonecrosis include the femoral head (the most common), the femoral condyles of the knee, the proximal tibia, the humeral head, the small bones of the foot and ankle, the wrist and hand bones, the vertebrae, and (less commonly) the facial bones.⁴

DIAGNOSIS

The clinical diagnosis of osteonecrosis is often substantially delayed. The primary reason for this is the insensitivity of radiography for its earliest features. Radiography may instead reveal minor osteoarthritic changes, to

which the pain is often misattributed. Indeed, the development of osteonecrosis in a joint with a prior diagnosis of osteoarthritis poses a particular clinical conundrum. Thus the presence of red flag clinical features should prompt a more sensitive imaging investigation, currently MRI.

A history of use of specific medications should raise the prior probability for this diagnosis in patients with known risk factors. These include exposures such as alcohol and corticosteroid use and diagnoses such as SLE or sickle cell or hemoglobin SC disease. Certain clinical scenarios should also increase vigilance for osteonecrosis, such as high-dose corticosteroid therapy in patients with SLE, acute hip pain in women in the third trimester of pregnancy, and a dramatic escalation of knee pain in individuals with knee osteoarthritis.

In general, the diagnosis of osteonecrosis is made through clinical evaluation and imaging. Blood tests may contribute information by establishing the presence of predisposing factors such as autoimmune disease, hemoglobinopathies, dyslipidemias, and systemic inflammatory disorders.

DIFFERENTIAL DIAGNOSIS

Among the subtypes of osteonecrosis are a small number that can be differentiated through their distinctive manifestations and that may represent separate disease entities. These include spontaneous osteonecrosis of the knee, subchondral fractures, osteonecrosis of pregnancy/transient osteoporosis of the hip, and transient regional osteoporosis. Other diagnoses that should be considered in the evaluation of severe joint pain include acute synovitis, soft tissue trauma (e.g., tear of the hip joint labrum), severe osteoarthritis, algodystrophy, and referred pain.

Bone infarct

Osteonecrosis is referred to as a *bone infarct* when it occurs within the diaphysis or metadiaphysis of the bone. The characteristics of bone infarcts differ somewhat from typical epiphyseal osteonecrosis but share many of the predisposing factors. The MRI appearance of focal bone infarcts contrasts with epiphyseal osteonecrosis because of differences between yellow and red marrow. Bone infarcts tend to reflect the characteristic bone marrow edema pattern seen in epiphyseal osteonecrosis (dark on T1-weighted and bright on T2-weighted sequences, with a geographic morphology). The T2-signal heterogeneity typical of epiphyseal osteonecrosis is not evident in bone infarcts. Radiographically, bone infarcts demonstrate a lytic appearance with serpiginous, well-defined geographic sclerotic borders.

Spontaneous osteonecrosis of the knee

Spontaneous osteonecrosis of the knee (SPONK), typically involving the medial or lateral tibial plateau and associated with severe knee pain, has been viewed as sharing the same pathologic basis as osteonecrosis of the femoral head (Fig. 184.2).⁴⁴ However, the syndrome may be somewhat heterogeneous in its manifestations⁴⁵ and may lack the typical features of epiphyseal osteonecrosis, which include a demarcation rim or reactive interface.⁴⁶ Recent scrutiny of histologic sections following knee arthroplasty performed for SPONK revealed that the pathologic process may originate as a form of subchondral stress fracture.⁴⁶ Subchondral fractures could result in infiltration of joint fluid into the trabecular space, causing a localized increase in medullary pressure and osteonecrosis. Some cases of SPONK have resolved without surgical intervention. Features on MRI that may indicate a benign course include the absence of focal epiphyseal contour depression or lines of low signal intensity deep in the condyle.⁴⁶

Osteonecrosis during pregnancy

Osteonecrosis of the hip occurring in pregnancy in women without any traditional risk factors for the disease is a rare but recognized phenomenon.⁴⁷⁻⁵⁰ No clear clinical patterns or associations are evident from the small number of cases described in the literature. The problem manifests as hip pain and is diagnosed using MRI or later becomes apparent on radiographs with clinical progression. Many cases have been treated with surgical intervention. Osteonecrosis during pregnancy can be confused with transient osteoporosis of the hip during pregnancy.⁴⁷

Idiopathic transient osteoporosis of the hip

Transient osteoporosis of the hip is a self-limiting skeletal disorder, usually affecting women in their third trimester of pregnancy, that resolves spontaneously within 12 months postpartum.⁵¹ It has been viewed as a variant of

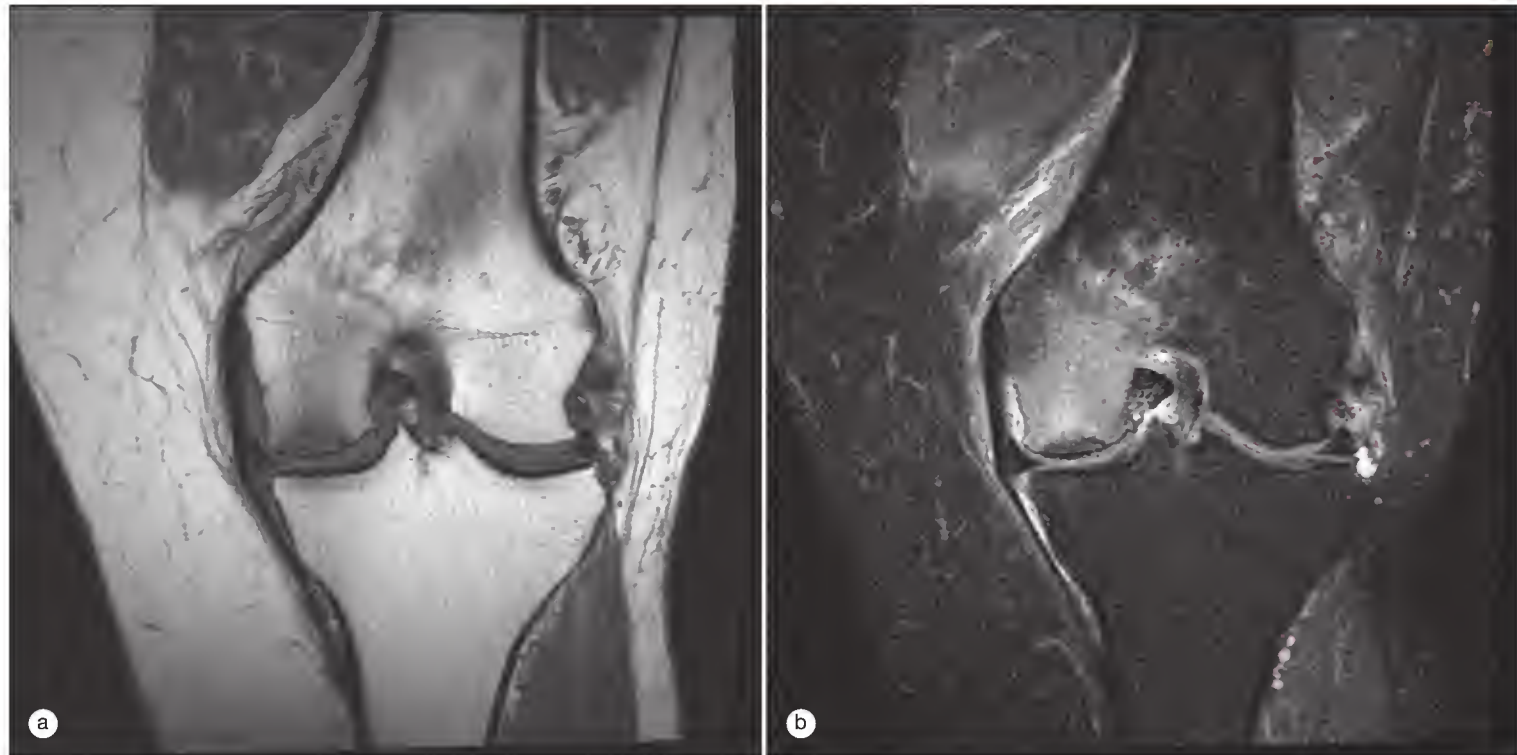


Fig. 184.2 T1-weighted coronal magnetic resonance image of the knee (left) demonstrates subchondral linear dark signal with associated ill-defined low signal representing marrow edema. The proton-density fat-saturated coronal image (right) demonstrates marked marrow signal abnormality involving the medial femoral condyle with subchondral dark signal paralleling the articular surface. These findings indicate the presence of the now controversial entity known as *spontaneous osteonecrosis of the knee*.

Sudeck atrophy,⁵¹ but the exact cause remains unknown. It is characterized by disabling pain in the hip without prior trauma and by striking radiographic evidence of osteopenia that is limited to the hip. MRI shows bone marrow edema and occasionally joint effusion (Fig. 184.3). Bone mineral density is reduced, and this can be systemic.^{52,53} Clinical and radiographic findings regress spontaneously after pregnancy and generally without late sequelae. However, there are reports of cases complicated by pathologic fracture.⁵⁴ Transient osteoporosis of the hip has been described postpartum⁵⁵ and in a nonpregnant woman.⁵⁶ The condition has many clinical similarities to another rare disorder, *transient regional osteoporosis*, in which localized pain and osteopenia migrate from one skeletal site to another.⁵⁷ Treatment for idiopathic transient osteoporosis of the hip consists of joint protection with limited weight bearing, range-of-motion exercise, progressive ambulation, and analgesics. Antiresorptive agents have been used in some cases with reported benefit.⁵⁸

IMAGING

Historically, radiographs have been widely used for the diagnosis and evaluation of osteonecrosis. Definitive radiographic features of osteonecrosis (e.g., the crescent sign) are highly specific late in the disease but insensitive during the early phase (Fig. 184.4). Before the widespread availability of MRI, bone scintigraphy was advocated as a more sensitive test for early osteonecrosis. The technique offered advantages over plain radiography⁵⁹ and with optimal conditions may be more sensitive than conventional MRI, albeit less specific.⁶⁰ However, the technique is cumbersome, exposes people to ionizing radiation, provides low resolution, and discriminates poorly among osteonecrosis, fractures, transient osteoporosis, and other conditions. Current practice in the diagnosis of early-stage osteonecrosis requires an MRI scan. MRI scans have the greatest detection sensitivity for osteonecrosis and are less hazardous than radionuclide bone scans.

The American College of Radiology recommends anteroposterior and frog-leg radiography for initial evaluation of osteonecrosis of the hip.⁶¹ These two views provide an approximation of orthogonal views with which to evaluate the morphology and quality of the femoral head. If collapse is identified and immediate surgery is contemplated, the American College of Radiology recommends MRI to evaluate for occult osteonecrosis of the contralateral hip. In cases in which the morphology of the affected side is maintained but the head appears sclerotic or mottled, MRI should be performed to confirm the diagnosis of osteonecrosis. Negative radiographic

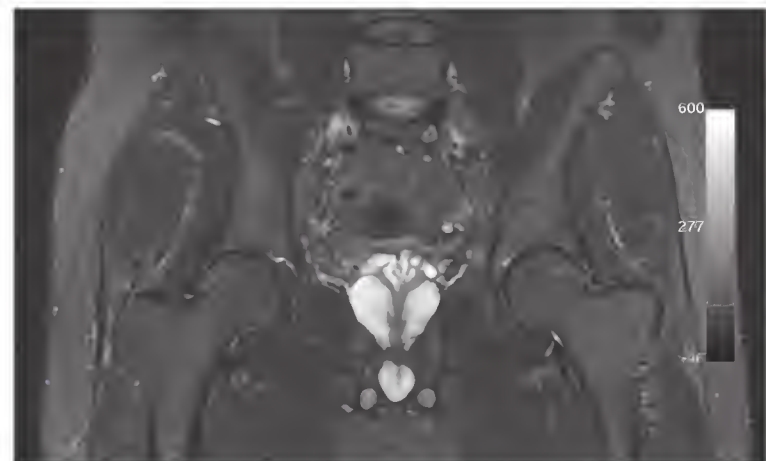


Fig. 184.3 Baseline magnetic resonance image showing increased signal in the left femoral head in a 30-year-old woman with idiopathic transient osteoporosis of the hip at 3 months postpartum.

findings in the setting of suspicion of femoral head osteonecrosis should always prompt an MRI examination. The American College of Radiology recommends the use of radionuclide bone scan as a second-line substitute in patients with contraindications to MRI.

Radiography

In the early stages of osteonecrosis plain radiographs typically show normal or negative findings. The earliest radiographic changes include diffuse osteopenia, serpiginous areas of radiolucency with a sclerotic border, and linear sclerosis typically adjacent to the joint margin. Later the subchondral radiolucency can organize into a crescent sign, and the appearance is pathognomonic for osteonecrosis (see Fig. 184.4). Later changes include flattening of the articular surface and sometimes gross collapse (see Fig. 184.4). Initially the joint space is normal, but structural collapse adjacent to articular cartilage typically leads to secondary osteoarthritis. In some cases this process results in total destruction of the involved structure such as the femoral head or humeral head.

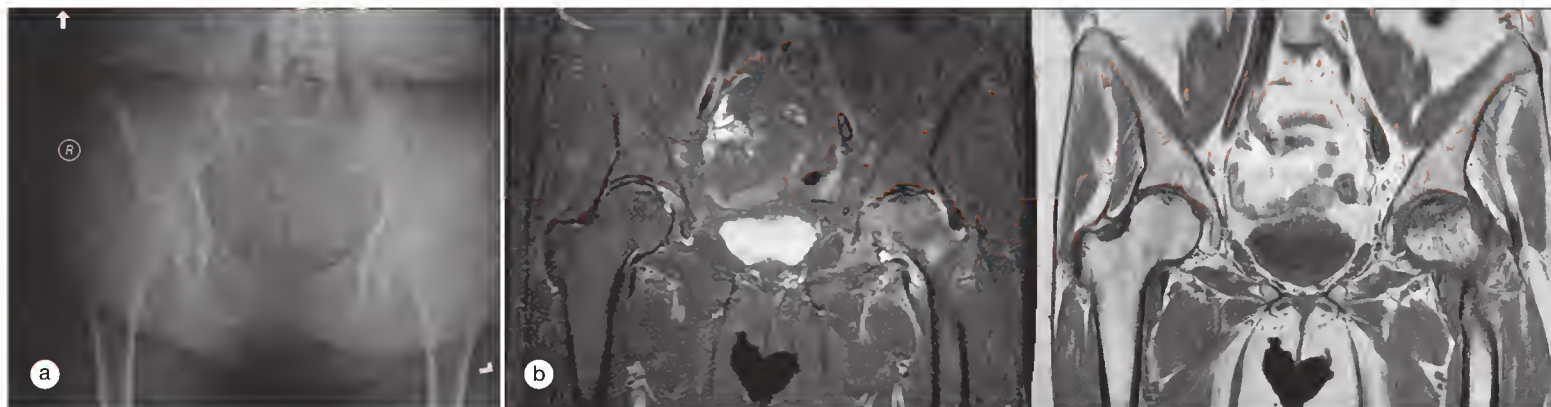


Fig. 184.4 (a) Single view of the pelvis demonstrating vague increased density of the left femoral head raising suspicion of osteonecrosis. Magnetic resonance imaging was recommended for both hips to confirm the finding on the left and potentially identify early osteonecrosis in the contralateral femoral head before collapse. (b) Coronal short tau inversion recovery image (left) confirming avascular necrosis on the left characterized by a geographic lesion on the weight-bearing surface of the left femoral head. Coronal T1-weighted image (right) illustrating the typical pattern of bilateral geographic lesions low in signal. Of interest is the early osteonecrosis involving the radiographically normal right femoral head.

Radionuclide bone scan

Radionuclide bone scans were used to detect early osteonecrosis before the advance of clinical MRI. Bone scans obtained using methylene bisphosphonate labeled with technetium-99m were useful because they can exhibit increased uptake in the region of osteonecrosis before changes emerge on the radiograph. Bone scans may still have utility in situations in which MRI is contraindicated. However, the changes on bone scan are somewhat non-specific, it is not as sensitive as MRI, and it exposes the patient to radiation hazard.

Computed tomography

Computed tomography (CT) offer advantages over radiography due to multiplanar reformatting and improved contrast. CT is useful in defining the extent of cortical collapse in late disease as well as assessing the severity of secondary osteoarthritis. Such information is essential to determine surgical treatment options, which range from osteotomy to total hip arthroplasty. CT may be used in the setting of potential acute on chronic osteonecrosis to evaluate new-onset subtle articular collapse.

Magnetic resonance imaging

The characteristic appearance on MRI varies according to location. Within epiphyseal lesions, such as osteonecrosis of the hip, a typical area of normal marrow signal on T1 and T2 weighting is bordered by a dark line or rim (see Fig. 184.4). The line has been described as having a geographic appearance because it mimics the morphology of a coastline with its interstices. Over time, T2-bright signal parallels the inside margin of the lesion. This is often referred to as the characteristic *double-line sign*. The double-line sign is seen in approximately 75% of cases.⁶² The double-line sign likely represents chemical shift artifact related to the misregistration of adjacent fluid and fat voxels owing to their slightly differing precessional frequencies. As the lesion evolves, it is common to identify subchondral fracture just before collapse. The subchondral fracture line may appear bright on T2-weighted and dark on T1-weighted images. The signal characteristics of the lesion are highly variable. Over time, the lesion, if not revascularized, will appear dark on both T1- and T2-weighted images. Additionally, researchers have identified effusion in approximately 60% of cases.⁶³

MRI has its greatest utility in the early diagnosis of osteonecrosis in a variety of anatomic locations (Figs. 184.5 to 184.8) and also can detect a variety of disorders that can cause diagnostic confusion, such as subchondral insufficiency fracture (see Fig. 184.2) and bone infarcts (Fig. 184.9).

Staging systems

Several different staging classifications have been used to evaluate osteonecrosis. The most widely used system based on conventional radiographic findings is the Ficat staging system described by Ficat and Arlet (Table 184.1).⁶⁴ Over time, this classification system has been modified by other groups to assist in assignment of patients into one of two arms of therapy, intraosseous pressure reduction or joint reconstruction. Steinberg proposed a classification system that refines the Ficat system by including the findings



Fig. 184.5 Coronal proton-density magnetic resonance image of the shoulder illustrating collapse of the articular surface with a characteristic subchondral, low-signal, linear geographic pattern and adjacent marrow signal abnormality that was found to be osteonecrosis on pathologic analysis. (Courtesy Christopher G. Roth, MD.)

of bone scan and MRI as well as emphasizing volumetric assessment of femoral head involvement (Table 184.2). The Association Research Circulation Osseus, in its International Classification of Osteonecrosis of the Femoral Head, has also recently adopted an osteonecrosis staging system (Box 184.2).

MANAGEMENT

Although it is prudent to avoid risk factors such as glucocorticoid use and weight bearing on the affected limb, no conservative medical approaches are known to influence the outcome of osteonecrosis.⁴ Medical treatment options are also limited in scope. There is a long-standing view that load on the affected region should be reduced for 4 to 8 weeks. Crutches can be prescribed to accomplish this, but their effectiveness is unclear. Other

suggested interventions include physical therapy to maintain muscle strength and prevent contractures, and judicious use of analgesics.

Thus the critical management decisions for an individual with newly diagnosed osteonecrosis relate to whether to intervene surgically and which procedure to deploy. Conservative approaches have been tested in clinical trials and are advocated when the affected segment involves less than 15%

of the articular margin and is remote from the weight-bearing region.⁶⁵⁻⁶⁷ However, these conservative approaches do not generally prevent disease progression, which is the primary goal of any osteonecrosis intervention therapy. Overall, the clinical trials and retrospective observational studies comparing conservative treatment to surgical interventions of various types for hip joint osteonecrosis indicate that surgically treated joints generally have better outcomes.

■ **TABLE 184.1**

Ficat staging system

Stage I	Normal radiographic findings
Stage II	Sclerotic or cystic lesions
Stage III	Subchondral collapse
Stage IV	Osteoarthritis with articular collapse

Core decompression

The goals of core decompression are to reduce elevated intramedullary pressure, improve oxygenation of the ischemic region of the bone, and allow adjacent living bone to contribute to the reparative process. The procedure provides swift pain relief and appears to yield favorable results when performed at an early stage of osteonecrosis development. However, a meta-analysis of clinical trials of core decompression suggested that this intervention was superior to conservative treatment only when used to treat stage I

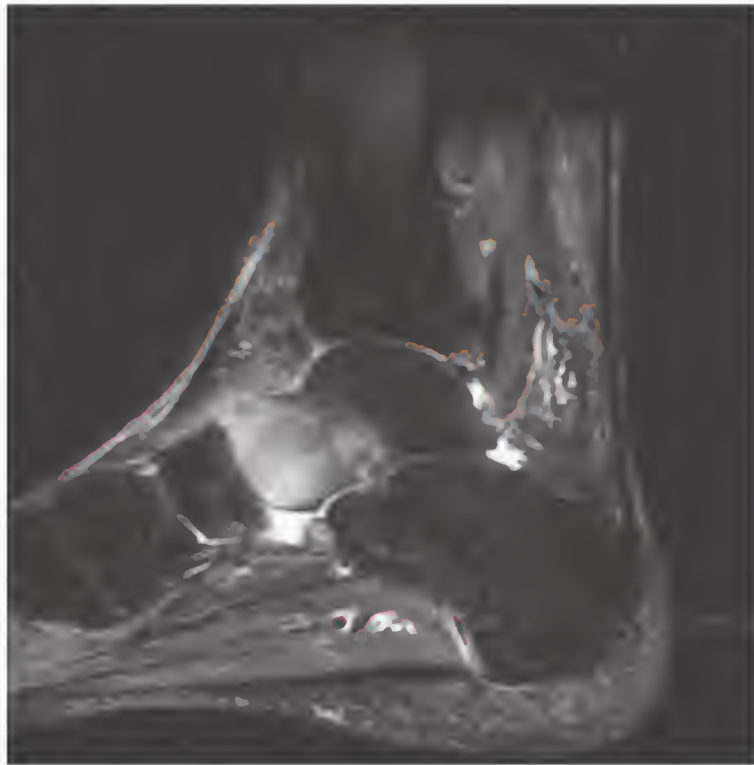


Fig. 184.6 Sagittal proton-density magnetic resonance image of the ankle demonstrating marked marrow signal change within the head of the talus. Differential considerations include fracture and osteonecrosis. The follow-up plain radiograph for this patient indicated avascular necrosis. (Courtesy Christopher G. Roth, MD.)



Fig. 184.7 Axial short tau inversion recovery (STIR) magnetic resonance image demonstrating bilateral avascular necrosis (AVN). Bilateral AVN is apparent on this coronal STIR image. A double-line sign is apparent on the right. Recent thinking attributes the sign to chemical shift artifact, a phenomenon that arises because of misregistration of adjacent fat and water due to slightly differing processing frequencies at a given field strength.

Fig. 184.8 Sagittal T1-weighted magnetic resonance image of the ankle (left) shows marked diffuse low signal of the navicular. The sagittal T2-weighted fat-saturated image (right) demonstrates corresponding diffuse high signal of the navicular, which suggests osteonecrosis. (Courtesy Christopher G. Roth, MD.)

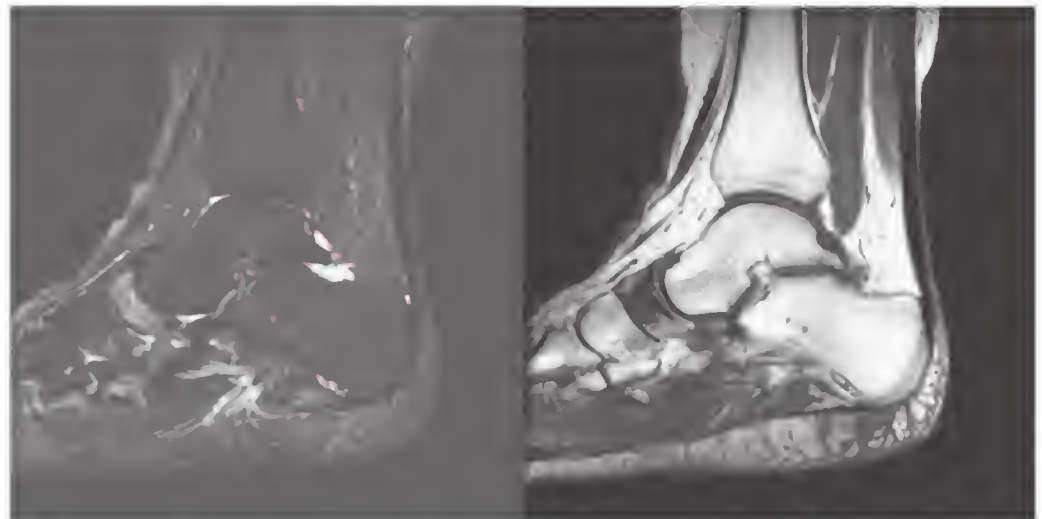




Fig. 184.9 T1-weighted coronal magnetic resonance image of the knee illustrating a geographic lesion in the tibial metaphysis consistent with a bone infarct. (Courtesy Christopher G. Roth, MD.)

TABLE 184.2
Steinberg staging system

Stage I	Normal radiographic findings; abnormal bone scan and/or magnetic resonance imaging findings Mild (<15% of head affected) Moderate (15%-30% of head affected) Severe (>30% of head affected)
Stage II	Lucent and sclerotic changes in the femoral head Mild (<15% of head affected) Moderate (15%-30% of head affected) Severe (>30% of head affected)
Stage III	Subchondral collapse without flattening Mild (<15% of head affected) Moderate (15%-30% of head affected) Severe (>30% of head affected)
Stage IV	Flattening of the femoral head Mild (<15% of head affected) Moderate (15%-30% of head affected) Severe (>30% of head affected)
Stage V	Joint narrowing and/or acetabular changes Mild Moderate Severe
Stage VI	Advanced degenerative changes

BOX 184.2 INTERNATIONAL CLASSIFICATION OF OSTEONECROSIS OF THE FEMORAL HEAD (ASSOCIATION RESEARCH CIRCULATION OSSEUS)

Stage 0: Bone biopsy results consistent with osteonecrosis; other test results normal

Stage I: Positive findings on bone scan, magnetic resonance imaging (MRI), or both

A: <15% involvement of the femoral head (MRI)

B: 15% to 30% involvement

C: >30% involvement

Stage II: Mottled appearance of femoral head, osteosclerosis, cyst formation, and osteopenia on radiographs; no signs of collapse of femoral head on radiographic or computed tomographic study; positive findings on bone scan and MRI; no changes in acetabulum

A: <15% involvement of the femoral head (MRI)

B: 15% to 30% involvement

C: >30% involvement

Stage III: Presence of crescent sign lesions classified on basis of appearance on anteroposterior and lateral radiographs

A: <15% crescent sign or <2-mm depression of femoral head

B: 15% to 30% crescent sign or 2- to 4-mm depression

C: >30% crescent sign or >4-mm depression

Stage IV: Articular surface flattened; joint space shows narrowing; changes in acetabulum with evidence of osteosclerosis, cyst formation, and marginal osteophytes

lesions.⁶⁸ The procedure also carries risks, which include hip fracture, post-operative infection, and suboptimal results.

Other orthopedic interventions for osteonecrosis

A variety of bone graft procedures, often in combination with other operative techniques, can be performed with the intent of delaying the need for arthroplasty. Various types of osteotomies are also performed to shift the necrotic bone segments away from the weight-bearing zone. Long-term outcome data for these procedures are scarce.

Arthroplasty

The development of substantial joint damage and secondary osteoarthritis leaves arthroplasty as the treatment of choice. The stage and extent of disease, as well as the age of the patient, all determine the type of arthroplasty procedure. Unfortunately, patients with osteonecrosis have poorer outcomes following total hip arthroplasty than individuals with osteoarthritis.⁶⁹

Experimental therapies

Various attempts have been made to enhance the healing of osseous defects in the femoral head before collapse occurs. In a recent clinical trial, low-molecular-weight heparin appeared to slow progression of osteonecrosis in patients with early-stage disease.³⁴ Other candidate noninvasive treatment modalities include pharmacologic measures, electrical stimulation, shock wave therapy, and electromagnetic field therapy.⁶⁷ Clofibrate is capable of abrogating the increase in fat content in the femoral head that precedes the development of osteonecrosis in a rabbit model.²⁹ The cholesterol-lowering agent lovastatin has also shown promise *in vitro* and *in vivo* for preventing the development of steroid-induced osteonecrosis.^{28,70} Puerarin, a compound with antioxidative and antithrombotic effects, has been proposed as a preventative for alcohol-induced adipogenesis and osteonecrosis.⁷¹ Future directions may involve growth and differentiation factors, cytokines, angiogenic factors, and bone morphogenetic proteins.

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Rare osteoarthritis: ochronosis and Kashin-Beck disease

■ VIRGINIA BYERS KRAUS

OCHRONOSIS

- Ochronosis is a rare autosomal recessive disorder resulting from a constitutional lack of homogentisic acid oxidase.
- In ochronosis, homogentisic acid undergoes autooxidation as well as enzymatic oxidation and polymerization to form an ochronotic pigment that accumulates in cartilage and connective tissues.
- The endogenous form of ochronosis may be confused with exogenous ochronosis, a limited hyperpigmentation of skin caused by various drugs and chemicals.
- Clinical features of ochronosis include homogentisic aciduria, pigmentation of cartilages and other connective tissues, and, in later years, generalized osteoarthritis of the spine and large joints, termed *ochronotic arthropathies*.

KASHIN-BECK DISEASE

- Kashin-Beck disease is a severe, progressive osteoarthropathy of unknown cause endemic to China and Tibet, with onset in childhood.
- Three interacting causal mechanisms have been proposed, including a deficiency in trace elements (selenium and iodine), exposure to organic matter in contaminated drinking water, and contamination of food by noxious mycotoxins.
- The disease is characterized by necrosis and remodeling of cartilage including growth plates.
- Clinical features of Kashin-Beck disease include generalized osteoarthropathy involving the ankles, knees, interphalangeal joints, wrists, and elbows with foreshortened phalanges; more severe involvement of distal and lower limbs; and an association with short stature.

INTRODUCTION

Osteoarthritis (OA) comprises a heterogeneous group of joint diseases, some of common and some of rare occurrence. Although the rare forms discussed here impact individuals infrequently or in specific and circumscribed geographic regions, nevertheless an understanding of these rare forms of OA may provide useful insights into the nature and pathogenesis of the more common varieties of OA. These rare forms of OA are thought to derive from diverse causes that include genetic determinants (ochronosis), and a combination of genetic, nutritional, and biogeochemical factors (Kashin-Beck disease). This diversity of causes is itself illustrative of the multiple pathways to the syndrome of joint failure that we recognize as OA. Although each of these diseases presents clinically as a form of OA, there are differentiating manifestations by which these arthropathies can be distinguished from one another. An appreciation of these subtleties is key to the recognition and management of these disorders.

OCHRONOSIS

History

Ochronosis and *alkaptonuria* are two names that refer to different manifestations of the same condition resulting from an inborn error of tyrosine

metabolism—a deficiency of the enzyme homogentisate 1,2-dioxygenase (HGO) (Fig. 185.1). The connection between these two entities was recognized by Albrecht in 1902.¹ Simultaneously, this was the first human disorder found to conform to the principles of mendelian autosomal recessive inheritance.² In 1908 the term *inborn errors of metabolism* was first coined by Archibald Garrod to describe this and three other diseases.³ The absence of the HGO enzyme, normally highly expressed in hepatocytes,⁴ leads to the accumulation of metabolites of homogentisic acid in the connective tissues of individuals who are affected; this deposition causes an ochrelike pigmentation in the skin, sclera, and cartilages of the body (Fig. 185.2) and is the characteristic for which the disease was named *ochronosis* by Virchow. Only a small proportion of the homogentisic acid formed endogenously is normally retained in the body because of its high renal clearance⁵; the absence of the HGO enzyme leads to abundant urinary excretion of homogentisic acid, which darkens slowly upon oxidation by prolonged exposure to air. The darkening is hastened by the addition of alkali to the urine and is reflected in the original term for homogentisic acid, *alkapton*, which refers to its avidity for alkali. The distinctiveness of alkaptonuria accounts for reports of dark urine, including urine “as black as ink,” dating as far back as the Middle Ages.¹ There has even been biochemical confirmation that ochronotic pigment in the bone and articular hip cartilage of an Egyptian mummy originated from homogentisic acid, which demonstrates that this disorder has afflicted humans since ancient times.⁶

Epidemiology

Alkaptonuria/ochronosis is one of the rare diseases that affect human beings on a worldwide scale.⁷ In the United States, alkaptonuria has a prevalence of 1 case per 250,000 to 1 million live births.⁸ This disorder occurs worldwide, with the highest frequencies reported in Slovakia and the Dominican Republic, in which the prevalence approaches 1 case per 19,000 inhabitants,⁹ and in a single village in southern Jordan with large number of cases (40 individuals in 17 families) considered a probable consequence of the high rates of consanguineous marriages in Jordan.¹⁰

Clinical features

The patient with ochronosis is distinguished by the triad of dark urine on addition of alkali, ochronotic pigmentation, and arthritis.¹¹ Alkaptonuria is present at birth and is often diagnosed by discoloration of the diapers. This is the only sign of the disorder in the pediatric age group,¹² and many patients remain undiagnosed until adulthood because 25% do not have the characteristic dark urine staining.¹³ It is possible that many of the early manifestations of this disorder may go unnoticed by the patient, including dark urine and dark cerumen at birth, axillary pigmentation at puberty, and earlobe skin and scleral pigmentation at 20 to 40 years of age.¹⁴ Cases that escape detection in childhood are usually diagnosed on the basis of chronic joint pain, which typically develops in the third decade of life.² The delay in appearance of the ochronotic arthropathy until after midlife is often ascribed to a waning efficiency of the renal clearance of homogentisic acid leading to an accelerated accumulation of homogentisic acid oxidation byproducts with aging.¹⁵

The arthropathy that develops affects the spine and large joints. The low back is frequently the signal anatomic site. The spine involvement resembles ankylosing spondylitis but differs in sparing the sacroiliac joints.² The pattern of spine involvement is reported to differ from typical OA in that thoracolumbar changes predominate rather than lumbosacral degeneration,¹⁵ although the severity of lumbar spine involvement had the strongest correlation with disability measures in a study of 53 patients.¹⁶ Narrowing and dense, waferlike calcification of the intervertebral disks are the most

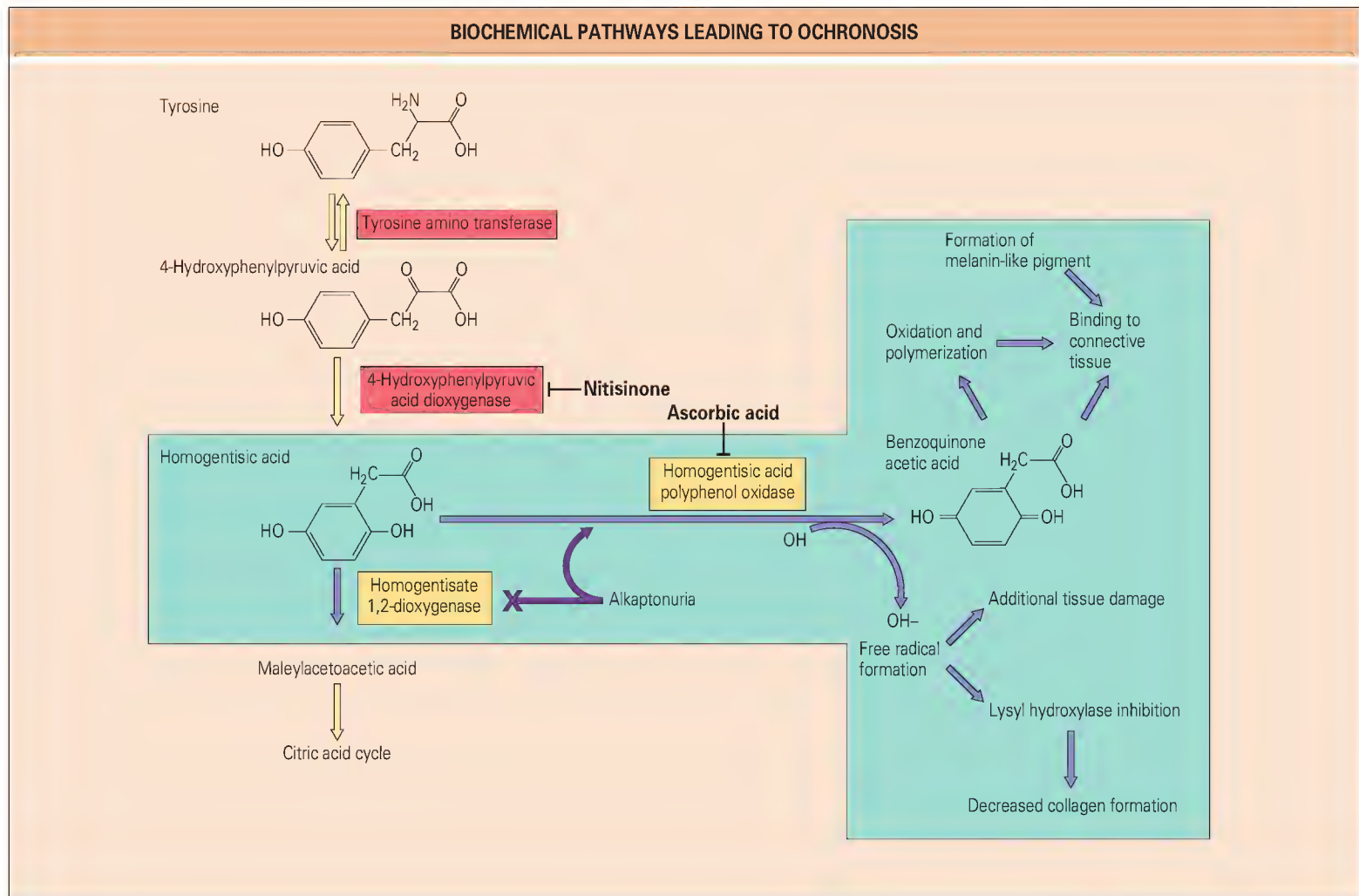


Fig. 185.1 Ochronosis. Pathways leading to pathologic manifestations of ochronosis (alkaptonuria). (Adapted from references 2, 8, and 19.)



Fig. 185.2 Ochronosis. Black-gray pigmentation of the ear cartilage in a patient with ochronosis.

characteristic findings in the spine (Fig. 185.3), and osteophytes are said to be usually absent or of small size.^{17,18} The peripheral arthritis closely resembles that of OA; however, hands and feet are usually spared.¹⁹ Arthritis of the peripheral joints is generally observed about 10 years after spinal changes (Fig. 185.4). The main differences between ochronotic arthropathy, primary OA, and ankylosing spondylitis are summarized in Table 185.1. Tendon involvement is typically symmetric and involves traction tendons and their insertion sites with characteristic changes of enthesopathy, in general sparing tendons with synovial sheaths.²⁰ Tendon and ligament ruptures are reported to occur with minimal provocation.^{2,21} Pain, stiffness, crepitation, flexion contractures, and limitation of motion are the most common clinical features.¹⁸ Loose (osteochondral) bodies may cause joint-locking episodes.¹⁸

Increased bone resorption and osteoporosis have also been documented in association with ochronosis, even in the absence of immobility.²² Other disease manifestations include renal and prostate stones, aortic valve calcification and stenosis, and coronary artery calcification.⁸ Because intense pigment deposition is found in the aortic root and minimal pigmentation is seen in the venous circulation, a role has been posited for blood pressure and hemodynamic factors in explaining the differential tissue susceptibility to ochronotic pigmentation and pathologic changes.²³

Investigations

Noninvasive

The diagnosis of alkaptonuria/ochronosis is suspected when there is bluish black pigmentation of the sclerae and the cartilages of the ears and nose, and darkening of the urine on standing in air or with the addition of alkali (10 drops of 10% NaOH to 20 mL urine per Zhao²⁴). The diagnosis is

■ **TABLE 185.1**
Characteristics of ochronotic arthropathy versus primary osteoarthritis and ankylosing spondylitis

	Ochronosis	Osteoarthritis (primary)	Ankylosing spondylitis
Joints involved	Spine+++ Knees+++ Hips++ Shoulders+	Spine+++ Knees++ Hips++ Hands+++	Spine+++ Knees+ Hips+
Distinguishing spine features			
Sacroiliac joints	Spared	Spared	Involved
Osteophytosis	Sparse	Prominent	None
Disk calcification	Dense/waferlike	Mild-moderate	Mild-moderate
Multiple vacuum disks	Common	Rare	Rare
Syndesmophytes	Broad	None	Thin + vertical
Apophyseal facet joint disease	Mild	Mild-severe	Severe
Ligamentous ossification	Prominent	Scarce	Scarce

Adopted from Konttinen YT, Hoikko V, Lomdmon M, et al. Ochronosis: a report of a case and a review of literature. Clin Exp Rheumatol 1989;7:435-44.



Fig. 185.3 Ochronosis. Radiographs of the spine showing narrowing and calcification of the intervertebral disks.

confirmed by 24-hour urinary excretion of homogentisic acid, measured by gas chromatography or high-performance liquid chromatography, that is higher than 0.030 to 0.040 mmol/mmol creatinine for children aged 1 to 6 years and 0.017 mmol/mmol creatinine for individuals from age 7 years through adulthood.²⁵ In addition, significant laboratory artifacts in alkaptonuria include the following: a false-positive urine Clinitest result for sugars caused by the reduction of copper by homogentisic acid¹⁸ and a falsely low urinary creatinine level if measured by an enzymatic method due to interference by homogentisic acid.²⁶

The extent of arthropathy is typically documented radiographically, and profound osteoarthritic changes in the large joints and the spine with extensive calcification of intervertebral disks characteristically are seen. Magnetic resonance imaging can readily detect ligamentous lesions.²⁷ Bone turnover and bone mass can be determined by quantification of N-telopeptides of type I collagen in the urine and by dual-energy x-ray absorptiometry (DXA) of the femur but not by DXA of the spine, for which bone mineral density measurements are spuriously overestimated due to intervertebral disk calcification and osteophyte formation.²²

Invasive

Macroscopic inspection of the joint during surgery shows darkened cartilage. Biopsy of affected tissues reveals the characteristic yellow-brown pigment in unstained sections, both free and intracellularly; the pigment typically is seen in macrophages, but researchers have also found pigment in chondrocytes, osteocytes, osteoblasts, osteoclasts, and fibroblasts.^{28,29} In cartilage the ochronotic pigmentation is most severe in the deep layer of cartilage, known to be a region of low protein turnover, whereas the articular surface, the region with the highest level of protein turnover, shows little pigmentation (Fig. 185.5a).³⁰ Ochronotic fragments of cartilage are found embedded in synovium where they evoke foreign body reactions with multinucleated giant cells.³¹ Ochronotic fragments of cartilage are also found in the joint cavity where they form a nidus for the development of osteochondral bodies.¹¹ Although the molecular basis for this is unclear, by electron microscopy ochronotic pigment has been observed deposited on collagen fibrils of joint capsule and cartilage, often in a distinctive pattern with some association with the periodicity of collagen cross banding (Fig. 185.5b).^{29,32}

as well as pigment invasion and disordering of collagen structure.³³ This distinct pattern of ochronotic pigment deposition can be reproduced by 5 to 7 days of *in vitro* culture of osteosarcoma cell lines and chondrocytes in a culture medium supplemented with homogentisic acid.^{28,34} Interestingly, bone collagen is largely unaffected, which indicates that mineralization of the collagen fibers *in vivo* prevents deposition of ochronotic pigment.³⁵ Homogentisic acid, the toxic agent in alkaptonuria, was recently identified as a member of a new chemical group of fibroblast growth inhibitors,³⁶ which suggests that the pigment itself may have some antianabolic characteristics that would inhibit the ability of joint tissue to respond to the pathologic insult induced by the deposition of pigment. This may, at least in part, explain the general lack of osteophyte formation as described earlier. It has recently been demonstrated that ochronotic pigment colocalizes with amyloid in osteoarticular tissues and is associated with high plasma levels

of serum amyloid A and P proteins,³⁷ which suggests that secondary amyloidosis occurs in response to the inflammation invoked by ochronotic pigment. Synovial effusions are reported in about half of cases, with cell counts of 100 to 700 cells/mm³ and a predominance of mononuclear cells.^{15,18} In one report, an aspirate from an affected joint yielded a synovial fluid with a speckled “ground pepper” appearance and dark cytoplasmic inclusions in mononuclear and polymorphonuclear cells.¹¹ Unlike urine, synovial fluids reportedly have low concentrations of homogentisic acid and fail to darken upon addition of alkali.¹¹ Homogentisic acid and its oxidation byproduct, benzoquinone acetic acid, react positively with Nile blue sulfate variant I stain, originally developed for identification of melanin,³⁸ and also turn black when stained with methylene blue or cresyl violet.¹⁸

Differential diagnosis

Alkaptonuria may be confused with several other conditions that cause dark urine, including porphyrias, the ingestion of indole compounds, myoglobinuria, hemoglobinuria, hematuria, bilirubinuria, and the presence of urobilinogen when oxidized to urobilin.¹⁸ The endogenous form of ochronosis may also be confused with exogenous ochronosis. Exogenous ochronosis refers to ochrelike pigment deposition in the skin, and sometimes in cartilages or other organs, as a result of exposure to a variety of exogenous compounds. Compounds implicated as causative agents of exogenous ochronosis include topical phenol formerly used as an antiseptic, topical hydroquinone bleaching creams, quinine injections, oral antimalarial drugs, amiodarone, cytotoxic drugs, minocycline,³⁹ and levodopa and methyldopa used in the treatment of Parkinson disease.⁴⁰ In most cases, long-term exposure to the inciting agent is necessary for the development of hyperpigmentation. Reversal is slow or nonexistent. These cases are distinguished from endogenous ochronosis by lack of urinary homogentisic acid excretion, genetics, and, in some cases, biopsy findings. No clear clinical effects beyond the cosmetic ones have been delineated for exogenous ochronosis. Thus it is necessary to appropriately distinguish exogenous from endogenous ochronosis, both to determine prognosis, which is more favorable for exogenous ochronosis, and to recommend the appropriate therapy, as described later, for an individual with endogenous ochronosis.

Pathogenesis

The tissue accumulation of homogentisic acid and its oxidation byproduct, benzoquinone acetic acid, is thought to be responsible for the clinical manifestations and severe arthropathy of ochronosis.⁴¹ Homogentisic acid can



Fig. 185.4 Ochronotic arthritis of the shoulder. Radiograph demonstrating characteristic osteoarthritis pathologic features including narrowing of the joint space, marked subchondral sclerosis, and small osteophytes.

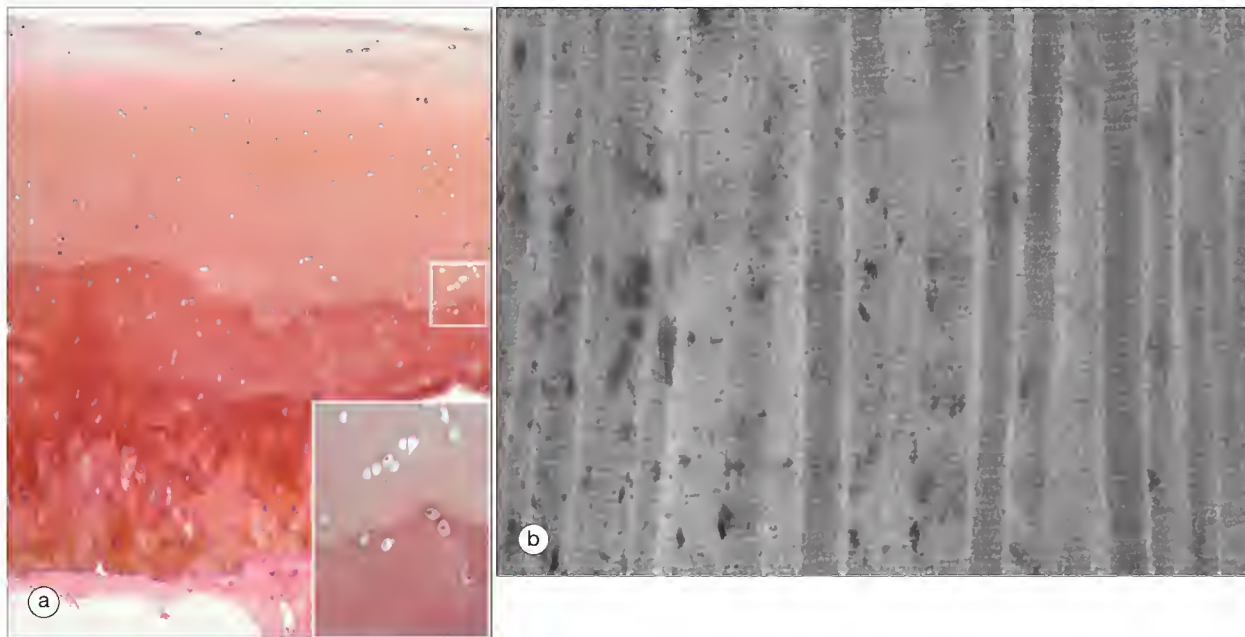


Fig. 185.5 Ochronosis. (a) Photomicrograph showing the presence of ochronotic pigment in the cartilage from a femoral condyle of a patient with alkaptonuria. Pigmentation appears as a gradient and is most severe in the deep layers of cartilage; the articular surface shows little pigmentation (hematoxylin-eosin, $\times 4$). Inset: Chondrocytes located on the border between dense and light extracellular pigment. Chondrocytes show intracellular pigmentation and in some instances signs of necrosis (hematoxylin-eosin, $\times 10$). The evidence suggests that pigmentation occurs initially at the deep layers of cartilage before progressing toward the articular surface. (b) Transmission electron micrograph showing collagen fibers of ligamentous capsule from a patient with alkaptonuria. Collagen fibers have numerous electron-dense deposits of ochronotic pigment located along the fiber body. Deposits show some association with collagen cross banding. Not all fibers have deposits (stained using 1% aqueous osmium tetroxide solution and 5% alcoholic uranyl acetate, post-stained using lead citrate and uranyl acetate, $\times 60,000$). (Courtesy Dr. Adam M. Taylor, findAKUre project, University of Liverpool.)

undergo both autooxidation and enzymatic oxidation and polymerization to form an ochronotic pigment in the presence of the enzyme homogentisic acid polyphenol oxidase, present in skin and cartilage⁴¹ (see Fig. 185.1). High levels of homogentisic acid perturb collagen assembly and structure *in vivo* and *in vitro*.^{32,33} The infiltrated cartilaginous tissues become stiff³⁰ and brittle, and fissure and fragment readily. In addition, benzoquinone acetic acid may inhibit lysyl hydroxylase,¹ thereby reducing cross-linking of types I and II collagen and further impairing the ability of menisci and articular cartilage to resist stress and shearing injury. Finally, homogentisic acid also inhibits cell growth *in vitro* in a dose-dependent manner.¹ The concentrations of homogentisic acid (1 to 5 µg/mL) that proved to be cytotoxic in one *in vitro* study⁴² corresponded to plasma concentrations reported for patients with alkaptonuria (3.0 to 27.8 µg/mL).² Injected in high concentrations into joints of rabbits, homogentisic acid caused swelling, limitation of motion, and articular cartilage necrosis.⁴³

Genetics

In 1901 Garrod suggested an inherited cause of alkaptonuria⁵ based on observation of a family with two affected siblings and consanguinity of the parents. In 2007, clinical images of the eye, ear, and spine were published showing the progression to ochronosis by age 60 of the infant with alkaptonuria originally identified by Garrod.⁹ It is now well established that the accumulation of homogentisic acid and its oxidation products occurs through a deficiency of the HGO enzyme. The HGO enzyme is a hexamer consisting of two trimeric subunits.¹ The proper folding or association of the HGO subunits can be readily abolished by nonsynonymous (affecting a change in an amino acid) point mutations in the HGO gene on chromosome arm 3q, which eliminates the function of the HGO enzyme at the sites of its tissue expression: liver, kidney, small intestine, colon, and prostate⁴⁴—and, as recently described, chondrocytes, synoviocytes, and osteoblasts.⁴⁵ To date, a total of 119 different HGO mutations have been reported.^{46,47} With the exception of several mutations affecting individuals from the high-prevalence areas of Slovakia and the Dominican Republic, most of these HGO mutations are unique and specific to particular families with the disorder. The occurrence of a few specific mutations in the high-prevalence areas is taken as evidence for mutational hot spots within the HGO gene or founder effects^{2,9}—the consequence of a population arising from a small number of genetically isolated individuals, one or more of whom had the gene mutation. To date, no apparent correlation has been discerned between a patient's genotype and the level of excreted homogentisic acid,⁴⁸ nor have there been clear correlations between specific genotypes and clinical manifestations, including age of onset of symptoms²; a functional enzyme assay is thought to be required to accurately predict the pathogenicity of specific HGO variants.⁴⁸

Animal models

The mouse gene homologue of human alkaptonuria was mapped in 1994 through creation of a mutant mouse strain.⁴⁹ In another animal model, an arthropathy resembling ochronosis was induced in rats by feeding a diet with 8% L-tyrosine for 9 or more months starting at 1 month of age.³⁸ In a third animal model, injection of homogentisic acid into the joints of rabbits produced joint lesions that were similar to those of ochronosis, including the deposition of pigment within the synovium, synovial thickening, and granulomatous reaction in response to embedded fragments of damaged cartilage or tendon. This pathologic process could be ascribed directly to homogentisic acid rather than acidity because similar results were observed with both unbuffered and buffered (pH 7) homogentisic acid solutions.⁴³ Finally, a recent report documented the first histologic evidence for ochronosis of tissues in a murine transgenic model of alkaptonuria⁵⁰; of note, macroscopic and microscopic evidence of ochronosis was first observed at 13 months of age and was most readily identified by Schmorl staining. These animal models, the latter in particular, may be of use for studies of the pathogenesis of this disorder and provide model systems in which to evaluate potential therapies.

Management

The current approach to the treatment of musculoskeletal manifestations of alkaptonuria consists of standard therapy for OA with judicious use of joint replacement when warranted. In one prospective study of the natural history of the ochronotic disease process, the average age of joint replacement in patients was lower (53 years) than the national mean (67 years).¹⁶ This study also noted that a history of regular swimming correlated with less kyphosis and scoliosis and a trend toward higher vitality, physical role, and

mental health scores on the SF-36 Health Survey. Based on this study, treatments likely to benefit the physical function of these individuals include regular swimming, spine mobilization, and development of good truncal strength initiated early in the disease process.¹⁶ There has been one report of the disappearance of alkaptonuria and the cessation of ochronotic lesions following liver transplantation for hepatitis B-related cirrhosis.⁴ Surveillance for aortic dilatation and valvular calcification is recommended, as well as intervention for prostate and renal stones as needed.⁵¹

Although no specific pharmacologic therapy yet exists, the compound nitisinone (Orfadin), which has the chemical name 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione and was approved by the U.S. Food and Drug Administration in 2002 for the treatment of hereditary tyrosinemia, has been investigated for use in ochronosis.^{2,52,53} This drug inhibits the enzyme 4-hydroxyphenylpyruvic acid dioxygenase that produces homogentisic acid (see Fig. 185.1). A prospective randomized clinical trial involving 40 patients who were treated for 3 years with 2 mg nitisinone orally once daily showed a reduction of 95% or more in urine and plasma homogentisic acid levels and few adverse effects (one case each of corneal keratopathy and hepatotoxicity); however, hip range of motion and musculoskeletal function were not significantly different between treated and nontreated groups, although the trend in all these outcome measures favored the nitisinone group at study completion.⁵³ Of patients lacking aortic stenosis at baseline, none of the 18 nitisinone-treated patients compared with 7 of 17 control patients developed aortic sclerosis or stenosis by study completion.⁵³ Of note, patients could not be masked as to their treatment group because their urine color revealed the impact of nitisinone. These results suggest that this therapy is worth further study, but a longer trial, different primary endpoints, and/or a younger patient group may be required to demonstrate clinical efficacy. The estimated half-life of nitisinone of 54 hours may ultimately permit even less frequent dosing than once daily. Standardized clinical assessment tools for alkaptonuria have been developed^{54,55}; these are expected to facilitate longitudinal clinical assessments of patients.

Other treatments have included dietary restriction of protein to limit tyrosine and phenylalanine intake, although this was not required in the clinical trial described earlier. Compliance with these restrictions is reported to be difficult for adults, and long-term clinical trials of dietary therapy for alkaptonuria/ochronosis have not been conducted. Low-dose methotrexate was recently suggested to potentially inhibit the secondary production of amyloid in patients with alkaptonuria.³⁷ Antioxidants have also been proposed for the treatment of alkaptonuria based on the ability to counteract both the polymerization and accumulation of homogentisic acid, and the deleterious effects of free radicals generated in the course of homogentisic acid oxidation.¹ Antioxidants studied to some extent to date include ascorbic acid (vitamin C), N-acetylcysteine, phytic acid, and vitamin E as well as taurine, ferulic acid, and lipoic acid.^{56,57}

For many years ascorbic acid was considered a potential therapy for ochronosis based on a mechanism of action of inhibition of homogentisic acid polyphenol oxidase⁵⁸ responsible for producing the oxidized and polymerized byproducts of homogentisic acid (see Fig. 185.1). Consistent with this proposed mechanism of action, ascorbic acid inhibited the binding of a radiolabel derived from a homogentisic acid precursor to connective tissues in a rat model of alkaptonuria⁵⁹ and decreased the excretion of benzoquinone acetic acid in the urine.⁶⁰ In one report, transient (about 12-day) enhancement of homogentisic acid urinary excretion was achieved by ascorbic acid (500 mg twice daily) in 2 of 3 patients.¹⁹ On a cautionary note, ascorbic acid may serve as a cofactor for 4-hydroxyphenylpyruvic acid dioxygenase (see Fig. 185.1) and therefore may increase the production of homogentisic acid in alkaptonuria through this mechanism.⁶¹ Clinical outcomes of long-term treatment with ascorbic acid (0.25 to 4 g/day) have varied, and overall it has not been dramatically effective; however, controlled trials have never been conducted.

KASHIN-BECK DISEASE

History

Kashin-Beck disease (KBD) was first reported in Siberia in 1849 by a Russian surveyor, M. Jurenskij, who noted that some residents of the Urov River Valley of Russia had shortened fingers, showed a characteristic gait, and could neither walk nor work properly.⁶² In 1859 the physician Nikolai Kashin, assigned to a Cossack brigade, was ordered to investigate the disease causing deformities that prevented a segment of the local population from serving in the army.⁶² He concluded that “goiter, rheumatic pain, and cretinism” was an endemic disease, and it came to be known as *Urov disease*.

Evgeny Beck later added a systematic epidemiologic survey of this disorder in 1906, noting a prevalence of 6% to 46% (mean, 32%). KBD was first reported in China in 1908.⁶³ The world's literature on KBD was summarized in 1994 by Allander.⁶⁴ Skeletal remains indicate that it goes back to at least the 16th century.⁶⁴

Epidemiology

KBD is endemic in a region extending diagonally from northeastern China to Tibet in the southwest, with additional endemic regions in neighboring areas of Russia and some regions of Vietnam and Korea.⁶⁵ According to the 2008 health statistics issued by the Chinese Ministry of Health, there are currently 714,822 individuals affected by KBD in 2253 villages; this represents a KBD prevalence of 0.2% in the endemic villages (www.moh.gov.cn/publicfiles/business/htmlfiles/zwgkzt/ptjty/200805/35671.htm). In nongovernmental reports, the prevalence of KBD is described to be 8% to 43% in heavily affected areas.⁶⁶ KBD is mainly a disease of poor farming families,⁶⁷ on whom it imposes a severe socioeconomic stress.⁶⁸ These endemic regions are known for especially low environmental levels of the essential trace element selenium⁶⁹ and, consequently, low selenium levels in the blood and tissues of the native peoples consuming food from these areas.⁷⁰ The population mean serum selenium concentration in this region is less than 0.020 mg/L,⁷¹ whereas serum selenium concentrations in healthy persons have been found to average 0.066 to 0.104 mg/L.⁷² In China, the geographic distribution of KBD corresponds most closely to the areas of lowest selenium in water, soil, and food grains,^{69,73} and fluctuations in disease status are reported to correspond to fluctuations in serum selenium concentration,⁶⁹ the so-called wave character in morbidity.⁶² The daily intake of selenium in the Shaanxi KBD endemic area of China was quantified as 4.6 µg/day compared with 10.5 µg/day for nonendemic areas.⁷⁴ Both levels are well below the U.S. recommended daily allowance (RDA) of 70 µg for men and 55 µg for women. Within low-selenium areas, the reliance on river water for drinking has been associated with increased risk of disease in KBD areas, although selenium levels of the various water sources under study were not cited.⁷⁵ Eating corn, wheat, and barley has also been associated with KBD, whereas eating rice appears to be protective^{67,69}; interestingly, rice grown in KBD-endemic areas has a higher selenium content and selenium bioavailability than corn or wheat, which possibly accounts for its apparent protective effect.

Although a geographic association between KBD and selenium deficiency has been reported, KBD does not occur in every selenium-deficient area of China.⁷¹ Therefore, to gain a comprehensive understanding of risk factors for KBD, a cross-sectional epidemiologic study was conducted in 12 rural villages in Tibet in which 575 children aged 5 to 15 years were examined. The variables independently associated with KBD were found to be higher age, male gender, low socioeconomic status, a poorly diversified diet, iodine deficiency, and the use of smaller water containers.⁶⁷ Individuals were also at greatest risk of KBD if they had a sibling with the disease. In this study, selenium deficiency was severe in both KBD-affected and unaffected children, whereas low urinary iodine, high serum thyrotropin, and low serum thyroxine-binding globulin values were associated with an increased risk of KBD. Goiter secondary to iodine deficiency was found more often in villages affected by KBD than in control villages.⁷⁶ In general, selenium deficiency is closely associated with iodine deficiency in KBD areas.^{71,76} In one KBD-endemic area of China, urinary iodine levels were found to be 40% lower in KBD-affected children than in unaffected children.⁷⁷ Although iodine deficiency doubled the odds of KBD in this Chinese cohort, selenium deficiency was associated with a 61-fold increase in the odds of KBD.

In China, foodstuffs such as corn have commonly been stored in cave dwellings, where it is thought mycotoxins enter the food chain. In Tibet, too, a striking association was found between KBD and moldy grain from storage in a tent out of doors, which further suggests a pathogenic role for mycotoxins.⁶⁷ Fungal contamination of barley grain was related to the highest percentage of KBD cases (65%). Three fungal taxa isolated from barley samples were independently associated with KBD (*Trichothecium roseum*, *Alternaria* species, and *Dreschlera* species). The KBD prevalence rate increased dramatically from 13% if none of these taxa was isolated to 51% if one taxon was found and 89% if two or more taxa were isolated. This study provided strong support for a multifactorial cause of KBD in Tibet. Since then, numerous *in vitro* and animal studies have documented the deleterious effect of mycotoxins on cartilage.⁷⁸⁻⁸³

Evidence for hyposelenosis in non-KBD areas suggests that other risk factors, in addition to selenium deficiency, contribute to the pathogenesis of KBD. For instance, hyposelenosis exists in non-KBD areas such as Scandinavia, New Zealand,⁸⁴ Poland,⁸⁵ Central Africa, and the Democratic

Republic of the Congo,^{71,86} although the degree of deficiency in these areas may not be as profound as in the KBD-endemic areas.⁸⁶ Nevertheless, recent data suggest that milder degrees of selenium deficiency are associated with deleterious musculoskeletal consequences. In a population-based study in Johnston County, North Carolina, low selenium levels have been associated with increased odds of knee and hip OA.⁸⁷ In this regard, it is interesting to note an observation attributed to Kravencho in 1959 that an inordinate degree of OA developed in individuals who moved into endemic areas of KBD after the age of 25.⁸⁸ In addition, selenium levels were found to be significantly lower in men than in women in this American cohort.⁸⁷ As for many essential nutrients, the RDA for selenium is higher for men than for women to compensate for their larger body mass. Thus it is possible that selenium levels in men may more readily fall below a critical level necessary for joint tissue health under conditions of severely limited intake. The possibility that insufficient selenium intake may impact males more readily suggests a possible rationale for the consistent reports of a higher prevalence of KBD in males.

Clinical features

KBD usually becomes evident in children between 5 and 15 years of age.⁷⁶ Joint pain is the earliest symptom. For purposes of epidemiologic studies, a diagnosis of KBD has required symptom onset before the age of 30 years to clearly differentiate it from primary OA.⁸⁹ An increasing number of joints are involved from childhood to the age of 25 years in a slowly progressive osteoarthropathy.⁹⁰ The particular manifestations of the disease are symmetric and may vary with the time in life of exposure to the endemic environment. The arthropathy progresses to severe joint dysfunction, enlargement, and deformity. The Chinese characters for this disease, when literally translated, mean "big joint disease"⁶⁴ (Fig. 185.6). The most distal joints of the upper and lower limbs (lower more than upper) are most often and most severely affected,^{91,92} including the ankles, knees, interphalangeal joints, wrists, and elbows.⁸⁹ The foot and ankle are involved in 90% of cases. In fact, it is said that the absence of talus involvement in an adult is cause to reject the diagnosis of KBD.⁹⁰ The hand develops enlargement of interphalangeal joints reminiscent of Heberden and Bouchard nodes; however, the middle and distal phalanges are shortened, termed *brachydactyly* (Fig. 185.7 shows a photograph and a radiograph of a hand with KBD), resembling the foreshortened distal and middle phalanges caused by frostbite injury in children.⁹³ The carpal bones, in particular the capitate and hamate, are more likely to be involved with worsening severity of KBD involvement of the hand.⁹⁴ Short stature is one of the main features of the disease, and dwarfism is sometimes marked, involving a disproportionate shortening of the extremities.⁸⁸

Standardized national clinical and radiologic diagnostic criteria for KBD have been available in China since 1995 (clinical GB16003-1995) (Table 185.2) and 2001 (radiologic W/T 207-2001) (Table 185.3); their correlation with other features of KBD, including brachydactyly, has been evaluated.⁹⁵ In addition, other staging systems have been devised for this disorder based on clinical^{64,89,96} or radiologic^{90,91,94} features (see Tables 185.1 and 185.2). A significant correlation has been shown between the clinical classification system of Mathieu⁸⁹ and the radiologic classification system of Hinsen-kamp.⁹¹ Although the clinical criteria are more sensitive, the radiologic criteria are more specific for KBD.⁹¹ An instrument for assessing quality of life has recently been developed and validated for use in KBD patient populations.⁹⁷

Investigations

Noninvasive

The abnormalities of growth and development and the radiographic appearance of this disease have been ascribed to pathologic endochondral growth at epiphyseal and acrophyseal sites.⁹⁸ The radiologic features of KBD have been reported to resemble the lesions of osteochondrosis,⁶⁴ a group of diseases of children and adolescents that are caused by insufficient blood supply to the epiphyses and lead to localized tissue necrosis at the growing ends of bones during the years of rapid bone growth. The radiologic joint features deemed diagnostic of KBD include irregularities of bony margins, sclerosis, and a cone-shaped, fused, or fragmented metaphysis.⁹¹ Several serum and urine OA-related biomarkers have been shown to be associated with the presence or severity of KBD, including chondroitin sulfate and proteoglycan-related epitopes, pyridinoline, serum nitric oxide, CD44, matrix metalloproteinase-1 (MMP-1), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), cartilage oligomeric matrix protein, and type II collagen.⁹⁹⁻¹⁰² Proteomic studies comparing KBD and control sera are ongoing to identify diagnostic biomarkers for KBD.^{103,104}



Fig. 185.6 Kashin-Beck disease manifested as bony enlargement of the elbows (a) and knees (b) exemplifying the characteristic for which the disease is named *large joint disease* in China. (Courtesy Drs. Virginia Byers Kraus and Junling Cao.)



Fig. 185.7 Kashin-Beck Disease of the hand. (a) Photograph of a hand with the brachydactyly of Kashin-Beck disease (on left) compared with a reference hand of a Chinese individual without Kashin-Beck disease (on right). (b) Radiograph of the hand of an individual with Kashin-Beck disease demonstrating shortened middle and distal phalanges, cone-shaped metaphyses, and “pumice stone” deformity of carpal bones. (a, Courtesy Dr. Junling Cao; b, courtesy Dr. Xiong Guo.)

Invasive

The initial pathologic change in KBD is necrosis of cartilage and secondary repair and remodeling of cartilages of the metaphyses, bone ends, epiphyses, and carpal bones⁹⁰ leading to disturbed mineralization, impaired skeletal development, disfiguration of joints, and chronic deforming OA.^{96,105} Because the metaphyseal side of the growth plate is the most active site of bone growth and development during childhood, it is the site affected

earliest and most frequently with cartilage necrosis (chondronecrosis).⁹⁰ Apoptotic chondrocytes are found more frequently in KBD than in control cartilage¹⁰⁶ and at a rate comparable to that in OA. The histologic features of KBD lesions have included the absence of vascularization within the proximal cartilage endplate.¹⁰⁷ *In vitro* studies of cartilage or chondrocytes have demonstrated increased hydroxyproline content, decreased thermal stability of collagen II, and increased levels of precursor collagen (procollagen II) thought possibly due to inhibition of conversion to the mature

TABLE 185.2

Staging systems for Kashin-Beck disease

Clinical staging system based on the Chinese National Criteria					
Stage	Signs				
Early	Flexion of the terminal part of the fingers or crooked fingers and arthritis pain in knee and ankle joints without enlarged finger joints				
First stage	Enlarged finger joints and clinical symptoms of the early stage				
Second stage	Shortened fingers and clinical symptoms of the first stage				
Third stage	Retarded growth or dwarfism and clinical symptoms of the second stage				
Clinical staging system of Mathieu					
Stage	Age	Joint enlargement (due to metaphyseal widening)	Joint pain	Severity of motion restriction of most affected joint	Associated symptoms*
I	<15 yr	–	+	Grade 0	–
I	All ages	+	–	Grade 0	–
II	All ages	+	+	Grade 1-2	–
III	All ages	+	+	Grade 1-2	+
Clinical staging criteria of Beck					
Stage	Severity	Joint pathology	Joint pain	Range of motion	Other findings
I	Mild	Deformation/thickening of fingers 2-4	+ (AM and with activity)	Slight limitation of interphalangeal and fine crepitation of larger joints (elbow, knee, ankle)	–
II	Moderate	Deformation/thickening of all fingers, elbow, knee, ankle, wrist, and 1-2 large joints; brachydactyly	+	Limited wrist motion and finger extension	Intraarticular loose bodies, muscle atrophy
III	Severe	Marked deformation/thickening of finger joints; distinct brachydactyly	+	Unable to make a fist; very limited motion or fused large joints	Platypodia (splayfoot); short/deformed sole

**Associated symptoms are tiredness, muscle weakness, inability to work, pes planus, waddling gait, and dwarfism.
Data for Chinese National Criteria–based staging system from document GB16003-1995 in [reference 154](#); data for Mathieu staging system from [reference 89](#); data for Beck criteria (1906) from [reference 62](#).*

TABLE 185.3

Radiologic staging systems for Kashin-Beck disease

Radiologic staging system based on the Chinese National Criteria			
Grade	Basis for grade (features scored below)		
Normal	0 points		
Mild	1-4 points		
Moderate	5-7 points		
Severe	8-10 points		
Possible points	Radiologic features		
3	Osteophyte: absent = 0; <2 mm = 1; 2 to <4 mm = 2; ≥4 mm = 3		
3	Joint space narrowing: absent = 0; narrowed by >½ normal joint space = 1; <½ normal joint space but joint surfaces did not contact = 2; joint surfaces contacted or loose bodies found in the joint = 3		
1	Sclerosis of bony margins: absent = 0; present = 1		
1	Depression of bony margins: absent = 0; present = 1		
1	Transverse deformation of joint: absent = 0; present = 1		
1	Cysts under bony articular surface: absent = 0; present = 1		
Radiologic staging system of Hinsenkamp*			
Grade	Radiologic feature	Total score	Stage
Grade 0	No radiologic change	0	0
Grade 1	Radiologic changes of the epiphysis or metaphysis	1-10	I
Grade 2	Radiologic changes of the epiphysis or metaphysis without fusion	11-20	II
Grade 3	Local fusion of the metaphyseal growth plate	21-36	III

**In the Hinsenkamp system, six sites (hands/wrists, elbows, shoulders, ankles, knees, and hips) are graded on the 0-3 scale yielding a total score of 0-36 and then a stage of disease is assigned. Data for Chinese National Criteria–based staging system from document WS/T 207-2001 in [reference 154](#); data for Hinsenkamp staging system from [reference 91](#).*

collagen II,⁶⁵ as well as decreased collagen II levels; increased levels of collagens I, II, and X; increased MMP-13 levels^{108,109}; and increased aggrecanase-mediated proteoglycan loss from cartilage.¹⁰¹ These effects were ascribed to fulvic acid toxicity and possibly other environmental exposures.

Differential diagnosis

Selenium and iodine deficiency are linked geographically. Distinguishing between the radiologic features of hypothyroidism and KBD can be difficult.⁷¹ It has been thought possible that some of the musculoskeletal abnormalities of KBD may be related to thyroid dysfunction early in life,⁷⁶ because hypothyroidism in children is associated with epiphyseal dysgenesis, delay of bone development, and reduced endochondral ossification. Of note, selenium plays an indispensable role in thyroid hormone synthesis because it is required for iodothyronine deiodinase activity that converts thyroxine to triiodothyronine.⁸⁵ Thus a closer examination of the role of thyroid hormone abnormalities in the pathogenesis of KBD would appear to be warranted.

Pathogenesis

To date, no consensus has been reached on the cause of KBD. Early residents of the Urov River Valley associated it with “bad” drinking water and had a notion that the disease could be passed down from generation to generation in “diseased families.”⁶² Three causal mechanisms have been proposed to interact to cause KBD: a deficiency in trace elements (selenium and iodine),¹¹⁰ the presence of organic matter in drinking water (fulvic and humic acid produced by chemical and microbial decomposition of plants and animals),^{69,75} and contamination of food by noxious mycotoxins.¹¹¹⁻¹¹³ Cold exposure and occupational microtrauma have also been implicated in disease severity.⁹² In this model, low selenium level is an essential but insufficient condition for the development of KBD.⁶⁹ It is posited that free radicals, generated by mycotoxins and fulvic acid or other environmental factors, damage chondrocytes under conditions of inadequate antioxidant defense, iodine deficiency, and possible protein-calorie malnutrition.⁶⁷ Inadequate antioxidant defense derives from a lack of selenoprotein antioxidants such as glutathione peroxidase and thioredoxin reductase. Selenium can partially counteract adverse chondral effects of the fungal toxin T-2¹¹⁴ and IL-1,¹¹⁵ and suppression of the selenoprotein iodothyronine deiodinase-2 (responsible for conversion of thyroid hormone to its active form) results in strong proinflammatory effects with increased expression of inflammatory mediators, IL-1 β , and cyclooxygenase-2 (COX-2).¹¹⁶ These results underscore the key antiinflammatory role performed by selenium in cartilage. In the absence of adequate selenium and antioxidant defense, the final common pathway of pathogenesis is necrosis of the hypertrophic chondrocytes at the base of the articular and growth plate cartilages.¹¹⁷

Selenium is necessary for the growth of cells in tissue culture⁸⁴ and is commonly used (in the form of selenite) as a supplement for chondrocyte culture in combination with insulin and transferrin.¹¹⁸ Selenium bioavailability ultimately depends on both intestinal absorption of selenium and its conversion into a biochemically active form.¹¹⁹ Selenomethionine is 50% more bioavailable than selenite.¹²⁰ Brief (24-hour) exposure of chondrocytes *in vitro* to selenomethionine (0.5 to 1.0 $\mu\text{mol/L}$) has been shown to block IL-1-mediated inhibition of cartilage matrix macromolecule (collagen II, aggrecan) synthesis and transforming growth factor- β 2 receptor synthesis,¹²¹ as well as induced nitric oxide synthase and COX-2 expression and nitric oxide and prostaglandin E₂ production.¹¹⁵

Some chondrotoxic effects and other pathologic effects have been attributed to mycotoxins and fulvic acid. Nivalenol, a mycotoxin produced by *Fusarium*, inhibits protein synthesis by binding to the ribosome. Added to cartilage grafts *in vitro*, nivalenol inhibits glycosaminoglycan synthesis and retention in the extracellular matrix, overall reducing the chondroitin sulfate content of cartilage.^{122,123} It has been hypothesized that mycotoxins may inhibit angiogenesis,⁹¹ block thyroid hormone function,⁶⁷ and bind thyroid receptors in bone cells.⁶⁷ When added to the diet of rats, fungal extracts inhibit glutathione peroxidase and superoxide dismutase activities and accelerate lipid peroxidation.⁹¹ Similarly, it is hypothesized that organic matter in the form of fulvic acid may accumulate in musculoskeletal tissues and induce superoxide production via its semiquinone radicals¹²⁴ and lipid peroxidation.¹²⁵ These, in turn, would be poorly scavenged in a selenium-deficient host with low levels of glutathione peroxidase activity. *In vitro*, fulvic acid stimulates the generation of H₂O₂ by chondrocytes and increases collagen secretion in a H₂O₂-dependent manner.¹²⁶ Fulvic acid has also been shown to inhibit the conversion of procollagen II to mature collagen II.⁶⁵ However, the levels used in these experiments have not been equated to blood or tissue levels of affected individuals in endemic areas. Finally, this

family of organic acids may interfere with selenium absorption from the intestine.¹²⁷

Genetics

As described earlier, hyposelenosis may be necessary but not sufficient to cause disease. Within the low-selenium belt in China, there are some places and individuals without KBD even though selenium concentrations in the soil, food grains, and hair are low.^{128,129} The mosaic character of disease prevalence (affected villages next to healthy ones) was noted as early as 1939.⁶² In his extensive review of the KBD literature from 1849 to 1992,⁶⁴ Allander noted instances in which Chinese villages where KBD was endemic were within 30 to 50 miles of villages where KBD was nonexistent. This suggests that other environmental or as yet unknown genetic factors are required for full manifestation of the syndrome. Clustering within families has been noted.^{67,117} Genetic factors, common environmental risk factors, or a combination of both could account for this clustering. A 2006-2007 survey of 212 case and 212 control families (total of 3848 individuals) reported that use of river water as the main source of drinking water clustered in KBD families and accounted for a sixfold increase in the odds of KBD.⁷⁵ The proportion of KBD-affected relatives among the probands' families was substantial and significantly higher than that in the control families (55.4% versus 10.2%, respectively; $P = .0001$).⁷⁵ Neither drinking river water alone nor other dietary factors fully explained the familial aggregation of KBD. In a companion study, the heritability of KBD was estimated to be 29% in Linyou County, Shaanxi, China.¹³⁰ These observations suggest that other factors influence the development of disease. Nevertheless, until recently the possibility of a genetic component of disease susceptibility has generally been overlooked in favor of environmental risk factors. Given the association of selenium deficiency with KBD, the possibility of genetic variation in the regulation of selenium absorption and metabolism has been of interest. It is estimated that there are 25 selenoproteins in the human genome.^{84,131} Several of these selenium-containing proteins have known and crucial functions *in vivo*: glutathione peroxidase protects tissues against reactive oxygen damage; iodothyronine deiodinase converts thyroxine to the biologically active form, 3,4,3'-triiodothyronine¹²⁴; and selenoprotein P, produced primarily in the liver,¹²⁰ plays a key role in whole-body selenium metabolism⁸⁴ and carries 60% to 70% of the circulating selenium.¹³² Moreover, selenoprotein P is a negative acute-phase protein,¹³² leading possibly to further limitation of selenium bioavailability during periods of acute illness and thus possibly potentiating KBD. To date, genes reported to contain genetic variants associated with KBD have included *HLA-DRB1*,¹³³ *TNF- α* ,¹³⁴ glutathione peroxidase 4 (*GPX4*),¹³⁵ and glutathione peroxidase 1 (*GPX1*).¹³⁶ Preliminary association analysis of one polymorphism in selenoprotein P (*SEPP1*) yielded negative results.¹³⁷

Animal models

Mice fed for two generations on a selenium-deficient diet supplemented with fulvic acid in the drinking water demonstrated disturbed development of the articular space and meniscus, disturbed subchondral ossification, overly hydroxylated collagens I and II with less thermal stability, and low bone formation activity.^{124,138} Second-generation rats fed a selenium-deficient diet showed growth retardation, a reduction in pituitary growth hormone and plasma insulin-like growth factor I levels, and impaired bone metabolism and osteopenia.¹³⁹ Chronic selenium deficiency in rats was also associated with abnormalities of chondrocytes in the deep cartilage layers consisting of nuclear degeneration and ballooning of the endoplasmic reticulum.¹⁴⁰ Combined selenium and iodine deficiency in rats significantly impaired the growth of bone and cartilage.¹⁴¹ Rats developed chondronecrosis when fed a selenium-deficient diet for 2 months followed by a 1-month oral challenge with bacterial A-1 toxin (from a bacterial contaminant of local grain).¹⁴² Conversely, mice prone to OA (the STR/IN strain) were protected from disease while on a diet enriched with vitamins (C, E, A, and B₆) and selenium.¹⁴³ The role played by muscle in this disease has also been questioned. Severe white muscle lesions develop in sheep in response to low selenium levels. Therefore the possibility has been raised that muscle weakness may contribute directly to the musculoskeletal abnormalities of KBD.⁶⁴

Strong support for a definitive role of selenium deficiency in KBD has recently been provided by a mouse model in which the gene encoding the selenocysteine transfer RNA, essential for selenoprotein expression, has been deleted from chondrocytes.¹⁴⁴ The mice manifested a number of pathologic features typical of KBD (chondronecrosis of articular cartilage, ear cartilage, and tracheal cartilage; small spine size; disproportionate widening of the epiphyseal growth plates) and died by 7 weeks of age due to respiratory distress from tracheomalacia.

TABLE 185.4
Methods of selenium supplementation for populations in China

Form of selenium	Dose or concentration
Sodium selenite (oral)*	1 mg/wk for children aged 3-10 yr 2 mg/wk for children aged 11-13 yr
Selenized table salt	16.7 mg/kg salt, which provided a calculated average intake of 50 µg selenium/day
Sodium selenite (fertilizer spray)	15 g/hectare

*Representative of the most common selenium dosage regimen of the clinical trials performed to date in China for Kashin-Beck disease per Zou et al.⁶⁶ The U.S. recommended daily allowance of selenium for adults is 70 µg/day for men and 55 µg/day for women. Adopted from references 64, 66, and 120.

Management

Individuals with radiologic lesions have more advanced stages of the disease and are expected to be less influenced by selenium treatment than individuals without radiologic lesions.¹¹⁰ Therefore the key to managing KBD is to prevent its occurrence. The strategy of selenium supplementation is considered the mainstay of therapy for KBD in China. Daily intakes of selenium below 20 µg are considered insufficient.¹³² The U.S. RDA is based on optimization of plasma glutathione peroxidase concentrations; however, the amount of selenium needed to optimize selenoprotein P levels may be greater than the current U.S. RDA.¹²⁰ The plasma selenium concentration is often used to assess selenium nutritional status. At plasma concentrations of about 0.08 mg/L (0.4 µmol/L), the selenoproteins glutathione peroxidase and selenoprotein P are considered optimized.¹²⁰ Selenium supplementation in China has been effected through the distribution of selenium-enriched table salt, the distribution of selenium tablets to children,⁷³ and the use of selenium-enriched fertilizer.^{64,74} (Table 185.4). Selenomethionine, the major form of selenium found in food, has almost twice the bioavailability of selenium in the form of selenite.¹²⁰ The use of selenium-enriched fertilizer in selenium-deficient areas has been shown to increase the average daily intake of selenium as much as fourfold to 16.8 µg/day.⁷⁴ Two meta-analyses have summarized the results of the known trials of selenium supplementation for KBD performed to date (5 randomized, 10 nonrandomized), conducted in China from 1982 to 1994.^{66,145} These trials involved more than

2000 participants ranging in age from 0 to 16 years with 10 months to 6 years of follow-up. Based on radiographic and physical examination outcomes (national KBD criteria), selenium reduced the odds of initial KBD manifestations by 80% (odds ratios of 0.13 and 0.16 for the randomized trials and nonrandomized trials, respectively). Although few of these trials reported adverse effects, one trial that administered 1 to 2 mg/day (rather than per week) for the first week reported nausea and vomiting at the beginning of the trial. Excess selenium is toxic, so dosages must be carefully regulated. Both selenium-deficient and selenium-excess diets have adverse effects on the mechanical properties of bones.¹⁰³ Other toxic effects of selenium excess include hair and nail loss,¹⁴⁶ neurologic dysfunction and respiratory distress,¹⁴⁷ and death.⁷² The toxicity limit is estimated to be 600 to 800 µg/day.^{132,146}

In KBD-affected areas of Tibet, where both selenium and iodine deficiency are endemic, supplementation of iodine over 12 months was primarily responsible for stimulating the growth of a population of 10-year-old children.¹¹⁰ As described earlier, a 12-month study of Tibetan children showed the beneficial effects of supplementing iodine in cases of KBD associated with both iodine and selenium deficiency. Because selenium repletion may aggravate hypothyroidism,¹¹⁰ iodine must be administered before selenium in cases in which both are deficient.¹¹⁰ This study has suggested the importance of iodine deficiency as an etiologic factor for KBD manifestations in some areas. In this study, new radiologic lesions occurred only in the group given placebo and iodine group and not in the group given both selenium and iodine, which suggests a potential role for selenium therapy as well.

Other preventive efforts include providing better storage of crops, drying corn, shifting to other crops less susceptible to fungal contamination and with greater bioavailability of selenium (e.g., from corn to rice),^{64,91} and improving the quality of drinking water.⁶⁵ Standard treatments for OA, including physical therapy, nonsteroidal antiinflammatory agents, glucosamine, and intraarticular hyaluronan, can also be of benefit in cases of established KBD.¹⁴⁸⁻¹⁵¹ Some individuals undergo osteotomy¹⁵² or extraction of loose bodies and joint lavage by arthroscopy,¹⁵³ but currently joint replacement is uncommon due to cost barriers.

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CRYSTAL-RELATED ARTHROPATHIES

186

Epidemiology of gout

■ HYON K. CHOI

- In most current societies, with abundantly available food and a strong tendency toward a sedentary lifestyle, gout has changed in epidemiology from a "disease of kings" to a "disease of commoners."
- A number of epidemiologic studies from a diverse range of countries consistently suggest that gout has increased in prevalence and incidence in the last few decades and has become the most common inflammatory arthritis.
- Purine loading and insulin resistance are two key mediating mechanisms underlying the action of many modifiable lifestyle risk factors for gout.
- Lifestyle modifications for gout should consider both the associated benefits and risks in a holistic manner because gout is often associated with many cardiovascular-metabolic comorbid conditions and sequelae.
- Reducing adiposity with daily exercise and limiting intake of red meat and sugary beverages help reduce uric acid levels, risk for gout, insulin resistance, and comorbid conditions, whereas dairy products, vegetables, nuts, legumes, fruits (less sugary ones), and whole grains are healthy dietary choices for patients with gout.

HISTORICAL PERSPECTIVE

Gout is an inflammatory arthritis caused by the crystallization of uric acid within joints and is associated with hyperuricemia. Once known as a "disease of kings and king of diseases," gout has affected figures such as Alexander the Great, Charlemagne, Henry VIII, Emperor Charles V, Benjamin Franklin, Alexander Hamilton, Tennyson, Coleridge, Voltaire, Isaac Newton, Charles Darwin, and Leonardo da Vinci.¹ Also described by Hippocrates during the Golden Age of Greece, gout was previously considered a disease of the affluent and observed primarily in middle-aged men of the wealthy upper class ("the patrician malady").¹⁻³ As is appreciable in these historical descriptions, gout had often afflicted the wealthy and the educated, particularly those who not only could afford the comforts of life but also enjoyed its excesses with lifestyles that bordered on overindulgence, gluttony, and intemperance.¹ As these lifestyles have become affordable and prevalent among the general public in the modern era, particularly in Western societies with abundantly available food and a strong tendency toward a sedentary lifestyle, gout has changed in epidemiology from a "disease of kings" to a "disease of commoners."

WESTERNIZATION AND GOUT TRENDS

Humans are the only mammals in which gout is known to develop spontaneously, probably because hyperuricemia commonly develops only in

humans.^{1,4} In most fish, amphibians, and nonprimate mammals, the uric acid generated from purine metabolism undergoes oxidative degradation via the enzyme uricase, which produces the more soluble compound allantoin.⁴ The impact of diet on uric acid levels in species that lack uricase may also provide insight into why serum uric acid levels in the great apes¹ (1.5 to 3.0 mg/dL) are substantially lower than those in humans in the modern era (6.1 mg/dL in men in the U.S. general population).⁵ The great apes primarily consume vegetables and fruit, and their animal protein intake is minimal.¹ Early humans in indigenous scavenging and gathering societies who lived on traditional diets primarily derived from vegetables and fruits with sporadic additions of fish and game probably had serum uric acid levels similar to those of the great apes.¹

A number of epidemiologic studies from various countries suggest that the prevalence of gout has increased in the last few decades.⁶ This increase is probably explained by trends in lifestyle factors associated with westernization.^{4,7} For example, since the introduction of Western culture and dietary habits, gout has become epidemic among some native peoples, such as the Maori of New Zealand.^{1,8,9} After the introduction of a diet high in fatty meats and carbohydrates and low in dairy products in the early 1900s, an epidemic of obesity and gout developed.^{1,8,9} Three similarly conducted serial surveys in New Zealand showed an increase in the prevalence of gout in both European, U.S., and Maori descendants (Table 186.1).⁸⁻¹⁰ Findings from the United States, United Kingdom, and China also suggest that the disease burden of gout is similarly increasing (see Table 186.1).⁸⁻¹⁸

Correspondingly, gout was rare among blacks in Africa, especially in rural areas where traditional agricultural and dairy-based diets were common, but its frequency has been increasing, particularly in urban communities.¹ Gout was considered rare in African Americans in the early 1900s, but changes in diet have led to the rapid development of obesity, diabetes, and hypertension. Today, mean serum uric levels are higher and gout is more common in African Americans than in whites.^{1,19} Furthermore, ecologic studies of Japanese and Filipino populations have found that U.S. immigrants from these countries had increases in serum uric acid levels, the incidence of gout, or both in comparison to their nonmigrant counterparts.¹

CASE DEFINITIONS IN GOUT EPIDEMIOLOGY

Epidemiologic estimates of the disease burden of gout (e.g., prevalence or incidence) depend on case definitions, as with any other condition. Definitive diagnosis of gout requires either the presence of monosodium urate monohydrate crystals in joint fluid or the presence of tophi.²⁰ However, in population surveys designed to estimate the prevalence of gout, this method of identification is impractical. For this reason, several gout case definitions have been developed, including self-reports, the Rome criteria, the New York criteria, and the American College of Rheumatology (ACR) preliminary criteria.²⁰⁻²² For example, the prevalence of gout has been estimated from self-reported data derived from various years of the U.S. National

■ TABLE 186.1

Prevalence of gout

Source/year	Gout definition	Prevalence (per 1000)
United States		
<i>National Health Interview Surveys (1-yr prevalence)*</i>		
1969	Self-report*	4.8
1976	Self-report*	7.8
1988	Self-report*	8.5
1996	Self-report*	9.4
<i>NHANES III (lifetime prevalence)†</i>		
1988-1994	Self-report*	27
2006-2007	Self-report	39
New Zealand (random community sample)		
1958 ⁸	Interview and examination	European 3, Maori 27
1966 ¹⁰	Interview and examination	European 9, Maori 60
1992 ⁹	Interview and examination; 1977 ACR criteria	European 29, Maori 64
United Kingdom (GP records)		
1975 ¹¹	GP diagnosis	2.6
1987 ¹²	GP diagnosis	3.4
1993 ¹³	GP diagnosis	9.5
1999 ¹⁴	GP diagnosis	14
IMS Disease Analyzer, 2000-2005 ¹⁵	GP diagnosis	14
China (random community sample)		
2002 ¹⁶	Self-report, medical records	3.6
2004 ¹⁷	Self-report, examination, 1977 ACR Criteria	5.3
Taiwan		
Nutrition and Health Survey, 1993-1996 ¹⁸	Interview and examination	34

*One-year prevalence of gout obtained by asking the question "Have you or any member of your household had gout within the past year?"
†Lifetime prevalence of gout obtained by asking the question "Has a doctor ever told you that you had gout?"
ACR, American College of Rheumatology (formerly American Rheumatism Association); GP, general practice; NHANES, National Health and Nutrition Examination Survey.

Health Interviews Surveys. Data from the Sudbury study showed that 44% of self-reported cases could be validated according to the Rome or New York criteria.²³ However, the validation rate from a physician cohort (Johns Hopkins Precursor Study) was much higher—80% according to the ACR survey criteria applied by mail and 100% by mail combined with medical record review.²⁴ Similarly, the validation rate of self-reported gout in a recent large prospective cohort of male health professionals was approximately 70% according to the ACR survey criteria assessed by a mailed survey.²⁵ The difference in the validation rates of self-reported gout between these studies probably reflects differences in the level of general health knowledge in the study populations.

PREVALENCE OF GOUT

Estimates of prevalence from various countries and time frames, along with their definitions of gout, are summarized in Table 186.1. The latest lifetime prevalence of self-reported gout (diagnosed by health professionals) in the United States was estimated in 2007-2008 to be 3.9% of U.S. adults, which translates into 8.3 million individuals.⁵ This prevalence increased with age to 9.3% of U.S. adults older than 60 years (4.7 million). This recent prevalence estimate is significantly higher than the 1988-1994 estimate (2.7%, an absolute difference of 1.2%).⁵ Furthermore, the prevalence of

hyperuricemia and mean serum urate levels in 2007-2008 were significantly higher than the 1988-1994 estimates. Similarly, serial U.S. National Health Interview Surveys that used the same survey instrument showed that the annual prevalence of gout doubled between 1969 and 1996 and that the steepest increase occurred between 1969 and 1976 (see Table 186.1).^{5,26} U.K. studies based on general practice diagnostic indices found similarly increasing prevalence estimates of gout between the 1970s¹¹ and 1990s¹³ (see Table 186.1).
Studies conducted in the UK-General Practice Research Database in 1999¹⁴ and the IMS Disease Analyzer from 2000 to 2005¹⁵ both found the prevalence of gout to be 1.4%. A Taiwanese Nutrition and Health Survey conducted during the mid-1990s found a prevalence similar to that in the United States (3.4%).¹⁸

INCIDENCE OF GOUT

Several prospective cohort studies have estimated the incidence of gout.⁶ The Johns Hopkins Precursors Study documented 60 cases of self-reported incident gout in 1216 male physicians observed over a median of 29 years (incidence, 1.73 per 1000 patient-years).^{6,27} The Health Professionals Follow Up Study monitored 47,150 male health professionals for 12 years and identified 730 cases of incident gout (incidence, 1.50 per 1000 patient-years according to the ACR survey criteria²⁰).²⁵ The Framingham Heart Study monitored 5209 people for a median of 28 years and documented 104 incident cases of gout (diagnosed clinically by typical symptoms and medications) in women and 200 cases in men for incidence rates of 1.4 and 4.0 per 1000 person-years, respectively.²⁸
Serial investigations of computerized medical records from the Rochester Epidemiology Project showed that the incidence of gout in individuals not exposed to diuretics (using the ACR survey criteria²⁰) more than doubled from 20.2 per 100,000 in 1977/1978 to 45.9 per 100,000 in 1995/1996, whereas the proportion of gout associated with diuretic use decreased significantly during that period.²⁹
Two studies of general practice databases in the United Kingdom estimated the incidence of gout (physician recorded) in the 1990s and 2000s. The first, based on data from 1990 to 1999, found that the incidence of gout ranged from a low of 119 cases per 100,000 patient-years in 1991 to a high of 180 cases per 100,000 patient-years in 1994.¹⁴ The second study, which was based on data from 2000 to 2007, found that the mean annual incidence of gout was 268 per 100,000 patient-years. Both studies reported that the incidence of gout was higher in men than in women and increased with age regardless of sex.³⁰

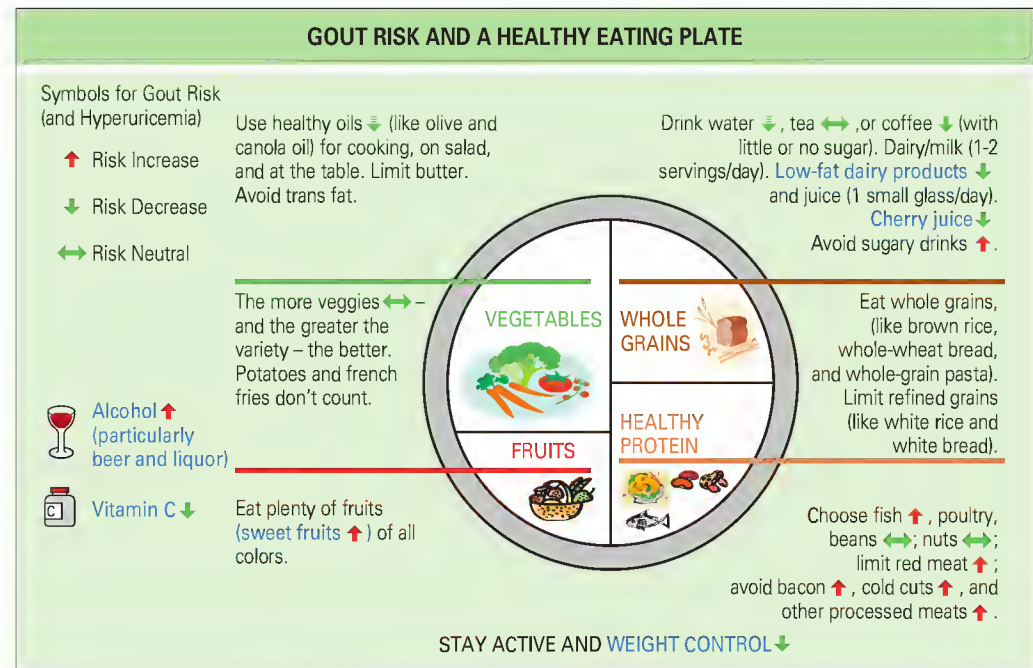
RISK FACTORS FOR HYPERURICEMIA AND GOUT

It has been well established that hyperuricemia is the causal precursor in the development of gout. Population studies show a direct positive (linear to exponential) relationship between serum urate levels and future risk for gout.⁴ Conversely, effective management of hyperuricemia prevents gout.⁴ Thus, this section summarizes the risk factors for hyperuricemia and gout together.

Demographics: sex, age, and ethnicity

Serum urate concentrations in men average about 1 mg/dL higher than in women in adult life, which is probably due to increased renal urate clearance by estrogen in women. This leads to a substantially higher risk for gout in men than in women, particularly before menopause.³¹ A Japanese study showed that combined use of estrogen and progesterone resulted in a significant drop in serum uric acid in postmenopausal hyperuricemic women whereas no drop occurred in controls.³² A U.S. nationwide study found that menopause was associated with increased serum uric acid levels and postmenopausal hormone replacement therapy with decreased uric acid levels,³³ and a prospective study showed consistent findings with the risk for incident gout in 92,535 women.³⁴
Age appears to have an influence only in women, in whom serum uric acid levels steadily increase with age.³⁵ In the aforementioned U.S. nationwide study, the increase attenuated substantially after adjusting for menopausal status but remained significant, thus suggesting that menopause explains a substantial portion, but not all of the age-associated increase in women.³³ The remaining age-associated increase was explained by other age-related factors such as declining renal function, diuretic use, and hypertension.³³

Fig. 186.1 Impact of lifestyle factors on risk for gout and their implications within a healthy eating plate. Directional arrows and blue font information are specific to gout and are not found in the original healthy eating plate. Upward red arrows denote an increased risk for gout, whereas downward green arrows denote a decreased risk. Horizontal green arrows denote no influence on risk for gout. Striped green arrows denote a potential effect, but without prospective evidence for the outcome of gout. References on the relationship between diet and risk for gout are listed in Table 186.2. (Adapted from <http://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/>.)



Serum uric acid levels appear to vary by race or ethnicity. African Americans have higher serum uric acid levels than white Americans do,¹⁹ which has been linked to the increased prevalence of hypertension in the former.³⁶ In addition, serum uric acid levels are higher in certain aboriginal people such as the Maori³⁷ and Taiwanese³⁸ aborigines.

Lifestyle factors

Gout is a metabolically driven arthropathy that can be controlled substantially through lifestyle modifications. The following sections review the epidemiologic evidence on modifiable lifestyle risk factors for gout, as well as their implications for general health (Fig. 186.1).

Adiposity

Adiposity is one of the strongest risk factors for hyperuricemia and gout. Prospective cohort studies have consistently found a strong relationship between higher adiposity (or weight gain) and increased risk for both hyperuricemia and incident gout.^{27,28,39-41} A recent study also documented that weight reduction leads to a considerable decrease in serum urate levels.⁴² Similarly, in the Swedish Bariatric Surgery Outcome study, gastric surgery–induced weight reduction was associated with substantially lower odds for the development of hyperuricemia.⁴³ Finally, men who have lost weight have shown a significantly lower risk for incident gout.⁴⁰ Adiposity probably increases uric acid levels both by decreasing renal excretion of urate and by increasing urate production.⁴⁴⁻⁴⁶

Meat and seafood

Meat intake (particularly red meat) contributes to an increased risk for gout,²⁴ probably because its high purine content raises urate levels, as demonstrated by short-term metabolic experiments of purine loading in animals and humans.^{24,47,48} Furthermore, red meat is a key source of saturated fat, which is associated with increased insulin resistance, which in turn reduces renal excretion of urate.⁴⁹ Indeed, higher consumption of meat is associated with hyperuricemia,⁵⁰ and men in the highest quintile of meat intake were found to have a 41% higher future risk for gout than men in the lowest quintile (Table 186.2, and see Fig. 186.1).*

Seafood intake (including fish and shellfish) can also increase the risk for gout²⁵ through its high purine content despite not being associated with increased insulin resistance like red meat. Men in the highest quintile of seafood intake were found to have a 51% higher risk for gout than those in the lowest quintile.²⁵ Furthermore, a prospective Internet-based case-crossover study of 633 gout patients showed that purine intake from animal sources was associated with up to a 2.4-fold increased risk for recurrent gout.⁷⁵

Dairy intake

A large prospective study showed that men in the highest quintile of dairy intake had a 44% lower risk for gout than did men in the lowest quintile. When dairy intake was stratified by fat content, the protective association persisted with low-fat dairy consumption but became null with high-fat dairy consumption.²⁵ Consistently, dairy consumption was found to be inversely associated with uric acid levels.⁵⁰ Furthermore, recent randomized trials have shown that intact milk intake has an acute urate-lowering effect⁷⁶ and that skim milk powder derivatives may have antiinflammatory effects against acute gout flares.⁷⁷ Thus, dairy products may exert their urate-lowering or antiinflammatory effects without the concomitant purine load contained in other animal protein sources such as meat and seafood.^{76,78}

Purine-rich vegetables, vegetable protein, and cherries

Contrary to traditional dietary approaches, consumption of purine-rich vegetables was not found to be associated with risk for incident gout (see Table 186.2 and Fig. 186.1).²⁵ Correspondingly, individual purine-rich plant food items such as nuts, legumes, spinach, mushrooms, oatmeal, and cauliflower were not associated with risk for gout. Men in the highest quintile of vegetable protein consumption actually showed a 27% lower risk for gout than did the lowest quintile.²⁵ Furthermore, the short-term impact of purine from plant sources on risk for recurrent gout attacks was found to be minimal.⁷⁵ These findings may be explained by insufficient amounts or bioavailability of purine in these plant food items²⁵ and by other healthy constituents (fiber or healthy fat) that may reduce insulin resistance and risk for gout.⁷⁹

The aforementioned study of preexisting gout patients also found that cherry intake over a 2-day period was associated with a 35% lower risk for gout attacks than was no intake.⁸⁰ Although previous small studies suggested urate-lowering or antiinflammatory effects of cherries or associated anthocyanins, these findings call for confirmation.⁸⁰

Alcoholic beverages

Increasing alcohol intake was found to be associated with increasing risk for gout in a dose-dependent manner.⁵² Among different types of alcoholic beverages, beer had the largest impact.⁵³ A nationwide study showed the same pattern of associations with uric acid levels.⁵³ Similarly, the aforementioned study of preexisting gout patients also confirmed that alcohol consumption triggers recurrent gout attacks in gout patients.⁸¹

Alcohol can induce hyperuricemia, probably through both increased urate production⁸² and decreased urate excretion. Ethanol administration can increase uric acid production by increasing degradation of adenosine triphosphate (ATP) to adenosine monophosphate (AMP), a uric acid precursor.⁸² Decreased urate excretion occurs via conversion of alcohol to lactic acid, as well as the confounding effects of fasting-induced acetoacetic and β -hydroxybutyric acidemia, which both reduce renal uric acid excretion by competitively inhibiting uric acid secretion by the proximal

*References 25, 27, 28, 30, 39-41, 43, 50-74.

TABLE 186.2
Modifiable risk factors of hyperuricemia and gout

Risk factors	Direction of effects		References
	Serum uric acid levels	Risk for gout	
Adiposity			27, 28, 39-41, 43, 51
Body mass index	↑	↑	
Waist-to-hip ratio	↑	↑	
Weight gain	↑	↑	
Weight loss	↓	↓	
Purine-rich food			25, 50
Meat	↑	↑	
Seafood	↑	↑	
Purine-rich vegetables/nuts		↔	
Alcohol	↑	↑	52, 53
Fructose	↑	↑	54-58
Sugar-sweetened beverages	↑	↑	
Sweet fruits/fruit juices	↑	↑	
Coffee/decaffeinated coffee	↓	↓	59-63
Dairy products	↓		25, 50
Low-fat dairy products		↓	
High-fat dairy products		↔	
Vitamin C supplements	↓	↓	64-67
Medications and substances			
Low-dose salicylate, diuretics	↑	↑	68
Calcium channel blockers, losartan	↓	↓	68
β-Blockers, angiotensin-converting enzyme inhibitors	↑	↑	68
Lead (including low-dose exposure)	↑	↑	69, 70
Insulin resistance/metabolic syndrome	↑	↑	41, 71, 72
Renal insufficiency	↑	↑	40, 41
Hypertension, ischemic heart disease, hyperlipidemia	↑	↑	30, 40, 41
Psoriasis	↑	↑	30
Diabetes (type 1 or 2)	↓	↓	73, 74

tubule.^{83,84} Furthermore, among individual alcoholic beverages, beer has a high purine content, which is predominantly guanosine, a readily absorbable nucleoside.^{83,85}

Sugar-sweetened sodas and fructose-rich foods

The doubling of the prevalence^{5,26} and incidence²⁹ of gout over the last few decades in the United States has coincided with a substantial increase in soft drink and fructose consumption.^{54,55} Furthermore, two large cohort studies found that consumption of sugar-sweetened soft drinks and fructose is associated with increased risk for gout in both sexes (see Table 186.2 and Fig. 186.1).^{54,55} In contrast, diet soft drinks were not associated with risk for gout. Other major contributors to fructose intake such as sugary fruit juice or fructose-rich fruits (i.e., apples and oranges) were associated with a modestly increased risk for gout in men⁵⁴ but not in women.⁵⁵ Correspondingly, serum urate levels were found to increase with increasing intake of sugar-sweetened soft drinks, whereas diet soft drink consumption was not associated with increased serum urate levels.⁵⁶ Furthermore, added sugar intake was also associated with increased serum urate levels.⁵⁷

Fructose intake can raise serum urate levels by increasing the degradation of ATP to AMP, thereby prompting activation of the pathway of purine degradation to uric acid.^{53,86} Furthermore, fructose intake is associated with increased serum insulin levels and insulin resistance⁸⁷ and could therefore indirectly increase serum urate levels and risk for gout.

Coffee, tea, and caffeine

Coffee consumption may lower serum uric acid levels and risk for gout in the long term via various mechanisms.^{59,88} For example, caffeine (1,3,7-trimethylxanthine) is a methylxanthine and may be a competitive inhibitor of xanthine oxidase.^{88,89} Long-term intake of coffee and caffeine may also lower insulin levels⁹⁰ and increase insulin sensitivity.⁹¹ Japanese studies and a U.S. nationwide study found that serum uric acid levels decreased with increasing coffee intake.⁶⁰⁻⁶² Furthermore, coffee consumption was associated with a decreased risk for gout in men⁵⁹ and women,⁸⁸ whereas tea intake was

not associated with hyperuricemia or risk for gout in either sex.^{59,88} A modest inverse association was also found for decaffeinated coffee.^{59,88}

Vitamin C

Randomized trials have demonstrated a urate-lowering effect of vitamin C via its uricosuric properties.^{64,65} Supplementation with 500 mg/day of vitamin C for 2 months was shown to reduce serum urate levels by 0.5 mg/dL. Several observational studies from Taiwan⁹² and the United States^{66,67} have extended evidence of an inverse link between vitamin C intake and risk for hyperuricemia or incident gout.

Medications and lead exposure

Several commonly used medications can affect serum uric acid levels and potentially the risk for gout, including aspirin, fenofibrate, diuretics, female hormones, and antihypertensives.⁴ A study found that low doses of salicylate (75, 150, and 325 mg daily) decreased uric acid excretion (by 1.35, 0.85, and 0.65 mL/min) and increased serum uric acid levels (by 0.27, 0.21, and 0.04 mg/dL, respectively).⁹³ Similarly, fenofibrate was found to have urate-lowering benefits in addition to its primary lipid-lowering effects.⁴

Certain antihypertensive medications also increase serum uric acid levels and thus may contribute to risk for gout. For example, beyond the well-known phenomena of diuretic-induced hyperuricemia and gout, β-blockers have been shown to increase serum uric acid levels in short-term trials.^{4,94} Conversely, calcium channel blockers and losartan have been found to lower serum uric acid levels^{4,94} and therefore have the potential to lower the risk for gout. Compatible with these urate-affecting properties, a recent population-based study revealed that calcium channel blockers and losartan were associated with a lower risk for incident gout in individuals with hypertension (see Table 186.2).⁶⁸ In contrast, diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers other than losartan were associated with increased risk for gout.⁶⁸

Even though chronic lead intoxication is known to cause hyperuricemia and gout (i.e., saturnine gout), recent study findings suggest that

low-level exposure to lead is also associated with an increased prevalence of hyperuricemia and gout.⁶⁹ A U.S. community-based cohort study found a positive association between the long-term accumulation of lead (contained in bone) and uric acid levels⁷⁰; however, no such association with risk for gout was evident at the levels arising from community exposure.

Key mediating mechanisms of lifestyle factors: purine and insulin resistance

As discussed earlier, both purine loading and insulin resistance are key mediating mechanisms underlying the actions of adiposity and many lifestyle factors on gout. Traditional lifestyle approaches to prevent gout have almost exclusively focused on purine-loading risk factors. However, factors that increase insulin resistance and thus decrease renal excretion of urate can increase uric acid levels and risk for gout.⁴⁹ Furthermore, because insulin resistance syndrome is highly prevalent in patients with gout or hyperuricemic^{41,71,95} and has cardiovascular-metabolic consequences,^{72,96-99} it is important to consider factors that can affect insulin resistance, particularly in long-term lifestyle recommendations.

Cardiovascular-metabolic conditions and other disorders

Many medical conditions can elevate serum uric acid levels and risk for gout, including cardiovascular-metabolic conditions, renal disorders, and other conditions associated with severe tissue hypoxia, such as proliferative and inflammatory disorders associated with increased cell turnover.⁸ Recent epidemiologic studies have quantified the potential impact of medical conditions on the risk for incident gout, including hypertension, renal insufficiency,^{40,41} ischemic heart disease, hyperlipidemia, and psoriasis.³⁰ Although these conditions are associated with an increased risk for gout, type 1 or 2 diabetes is associated with a decreased risk for gout,⁷³ probably through the uricosuric effect of glycosuria or the impaired inflammatory response associated with diabetes (see Table 186.2).⁷⁴

Beyond the potential excess risk for gout brought on by these other medical conditions, gout and hyperuricemia are metabolic conditions associated with multiple cardiovascular-metabolic comorbid conditions and complications.^{72,96-99} These comorbidities of gout and independent risks for adverse cardiovascular outcomes and premature mortality provide a strong rationale for serious consideration of these issues when determining appropriate lifestyle approaches for patients with gout (see Fig. 186.1).

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Etiology and pathogenesis of gout

■ LACHY McLEAN ■ NICOLA DALBETH

- Gout (monosodium urate crystal deposition disease) is an inflammatory arthritis resulting from the deposition of monosodium urate crystals from extracellular fluids saturated with urate, the end product of human purine metabolism.
- Acute gout is a severe but self-limited arthritis caused by the inflammatory response to urate crystals. Repeated acute attacks and persistent crystal deposition can lead to chronic arthropathy and deforming tophaceous gout.
- Hyperuricemia is a serum urate concentration exceeding approximately 6.8 mg/dL ($\approx 400 \mu\text{M}$) and reflects the tissue urate saturation that is the central biochemical precursor for gout.
- Defects in purine metabolic enzymes (such as hypoxanthine-guanine phosphoribosyltransferase and 5-phosphoribosyl 1-pyrophosphate synthetase 1) are well-characterized causes of gout with urate overproduction but account for less than 1% of cases of gout. Large genetic studies have revealed many candidates involving urate transport, metabolic pathways, and regulation of inflammation. The known genes still explain only a minority of the strong heritability of hyperuricemia and gout.
- In most patients with gout, hyperuricemia results from relative impairment of renal uric acid excretion, often exacerbated by dietary excess, diuretics, and alcohol. Variation in one or more of the proximal tubular urate transporters (such as GLUT9 and URAT1) also contributes to hyperuricemia.
- Acute gouty inflammation is initiated by resident synovial cells, including phagocytes, which secrete chemokines and cytokines to attract and activate the neutrophils that predominate in acute gout.
- Activation of the NLRP3 inflammasome by monosodium urate crystals and the resultant release of mature interleukin-1 β are central to initiation of acute gouty inflammation.
- Joint damage in chronic gout is strongly linked to intraarticular tophi, with activation of catabolic pathways leading to cartilage and bone degradation.

Gout is a painful and potentially destructive rheumatic disorder that arises in the setting of hyperuricemia, a condition defined by saturation of serum with urate. Urate is the obligatory end product of human purine metabolism. The clinical manifestations of gout arise as a consequence of urate or uric acid crystal deposition and include acute gouty arthritis, chronic gouty arthropathy, tophi, renal functional impairment, and urolithiasis (kidney and bladder stones). This chapter focuses on the articular manifestations of gout.

URATE PHYSIOLOGY

Gout is the result of inflammatory responses to crystals deposited because of one or more derangements in the physiology of urate. In contrast to most mammals, urate is the final oxidative degradation product of purine metabolism in humans and higher primate species because the gene encoding the enzyme uricase (urate oxidase) has been silenced by mutations.¹ Urate is the most abundant natural antioxidant in the human body (Table 187.1). The traditional view has been that a major physiologic role of urate is to remove reactive oxygen species, thereby possibly providing protection

against oxidant-induced neurologic and cardiovascular degenerative processes. However, administration of pegloticase, which leads to dramatic reductions in urate concentrations, did not result in increased lipid or protein oxidation, thus suggesting that urate is not a major factor controlling oxidative stress *in vivo*.²

Urate may also have an important role in immune surveillance. Distressed and dying cells produce locally high urate concentrations as a “danger” signal, which acts as an endogenous adjuvant to help trigger inflammatory and both innate and specific immune responses (discussed in more detail later).³ Urate may also have had an evolutionary role in maintenance of blood pressure and intravascular volume.⁴

Forms of uric acid

Uric acid ($\text{C}_5\text{H}_4\text{N}_4\text{O}_3$; 2,6,8-trioxypurine) is a weak organic acid ionized at position 9 with a functional $\text{pK}_{\text{a}1}$ in serum of 5.75. Urate exists in biologic systems in two forms with limited solubility (Fig. 187.1). At the 7.4 pH of most body fluids, urate ion levels exceed those of un-ionized uric acid in a ratio of approximately 50:1. Because of the high concentration of sodium in extracellular fluid, urate functions mainly as monosodium urate (MSU). As a consequence, the high solubility of the urate ion (120 mg/dL, 7 mM) is replaced by the much lower solubility of MSU ($\approx 6.8 \text{ mg/dL}$ or $400 \mu\text{M}$).

Serum urate concentrations exceeding 6.8 mg/dL are saturating, a condition referred to as *hyperuricemia*. Persistent hyperuricemia reflects saturation of extracellular fluid with urate. Increasing levels of hyperuricemia impart increasing (but not linearly related) risk for urate crystal deposition and the associated clinical consequences.⁵ Hyperuricemia is very common and affects more than 20% of adult white males in the United States⁶; it is even more common in certain ethnicities. Even though hyperuricemia most often does not evolve into clinical gout, it is associated with several highly prevalent chronic disorders, as discussed in Chapter 186.

In acidic body fluids, nonionized uric acid predominates. For example, at pH 5.0 (common in urine), the solubility of uric acid is only approximately 10 to 15 mg/dL (≈ 600 to $900 \mu\text{M}$), a range often exceeded in the urine of normal, as well as gouty, individuals. This explains the formation of uric acid crystals and stones in the urinary tract, in contrast to MSU monohydrate crystals, which are deposited in joints, tophi, renal interstitium, and other tissues of gouty patients.

Urate balance

The diet contains little urate, and dietary urate is poorly absorbed. Ingestion of other purines, endogenous synthesis of purines from small-molecule nonpurine precursors, and reutilization of preformed body purine compounds are more important sources.⁷ Purines other than urate are more abundant in foods and beverages and can, along with dietary nonpurine components (discussed later), contribute significantly to purine disposition (Box 187.1).^{8,9}

Nevertheless, the bulk of urate is usually derived from endogenous synthesis, which occurs mainly in the liver with a smaller contribution by the small intestine. The urate released from cells circulates relatively free (<4%) of serum protein binding,⁷ so all or nearly all circulating urate is filtered at the glomerulus.

Under steady-state conditions, urate production is balanced by uric acid disposal, largely through renal excretion (equivalent to about $\frac{2}{3}$ of daily production), as discussed below. Urate secretion into the small intestine, with breakdown of urate by gut bacteria (intestinal uricolysis), accounts for nearly all the rest of urate disposal. The body pool of urate is expanded in hyperuricemic states resulting from urate overproduction or impaired disposal.

■ TABLE 187.1

Factors influencing hyperuricemia and gout

Dietary influences*		Clinical associations		Drugs	
Chemical composition	Total caloric intake (obesity, leptin)	Age		Induce or worsen hyperuricemia or precipitate acute gout	Aspirin (low dose) Chemotherapeutic cytotoxics Diuretics (especially thiazides) Ethambutol Tacrolimus
	Triglycerides	Male or postmenopausal female			
Specific food examples	Carbohydrates (insulin)	Direct causal link	X chromosome-linked enzyme defects		
	Protein (aspartate, glutamine, glycine)		HPRT deficiencies:		
	DNA (cellularity, nucleus-cytoplasm ratio)		Complete (Lesch-Nyhan syndrome)	Urate-lowering or antihyperuricemic	Allopurinol, oxypurinol, febuxostat
	RNA (transcriptional activity, messengers)		Partial (Kelley-Seegmiller syndrome)	xanthine oxidase inhibitors	
	Red meat†		PRPP synthetase overactivity		
	Beer		Autosome-linked enzyme defects		
	Liver		Glucose-6-phosphatase deficiency		
	Shellfish		Fructose-1-phosphate aldolase deficiency		
	Thymus, pancreas		Myogenic glycogenoses (types III, V, VII)	Uricosuric agents	Ethanol Benzbromarone, probenecid, lesinurad, sulfapyrazone, losartan, fenofibrate, leflunomide, calcium channel blockers
	Yeast extracts		Uromodulin-associated kidney disease		
Associated with lower urate level	Fructose		FJHN		
	Sugar-sweetened drinks		MCKD types 1 and 2		
Associated with lower urate level	Low-fat dairy products		Hemolytic disorders		
	Cherries		Hemopoietic malignancies; tumor lysis		
	Vitamin C		Lactic acidosis or ketoacidosis; hypoxemic states		
			Lead nephropathy, chronic low-level exposure		
			Preeclampsia‡	Uricase preparations	rasburicase, pegloticase
			Renal impairment§		
			Systemic inflammatory conditions (including psoriasis)		
			Vasopressin-resistant diabetes insipidus		
			Bartter, Gitelman, Down syndromes		
			Hypothyroidism; hyperparathyroidism	Other mechanisms	Sevelamer Effects of lactate on transporters
Associated with lower urate level			Hypertiglyceridemia		
			Hypertension		
			Hypothyroidism		
			Obesity		
			Cardiovascular disease		
			Aggressive introduction of hypouricemic therapy	Role of alcohol	Direct renal tubular effect by ethanol?
			Alcohol or shellfish binges		Hypertension
			Sepsis, myocardial infarction, acute severe illness		Adenosine triphosphate turnover
			Sudden cessation of hypouricemic therapy		Guanosine content (beer)
			Trauma, surgery, dehydration, parenteral nutrition		Poor compliance with therapy

*In addition to the direct contributions of dietary purines and protein as uric acid precursors, diet can adversely influence renal urate excretion. The renal actions of insulin, leptin, and other systemic factors may mediate some of these effects.

†Intake of purine-rich vegetables is not associated with gout.

‡Hyperuricemia is a sensitive indicator of both effective volume status and tubular dysfunction.

§Uremia appears to blunt the inflammatory response to urate crystals, so gout is less common than might be expected for a given degree of hyperuricemia in patients with advanced renal dysfunction.

*A causal relationship has not been established with the associated disorders (see text).

FJHN, familial juvenile hyperuricemic nephropathy; HPRT, hypoxanthine-guanine phosphoribosyltransferase; MCKD, medullary cystic kidney disease; PRPP, 5-phosphoribosyl 1-pyrophosphate.

URIC ACID AND THE URATE ANION

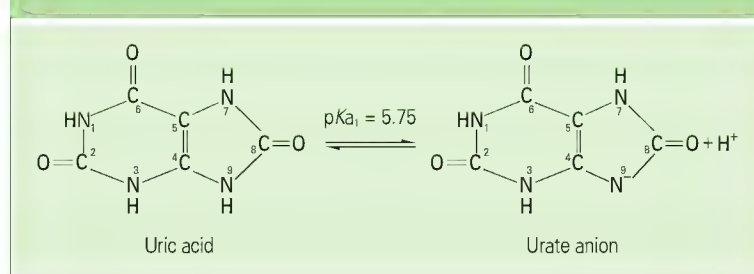


Fig. 187.1 At physiologic pH (7.4), urate predominates at about 50:1 over unionized uric acid. Urate ion solubility is functionally reduced at the high sodium concentration of extracellular fluids, so monosodium urate and uric acid have relatively low solubility in biologic fluids.

BOX 187.1 PHYSIOLOGIC FUNCTIONS OF PURINES

- Antioxidation (urate)
- Nucleotide building blocks for nucleic acids (DNA and RNA)
- Nucleotide components of coenzymes (e.g., coenzyme A, flavin adenine dinucleotide [FAD], nicotinamide adenine dinucleotide [NAD])
- High-energy phosphate donors in enzyme reactions (e.g., adenosine triphosphate [ATP])
- Metabolic regulators (e.g., cyclic adenosine monophosphate [AMP], cyclic guanosine monophosphate [GMP])
- Neurotransmitters
- Extracellular messengers (e.g., adenosine, ATP)
- Intracellular second messengers (e.g., G protein-coupled receptors)
- Immunologic adjuvants, endogenous "danger" signal for innate immunity
- Maintenance of extracellular volume, vascular tone (urate) (hypothesized)

Urate pools in normal men range from about 800 to 1500 mg and in women from 500 to 1000 mg. Daily turnover of the body's urate pool (balanced production and disposal) is considerable and averages 60% to 70% of the pool (0.5 to 1 g) every day. Urate saturation of extracellular fluids (for which hyperuricemia is a surrogate marker) predisposes to urate crystal formation and deposition, events required for clinical expression of gout.

Serum urate concentrations in children are lower than those in adults. During male puberty, values increase into the adult male range. Serum urate levels remain lower in women of reproductive age than in their male counterparts.¹⁰ This gender difference results mostly from the action of estrogens,¹¹ which alter the activity of key renal urate transporters. This results in less renal tubular uric acid reabsorption and thus increased urate clearance in women.

With the onset of menopause, serum urate values in women increase and approach or equal those of men. This physiologic change in women is partly reversed by estrogen-containing hormone replacement therapy and is accompanied by increases in the incidence of hyperuricemia and, over the succeeding 2 to 3 decades, gout.

HYPERURICEMIA

Conditioning factors

Several genetic and physiologic circumstances predispose all humans to the development of hyperuricemia and gout: the species-wide deficiency of uricase, the enzyme catalyzing the conversion of uric acid to the much more soluble excretory product allantoin; net reabsorption of 90% of the urate filtered at the glomerulus; and the limited solubility of both uric acid and MSU in body fluids.

Despite these conditioning factors, most people do not display the sustained hyperuricemia that reflects extracellular fluid saturation, and MSU crystal deposition disease develops in even fewer. The many processes influencing the development of hyperuricemia (Fig. 187.2; also see Table 187.1) operate through impaired renal uric acid excretion (most commonly), excessive urate production, or a combination of these two mechanisms.¹²

With increased urate production or decreased renal uric acid excretion, intestinal uricolytic increases to as much as half of the total urate disposal. In contrast, when intestinal urate excretion is impaired, the kidneys are confronted with a higher urate load.⁷ The transporter ABCG2 (ATP-binding cassette sub-family G, member 2) plays a central role in intestinal urate transport.¹³

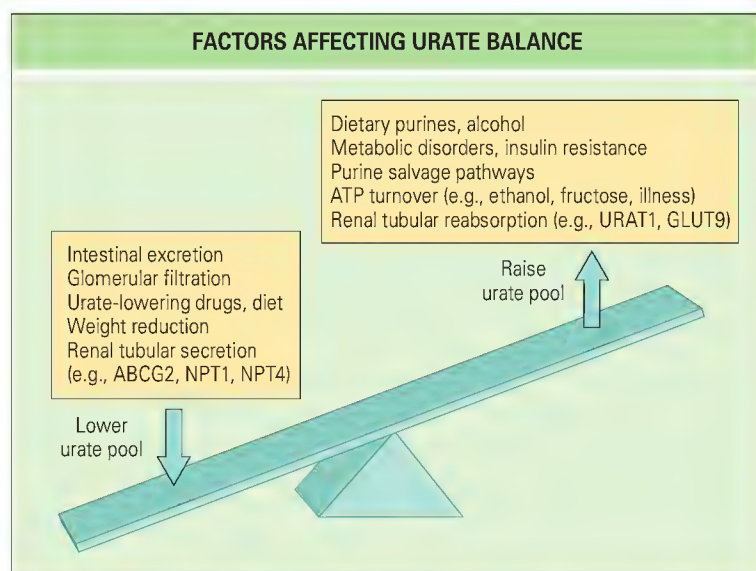


Fig. 187.2 The systemic urate pool and the likelihood of gout are determined by the dynamic balance between dietary purines, endogenous synthesis and recycling, and disposal by the kidney and gut. ABCG2, ATP-binding cassette sub-family G member 2; ATP, adenosine triphosphate; URAT1, urate transporter 1; GLUT9, glucose transporter 9; NPT, sodium-dependent phosphate cotransporter.

Classification of hyperuricemia

Hyperuricemia and gout may arise in individuals with or without an underlying clinical disorder or toxic or drug exposure. When a specific process resulting in hyperuricemia is identifiable, it is said to be *secondary* (see Table 187.1). When no such process is evident, the hyperuricemia is termed *primary* or idiopathic. Several diseases, toxic states, and medications lead to hyperuricemia as a result of urate overproduction. Foremost among these are diseases associated with cellular proliferation and destruction, such as acute leukemias and lymphomas, tumor lysis syndromes, hemolytic states, and psoriasis.

The causes of hyperuricemia have traditionally also been divided into *overproduction* causes (mainly consisting of metabolic factors) and *underexcretion* causes (mostly renal). Many patients with gout have a combination, with relative urate underexcretion by the kidneys contributing the most. Analysis of the role of ABCG2 in intestinal handling of urate has challenged the conventional concept of overproduction-induced hyperuricemia.¹³ ABCG2 knockout mice have reduced intestinal urate excretion, which leads to higher serum urate levels. Despite also lacking ABCG2 in the kidneys, renal urate excretion in this situation is still higher than normal, thus indicating that other transporters in the kidney can partially compensate.

Urate overproduction may be better described as a type of “renal overload,” which in turn consists of the subtypes *extrarenal underexcretion* and *genuine urate overproduction*.¹³

PURINE METABOLISM: PATHWAYS AND REGULATION OF URATE PRODUCTION

Purines are compounds that possess a nine-member purine nucleus composed of fused pyrimidine and imidazole rings. Purines fulfill essential functions in all living cells (see Box 187.1). Most functions of purines are carried out by nucleotide and nucleoside derivatives of the purine bases adenine, hypoxanthine, and guanine. Representative structures of purine bases, nucleosides, and nucleotides are shown in Figure 187.3.

Purine synthetic pathways

The sole sources of new purines in the body are the diet and endogenous synthesis of purines from nonpurine precursors. The dietary contribution to urate production and turnover is significant. Removal of purines from the diet of normal individuals for 10 days can reduce serum urate levels by 25% and urinary uric acid excretion by as much as 50%.

However, purine-free or heavily purine-restricted diets are unpalatable and require substitution by potentially atherogenic dietary components to maintain caloric balance. Severe dietary purine restriction is seldom successful as a first line of therapy for the hyperuricemia of gout. On the other hand, diets high in fructose, meat, and fish content,¹⁴ as well as beer and distilled alcohol intake,¹⁵ promote hyperuricemia and increase the risk for gout, whereas vitamin C and cow's milk may reduce the risk.

The biochemical pathways of purine metabolism and their regulation are discussed in more detail elsewhere.¹⁴ The only endogenous pathway of net purine production (Fig. 187.4) is called purine synthesis *de novo* and involves 10 steps. The purine ring is synthesized on a backbone of ribose-5-phosphate donated by the key regulatory substrate *5-phosphoribosyl 1-pyrophosphate* (PRPP) from the pentose phosphate sugar pathway. The end product of this pathway is the nucleotide *inosine monophosphate* (IMP). IMP serves as a branch point in the conversion of new purines into the adenylate and guanylate classes of purine nucleotides or, alternatively, into the purine degradation pathway culminating in urate formation.

Purine synthesis *de novo* is an energy-costly process. Considerable saving in cellular energy expenditure is achieved by an extensive network of reactions that interconvert and salvage purine nucleotides, nucleosides, and bases. This saves energy and provides flexibility in the provision of specific purines for a wide array of cellular functions.

Degradation of purines to urate

Degradation of purine nucleotides and nucleosides to purine bases culminates in the key urate precursors *hypoxanthine* and *guanine*. They are mostly reused in salvage reactions with PRPP, catalyzed by the enzyme *hypoxanthine-guanine phosphoribosyltransferase* (HPRP). The remainder of guanine is deaminated to *xanthine*. Unsalvaged hypoxanthine is oxidized to xanthine, which undergoes further oxidation to urate. The enzyme *xanthine oxidoreductase* (XOR) catalyzes the conversion of both hypoxanthine to xanthine and xanthine to urate.

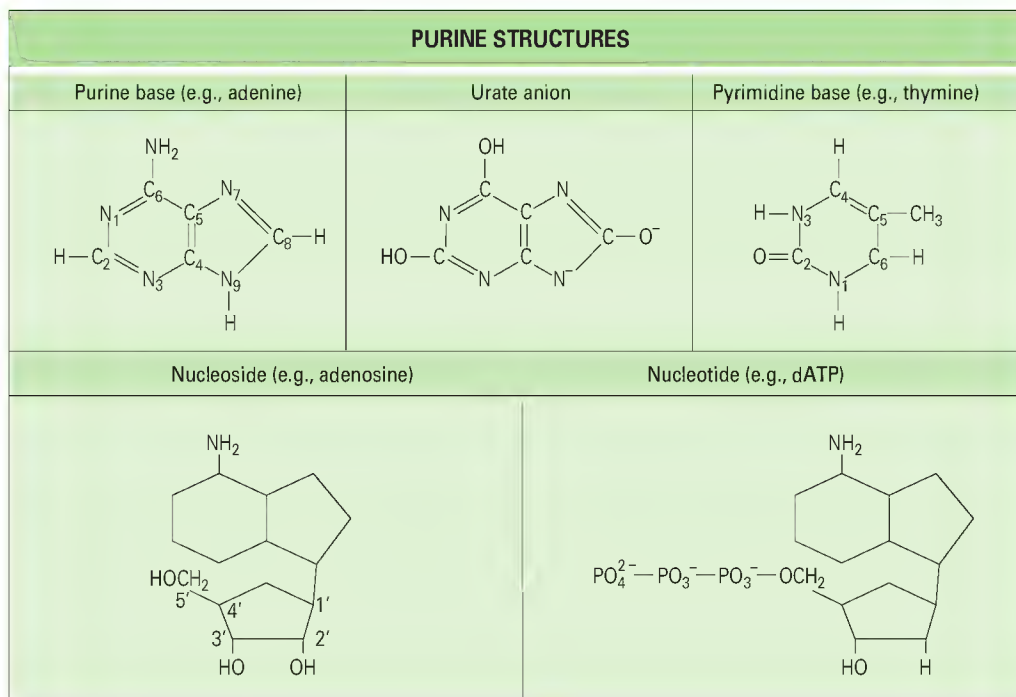


Fig. 187.3 Purine ring atoms are numbered 1 to 9, as shown in the upper left panel. Pentose sugar carbon atoms are numbered 1' to 5', as shown in the lower left panel. In purine *nucleosides*, a purine base is joined to a pentose ring through an N-glycoside bond between the purine 9 and pentose 1' atoms. *Nucleotides* are phosphate esters of the nucleoside that contain one, two, or three phosphate groups (nucleoside monophosphate, diphosphate, or triphosphate, respectively) attached at the 5' carbon of the sugar. *Nucleotidases* remove phosphate groups. *Phosphorylases* remove both the phosphate groups and the sugar. *Kinases* transfer a high-energy phosphate group (usually donated by ATP). The nucleoside of hypoxanthine is known as inosine, and the respective nucleotide is inosine monophosphate. dATP, deoxyadenosine triphosphate.

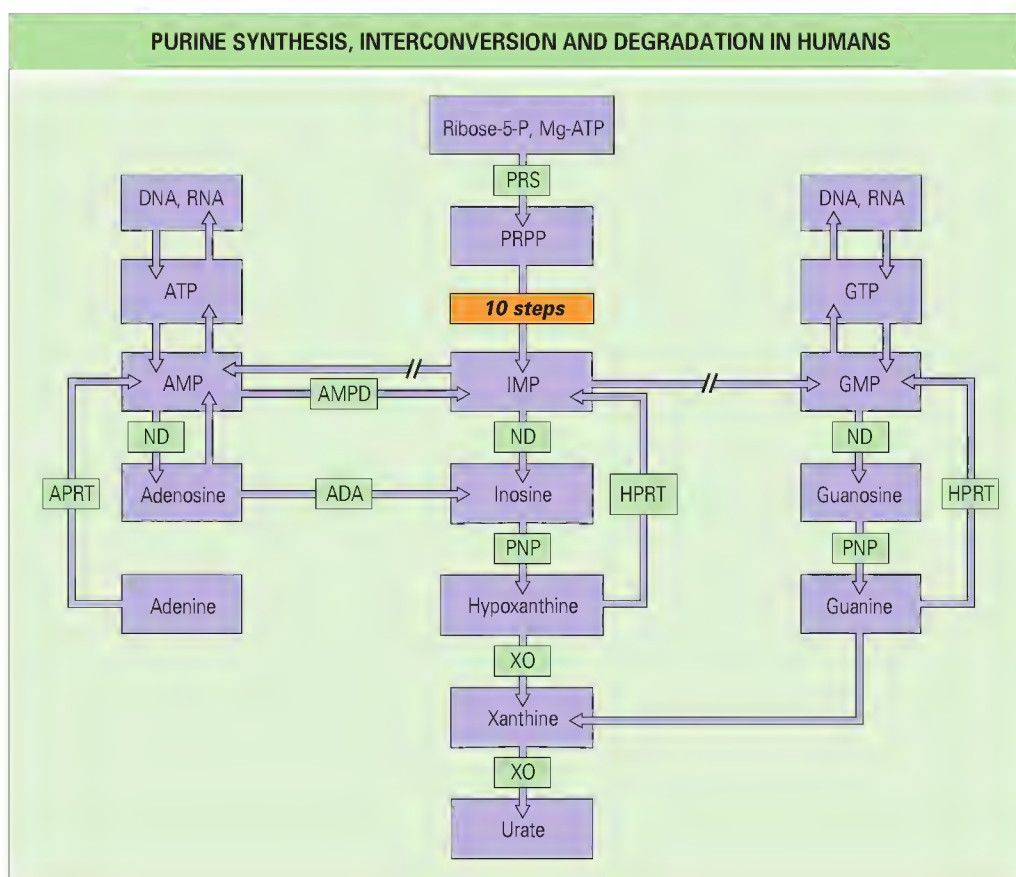


Fig. 187.4 The gene for uricase (urate oxidase) has been inactivated in humans and other primate species such that urate is the end product of purine metabolism. Intermediates and enzymes not pertinent to hyperuricemia and gout have been omitted for simplicity ("10 steps"). ADA, adenosine deaminase; AMP, adenosine monophosphate; AMPD, AMP deaminase; APRT, adenine phosphoribosyltransferase; ATP, adenosine triphosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate; ND, 5'-nucleotidase; PNP, purine nucleoside phosphorylase; PRPP, 5-phosphoribosyl 1-pyrophosphate; XMP, xanthosine monophosphate; XO, xanthine oxidase (oxidoreductase).

XOR is a molybdenum-pterin and iron sulfide cluster-containing flavo-protein that exists in interconvertible forms: an *oxidase* form (xanthine oxidase, XO) which uses oxygen (O_2) to convert hypoxanthine and xanthine to urate; and a *dehydrogenase* form (XDH), which uses the nucleotide oxidized nicotinamide adenine dinucleotide (NAD^+).

The catalytic events in purine base conversion involve binding and oxidation of the substrate (the purine base) at the active site of the oxidase form of XOR. This is accompanied by reduction of molybdenum from valence +6 to +4 by electrons donated by the purine. These electrons are then transferred to the iron sulfide cluster and then to the flavin center. Reoxidation of the flavin moiety by O_2 is accompanied by release of the product (xanthine, urate), including generation of the reactive metabolites H_2O_2 and superoxide ($O_2^{\bullet-}$).

Inhibition of XOR activity is the major action of the class of agents most commonly used for lowering urate levels in patients with gout.¹⁵ Other roles for XOR have also been proposed—protection from infection and tissue injury (because of the generation of unstable oxygen radicals) during and after ischemia.

Purine nucleotide synthesis and degradation are both carefully regulated processes. The major purine synthetic steps targeted by regulation are (1) synthesis of PRPP in the PRPP synthetase (PRS) reaction and (2) use of PRPP in the first step of purine synthesis *de novo* in the amidophosphoribosyltransferase (ATase) reaction (Fig. 187.5).¹⁴ ATase is allosterically inhibited by purine nucleotide products of the pathway and activated by PRPP.¹⁶

When this antagonistic control mechanism malfunctions, increased cellular levels of PRPP result in accelerated purine nucleotide and urate production. This occurs in two rare X chromosome-linked disorders: deficiency of the salvage enzyme HPRT and overactivity of PRS1.¹⁴ Similarly, excessive cellular adenosine triphosphate (ATP) depletion (for example, with tissue hypoxia or acute alcohol intoxication) can lead to reduced inhibitory nucleotide concentrations and consequent urate overproduction. Other states of excessive urate production in patients with gout are not as well characterized at the pathway level. They are likely to involve disruption of the regulatory mechanism for the antagonistic interaction of PRPP and purine nucleotides on amido-PRT.

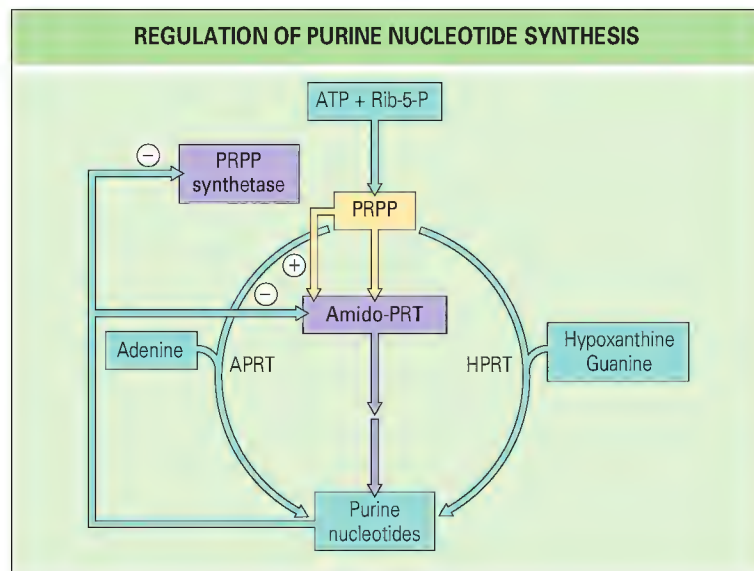


Fig. 187.5 Rates of the 10-step *de novo* pathway of purine nucleotide synthesis (vertical arrows) are regulated by activity of the enzyme amidophosphoribosyltransferase (ATase), which catalyzes the first step. ATase activity is allosterically controlled by the antagonistic interaction of pathway purine nucleotide products that inhibit (–) the enzyme and the regulatory substrate PRPP that activates (+) amido-PRT. Purine nucleotides also inhibit (–) PRPP synthetase, the enzyme catalyzing the synthesis of PRPP. Regulation directed at these sequential reactions provides a flexible means of controlling purine nucleotide production in an economic manner, a process potentiated by preferential single-step salvage of preformed purine bases in reactions with PRPP catalyzed by the phosphoribosyltransferase enzymes HPRT and APRT (depicted by the curved arrows). APRT, adenine phosphoribosyltransferase; ATP, adenosine triphosphate; HPRP, hypoxanthine-guanine phosphoribosyltransferase; PRPP, 5-phosphoribosyl 1-pyrophosphate; Rib-5-P, ribose-5-phosphate.

RENAL URIC ACID EXCRETION

Models of renal uric acid handling

Despite nearly complete filtration of urate at the glomerulus, clearance of uric acid in adults averages only 5% to 10% that of creatinine clearance, which reflects net renal tubular reabsorption of about 90% of the filtered urate. A four-compartment model for renal uric acid handling has been proposed (Fig. 187.6). This model incorporates glomerular filtration and three proximal tubular processes: urate reabsorption, secretion of reabsorbed urate, and postsecretory reabsorption.

Urate transporters

GLUT9

Molecular and genomic approaches have identified several transporters involved in renal uric acid excretion, including some with substantial specificity for urate.¹⁷ Two of these transporters, glucose transporter 9 (GLUT9) and urate transporter 1 (URAT1), are members of the organic acid transporter (OAT) family and have strong effects on serum urate levels.

GLUT9 is the product of the *SLC2A9* gene. It is a voltage-driven urate transporter that mediates urate reabsorption from the tubular cell to the circulation. In humans, GLUT9 exists in two isoforms: GLUT9L, identified on the basolateral aspects (“blood” side) of the proximal renal tubular epithelial cell, and GLUT9S, located on the apical (“urine”) side.^{18–20} As with URAT1, mediation of urate reabsorption by GLUT9 is inhibited by the uricosuric agents probenecid and benzbromarone.

GLUT9 is also expressed in the basolateral membrane of hepatocytes and regulates serum urate concentrations through dual roles in urate handling in the kidney and uptake in the liver.²¹ Mice with systemic “knockout” of *GLUT9* have moderate hyperuricemia, massive hyperuricosuria, and early-onset nephropathy. In contrast, specific inactivation of the *GLUT9* gene in the liver of adult mice leads to severe hyperuricemia and hyperuricosuria, but without the renal disease.²¹

GLUT9 also transports the sugars glucose and fructose, which may be pertinent to the dietary influences of these compounds on hyperuricemia and gout. A substantial role for GLUT9 in the physiologic regulation of serum or plasma urate levels is further suggested by the results of genome-wide association and candidate gene studies. Such studies show that the *SLC2A9* locus and certain polymorphisms are associated with an increased risk for hyperuricemia and gout.^{22,23} Different mutations of *SCL2A9* have also been linked with renal *hypouricemia*, particularly in patients with intact URAT1.²⁰

URAT1

URAT1 is encoded by the *SLC22A12* gene and has a typical OAT structure.²⁴ URAT1 is highly specific for urate. It mediates the exchange of urate for a variety of endogenous and drug anions known to affect renal uric acid transport. URAT1 can transport urate in either direction across the tubular cell membrane, depending on the relative concentrations of urate and other ions on each side of the membrane. Like GLUT9S, URAT1 localizes to the apical brush border membrane of proximal tubular epithelial cells.

People with mutations in the *SLC22A12* gene (resulting in decreased URAT1 activity) have hypouricemia and hyperuricosuria, as well as exercise-induced renal functional impairment.²⁵ This suggests that URAT1 is important in the renal regulation of serum urate levels in normal individuals.²⁴ The uricosuric drugs probenecid, benzbromarone, and lesinurad increase urate excretion by inhibiting URAT1 and other OATs.^{24,26} Urate transporters may also play other roles in urate metabolism, for example, in the transport of urate across hepatic cell membranes.

URAT1 interacts with the scaffolding protein PDZK1. PDZ motifs are typically involved in the protein-protein interactions that support intracellular signaling and are also present in other urate transporters, including OAT4 and NPT1 (discussed later). This suggests that a more extensive multiprotein complex (the “urate transportosome,” which contains transport and transport regulatory molecules, hormone receptors, and intracellular signaling elements) may be involved in regulated bidirectional transport of urate across the renal tubular epithelial cell. Fractional renal excretion of urate ($FE_{ur} = \text{uric acid clearance/creatinine clearance} \times 100$) in URAT1 knockout mice²⁷ remains substantially less than 100%. This confirms that there are multiple mechanisms of uric acid reabsorption.

Other urate transporters

Many urate transporters are known. ABCG2 functions in both the kidney and intestine, and dysfunction is associated with hyperuricemia and gout.²⁸ The *sodium-dependent phosphate cotransporters* types 1 and 4 (NPT1 and NPT4; encoded by *SLC17A1* and *SLC17A3*, respectively) are located at the

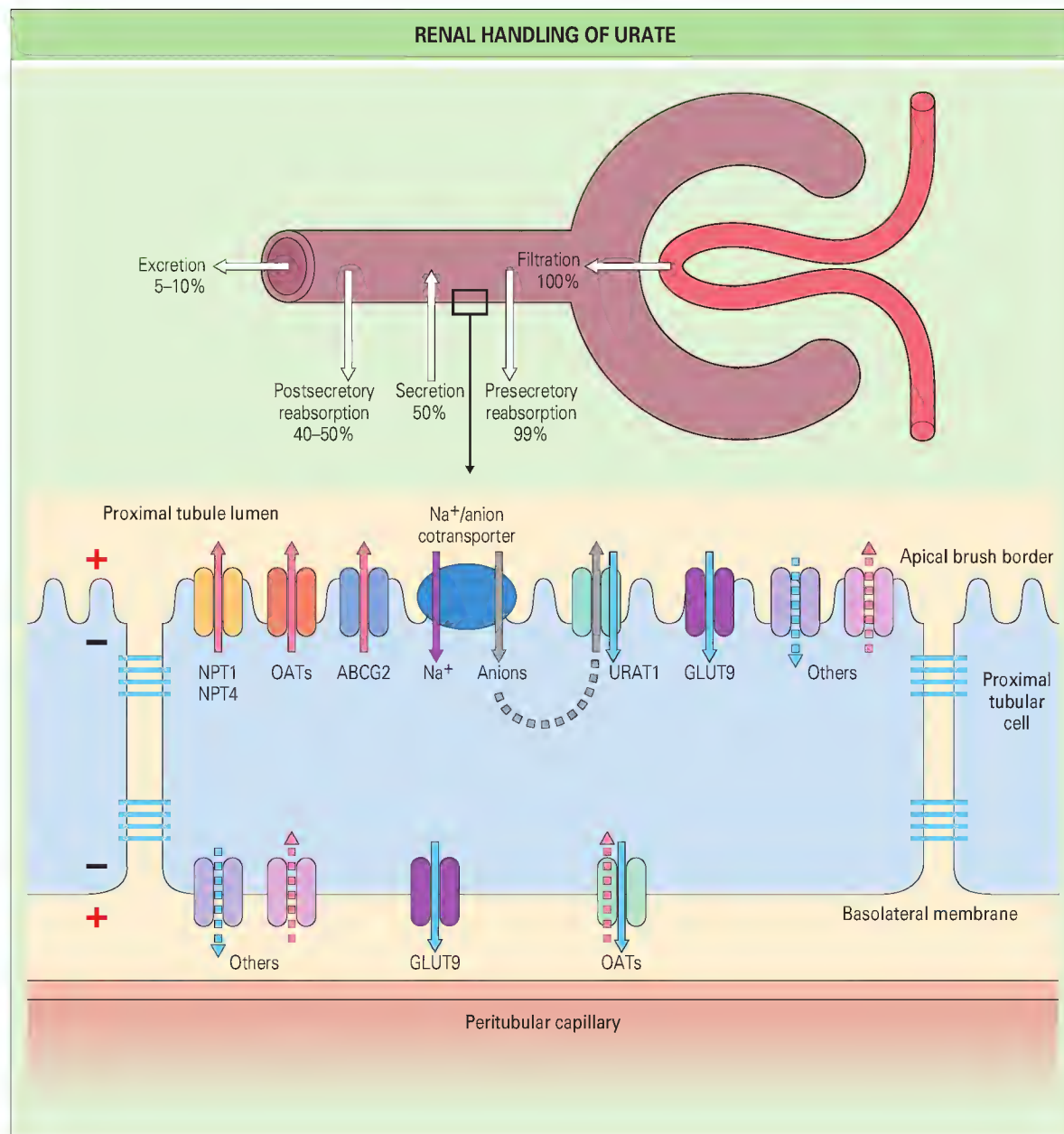


Fig. 187.6 The upper panel illustrates renal uric acid movement as historically divided into four physiologic compartments: glomerular filtration, tubular reabsorption, tubular secretion, and a second round of “postsecretory” reabsorption. The existence of a discrete fourth compartment of postsecretory reabsorption for fine-tuning of net uric acid excretion was controversial, and the anatomic correlates of these four compartments were uncertain. This classic model has declined in significance as the mechanisms underlying renal uric acid handling have become better understood at a molecular level (see text and lower panel). The lower panel indicates some of the key players in reabsorption and secretion of urate across the proximal tubule epithelial cell. Exchange of uric acid for other anions is mediated by specialized channels and transport proteins embedded in the tubular cell membrane. URAT1 and glucose transporter 9 (GLUT9) are significant contributors to uric acid absorption (such that defective function is associated with hypouricemia), whereas ABCG2, sodium-dependent phosphate cotransporter 1 (NPT1), and NPT4 are associated with net uric acid excretion. Uric acid transport is driven in part by a pH gradient produced by active sodium/hydrogen ion exchange. Several other organic acid transporters (OATs) have been implicated in uric acid transport. Transporters may be linked with each other and with regulatory and signaling elements by the PDZK1 scaffolding proteins making up the urate transportosome. Many of the drugs and endogenous mediators that affect renal uric acid disposition interact with these proteins; for example, the uricosuric drugs probenecid, benzbromarone and lesinurad inhibit uric acid reabsorption by URAT1.

luminal membrane of the proximal tubule and mediate net tubular urate secretion.²⁹

The relative importance of the many other OATs and exchangers in human renal urate handling is also uncertain. For example, OAT4, encoded by *SLC22A11* and localized at the apical membrane of the proximal tubules, is also associated with serum urate levels,³⁰ and OAT10 is a secondary target for the uricosurics probenecid and lesinurad.

IMPAIRED RENAL URIC ACID EXCRETION IN GOUT

Most people with hyperuricemia resulting from impaired renal uric acid excretion have normal amounts of uric acid in urine but selectively reduced

uric acid clearance.^{12,31} Excretion of “normal” amounts of uric acid is accomplished by gout patients only when serum urate levels are 2 to 3 mg/dL (120 to 180 μ M) higher than in healthy people excreting the same amount of uric acid. The hyperuricemia that results from this is the prime risk factor for the development of gout. Many mechanisms contribute to net urate excretion. It seems unlikely that a single mechanism for renal hyperuricemia explains the majority of primary renal gout.

Regulation of urate excretion

Renal uric acid processing has been further elucidated by molecular and genetic analyses such as those used to evaluate the role of variants in the GLUT9 and URAT1 transporters in gout patients and as determinants of serum urate or renal uric acid excretion in normal individuals. Alterations

in urate movement may be due to changes in the transporter itself, to changes in associated proteins or ion cotransporters, or to regulation of transport function.

Potential endogenous regulators of urate transport include insulin, leptin, adiponectin, and estrogens. In addition, the likelihood that renal urate transport normally regulates serum urate levels^{24,25,32} suggests that new classes of uricosuric agents acting with more selective action on particular urate transporters or associated molecules could emerge as targeted treatments.

Familial juvenile hyperuricemic nephropathy and medullary cystic kidney disease

Additional insight into uric acid handling has been provided by studies of familial juvenile hyperuricemic nephropathy (FJHN) and medullary cystic kidney disease (MCKD). These autosomal dominantly inherited disorders are characterized by early onset of hyperuricemia (with or without gout), hypertension, and progressive tubulointerstitial inflammation and fibrosis. This culminates in end-stage renal disease, often by 40 years of age.

Most families with FJHN show mutation in the chromosome 16p13-p11 *UMOD* gene,³³ usually affecting exons 4 and 5, which encodes cysteine-rich regions³⁴ of uromodulin, long known as Tamm-Horsfall urinary glycoprotein. More than 60 different *UMOD* mutations have been described. Uromodulin is an abundant disulfide bond–rich urinary protein with several putative proinflammatory and antioxidant properties. It is hypothesized to play a role in maintaining the structural and functional integrity of the ascending loop of Henle by forming a protective gel-like lattice that coats the luminal (urine) side of the tubule.

Mutant uromodulin accumulates in the endoplasmic reticulum. Defects in the protective lattice alter solute fluxes and thereby reduce reabsorption of Na⁺ and Cl[−]. This results in a contracted extracellular volume and compensatory enhancement of sodium-dependent urate transport in the proximal tubule.³⁵

Disorders resembling FJHN and MCKD type 2 at the clinical level have been associated with mutations in other genes, including the preprorenin signal peptide and the *HNF1B* gene.^{36,37}

URATE CRYSTAL FORMATION

Formation of MSU crystals requires sustained high (supersaturated) concentrations of urate. Crystal formation is influenced by many other factors, including the presence of particulate seed nuclei such as cartilage debris, collagen, chondroitin, and hyaluronate released by joint trauma or osteoarthritis (OA); local cation concentrations; pH, temperature, and dehydration; and the balance between macromolecular inhibitors and promoters of crystal formation (Table 187.2).³⁸ IgG and IgM may also aid crystal formation and growth in gout patients.^{39,40} MSU crystals preferentially form at certain sites, particularly the first metatarsophalangeal joint, midfoot, and Achilles tendon.⁴¹

Mounting evidence suggests a link between the presence of OA and sites of MSU crystal deposition.⁴² A cadaveric study reported that urate crystals were nearly always located within or adjacent to OA cartilage lesions.⁴³ A joint with OA has increased levels of cartilage degradation products, such as chondroitin sulfate, which lowers urate solubility and promotes the nucleation and growth of urate crystals.^{44–46}

One reason why gout does not develop in most persistently hyperuricemic people may lie in individual variation in the propensity for forming crystals. However, microscopic and imaging studies have shown that many people with asymptomatic hyperuricemia have evidence of urate crystals within joints,⁴⁷ thus suggesting that crystals may be present within the joint for long periods without eliciting an overt inflammatory response leading to the development of gout.

THE INFLAMMATORY RESPONSE TO URATE CRYSTALS

An acute gout attack occurs when urate microcrystals interact with host cells to initiate an inflammatory response (Fig. 187.7). The crystals triggering the acute gout flare are most likely shed from small preexisting synovial tophi rather than being freshly formed *in situ*. Whether crystals initiate clinically significant inflammation depends on multiple factors, including crystal size, the proteins and other molecules coating them, and the cells that they first encounter. *In-vitro* and animal model data suggest that urate crystals can activate the inflammatory response through several pathways.

■ TABLE 187.2

Gout promoters and inhibitors

Crystal formation	Seed nucleus (particulate) Immunoglobulin Phagocytes Low temperature Low pH Cation concentration Intraarticular dehydration Other (unknown) macromolecules
Triggering the acute flare (local factors)	Rapid change in urate level Microcrystal release IgG coat (apolipoproteins B, E inhibitory) Complement activation (classical, alternate, MAC) Inflammasome activation Cytokine and chemokine release Endothelial activation (e-selectin, ICAM-1, VCAM-1) Local trauma?
Presence of susceptible phagocytes, mast cells (systemic events)	Surgery, trauma Infections, other intercurrent systemic illness Alcohol, dietary intake Drugs that raise or lower circulating urate level

A diverse array of proteins and other mediators have been identified on the surfaces of urate crystals. In addition to their proinflammatory effect through opsonizing existing crystals, IgM and IgG antibodies may promote crystal formation by providing a stable molecular platform for crystal nucleation and growth. Apolipoproteins are the best characterized of the antiinflammatory molecules that coat crystals. The characteristics of the phagocytes encountering the crystals may be crucial; macrophages that are more differentiated are less likely to elicit proinflammatory cytokines. ICAM-1, intercellular adhesion molecule 1; MAC, membrane attack complex; VCAM-1, vascular cell adhesion molecule 1.

Which pathway predominates *in vivo* in acute gouty inflammation is uncertain.

In acute gout the predominant inflammatory cell in synovial fluid and the synovial membrane is the neutrophil, and activation of neutrophils seems to contribute the bulk of the proinflammatory stimulus. However, healthy joints do not contain a significant resident population of neutrophils. Urate crystals have their initial interaction with cells normally resident in the tissue.^{48,49}

The resident macrophages within the synovial membrane play a central role in instigating and driving the initial inflammatory response to urate crystals within the joint. Other cells such as synovial fibroblasts, antigen-presenting dendritic cells (DCs), eosinophils, and mast cells may also play a role in the initiation phase of acute gouty inflammation.

Crystal phagocytosis

Despite potent proinflammatory potential, urate crystals do not necessarily trigger acute inflammation. Gout patients and healthy hyperuricemic individuals may have urate crystals in clinically uninvolved joints. Heavily crystal-laden fluids (“urate milk”) are sometimes found in relatively uninfamed bursae and joints. The dense masses of urate crystals in tophi can reach massive dimensions, often with little apparent inflammatory response. In confined spaces such as axial or visceral sites, tophi can enlarge progressively without eliciting symptoms until critical compression of neighboring tissues ensues.

Similarly, patients with intercritical and chronic gout may have prolonged periods with absent or relatively low-grade synovitis despite the ongoing presence of urate crystals in the synovial environment. Thus, for urate crystals to trigger acute inflammation, additional determinants such as crystal size, crystal coatings, the local cytokine milieu, and encounters with particular cell types are necessary.

Microcrystals first need to be released from larger crystals or from tophi (Fig. 187.8). This fits with the clinical observation that gout flares are associated more with rapid changes in urate concentration than with absolute serum urate levels. For example, rapid and large urate reduction with intensive urate-lowering therapy is more likely to precipitate gout flares than a gradual approach. It is thought that rapid reductions in the urate concentration partially redissolve the margins of larger deposits and release fresh microcrystals. Crystal masses located within synovial tophi are surrounded by a protein coat, and dissolution of synovial tophi may serve to expose uncoated crystal surfaces.

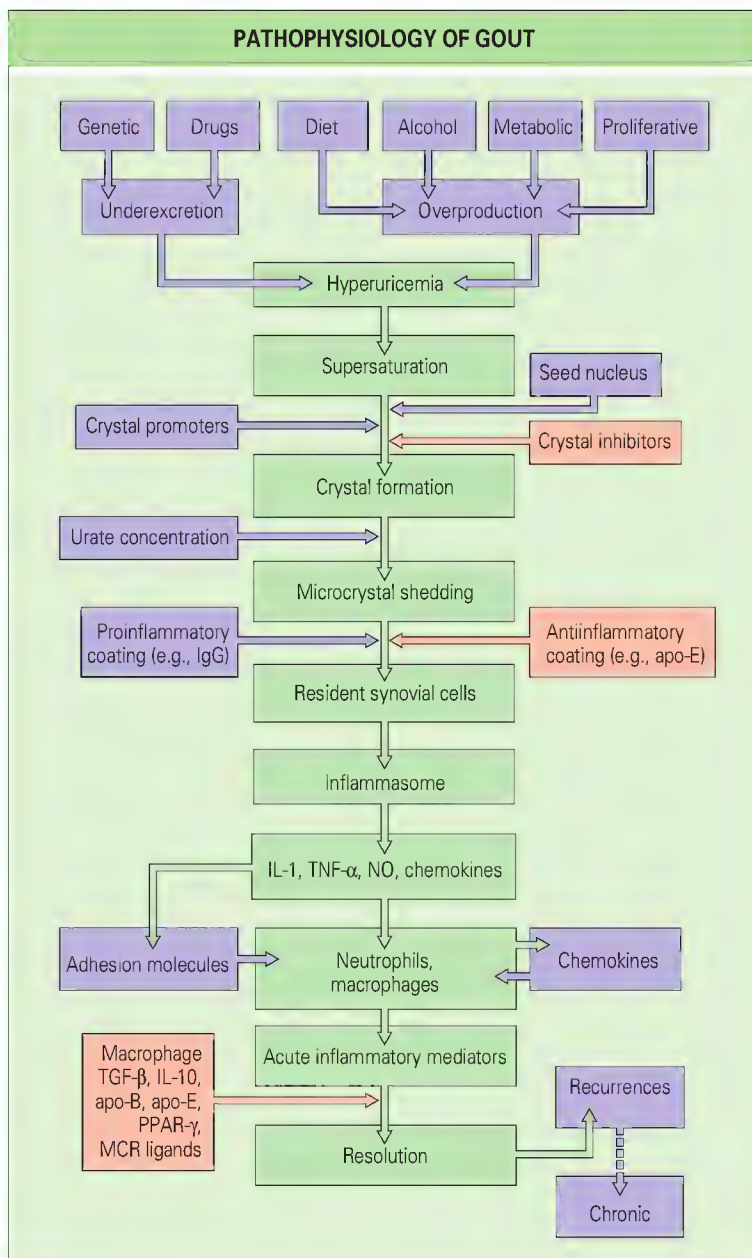


Fig. 187.7 Many signals have an impact at critical points in this pathway. Urate crystals do not necessarily form in hyperuricemic patients. Crystals ingested by phagocytes sometimes elicit remarkably little inflammation, and inflammation is often low grade or clinically inapparent in chronic gout, thus indicating robust regulation of the pathways shown. Factors leading to spontaneous termination of an acute gout attack are incompletely understood. Apo-B, apolipoprotein B; IL-1, interleukin-1; MCR, melanocortin receptor; NO, nitric oxide; PPAR- γ , peroxisome proliferator-activated receptor- γ ; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α .

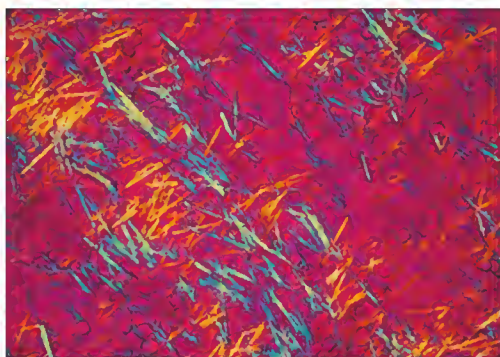


Fig. 187.8 Monosodium urate crystals aspirated from a subcutaneous tophus. The crystals are visualized with polarized transmission white (halogen) light, a 90-degree extinction filter, and a 530-nm first-order compensator.

Proteins binding to urate crystals

MSU crystals are composed of a highly ordered, regular array of urate and sodium ions and water molecules. Although the MSU crystal surface has a net negative charge, some positive charges are also exposed. MSU crystal surfaces can bind a variety of lipids, lipoproteins, and proteins,⁵⁰ including immunoglobulin G (IgG), which attaches via both charge interactions and hydrogen bonding. The resulting conformational change in IgG encourages phagocytosis by cells with Fc γ receptors (e.g., Fc γ RIII, CD16).

The complement system is involved in acute gout inflammation at several levels. Crystal-bound IgG activates the classical complement pathway. Urate crystals also activate complement directly through both the classical and alternative complement pathways. These pathways promote further opsonization via deposition of the complement split product C3b on the crystal exterior. C3b decays to iC3b and interacts with complement receptor CR3 (CD11b/CD18).

The soluble complement split products C3a and C5a act as additional chemoattractants. The complement “membrane attack complex” (MAC), which consists of the terminal complement components C5b through C9, may play an important role; rabbits lacking the MAC component C6 have reduced neutrophil responses to urate crystals.⁵¹

Coating of MSU crystals with apolipoprotein can counter the opsonic effects of IgG Fc and complement by decreasing the attractiveness of urate crystals to phagocytes.⁵² Apolipoprotein B (apo-B) is a major component of the serum low-density lipoprotein fraction and can coat crystals to inhibit stimulation of neutrophils. Apo-E has similar effects and can be made locally by synovial macrophages.

Other proteins detected on urate crystal surfaces include further complement activation products, lysosomal enzymes, and the antiinflammatory cytokine transforming growth factor- β (TGF- β). The inflammatory potential of MSU crystals reflects the balance between the proinflammatory and anti-inflammatory elements of this coating.

Phagocyte responsiveness

In addition to crystal size and coating, the host cell making first contact with the crystal is a crucial determinant of the inflammatory response (Box 187.2, Fig. 187.9; also see Fig. 187.7). Synovial fluid phagocytes from gout patients' noninflamed joints often contain urate crystals.⁵³ This indicates that crystals in the synovial compartment do not necessarily elicit overt inflammation despite active engagement with phagocytes.

Immature macrophages and blood monocytes mount a vigorous response to urate crystals. In contrast, more differentiated macrophages that release TGF- β show a greatly reduced proinflammatory mediator response despite equally efficient crystal internalization.⁵⁴ Most phagocytes in “normal” joints are macrophages rather than neutrophils.⁵⁵

Some mature phagocytes residing in human synovium may thus be able to ingest MSU crystals without triggering inflammation, whereas any circumstance that promotes the entry of fresh monocytes or neutrophils into the joint is more conducive to causing an acute gout attack.

THE ACUTE ATTACK OF GOUT

Urate crystals are a potent inflammatory stimulus that have multiple mechanisms for interacting with cells (reviewed elsewhere⁵⁶). The interaction of MSU crystals with phagocytes involves two broad mechanisms that depend on crystal concentration and surface reactivity. First, crystals can activate cells through the “conventional” route as opsonized and phagocytosed particles, analogous to the response seen with phagocytosed microorganisms. This process elicits the stereotypic phagocyte response of lysosomal fusion, respiratory burst, and release of inflammatory mediators.

A second and perhaps predominant mechanism involves the particular properties of the negatively charged MSU crystal surface. Their strong surface reactivity enables MSU crystals to cross-link membrane glycoproteins and directly activate proinflammatory signaling pathways at several levels within the phagocyte. The crystals interact directly with signaling proteins in the cell membrane (see Box 187.2 and Fig. 187.9) and bypass mechanisms that should normally regulate these pathways. Such mechanisms include integrins such as the CD11b/CD18 complex on leukocytes and $\alpha_{IIb}\beta_3$ on platelets, the Fc γ receptor CD16,⁵⁷ CD14, phospholipases, chemokine receptors, and receptor tyrosine kinases.

Although the phagocyte Toll-like receptors TLR2 and TLR4 (important in triggering innate immune responses via the adaptor protein Myd88) may also be involved in urate crystal inflammation, their exact role has been contentious.^{48,58} Certain free fatty acids such as C18:0 appear to synergize

BOX 187.2 INFLAMMATORY EVENTS IN AN ACUTE GOUT ATTACK

- a. Sequence of cellular events
 1. Deposition of urate crystals and release of microcrystals
 2. Proinflammatory coating (e.g., IgG, complement)
 3. Initial interaction with resident cells: tissue macrophages ± fibroblasts, mast cells, others
 4. Activation of membrane signaling molecules (TLR, CD14, TREM)
 5. Release of cytokines, especially IL-1, TNF- α , and chemokines
 6. Activation of endothelial cell adhesion molecules
 7. Emigration, attraction, and activation of neutrophils
 8. Phagocytosis of crystals by neutrophils
 9. Delayed neutrophil apoptosis
 10. Cross-linking of inflammatory signaling proteins
 11. Removal of crystal coating, membrane damage, phagolysosome rupture
 12. Activation of NLRP3 inflammasome, production of active IL-1 and IL-18
 13. Enzyme and mediator release
 14. Resolution—cytokines (e.g., TGF- β), MCR and PPAR- γ ligands, mature macrophages
- b. Membrane mediators
 - Fc γ receptors (Fc γ RIII/CD16)
 - GPCRs (e.g., chemokine receptors)
 - Toll-like receptors (TLR2, TLR4)
 - Complement receptors
 - Integrins
- c. Intracellular signaling
 - NLRP3 inflammasome
 - Tyrosine kinases (Syk, Src, Pyk-2)
 - Mitogen-activated protein kinases (p38, JNK, ERK-1, ERK-2)
 - Downstream TLR pathway (Myd88, IRAK-1, TRAF-6, IK- κ B)
 - Nuclear factors (NF- κ B, AP-1)
 - Lipid kinase PI3K
- d. Soluble mediators released
 - Chemokines: CXCL (e.g., IL-8), CCL (e.g., MCP-1)
 - Complement split products
 - TNF- α
 - Kinins
 - Metalloproteinases
 - Reactive nitrogen species (NO)
 - S100 proteins (S100A8/9; MRP 8/14)
 - TGF- β
 - RANKL
 - IL-1
 - Endothelins
 - IL-6
 - Leukotrienes
 - Reactive oxygen species
 - Prostaglandins
 - Substance P

Urate crystals can activate many cell types and trigger the release of a diverse array of proinflammatory mediators. Multiple pathways have been implicated in different experimental systems and based on the detection of mediators in gout patients, and it is likely that some of these mechanisms operate in parallel. The clinical efficacy of the inhibition of prostanooids and of IL-1 in preventing and reducing the inflammation of acute gout has established their role beyond doubt. Intervention *in vivo* with selective inhibitors of other mediators to “prove” their significance in humans has not been reported, and it is more difficult to be certain of the size of their contribution.

AP-1, activator protein-1; ERK, extracellular signal-regulated kinase; GPCR, G-protein coupled receptor; K- κ B, inhibitor of NF- κ B; IL-1, interleukin-1; IRAK, interleukin-1 receptor-associated kinase; JNK, Jun N-terminal kinase; MCP-1, monocyte chemoattractant protein-1; MCR, melanocortin receptor; MRP, myeloid release protein; NF- κ B, nuclear factor- κ B; NO, nitric oxide; PI3K, phosphatidylinositol 3'-kinase; PPAR- γ , peroxisome proliferator-activated receptor- γ ; RANKL, receptor activator of NF- κ B ligand; TGF- β , transforming growth factor- β ; TLR, Toll-like receptor; TNF- α , tumor necrosis factor- α ; TRAF, TNF receptor-associated factor; TREM, triggering receptor expressed on myeloid cells.

with urate crystals to engage TLR2 and induce release of interleukin-1 β (IL-1 β),⁵⁹ thus suggesting a further potential explanation of gout flares triggered by dietary excess.

Intracellular messengers

Once inside the phagocyte, urate crystals damage the phagosome membrane and hence lead to its rupture. The released phagosome contents then

activate the nucleotide-binding oligomerization domain-like receptor (NLR) NLRP3 inflammasome.⁶⁰ The inflammasome is a multiprotein cytoplasmic complex that senses cell damage and the presence of microbial products. It consists of the sensor protein NLRP3 (also known as cryopyrin and encoded by the *NLRP3* gene) and adaptor proteins CARD8/TUCAN (encoded by the *CARD8* gene) and ASC, which convert procaspase-1 into its active enzyme form.

Caspase-1 then cleaves pro-IL-1 β and pro-IL-18 into their active, inflammation-promoting forms. Release of IL-1 and IL-18 is in turn modulated by interactions between extracellular ATP and purinergic receptors on the cell surface. Further support for the central importance of the inflammasome/IL-1 pathway comes from the efficacy of IL-1 antagonists such as canakinumab and rilonacept in both treating and preventing acute gout flares.

For most external stimuli that activate inflammatory cells, signal transduction from receptors on the cell surface requires a carefully coordinated cascade of tyrosine kinase phosphorylation and interconnections with other messenger systems. MSU crystals can again bypass these “normal” routes and directly activate second-messenger systems.⁶¹

As with other steps in crystal-induced inflammation, multiple intracellular signaling pathways have been implicated (see Box 187.2). It is likely that these pathways operate in parallel. The p38 mitogen-activated protein kinase is a key regulatory point for many of the cytokines implicated in various forms of inflammatory arthritis and is involved in cell activation by MSU crystals.⁶² Both MSU and calcium pyrophosphate dihydrate crystals also activate the kinases Jun N-terminal kinase (JNK), extracellular signal-regulated kinase 1 (ERK-1), and ERK-2.

These pathways lead to the binding of nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1) to the promoter regions of genes encoding proinflammatory cytokines, chemokines, inducible nitric oxide (NO) synthase (iNOS), and metalloproteinases.⁶³ Similarly, activation through TLR proteins proceeds via Myd88 and a chain of intracellular mediators (see Box 187.2) that also converge on NF- κ B. Other adaptor molecules in the TLR2 and TLR4 signaling pathways (e.g., CD14) may also play a role.

Although the inflammation that urate crystals trigger via the inflammasome is clearly detrimental in the context of acute gout, it may play a physiologic role in activating the innate immune response by providing a “danger” signal.³ Cell injury results in the release of urate, which accumulates in the microenvironment. Free urate or MSU crystals can then stimulate phagocytes and other resident cells. Danger signals from urate crystals and from other purines (e.g., ATP) may also help trigger the adaptive immune response by activating antigen-presenting DCs.³ DCs provide stimulatory signals that help drive the activation of T lymphocytes, including type 17 helper T-cell (Th17) differentiation.

Acute inflammatory mediators

Activation of cells by urate microcrystals leads to the production of a diverse array of mediators. The S100 protein heterodimer formed by the calgranulin proteins S100A8 and S100A9 (formerly “myeloid release proteins” MRP8 and MRP14) is among the earliest inflammatory mediators produced in response to urate crystals. S100A8/9 is one of the most abundant proteins in the neutrophil cytoplasm.

S100A8/9 is also elevated in synovial fluid and serum during acute gout and may be an important initial stimulus to attract and activate other cells.⁶⁴ Release of S100A8/9 involves the Src-family tyrosine kinase Syk and phosphatidylinositol-3'-kinase pathways and also appears to be dependent on the CD11b and Fc γ RIII (CD16) receptors.

IL-1, IL-6, chemokines (see the next section), granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor- α (TNF- α) are among the mediators released starting within 30 minutes after exposure of cells to MSU crystals.

Another early response to cytokine release is increased expression of E-selectin on nearby vascular endothelial cells. A further mediator involved in experimental crystal-induced inflammation is endothelin-1, a peptide modulator of neutrophil migration produced by vascular endothelium.⁶⁵ These mediators contribute to massive neutrophil migration toward the MSU crystals that have triggered the episode.

Chemokines

Chemokines of the CXC family are important for attracting and activating neutrophils and are the major cytokines in acute gouty synovial fluid. Mice with a targeted disruption (“knockout”) of the gene for the chemokine receptor CXCR2 have a reduced neutrophil component in response to MSU crystals⁶⁶ (Fig. 187.10; also see Fig. 187.9 and Box 187.2). In addition,

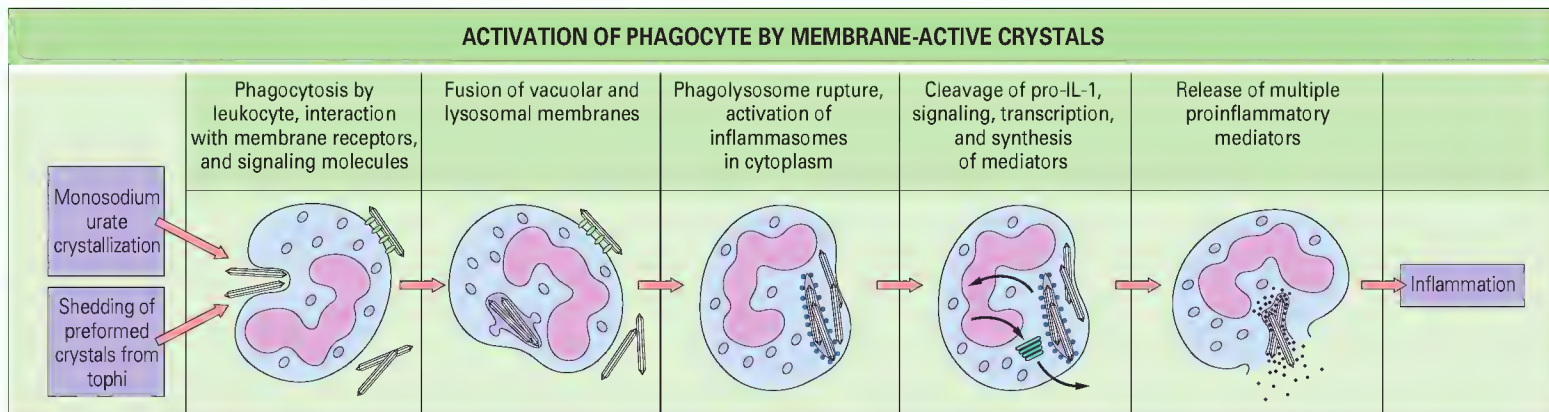


Fig. 187.9 Crystals interact with cell-surface receptors and their associated signaling complexes and are phagocytosed by the cell. Rupture of the phagolysosome releases the crystals into the cytoplasm, which allows interaction with the inflammasome and leads to activation and release of interleukin-1 (IL-1). Signaling protein kinases and promoters for cytokines and other proinflammatory genes are activated, with the release of a diverse array of inflammatory mediators (see text). Urate and other crystals also interact with lipid membranes and bind to cytosolic and membrane-bound proteins, thereby acting directly at important steps controlling proinflammatory signaling.

CXCL-8, CXCL-1 (growth regulated α , [Gro- α]), CXCL-2 (macrophage inflammatory protein-2 α [MIP-2 α], Gro- β), and CXCL-3 (MIP-2 β , Gro- γ) have been implicated.

The chemokine CCL-2 (monocyte chemoattractant factor-1 [MCP-1]) aids in recruitment of monocytes to the sites of inflammation induced by urate crystals.⁶⁷ As with other mediators, assigning relative significance to individual chemokines is difficult—the chemokine family is large and there is substantial overlap between the various chemokines binding a given receptor, redundancy in the functions assigned to different chemokines and receptors, and incomplete translation between mediator actions *in vitro* and in animal models and their functions in human disease.

Other mediators

MSU crystals activate *de novo* synthesis of inducible cyclooxygenase-2 (COX-2) and phospholipase A₂ and produce the inflammatory prostanoids prostaglandin E₂ and thromboxane A₂ in phagocytes.^{62,68} Prostaglandin E₂ causes vasodilatation, edema, and further leukocyte immigration. The clinical efficacy of COX inhibition in treating acute gout confirms a significant role for prostanoids in urate crystal inflammation.

Urate crystals stimulate neutrophils to undergo the respiratory burst and produce reactive oxygen species, particularly O₂^{•-}.⁶⁹ Urate crystals also incite NO production.⁶³ NO synthesis by iNOS (NOS2) has been demonstrated in cells relevant to the inflammation of acute gout, including macrophages, fibroblasts, chondrocytes, and endothelia.

Release of NO involves signaling pathways similar to those of the proinflammatory cytokines. Depending on its concentration and microenvironment, NO can mediate regulatory or direct toxic effects and can influence neutrophil activation and apoptosis.

Neutrophil activation

Resident synovial cells and trafficking monocytes contribute to the initial burst of proinflammatory mediators important in the initiation of gouty arthritis. Much of the full-blown response observed clinically is mediated by neutrophils. Synovial fluid aspirated during attacks of acute gout reveals neutrophil counts in a range up to that seen in acute pyogenic septic arthritis.

Neutrophils initially attach to the synovial vascular endothelium through their selectin ligands. Stronger adhesion occurs when the vascular endothelia express integrin molecules in response to the chemokines and cytokines produced in adjacent tissues.

The neutrophils then exit the synovial capillaries and migrate through the synovial matrix to the joint cavity, aided by the chemotactic gradient. The proinflammatory cytokines prime the neutrophil for an amplified oxidative and degranulation response to crystals.

Neutrophils have a shorter half-life (hours) than any other circulating leukocyte. Unless they are activated, normal neutrophils soon die. Inflammatory mediators implicated in gout, particularly colony-stimulating factors, IL-1, IL-6, chemokines, and prostaglandins, prolong neutrophil survival by inhibiting spontaneous apoptosis.

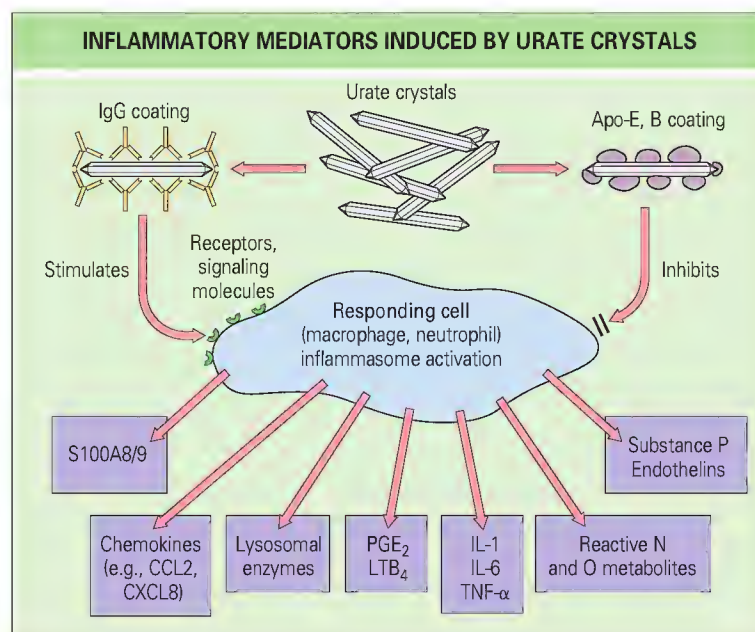


Fig. 187.10 Urate crystals can stimulate a variety of cells to produce a diverse array of inflammatory mediators, depending on the coating of the crystal and the receptiveness of the cell. Many mediators have been implicated in experimental settings, but the dominant mediators in human gout are uncertain; the clinical response of acute gout to nonsteroidal antiinflammatory drugs/coxibs and to specific interleukin-1 (IL-1) antagonists supports key roles for prostanoids and for IL-1, respectively. CCL2: MCP-1, macrophage chemoattractant factor 1; CXCL8: IL-8; LTB₄, leukotriene B₄; N, nitrogen; O, oxygen; PGE₂, prostaglandin E₂; TNF- α , tumor necrosis factor- α .

Neutrophils and macrophages within synovial fluid avidly engulf urate crystals. Lysosomal enzymes then remove the protein coating that the crystal has acquired in the synovial membrane and cavity. In the uncoated state, MSU crystals have increased reactivity with proteins and membranes. Neutrophil activation is marked by activation of phospholipases and by inositol triphosphate production, which leads to cytoplasmic calcium flux. Urate crystals also induce leukotriene production.

Depending on crystal concentration and coating, MSU crystals can then lyse the phagolysosomal membrane and spill the phagocytosed crystals and toxic lysosomal contents (proteases, reactive oxygen species) into the neutrophil cytoplasm (see Fig. 187.9). Phagosome lysis allows the urate crystals to interact with the inflammasome but can also lead to death of the phagocyte; this releases the lysosomal contents together with newly synthesized acute inflammatory mediators.

According to the intensity of the response and the size and number of joints affected, cytokines, including S100A8/9, IL-1, IL-6, IL-8, MCP-1, and TNF- α , are produced in sufficient quantity to enter the circulation and stimulate an acute-phase response. Patients with acute gout are often systemically unwell, with fever and leukocytosis, and in some cases display a systemic inflammatory response syndrome easily confused with sepsis (see Chapter 188).

The clinical response of acute gout to COX-2 inhibitors and IL-1 antagonists suggests that prostanoids and IL-1 (see Chapter 189) are prominent mediators of the intense acute inflammation characteristic of acute gout.⁷⁰ Other pain mediators include kinins, neuropeptides such as substance P, and mast cell products.

Termination of the acute attack

Even without medical intervention, acute gout is almost always self-limited. The classic attack resolves spontaneously within a week or two. This is an intriguing paradox given the overlap between gout and other arthropathies at the level of the molecular mediators involved and the persistence of the crystals that initiated the attack.

The increase in vascular permeability once acute synovitis has begun allows increased entry of antiinflammatory crystal-coating macromolecules from plasma, such as apo-B. Increasing urate crystal coating with apo-B and locally produced apo-E and TGF- β can inhibit neutrophil activation.

Systemic antiinflammatory mediators include the melanocortins, products of the hypothalamic-pituitary axis, including adrenocorticotropin (ACTH) and melanocyte-stimulating hormone (MSH). ACTH stimulates the release of corticosteroids from the adrenal cortex. Melanocortins also have a direct antiinflammatory effect on macrophages in the inflamed joint via macrophage melanocortin receptors.⁷¹

A number of antiinflammatory mediators have been implicated in the resolution phase of an acute gout attack. These mediators include apo-E, TGF- β , IL-10, IL-1 receptor antagonist, soluble TNF receptors, intracellular cytokine inducible SH2-containing protein (CIS) and suppressor of cytokine signaling 3 (SOCS3),⁷² and inducers of the nuclear hormone receptor peroxisome proliferator-activated receptor (PPAR- γ)⁷³ (see Fig. 187.7).

Resolution of the acute attack may be aided by the presence of progressively more differentiated macrophages arising in response to the cytokine milieu,⁷⁴ although other studies suggest that mature macrophages are as capable as monocytes of initiating responses to urate crystals⁴⁹ and removing neutrophils through apoptosis and phagocytosis.

CHRONIC GOUTY ARTHRITIS

Other than the serum urate level, risk factors for recurrence during the intercritical phase have not been studied in detail but are likely to be similar to

those for the initial development of gout. Hyperuricemia, synovial membrane microtophi, and synovial fluid crystals persist in a large proportion of these patients. At a clinical level, some chronic gout patients have no overt synovitis, whereas others have ongoing but relatively low-grade inflammation.

Persistent nests of crystals are enveloped by a granuloma-like chronic inflammatory response, with a corona zone of differentiated macrophages and multinucleated giant cells surrounded in turn by a fibrous layer. Both adaptive and innate immune cells are present within the tophus, and proinflammatory cytokines, including IL-1 and TNF- α , are expressed within the corona zone (Fig. 187-11).⁷⁵

Erosion of bone occurs frequently in chronic gout, particularly in proximity to intraarticular or periarticular tophi, and generally has a radiographic appearance distinct from that seen with the erosions of rheumatoid arthritis. Patients with severe erosive and tophaceous gout have elevated circulating levels of receptor activator of NF- κ B ligand (RANKL) and macrophage colony-stimulating factor, factors that aid the maturation of bone-resorbing osteoclasts.⁷⁶ T cells present within the tophus express RANKL and may contribute to joint damage.⁷⁷

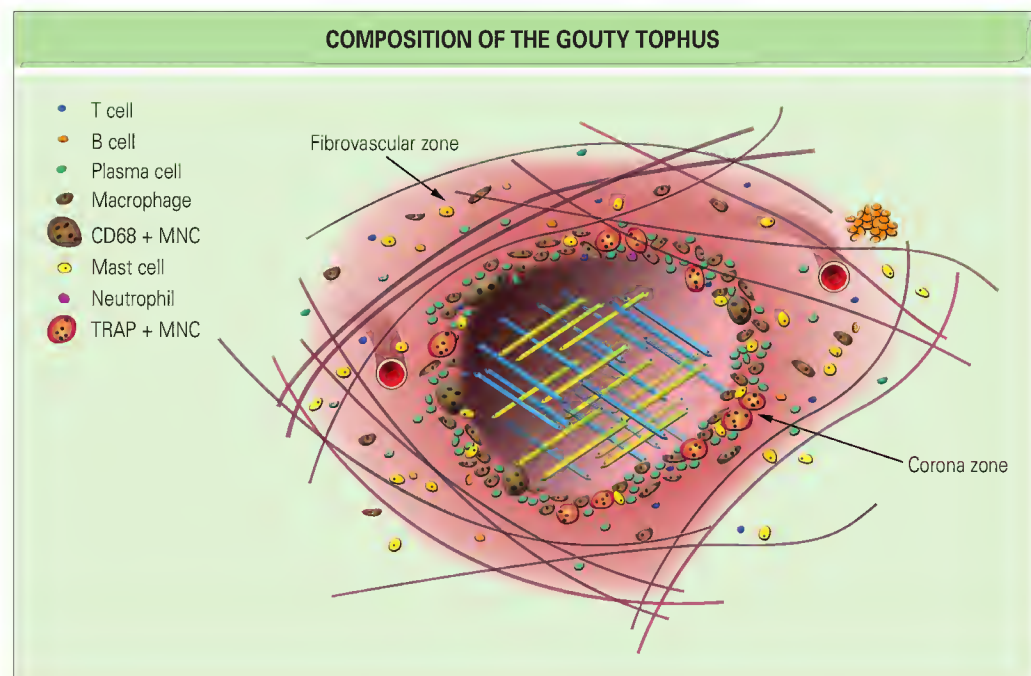
Urate crystals also have profound effects on osteoblasts and cause reduced cell viability, function, and differentiation.⁷⁸ In addition, these crystals reduce the expression of osteoprotegerin, a decoy receptor that inhibits osteoclastogenesis by preventing the binding of RANK to its ligand. High numbers of osteoclasts and infrequent osteoblasts are present at the bone-tophus interface in patients with chronic gout.^{76,78} Together, these data suggest that the bone erosion in gout is due to uncoupling of osteoclast and osteoblast function, which in turn promotes bone resorption at sites of urate crystal deposition.

Cartilage damage, characterized by radiographic joint space narrowing, is a relatively late manifestation of chronic gout. Histologic studies have shown that urate crystals are deposited radially in the superficial layers of articular cartilage, and cartilage surfaces in chronic gout are often described as being diffusely “dusted” with white crystal deposits.⁷⁹ Ultrasound studies have highlighted the close relationship between urate crystals and articular cartilage. The “double-contour” ultrasound sign can be visualized over the superficial margin of the articular cartilage in gouty joints and is thought to represent urate crystal deposition.⁸⁰

Urate crystals interact with chondrocytes to promote degradation of the cartilage matrix by inducing NO generation and expression of matrix metalloproteinase-3 (MMP-3) in articular chondrocytes through TLR2 signaling and upregulation of NF- κ B.⁸¹ Increased expression of other MMPs has also been observed in synovial fibroblasts stimulated with urate crystals⁸² and in macrophages obtained from gouty synovial tissue and within the tophus.⁸³

Findings on magnetic resonance imaging and ultrasound suggest that a high proportion of patients with gout and normal plain radiographs have occult joint damage.⁸⁴ Joints with persistent crystals may be subject to ongoing progressive damage even in the absence of acute flares.

Fig. 187.11 The central mass of monosodium urate crystals is surrounded by a corona of cells, including mature macrophages and multinucleated giant cells. Cells of the adaptive immune response are also present: T and B lymphocytes and plasma cells. (Adapted with permission from Dalbeth N, Pool B, Gamble GD, et al. Cellular characterization of the gouty tophus: a quantitative analysis. *Arthritis Rheum* 2010;62:1549-56.)



MODELS OF GOUT

Hyperuricemia models

No naturally occurring mammalian models for gout are available because most nonprimate mammalian species have uricase activity and maintain much lower urate levels than humans, and uricase-lacking nonhuman primates are vegetarians. Rodents, the most used source of animal models of arthritis, do not suffer spontaneous gout. Urate balance has been manipulated in several rodent models.

Mice with a homozygous urate oxidase gene knockout have severe hyperuricemia. Half die before 4 weeks of age as a result of renal failure and nephrogenic diabetes insipidus caused by uric acid crystal deposition within the kidneys.⁸⁵ Gout does not develop in surviving animals. Mice deficient in HPRT (the enzyme defect underlying Lesch-Nyhan and Kelley-Seegmiller syndromes in humans) or in both HPRT and adenine phosphoribosyltransferase (APRT) have normal urate excretion rates and no overt behavioral changes.⁸⁶

Oxonic acid, an inhibitor of urate oxidase, has been used to study the direct effects of urate on the vasculature. Treating rats with oxonate produces elevations in plasma urate levels that are modest by human standards and not associated with overt tissue deposition of urate crystals or with gout-like inflammation.

Urate crystal injection models

Injection of MSU crystals allows the study of crystal-induced inflammation under controlled circumstances. Urate crystals have been injected locally into several species, including rodents, rabbits, pigs, guinea pigs, dogs, and humans. They provoke a transient dose-dependent acute inflammatory response. Injection routes include intradermal, subcutaneous, palatal, intra-peritoneal, intraarticular, and into subcutaneous pouches produced by repeated injection of air.

An example of the use of urate crystals to study human inflammation is shown in Figure 187.12. Inflammation becomes clinically apparent within 2 to 4 hours of intradermal injection, peaks at 8 to 24 hours, and then subsides spontaneously with no significant sequelae. This and similar models provide safe and reasonably quantifiable systems to study aspects of cell trafficking, inflammatory regulation, mediator release, and pharmacologic inhibitors *in vivo*.

Although crystal injection models have allowed exploration of certain aspects of the inflammatory response, there are important caveats. In addition to the generally poor track record of extrapolating between induced preclinical models and spontaneous human arthritis, synthetic crystal preparations cannot easily mimic the protein, apolipoprotein, and lipid coatings acquired when urate crystals form *in vivo*. Injection into sites other than joints means an initial encounter with responding cells that are unlike those in the synovium.

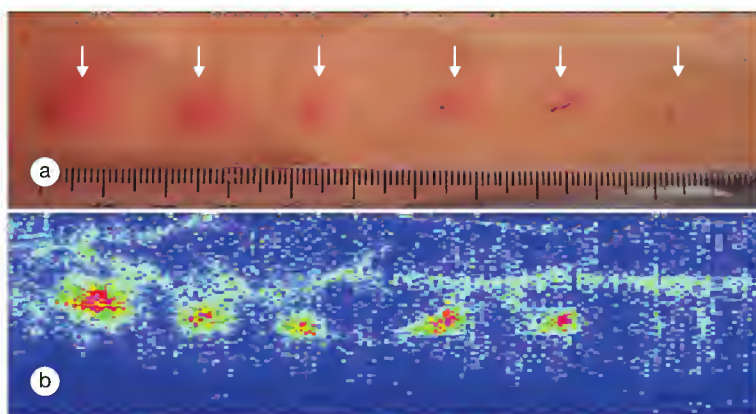


Fig. 187.12 Crystal-induced experimental inflammation: example of a model system for studying inflammatory events triggered by monosodium urate crystals in human volunteers. (a) Erythema visible 8 hours after the intradermal injection of graded doses of crystals (from left: 2.5, 1.25, 0.63, 0.32, 0.16 mg, and saline control). (b) Measurement of increased skin blood flow in this subject via laser Doppler flux. Urate crystals have been injected into skin and other accessible sites in humans and experimental animals to provide models of acute inflammation driven by cytokines (particularly interleukin-1 [IL-1], IL-6, and tumor necrosis factor- α [TNF- α]), chemokines (particularly IL-8), and prostanooids.

Most experimental animal species possess uricase. This limits the development of a model of chronic gouty arthropathy to further examine the mechanisms of bone and joint disease in chronic gout.

THE GENETICS OF GOUT

A familial diathesis to gout was first noted by Seneca 2 millennia ago. A positive family history has been reported in as few as 10% and as many as 80% of gout patients. This range reflects differences in the populations studied, the definitions used, and the vigor applied to ascertainment. Genetic influences on hyperuricemia and gout are, in most instances, multigenic.

Environmental factors are often required to exacerbate an underlying predisposition. For example, gout in Tokelau Islanders increased ninefold after migrating to New Zealand and adopting aspects of a Western industrialized lifestyle.⁸⁷ Assessing the relative contributions of genes and environment is difficult because certain pertinent “nongenetic” factors have a strongly heritable component, including dietary preferences and alcohol intake, and environmental exposures may be needed to “unmask” certain genetic influences. Contemporary estimates of the heritability of serum uric acid levels have ranged from 40% to 63%.⁸⁸

Genes that influence gout could in principle act at any one of several checkpoints on the path to crystal-induced inflammation. For example, they could affect urate production, renal handling of urate, crystal nucleation and enlargement, the crystal coating, or the cellular and soluble mediator components of the acute response when cell meets crystal or the amplification of this response. In support of the importance of genes influencing urate excretion, monozygotic twins show a tighter concordance than dizygotic twins for fractional renal uric acid clearance.⁸⁹ Genome-wide association studies (GWASs) indicate roles for genes involved in urate production, urate excretion, and control of inflammation.⁹⁰

Large, well-powered GWASs have revealed associations of many other genes encoding renal urate transporters (including *ABCG2*, *SLC2A12*, *SLC16A9*, *SLC17A1*, *SLC17A3*, and *SLC22A11*) with serum urate concentrations and gout.^{30,90} *SLC2A9* has the strongest effect on serum urate levels. Genetic associations between the serum urate level and the *PDZK1* gene³⁰ further support the importance of the URAT1-PDZ-NPT complex in controlling net urate reabsorption and secretion.

Consistent with a significant role in urate excretion, homozygosity for a loss-of-function mutation in *URAT1/SLC22A12*, the gene for the renal urate anion exchanger (see earlier), is the most common cause of renal hypouricemia (Online Mendelian Inheritance in Man [OMIM] 607096, 220150) in Japanese patients.²⁵ This polymorphism is more common in healthy Japanese than in gout patients, thus suggesting that it provides protection against gout.⁹¹

SLC2A9 has a stronger effect in women than in men and *ABCG2* a stronger effect in men.^{30,92} The promoter regions for some of the urate transporter genes contain hormone-responsive elements, which may underlie these effects.

Metabolic genes

Several well-defined purine metabolic enzyme defects lead to overproduction of urate (see Table 187.2), but they are uncommon. Other metabolic genes have effects that are less direct and less dramatic. There is an association between the serum urate level and *GCKR*, which encodes glucokinase regulatory protein, a regulator of glucokinase.⁹³ Glucokinase is an important enzyme in the glycolytic pathway and acts as a glucose sensor. *GKCR* has in turn been linked with metabolic traits associated with gout, including insulin resistance and hyperlipidemia. Other implicated genes are involved in sugar metabolism and in the production of purine precursors through the pentose phosphate pathway.⁹⁰

Genes influencing crystal formation and crystal-triggered inflammation

Gout does not develop in many hyperuricemic people. Moreover, the genes currently known to influence urate levels account for just a small proportion of the heritability of gout (less than 10% when stringent criteria are applied). This suggests that diverse mutations or a combination of many individually “weak” genes contribute to the genetic predisposition to gout. Despite powerful contemporary epidemiologic and genetic techniques, the relative contributions of genes versus environment (“nature vs. nurture”) remain uncertain.

Numerous polymorphisms have been identified in the promoter and structural regions of the genes for inflammatory cytokines, cytokine

receptors, and cellular signaling molecules, including NLRP3 and members of the IL-1 family. Expression of one or more of these genes might modulate the inflammatory response to urate crystals. GWASs have also implicated several genes involved in the regulation of inflammation.⁹⁰ Associations between gout and cytokine gene polymorphisms have not been explored as robustly as, for example, the *URAT1* and *SLC2A9* associations.

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Clinical gout

■ N. LAWRENCE EDWARDS

- Gout has an abrupt initial onset involving, most commonly, the big toe, ankle, or other joints of the foot.
- Upper limbs, especially the distal interphalangeal joint, are affected in chronic tophaceous or recurrent acute gout.
- Men in middle life who are obese and drink alcohol regularly are the most susceptible.
- Women, when affected, are most commonly taking diuretics or postmenopausal.
- Hypertension, hypertriglyceridemia, insulin resistance, and mild renal impairment can be associated.
- Hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosylpyrophosphate synthetase overactivity, or hereditary renal disease should be suspected in children, adolescents, or young adults with gout.

INTRODUCTION

Gout is by far the most common inflammatory arthritis that affects humans. Despite this, there are many widely held misconceptions about the disease, its causes, and its treatments. From a clinical perspective, gout is frequently perceived as a painful intermittent nuisance rather than the progressive, and ultimately destructive, form of arthritis that it is.

The gouty process actually begins years or decades before the patient develops any gout symptoms. When gout is viewed in this way, it becomes clear how, if it is left untreated, the process of urate accumulation over time will lead to greater destruction and will make treatment more difficult.

CLINICAL STAGES OF GOUT

Gout is a clinical disease associated with hyperuricemia and caused by the deposition of monosodium urate crystals in and around the tissues of joints. Gout is frequently epitomized by an acutely painful and swollen toe or foot. This is, however, only a single stage in the progression of urate deposition disease in the soft tissues and joints. Typical gout progresses from a usually prolonged initial period of asymptomatic accumulation of monosodium urate crystals in and around joints to a phase of acutely painful but self-limited episodes of monoarthritis or oligoarthritis to a final phase of chronically painful, deforming, and debilitating polyarthritis associated with the visible presence of soft tissue monosodium urate crystal deposits known as *tophi* (Fig. 188.1). Although it is traditional to think of the natural progression of gout in these three stages, it is more correct to view gout as a steady accumulation of monosodium urate crystals in and around joints from the earliest onset of hyperuricemia. Gout is a disease of urate burden.

The duration of each stage of gout can vary greatly from one person to another depending on numerous endogenous and exogenous factors. The most important of these factors is the degree of hyperuricemia.

Asymptomatic hyperuricemia

Definition

Hyperuricemia is a common biochemical abnormality that has become much more common over the past 40 years. In extracellular fluids, 98% of uric acid is in the form of the urate ion at pH 7.4. Hence it is conventional

to refer to the serum and synovial fluid forms as *urate* but the urinary form as *uric acid*. The physiologic definition of hyperuricemia is a concentration of serum urate above 6.8 mg/dL (402 μ mol/L) because this level defines the saturation point of the sodium urate salt in biologic fluids at physiologic pH and temperature.¹ Inappropriately, commercial medical laboratories define the “normal” range of serum urate based on the population mean and its 95% confidence intervals. This definition of hyperuricemia clearly has no bearing on the pathologic potential of uric acid.

Demographic risk factors

The prevalence of hyperuricemia varies from country to country, but worldwide the percentage of adults with hyperuricemia has been increasing over the past four decades. In the United States, the Framingham study found the prevalence of serum urate levels higher than 7.0 mg/dL to be 4.8% in adults in the early 1970s, whereas the National Health and Nutrition Examination Survey (NHANES) for 2007-2008 reported hyperuricemia in 21% of both men and women.²

Many factors contribute to this observed rise in serum urate levels around the world, and the importance of individual factors can vary among countries and populations. Age is by far the most important risk factor in explaining the increased number of cases of hyperuricemia and gout. Men usually attain their adult serum urate levels shortly after puberty and maintain this level throughout life with modification only by diet, disease, and medications. When the percentage of the population over the age of 65 increases, as it has done in most industrialized nations, then the prevalence of hyperuricemia also increases. The effect of longevity on the prevalence of hyperuricemia is even more profound in women.³ Women's serum urate levels remain relatively low throughout most of their adult lives because of the uricosuric effect of estrogens. After menopause, the gap between male and female urate levels narrows, and a far higher percentage of elderly women than of young adult women have hyperuricemia and gout.

Kidney disease

The rising frequency of solid organ transplantation and the survival of patients with severe chronic kidney disease also contribute to the higher prevalence of hyperuricemia. The calcineurin inhibitors cyclosporine and tacrolimus have potent effects on serum urate levels by preventing uric acid secretion by transporters in the proximal convoluted tubules of the kidney and by diminishing glomerular filtration.^{4,5} In one study of renal transplant patients taking prednisone and either cyclosporine or azathioprine, the prevalence of hyperuricemia was 84% in those taking cyclosporine, whereas it was 30% in those taking azathioprine.⁶ Patients with advanced kidney disease have a high likelihood of being hyperuricemic even if they do not undergo renal transplantation. The survival of these patients has greatly improved over the past 4 decades, and therefore the contribution of kidney failure to the rising prevalence of hyperuricemia over the same period of time is substantial.

Influence of diet

Dietary trends have also been part of this epidemic of hyperuricemia. Western countries consume more meat and seafood, less dairy products, more sugar-sweetened beverages, and a higher proportion of beer compared with other alcoholic beverages than in decades past. All of these dietary changes promote higher uric acid levels.^{7,8} Serum urate levels have been shown to independently predict the development of hypertension⁹ as well as cardiovascular disease, cardiac failure, stroke, and kidney disease.^{10,11} Thus this period of asymptomatic hyperuricemia may not be the quiescent and benign initial phase of clinical gout that it was once considered to be. Similarly, the requisite changes in the joints and soft tissues of hyperuricemic patients that will ultimately go on to develop gout are taking place

THE STAGES OF GOUT

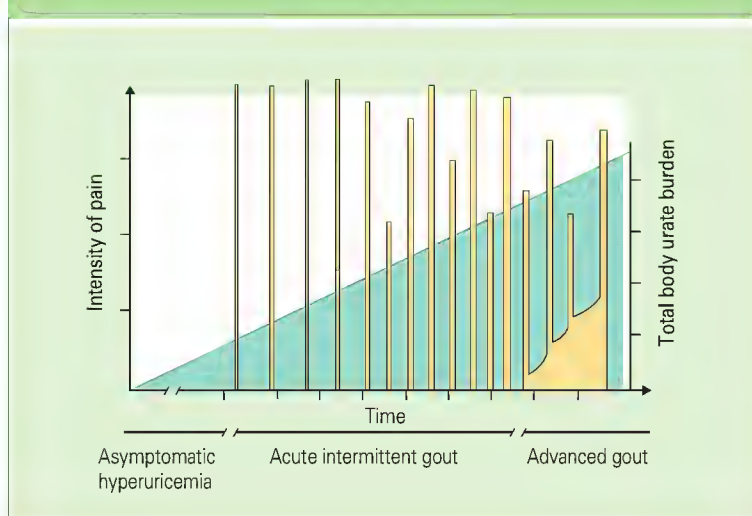


Fig. 188.1 A period of asymptomatic hyperuricemia is an obligatory precursor to clinical gout. The duration of this initial phase varies directly with the degree of serum urate elevation. A period of acute intermittent gout, lasting a decade or longer, is characterized by acute flares separated by asymptomatic intervals. If the disease is not treated, the majority of individuals progress to a chronic debilitating arthritis with clinically apparent soft tissue tophi—collectively referred to as *advanced gout*. Underlying the clinical manifestations of gout, the clinical course of untreated gout is one of gradual accumulation of urate stores throughout the body (shaded area).

during this time of asymptomatic hyperuricemia. The supersaturation of urate in synovial fluid leads to crystallization of monosodium urate, and these crystals gradually form small microtophi on the cartilage surface and in the synovium years to decades before the first clinical attack of gout. The presence of these preexisting microtophi has been demonstrated directly by arthroscopy¹² and indirectly by ultrasonography and magnetic resonance imaging.^{13,14}

Other risk factors

Obesity is another major risk factor related to the increasing prevalence of hyperuricemia and gout. In fact, the obesity epidemic in most Western countries is closely paralleled by the increased prevalence of hyperuricemia and gout.¹⁵ Uric acid levels are raised in the setting of obesity because of both diminished renal elimination of uric acid and increased production of uric acid in the body.¹⁶

A number of medications in common use also contribute to the higher prevalence of hyperuricemia. Low-dose aspirin and diuretics are widely used by adults who have hypertension or are at risk of cardiovascular disease. Aspirin dosages as low as 75 mg/day have been shown to have an impact on serum urate levels¹⁷ and are taken by more than half of all persons at high risk of cardiovascular events.¹⁸ Similarly, thiazide diuretics alone or in combination with other antihypertensives are among the most commonly prescribed of all medications.

Hyperuricemia and onset of gout

Although the initial stage of gout, asymptomatic hyperuricemia, goes unrecognized clinically in the vast majority of gout patients, it is an important period in altering structural anatomy and fostering the development of the comorbid medical conditions associated with gout. The period of asymptomatic hyperuricemia typically lasts for several decades but may be considerably shorter in patients with marked elevations of serum urate levels. This is especially true in patients with certain inborn metabolic errors and in patients taking cyclosporine, in whom the period of hyperuricemia preceding clinical gout may be as short as several years.¹⁹ Not everyone with hyperuricemia eventually has gout. In the Framingham study, gout developed in only 12% of patients with urate levels between 7.0 and 7.9 mg/dL over a 14-year period.²⁰ Patients with urate levels higher than 9.0 mg/dL had a sixfold greater likelihood of progressing to clinical gout.

Acute intermittent gout

The initial attack of acute gout usually occurs in men between the fourth and sixth decades of life. In women, the age at onset is later and varies with

BOX 188.1 KEY COMPONENTS OF GOUT FLARES

- Marked tenderness and swelling of affected joint
- Acute onset with maximum pain in 4 to 12 hours
- Recurrent pattern of similar attacks
- Marked impairment of physical function
- Resolution of symptoms within 3 to 14 days



Fig. 188.2 Podagra or acute gout of the first metatarsophalangeal joint is shown. The hyperintense erythema with a dusky hue is characteristic. The area of inflammation usually extends beyond the region of the involved joint.

several factors, the most important of which is the age of menopause. The typical gouty attack is usually heralded by the rapid development of warmth, swelling, erythema, and exquisite pain in the affected joint. These symptoms can appear at any time of the day, but there is a slightly higher incidence of onset during the sleeping hours.²¹ Pain escalates from faint twinges to its most intense level over a short 4- to 12-hour period. The initial attacks are usually monoarticular, and in approximately half of the cases the arthritis involves the first metatarsophalangeal joint. Eventually this joint is affected in 90% of individuals with gout. Other joints that are frequently affected in the early phase of acute intermittent gout are the midfoot, ankle, heel, and knees. After the first five to eight episodes of acute gout, other joints, including the fingers, wrists, and elbows, can also be affected. Classically, patients cannot stand even the lightest of touches or bed sheets on the affected joint, and most patients find walking difficult or impossible when lower extremity joints are involved.

A recent study attempted to provide criteria for defining a gout flare from the perspective of gout experts and patients alike.²² In general, the description clusters of classic joint inflammation, the marked severity of joint symptoms, and the stereotypical nature of the onset and resolution of an acute attack were found to be the most meaningful clinical clues that can help distinguish a gout flare from other forms of acute monoarthritis (Box 188.1).

The initial flares of gout occur with explosive suddenness, and within 4 to 12 hours the gouty individual is not capable of walking. In an acute attack the skin over the affected joint soon becomes reddened and warm with extreme tenderness to touch or movement of the joint (Fig. 188.2). As suggested over a 100 years ago by Sir William Osler, a distinguishing characteristic differentiating an acute gouty joint from a septic joint is the appearance of the overlying skin: a gouty joint has shiny, tense skin with a cyanotic or mauve hue, whereas a fiery red color is more characteristic of a septic joint. Although this difference has not been subjected to a formal investigation, it is widely accepted. Systemic symptoms such as

fevers, chills, and malaise may also accompany acute gout and may lead to some confusion when trying to distinguish acute gout from a septic joint.

The previous clinical description refers to the classic presentation of acute gout. There are other forms. McCarty^{22a} described a much milder variation with trivial episodes of pain (“petite attacks”) lasting only minutes to hours and sometimes recurrent over several years before the first dramatic gouty attack. Another atypical presentation of acute gout occurs more often in elderly women. In these women, the initial flares are in the upper extremity joints and may involve several joints. Early onset of upper extremity involvement and the occurrence of oligoarticular or polyarticular flares are seen more commonly in women than in men.²³

Factors precipitating flares

Factors capable of provoking an acute flare include anything that can alter the usual stable microenvironment surrounding the microtophi in the joint space. The physical factors that are most commonly altered to provoke an attack are the pH of the surrounding synovial fluid and the concentration of urate. Destabilization of the microtophi leads to shedding of crystals into the joint space and initiation of the acute attack. Trauma to the joint with or without intraarticular bleeding or systemic acidosis associated with surgery can both change the intraarticular pH enough to foster a flare. Similarly, any condition or medication that dramatically raises or lowers urate levels in the synovial fluid will also destabilize the microtophi, resulting in “mobilization flares.” Dietary exposures such as abnormally high intake of meat, seafood (especially shellfish), and alcohol (especially beer) raise urate levels and cause crystal shedding. Crystal shedding can also be induced by factors that rapidly reduce serum urate levels, such as allopurinol. Interestingly, factors that cause sudden lowering of serum urate levels are more likely to trigger attacks than those that raise urate levels.

Natural history of acute attack

One of the hallmarks of the acute gout flare is its self-limited nature. In fact, a clear and detailed history of an acute arthritic attack followed by a completely asymptomatic intercritical period before a recurrence of a similar attack is valuable in pointing toward a clinical diagnosis of gout. The initial attacks themselves last between 5 and 10 days. The intercritical period separating early attacks may last several months or up to several years, with a mean duration of 11 months. As the disease progresses in the untreated patient, acute attacks occur with increasing frequency and are often oligoarticular or polyarticular, more severe, and longer lasting (see Fig. 188.1). The corollary to this pattern of flares is that the length of the intercritical period becomes progressively shorter. Even when the acute gouty flare has completely subsided, monosodium urate crystals remain in the synovial fluid,²⁴ and low-grade inflammation persists within the joint, as evidenced by white blood cell counts in the range of 1000 to 2000/mm³. Thus the entire stage of acute intermittent gout is one of persistent low-grade inflammation with relatively short periods of acute severe inflammation. This stage usually persists for 10 years or longer before progression to the chronically symptomatic stage of advanced gout. However, depending on the cause and degree of hyperuricemia, the acute intermittent stage of gout may last for as short as 3 to 4 years or for longer than 20 years.

Advanced gouty arthritis

The transition from acute intermittent gout to advanced gout occurs when the intercritical period between flares is no longer associated with freedom from pain (see Fig. 188.1). This stage was previously called *chronic tophaceous gout*; however, although the subcutaneous tophus is the most characteristic lesion of advanced gouty arthritis, it is not always present. In addition, patients have been reported who have tophi as their initial clinical manifestation.²⁵ In this stage of gout, the involved joints are persistently uncomfortable and swollen, although the intensity of these symptoms is much less than during the acute flares. Flares can continue to occur against this painful background, and without therapy they will recur as often as every few weeks. The level of background pain may also steadily increase with time if appropriate therapies are not instituted. Macrotophi or clinically evident tophi may or may not be detected on physical examination in the early phases of advanced gout, but bony or periarticular tophi are almost always detected by ultrasonography or magnetic resonance imaging.¹⁴ Polyarticular involvement becomes much more frequent at this time. With diffuse and symmetric involvement of small joints in the hands and feet, advanced gout can occasionally be confused with the symmetric polyarthritis of rheumatoid arthritis (Fig. 188.3). The severity of and disability associated with the erosions and bony destruction of advanced gouty arthritis are similar to those observed with rheumatoid arthritis.²⁶



Fig. 188.3 Advanced gout of the hands and wrists demonstrates an asymmetric arthritis with articular and interarticular tophi. The large tophus involving the distal left fourth digit shows very superficial crystalline deposits.

Role of subcutaneous tophi

A subcutaneous tophus is a well-organized collection of monosodium urate crystals and is pathognomonic for gout, as is the destructive arthritis of advanced gout. Tophi can lead to pain and dysfunction in their own right. Similar-appearing nodules are clinically observed in other rheumatic disorders such as rheumatoid arthritis and multicentric reticulohistiocytosis, which may lead to diagnostic confusion. Besides their appearance, there are other parallels between gouty tophi and rheumatoid nodules. The nodular aspects of both diseases are generally observed in the most chronic and severe cases but are not a universal consequence of the disease process. The presence of both types of nodules is also closely correlated with high titers of their respective serologic markers: serum urate in the case of gout and rheumatoid factor in the case of rheumatoid arthritis.

Subcutaneous gouty tophi may be found anywhere in the body but occur most commonly in the fingers, wrists, ears (Fig. 188.4), knees, olecranon bursae, and pressure points such as the ulnar aspect of the forearm and the Achilles tendon. In patients with coexisting nodal osteoarthritis, tophi have a propensity for forming in Heberden nodes (Fig. 188.5). Tophi may also occur in connective tissues at other sites such as the renal pyramids, heart valves, and sclerae.²⁷

Before the advent of urate-lowering therapies in the 1950s and 1960s, as many as 50% of patients with gout eventually developed clinical evidence of tophi.²⁸ With the introduction of allopurinol and probenecid, the incidence of tophaceous gout has declined.

Nonclassic gout

The descriptions of the three stages of classic gout in the previous section are most relevant to the typical middle-aged man who is obese and has one or more of the comorbid medical conditions associated with gout, such as hypertension, cardiovascular disease, renal insufficiency, or dyslipidemia. There are other presentations of gout that do not fit this profile and whose manifestations are atypical enough that the clinician may miss the diagnosis.

Early-onset gout

Approximately 5% of all patients with gout experience the onset of their symptoms before the age of 25. These patients with early-onset gout are a special subset who usually do not have obesity or the comorbidities of gout, experience a more accelerated clinical course, generally have a strong family history of gout, and require more aggressive antihyperuricemic therapy than do typical individuals with gout. In large epidemiologic studies, a family history of gout and/or nephrolithiasis is present in 25% to 30% of patients with classic gout. In early-onset gout, a family history is found in about 80%. In this younger group, detailed questioning about the patient's family history over several generations may yield enough information to suggest a



Fig. 188.4 Subcutaneous tophi along the helix of the ear are uncommon but are ready sources of monosodium urate crystals for microscopic confirmation of gout.



Fig. 188.5 Large tophi involving the distal interphalangeal joints are commonly seen in gouty patients with preexisting Heberden nodes. This is particularly characteristic of late-onset gout.

mode of inheritance (X-linked or autosomal dominant or recessive). The measurement of 24-hour urine uric acid excretion and calculation of the urate clearance is also very helpful in classifying these patients with early-onset gout into the subgroups of uric acid overproducers and those with diminished fractional uric acid excretion (uric acid underexcretors).

Specific genetic deficiencies

Diseases associated with urate overproduction in children and young adults include enzymatic defects in the purine pathway, glycogen storage diseases, some genetic errors of urate transport in the kidney, as well as hematologic disorders such as hemoglobinopathies and leukemias.

The two inborn errors of purine metabolism that are associated with urate overproduction are both X-linked and both have severe phenotypes in which the very early onset of gout and kidney stones is combined with neurobehavioral and neurodevelopmental impairments. Both enzymatic abnormalities also have milder phenotypes with slightly later onset of gout and nephrolithiasis and milder or no neurologic impairments.

- A complete deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) is an inherited X-linked condition with the characteristic presentation known as *Lesch-Nyhan syndrome*.²⁹ These boys develop gout and kidney stones in the first decade of life if not treated very early. They also develop severe neurologic manifestations in infancy or early childhood consisting of variable mental retardation, dystonia, and compulsive self-mutilating behavior. A milder phenotype is found in boys with a partial deficiency of the HPRT enzyme. This usually manifests as the development of gout and/or kidney stones in male teenagers who are free of neurologic abnormalities. This X-linked partial deficiency of HPRT is referred to as *Kelley-Seegmiller syndrome*.³⁰
- The other purine enzyme abnormality associated with early-onset gout is phosphoribosylpyrophosphate (PRPP) synthetase overactivity. One of the two phenotypes of this X-linked disease is the infantile-onset form in which gout and uric acid nephrolithiasis are combined with neurodevelopmental impairment, including sensorineural hearing loss. It is caused by a point mutation in the PRPP synthetase gene that makes it insensitive to allosteric downregulation by purine nucleotides. The milder phenotype of this enzyme overactivity can be seen in older children, who have gout, kidney stones, and either mild or no neurologic impairment. This form of PRPP synthetase overactivity is caused by overexpression of a normal (nonmutated) PRPP synthetase gene.³¹

Glycogen storage disease (GSD) types I, III, V, and VII are associated with early-onset gout and are inherited as autosomal recessive diseases.^{32,33} In the hepatic form of von Gierke disease (GSD type IA) or glucose-6-phosphatase deficiency, childhood hyperuricemia can lead to acute and chronic gout in the adolescent years. The other components of this phenotype include short stature, hepatomegaly, hypertriglyceridemia, and fasting hypoglycemia. The reason for hyperuricemia in these children is an accelerated degradation of adenosine triphosphate in the liver. In the other forms of GSD the hyperuricemia is a less consistent finding, and documented cases of childhood or adolescent gout are much rarer. Type III disease, or Cori or Forbes disease, has a clinical picture very similar to that of type I disease except that serum urate and lactate levels are generally normal in the very young and in nonexercising older children. The glycogen debrancher enzyme is deficient in GSD type III. GSD type V (McArdle disease) and the very rare GSD type VII (Tarui disease) are enzymatic deficiencies in which the primary disturbance in glycogen homeostasis occurs in skeletal muscle. In McArdle disease, the deficient enzyme is muscle glycogen phosphorylase; the disorder manifests as exercise-induced cramps and can lead to rhabdomyolysis and renal failure. Accelerated adenosine triphosphate breakdown and enhanced lactic acid formation can lead to hyperuricemia and gout. Tarui disease, on the other hand, is caused by phosphofructokinase deficiency, which leads to enhanced purine nucleotide formation and turnover.

Childhood kidney disease

Although any form of childhood kidney disease that results in reduced glomerular filtration rate can cause hyperuricemia, there are only two diseases that consistently lead to gout in individuals in their teens and 20s. Familial juvenile hyperuricemic nephropathy (FJHN) is a rare autosomal dominant trait that inevitably causes childhood hyperuricemia, frequently resulting in gout in postpubertal adolescents.³⁴ The functional reason for hyperuricemia in children with FJHN is that the fractional excretion of urate by their kidneys is only half that seen in normal kidneys. In time, this deficiency leads to end-stage renal disease, usually by midlife. Autosomal dominant medullary cystic kidney disease (MCKD) is another inherited nephropathy that frequently results in gout. The gout associated with MCKD typically occurs in the third and fourth decades of life—much later than in FJHN. Multigenerational linkage analysis of MCKD shows at least two genetic abnormalities: one on chromosome 1 and the other on chromosome 16. Interestingly, the abnormal genetic locus on chromosome 16 found in some patients with MCKD is the same locus associated with FJHN. The chromosome 16p12 locus that contains the candidate intervals for FJHN and MCKD type II represents six genes, including the uromodulin gene (*UMOD*). The precise mechanism by which the uromodulin gene and its product, the Tamm-Horsfall protein, causes hyperuricemia remains unclear.

Female gout

Gout is considered a disease of men, and in most epidemiologic studies women have represented only 5% of the total gout population.³⁵ There has been a doubling of the incidence of gout in women over the past 20 years, however, with the incidence in postmenopausal women equaling that of similarly aged men.³⁶ Premenopausal levels of estrogen promote an increased fractional excretion of uric acid by the kidneys. Natural and surgical menopause are associated with increased uric acid levels, and the use of estrogen replacement therapy in postmenopausal women is associated with decreased uric acid levels.³⁷

The comparative clinical features in male and female gout patients have been examined in four small studies.³⁸ All agree that women develop gout at a later age (approximately 7 years later than men) and have more comorbidities, especially hypertension and renal insufficiency.³ Two of the studies found that women were more likely to have advanced disease at the time of presentation, as manifested by more tophi and polyarticular disease and a greater frequency of upper extremity gout involvement. Several associated characteristics are seen almost twice as frequently in female gout patients than in their male counterparts. These include diuretic use (95%), hypertension (73%), renal insufficiency (50%), and preexisting osteoarthritis (38%). The relationship to nodal osteoarthritis of the hands is interesting because there have been many clinical reports of patients in whom the initial presentation of postmenopausal gout occurred as a tophus developing in a preexisting Heberden node or Bouchard node (see Fig. 188.5).³⁸ In the rare case of gout in a premenopausal woman who is not taking a diuretic and does not have renal failure, the patient should be evaluated for the autosomally inherited causes of early-onset gout discussed in the preceding section.

Transplantation gout

Solid organ transplantation is a field of medicine that has blossomed in the 25 years since the introduction of the calcineurin inhibitor cyclosporine as an antirejection medication. Heart, kidney, and liver transplantations have improved and saved many lives, but the drug cyclosporine and its newer relative tacrolimus have also created many problems. Both drugs can cause renal dysfunction and hypertension and can dramatically reduce the kidney's ability to excrete uric acid.³⁹ Hyperuricemia develops in 75% to 80% of heart transplant recipients who routinely take cyclosporine to prevent allograft rejection.⁴⁰ The clinical course of gout associated with organ transplantation is markedly accelerated compared with the classic progression of primary gout. The stage of asymptomatic hyperuricemia lasts for 20 to 30 years in classic gout but is present for only 6 months to 4 years in cyclosporine-induced disease. Similarly, the duration of the acute intermittent gout stage is only 1 to 4 years in transplant recipients, whereas it may last 8 to 15 years in classic gout.⁴¹

Saturnine gout

Hyperuricemia and gout are well-recognized complications of chronic lead intoxication. The mechanism of lead-induced hyperuricemia is poorly understood but does appear to involve diminished uric acid excretion by the renal tubule. This form of secondary gout caused by excessive lead ingestion is referred to as *saturnine gout*. The term *saturnine* is derived from the word *saturnus*, the ancient alchemist's name for lead, which was considered to be very cold like the planet Saturn.⁴²

COMORBID DISEASES ASSOCIATED WITH HYPERURICEMIA AND GOUT

For more than a century, gout has been associated with hypertension, diabetes, obesity, cardiovascular disease, and kidney disease. In fact, the

prevalence of gout and the prevalence of these comorbid conditions have risen in parallel over the past 100 years, and they have spread from one culture to the next in a linked fashion. More recently, the dyslipidemia, obesity, and insulin resistance that make up metabolic syndrome have been directly tied to both hyperuricemia and gout.

Hypertension

Studies from the 1950s and 1960s established a close link between hypertension and both hyperuricemia and gout. There have been seven large epidemiologic studies since 2003 that have demonstrated serum urate level to be a consistent predictor of the later development of hypertension.⁴³ The Normative Aging Study showed that serum urate concentration independently predicted the development of hypertension when age-adjusted and multivariate models were used that included body mass, abdominal girth, alcohol use, serum lipid levels, plasma glucose level, and smoking status.⁴⁴ In fact, the preponderance of recent epidemiologic studies looking at the link between hypertension and hyperuricemia have concluded that a high uric acid level is an independent risk factor for the development of hypertension.

Kidney disease

Aside from the musculoskeletal system, the deleterious effect of hyperuricemia is most often manifested in the kidneys. Significant impairment of renal function was reported in up to 40% of patients with gout in studies conducted before the advent of effective urate-lowering therapies. Two large prospective studies in Japan looked at the relationship between baseline serum urate level and the eventual development of end-stage renal disease (ESRD)³⁵ or renal failure. The calculated incidence of ESRD per thousand persons was 1.2 for men without hyperuricemia and 4.6 for men with hyperuricemia. The effect was even more dramatic in women: the adjusted hazard ratio for developing ESRD due to hyperuricemia was 2.0 in men and 5.8 in women.⁴⁵

Cardiovascular disease

Hyperuricemia and gout are recognized as a significant risk factor for atherosclerotic disease in general and for coronary artery disease in particular.⁴⁶ NHANES-III showed that a serum urate level in excess of 6 mg/dL was an independent risk factor for coronary artery disease and that a serum urate level above 7 mg/dL was an independent risk factor for stroke.⁴⁷ Multiple studies have now confirmed this relationship between hyperuricemia, gout, and cardiovascular disease, although a direct causal mechanism has yet to be determined.

Metabolic syndrome

Hyperuricemia and gout are highly correlated with body mass index for both men and women. Metabolic syndrome is a constellation of disorders characterized by insulin-resistant hyperglycemia, hypertension, hypertriglyceridemia, and obesity. Although 20% to 25% of the adult population in the United States has metabolic syndrome, one study showed that 86% of gout patients met the criteria for metabolic syndrome.⁴⁸ In another recent study, nonobese individuals who developed metabolic syndrome were 10 times more likely to be hyperuricemic than a body mass index-matched cohort without metabolic syndrome.⁴³

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Management of gout and hyperuricemia

■ ROBERT TERKELTAUB

- Therapeutic strategies for gout and hyperuricemia were subjected to a systematic and formal consensus review process and recently disseminated in the 2012 American College of Rheumatology guidelines.^{1,2}
- Management strategies involve distinct but linked arms, with attention to safety and improved quality of life:
 - Antiinflammatory treatment and prophylaxis of gouty arthritis. Treatment options are designed to either prevent acute gout flares or treat active inflammation of acute and chronic gouty arthritis.
 - Urate-lowering therapy. Treatment options aim to lower serum urate levels, as well as to achieve ultimate resolution of tophi and prevent the disabling tissue consequences of urate crystal deposition. Risk management of urolithiasis is an added objective in some.
 - Treatment of identified, significant comorbid conditions in patients with gout to bring about improved overall health and added, potential serum urate lowering and fewer acute gout attacks. Direct, pharmacologic treatment of asymptomatic hyperuricemia is not yet evidence based, but other measures to lower serum urate levels are appropriate.

TREATMENT OF ACUTE GOUTY INFLAMMATION

Therapeutic targets

Acute gouty arthritis is triggered by initial activation of resident cells, such as mast cells and synovial lining cells, and driven by monocyte ingress and a continuing cycle of neutrophil ingress and intraarticular neutrophil activation.³ Current evidence-based treatment strategies rely on broad inhibition (by nonsteroidal antiinflammatory drugs [NSAIDs], corticosteroids, and colchicine) of different combinations of cell adhesion to endothelium, phagocyte chemotaxis and activation, and expression and signaling by multiple mediators, including leukotriene B₄, interleukin-1 (IL-1), IL-8, and other inflammatory cytokines.³⁻⁵

Primary treatment objectives

The principal immediate goal of therapy in patients with acute gout is rapid, safe improvement in pain and inflammation. Long-term objectives include limiting recurrences of acute gouty arthritis and inhibiting chronic gouty synovitis and its associated connective tissue destruction. Treatment of both the pain and inflammation associated with acute gout is achieved with antiinflammatory agents. Other modalities (e.g., topical ice packs, acetaminophen, and in selected circumstances, opiates) are adjunctive measures.

Choice of drug and treatment regimens

Multiple effective drug options and dosing regimens for antiinflammatory treatment can be used for acute gout^{2,6-8} (Table 189.1). Selection of the appropriate option is influenced by the patient's comorbid conditions (e.g., renal, cardiac, hepatic, or gastrointestinal [GI] disease), drug interactions, attack duration, and number and accessibility to injection of the joints involved.² The typical response of acute gout to first-line options (NSAIDs,

systemic glucocorticosteroids, colchicine) is rapid but incomplete such that only approximately 50% pain reduction is achieved by 2 to 3 days in most subjects (grade A).⁹

Nonsteroidal antiinflammatory drugs

In appropriately designed clinical trials, multiple NSAIDs (e.g., Table 189.1) have been demonstrated to be effective for acute gout.² NSAIDs are typically given in full doses for at least 3 days and then tapered until the acute gouty arthritis subsides. GI and CNS side effects often limit the use of indomethacin. The author prefers naproxen to treat acute gout,⁶ but numerous other NSAIDs are effective alternatives²; those with a relatively short half-life are preferred. Some cyclooxygenase-2 inhibitors, such as etoricoxib⁹ and celecoxib, are effective for acute gout, but dosing and cardiovascular safety remain under review, as they are for NSAIDs. High-dose aspirin and non-acetylated salicylates are not recommended.

Corticosteroids

Prednisolone (30 to 35 mg daily for 5 days) appears to be at least comparable in efficacy and tolerance to NSAIDs in the first days of acute gout treatment.^{6,7} High starting doses of systemic antiinflammatory corticosteroids are needed for acute gout (e.g., ≥0.5 mg/kg daily for oral prednisone), especially with severe polyarticular flares.^{2,6,7} Triamcinolone (60 mg intramuscularly once) or a methylprednisolone dose pack can be used as starting therapy for acute gout.² The effectiveness of intraarticular injection of a depot corticosteroid for gout involving one or two large joints has been supported by small, open studies.² Initiation of adjunctive, daily low-dose prophylactic colchicine with systemic corticosteroids can inhibit the occurrence of rebound gout flares after stopping corticosteroid therapy that may be driven by corticosteroid induction of the inflammasome constituent NLRP3.¹⁰

Adrenocorticotrophic hormone

Adrenocorticotrophic hormone (ACTH) not only induces adrenal glucocorticosteroid production but also has a distinct peripheral antiinflammatory effect via the melanocortin 3 receptor.¹¹ ACTH is an effective option for acute gout in patients without preexisting adrenal suppression, particularly for those unable to ingest anything orally.² Synthetic ACTH is preferred to reduce the risk for hypersensitivity.

Colchicine

Clinical pharmacology of colchicine and drug-drug interactions

Via uptake in the jejunum and ileum, colchicine is readily bioavailable after oral administration. The lipophilic nature of colchicine facilitates cell uptake by allowing colchicine to bind tubulin, its primary target.¹² Colchicine is predominantly eliminated by biliary and fecal excretion. Extrusion of colchicine from cells (including gut-lining cells), enterohepatic recirculation, and marked drug enrichment in bile are critical for drug elimination, with ABCB1 (P-glycoprotein multidrug resistance transporter) playing a central role (Fig. 189.1).¹² Plasma membrane ABCB1 pumps multiple classes of substrates out of cells, thereby mediating multiple drug-drug interactions that can develop even with low colchicine doses (grade A).^{12,13} Clarithromycin and cyclosporine are examples of potent ABCB1 inhibitors.⁷ Most ABCB1 inhibitors also inhibit cytochrome P450 3E4 (CYP3A4), which carries out hepatic demethylation of colchicine to inactive metabolites before hepatobiliary excretion of the colchicine.^{12,13} Colchicine neuromyopathy can develop weeks after the initiation of cyclosporine.¹² Two macrolide antibiotics, clarithromycin and erythromycin, are known to promote serious colchicine toxicity, including death.^{12,13} In contrast, another macrolide, azithromycin, inhibits ABCB1 only weakly, does not significantly increase plasma concentrations of colchicine in healthy volunteers, and

TABLE 189.1
Therapeutic options for acute gouty inflammation

Drug option	Typical regimens
COX-nonselective NSAIDs (grade A evidence for each regimen listed)	Naproxen, 750-1000 mg PO daily for 3 days, then 500-750 mg total daily for 4-7 days Sulindac, 300-400 mg daily for 7-10 days Indomethacin, 150-200 mg PO daily for 3 days, then 100 mg PO daily for 4-7 days
Off-label use: COX-2-selective NSAIDs (grade A evidence for etoricoxib, a drug not approved in many countries)	Celecoxib, 800 mg then 400 mg on day 1, followed by 400 mg bid for 7 days
Systemic corticosteroids (grade A evidence for oral prednisolone, 35 mg daily for 5-6 doses; lower evidence grades for other regimens)	Prednisone, 30-60 mg daily for 3 days, then taper by 10-15 mg/day every 3 days until discontinuation Oral prednisolone, 35 mg daily for 5 days Medrol dose pack (for less severe flares) or to initiate therapy In an NPO patient: Triamcinolone, 60 mg IM once, with additional corticosteroid treatment as needed Methylprednisolone, 100-150 mg IV for 1-2 days
Intraarticular corticosteroids (grade C evidence)	Particularly useful for flares in a single large joint Triamcinolone acetonide preparations are especially useful Dose titrated to the size of the joint
Off-label use: synthetic ACTH (grade C evidence)	25 USP units of synthetic ACTH SC for less severe flares; 40 USP units IM or IV once for more severe flares (including larger joint flares and polyarticular gout) 1-2 repeated doses of synthetic ACTH at intervals of 12 hours are often required with each of these regimens
Oral colchicine (grade A evidence for U.S. FDA-approved regimen)	In the United States: to treat an early acute gout flare: 1.2 mg once followed by 0.6 mg in 1 hour, then 12 hours later, oral low-dose colchicine at prophylaxis doses until the acute gout attack resolves Outside the United States: 0.5 mg tid for several days is the EULAR-recommended dosing regimen Oral colchicine treatment of acute gout should be avoided in those already taking a maintenance low dose of colchicine
Off-label use: IL-1 antagonism (grade C for anakinra, grade A for canakinumab)	Use of anakinra (e.g., 100 mg SC daily for 3 days) for gout is not approved by the FDA

ACTH, adrenocorticotrophic hormone; COX, cyclooxygenase; EULAR, European League Against Rheumatism; FDA, Food and Drug Administration; IL-1, interleukin-1; IM, intramuscularly; IV, intravenously; NPO, nothing by mouth; NSAID, nonsteroidal antiinflammatory drug; PO, orally; SC, subcutaneously.

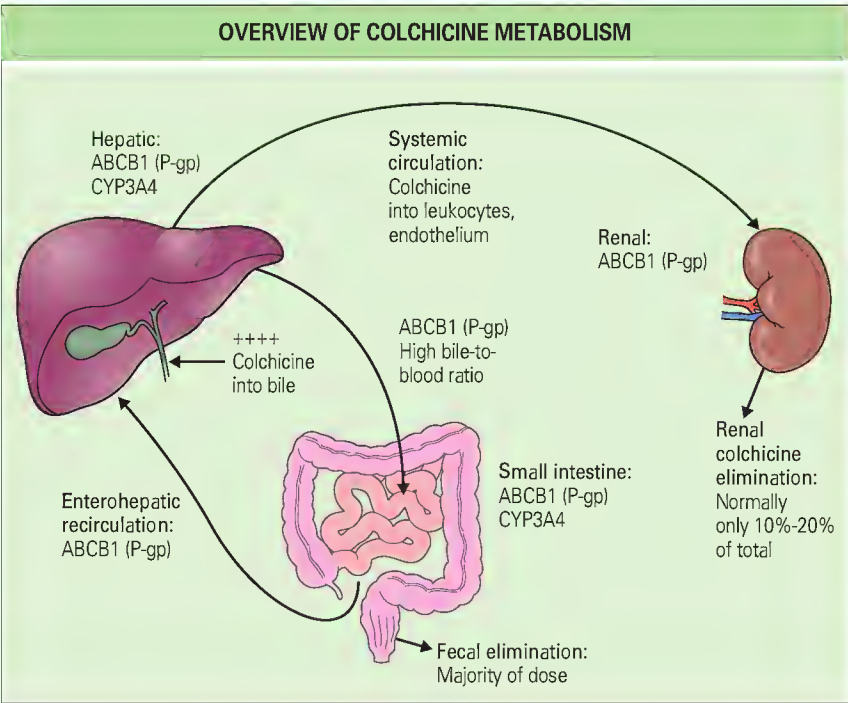


Fig. 189.1 Colchicine is readily bioavailable after oral administration via uptake in the jejunum and ileum, and the lipophilic nature of colchicine allows ready absorption by multiple cell types and binding to its primary target tubulin, which serves as a drug reservoir. Colchicine is predominantly eliminated by biliary and fecal excretion, with a major role played by extrusion of colchicine from cells mediated by the multidrug resistance transporter molecule ABCB1 (P-glycoprotein [P-gp]). Catalysis of demethylation of colchicine to inactive metabolites by enteric and hepatic cytochrome P450 3E4 (CYP3A4) and renal elimination normally play lesser but significant roles (<10%, and 10% to 20%, respectively) in colchicine metabolism. However, CYP3A4 and renal disposition of colchicine become more critical with certain drug-drug interactions that affect ABCB1 and with aging and hepatobiliary dysfunction. Importantly, colchicine undergoes hepatobiliary excretion against the bile-to-blood concentration gradient, mediated in part by ABCB1 and normally achieving at least 70:1 enrichment in bile relative to blood. Colchicine elimination driven by hepatic metabolism and intestinal excretion follows a first-order process, with enterohepatic circulation playing a substantial role. (Modified from Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum* 2009;38:411-9, with permission.)

appears to be safe to use with colchicine.¹³ Both renal disposition of colchicine and CYP3A4 metabolism are more important in patients with hepatobiliary dysfunction and potentially in those with aging (because of decreased ABCB1 expression).¹² Finally, colchicine and multiple statins have the potential to synergistically potentiate myopathy (including rhabdomyolysis).¹²

Mechanism of action

Colchicine binds tightly to unpolymerized tubulin and forms a tubulin-colchicine complex that regulates microtubule and cytoskeleton function.¹²

Binding of the tubulin-colchicine complex at the ends of microtubules physically acts on elongation of the microtubule polymer.¹² Colchicine thereby regulates cell proliferation, signal transduction, gene expression, chemotaxis, and neutrophil secretion of granule contents.¹² Colchicine acts disproportionately on highly proliferating cells (e.g., bone marrow, GI tract lining).¹² It also concentrates in neutrophils, possibly related to low ABCB1 expression.¹² Nanomolar colchicine, achievable in plasma with low daily prophylactic doses of colchicine, suppresses E-selectin redistribution in the endothelial cell plasma membrane, thereby suppressing neutrophil adhesion.¹²

Evidence basis and colchicine dosing for treatment of acute gout

Oral colchicine is believed to be more effective when given in the first 36 hours of gout flares.² European League Against Rheumatism (EULAR) consensus guidelines for treatment of acute gout with colchicine call for a maximum of three colchicine (0.5 mg) tablets per 24-hour period (grade A).¹⁴ A large, randomized, controlled multicenter trial found that a low-dose colchicine regimen of 1.2 mg followed by 0.6 mg in 1 hour (1.8 mg total, patient administered within 12 hours of onset of the acute gout attack) was equally effective and much better tolerated than higher-dose colchicine (grade A).⁸ Based on pharmacokinetics,⁸ this regimen can be followed 12 hours later by prophylactic dosing of colchicine (see later) until the acute gout attack resolves.

Side effects

GI toxicity (diarrhea, sometimes severe, nausea, and to a lesser degree, vomiting) is the most frequent adverse event with oral colchicine.^{8,12} Bone marrow depression is common with colchicine overdose, with the nadir occurring 1 week after drug initiation. Cardiac toxicity with more severe overdosing can include arrhythmia. Cardiovascular collapse can occur as well. Colchicine overdose is also hepatotoxic and can cause alopecia. Colchicine myopathy, which affects proximal more than distal muscles and is accompanied by elevated creatine kinase in the early phase and by varying neuropathy, can mimic inflammatory muscle disease. Colchicine is, at most, weakly dialyzable. Severe cases of colchicine intoxication are treated by supportive care and can be lethal.¹²

Colchicine and other antiinflammatory drugs for prophylaxis of acute gout

Limitation of the subclinical joint inflammation in gout underpins the prophylactic effect of colchicine.¹² The most common adverse event on initiation of urate-lowering therapy (ULT) is acute gout flare (grade A).^{2,15} More intense ULT regimens precipitate more acute flares early in therapy, probably because of the local inflammatory effects of urate crystal deposit remodeling. For prophylaxis of acute gout, low-dose colchicine therapy is the first choice; it is commenced 1 week before initiation of serum ULT and typically continued for 6 months (if ULT is successful within that period) or until the clinically detected tophi resolve (grades A and B).^{1,2,16,17} Low-dose NSAID therapy is a sound alternative first-line choice if NSAID risk management is appropriate, although the evidence is limited.¹⁷ Low-dose prednisone therapy should be avoided but is sometimes necessary as a last resort.² The recommended dosage of colchicine is 0.6 mg twice daily in an average-sized younger patient with preserved renal and hepatobiliary function. Specific severe drug interactions (e.g., with clarithromycin, erythromycin, or cyclosporine) should be avoided.¹³ Low-dose prophylactic colchicine dosing should be reduced by 50% in patients with a glomerular filtration rate (GFR) lower than 50 and even more so in those with end-stage kidney disease.¹²

Drugs in clinical development for the treatment and prophylaxis of gouty arthritis

IL-1 β plays a more central role than tumor necrosis factor- α in urate crystal-induced inflammation (grade B).¹⁸ In refractory cases of gouty arthritis, the off-label use of IL-1 antagonists (e.g., the soluble IL-1 receptor antagonist anakinra, 100 mg daily subcutaneously for 3 days) has shown evidence of efficacy.¹⁸ IL-1 antagonists are in advanced clinical trials for the treatment (canakinumab) and prophylaxis (rilonacept) of acute gout, but the risk-benefit ratio is uncertain at this point.²

TREATMENT OF HYPERURICEMIA IN GOUT

Nonpharmacologic measures

In certain gout patients, serum urate can be improved or normalized by measures such as substitution of an alternative antihypertensive for a thiazide, better control of hypertension, reduction of obesity, appropriate moderation of specific portions in the diet, and limited consumption of alcohol, particularly beer.¹ Dietary advice to gout patients is often first tailored to their comorbid conditions, such as diabetes, atherosclerosis, hypertension, and chronic kidney disease (CKD).¹ A low-carbohydrate, weight reduction diet tailored to treat metabolic syndrome can lower serum urate levels, but only by approximately 18% at most (grade B).¹⁹ Broadly, purine-restricted diets are typically less effective than that and largely unpalatable, and ample vegetable consumption (including vegetables with high purine content) is

a valuable health measure that is associated with lower serum urate. Decreased consumption of high-fructose corn syrup-sweetened beverages (e.g., sodas, energy drinks) has potential salutary effects on hyperuricemia.¹ In patients with advanced CKD, it has been noted that hemodialysis significantly reduces body urate stores, and gouty arthritis often quiets down clinically in hemodialysis patients. Finally, asymptomatic hyperuricemia is not yet an evidence-based indication for direct pharmacologic treatment, except for prevention of tumor lysis syndrome.

Indications for pharmacologic urate-lowering therapy for gout and drug choices

Figure 189.2 presents an algorithm for pharmacologic urate-lowering therapy (ULT) in patients with gout and highlights the indications and choices. Gout ULT is most effective when continued indefinitely so that serum urate levels remain lower than 6.0 mg/dL.¹ Patient education is critical for ULT.²⁰ Conveying to the patient early in therapy that gout is caused by excessive body stores of uric acid and that only ULT is “curative” appears to facilitate appropriate adherence to and success of ULT²⁰ (grade B). Therapy goals and the risk-benefit ratio of treatment should be considered individually.¹ ULT should not be initiated until acute gouty inflammation is under adequate antiinflammatory control, but once established, the ULT should not be interrupted during acute gout flares. First-line pharmacologic ULT consists of targeting uric acid formation by xanthine oxidase inhibition

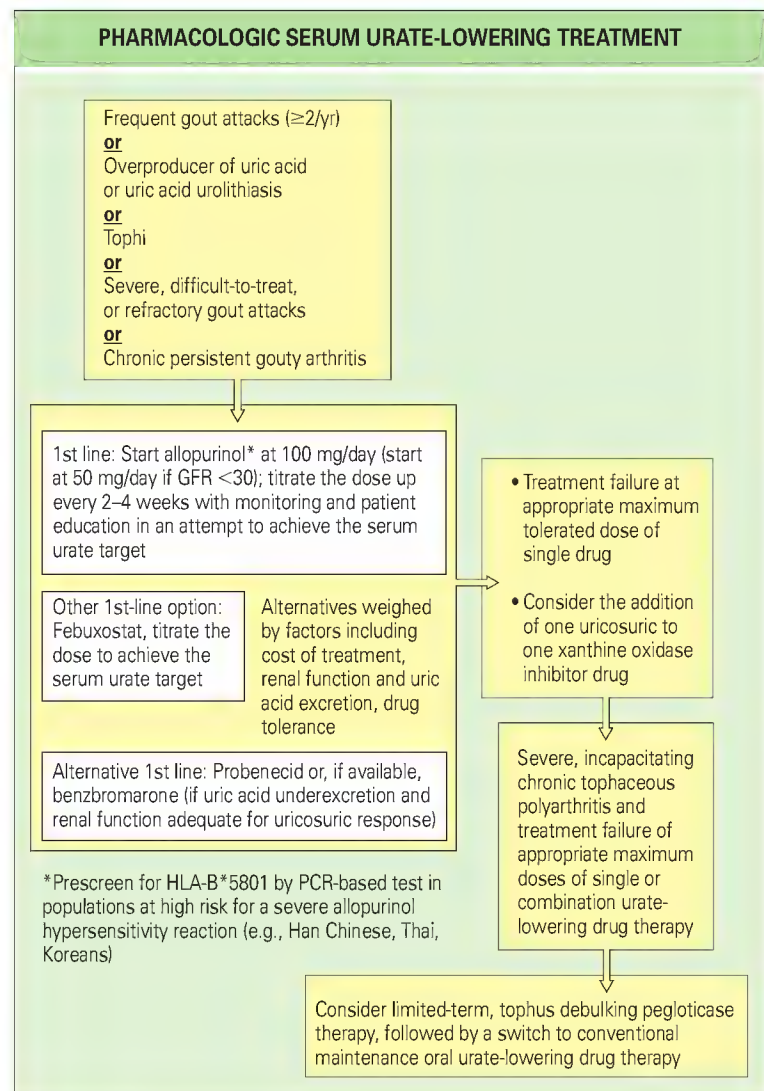


Fig. 189.2 Algorithm for pharmacologic serum urate-lowering treatment of hyperuricemia in patients with a confirmed diagnosis of gout. The algorithm, discussed in text, summarizes the first-, second-, and third-line approaches to pharmacologic urate-lowering therapy, including management of refractory hyperuricemia in difficult gout. GFR, glomerular filtration rate; PCR, polymerase chain reaction.

(XOI) with allopurinol or febuxostat^{1,15} (see Fig. 189.2). Because of large cost differences, allopurinol is often started first, with febuxostat substituted in those intolerant of allopurinol or failing maximum, appropriate doses of allopurinol despite adequate adherence to treatment. Monotherapy with a potent uricosuric is a sound alternative first-line approach in many patients (grade B),²¹ and probenecid is the most widely available drug with potent uricosuric action. Benzbromarone is a particularly potent and effective uricosuric,²¹ but hepatic safety issues have led to restrictions in availability and use of the drug, and it is not approved in the United States. Targeting the uric acid underexcretion that drives hyperuricemia in most patients can robustly decrease body urate stores.¹ However, effective urolithiasis risk management needs to be in place. Little published evidence is available on efficacy and safety of probenecid for stage 3 CKD, whereas benzbromarone remains effective for stage 3 CKD. Uricosurics should not be used in patients with a creatinine clearance of less than 30 mL/min.

Strategies for treatment-refractory hyperuricemia

Since effective XOI treatment robustly lowers total urinary uric acid excretion, addition of a uricosuric agent to patients with hyperuricemia refractory to XOI provides an additive serum urate-lowering effect (grades A and B).^{22,23} Probenecid is useful in this setting,²¹ as can be agents with less potent uricosuric effects, such as fenofibrate and losartan.¹ Fenofibrate can lower serum urate by up to 20%, an effect less potent than that of primary uricosurics but potentially useful as an adjunct in patients with hypertriglyceridemia. The uricosuric effects of losartan become maximal at 50 mg daily, but the urate lowering may be transitory, and in most patients losartan does not lower serum urate by more than 10%.

A serum urate target of less than 6 mg/dL (<360 mmol/L) is the minimum acceptable target level, with a lower level being appropriate for chronic tophaceous gouty arthritis. Beyond tophus debulking and fewer acute gout attacks, improved health-related quality of life and a reduction in functional, occupational, and social disability are ultimately achieved with effective ULT.¹ The solubility of urate in physiologic solutions is low (i.e., ≈6.7 to 7.0 mg/dL). Concordantly, current guidelines for decreasing total body urate stores, debulking and resolving tophi, reducing the ultimate frequency of gout flares, and decreasing the risk for ongoing precipitation of urate crystals support continuing (lifelong) reduction in serum urate to less than 6 mg/dL.¹ There may be salutary indirect or direct effects on renal function and blood pressure by achieving this target level in gout patients via XOI, potentially mediated by antioxidant effects or serum urate lowering.²⁴

More aggressive oral ULT to decrease serum urate to less than 4.0 mg/dL, including combining XOI and uricosuric treatment, accelerated the velocity of reducing tophus size by approximately 2 mm/mo for index tophi with mean size of 27 mm in one study²⁵ (Fig. 189.3). Achieving a serum urate level in the 0- to 4-mg/dL range is appropriate with moderate to severe chronic tophaceous gouty arthritis.¹ To do so, a more intensive and expensive “biologic” strategy, appropriate only for carefully selected, more difficult cases of severe or treatment-refractory chronic tophaceous arthritis, is to use intravenous pegloticase, a recombinant pegylated uricase that directly degrades urate (grade A).²⁵ This approach has the potential to rapidly decrease the miscible body urate pool size and resolve tophi in months rather than years with most XOI or uricosuric monotherapy.

Allopurinol

Clinical pharmacology and mechanism of action

Allopurinol undergoes hepatic conversion to the active metabolite oxypurinol, whose half-life is normally 24 hours.²⁶ This allows allopurinol, at doses of up to 300 mg/day, to be given once daily. Because of primary renal clearance of oxypurinol, its half-life rises substantially in those with renal impairment. Allopurinol and oxypurinol lower serum urate not only by inhibiting xanthine oxidase but also by competing for phosphoribosylpyrophosphate in the salvage pathway and by the suppressive effects of drug nucleotides on amidotransferase activity, the rate-limiting step in purine synthesis. Allopurinol nonselectively interferes with pyrimidine metabolism.

Side effects

Lack of selectivity of allopurinol contributes to a wide range of potential toxicities, with significant drug intolerance developing in about 5% to 10%, including dose-dependent GI side effects such as nausea or diarrhea, elevated liver transaminases in approximately 3% to 5%, and variable CNS side effects.²⁶ Severe allopurinol-associated hepatic disease (granulomatous hepatitis, cholestatic jaundice, and severe liver necrosis) can occur, but this

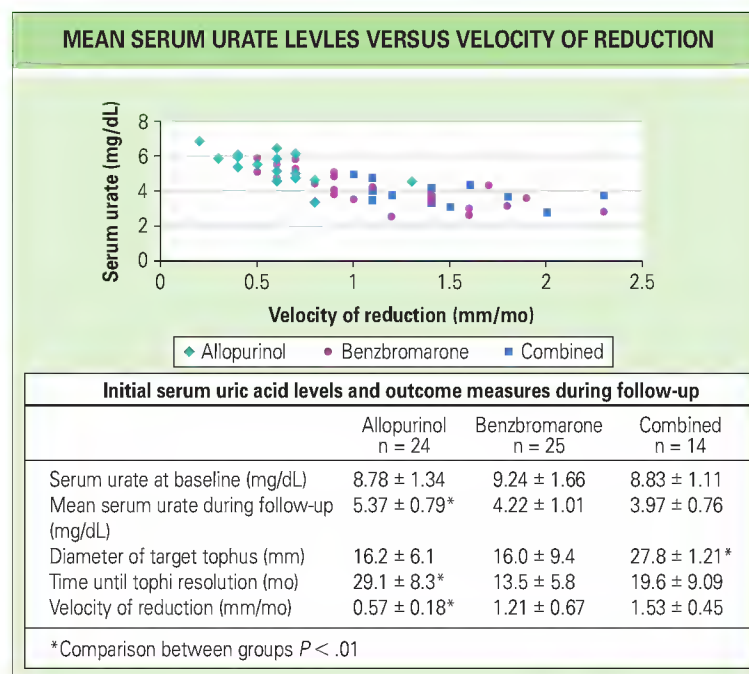


Fig. 189.3 Mean serum urate levels and the velocity of reduction of tophi have a linear relationship, and the rate of acceleration of tophus debulking increases to greater than 2 mm/mo when serum urate is lowered below 4 mg/dL ($r = -.62$, $r^2 = -.48$; $P < .05$). Subjects were treated with allopurinol, the potent uricosuric benzbromarone (a drug not available in the United States), or a combination of the two. (From Perez-Ruiz F, Calabozo M, Pijoan JL, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002;7:56-60. Reprinted with permission.)

is rare.²⁶ Allopurinol induces rash, typically pruritic and maculopapular, in about 2% of patients. Pruritus alone is a classic premonitory sign of rash and by itself is a valuable indication for a previously informed patient to immediately stop taking allopurinol.²⁶ Bone marrow suppression is uncommon with allopurinol but may occur at higher doses. Allopurinol has major drug interactions with azathioprine, 6-mercaptopurine, and theophylline, whose metabolism is mediated by xanthine oxidase. Patients taking warfarin need careful observation of their anticoagulation status. In addition, ampicillin and amoxicillin trigger a rash in at least 20% of allopurinol-treated patients. Appropriate clinical practice is to periodically monitor the liver panel, chemistry profile, and eosinophil and other blood counts in conjunction with serum urate levels before and after allopurinol is initiated, especially in patients with CKD.

Severe allopurinol hypersensitivity reaction: clinical features and risk management

The constellation and clinical reporting criteria for major allopurinol hypersensitivity (AHS) reactions include severe cutaneous adverse reactions to allopurinol (such as Stevens-Johnson syndrome or toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic symptoms (DRESS) (which can include severe multiorgan disease and combinations of vasculitis, various rashes, and hepatic and renal dysfunction, with approximately 20% to 25% mortality [grade B]²⁷) (Box 189.1). Risk factors (Table 189.2) include HLA-B*5801,²⁸ the starting dose of allopurinol, CKD,²⁷ and concurrent use of thiazide diuretics, which may act partly by increasing renal oxypurinol reabsorption.

The highest risk for AHS occurs in the first 60 days after initiation of allopurinol.²⁷ The direct toxic effects of accumulation of oxypurinol and T-cell activation responses to allopurinol and oxypurinol appear to contribute to the pathophysiology of AHS.²⁶ Recent studies show no association between the maintenance dose of allopurinol and the likelihood of AHS developing,²⁷ and maintenance doses of allopurinol below 300 mg daily do not achieve the serum urate target level in the majority of subjects.^{1,15} In contrast, adjusting the starting dose of allopurinol so that it is low (especially in those with renal impairment) and steadily titrating allopurinol

BOX 189.1 MAJOR RISK FACTORS AND PROPOSED CRITERIA* FOR ALLOPURINOL HYPERSENSITIVITY SYNDROME

Major risk factors

Starting dose of allopurinol higher than 1.5 (measured as the starting dose of allopurinol in milligrams per estimated GFR [mL/min]; e.g., a starting dose of allopurinol of 100 mg daily with an estimated GFR of 66 = 1.5)
Chronic kidney disease
Concurrent thiazide use
HLA-B*5801

General recommendations

1. Start allopurinol at no more than 100 mg daily in those with a GFR of 60 or higher, and increase by 100 mg every 2 to 4 weeks, along with patient education and monitoring, in an attempt to achieve the serum urate target
2. Decrease the starting dose to no more than 50 mg daily with an EGFR of 30 or less, and increase by 50 mg every 2 to 4 weeks in an attempt to achieve the serum urate target
3. The maximum FDA-approved maintenance dose is 800 mg daily
4. Progressively decrease the maximum allopurinol dose with progressively worse chronic kidney disease, but 300 mg daily can be exceeded with patient education and monitoring

Major criteria

1. Rash (e.g., diffuse maculopapular, exfoliative, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). Some patients have more than one type of rash
2. Worsening renal impairment
3. Acute hepatocellular injury

Minor criteria

1. Fever
2. Eosinophilia
3. Leukocytosis

Criteria fulfillment

At least two major criteria or one major and at least one minor criteria or Rash only and/or more minor criteria
Renal only and/or more minor criteria

*Criteria reprinted with permission from Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheum* 2012;64:2529-36.
EGFR, estimated GFR; FDA, Food and Drug Administration; GFR, glomerular filtration rate.

TABLE 189.2
HLA-B*5801 and risk for allopurinol hypersensitivity syndrome

Population: HLA-B*5801 prevalence	Odds ratio for AHS with HLA-B*5801
Han Chinese: 9%	≈580:1
Koreans: 12.2%	≈380:1 with stage 3–5 chronic kidney disease
Thai: >6%	≈350:1
Whites: 1%–3% in most	Up to ≈80:1 (lower negative predictive value)

Meta-analysis: HLA-B*5801 and risk for AHS*

Matched control studies: OR = 96.60; 95% CI, 24.49–381.00; *P* < .001
Population control studies: OR = 79.28; 95% CI, 41.51–151.35; *P* < .001
Subgroup analysis for Asian and non-Asian population found increased OR

Recommendations by the author

1. HLA-B*5801 screening is appropriate for AHS high-risk/high-HLA-B*5801 prevalence groups (particularly Han Chinese, Thai, Koreans) by rapid, inexpensive PCR-based methodology (followed by PCR sequencing of inconclusive results, which typically occur in ≈10% of PCR screening tests for HLA-B*5801)
2. Populations at high risk for AHS continue to be defined
3. Those with a known positive HLA-B*5801 test should not receive allopurinol

*Samkrua R, Eichman EE, Saokaew S, Lahitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet*. 2011;12:118.
AHS, allopurinol hypersensitivity syndrome; CI, confidence interval; OR, odds ratio; PCR, polymerase chain reaction.

upward are core aspects of using the drug both safely and effectively (see Box 189.1).¹

The incidence of AHS is approximately 0.1% to 0.4%, apparently highest in Southeast Asian subpopulations. HLA-B*5801 is most common in Southeast and East Asians (up to ≈8%) and those of African ancestry (up to ≈4%), but it is only about 2% in most white individuals. The HLA-B*5801-associated hazard ratio for AHS is several hundred to one in Han Chinese and Thai, irrespective of renal function, and in Koreans with an estimated GFR of less than 60 (stage 3 CKD or worse).²⁸ The HLA-B*5801 hazard ratio for AHS is approximately 80:1 in white people studied to date, but the predictive value of HLA-B*5801 is substantially less in whites than in Southeast Asians.²⁸ The author recommends prescreening subpopulations at high risk for severe AHS via rapid and relatively inexpensive single polymerase chain reaction–based testing for HLA-B*5801 as an appropriate measure to consider^{11,28} (see Table 189.2).

Allopurinol dosing, including dosing in those with chronic kidney disease

Clinical trial data indicate that allopurinol (300 mg daily) lowers serum urate by about 33% in populations of gout patients in which about 25% to 30% have tophi on physical examination and serum urate is approximately 9.5 to 10 mg/dL, with largely intact renal function.¹⁵ Daily doses of allopurinol needed to normalize serum urate in the average patient are close to 400 mg (grade A).²⁹ However, allopurinol is frequently underdosed in clinical practice, particularly in those with CKD (i.e., the vast majority of allopurinol prescriptions are for ≤300 mg daily). Previous maintenance dosing guidelines for allopurinol in patients with CKD (calibrated for their estimated GFR) are not evidence based, fail to adequately treat hyperuricemia, and also fail to prevent many cases of AHS.²⁹

In “start low, go slow” dosing of allopurinol in patients with normal renal function, a starting dose of allopurinol of 100 mg daily is used in the average patient (in accordance with Food and Drug Administration [FDA] and rheumatology society guidelines).^{1,27} With a GFR lower than 30 mL/min, the allopurinol starting dose is reduced so that it is no higher than 50 mg/day.²⁷ As long as the drug is well tolerated, the author titrates the maintenance dose upward by 100 mg daily (with normal renal function, but only by 50 mg daily in those with a GFR <30) every 2 to 4 weeks after starting allopurinol²⁹ (see Fig. 189.2). This is done until the serum urate target level or an appropriate maximum dose of allopurinol is reached. Allopurinol has been approved by the FDA at a maximum dose of 800 mg daily. The author, in accordance with current guidelines,^{1,14} titrates allopurinol above the previous renal dosing adjusted recommendations and increases the dose to above 300 mg daily even with CKD, a strategy often effective in achieving the serum urate target level.²⁹

The “start low, go slow” recommendation for dosing of allopurinol can help reduce gout attacks in early ULT. Patient education and monitoring (e.g., serum urate level, liver function tests) include instructions to stop taking allopurinol immediately if pruritus or rash develops. However, long-term safety data for allopurinol dosages higher than 300 mg daily are sparse. Reduced maximum allopurinol doses in patients with CKD are strongly supported by retrospective analysis of renal function–adjusted dosing and allopurinol toxicities, in which adverse events increased with dosages higher than 400 mg/day and particularly so at higher than 600 mg/day calibrated to a creatinine clearance of 100 mL/min (grade B).³⁰

At doses of 300 mg daily or less, allopurinol is given once daily in the morning. Above 300 mg daily, the drug is divided into two daily doses to improve GI tolerance. Since adherence to allopurinol therapy is often poor in clinical practice (grade B),³¹ pill counts or measurement of serum oxypurinol levels can be helpful to confirm suspected nonadherence. Particularly with CKD, oxypurinol levels may need to be above the average therapeutic range to achieve adequate lowering of serum levels (grade B).³²

Febuxostat

Febuxostat is a selective inhibitor of xanthine oxidase that occupies the access channel to the molybdenum-pterin active site of the enzyme.³³ Unlike allopurinol and oxypurinol, febuxostat does not have a purinelike backbone (Fig. 189.4). Furthermore, febuxostat, unlike allopurinol, is metabolized primarily by oxidation and glucuronidation in the liver, and renal elimination plays a minor role in febuxostat pharmacokinetics. Febuxostat, unlike

COMPARISON OF ALLOPURINOL, OXYPURINOL, PURINE BASE, AND FEBUXOSTAT STRUCTURES

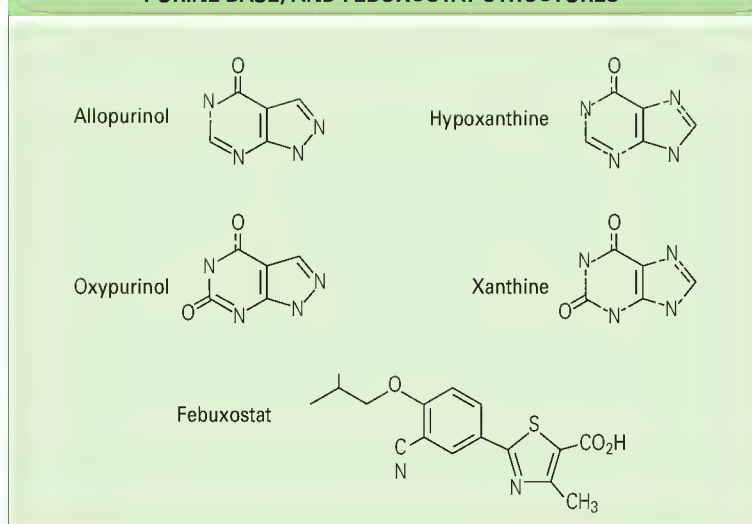


Fig. 189.4 The purine base hypoxanthine and subsequently xanthine (both pictured here) are oxidized by xanthine oxidase in the chemical reactions that generate uric acid. Xanthine oxidase is inhibited by allopurinol and its major, long-lived active metabolite oxypurinol (both pictured here). Oxypurinol has a half-life much longer than that of allopurinol (up to 24 hours in subjects with normal renal function; longer with renal impairment). Febuxostat (pictured) is a xanthine oxidase inhibitor that unlike allopurinol and oxypurinol, does not have a purinelike backbone.

allopurinol, does not affect pyrimidine metabolism and is not reincorporated into nucleotides.

Febuxostat is labeled in the United States for use at 40 mg once daily, and if serum urate levels do not become normalized after at least 2 weeks of therapy, the dose is increased to 80 mg once daily. In Europe and many other countries, febuxostat is approved at doses of up to 120 mg once daily. Febuxostat has been analyzed in randomized, large clinical trials in which a maximum dose of 300 mg of allopurinol was used as a comparator.^{1,15} Overall, both 80 and 120 mg febuxostat achieved the serum urate target level of less than 6 mg/dL more often than allopurinol, 300 mg daily, did.¹⁴ The results of serum urate lowering were comparable overall for allopurinol, 300 mg daily, and febuxostat, 40 mg daily, in those with normal renal function. In subjects with stage 2 to 3 CKD, 80 mg febuxostat daily achieved a serum urate target level of less than 6 mg/dL approximately twice as frequently as did renally dose-adjusted allopurinol (200 to 300 mg daily), and 40 mg febuxostat was superior to renally dose-adjusted allopurinol (grade A).³⁴ Adverse effects of febuxostat include rash in less than 2% and elevation of hepatic enzymes, diarrhea, and dizziness in small proportions of treated patients,^{15,34} but there does not appear to be cross-reactivity with allopurinol. Via XO1 by febuxostat, there is a potential for major drug interactions with azathioprine and 6-mercaptopurine.

Outcomes with febuxostat

At 1 year, gout flare rates declined comparably in patients treated with allopurinol, 300 mg daily, and febuxostat, 80 to 120 mg daily.¹⁵ In a small open-label extension study of patients with tophi who kept taking febuxostat, about half achieved elimination of the tophi by 2 years and more than two thirds by 5 years (grade B).³⁵

Probenecid

Mechanism of action

Primary uricosurics such as probenecid, as well as certain other drugs with less potent uricosuric activity (e.g., losartan), inhibit the urate anion exchanger SLC22A12, which is localized at the apical (brush border) membrane of the renal proximal tubule epithelial cell.³⁶ Probenecid also inhibits voltage-dependent urate anion reabsorption into the peritubular interstitium by SLC2A9 at the proximal renal tubular epithelial cell basolateral membrane.³⁷

Dosing recommendations and side effects

Probenecid is started at 250 mg orally twice daily and titrated up to 1000 mg twice daily in most patients and occasionally up to 3 g daily if

tolerated. The risk for urolithiasis with potent uricosuric monotherapy such as probenecid and benzbromarone can be 9% to 11%. All patients should be able to adequately hydrate themselves and increase oral hydration, particularly during early treatment. Inhibition of uric acid urolithiasis by urine alkalinization adds complexity to the treatment regimen. Uricosuric risk management requires 24-hour urine uric acid assays to rule out overproduction of uric acid,¹ which along with urolithiasis, is a contraindication to such monotherapy. Acidic urine pH is a major risk factor for urolithiasis in patients with gout, as is urine-undissociated uric acid concentrations higher than 20 mg/dL (roughly equivalent to >40 mg/dL total uric acid in acidic urine) before or while receiving uricosuric therapy (grade B).³⁸ Probenecid modifies the renal clearance of methotrexate, penicillins and cephalosporins, salicylates, indomethacin, ketorolac, heparin, zidovudine, nitrofurantoin, and certain other drugs. Low-dose acetylsalicylic acid does not appear to robustly block the antihyperuricemic action of probenecid.

The uricase pegloticase for refractory hyperuricemia in patients with severe, chronic gout

Mechanism of action

Uricase is the final catalyst of purine degradation in nonprimate mammals and lower primates, but uricase expression was lost in humans and higher primates in evolution. Uricases directly degrade relatively insoluble uric acid by catalyzing its conversion to highly soluble allantoin (Fig. 189.5) (grade A).²⁵ Although uricases generate 1 mol of the oxidant hydrogen peroxide for each mole of uric acid degraded (see Fig. 189.5), erythrocyte and plasma antioxidant defenses normally prevent plasma oxidative stress³⁹ and associated methemoglobinemia and hemolysis.

Pegloticase for refractory hyperuricemia of gout

Pegylation of the recombinant porcine-baboon uricase pegloticase results in a circulating half-life of days to weeks and decreases but does not eliminate immunogenicity.²⁵ Intravenous administration of pegloticase consistently produces a marked initial reduction in serum urate, but serum urate begins to increase over a several month period in a substantial fraction of patients.²⁵ Preinfusion of an antihistamine, acetaminophen, and a corticosteroid such as hydrocortisone (200 mg) is used to decrease infusion reactions to pegloticase.²⁵ In phase 3 studies of particularly severe gout (≈70% with visible tophi), intravenous pegloticase (8 mg every 2 weeks) lowered serum urate levels to less than 6 mg/dL in approximately 42% of subjects by 6 months.²⁵ Significantly, such treatment promoted complete resolution of one or more tophi in 20% of patients by 13 weeks and in more than 40% by 25 weeks.²⁵

Side effects

Even with the use of gout attack prophylaxis, acute gout flares are seen in up to 80% of pegloticase-treated patients in the first few months of treatment, with flares tapering off later.²⁴ Moderate to severe infusion reactions were common (8% to 11%) in phase 3 trials of pegloticase infusion.²⁵ Flushing, urticaria, and hypotension occurred in some and anaphylaxis in approximately 2%.²⁵ Pegloticase infusion reactions can also include severe muscle pain or cramping, driven by undefined mechanisms. Glucose-6-phosphate dehydrogenase (G6PD) deficiency should be screened for before use of pegloticase since uricases can induce methemoglobinemia or hemolysis, which is linked to G6PD deficiency in some but not all affected subjects. Caution with pegloticase is prudent in patients with congestive heart failure.

Antibodies to pegloticase

Antibodies to pegloticase frequently emerge as treatment evolves over the first few months.²⁵ For pegloticase these include IgM and IgG antibodies, which do not directly neutralize uricase enzymatic activity but adversely alter its pharmacokinetics and pharmacodynamics.²⁵ Such antibodies, seen in elevated titer in the majority of nonresponders but in few responders, are associated with infusion reactions.²⁵ Importantly, loss of the serum urate normalization response (i.e., below 6 mg/dL) to pegloticase on one or more occasions indicates that the drug treatment course should be stopped; about 79% of infusion reactions in phase 3 studies occurred after the serum urate normalization response was lost.²⁵ To avoid masking loss of pegloticase ULT activity, potent oral ULT must be stopped in those taking pegloticase.

Acknowledgements

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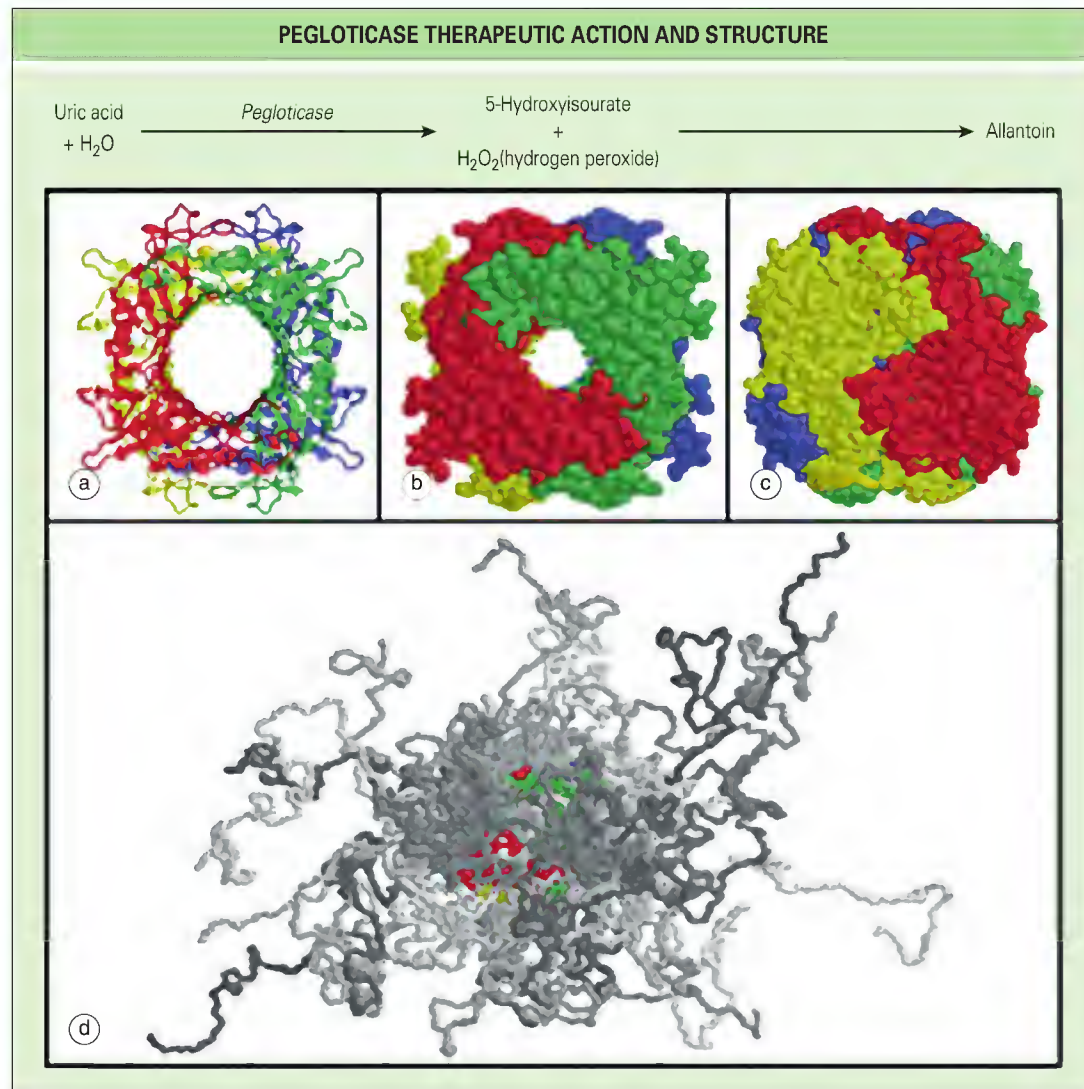


Fig. 189.5 (Top) Uricases such as pegloticase oxidize sparingly soluble uric acid to an intermediate degraded to highly soluble allantoin, which is more readily excreted in urine. This chemical reaction generates 1 mol of hydrogen peroxide per mole of uric acid degraded. (Bottom) The uricase tetramer structure is modeled in panels a to c. The purified recombinant porcine-baboon uricase pegloticase is modified by covalent attachment of 9 ± 1 strands of methoxy-polyethylene glycol per enzyme subunit, as depicted in panel d. Pegloticase contains 36 strands of 10-kDa polyethylene glycol (PEG) per uricase tetramer. This measure prolongs the enzyme's half-life and reduces, but does not eliminate immunogenicity. (a) Cartoon model of the uricase tetramer based on the crystal structure of *Aspergillus flavus* uricase. Each subunit is shown in a different color (red, blue, green, or yellow). (b) Space-filling model of the *A. flavus* uricase tetramer showing the tunnel. (c) Space-filling model of the *A. flavus* uricase tetramer rotated around the vertical axis so that the tunnel is not visible. (d) The structures of the PEG strands (shown in various shades of gray) were generated with a computer program. The scale of panel d is about half that of panels a to c. (From Sherman MR, Saifer MG, Perez-Ruiz F. PEG-uricase in the management of treatment-resistant gout and hyperuricemia. *Adv Drug Deliv Rev* 2008;60:59-68. Reprinted with permission.)

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Calcium pyrophosphate crystal-associated arthropathy

■ ABHISHEK ABHISHEK ■ MICHAEL DOHERTY

- Calcium pyrophosphate (CPP) crystal-associated arthropathy is characterized by locomotor conditions associated with CPP crystal deposition.
- Sporadic, familial, and metabolic disease-associated forms are recognized.
- It predominantly affects the elderly.
- Clinical findings include the following:
 - Acute, self-limited synovitis, which is termed acute CPP crystal arthritis (formerly “pseudogout”)
 - Chronic arthropathy, which shows an association and overlap with osteoarthritis
 - Chronic CPP crystal-associated inflammatory arthritis
- Target joints include the knees, wrists, shoulders, and hips.

HISTORY AND NOMENCLATURE

Adams (1857) is credited with the first description of articular cartilage calcification (chondrocalcinosis [CC]) in pathologic specimens.¹ With the advent of radiography, it became apparent that CC is common and occurs alone or in association with arthritis. Mandl (1927) emphasized the clinical and pathologic diversity of CC at the knee and distinguished primary (asymptomatic, bilateral, no cartilage damage) from secondary CC (symptomatic, localized, often posttraumatic with cartilage fibrillation). In 1957, Sitaj and Zitnan used CC as a diagnostic feature for arthritis in five Czech families and coined the term *chondrocalcinosis polyarticularis*. The observation that CC often preceded the development of radiographic damage in these families reinforced previous contentions that CC causes arthritis. Undoubtedly, a major milestone occurred in 1962 when McCarty and colleagues discovered nonurate crystals, identified by x-ray diffraction as calcium pyrophosphate (CPP) dihydrate ($\text{Ca}_2\text{P}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$), in the knee fluid of patients with acute synovitis and CC. The clinical similarity to gout prompted the term *pseudogout* for this new “crystal-induced arthropathy.”² Cadaveric studies subsequently established CPP as the most common, but not exclusive cause of CC, which resulted in the term CC often being used synonymously with CPP crystal deposition (CPPD). The perspective of CPP crystals as primary, causal agents in joint disease was readily supported by the demonstration of CPP crystals in patients with acute arthritis, *in vitro* evidence that CPP crystals are potent inflammatory agents, and induction of synovitis by injection of CPP crystals into normal joints. The finding of metabolic disease associations and various forms of familial predisposition reinforced the analogy to gout. Consequently, CPP crystal-associated arthropathy was separated into hereditary, metabolic disease-associated, and sporadic/idiopathic forms.

Following the initial descriptions of *pseudogout*, a variety of other clinical manifestations of CPPD were reported. Many appeared to mimic other forms of arthritis, thus encouraging the proliferation of numerous “pseudo” syndromes and a complex clinical classification: “pseudogout” (type A), “pseudo-rheumatoid arthritis” (type B), “pseudo-osteoarthritis” (with acute attacks, type C; without inflammation, type D), “lathanic or asymptomatic” (type E), and “pseudoneuropathic” (type F), to which other forms were added later.³ In an attempt to simplify matters, *calcium pyrophosphate dihydrate crystal deposition disease* (to incorporate all instances of CPP crystal deposition) and *pyrophosphate arthropathy* (for cases with both structural changes of osteoarthritis [OA], e.g., cartilage loss, osteophytes, and cysts,

and intraarticular CPP crystal deposition) were used. Recently, the European League Against Rheumatism (EULAR) developed a simplified terminology for CPP crystal deposition⁴:

- CPP crystals: the simplified term for calcium pyrophosphate dihydrate crystals (similar to “sodium urate” for monosodium urate [MSU] monohydrate crystals)
- CPPD: the umbrella term for all instances of occurrence of CPP crystals
- CC: cartilage calcification, identified by imaging or histologic examination—mainly but not always caused by CPPD
- Clinical presentations associated with CPPD:
 - Asymptomatic CPPD: no apparent clinical consequences
 - Acute CPP crystal arthritis: acute self-limited synovitis (replaces “pseudogout”)
 - OA with CPPD: CPPD in a joint that also shows changes of OA
 - Chronic CPP crystal inflammatory arthritis: chronic inflammatory arthritis associated with CPPD

EPIDEMIOLOGY

Prevalence

Data on the prevalence of CC are largely confined to the knees, wrists, and hips.⁵⁻¹⁰ CC is strongly associated with age, the prevalence being low in those younger than 50 years, but it rises from 10% to 15% in those aged 65 to 75 years to 30% to 60% in those older than 85 years. Previous reports suggested a female preponderance. This may be due to confounding by age and OA, and the age-specific prevalence does not differ between men and women.⁶⁻⁸ CC is reported in most countries and racial groups but appears to be less common in the Chinese and possibly in people from the Middle East.^{10,11} A community-based study of the prevalence of knee OA with CPPD gave an estimate of 2.4% (age, sex, and knee pain standardized for Nottingham, United Kingdom, residents older than 40 years).⁷

Predisposing factors

Age

Age is a major predisposing factor but the precise mechanism is unknown. Although overall levels of inorganic synovial fluid pyrophosphate (PPi) from normal knees does not increase with age, chondrocytes from older individuals secrete more PPi than do those from younger individuals on stimulation by transforming growth factor- β (TGF- β),¹² and several key enzymes and transport proteins involved in PPi metabolism and transport are upregulated in the elderly, thus suggesting that increased tissue levels of PPi may have a role. Age-related changes in cartilage matrix may also contribute.

Heredity

Several reports indicate increased familial risk, as well as ethnic variation in occurrence, both of which support a genetic predisposition.¹³⁻¹⁸ The pattern of inheritance of familial CC varies, although autosomal dominance is usual. Two familial phenotypes have been emphasized:

- Early onset (3rd to 4th decade): florid polyarticular CC and variable severity of arthropathy ranging from mild to destructive
- Late onset (6th to 7th decade): oligoarticular CC mainly confined to the knees and arthritis resembling sporadic OA with CPPD

The latter may be more common than recognized. The late onset of disease expression and geographic dispersal of families pose difficulties in this

respect. Recombination mapping in British, French, and Argentinian families with CPPD identified the CC gene 2 (CCAL2) on chromosome 5p15.¹⁹ This was subsequently identified as the ANKH (ankylosis human) gene. The other reported locus (CCAL1) in one American family with premature OA and CPPD is on chromosome 8q.²⁰ No specific gene has been identified at the CCAL1 locus, which spans a genetic interval of 30 cM (physical distance of 25 Mbp). A case-control study suggested that the -4 bp G-to-A transition in 5' untranslated region of ANKH that upregulates its expression is associated with apparently sporadic CC.²¹ However, a larger community-based sibling study suggested that there is no significant heritable contribution to apparently sporadic CC and to OA with CPPD.²² Thus, although hereditary CPPD exists, most patients have sporadic disease.

Association with metabolic diseases

Numerous metabolic disease associations have been suggested, but many reflect a chance concurrence of common age-related conditions, as suggested by negative results from controlled studies looking for previously reported associations with diabetes, hypothyroidism, uremia, and Paget disease.²³⁻²⁵ The strongest evidence for association relates to hyperparathyroidism, hemochromatosis, hypomagnesemia (as a result of renal loss, e.g., the Gitelman variant of Bartter syndrome, or gastrointestinal loss, e.g., short bowel syndrome, intestinal failure), and hypophosphatasia, which associate with both CC and acute CPP crystal arthritis.²³⁻²⁶ However, for rarer metabolic conditions, such as Wilson disease, evidence is necessarily limited to the occurrence of premature CC in just a few cases.²³ Other metabolic diseases, such as ochronosis and acromegaly, rarely associate with CC and acute CPP crystal arthritis, whereas familial hypocalciuric hypercalcemia does associate with CC. Hemochromatosis is the only metabolic disease that causes structural arthropathy with CPPD. CC is reported to be more frequent in young H63D homozygotes (<65 years) and old H63D/C282Y compound heterozygotes (>65 years) than in C282Y homozygotes of the high ferritin (HFE) gene,²⁷ thus implying variable penetrance of HFE mutations or suggesting that factors other than iron overload may be responsible.

Associations with metabolic diseases are explained through putative effects on PPI metabolism extrapolated largely from *in vitro* data.^{28,29} Mechanisms other than effects on PPI metabolism may also be operative. Bone and cartilage changes may be present, and CPPD may be mediated via alterations in cartilage matrix. Suggested mechanisms include the following:

- Reduced breakdown of PPI by tissue nonspecific alkaline phosphatase (TNAP) as a result of
 - Reduced levels of TNAP (hypophosphatasia)
 - Presence of inhibitory ions (calcium, iron, or copper in hyperparathyroidism, hemochromatosis, or Wilson disease, respectively)
 - Impaired complexing of PPI and Mg (hypomagnesemia)
- Enhanced nucleation of CPP crystals by increased iron (hemochromatosis) or copper (Wilson disease)
- Increased calcium concentration (hyperparathyroidism)
- Increased PPI production through stimulation of adenylate cyclase by parathyroid hormone (hyperparathyroidism)

ASSOCIATION WITH OSTEOARTHRITIS AND JOINT INSULT

The relationship between CPPD and OA remains unclear. The strong overlap with OA has led many to consider OA with CPPD to be a "subset" of OA itself. The dose-response relationship between the concentration of CPP crystals in knee synovial fluid and the severity of radiographic OA (Fig. 190.1) also supports this view.³⁰ However, this relationship is complex inasmuch as CPPD and OA are both associated with increasing age, which could be a confounding factor, and each can occur without the other. Nevertheless, there is convincing evidence for a strong association between OA and CC at the knee, wrist, and metacarpophalangeal (MCP) joints.^{7,31} A U.K. study confirmed an increased rate of radiographic OA in those with CC (age-sex-adjusted odds ratio [OR] of 2.1 at the patellofemoral joint and 2.0 at the tibiofemoral joint).⁷ This appeared to operate principally through an association with osteophytosis rather than joint space narrowing. Such observations have prompted the hypothesis that CPPD in the context of OA may act as a marker for individuals with a "hypertrophic" and thus potentially reparative tissue response to joint injury. That this may be a generalized skeletal response with a predisposition to both osteophyte and enthesophyte formation is suggested by small uncontrolled case

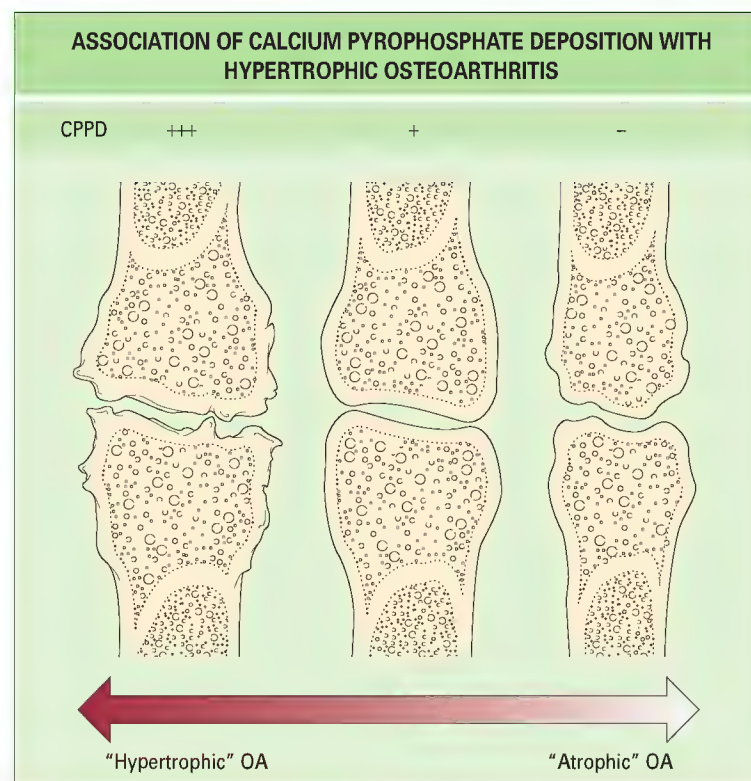


Fig. 190.1 Association of calcium pyrophosphate deposition with hypertrophic osteoarthritis.

series in which a higher than expected concordance of CC and vertebral hyperostosis is reported.³² The association between CC and OA may be joint specific. For example, a community-based study suggested that hip OA does not associate with CC at knee, hip, or symphysis pubis whereas knee OA does.⁸ Basic calcium phosphate (BCP) and CPP crystals frequently coexist in the same joint (see Chapter 191), and cartilage mineralization as a result of deposition of both CPP and BCP crystals ("mixed crystal deposition") in varying proportions is common in end-stage OA. Indeed, BCP crystals, particularly apatite, are universal in end-stage OA, whereas CPP crystals were present in 18% of knee joints and 10% of hip joints analyzed.^{33,34}

Several observations support a relationship between preceding joint insult and the subsequent development of CC, for example, the high frequency of CC (often localized, premature) in knees that have undergone surgery; the frequency of CPPD in lumbar disk fibrocartilage removed at revision surgery; and reports of localized OA with CPPD as a late complication of juvenile chronic arthritis, joint instability, or trauma.³⁵ Similarly, constitutional varus malalignment of the knee in early adult life predisposes to subsequent knee CC.³⁶ Controlled radiographic and synovial fluid surveys suggest an inverse correlation between CPPD and rheumatoid arthritis (RA).³⁷

Mechanism

The mechanisms that link CPPD and osteophyte formation remain speculative but may include shared chemical or mechanical predisposing factors. For example, TGF- β stimulates osteophyte formation and also enhances elaboration of PPI by hypertrophic chondrocytes, thus predisposing to pericellular CPP crystal formation.³⁸ The occurrence of atypical osteoarthritic radiographic features in patients with coexistent disease further suggests that the primary association of CPPD is with the hypertrophic tissue response or OA. The "amplification loop" hypothesis may explain the variable interrelationship between OA and CPPD (Fig. 190.2). This hypothesis suggests that CPPD may be enhanced by the tissue changes that accompany OA and that once formed, the CPP crystals hasten further joint damage via inflammatory and mechanical effects.³⁵

The characteristic distribution of joints with structural changes in patients with OA and CPPD versus those who have OA alone remains unexplained. Age and gender, however, could be important confounders in that the prevalence of both OA at different joint sites and CPPD varies markedly according to these factors. The glenohumeral joint, for example,

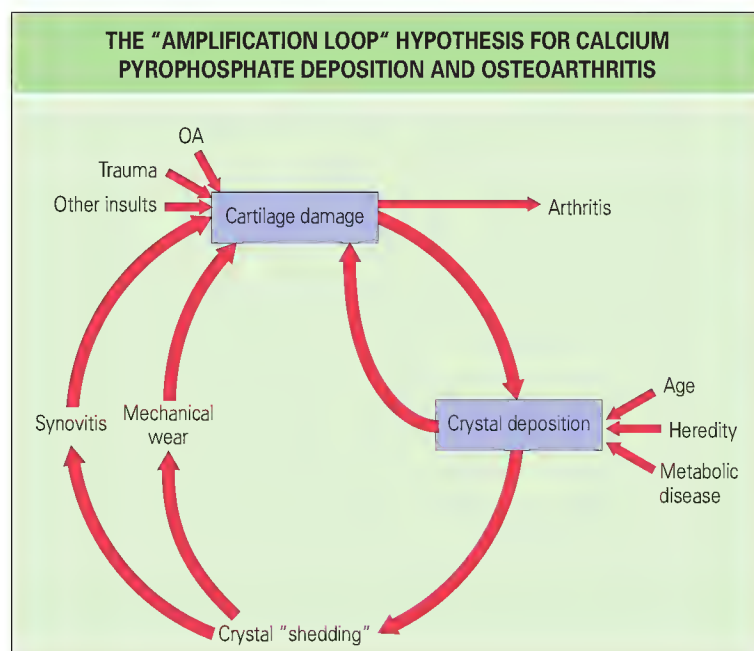


Fig. 190.2 The "amplification loop" hypothesis explains association between calcium pyrophosphate deposition and osteoarthritis.

may appear to be a target site for OA with CPPD because it becomes a common site for OA only in elderly people.

CLINICAL FEATURES

CC can be an incidental finding, but the common manifestations of CPPD are acute synovitis and chronic arthritis.^{3,35,39,40} Others are rare.

Acute calcium pyrophosphate crystal arthritis

This is the most common cause of acute monoarthritis in the elderly. Acute attacks may be the only manifestation of otherwise asymptomatic CPPD. In older, mainly female patients, however, they are often superimposed on chronic symptomatic arthropathy. Any joint may be involved, including the first metatarsophalangeal joint simulating gout ("pseudopodagra"), but the knee is by far the most common site (Fig. 190.3), followed by the wrist, shoulder, ankle, and elbow. Concurrent attacks in more than one joint are unusual (<10% of cases), and polyarticular attacks are rare. The typical attack develops rapidly and is associated with severe pain, stiffness, and swelling, maximal within just 6 to 24 hours of onset. As with gout, the patient may describe the pain as the "worst ever" and be unable to tolerate even light pressure from clothing or bedding. Overlying erythema may occur but is less common than in gout. Examination reveals a tender joint with signs of marked synovitis—increased warmth, a large or tense effusion, joint line tenderness, and restricted movement with stress pain. Pitting periarticular edema is common, especially in those with wrist, ankle, and midfoot involvement. Fever is common and occasionally marked. Elderly patients may appear unwell and mildly confused, especially with knee or multiple joint involvement. Acute attacks are self-limited and usually resolve within 1 to 3 weeks. Transient, less severe "petit" attacks are probably common but difficult to confirm. Most episodes develop spontaneously, but several provoking factors may precede the attack by 1 to 3 days (Box 190.1), the most common being a stress response to intercurrent illness or surgery.

Chronic arthropathy

Symptomatic patients are mainly elderly and female. Large and medium-sized joints are targeted, with the knees being the most frequently and severely affected site, followed by the wrist, shoulder, elbow, hip, and mid-tarsal joints (Figs. 190.4 and 190.5). In the hand, the MCP joints (particularly the second and third) are the most severely affected sites. Symptoms are often restricted to just a few joints, although single or multiple joint involvement also occurs. The chronic arthropathy associated with CPPD may be manifested as OA with CPPD or as chronic CPP crystal inflammatory



Fig. 190.3 Acute calcium pyrophosphate crystal arthritis affecting the knee. Seen here in an elderly woman with background osteoarthritis and calcium pyrophosphate deposition. Bloodstaining of synovial fluid is common in this situation.



Fig. 190.4 Osteoarthritis with calcium pyrophosphate deposition.

BOX 190.1 SITUATIONS THAT MAY TRIGGER ACUTE CALCIUM PYROPHOSPHATE CRYSTAL ARTHRITIS

Definite

- Direct trauma to a joint
- Intercurrent medical illness (e.g., chest infection, urinary tract infection, myocardial infarction)
- Surgery (especially parathyroidectomy)
- Blood transfusion, parenteral fluid administration
- Joint lavage

Possible

- Institution of thyroxine replacement therapy
- Intraarticular injection of hyaluronan
- Bisphosphonate treatment

Note: Most cases of acute calcium pyrophosphate crystal synovitis develop spontaneously.

arthritis. The two forms may coexist in different joints in the same patient, and a single joint may evolve from one to the other.

Osteoarthritis with calcium pyrophosphate crystal deposition

OA with CPPD targets the knees in particular and is characterized by chronic symptoms with or without acute attacks of crystal-induced inflammation. When compared with OA without CPPD, it may be associated with more inflammatory symptoms and signs (e.g., more stiffness and effusion) and an atypical distribution (e.g., involvement of the MCP, radiocarpal,

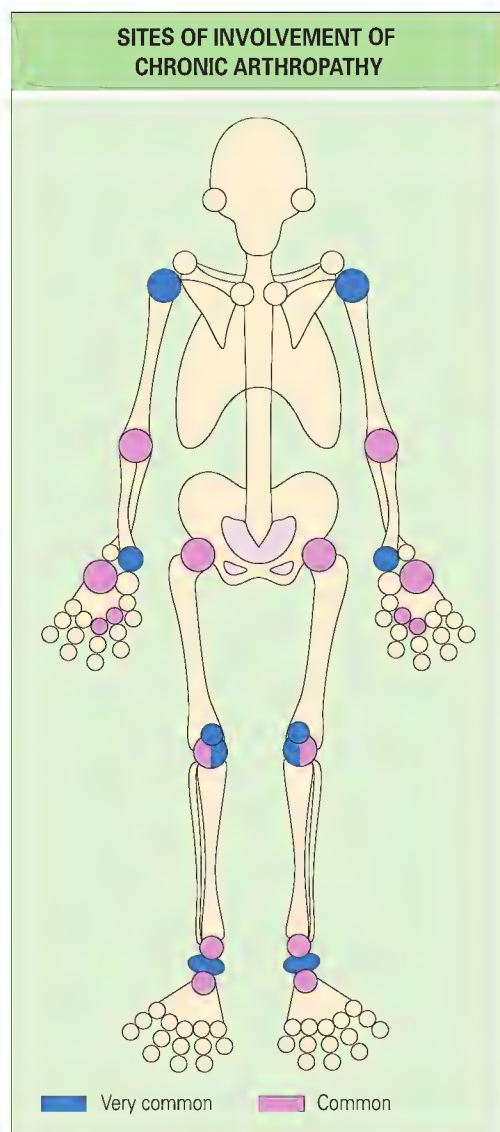


Fig. 190.5 Chronic arthropathy—common sites of involvement.

midcarpal, glenohumeral, ankle, and midfoot joints).⁴ Examination, particularly of elderly women, often reveals more widespread but asymptomatic OA changes. Generalized OA with Heberden nodes, for example, is common. Though less well documented, it is likely that asymptomatic OA with CPPD is also common in the 8th and 9th decades, as is asymptomatic OA.

Chronic calcium pyrophosphate crystal inflammatory arthritis

Chronic CPP crystal inflammatory arthritis is manifested as chronic oligoarthritis or polyarthritis with inflammatory symptoms and signs and occasional systemic upset (with elevation of C-reactive protein [CRP] and the erythrocyte sedimentation rate [ESR]); superimposed flares with the characteristics of crystal inflammation support this diagnosis. It should be considered in the differential diagnosis of RA and other chronic inflammatory joint diseases in older adults.⁴¹ Apart from signs of OA, which may be widespread, signs of synovitis may be present, such as increased warmth, joint line or capsular tenderness, stress pain, effusion, and marked soft tissue thickening. It is usually most evident clinically at the knee, radiocarpal, or glenohumeral joints.

NATURAL HISTORY OF CHRONIC CALCIUM PYROPHOSPHATE CRYSTAL DEPOSITION—ASSOCIATED ARTHROPATHY

The natural history of chronic CPPD-associated arthropathy is poorly documented. However, despite the presence of often severe symptoms and structural changes at initial evaluation, one 5-year hospital-based study suggested

that most patients have a benign course, particularly with respect to involvement of small and medium-sized joints.⁴² As expected, most symptom progression in this study occurred in large, lower limb joints, but even in severely affected knees (the usual site of occurrence), 60% showed stabilization or improvement of their symptoms. However, in another hospital-based prospective study of 350 knees with OA, the presence of synovial fluid CPP crystals or CC associated with radiographic progression, especially bone attrition (OR = 3.44; 95% CI, 1.97 to 6.02) and clinical deterioration, suggested that CPPD may be a marker for a poor prognosis in patients with knee OA.⁴³ Against this is a report suggesting that the presence of CC in patients with knee OA has a protective effect on joint space narrowing over a 2.5- to 3-year period.⁴⁴ This observation might be expected if the association between CC and OA is mediated by a predisposition to osteophytosis.⁷ Nevertheless, the occasional development of rapidly progressive arthropathy, particularly at the knee, shoulder, or hip, is well recognized. This is virtually confined to elderly women and is generally accompanied by severe night and rest pain and associated with a poor outcome.^{3,45,46} Some such patients have problematic recurrent hemarthrosis, particularly of the shoulder and knee; joint leakage may cause extensive bleeding, swelling, and bruising of adjacent tissues. Interestingly, the occurrence of rapidly destructive arthritis at the hip (without local CPPD) appears to be more common in patients with CPPD at other sites, although the mechanism for this is obscure.³⁵

Uncommon manifestations

Atypical arthropathy and axial involvement

Marked proximal stiffness accompanying glenohumeral and polyarticular involvement may rarely suggest polymyalgia rheumatica. Severe spinal stiffness, particularly in Czech, Chilean, and other familial forms, may be manifested as “pseudo-ankylosing spondylitis”; indeed, spinal ankylosis may occur in these Chilean families.⁴⁷ The putative association with diffuse idiopathic skeletal hyperostosis may further complicate this issue. Acute attacks in axial joints are difficult to confirm, and some self-limited spinal syndromes, described in relation to the periodontium (crowned dens syndrome)⁴⁸ and cervical and lumbar regions, may reflect acute CPP crystal attacks. Certainly in elderly subjects, acute self-limited meningitic episodes may occur in relation to CPPD in degenerative ligamenta flava and cervical disks; such deposits rarely associate with chronic myeloradiculopathy. Preferential deposition of CPP in the ligamenta flava at C3–C6 remains unexplained but corresponds to the level of greatest mobility.

Tendinitis and tenosynovitis

Acute inflammatory episodes have been described for the triceps, flexor digitorum, and Achilles tendons, and tenosynovitis has been reported in the hand flexors and extensors.⁴⁹ Tendinitis and tenosynovitis usually, but not inevitably occur in patients with intraarticular CPPD. Flexor tendon involvement may be associated with carpal tunnel syndrome and, less frequently, with combined median and ulnar nerve entrapment at the wrist, with the entrapment appearing to relate more to soft tissue factors than to structural arthropathy. Tendon rupture (hand extensors, Achilles) is a rare complication.

Bursitis

Olecranon, infrapatellar, and retrocalcaneal bursitis is a rare clinical manifestation that predominates in patients with widespread CPPD. It is thought most likely that CPP crystals migrate to bursal tissues from the adjacent cartilage and capsule of tendons rather than deposit *de novo* in soft tissues.

Tophaceous calcium pyrophosphate crystal deposition

Tophaceous (“tumoral”) CPPD is rare but has been reported in intraarticular or periarticular sites, including the temporomandibular joint, hand, cervical spine, foot, hip, acromioclavicular joint, knee, and elbow. Tophaceous CPPD is most common at the temporomandibular joint.⁵⁰ Lesions are solitary and usually develop in areas of chondroid metaplasia without predisposing metabolic abnormality or CPPD elsewhere. Malignancy is often suspected and the diagnosis follows examination of excised material. Rarely, bone erosion and destruction may occur with tophaceous CPPD (e.g., at the temporomandibular joint).

INVESTIGATIONS

Central investigations for diagnosis are (1) fluid and tissue analysis (primarily synovial fluid and rarely bursal or tenosynovial aspirates and biopsy material) for the presence of CPP crystals and (2) plain radiographs. Other



Fig. 190.6 Calcium pyrophosphate crystals in synovial fluid.

investigations may be undertaken to exclude alternative or coexisting arthropathy, and once the diagnosis is confirmed, further investigation for predisposing metabolic diseases may be indicated.

Fluid and tissue analysis

In acute CPP crystal arthritis, aspirated fluid is often turbid or bloodstained, with diminished viscosity and greatly elevated cell counts (usually >90% neutrophils). Macroscopic appearance, viscosity, and cell counts in chronic arthropathy are more variable and range from “inflammatory” to “noninflammatory.” The initial search for CPP crystals should be carried out under light microscopy (400× or 1000×) since most (80%) are nonbirefringent and may not be visualized under noncompensated polarized light microscopy.⁵¹ However, once a crystal is identified by its morphologic characteristics, it should be examined under polarized light to see whether it also displays birefringence.

CPP crystals are recognized primarily by their morphology, generally rhomboids or rods, occasionally acicular, and approximately 2 to 10 μm long. A minority also show weak positive birefringence and inclined extinction (15 to 20 degrees) under compensated polarized microscopy (Fig. 190.6). “Twinning” of crystals, with a chip left at one corner, is occasionally seen. CPP crystals are less readily identified and often less numerous than MSU crystals, and they can often be missed. A careful search in areas of cellular debris and fibrin, as well as examination of a spun deposit, may increase detection. Although the crystals are robust, early examination of fresh fluid avoids problems of dissolution and postaspiration artifact. The Diff Quik stain using eosin G and thiazine is as effective as wet mount examination for detecting CPP crystals and can facilitate delayed examination of stained slides for quality control checks for up to 12 months.⁵² Dried cytospin preparations of synovial fluid are also stable for long-term storage and delayed crystal analysis for up to 12 months.⁵³ This is particularly attractive since crystal detection rates improve with centrifugation, freezing of slides is not required, and subsequent staining is possible.⁵³

For histologic samples, neutral buffers should be used to avoid dissolution because crystals may readily be lost during decalcification (often done for tissue submitted with bone). Stains such as alizarin red S improve detection. As with other synovial fluid particles, identification by polarized light microscopy is associated with both false positives and false negatives. Identification via more definitive analytic means (e.g., infrared spectrophotometry, electron microscopic methods, x-ray diffraction) is ideal. However, such methods often require a high crystal load for analysis, are expensive, and take time. Therefore, for routine clinical purposes, polarized microscopy of fresh synovial fluid represents a convenient, rapid, and adequate compromise.

Imaging

Plain radiographic features

Radiographic aspects relate to both the calcification and arthropathy associated with CPPD.⁵⁴

Calcification

CC most commonly affects fibrocartilage (particularly the knee menisci, wrist triangular cartilage, symphysis pubis, and hip labrum) but also occurs in hyaline cartilage (particularly the knee, shoulder, and hip) as thick linear deposits parallel to and separate from subchondral bone (Fig. 190.7). Though occasionally localized to a single joint, such as one knee, CC usually affects several joints. If absent from the knees, wrists, hips, or symphysis pubis, it is unlikely to be present elsewhere. Capsular (“linear”) and synovial (“cloudy”) calcification is less common than CC and is generally most obvious at the MCP joints (Fig. 190.8) and the knee. Florid synovial calcification occasionally simulates synovial osteochondromatosis—most



Fig. 190.7 Knee radiograph showing chondrocalcinosis of both fibrocartilage (meniscus) and hyaline cartilage.



Fig. 190.8 Calcification affecting the metacarpophalangeal joints.

frequently at the knee. Deposition in tendon insertions particularly favors the Achilles (Fig. 190.9), triceps, and obturators and is typically linear and extensive, as opposed to the discrete nummular calcification of apatite.^{55,56} Diffuse calcification of bursae and ligaments may occur. Both CC and calcification are dynamic and may increase or decrease with time. CC may become less evident, particularly if cartilage thickness is lost or if crystals are “shed” during acute or recurrent inflammatory episodes.

Structural changes

The changes of CPPD with OA include cartilage loss, sclerosis, cysts, and osteophytes.^{35,54} Characteristics purported to aid distinction, however, include the following:

- Joint distribution and involvement within articulations that are atypical of OA (e.g., glenohumeral, MCP, ankle, or elbow; isolated or predominant involvement of the patellofemoral compartment; radiocarpal joint [sometimes with characteristic scapholunate dissociation]; midfoot (Fig. 190.10); or talocalcaneonavicular articulation)
- Often prominent, exuberant osteophyte (Fig. 190.11; see also Fig. 190.10) and cyst formation (Fig. 190.12), particularly at the knee and wrist.

Many cases of OA with CPPD appear to be similar to “uncomplicated” OA with respect to structural change (and vice versa), and a recent meta-analysis suggested that osteophytosis, joint space narrowing, and cysts do not specifically associate with coexistent OA and CPPD as opposed to OA alone.⁴ Sequential radiographic changes are variable. The few patients with destructive arthropathy show marked attrition of cartilage and bone with occasional fragmentation and loose osseous bodies that may resemble the “disorganization” of a Charcot joint; such cases may show rapid, progressive change (Fig. 190.13).

Marginal erosions are not a feature, although smooth “pressure” erosions (reflecting chronic effusions or bone “wear”) are not infrequent, particularly on the anterior aspect of the distal end of the femur and around the distal inferior radioulnar and radiocarpal joints. Patients with coexistent RA and



Fig. 190.9 Calcification of the Achilles tendon.

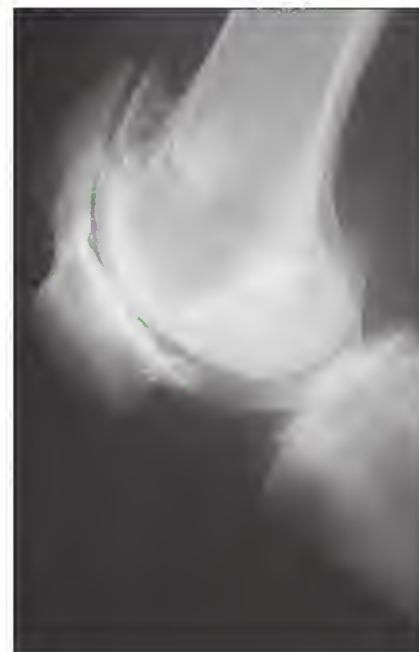


Fig. 190.11 Knee radiograph showing hypertrophic osteoarthritis. Note the prominent patellofemoral involvement typical of osteoarthritis with calcium pyrophosphate deposition.

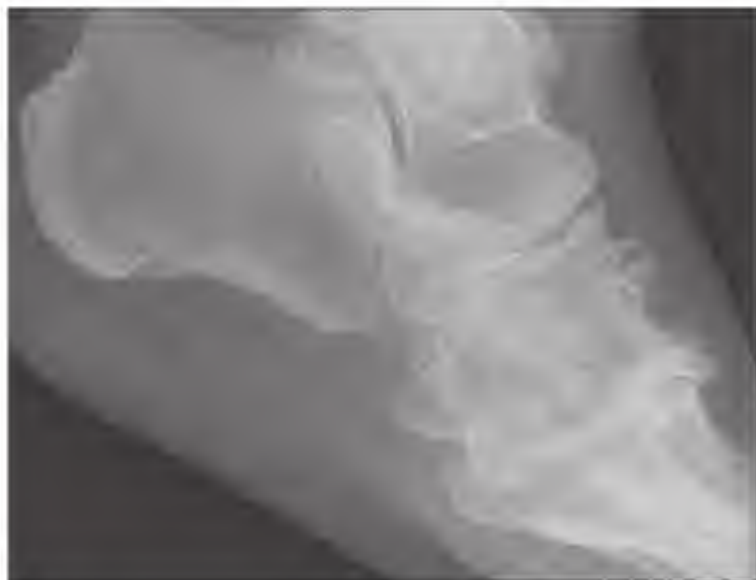


Fig. 190.10 Midfoot radiograph showing hypertrophic osteoarthritis. Note the prominent osteophytosis typical of osteoarthritis with calcium pyrophosphate deposition.



Fig. 190.12 Hand radiograph showing the typical radiocarpal involvement. Note the prominent cyst formation, chondrocalcinosis of the triangular ligament, and "pressure erosion" of the distal end of the radius.

CPPD may have a modified radiographic appearance (Fig. 190.14) characterized by retained bone density, prominent osteophytes, prominent well-corticated cysts, and a paucity of erosion (i.e., predominance of reparative OA rather than atrophic destructive change).³⁷

Arthropathy in patients with hemochromatosis may be accompanied by similar radiographic changes, although possible differentiating features include more widespread MCP joint involvement, with the greatest difference in involvement occurring in the fourth and fifth digits; radial hook osteophytes at the MCP joint; absence of scapholunate dissociation; involvement of the MCP joint in the absence of radiocarpal arthropathy; more frequent multiple "ring cysts" in large joints; and subchondral bone fragmentation at the hip.⁵⁷

Computed tomography

Computed tomography (CT) is particularly useful in the evaluation of CPPD in the spine. CT of the cervico-occipital junction may show periodontal calcification, subchondral cysts, and erosion in patients with crowned dens syndrome. Magnetic resonance imaging (MRI) may be used for further evaluation of patients with neurologic symptoms.

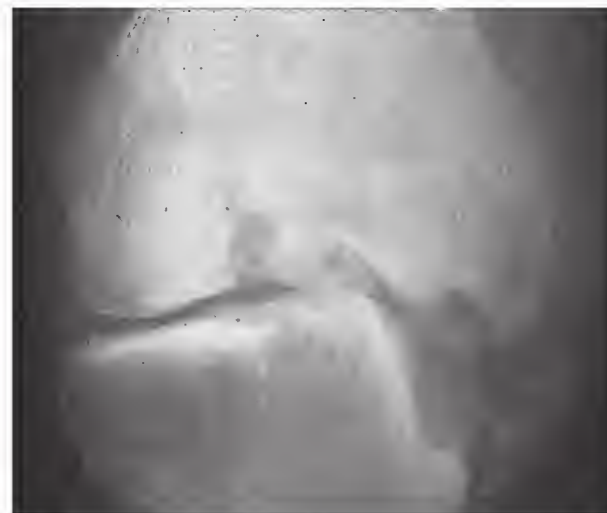


Fig. 190.13 Rapidly destructive knee arthropathy in an elderly woman. Note the marked bone attrition, bony "loose bodies," and chondrocalcinosis.

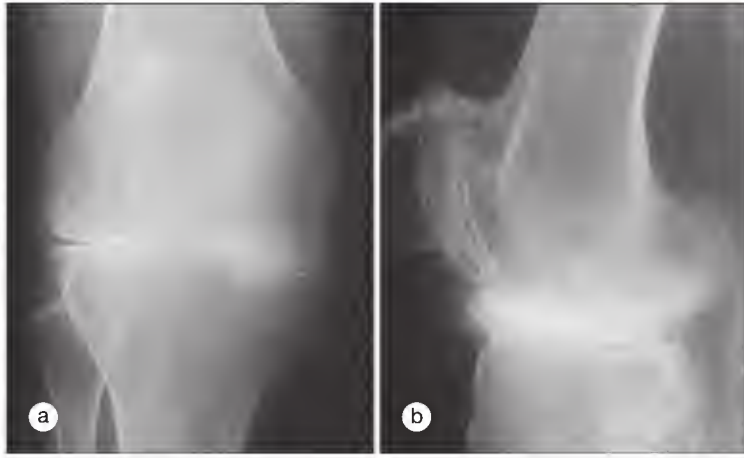


Fig. 190.14 Knee radiograph of patient with coexistent rheumatoid arthritis and calcium pyrophosphate deposition. On the anteroposterior view (a), widespread cartilage loss is evident, but the lateral view (b) shows marked new bone formation atypical of rheumatoid arthritis.

Ultrasound

High-frequency ultrasound (US) can demonstrate CPPD in hyaline cartilage and fibrocartilage and in and around tendons. CC appears as isolated or extensive linear hyperechoic deposits within the substance of hyaline articular cartilage and as rounded or amorphous deposits in fibrocartilage. In contrast, urate crystals are seen as hyperechoic linear deposits on the surface of articular cartilage. Articular CPP deposits are generally not dense enough to cast an acoustic shadow. Musculoskeletal US has high specificity (96.4% to 97.6%) and moderate to high sensitivity (68.7% to 86.7%) for the detection of CC at the knee⁵⁸ and performs better than plain radiography.^{4,59} However, MRI is relatively insensitive and detects only sizable CPP deposits.⁶⁰

Additional investigations

In acute CPP crystal arthritis, Gram stain and culture should always be performed on aspirated synovial fluid. Septic arthritis is the principal differential diagnosis, and concurrence with acute CPP crystal arthritis is reported. Other synovial fluid investigations are of little diagnostic value. Acute CPP crystal arthritis commonly triggers an acute-phase response consisting of elevation of plasma viscosity, ESR, acute-phase reactants (e.g., CRP), and the peripheral white blood cell count (predominantly neutrophils). Such changes are occasionally impressive, particularly with attacks affecting multiple large joints and in patients with triggering intercurrent illness.

In chronic CPP inflammatory arthritis, mild anemia with a modest elevation in acute-phase reactants (including ferritin) is not uncommon. The frequency of other biochemical and serologic abnormalities, however, is no different from that in other subjects of the same age.

Screening for predisposing metabolic disease

Metabolic disease predisposition is rare, and routine screening of all patients with CPPD is unrewarding. Nevertheless, CC and arthritis may be the initial feature of metabolic disease, and screening tests are warranted in the following circumstances:

- Early-onset arthritis (younger than 65 years)
- Florid polyarticular CC
- Recurrent acute attacks more than chronic arthropathy
- Presence of additional clinical or radiographic clues that suggest the diagnosis

Screening tests include calcium, alkaline phosphatase, magnesium, ferritin and transferrin saturation, and liver function tests.

DIFFERENTIAL DIAGNOSIS

Acute calcium pyrophosphate crystal arthritis

The occurrence of acute synovitis in one or a few joints, overlying erythema, pyrexia, systemic upset, and purulent joint fluid (particularly in the setting

of preceding surgery, trauma, or infective illness) should always lead to consideration and exclusion of septic arthritis. Because septic arthritis may coexist with crystal synovitis, Gram stain and culture of joint fluid should always be undertaken in an ill patient in a hospital setting (culture of blood and other body fluids may also be appropriate), even once CPP crystals are identified or radiographic CC demonstrated. Gout is the other principal condition to consider, with the diagnosis resting on synovial fluid analysis. Occasionally, heavy bloodstaining of joint fluid may lead to consideration of other causes of hemarthrosis, especially a bleeding disorder (low vitamin C levels in the elderly may encourage hemarthrosis) or subchondral fracture (particularly with preceding, provoking trauma). However, if CPP crystals are identified, results of the clotting screen are normal, no lipid is found in the aspirated fluid, and no radiographic fracture is present, the diagnosis of acute CPP crystal arthritis alone can be accepted. If localized tenderness and pain on weight bearing persist following the resolution of synovitis, repeated radiographs (with or without a subsequent bone scan) may be justified to detect missed fracture.

Chronic arthropathy

In most cases the characteristic distribution, radiographic features, and joint fluid findings permit a ready diagnosis. In older patients, however, a marked inflammatory component, polyarthritis with MCP joint involvement, and modest elevation of the ESR may lead to consideration of RA, particularly since large-joint involvement may predominate in elderly patients with RA. Nevertheless, the following considerations usually permit distinction: infrequency of metatarsophalangeal arthropathy, infrequency of tenosynovitis, absence of extraarticular features, lack of juxtaarticular osteopenia and marginal erosions, lack of strong seropositivity for rheumatoid factor and anti-CCP antibodies, and positive joint fluid and radiographic findings for CPPD-associated arthropathy.

Patients with marked proximal stiffness and an elevated ESR are differentiated from those with polymyalgia rheumatica mainly by careful locomotor examination and positive joint fluid and radiographic findings. Oral corticosteroids often improve the symptoms in such patients but rarely result in a rapid “cure” of polymyalgia; the response to local intraarticular corticosteroid may be more impressive. Differentiation from uncomplicated OA is often facilitated by the different pattern of distribution between and within articulations; the more florid inflammatory component; the presence of superimposed acute attacks; radiographic findings of an atypical distribution of joint involvement, CC, and prominent osteophyte and cyst formation; and synovial fluid CPP crystals.

Even though destructive CPPD arthropathy may resemble a neuropathic joint radiographically, such joints are severely symptomatic and arise in the absence of overt neurologic or serologic abnormality. Although the description of clinical manifestations by the addition of “pseudo” to other diagnostic labels suggests the close mimicry of other joint disease, the diagnosis is usually suspected on clinical grounds alone and confirmed by synovial fluid and radiographic findings. However, CPPD commonly coexists or is superimposed on other recognizable joint disease, thus making the prefix “pseudo” clearly inappropriate. The most common associated condition is OA (generalized, pauciarticular, or posttraumatic) affecting the same or distant joints, although coexistent gout, sepsis, RA, apatite-associated destructive arthropathy, or true Charcot arthropathy may all occur. In such cases the diagnostic label should reflect both conditions even though the relative contribution of each may vary at different sites in the same individual.

Though rare, tophaceous CPPD should be considered with malignancy and tophaceous gout in the differential diagnosis of calcified lesions involving periarticular soft tissues. Examination of biopsy material is required for correct diagnosis.

STRUCTURE AND FUNCTION

Pyrophosphate metabolism

Inorganic PPI is a byproduct of many biosynthetic reactions.⁶¹ Despite high turnover (about a few kilograms per day), both intracellular and extracellular concentrations of PPI are maintained at a low level by ubiquitous pyrophosphatases that metabolize PPI (complexed to Mg) to orthophosphate (Pi). Even with its high-energy phosphoester bond (implicated in the biochemical origin of life), PPI is not known to be an energy source in mammals, nor is it synthesized *de novo*.

Numerous biologic roles for PPI are now recognized, including participation in intracellular Ca²⁺ traffic, mediation of nucleotide and iron transport,

modulation of enzyme systems, storage of molecules in cellular granules, and effects on mitogenesis.⁶¹ In locomotor tissues, however, modulation of apatite mineralization is a key role.⁶² A certain level of PPi is required for the initial nucleation of apatite from amorphous calcium phosphate and for subsequent crystal growth. Paradoxically, a high level of PPi inhibits these processes by preventing nucleation and adsorbing to the surface of apatite crystals, thereby preventing further crystal growth.⁶² In a chicken embryo growth plate matrix vesicle model, CPP crystals formed exclusively when the Pi/PPi ratio was less than 6, and their formation was inhibited when the Pi/PPi ratio was higher than 28.4. In contrast, optimal formation of apatite crystals occurred when the Pi/PPi ratio was greater than 140 and their formation was completely inhibited when the Pi/PPi ratio was less than 70.⁶² This is how PPi inhibits abnormal calcification in the vasculature, saliva, and the urinary tract and is used industrially as a water softener.

Extracellular PPi (ePPi) may either be produced locally or result from the transport of intracellular stores. Because PPi cannot cross membranes passively, the multipass membrane transporter protein ANK regulates the passage of PPi to the exterior of the cell.⁶³ Loss-of-function defects in ANK can result in high intracellular PPi but low ePPi concentrations (Fig. 190.15). The subsequent low ePPi level promotes apatite formation and growth, which then results in abnormal mineralization of locomotor tissues—the “ankylosis” mouse phenotype from which the gene and its protein were first determined.⁶³ The ANKH gene (H = human) is the human homologue of ANK. Several ANKH mutations have been reported in familial CPPD, and it was proposed that the abnormality, instead of reducing, increases the activity of ANKH, which potentially results in high ePPi levels (see Fig. 190.15).^{19,21}

The family of phosphodiesterase nucleotide pyrophosphatase (PDNP) enzymes includes plasma cell membrane glycoprotein 1 (PC1, located on the cell membrane and matrix vesicles), autotaxin (secreted from cells), and PDNP3 (intracellular). All the PDNP enzymes hydrolyze the phosphodiesterase 1 bond of nucleoside triphosphates (NTPs).⁶⁴ The activity of surface 5'-nucleotidase may influence this reaction in favor of PPi production (Fig. 190.16). Of the three PDNP enzymes, PC1 is the most significant contributor to extracellular NTP, and studies in knockout mice suggests that PC1 and not ANKH is responsible for the majority of ePPi.⁶⁵

Adenosine triphosphate (ATP), the principal extracellular substrate for PC1, is released from chondrocytes following mechanical loading; during increased cell activity, cell division, and injury; and possibly during vesicular extrusion of matrix components and other products.^{61,66} Recently, ANKH has also been shown to export ATP.⁶⁷ The level of extracellular ATP together with PC1 activity determines ePPi levels and hence the possibility of CPP crystal formation.^{61,68} ePPi complexed with Mg is normally processed rapidly by surface TNAP to Pi, which can readily cross membranes. In organ culture,

adult hyaline cartilage and fibrocartilage, but not synovium or bone, elaborates ePPi. Increased PPi production occurs in growth plate cartilage and human OA cartilage.

The addition of ATP to cultured articular cartilage encourages CPP crystal formation, particularly around articular chondrocyte vesicles (ACVs).⁶⁸ These vesicles, analogous to the matrix vesicles of growing cartilage, are trilaminar, phospholipid membrane-limited structures adjacent to chondrocytes. They avidly bind calcium and are rich in all the enzymes that generate PPi and Pi. Cultured ACVs mineralize in the presence of calcium and ATP.⁶⁹ Depending on the PPi/Pi ratio (excess ATP producing a high ratio and restricted ATP producing a low ratio), ACVs produce CPP, BCP, or both types of crystals.^{62,69} Factors other than the ATP concentration can also influence ePPi elaboration in cartilage (Table 190.1). Frequently, complex mechanisms underlie these effects. For instance, the TGF- β -induced increase in ANK expression is mediated by the influx of Pi through the type III Na⁺/Pi channels PiT-1 and PiT-2 and by the influx of calcium by L-type or T-type voltage-dependent calcium channels—Ca²⁺ being required for the activation of extracellular signal-regulated kinase 1 and 2 (ERK1/2) and protein kinase C.^{70,71} Several other cell-signaling pathways may be of

TABLE 190.1
Regulation of pyrophosphate metabolism

Substrate	Factors increasing substrate expression	Factors decreasing substrate expression
PC1	TGF- β , [*] aging, thyroid hormone, retinoic acid [†]	IL-1 β , IGF-I [‡]
TNAP	IL-1 β , thyroid hormone	TGF- β [§]
ANKH	TGF- β	IGF-I, TNF
Transglutaminase	TGF- β , aging	IGF-I
CILP	TGF- β , aging	IGF-I

^{*}The effect of TGF- β on PC1 is antagonized by IL-1 β and IGF-I.

[†]The effect of retinoic acid on PC1 is mediated in part by activation of latent TGF- β .

[‡]The effect of IGF-I on PC1 is antagonized by CILP-1.

[§]The effect of TGF- β on TNAP is antagonized by IL-1 β .

CILP, cartilage intermediate layer protein; IGF-I, insulin-like growth factor type I; IL-1 β , interleukin-1 β ; PC1, plasma cell membrane glycoprotein 1; TGF- β , transforming growth factor- β ; TNAP, tissue nonspecific alkaline phosphatase; TNF, tumor necrosis factor. Adapted from Abhishek A, Doherty M. Pathophysiology of articular chondrocalcinosis—role of ANKH. *Nat Rev Rheumatol* 2011;7:96-104.

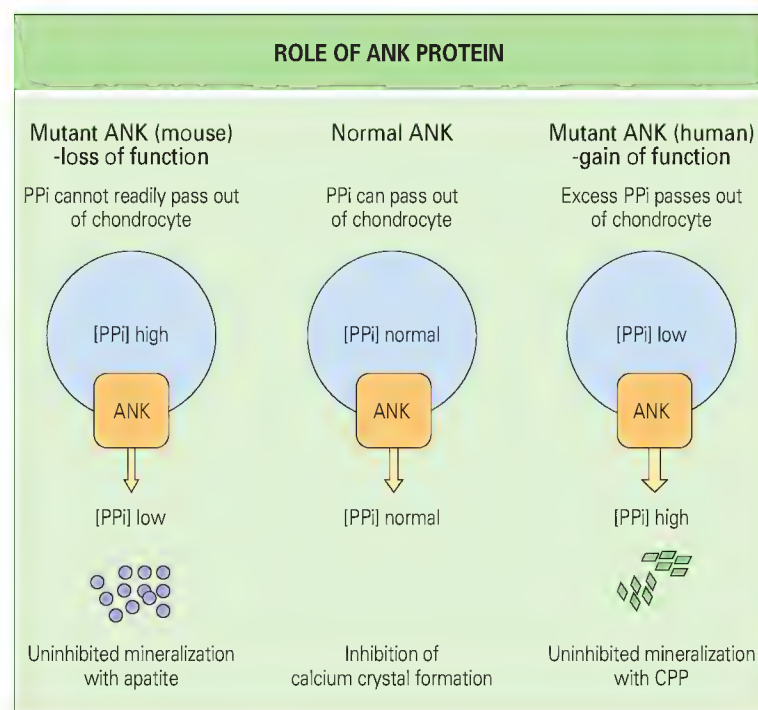


Fig. 190.15 ANK(H) regulates exit of pyrophosphate from cells, which inhibits mineralization with apatite.

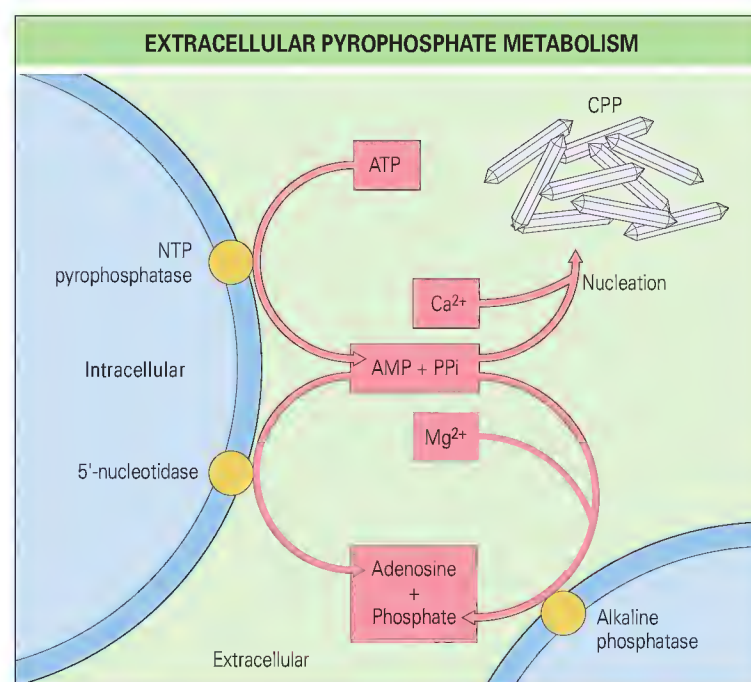


Fig. 190.16 Extracellular pyrophosphate metabolism. AMP, adenosine monophosphate; ATP, adenosine triphosphate; CPP, calcium pyrophosphate; NTP, nucleoside triphosphate.

relevance in moderating such responses; for example, protein kinase C activation stimulates and adenylyl cyclase stimulation diminishes PPI elaboration.⁷² Type 2 transglutaminase and factor XIIIa, both expressed in chondrocytes, increase CPP crystal formation.⁷³ This may be due to transglutaminase-mediated incorporation of latent TGF- β into the extracellular matrix and its activation, with post-translational modification of the extracellular matrix favoring crystal formation and stimulation of phospholipase A₂ leading to cartilage degradation and inhibition of TNAP.⁷⁴⁻⁷⁶ Dexamethasone increases the transcription of transglutaminase XIIIa, which leads to CPP crystal formation by cultured ACVs.⁷⁷ Osteopontin, a calcium-binding matricellular protein present in the pericellular location, also increases CPPD by activating transglutinases.⁷⁸

When compared with normal knees, elevated synovial fluid PPI concentrations are reported in both OA with CPPD and uncomplicated OA,⁶¹ the normal plasma and urinary concentrations in such cases supporting increased intraarticular production. Less impressive elevations in synovial fluid PPI are seen in acute CPP crystal arthritis, with subnormal levels in RA.⁶¹ These lower levels perhaps reflect increased clearance of PPI in inflamed states. Extracellular ATP, the major substrate for PPI, has been found in synovial fluid, with higher levels in OA with CPPD than in OA or RA.⁶¹

Pi and PPI levels are interrelated by several biofeedback mechanisms to maintain a physiological Pi/PPI ratio. For instance, a gain in ANKH activity increases the expression of PiT-1 and consequently results in high intracellular Pi levels, which then stimulates TNAP production, thereby lowering the ePPI concentration and promoting mineralization with hydroxyapatite.⁷⁹ Additionally, elevated extracellular Pi increases the effect of TGF- β on ANKH, PC1, and PiT-1 mRNA and protein expression, which increases ePPI.⁸⁰ The coexistence of BCP and CPP crystals in the same joint may be due to dynamic changes in the Pi/PPI ratio and result in the formation of both types of crystals.

Calcium pyrophosphate crystal formation

Factors likely to affect the formation, growth, and dissolution of CPP crystals are outlined in Figure 190.17. The formation of CPP crystal appears to be restricted principally to fibrocartilage and hyaline cartilage (less commonly the capsule and tendon), with only 2 of 12 known crystallographic forms occurring—the triclinic (t-CPP) and monoclinic (m-CPP) dimorphs. Unlike MSU crystals, which readily form in supersaturated solutions, CPP crystals require exacting conditions for formation. In addition, CPPD occurs

only in larger animals such as primates and dogs and does not occur in smaller animals. Thus, to date no animal model has been developed, and most knowledge has been derived from model systems using gels (nonbiologic gelatin or native collagen gels). From these systems the following generalities are implied. In addition to the product ($\text{Ca}^{2+} \times \text{PPI}$), the local Mg concentration importantly influences CPPD by inhibiting nucleation and growth and by enhancing dissolution. Pi, chondroitin sulfate, and proteoglycan are also inhibitory to nucleation and growth. With proteoglycan this effect depends on the spatial arrangement of carboxylate ligands, which may operate via calcium binding or spatial regulation of Mg, phosphate, or unidentified small-molecular-weight promoters and inhibitors.

Conversely, nucleating and growth-promoting factors include iron ($\text{Fe}^{3+} > \text{Fe}^{2+}$) and seeded MSU crystals. Interestingly, seeded apatite efficiently traps PPI, thereby leading to more stable CPP growth. A possible promoting role of collagen and acidic phospholipid has been suggested. Formation of m-CPP and t-CPP is slow and occurs via intermediate crystal species, with t-CPP being the final, most stable form.

Histologic studies suggest that CPP crystals form extracellularly in the pericellular area in the midzone of fibrocartilage and hyaline cartilage.⁸¹ A close association is reported with hypertrophic or metaplastic chondrocyte phenotypes containing Sudan-positive lipid granules, and similar lipid may occur around CPP crystals, the involved matrix often being depleted of proteoglycan and degenerate.⁸¹ Such findings support the importance of tissue (“soil”) factors, which implies that a reduction in inhibitors (e.g., proteoglycan) and an increase in promoters (e.g., lipid) combine to promote CPP crystal formation. Conversely, elevation of synovial fluid PPI, perhaps released from hypertrophic and metabolically active chondrocytes, argues in favor of “seed” components. The relative importance of these multiple factors may vary from time to time. With respect to dissolution, CPP crystals are extremely insoluble but can, however, be dissolved by TNAP. Mg enhances dissolution via both enzyme stimulation and enhanced release of PPI ions from the crystal surface.

PATHOGENESIS

Crystal-associated inflammation

Crystals of CPP, as with MSU, have been studied mainly in relation to acute inflammation.⁸² In general, laboratory-prepared CPP crystals are markedly phlogistic particles in a wide variety of *in vitro* and *in vivo* systems, though less so than MSU on an equal-weight comparison. Effects on humoral mediators, cytokines, cell-derived mediators, and cell membranes have been demonstrated.⁸² For example, CPP crystals activate complement *in vitro* via the classical and alternative pathways. Consequently, elevated synovial fluid complement breakdown products (C3d) occur with acute CPP crystal arthritis, though interestingly not with chronic arthropathy despite the presence of often marked clinical inflammation. Hageman factor is also activated and leads to the generation of kallikrein, bradykinin, plasmin, and other soluble mediators. A dramatic effect of CPP crystals is marked perturbation of plasma membranes, which causes membranolysis, as well as nonlytic platelet and neutrophil secretory responses. CPP crystals induce superoxide production by neutrophils and release of lysosomal enzymes, chemotactic factors, and lipoxygenase-derived products of arachidonic acid, including leukotriene B₄, following phagocytosis. CPP crystals engage the caspase-1-activating NALP3 inflammasome. This increases the production of interleukin-1 β (IL-1 β) and IL-18 by facilitating maturation of their precursors. CPP crystals appear to be equipotent to MSU crystals in activating the NALP3 inflammasome.⁸³ IL-1 β stimulates secretion of tumor necrosis factor- α and is chemotactic to neutrophils. Other CPP-cell interactions include the release of newly synthesized IL-6 from synoviocytes and monocytes (in accord with the high synovial fluid IL-6 levels demonstrated in acute CPP crystal arthritis). CPP crystals stimulate the ERK1/2 and p38 mitogen-activated protein kinase pathways and thereby result in the secretion of IL-8, which is important in neutrophil recruitment and activation. CPP crystals inhibit neutrophil apoptosis by inhibiting proapoptotic cysteine protease caspase-3 and activating ERK1/2, p38, and Akt.⁸⁴ This may explain the prolonged neutrophilic inflammatory response seen in patients with acute CPP crystal arthritis. CPP crystals activate Toll-like receptor 2 on the surface of articular chondrocytes, which leads to several changes (e.g., nitric oxide [NO] production) that may adversely affect the chondrocyte and the cartilage matrix.⁸⁵

Many of these effects result from direct crystal contact, although some (e.g., the classical pathway of complement activation) may be enhanced or mediated by adsorption of IgG onto the crystal surface (Fig. 190.18).⁸⁶ In biologic systems, CPP crystals avidly attract both anionic and cationic

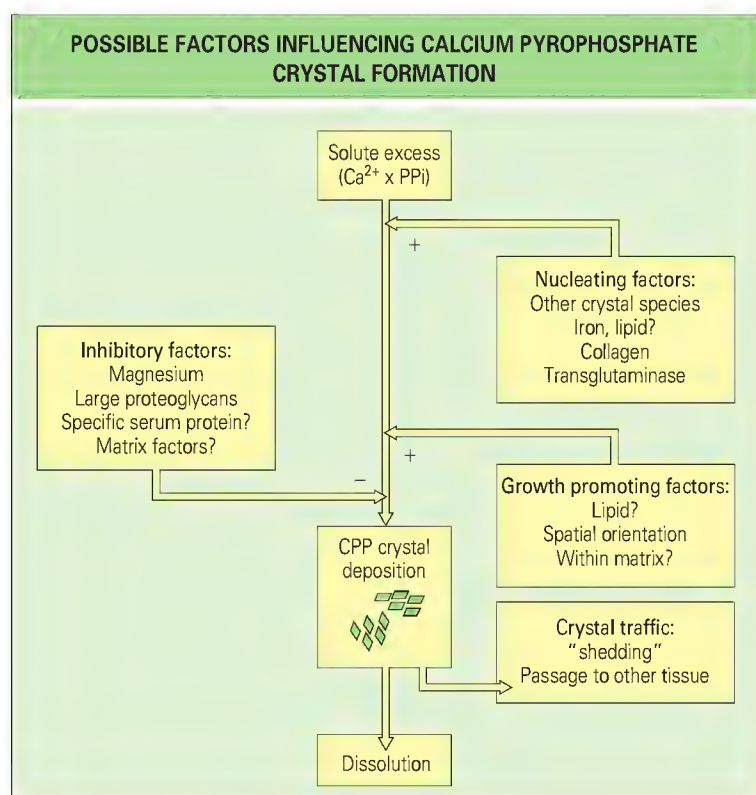


Fig. 190.17 Possible factors influencing calcium pyrophosphate crystal formation.

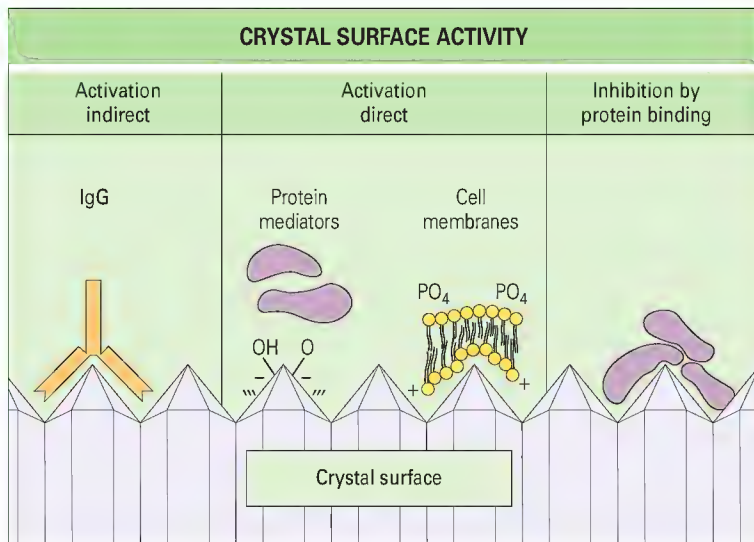


Fig. 190.18 Potential interactions and blocking at the crystal surface are shown.

proteins, with some preferential selection for immunoglobulin, especially IgG. Although the altered stereochemical configuration of adsorbed IgG may be proinflammatory, other protein binding may be inhibitory. Of most interest in this respect are apolipoprotein B-containing low-density and high-density lipoproteins, binding with which, for example, inhibits CPP-induced neutrophil lysis.

Certain physical characteristics of CPP and other crystals appear to relate to their inflammatory potential. In general, smaller crystals are more inflammatory than large ones and m-CPP crystals are more inflammatory than t-CPP crystals; this may result from mechanical effects (e.g., greater ease of phagocytosis) or merely reflect the greater surface area or weight presented for protein or membrane interaction. “Roughness” and net negative surface charge are also important. The crystal surfaces of inflammatory membranolytic crystals (MSU, CPP) are irregular and possess a high density of charged groups that give a high negative zeta potential, whereas the surfaces of noninflammatory crystals (diamond, stishovite) are smooth, with low or zero zeta potential; brushite and apatite are intermediate in these respects and are associated with more modest inflammatory effects.

Less is known of the tissue damage induced by chronic CPPD, although postulated mechanisms include matrix metalloproteinase expression, NO release, persistent synovial inflammation, altered cell metabolism, prostaglandin E₂ release, and altered osteoblast activity.⁸⁵ Intradermal injection of CPP causes a chronic “granulomatous” reaction that lasts several weeks; unlike acute inflammation, CPP is more potent than MSU in this respect.

Mechanical effects of crystals

Deposition of hard CPP crystals within the cartilage matrix might theoretically be disadvantageous for cartilage but might equally facilitate the transmission of impact forces, depending on the shape, size, extent, and orientation of the crystals.⁸⁷ However, the occurrence of free crystals at the cartilage-cartilage interface is likely to be damaging through their effects as “wear” (abrasive) particles.⁸⁸ Though usually cleared quickly from synovial fluid, the presence of even a small amount of CPP crystals may thus be more harmful than much larger deposits within cartilage.

Crystal shedding

Given the difficult physicochemical requirements for *in vitro* manufacture, nucleation and growth of CPP crystals in synovial fluid would seem unlikely, and the preferred mechanism to explain the occurrence of CPP crystals within synovial fluid is “shedding” from preformed deposits within cartilage.⁸⁹ This could be accomplished by a reduction in crystal size, fissuring of cartilage, or an alteration in the cartilage matrix that allows easier escape of the crystals. Circumstantial evidence to support each of these possibilities includes the provocation of acute attacks by the following:

- Joint lavage with crystal-solubilizing agents or situations (acute stress response, parathyroidectomy) associated with a reduction in ionized calcium (reduced crystal size)

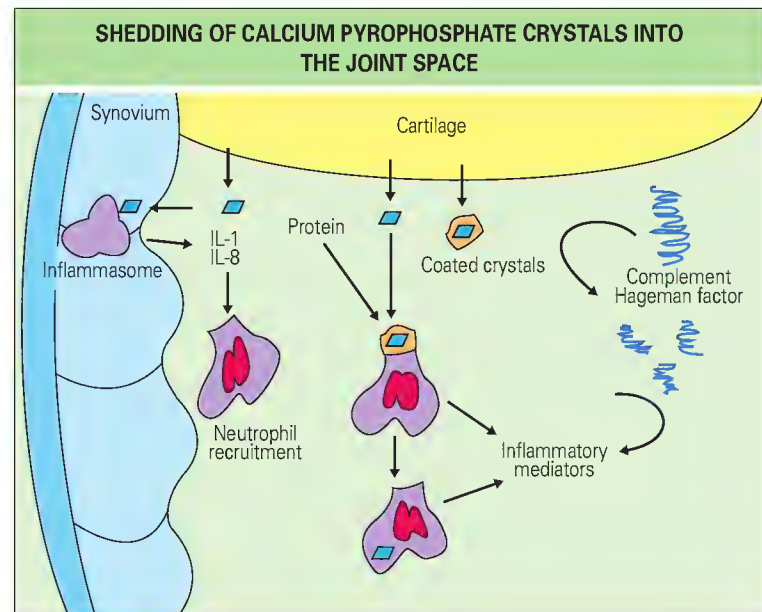


Fig. 190.19 The preformed calcium pyrophosphate (CPP) crystals initiate an acute attack but then become coated with protein and are processed by synoviocytes and inflammatory cells.

- Trauma (microfissuring, “shaking loose”)
- Thyroxine replacement (change in the cartilage gel matrix)
- Concurrence of acute CPP crystal arthritis and sepsis (“enzymatic strip mining”)

More direct evidence comes from the reduction in radiographic CC documented during acute CPP crystal arthritis and during follow-up of CPPD patients.^{39,89} Shedding from cartilage deposits might expose previously protected “naked” crystals to soluble mediators and cells and thus trigger the acute attack (Fig. 190.19). The CPP crystals are subsequently taken up and processed by neutrophils and synoviocytes; such “trafficking” through the joint, however, is slow, and CPP crystals are still identifiable in synovial fluid as the attack settles. What “turns off” the attack and permits inflammatory crystals to reside in synovial fluid during noninflamed intercritical periods remains unexplained. Nevertheless, coating by inhibitory proteins (some acute-phase reactants) appears to be more plausible than altered responsiveness or changes in the physical properties of CPP crystals.

PATHOLOGIC CHANGES

Unlike MSU, CPP crystals are not deposited in all connective tissues but are virtually confined to locomotor structures. Pathologic data largely support primary deposition in cartilage (less commonly, capsule, tendon, and ligament), with secondary release and uptake by synovium, tenosynovium, or bursae.

Microscopy of cartilage usually shows rounded, sharply demarcated crystal deposits within a granular matrix in the midzone.⁸¹ The earliest lesions are perilacunar, but with widespread CC, superficial cartilage may be involved, with tophus like deposits predominating in the midzone. Electron microscopy studies may dislodge CPP crystals, and those visualized often appear vacuolated and “foamy” (artifactual) with a bumpy contour, perhaps representing adsorbed protein. The surrounding cartilage may appear normal or show loss of metachromasia, chondrocyte cloning, or fibrillation; the occurrence of associated lipid-laden hypertrophic metaplastic chondrocytes has been particularly emphasized.⁸¹ With severe cartilage changes, subchondral bone may show thickened trabeculae with multiple cysts; cyst fracture occasionally results in bone fragmentation and collapse. In synovium, CPP crystals usually occur superficially in the interstitial space and synoviocyte vacuoles and are often surrounded by fibrocytes and connective tissue; neutrophil and lymphocyte infiltrates may be present, but the prominent response is lining cell hyperplasia. Tophus like deposits, surrounding giant cell reactions, and osteochondral bodies are occasional findings. In advanced disease, masses of CPP crystals may virtually replace ischemic-appearing villi. Changes in bursae and tendon sheaths resemble those in synovium.

MANAGEMENT

Recently, EULAR has developed consensus-driven, evidence-based guidelines for the management of CPPD.⁹⁰ Unlike gout, no treatment is available to reduce the CPP crystal load. Lavage with calcium-chelating agents (e.g., MgSO_4) provokes acute CPP crystal arthritis, perhaps through partial dissolution, which then encourages crystal shedding, and no compound capable of dissolving CPP crystals has come into use. Treatment of any underlying metabolic disease is appropriate. However, other than possibly for correction of hypomagnesemia, such treatment does not influence the outcome of CPP crystal-associated disease.

Acute calcium pyrophosphate crystal arthritis

The aims are to reduce symptoms, identify and treat triggering illness, and rapidly mobilize patients once the inflammation has settled. Rapid mobilization is important because many patients are elderly and prone to complications from prolonged immobility. In general, therefore, local rather than systemic therapy is preferred, particularly because acute CPP arthritis commonly affects only one or a few joints.

Aspiration and injection

In most cases, aspiration alone greatly relieves the symptoms and may be the only treatment required. Fluid reaccumulation, however, is common, particularly early in the attack. Therefore, for florid attacks, intraarticular injection of a long-acting corticosteroid is appropriate, either at the time of initial aspiration or as a second procedure following reaccumulation (some prefer the reassurance of a negative Gram stain or culture, or both, before injecting corticosteroid if septic arthritis is suspected). Joint lavage (normal saline, room temperature) can help settle attacks but is usually reserved for troublesome relapsing or prolonged episodes unresponsive to corticosteroid injection. Evidence for these treatments is anecdotal.

Other treatments

Ice packs may be applied for relief of symptoms. Simple analgesics and nonsteroidal antiinflammatory drugs (NSAIDs) may have additional benefits. NSAIDs are often contraindicated in the elderly. Oral colchicine may be effective but is rarely warranted; if used, it should be given at a low dose (e.g., 0.5 or 0.6 mg twice or three times daily) to reduce the incidence of gastrointestinal side effects, especially in elderly patients or in those with renal impairment. One small study of patients with recurrent acute CPP crystal arthritis ($N = 10$) suggested that colchicine may be effective in the prophylaxis of recurrent acute attacks.⁹¹ As for gout, colchicine, a microtubule assembly inhibitor, may work by inhibiting CPP crystal endocytosis or its presentation to the inflammasome.⁸³ In an elderly patient with acute CPP crystal arthritis, short courses of systemic corticosteroids may be preferred over NSAIDs and colchicine (once infection has been excluded as a trigger) and produce more rapid relief than possible with these oral agents.⁹² This approach is particularly suitable for severe polyarticular attacks unresponsive to aspiration and injection of the largest affected joints. In general, however, evidence for the use of pharmacologic agents is derived from observational and small controlled studies or by extrapolation from studies of patients with gout.

Anakinra (IL-1 receptor antagonist) has been used for the treatment and prophylaxis of polyarticular acute CPP crystal arthritis unresponsive to oral corticosteroids,⁹³ although the usefulness of this agent for prophylaxis was not confirmed in a recent case series consisting of just three patients.⁹⁴

Osteoarthritis with calcium pyrophosphate deposition

The aims of management and the choice of interventions are the same as for OA. A variety of strategies may be beneficial, although evidence for these

measures is extrapolated from OA trials (Chapter 181). Whether the presence of CPPD is a predictor of response to individual treatments of OA, however, has not been formally examined in clinical trials.

All patients should receive the following:

- Education concerning the nature of their arthritis
- Advice regarding both local strengthening and aerobic/fitness exercise
- Interventions aimed at minimizing adverse mechanical factors, such as reduction in obesity and appropriate footwear
- Simple analgesics such as paracetamol and topical NSAIDs, especially for the knee and hand

Recognition and management of depression and the use of coping strategies are applicable. Despite the presence of frequently marked structural abnormality, intraarticular corticosteroid injection often greatly improves the symptoms. Though often temporary, this may improve the patient's optimism, encourage adherence to other aspects of treatment, and provide a useful interval for effective physiotherapy or enjoyment of an important life event (e.g., holiday). One small, double-blind, placebo-controlled study reported a reduction in pain with oral magnesium.⁹⁵ However, no reduction in radiographic CC was found. A double-blind controlled study of intraarticular radiocolloid (yttrium 90) for CPPD with OA of the knee showed efficacy even in those with gross structural change.⁹⁶ The number needed to treat (NNT) was 2 for greater than 33.3% improvement in knee pain and 50% improvement in global knee symptoms. Radiosynovectomy is also useful for recurrent hemarthrosis, presumably by inducing synovial fibrosis.

Chronic calcium pyrophosphate crystal inflammatory arthritis

Oral NSAIDs (with gastroprotection) or colchicine (or both), low-dose corticosteroids, methotrexate, and hydroxychloroquine have been suggested as pharmacologic options for the treatment of chronic CPP crystal arthritis.⁹⁰ The use of NSAIDs and low-dose corticosteroids is based mainly on expert opinion. The use of colchicine is based on the findings of a study of patients with knee OA and persistent inflammation as a result of CPP crystals, in whom colchicine (0.5 mg twice daily for 8 weeks and then as necessary) resulted in greater than 30% improvement in pain (NNT = 2 at 4 months and 4 at 5 months). One small, double-blind, placebo-controlled study reported clinical benefit with oral hydroxychloroquine (NNT = 2 for a 30% reduction in swollen and tender joint counts).⁹⁷ In a retrospective review of patients with chronic CPP crystal inflammatory arthritis, methotrexate (median dose of 12.5 mg/wk) reduced symptoms, joint inflammation as assessed clinically, ESR, and CRP with a mean time to improvement of 7 to 8 weeks.⁹⁸ However, other retrospective studies have not confirmed this outcome,⁹⁹ and the results of prospective trials are awaited. Radiosynovectomy may be useful in the treatment of patients with monoarthritis or oligoarthritis. Rilonacept (IL-1 Trap), which is beneficial in the treatment of patients with chronic gouty arthritis, may be effective in patients with refractory CPP crystal-related arthritis.

Other treatment

Stronger analgesics such as opioids, NSAIDs, and coxibs may be required but carry an appreciable risk for side effects and drug interactions. Such drugs should be used with caution in the elderly. Patients should be clearly informed regarding optimal use, the requirement for drugs should be reviewed regularly, and "repeated" prescribing should be avoided.

Surgery

Patients with progressive or destructive large-joint arthropathy who require replacement appear to derive benefits equal to those with uncomplicated OA, without any increased risk for prosthetic failure.

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Basic calcium phosphate crystal deposition disease

■ GERALDINE MCCARTHY

- Calcific periarthritis is characterized by periarticular deposits of calcific material (hydroxyapatite), which may also result in calcific tendinitis or bursitis.
- Intraarticular deposits of basic calcium phosphate (BCP) crystals may be found in joint fluid, as well as in synovium and articular cartilage.
- In calcific periarthritis, the shoulder is the main site affected, but deposits have been described near many other joints. The deposits are often inert and asymptomatic.
- Deposits can rupture and cause local acute, crystal-induced inflammation.
- Deposits may also be associated with local chronic pain and functional impairment.
- With intraarticular deposition, deposits are often inert and asymptomatic.
- Deposits occur with increased frequency in patients with osteoarthritis.
- BCP crystals can occasionally be shed into the joint and result in an acute synovitis resembling gout.
- BCP crystals are also found in abundance in the joints of older patients with large joint destructive arthropathies such as the Milwaukee shoulder syndrome.

HISTORY

Calcific periarthritis

Calcific scapulohumeral periarthritis was first described in 1870, and radiographic demonstration of periarticular shoulder calcifications was accomplished by 1907.¹ These calcifications were initially regarded as having arisen in the subdeltoid bursa but were subsequently demonstrated to occur chiefly in the supraspinatus tendon or the shoulder joint capsule. Thirty years later, renewed interest in periarthritis of the shoulder led to further descriptions of the phenomenon, as well as recognition of periarticular calcifications at other sites.² After another 30 years, it was recognized that the calcific material consisted of hydroxyapatite,³ and the pathophysiologic theory of primary tendon necrosis leading to secondary calcification followed.⁴ Subsequently, aggregates of basic calcium phosphate (BCP) crystals with their various crystalline structures and chemical compositions were further defined via ultrastructural and physical microanalysis techniques, including analytic electron microscopy, x-ray diffraction, and Fourier transform infrared (FTIR) spectroscopy.⁵ Included in the term BCP are crystals of partially carbonate-substituted hydroxyapatite, octacalcium phosphate, and rarely, tricalcium phosphate.

Intraarticular basic calcium phosphate crystal deposition

The earliest description of the pathoanatomic features of the consequences of intraarticular BCP crystal deposition appears to have been by Robert Adams in 1857, who called it “chronic rheumatic arthritis of the shoulder.”⁶ In his 1934 monograph, Codman reported the case of a 51-year-old woman who had what he called “subacromial space hygroma.” He described recurrent swelling of the shoulder, absent rotator cuff, cartilaginous bodies attached to synovial tissue, and severe destructive glenohumeral arthritis.⁷ These clinical descriptions were made without the benefit of modern diagnostic tests. The condition has subsequently been known by many different

names. In the French-language literature, the terms *les caries séniles hémorragique de l'épaule* and *l'arthropathie destructrice rapide de l'épaule* have been used, and in the English-language literature, terms such as *cuff tear arthropathy* appear. All early descriptions stress the involvement of older females and localization to the shoulder joint.⁷

The association of intraarticular deposits of BCP crystals with joint disease is much more recent. The presence of solid deposits of BCP crystals in the menisci of postmortem knees was noted in 1966,⁸ but it was not until 1976 that the first description of BCP crystals in degenerative joint diseases was recorded. Clumps of BCP crystals were discovered in the synovial fluid of patients with osteoarthritis (OA) via analytic electron microscopy,⁹ a finding that was confirmed by others.^{10,11} In 1981, McCarty's group described a similar large-joint destructive arthropathy, seen most commonly in the shoulder joints of elderly women, and called it *Milwaukee shoulder*. They noted the presence of large quantities of BCP crystals associated with collagenase in synovial fluid and hypothesized that the BCP crystals caused the associated joint destruction.¹² Subsequently, others noted that many large joints could be involved and terms such as *apatite-associated destructive arthritis* and *idiopathic destructive arthritis of the shoulder* were added to the list of names. BCP crystals were also described in the joint fluid of a few patients with acute synovitis and other forms of arthropathy.¹¹

EPIDEMIOLOGY

Calcific periarthritis

Few systematic studies of the incidence or prevalence of juxtaarticular deposits of BCP crystals have been done. These deposits are often asymptomatic and most commonly noted by chance on a radiograph obtained for other reasons (Fig. 191.1). In a unique, large study of office workers published in 1941, a 2.7% prevalence of shoulder deposits was noted in a North American, predominantly white population, 34% to 45% of which were associated with clinical problems.¹³ Females were affected more commonly than males, and the prevalence was highest in those between 31 and 40 years of age (19.5%). No comparable epidemiologic data have been reported subsequently, although a number of smaller pathologic or radiographic studies have documented the relatively high frequency of periarticular calcification. Calcific periarthritis has been reported in children as young as 3 years but appears to be relatively uncommon in the elderly. This suggests that many of the deposits seen in young adults must disappear spontaneously.

Articular calcification

The prevalence of intraarticular BCP crystal deposition has not been established because it has not been adequately studied. Apatite crystals are detected in up to 60% of synovial fluid samples from patients with knee joint OA.^{14,15} BCP crystals were found in approximately 50% of 53 preoperative OA knees.¹⁶ The prevalence in normal joints at different ages is not known. Milwaukee shoulder syndrome and the related BCP crystal-associated destructive arthropathies are uncommon, tend to occur in elderly individuals, and are of unknown prevalence.

CLINICAL FEATURES

Calcific periarthritis

Periarticular calcific deposits are often asymptomatic. However, they are also associated with a number of clinical syndromes (Table 191.1). The most



Fig. 191.1 Anteroposterior radiograph of the shoulder joint showing a large calcific deposit in the supraspinatus tendon. The deposit is dense, homogenous, and well defined, findings characteristic of inert periarticular deposits of calcific material.

TABLE 191.1

Clinical syndromes that can be associated with the deposition of basic calcium phosphate crystals in and around joints

Subcutaneous deposits (e.g., calcification of the hands in scleroderma)	Asymptomatic chance finding Acute and chronic inflammation Skin ulceration Secondary infection Pressing necrosis of surrounding tissues Mechanical interference with function
Periarticular deposits (e.g., calcification of the supraspinatus tendon)	Asymptomatic chance finding Acute calcific periarthritis Chronic periarticular pain and/or dysfunction
Intraarticular deposits (e.g., synovial and cartilage deposits in damaged joints)	Asymptomatic chance finding Acute synovitis Severe osteoarthritis Destructive arthropathies of older people

striking clinical finding is acute calcific periarthritis, which most commonly involves the shoulder but can occur in almost any joint. The episode may be preceded by mild trauma or overuse, but most cases have a spontaneous onset.

Patients report a sudden onset of severe pain, and within hours the affected part is usually swollen with redness and warmth of the overlying skin. There is extreme local tenderness and associated loss of function. At the shoulder the pain is most marked around the subacromial region and radiates down the outside of the arm. Glenohumeral movement is usually severely restricted. Severe pain may last for several days, but the symptoms then generally resolve slowly over a period of 2 to 3 weeks. A “frozen shoulder” may result.

Calcific periarthritis is thought to be caused by rupture of a calcific deposit into an adjacent soft tissue space or bursa along with initiation of an acute inflammatory reaction. In the shoulder the crystals may induce intense inflammation in the subacromial bursa (Fig. 191.2). Radiographically, calcium deposits appear dense with well-defined borders before an attack. With the onset of an attack, however, these calcific deposits appear fluffy with poorly defined margins. Ultimately, there is a reduction in the size of the deposit seen radiographically, and it may disappear completely.

Calcific deposits in periarticular tissues are also associated with chronic pain syndromes without a history of a previous acute episode. However, in the shoulder, because both chronic shoulder pain and calcification are common and because previous damage to tendons may predispose to calcification, it is difficult to define what contribution, if any, the deposits themselves make to the clinical findings. Moderate to severe pain is described, with varying degrees of tenderness and restriction of motion. Pain usually radiates to the insertion of the deltoid and sometimes beyond to the forearm. Lying on the affected shoulder is painful and may interfere with sleep. In some patients, recurrent acute attacks around the shoulder, separated by pain-free periods lasting months or years, are followed by the development

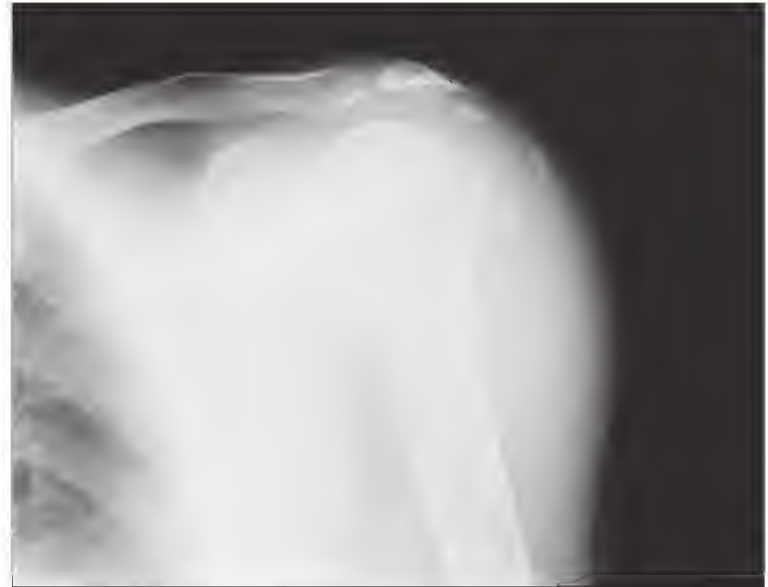


Fig. 191.2 Anteroposterior radiograph of the shoulder during an attack of severe acute calcific periarthritis. The deposit has become indistinct and ill defined as the crystals have been shed into the surrounding tissues. In this elderly patient, communication between the shoulder joint and the subacromial bursa led to a large effusion in the glenohumeral joint and a huge extension of the bursa into the upper part of the arm, as shown by the soft tissue swelling seen on the radiograph.

of chronic pain. Damage to the tendons and muscles of the rotator cuff may result and lead to total disruption of the cuff apparatus.

The shoulder is the most commonly affected site, followed by the hip, knee, elbow, wrist, and ankle joints. The joints of the feet and toes are less commonly involved (<1% of all reported cases), as are those of the hands and fingers.¹⁷ *Hydroxyapatite pseudopodagra* is a term used to describe acute calcific arthritis involving the first metatarsal phalangeal joint, usually in young women.¹⁸ Acute neck pain attributed to calcifications surrounding the odontoid process has been described and called the *crowned dens syndrome*. Calcifications appear to be composed of apatite, calcium pyrophosphate dihydrate (CPPD), or a combination of both.¹⁹

In some patients with multifocal deposits, symptoms develop at several sites, thus suggesting a more generalized condition rather than a chance localized process with resultant calcification. This manifestation can cause diagnostic confusion and may even mimic a seronegative polyarthritis. Several reports have described familial occurrences of calcific periarthritis.²⁰

Intraarticular basic calcium phosphate crystals

Our understanding of the exact relationship between intraarticular BCP crystals and joint pathology is incomplete, especially because special techniques are required to identify the crystals.²¹ Nonetheless, current data support the pathogenic role of BCP crystals in degeneration of articular tissue (Fig. 191.3). BCP crystals have been linked with several different diseases.

Acute synovitis

Acute attacks of arthritis associated with intraarticular BCP crystals in relatively young individuals have been described in the knee, as well as at other sites. The pain, swelling, and erythema resembled gout.²² These attacks appear to be rare, and the diagnosis is difficult to establish. Occasionally, crystals from a periarticular deposit can rupture into the joint itself and cause acute synovitis. This can occur in some older individuals who have a direct communication between the subacromial bursa and the glenohumeral joint.

Chronic monoarthritis, with or without erosions

A chronic, sometimes erosive monoarthritis has been linked with intraarticular BCP crystals. BCP crystals have been particularly implicated in finger joint arthropathies, including erosive or inflammatory forms of OA.²³ However, this phenomenon appears to be rare, and a direct contribution of BCP crystals to the observed pathology remains to be established.

SCHEMATIC REPRESENTATION OF THE POSSIBLE ASSOCIATIONS BETWEEN BCP CRYSTALS AND ARTHRITIS

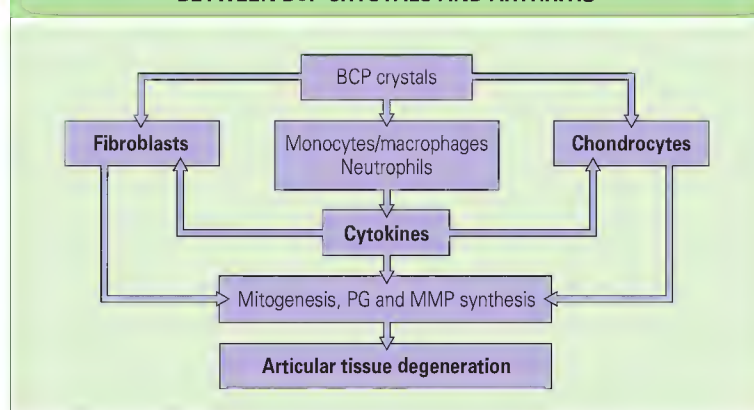


Fig. 191.3 BCP, basic calcium phosphate; MMP, matrix metalloproteinase; PG, prostaglandin.

Osteoarthritis

Co-occurrence of BCP crystals and OA is well established. Ample data support the role of BCP crystals in cartilage degeneration because their presence correlates strongly with the severity of radiographic OA²⁴ and larger joint effusions are seen in affected knee joints than in OA knees without crystals.²⁵ Although the basis of the cartilage damage by BCP crystals has been the subject of numerous investigations, there are ongoing controversies concerning the relationship between calcium-containing crystals and OA and whether the crystals cause cartilage damage or are present as a result of joint damage.

Large-joint destructive arthropathies

A distinctive type of destructive arthropathy has been described in elderly individuals that is associated with rotator cuff defects and numerous aggregates of BCP crystals in the fluid of affected joints and is called Milwaukee shoulder.¹²

The clinical picture is characteristic (Fig. 191.4a). Patients are nearly always 70 years or older, and approximately 90% are females. They usually have a history (months or years) of increasing pain, swelling, and loss of function of the affected joint, typically the shoulder. The dominant side is usually involved initially, although 60% have bilateral involvement.²⁶ The pain may be mild but is typically most apparent at night and with use of the joint. Examination shows extensive damage to periarticular soft tissues, as well as to cartilage and subchondral bone on both sides of the joint. Active range of motion is reduced in all affected joints, sometimes associated with pronounced joint instability. Crepitation and pain may be noted, especially when the humerus is grated passively against the glenoid. In general, the rotator cuff is completely destroyed. Joint effusion is typically present and may be massive and extend into the subdeltoid region. Aspiration of affected shoulder joints routinely yields 3 to 160 mL of synovial fluid that is frequently blood tinged and has a low, predominantly mononuclear cell count (Fig. 191.4b). Rupture of the effusion can lead to massive extravasation of blood and synovial fluid into the surrounding tissue. Although the shoulder predominates, the knee, hip, elbow, and other joints may be involved.²⁷

The natural history of the condition is unclear, but many cases seem to stabilize after a year or two, with reduction of symptoms, joint effusions, and no further radiographic changes.

Additional clinical manifestations

A number of secondary forms of BCP crystal-associated arthropathy have been described. BCP crystal deposits have been reported in the joints and periarticular tissue of patients with renal failure, mostly when undergoing dialysis. Intraarticular injection of triamcinolone hexacetonide has been associated with the formation of periarticular calcifications along the injection tract, which may become apparent months after the injection. Such calcification may be gradually resorbed over a period of months to years. Occasionally, severe neurologic damage has been followed by heterotopic ossification in periarticular tissues that may mimic arthritis.

BCP deposition is also associated with connective tissue diseases, particularly scleroderma and dermatomyositis. Following dermatomyositis in childhood, massive sheets of fascial calcification can occur. In scleroderma, the deposits are usually subcutaneous. They are associated with the CREST



Fig. 191.4 Basic calcium phosphate crystal-associated destructive arthritis (Milwaukee shoulder syndrome). This elderly patient has visible swelling in both shoulders (a). Aspiration revealed a large amount of blood-stained fluid (b) that contained numerous particles of basic calcium phosphate.

syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), but some patients have extensive calcification with little in the way of other features of the disease (calcinosis cutis) (Fig. 191.5). Occasionally, the hand calcification occurs on its own.

Tumoral calcinosis is a rare condition characterized by the progressive deposition of calcified masses in cutaneous and subcutaneous tissue; it is typically associated with chronic renal failure and hyperparathyroidism. Familial tumoral calcinosis is a heritable disorder typified by hyperphosphatemia, normal or elevated serum 1,25-dihydroxyvitamin D, and often severe ectopic calcifications. Mutations in the genes for both fibroblast growth factor-23 and GALNT3, which encodes a glycosyltransferase responsible for initiating mucin-type O-glycosylation, have been found in familial tumoral calcinosis. Finally, calciphylaxis is a dreaded complication of renal failure characterized by nodular subcutaneous calcification and painful tissue necrosis that often leads to ulceration, secondary infection, and high mortality rates.

INVESTIGATIONS

Imaging

A plain radiograph is the easiest method with which to detect and describe the calcific material of calcific periarthritis (Fig. 191.6). Anteroposterior and lateral radiographs are generally sufficient, but special views, with internal or external rotation of the shoulder, may be necessary to visualize retro-humeral deposits. The deposits are usually visualized in the rotator cuff, particularly the supraspinatus tendon a few centimeters from its insertion, but may also be seen in the subacromial bursa. Various appearances have been described with size varying from a few millimeters to several centimeters across. Other imaging investigations are rarely helpful in calcific periarthritis, although arthrography can be used to confirm cuff rupture and

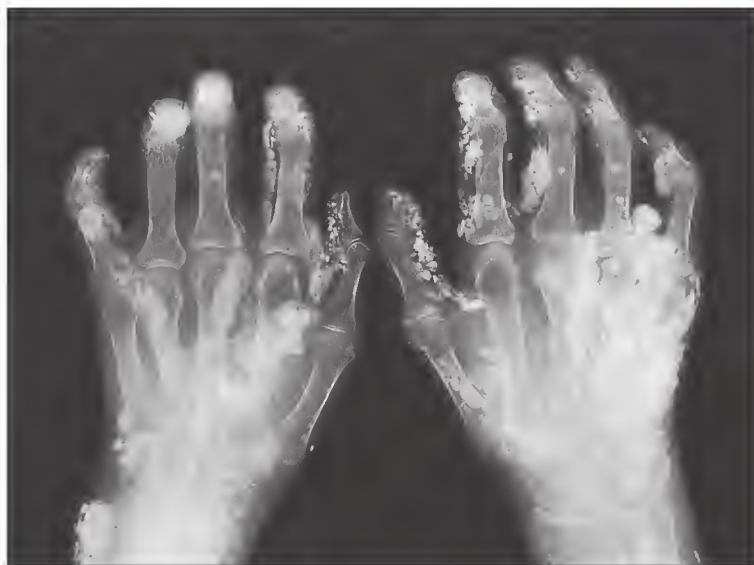


Fig. 191.5 Anteroposterior radiograph of the hands of a patient with severe subcutaneous calcification associated with mild scleroderma.



Fig. 191.6 Anteroposterior radiograph of the shoulder joint showing a small periarticular calcific deposit. Other views may be necessary to identify small deposits and the site of deposition.

techniques such as computed tomography or magnetic resonance imaging may help demonstrate small deposits or other changes in the tissues around the lesion. During acute attacks of peri-arthritis the deposits may change and disappear, only to reappear again subsequently.

Calcification around joints is sometimes mistaken for ossification, although the presence of trabeculae in the latter should allow differentiation. The only other differential diagnosis on the images is the very rare formation of periarticular deposits of CPPD crystals. They occasionally occur in peri-articular tendons, but as in joints, the deposits usually appear as linear rather than nummular shadows.

Intraarticular BCP deposits are rarely visible with any of the conventional imaging procedures. Occasionally, articular calcifications of a nummular sort are seen, in contrast to the linear deposits of chondrocalcinosis as a result of CPPD crystals. However, pathologic studies indicate that individual aggregates of crystals in cartilage synovium or synovial fluid are generally tiny and well below the size that gives any chance of their being visible on a radiograph.

Radiographs in patients with Milwaukee shoulder syndrome are striking (Fig. 191.7) and show upward subluxation of the humeral head or arthrographic evidence of rotator cuff defects in the majority of patients. Other



Fig. 191.7 Anteroposterior radiographs of a shoulder joint affected by basic calcium phosphate crystal-associated destructive arthritis (Milwaukee shoulder syndrome). Extensive destruction of periarticular tissues, including the rotator cuff, has led to instability of the shoulder. The upward subluxation (a) of the humerus can be overcome by traction on the shoulder (b). Note the extensive atrophic destruction and loss of bone in both the acromion and the glenohumeral joint.

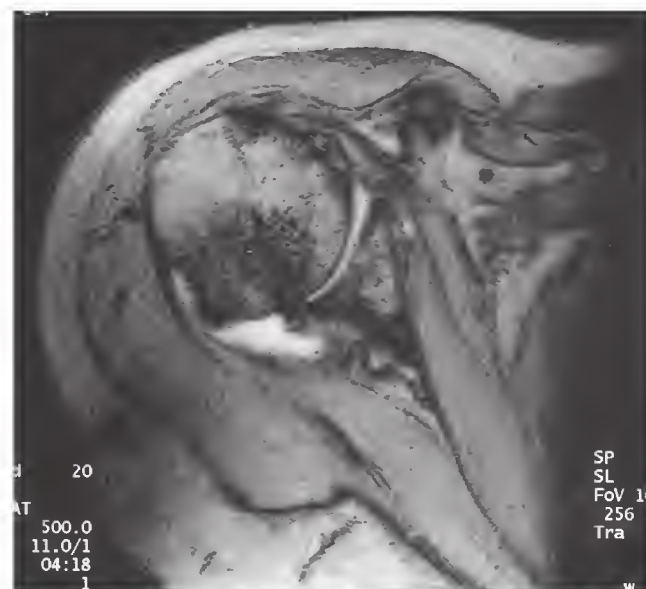


Fig. 191.8 Axial T2-weighted magnetic resonance image of a shoulder joint affected by basic calcium phosphate crystal-associated destructive arthritis (Milwaukee shoulder). There is advanced glenohumeral joint degeneration with loss of articular cartilage, truncation of the anterior and posterior labrum, narrowing of the joint space, osteophyte formation, muscle atrophy, and joint effusion.

findings may include cystic degeneration of the humeral tuberosities, erosions of cortical bone at the site of insertion of the rotator cuff, degenerative changes in the humeral head or glenoid of the scapula (or both), degenerative changes in the acromioclavicular joint, and calcification of the tendinous rotator cuff. Pseudarthrosis formation between the humeral head and the acromion and clavicle is common.

Magnetic resonance imaging can be used to further define the anatomic changes associated with Milwaukee shoulder syndrome, including loss of cartilage, periarticular bone marrow edema, rupture of the rotator cuff, synovial hypertrophy, and joint effusion (Fig. 191.8).

Biochemical

Apatite deposition usually occurs in the absence of any detectable metabolic abnormality. However, if multiple deposits are detected or if the deposits are unusually large or in unusual sites, calcium and phosphate levels, as well as renal function, should be checked. High serum phosphate levels seem

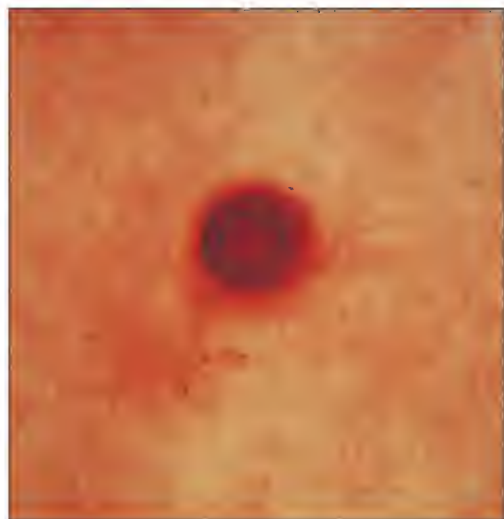


Fig. 191.9 Alizarin red S stain of a basic calcium phosphate particle isolated from the synovial fluid of a patient with osteoarthritis.

more likely to predispose to deposition than do abnormalities in calcium alone.

Synovial or bursal fluid

In acute calcific periarthritis it is sometimes possible to aspirate a mixture of calcium deposits and inflammatory matter from the bursa or periarticular tissue. It may look like toothpaste or be a creamy fluid, obviously full of “chalk.” In cases of intraarticular BCP crystal deposition, the synovial fluid findings vary. Usually, the fluids that contain BCP crystals have a low cell count, are viscous, and are much the same as fluids from any patient with OA. In the destructive arthropathies of the elderly there is frequent blood staining of the fluid. In addition, numerous cartilage fragments and other debris may be present, although the cell count is low.

Identification and characterization of basic calcium phosphate crystals

Study of BCP crystal-associated arthritis has been relatively difficult because of the lack of a simple, easily accessible, reliable diagnostic test.²¹ BCP crystals are not birefringent. Therefore, polarized light microscopy is not useful for detection of them because individual BCP crystals, which are typically needle shaped and less than 0.1 μm long, cannot be resolved by light microscopy and are randomly oriented in the much larger aggregates (2 to 19 μm) in which they are usually found. Plain and polarized light microscopy of samples containing apatite may show globular clumps of crystals, which can look like shiny coins, but the usual appearance of these crystals is nondescript.

Calcium stains such as alizarin red S have been used by some investigators to identify BCP crystals.²⁸ Clumps of crystals show up with a “halo” of stain (Fig. 191.9). Alizarin red S is highly sensitive, but frequent false-positive results suggest that it lacks sufficient specificity to qualify for routine identification of BCP crystals without some other type of confirmatory testing.

A semiquantitative binding assay for BCP crystals that uses [¹⁴C] ethane-1-hydroxy-1,1-diphosphonate (EHDP) has been described.¹⁰ Diphosphonates are analogues of inorganic pyrophosphate that adsorb to the surface of BCP crystals but not to monosodium urate, CPPD, cartilage fragments, or any other known particulates in joint fluid. This method is performed on a synovial fluid pellet resuspended in phosphate-buffered saline, and the results are expressed as micrograms per milliliter of hydroxyapatite standard. The limit of sensitivity is approximately 2 $\mu\text{g/mL}$ standard hydroxyapatite.

Electron microscopy can be used to visualize the crystals in synovial fluid pellets, and if elemental analysis or electron diffraction is possible, their identity can be confirmed (Fig. 191.10). If sufficient material is available, (e.g., from surgical specimens), other analytic techniques such as x-ray powder diffraction or FTIR spectroscopy can be used to identify the material. The latter has shown that BCP crystal deposits consist of mixtures of hydroxyapatite, octacalcium phosphate, and rarely tricalcium phosphate crystals. Combinations of both BCP and CPPD crystals are not infrequent.

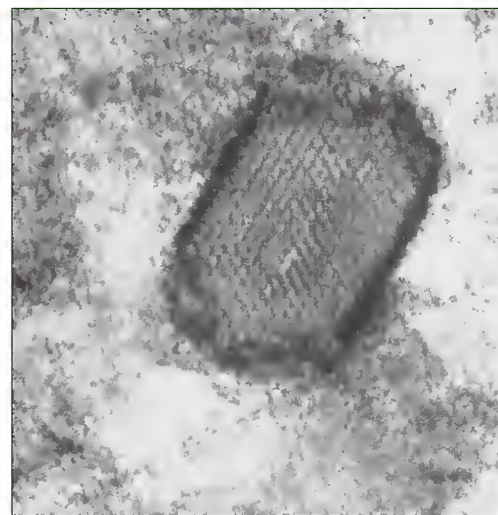


Fig. 191.10 High-magnification transmission electron micrograph of basic calcium phosphate crystals. The crystal lattice structure and morphology of the crystals are apparent.

Atomic force microscopy has been applied to the identification of synovial fluid microcrystals and is capable of achieving subnanometer resolution of crystal surface topology and measurement of lattice unit cell dimensions.²¹

More novel methods of identifying BCP crystals from synovial fluid include isolation using bisphosphonate-modified superparamagnetic beads and identification via oxytetracycline staining, which fluoresces under ultraviolet light. Synchrotron FTIR spectroscopy can accurately distinguish between CPPD and BCP crystals.²¹

The ability to identify apatite is less crucial than the identification of monosodium urate or CPPD crystals from a clinical perspective because no drug has yet been identified that specifically inhibits the pathologic effects of BCP crystals *in vivo*.

DIFFERENTIAL DIAGNOSIS

Acute calcific periarthritis

The differential diagnosis of acute calcific periarthritis should include gout, pseudogout, and sepsis. However, the distribution of the lesions and acute onset are often characteristic. Radiographs showing the evolution of the calcific deposit are virtually pathognomonic. The diagnosis can be confirmed if material can be aspirated from the area.

Chronic periarticular syndromes

The usual features are those of tendinitis, and the only way of implicating crystal deposition in the diagnosis is through visualization of the deposit on a radiograph. Other causes of tendinitis such as trauma, impingement, and inflammatory arthritis are possible differential diagnoses.

Acute and chronic arthritis

Acute inflammatory arthritis that may mimic gout, pseudogout, or other systemic inflammatory rheumatic diseases has been attributed to BCP crystals.^{9,22} BCP crystals are often detected in OA joints and appear to promote the degenerative process.^{24,25} Erosive arthritis with recurrent episodes of pain and swelling involving the wrists and finger joints has been associated with BCP crystal deposition.²³

Destructive arthropathies of the elderly

The main differential diagnoses include neuropathic or Charcot joints, chronic sepsis, advanced rheumatoid disease, osteonecrosis, and CPPD deposition disease. Radiographic involvement of both sides of the joint helps differentiate this condition from osteonecrosis. The absence of any neurologic deficit distinguishes it from Charcot arthropathy. Synovial fluid examination and culture will aid in differentiation from CPPD deposition disease and sepsis.

STRUCTURE AND FUNCTION

Nature of the crystals

Hydroxyapatite is a form of calcium phosphate represented by the formula $\text{Ca}_5(\text{PO}_4)_3\text{OH}\cdot 2\text{H}_2\text{O}$ and is usually found in partially substituted carbonated form. In periarticular calcific deposits, light microscopy generally shows multifocal aggregates of crystals separated by fibrocollagenous tissue. On transmission electron microscopy the deposits appear as rounded aggregates with isolated crystals in a matrix of fragmented collagen fibers (Fig. 191.11). On scanning electron microscopy they look like rocky bulks embedded in mortar (Fig. 191.12). The crystals are heterogeneous both within the sample and in different patients. Typically, they include compounds of varying crystallinity ranging from amorphous BCP to well-structured stable elements, similar to those of bone and teeth, but with a larger crystal size than most of the crystals seen in bone. In bone, poorly crystalline, partially carbonated crystals of hydroxyapatite, each about 500 Å in length, are the main mineral phase. The crystals of periarticular deposits are often more carbonated than bone crystals are, and high-resolution electron microscopy suggests that some of them are coated with electron-dense material.

In synovial fluid samples, mixed populations of BCP crystals have been reported, including partially carbonate-substituted hydroxyapatite, octacalcium phosphate ($\text{Ca}_8\text{H}_2(\text{PO}_4)_6\cdot 5\text{H}_2\text{O}$), and rarely, tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$). They frequently coexist with CPPD crystals and are associated with particulate collagens.²⁹ One report suggested that the crystals extracted from synovial fluid were more like those found in periarticular calcific deposits than in bone crystals, thus suggesting that they were derived from newly formed deposits and not from subchondral bone.³⁰

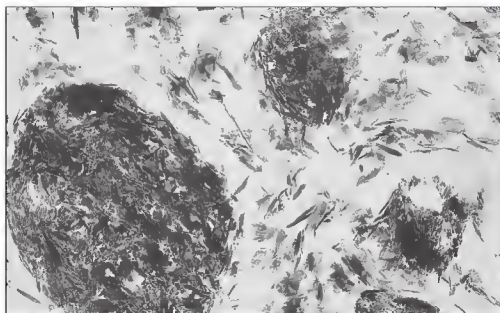


Fig. 191.11 Transmission electron micrograph of basic calcium phosphate crystals from a tendon deposit. Clumps of crystals, dense globular structures of various size, and isolated crystals can be seen.

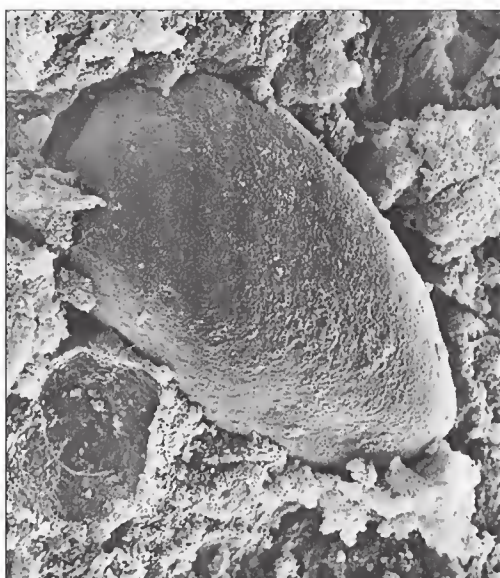


Fig. 191.12 Scanning electron micrograph of a calcific deposit isolated from a tendon.

Another form of BCP, magnesium whitlockite, has been identified in the superficial region of articular cartilage. Some studies suggest that it may be a frequent finding in normal and diseased hyaline cartilage.³¹ This observation, coupled with the identification of some hydroxyapatite crystals in normal cartilage, has led to speculation that some BCP minerals may have a physiologic rather than a pathologic role in cartilage homeostasis. However, whitlockite crystals elicit biologic cellular responses, including mitogenesis and matrix metalloproteinase production *in vitro*, that suggest potential pathogenicity in arthritis.³²

ETIOLOGY

The mechanism of periarticular calcification is largely unknown, although periarticular intratendinous deposits have been thought to be due to ectopic calcification of damaged tendons. In most patients, no obvious local, metabolic, or genetic cause of the calcification is found. The frequent occurrence of bilateral and multifocal deposits suggests the operation of a generalized predisposition, as well as local factors. This is supported by the fact that the sites of deposition in sporadic cases of calcific periarthritis are the same as those associated with a known systemic predisposition such as diabetes mellitus, hyperthyroidism, or parathyroid disorders. The classic description of a relationship between repetitive shoulder use and the formation of calcific deposits has not been established. There is no known relationship with any HLA specificity or other genetic marker despite the known occurrence of familial cases, some with extensive pedigrees.

PATHOGENESIS

Calcific periarthritis

Pathologic assessments have shown that the calcific deposits are located in tendons, peritendinous tissues, bursae, or ligaments. Original studies suggested that “dystrophic” tendon calcification occurs as a consequence of local trauma, ischemia, and necrosis of tendons. Calcific periarthritis frequently localizes to the supraspinatus tendon in a poorly vascularized area of the tendon sheath known as the “critical zone,” a few millimeters from the bone insertion. Similarly, calcification in other tendons seems to occur preferentially in hypovascular segments, which suggests local necrosis followed by ectopic calcification.

Some evidence has indicated that calcifying tendinitis is an active, cell-mediated process in which local vascular and mechanical changes result in focal transformation of tendinous tissue into fibrocartilaginous material containing chondrocytes. This is followed by local deposition of hydroxyapatite crystals within extracellular matrix vesicle-like structures derived from these chondrocytes.³³

Acute calcific periarthritis appears to be induced by rupture of the deposit and shedding of the crystals into more cellular vascular areas. BCP crystals have been shown to be intrinsically phlogistic. They are phagocytosed *in vitro*, which results in the release of inflammatory mediators.³⁴ Similarly, *in vivo* models of inflammation show a brisk inflammatory reaction to apatite, and injection into the tissues of human volunteers results in an inflammatory response.³⁵ Phagocytosis may be one of the main ways in which the crystals are removed.

Evidence indicates that coating of the crystals, which have highly adsorptive surfaces, can either stimulate or suppress the inflammatory response, depending on the nature of the proteins that attach to the crystals.³⁶ Immunoglobulins, for example, may activate inflammatory responses, whereas coating of apolipoproteins on the crystal surfaces will suppress such responses.

Tumoral calcinosis

Light microscopic and immunohistochemical studies have indicated that the calcifying process in tumoral calcinosis and calciphylaxis involves histiocytes and osteoclast-like giant cells of histiocytic origin. Hydroxyapatite crystal formation and calcification appeared to develop predominantly from intracytoplasmic membrane-bound vesicles and also from mitochondria.

Relationship with osteoarthritis and destructive arthropathies

Crystals of BCP are frequently found in OA cartilage, synovium, and synovial fluid. Evidence suggests that human osteoarticular cartilage contains matrix vesicles that are capable of progressive mineralization and can



Fig. 191.13 Bones from a patient with advanced basic calcium phosphate crystal-associated destructive arthritis. The humerus (a) shows the extensive bony attrition characteristic of this condition. The tibial condyles (b) show the characteristic destruction of the lateral tibiofemoral joint, with extensive loss of subchondral bone. L, lateral; M, medial.

generate either BCP or CPPD crystals *in vitro*.³⁷ However, more than one source of formation is likely. For example, the ANK gene product, a cell membrane protein, regulates extracellular inorganic pyrophosphate (ePPi). ePPi is an important inhibitor of nucleation and growth of BCP crystals. ANK-mediated control of ePPi levels is a possible mechanism of regulation of tissue calcification.³⁸ In support of this concept, the roles of the ANK gene and the *TNAP* gene, the product of which also regulates ePPi, have been investigated in patients with cuff tear arthropathy. Variant genotypes for both were observed more frequently in cases than in controls.³⁹

The degree of damage that can occur in apatite-associated destructive arthropathies is marked (Fig. 191.13), but the basis of the cartilage damage by calcium-containing crystals is still somewhat speculative. Theoretically, crystals in cartilage may directly injure chondrocytes. However, in pathologic specimens, crystals are rarely seen in immediate contact with chondrocytes and even less frequently found engulfed by chondrocytes.

It is more likely that cartilage damage ultimately results from effects of the crystals on synovial lining. *In vitro* properties of BCP crystals that emphasize their pathogenic potential have been observed.⁴⁰ BCP crystals induce cellular mitogenesis, a characteristic that presumably leads to synovial proliferation, characteristic of both Milwaukee shoulder syndrome and apatite-associated OA.⁴¹ They can induce the secretion of proteolytic enzymes that lead to the degradation of intraarticular collagenous structures.⁴⁰ Similarly, BCP crystals induce cyclooxygenase-1 (COX-1) and COX-2, followed by increased prostaglandin E₂, and induce proinflammatory cytokines and danger-associated molecules via activation of Syk and phosphatidylinositol 3'-kinase.^{35,42,43} Finally, recent evidence supports a role of the NLRP3 inflammasome in the pathogenesis of BCP crystal-associated arthropathies.⁴⁴

Despite the association of BCP crystals with OA and joint destruction and the biologic effects noted *in vitro*, the specific role of the crystals in joint degeneration is controversial. Some hypothesize that the BCP crystal aggregates found in association with destructive arthropathies actually originate from damaged subchondral bone and are merely an epiphenomenon. More studies will be necessary to further differentiate between crystals as a cause of cartilage damage and crystals as a result of cartilage damage. Improved understanding of the biologic effects of BCP crystals is essential for ultimate prevention or reversal of the consequences of deposition.

MANAGEMENT

Calcific periartthritis

Asymptomatic deposits require no treatment. Acute attacks of calcific periartthritis have been treated successfully with immobilization and a variety of nonsteroidal antiinflammatory drugs (NSAIDs) or colchicine. Most patients have markedly reduced symptoms within 5 days and virtually complete resolution within 1 to 3 weeks. Untreated attacks may last several weeks. Needle aspiration of the pasty calcific deposits with or without irrigation may be helpful. The use of corticosteroids is controversial; local corticosteroid injections will help resolve the acute attacks but may possibly make further calcification and recurrent attacks more likely.

For patients with chronic periarticular syndromes, treatment is in general much the same as it would be regardless of whether deposits are present. In chronic calcific tendinitis, ultrasound treatment helps resolve calcifications and is associated with short-term clinical improvement.⁴⁵ Treatment with disodium ethylenediaminetetraacetic acid can result in significant improvement in shoulder function and pain levels and the disappearance of calcifications with no adverse effects.⁴⁶

If the problem persists and large calcific deposits are present, other treatments can be considered. Local corticosteroid therapy should be used with caution because of the risk of disrupting the deposit or seeding further calcification. Needle aspiration is usually difficult in chronic cases, but arthroscopic or surgical removal may provide permanent symptomatic relief in refractory cases.

Tumoral calcinosis

Recently, successful treatment of both tumoral calcinosis and calciphylaxis with intravenous sodium thiosulfate has been reported.⁴⁷ The beneficial effect of sodium thiosulfate has been ascribed to the extremely high solubility of calcium thiosulfate salts, which results in inhibition of precipitation of calcium salts and dissolution of calcium deposits with subsequent mobilization of tumorlike masses. Whether this is in fact the mechanism of action is unknown, as is the optimal duration of treatment.

Articular basic calcium phosphate crystals

Currently, patients with OA complicated by BCP crystal deposition should be treated in the same manner as though they had simple OA because no specific treatment has been identified or tested. It is hoped that ongoing research endeavors will ultimately lead to the development of more specific treatment of apatite deposition.

At the time of diagnosis of BCP crystal-associated destructive arthropathies such as Milwaukee shoulder syndrome, advanced destructive changes are usually present and may even be asymptomatic. Treatment of symptomatic disease is generally unsatisfactory. A conservative approach that includes analgesics and NSAIDs, repeated shoulder aspirations, and decreased joint

use has sometimes controlled the symptoms satisfactorily. In theory, nonselective COX inhibition would be more effective because BCP crystals induce both COX-1 and COX-2. Surgical therapy is sometimes successful in relieving pain and restoring function but may be difficult because of the extent of damage to the joint and periarticular tissues. Surgical procedures include arthroscopic lavage or débridement (or both), humeral tuberopecty arthrodesis, arthroplasty, and hemiarthroplasty.⁷ Some patients have responded to closed-needle tidal-joint irrigation followed by the injection of methylprednisolone acetate (40 mg) and tranexamic acid (0.5 g).⁴⁸ Other pain-relieving measures such as suprascapular nerve blocks for shoulder disease or transcutaneous nerve stimulation have been used with some success. The pain may subside with time alone.

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Other crystal-related arthropathies

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- The clinical significance of non-monosodium urate monohydrate joint crystals, calcium pyrophosphate dihydrate crystals, and hydroxyapatite crystals varies widely, depending on the crystal.
- Oxalate and depot corticosteroid crystals have established pathogenic potential.
- Other crystalline material with possible pathogenic implications includes liquid lipid crystals, cholesterol, other lipids, hematoidin, immunoglobulins, Charcot-Leyden crystals, and foreign bodies.
- Crystal-like artifacts are potential sources of confusion.

HISTORY

Identification of the infrequently found joint, bursa, or subcutaneous crystals remains an evolving topic. This has been stimulated largely by the technique of polarized light microscopy introduced by Hollander and McCarty in the early 1960s and by the expanded use of microscopic examination of joint fluids as part of the routine diagnostic evaluation of arthritis. Oxalate crystals in joint fluids were first reported in 1982,¹ and depot corticosteroids have, since their introduction in 1951, been known to be able to cause inflammation occasionally.²

In this chapter the suggestive clinical features and appropriate investigations are described for these and several less common crystals.

Oxalate crystals

Oxalate crystals are found less often in synovial fluid than monosodium urate, calcium pyrophosphate dihydrate (CPPD), and apatite crystals are, even though they can be associated with acute or chronic arthritis. Oxalate crystal deposition disease is seen in patients with primary familial hyperoxaluria types 1 and 2 (PH1 and PH2) and in patients with end-stage renal disease (ESRD), especially in those maintained long-term on dialysis.³ In addition to deposition in joints and bones, oxalate crystal deposits are found mainly in the kidneys, skin, and vessels. Clinical and radiographic features include calcium oxalate osteopathy, acute and chronic arthropathy with chondrocalcinosis, synovial calcification, milium skin calcium oxalate deposits, and vascular calcifications that for some unknown reasons affect mainly the hands and feet.³

Oxalate is present in several edible plants and fruit. The gut does not absorb much oxalate from the diet because most will be metabolized by the flora or leave the body in stool. In patients with inflammatory bowel disease such as Crohn and ulcerative colitis, much dietary oxalate is absorbed with a resulting increase in serum oxalate levels.³ Variation in absorption of dietary oxalate can range from as little as 1% to 2% to as high as 50%.

Oxalate can be produced endogenously, and production can be increased as a result of enzyme imbalance because of genetic variation or differences in lifestyle with varying intake of vitamin B₆, magnesium, or thiamine. Increases in oxalate generation can also be a consequence of high doses of vitamin C or consumption of high levels of fructose.³

PH1 is a rare autosomal recessive metabolic disorder that results in the overproduction of plasma oxalate.⁴ Although the enzymatic defect resides in hepatocyte peroxisomes, uncontrolled levels of oxalate result in calcium oxalate deposition in multiple organs. Because the primary route of elimination of oxalate is renal excretion, high levels are found in urine. Patients typically have recurrent nephrolithiasis and nephrocalcinosis. If not

diagnosed early, ESRD and systemic calcium oxalate deposition can occur. Once ESRD develops, intensive dialysis therapy is unable to keep pace with the high oxalate production, and the preferred therapeutic intervention is combined kidney-liver transplantation. The diagnosis of PH1 must be considered in the differential diagnosis of patients with ESRD and a history of recurrent nephrolithiasis. Genomic DNA studies have identified the genetic defects leading to PH1 and PH2, thereby allowing precise early diagnosis.³

Oxalate deposition may complicate amyloid-induced renal failure in patients with rheumatoid arthritis.⁵ Total leukocyte and differential counts in synovial fluid vary but are generally less than 2000/mm³. Inflammatory reactions in tissue may be absent, or a granulomatous response around the crystals may be noted. Oxalates may also be found in intervertebral disks and contribute to disk destruction in dialysis patients.⁶ Because oxalosis is also generalized in many of these patients, crystal deposition can occur at other sites as well, including bone marrow.⁷ Oxalosis can thus cause vascular insufficiency with gangrene.⁸ Although oxalosis can occur as a result of small bowel resection or inflammatory bowel disease, oxalate-induced arthritis has not yet been reported as a complication of these causes.

Definitive diagnosis is achieved by identification of crystals in joint fluid or by biopsy of joints, bones, or other tissues. Synovial fluid crystals can be pleomorphic but characteristically include at least some with bipyramidal or envelope-like shapes (Fig. 192.1), a distinctive feature that helps in the differential diagnosis. Sizes range from 5 to 30 μ m. Most crystals are strongly birefringent, although some of the smaller rodlike ones can have positive elongation that could cause confusion with CPPD. Most also stain brightly with calcium stains such as alizarin red S, which might cause further confusion with the various apatite-like crystals or CPPD. Under electron microscopy, oxalates are electron dense and foamy and thus are indistinguishable from CPPD without elemental analysis, which shows that the oxalates contain calcium but no phosphorus. X-ray or electron diffraction, infrared spectroscopy with Fourier transformation, or Raman spectroscopy can be helpful in making the diagnosis when available and used by experienced operators.

Radiographs of joints can show calcifications. The opacification of articular structures seen with oxalates can be found in cartilage or soft tissue and can mimic either CPPD or apatite-associated diseases. Some patients with articular oxalates will have no calcification visible on radiographs. Oxalate-infiltrated bones show various patterns, including sclerosis and demineralization.

Depot corticosteroid crystals

The obvious clinical clue to this phenomenon is known or suspected recent intraarticular or bursal injection.^{9,10} If an inflammatory reaction occurs, it is most frequent during the first 8 hours after injection. Such reaction tends to help distinguish this phenomenon from an infection, which generally develops considerably more slowly.

Depot corticosteroid crystal-induced inflammation appears to be more common with triamcinolone hexacetonide than with other preparations. The former preparation is also less soluble, which may increase the chance of inducing acute inflammation. Inflammatory responses have been shown to vary among the different depot corticosteroids after injection into rat air pouches.¹¹ The inflammation may be transient because of corticosteroid suppression as it dissolves in the joint. Even joints in patients with osteoarthritis that are dramatically improved promptly after corticosteroid injection may transiently show depot corticosteroid crystal phagocytosis and mildly increased leukocyte counts in synovial fluid.¹² The diagnosis can be supported by aspiration and identification of pleomorphic crystals, which include irregular shapes, rods, and squares with intense positive or negative birefringence (Fig. 192.2). Phagocytosis of crystals by neutrophils and

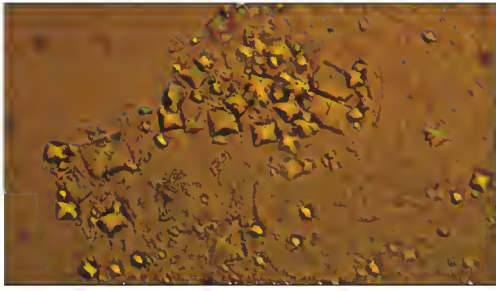


Fig. 192.1 Oxalate crystals from synovial fluid seen with regular, unpolarized light. Note that some crystals have the characteristic bipyramidal shape ($\times 400$).

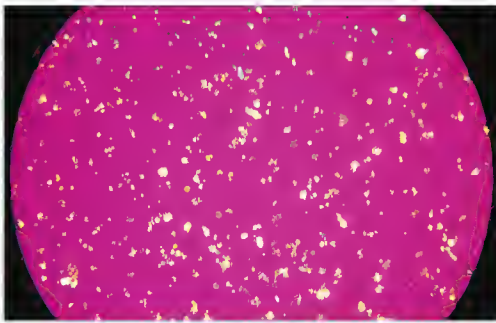


Fig. 192.2 Bright, irregular, depot corticosteroid crystals. Crystal morphology can vary widely with preparation, batch, and duration of storage (compensated polarized light, $\times 400$).

mononuclear cells can be observed.¹³ When acute inflammation develops after an injection, it may be necessary to perform a Gram stain and obtain material for culture to exclude infection. Radiographs are not helpful. Depot corticosteroids can also be artifacts as a result of contamination of specimens during handling if a corticosteroid is injected after arthrocentesis.

Lipid crystals

Lipid crystals may be pathogenic or potentially confusing factors when present in joint effusions.

Cholesterol crystals

Cholesterol crystals (Fig. 192.3) may be a complication of joint effusions resulting from rheumatoid arthritis (Fig. 192.4). Other less common causes include osteoarthritis, and crystals are also found in sites such as the olecranon bursae. Cholesterol crystals are most often seen as broad plates with a notched corner. Needle-shaped crystals with negative elongation (which are not monosodium urate crystals) may also be seen in cholesterol-laden fluid.¹⁴ Synovial fluid may have a glossy golden appearance. Cholesterol crystals may develop in rheumatoid nodules and gouty tophi and have been found in rheumatoid pericarditis.

There is some debate that although cholesterol crystals are often too large to undergo phagocytosis, they may contribute in some way to perpetuation of inflammation. Evidence in support of this comes from studies of injection of cholesterol crystals subcutaneously to stimulate inflammation.¹⁵ Similarly, injection into guinea pig gallbladders caused increases in interleukin-1, myeloperoxidase, prostaglandin E_2 , and prostaglandin F in luminal fluid.¹⁶ Cholesterol-containing subcutaneous tophi or ganglion-like nodules have also been described,¹⁷ and the sites involved may be related to repeated local microtrauma.

Lipid liquid crystals

Lipid liquid crystals are caused by lipid states with the characteristics of both liquids and solids; they form layered arrays that appear as birefringent microspherules.¹⁸⁻²⁰ They form from phospholipids released from red blood cells or other cells. Trauma with hemarthrosis has preceded some but has not been evident in all cases, so other sources of these lipid spherules should be considered, such as other antecedent inflammatory exudation. When present in large number, lipid liquid crystals resembling Maltese crosses may undergo phagocytosis and be associated with acute joint symptoms. Most patients have monoarthritis. The knees are most frequently involved, but wrist involvement and even polyarthritis, with possibly similar mechanisms,

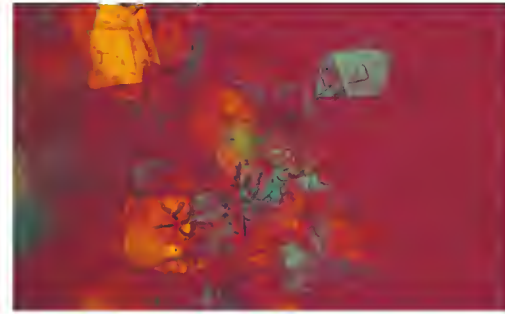


Fig. 192.3 Classic cholesterol plates with overlapping and some corner notching (compensated polarized light, $\times 400$).



Fig. 192.4 Red tender swelling at the first metatarsophalangeal joint in a patient with rheumatoid arthritis from which fluid with a large number of cholesterol crystals was aspirated.



Fig. 192.5 Positively birefringent Maltese cross-like lipid microspherules from the synovial fluid of a patient with otherwise unexplained acute arthritis (compensated polarized light, $\times 1000$).

have been reported. Synovial fluids have been inflammatory and contain 10,000 to 40,000 leukocytes/ mm^3 , with intracellular "Maltese crosses" identified in many samples. Polymorphonuclear leukocytes or macrophages are the predominant cells.

Lipid liquid crystals are readily identified under compensated polarized light as 2- to 20-mm Maltese cross-like spherules with the two blue parts of the cross lined up parallel to the axis of slow vibration of the compensator (positive elongation) (Fig. 192.5). Rare Maltese crosses are not clinically significant, but when they are frequent and intracellular, they should be considered as possible causes of the arthritis if no other explanation is

evident. Lipid liquid crystals need to be distinguished from starch derived from gloves, which has a more polygonal outline, and from rare urate microspherules, which have negative birefringence.

Other lipids

There is interest in whether lipid crystals can explain some of the arthritis and tenosynovitis reported to complicate type II and IV hyperlipoproteinemia. A case report describing incompletely characterized, brightly positively birefringent rodlike crystals in a tendon of a man with hypercholesterolemia and Achilles tendinitis is suggestive.²¹ Most hyperlipidemic patients do not have lipid crystals. Synovial xanthomatosis has been described with normal serum lipid levels.²² Synovial biopsy specimens can show infiltration with foam cells.

Nonbirefringent droplets composed largely of neutral lipids are common after trauma, with lymphatic obstruction, in pancreatic disease, and occasionally in type IV hyperlipoproteinemia. Fractures into joints can produce tomato soup–like bloody effusions with lipid droplets that will rise to the surface on centrifugation.²³ Chylous effusions secondary to lymphatic obstruction or trauma can be milky with chylomicrons.^{24,25} Needle-shaped crystals with negative elongation can precipitate in neutral lipid droplets, especially during storage, and can be a source of confusion with urates. Uricase digestion can be used to determine whether urate crystals are present, although this may be difficult to interpret if only rare urates are mixed with the lipid crystals. Crystalline lipids do not generally stain with fat stains as do neutral fat droplets.

Protein crystals

Data on protein crystals are limited, with most based on case reports. One interesting case report involved a patient who had chronic polyarthritis that appeared to be due to massive intraarticular crystalline precipitates of an IgG cryoprecipitable paraprotein.²⁶ This patient had an erosive arthritis with inflammatory synovial fluid (30,000 leukocytes/mm³, 90% polymorphonuclear neutrophilic leukocytes) and chronic inflammation in the synovium surrounding deposits of crystals. Another patient with multiple myeloma had polyarthritis with weakly birefringent rhomboid crystals that were not observed until the synovial fluid cooled.²⁷ Other patients with cryoglobulinemia may have arthritis without synovial fluid crystals. In vessels, crystallized cryoglobulin or myeloma proteins can cause vascular obliteration. Cryoglobulin crystals have been emphasized as a cause of both destructive arthritis and vasculopathy.²⁸ A mouse model of IgG3 cryocrystal globulinemia has been reported with deposits in kidneys.²⁹

Immunoglobulin crystals are pleomorphic and may be larger than 60 nm. However, they can also appear as smaller squares, hexagons, rhomboids, or rods and potentially be confused with known pathogenic crystals. Because they are proteins, they will stain with methylene blue (Fig. 192.6). Some crystals are negatively birefringent. Monoclonal antibodies can provide specific identification. Other protein crystals described in synovial fluid and other sites include Charcot-Leyden crystals,^{30–32} which are believed to be composed of lysophospholipase in eosinophil-laden fluid; hemoglobin; and hematoidin. Charcot-Leyden crystals have a characteristic spindle shape and are weakly birefringent with positive or negative elongation (Fig. 192.7). Hematoidin crystals (Fig. 192.8), derived from the breakdown of hemoglobin, are rhomboids very similar to CPPD, except for their golden color on regular light microscopy. Other golden debris and stellate arrays are rarely seen but have been identified as hematoidin at other sites.^{23,33,34} Their identification and possible modes of formation have been reviewed.^{33,34} Because hematoidin and Charcot-Leyden crystals can undergo phagocytosis, they may have phlogistic potential. Hemoglobin has also rarely been noted to crystallize out as rods in dried smears containing red cells.³³

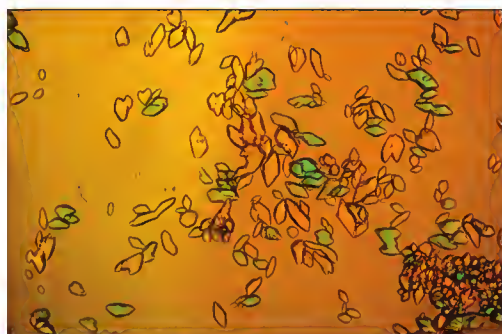


Fig. 192.6 Myeloma protein crystals (compensated polarized light, ×100).

Crystalline and other potentially confusing foreign material

Foreign bodies can cause acute or recurrent arthritis that is usually monoarticular. These bodies may be crystalline or poorly crystalline. The penetrating injury may not be recalled. Most foreign bodies become embedded or sequestered in synovial tissue and consequently are not seen in synovial fluid. Thus, arthroscopy or arthrotomy may be required for diagnosis. There are a number of examples of foreign bodies with such effects. Plant thorns can be associated with dramatic packing of cells and cellulose that is accentuated with polarized light. Calcium carbonate from sea urchin spines is birefringent and irregular. Birefringent fiberglass fibrils or polyethylene and methacrylate wear particles in patients with joint replacements have also been described in joint fluid.³⁵ Silicone wear particles can produce granulomatous reactions in synovium in patients with failure of finger implants.³⁶ Wear particles from metallic prosthetic implants can be dark metal shards.³⁷ Any of these particles can undergo phagocytosis and be a cause of low-grade inflammation.^{38,39} Aluminum crystals have been reported in joints in patients with systemic aluminum toxicity. Most foreign bodies are not radiopaque, and magnetic resonance imaging may help identify some of them. Patients with the rare inflammatory reactions after hyaluronate G-F 20 injections may have shiny, nonbirefringent inclusions in synovial fluid cells.⁴⁰

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Methods for investigation and differential diagnosis span the variety of techniques in use for the more commonly recognized crystal-associated syndromes. They can include regular and polarized light microscopy, electron microscopy, elemental analysis, x-ray or electron diffraction, Fourier transform infrared analysis, and atomic force microscopy. In addition, monoclonal antibodies can be used to stain immunoglobulin crystals, and the Fouchet stain can probably help identify hematoidin.²³ To exclude the more common diseases, uricase or pyrophosphatase digestion may be attempted. Artifacts seen on wet preparations with regular or polarized light have frequently been a source of diagnostic confusion (Box 192.1).⁴¹ Figures 192.9 to 192.12 illustrate some of the artifacts found.

ETIOLOGY AND PATHOGENESIS

As each new crystal of suspected pathogenic significance has been suggested, new techniques have been used by investigators to help establish



Fig. 192.7 Charcot-Leyden crystals (regular light microscopy, ×400).

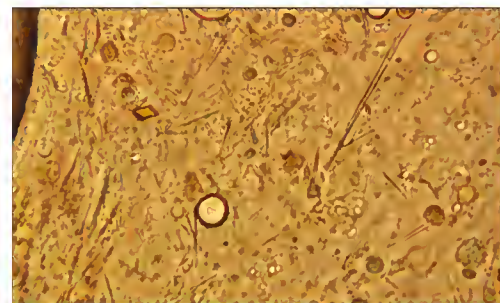


Fig. 192.8 Golden rhomboid-shaped hematoidin crystal along with many monosodium urate crystals (regular light microscopy, ×400).

BOX 192.1 CRYSTAL-LIKE ARTIFACTS SEEN IN SYNOVIAL FLUID WET PREPARATIONS

Depot corticosteroid crystals
 Glass fragments
 Nail polish from sealed coverslip edges
 Wood fragments from sticks used in transport
 Starch from gloves
 Anticoagulant crystals—sodium oxalate, lithium, heparin
 Precipitates from storage—calcium phosphates, oxalates, hemoglobin, hematoidin, lipids, unidentified material
 Dust
 Lens paper fibrils
 Polyester from yellow serum separator tubes



Fig. 192.9 Slivers of glass from coverslips can be needle shaped and mimic monosodium urate crystals, even to the point of having negative elongation in compensated polarized light ($\times 400$).

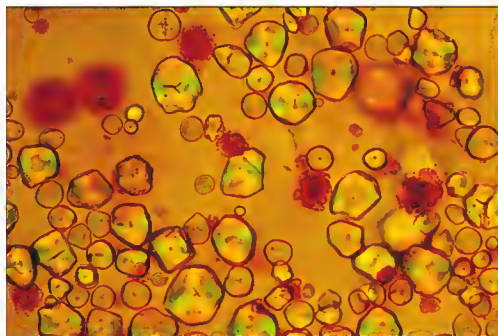


Fig. 192.10 Starch from gloves produces Maltese cross-like particles that are more angular than liquid lipid crystals. Calcium phosphates stained here with alizarin red S are also present in some powders (compensated polarized light, $\times 400$).

their identity and to test their inflammatory potential. Crystals can be tested for inflammatory properties by intraarticular injection, injection into the pleural space, or injection into air pouches on the dorsum of the rat, which produces a synovial-like space.⁴² *In vitro* incubation with various cells and chemotactic assays are also used. Some crystals may not produce acute, readily detectable inflammation but may interact with chronic inflammatory cells and still have a long-term impact. Studies may well be worth extending to better define any important roles of crystals such as cholesterol, lipid liquid crystals, and hematoidin and also to investigate prosthetic wear particles and polymethyl methacrylate cement, which may

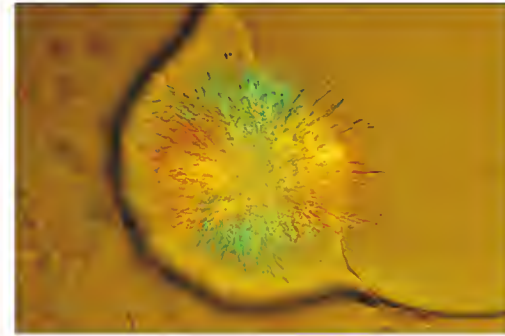


Fig. 192.11 Negatively birefringent needles precipitate in synovial fat droplets during storage. When they are released into joint fluid, they can mimic monosodium urate crystals (polarized light, $\times 400$).

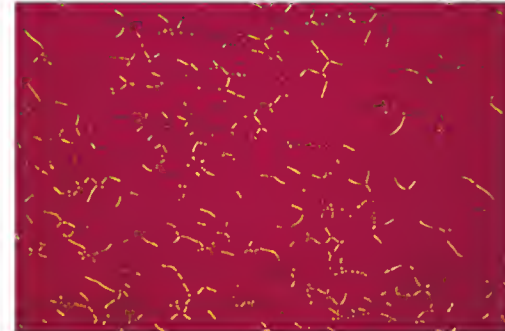


Fig. 192.12 As fluid dries, birefringent salts precipitate (compensated polarized light, $\times 100$).

produce inflammation in ways similar to crystals.^{39,42} Injection of polymethyl methacrylate cement into rat air pouches⁴² does produce inflammation. Cholesterol crystals can activate the inflammasome and complement,^{43,44} thus suggesting a process that might be involved in atherosclerotic plaque, as well as in joints or bursae. Surface charge, binding properties, and activation of the inflammasome can also be studied with other crystal or crystal-like particles. An organic matrix is associated with oxalate stones, and proteins may well also bind to oxalates in joints.

The reasons why only very few individuals have deposits of the crystals discussed earlier despite apparent similar risks are also potential areas for investigation. Some investigations suggest direct mechanisms for crystal production. Thus, lipid liquid crystals were shown to result from hemorrhage after blood was injected into joints and Maltese cross-like particles developed.⁴⁵

MANAGEMENT

Treatment of inflammatory episodes related to these less common crystals has not been studied systematically. When the clinical situation permits, nonsteroidal antiinflammatory drugs are generally used for oxalate-associated inflammation or to temporarily help with depot corticosteroid-induced bouts. Rarely, depot corticosteroid crystals have to be aspirated from unusually prolonged iatrogenic corticosteroid crystal-induced inflammation. Measures to deplete the crystals discussed here are not known. Oxalate accumulation in hemodialysis patients may be slowed by avoiding the use of vitamin C, which is metabolized to oxalate. Cryoglobulins can be decreased by treating the underlying disease, and one patient's arthritis improved with oral and intraarticular corticosteroids.²⁷ In a patient with Waldenström cryoglobulinemic vasculitis, rituximab initially increased cryoglobulin levels but then led to a response.⁴⁶ Foreign bodies, of course, are best managed by removal.

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ENDOCRINE AND HEMOGLOBIN-RELATED ARTHRITIS AND STORAGE DISEASES

193

Rheumatoid manifestations of endocrine and lipid disease

■ SIMON M. HELFGOTT

- Musculoskeletal abnormalities occur commonly in association with endocrine disease.
- Glandular dysfunction involving the adrenal, pituitary, pancreas, parathyroid, and thyroid may be manifested as rheumatologic disorders.
- Nonspecific rheumatic manifestations and more characteristic abnormalities may occur.
- Musculotendinous, bone, and joint abnormalities are more likely after periods of metabolic imbalance.
- Specific clinical problems (i.e., widened joint spaces, Dupuytren contracture, osteonecrosis, periosteal bone resorption, and muscle weakness) should prompt exclusion of particular disorders.
- Resolution or improvement of the clinical manifestations of rheumatic disease may occur on restoration of metabolic balance.
- Primary hyperlipidemias (hyperlipoproteinemias) result from abnormal metabolism of lipoproteins with an increase in their blood levels.
- Six types of hyperlipoproteinemias are recognized and differ on the basis of their lipoprotein profiles and musculoskeletal manifestations.
- Tendon xanthomas consist of lipid infiltrates, which results in irregular thickening of the involved tendon.
- They may be observed in type IIa and III hyperlipoproteinemia and can be associated with or be preceded by episodes of acute tendinitis, particularly in type IIa.
- Arthralgias or arthritis (or both) can be a feature of type IIa and type IV hyperlipoproteinemia.
- Osseous xanthomas, or aggregates of spumous macrophages, are rare and have been reported mainly in type III hyperlipoproteinemia.
- Hyperuricemia and gout can be associated with the hypertriglyceridemia of types I, IV, and V.
- Sicca-like syndromes, probably caused by fatty infiltration of the lacrimal and salivary glands with subsequent enlargement of the parotids, can develop in patients suffering from type II, IV, and V hyperlipoproteinemia.

ACROMEGALY

The articular manifestations of acromegaly are a leading cause of morbidity and functional disability in affected patients.^{1,2} At the time of diagnosis, most patients have signs or symptoms of joint disease.³⁻⁵ The duration of acromegaly does not appear to correlate with the severity of the arthropathy.³ The initial endocrine changes secondary to acromegaly are followed over time by the development of mechanical changes in the joints and the spine. Joint damage in patients with acromegaly occurs in three stages. The first

is characterized by continued, excessive proliferation and regeneration affecting chondrocyte activity and cartilage matrix growth. In the early course of the disease, elevated growth hormone and insulin-like growth factor type I levels promote the growth of articular cartilage and periarticular ligaments, which leads to cartilage thickening and joint space congestion. In this phase, joint space widening and periarticular soft tissue hypertrophy occur. Hyaline cartilage becomes thickened with clusters of large active basal chondrocytes; marginal osteophyte formation becomes excessive and periosteal fibrocartilaginous attachments hypertrophy and ossify. These changes account for the clinical features of acromegaly: large bones with remodeled shafts; thickened cartilage, tendon, and capsule attachments; and large marginal osteophytes (Fig. 193.1). The second stage consists of the development of specific cartilage ulcers at weight-bearing sites, presumably because of unequal cell proliferation and matrix formation in the cartilage midzone, which creates stress in the interterritorial areas and ultimately cartilage fissuring and ulceration. In the third stage, localized loss of cartilage substance takes place. As a repair mechanism, the resultant regenerating fibrocartilage layer is excessive and striking and forms a layer covering the old hyaline cartilage on the exposed bone. These structural alterations result in eburnation of subchondral bone and cyst formation resembling severe forms of osteoarthritis.

Clinical features

Joint pain is a common finding in patients with acromegaly (Box 193.1). Affected joints include those of the jaw, hands, shoulders, hips, knees, and cervical and lumbar spine (Fig. 193.2). Joint effusions are uncommon; rarely, some patients may experience episodes of pseudogout. Physical examination shows evidence of bony enlargement and soft tissue prominence surrounding affected joints. Radiographs demonstrate widened joint spaces with chondrocalcinosis, osteophyte formation, and calcification of ligamentous insertions. Prognathism is seen commonly and usually accompanied by widening of the interdental spaces.⁶ The Raynaud phenomenon has been described in about a quarter of patients.² Bilateral carpal tunnel syndrome is often present and symptomatic at initial evaluation.⁷ Magnetic resonance imaging has demonstrated increased edema of the median nerve in the carpal tunnel rather than extrinsic compression.⁷ A hallmark feature is vertebral enlargement with widened intervertebral spaces and osteophyte formation; however, facet joint hypertrophy is unusual.⁶ A high prevalence of vertebral fractures has been observed in men and postmenopausal women with acromegaly, regardless of their bone mineral density scores.⁸

DIABETES MELLITUS

Diabetes mellitus is associated with a range of musculoskeletal and rheumatologic problems (Table 193.1). Many studies have observed that the symptoms of hand pain and dysfunction occur more frequently in diabetic patients.⁹ A longer duration of diabetes rather than hemoglobin A_{1c} levels appears to correlate with a higher frequency of hand and shoulder

APPEARANCE OF THE HAND IN ACROMEGALY

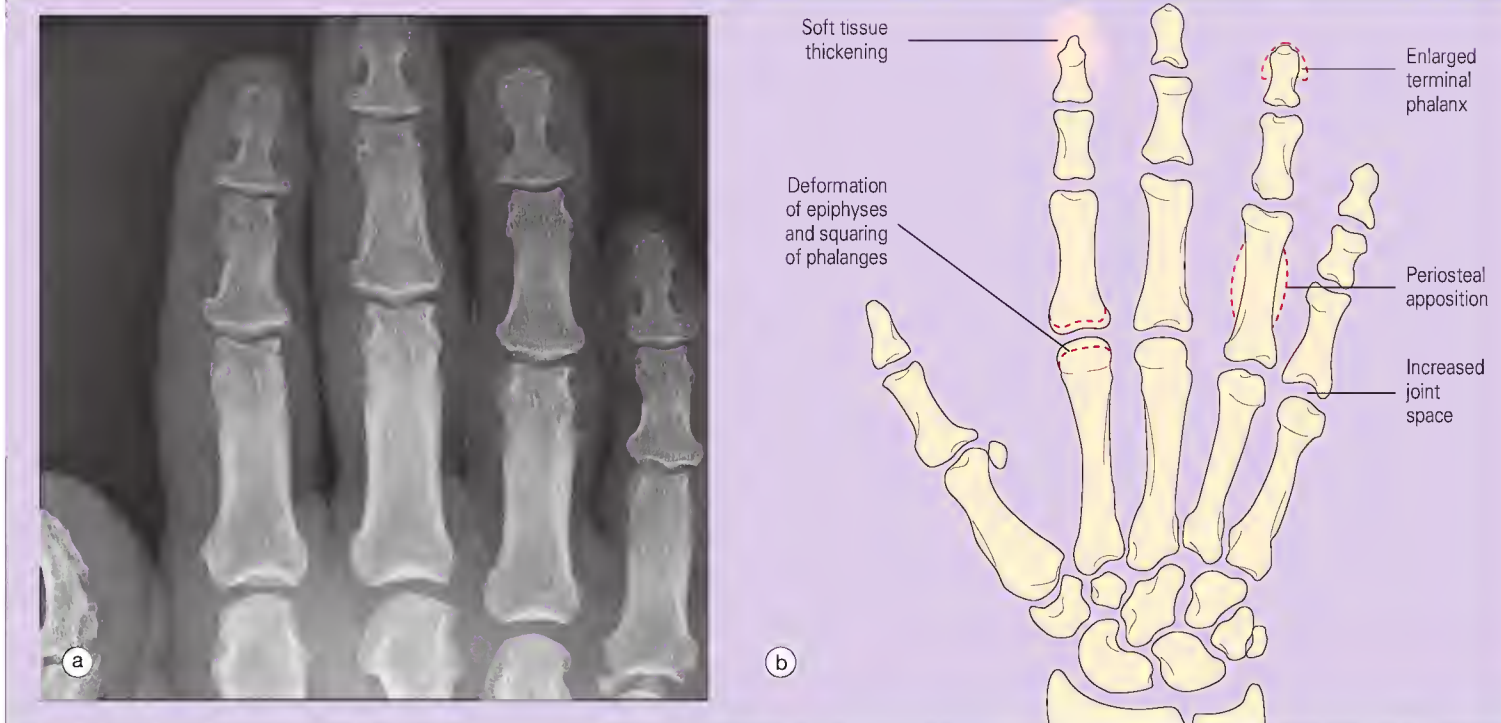


Fig. 193.1 (a) Apart from the soft tissue thickening of the hand, this radiograph also shows the increased joint space and enlargement and tufting of the terminal phalanges. (b) Examination of the hand is important for the diagnosis of acromegaly.

APPEARANCE OF THE LUMBAR SPINE IN ACROMEGALY

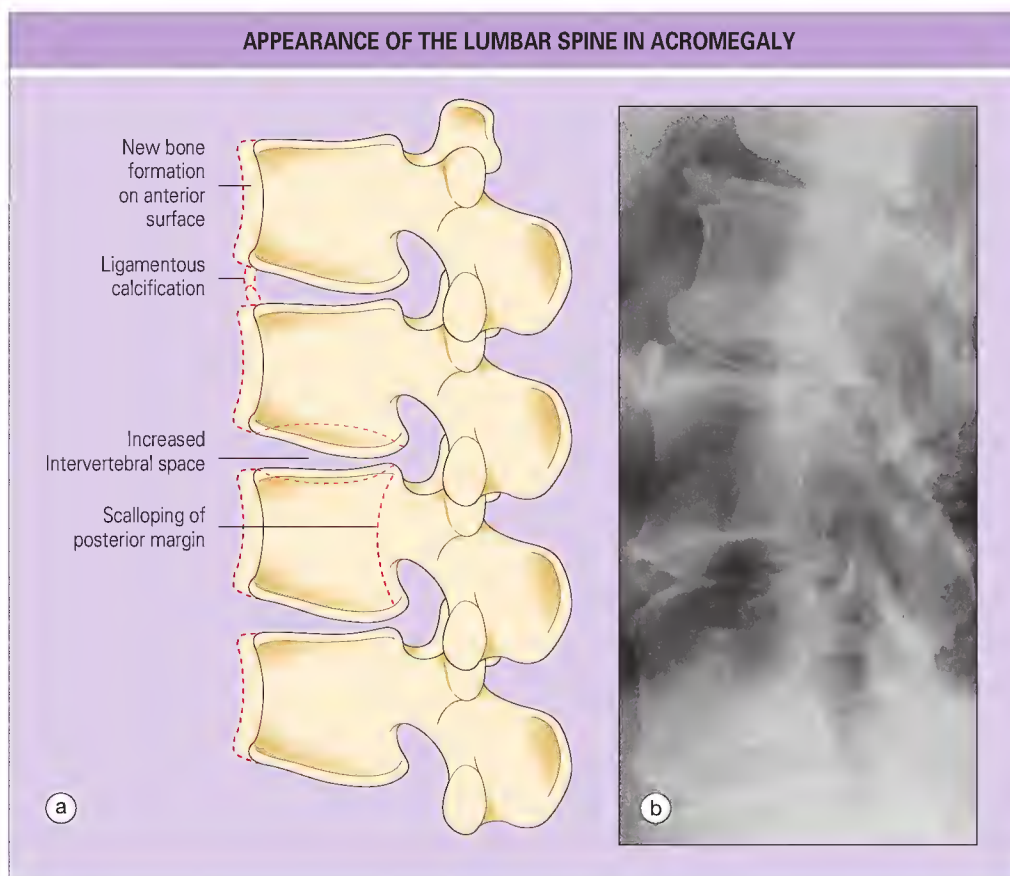


Fig. 193.2 (a) Typical changes include scalloping of the posterior margin of the vertebrae, new bone formation on the anterior surfaces, and increased intervertebral space. (b) A radiograph of the lumbar spine shows the decrease in disk height because of late degenerative disease.

BOX 193.1 MUSCULOSKELETAL FEATURES OF ACROMEGALY

Clinical features of acromegaly include large bones with remodeled shafts, thickened cartilage, enlarged tendon and capsule attachments, and large marginal osteophytes.

Pain and crepitus are common but rarely accompanied by restricted motion.

Despite frequent back pain, back mobility is maintained even with aging because the thickened intervertebral disk cartilage, together with lax hypertrophied paraspinal ligaments, contribute to increased spinal mobility.

A higher incidence of vertebral fractures may be observed.

Adapted from Bluestone R, Bywaters E, Hartog M, et al. Acromegalic arthropathy. *Ann Rheum Dis* 1971;30:243-58.

TABLE 193.1
Rheumatologic manifestations of diabetes

Disorder	Special features
Adhesive capsulitis	Unilateral shoulder pain Therapies include intraarticular corticosteroids, physical therapy
Limited joint mobility	Painless, "prayer sign" Occasionally associated with hand weakness Correlation with microvascular disease
Dupuytren contracture	Ring, middle finger involvement is more common May be less painful in patients with diabetes
Stenosing tenosynovitis	More common in females Bilateral, multidigit involvement with relative sparing of the index and small fingers
Carpal tunnel syndrome	Similar manifestation as in nondiabetics Bilateral involvement Surgical release may be less effective than in nondiabetics
Calcific tendonitis	Basic calcium pyrophosphate crystal deposition Acute and intensely painful Radiographs may demonstrate calcium deposition within tendons and soft tissues
Diffuse idiopathic skeletal hyperostosis	Seen more commonly in diabetics Typically an asymptomatic finding Anterior ligament ossification on radiographs Peripheral joint calcific enthesopathy
Charcot arthropathy	Unilateral foot involvement, usually the midfoot Seen in the context of severe peripheral neuropathy Osteolysis, joint destruction Role of proinflammatory cytokines?
Muscle infarction	Associated with long-standing disease Pain, swelling, and induration of the thigh High signal intensity noted on T2-weighted magnetic resonance images Resolves over time
Stiff person syndrome	Progressive axial stiffness may lead to an appearance mimicking spine ankylosis. Straightening of the lumbar lordosis "Startle" response (marked hardening of the muscle group in response to fright or surprise) present in most patients Association with raised titers of anti-GAD antibody

GAD, glutamic acid decarboxylase.

syndromes.⁹ A study of adolescents with type I diabetes mellitus found that plantar fascia thickness, as measured by ultrasound imaging, was a significant predictor of the subsequent development of complications in type I diabetes mellitus, thus suggesting that glycation and oxidation of collagen in soft tissues may be independent risk factors for microvascular complications.¹⁰ Similarly, the finding of limited joint mobility of the hands in patients with type I diabetes may indicate an increased risk for microvascular disease.¹¹ Patients with limited joint mobility typically have limited extension of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints, generally beginning in the ulnar digits and spreading

radially.¹² Patients are asked to hold their hands opposed to one another with the wrists extended and the elbows flexed (prayer sign); a positive test is indicated by the inability of patients to completely approximate the palmar surface of the digits. Dupuytren contracture consists of palmar and digital nodules and cords, palmar skin tethering, and digital contractures.¹² In contrast to nondiabetics, the condition is milder, the ring and middle digits are predominantly involved as opposed to the small and ring digits, and few patients complain of symptoms.¹³ Carpal tunnel syndrome has similar findings in diabetic and nondiabetic patients. However, many authors think that diabetic patients have poorer outcomes following carpal tunnel release than nondiabetic patients do.¹⁴

There may be subtle distinctions between the clinical manifestations of stenosing tenosynovitis (trigger finger) in diabetic versus nondiabetic patients. When compared with a nondiabetic population, trigger finger in diabetics is more commonly seen in females and more often bilateral and involving multiple digits with relative sparing of the index and small fingers.¹⁵ Corticosteroid injection is less effective in diabetics, and these patients require surgery more frequently. Adhesive capsulitis of the shoulder can be defined as unilateral shoulder pain of greater than 3 months' duration with an associated reduction in range of motion in all planes by at least 50%.⁹

A study attempting to quantify the prevalence of painful or stiff shoulder in diabetic patients found that shoulder pain was present in about a quarter of the patients as compared with just 5% of nondiabetic individuals.¹⁶ Frozen shoulder was observed in about 4% of patients versus less than 1% in the nondiabetic cohort.

Neuropathic (Charcot) arthropathy is typically characterized by pain and swelling of the midfoot in a patient with underlying peripheral neuropathy. Over time, evidence of severe osteolysis may be seen, and bone and joint destruction may follow. The condition is sometimes self-limited and one sided even though the neuropathy is permanent and symmetric.¹⁷ It has been proposed that activation of proinflammatory cytokines, including tumor necrosis factor- α and interleukin-1 β , together with RANKL-NF- κ B signaling, may result in bone lysis and calcification of the media of the arterial walls of blood vessels supplying the feet.¹⁷

Stiff person syndrome is an uncommon disorder seen in some type I diabetic patients. The condition is characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles with severe impairment of ambulation. In severe cases a fixed spinal deformity with pronounced lordosis is evident. The hallmark feature is the presence of superimposed, severe episodic muscle spasm precipitated by sudden movement, noise, or emotional upset (startle reflex). Stiff person syndrome and type I diabetes share some immunologic features, including the presence of antibodies to glutamic acid decarboxylase, although the magnitude of the antibody response and the selected epitopes that are recognized differ in these two diseases.¹⁸

THYROID DISEASE

Disorders of thyroid function can be accompanied by a variety of rheumatologic symptoms ranging from arthralgia and myalgia to weakness and digital vasospasm (Table 193.2). Thyroid deficiency is more frequently associated with musculoskeletal symptoms than hyperthyroidism is. In older patients, hypothyroidism may mimic a polymyalgia rheumatica-like disorder consisting of proximal achiness around the shoulder and pelvic girdle muscles and generalized stiffness. Other patients may have an associated myopathy¹⁹ with findings ranging from mild (delayed tendon reflex response) to severe (weakness, cramps, and severe stiffness). The latter has been termed Hoffman syndrome. This disorder may also be accompanied by muscle hypertrophy (pseudohypertrophy). Most symptoms improve or resolve following correction of the hypothyroidism.¹⁹ Carpal tunnel syndrome may also be associated with hypothyroidism and generally improves with thyroid hormone replacement.²⁰ Myoedema may occasionally be noted when the muscles of affected individuals are tapped with a reflex hammer; the resulting induration persists for several seconds. Rare patients may have a symmetric polyarthritis that involves the metacarpophalangeal and metatarsophalangeal joints, wrists, and knees and resembles seronegative rheumatoid arthritis. Synovial fluid analysis has demonstrated low white blood cell counts and normal fluid viscosity.²⁰

Hyperthyroidism secondary to Graves disease is associated with an unusual cutaneous manifestation known as pretibial myxedema. This dermopathy is an uncommon and late manifestation of Graves disease and is often seen concurrent with the development of Graves ophthalmopathy.²¹ It is generally asymptomatic and manifested as skin induration over the pretibial area, although other areas can be involved as well. The lesion is

TABLE 193.2
Rheumatologic manifestations of thyroid disorders

Manifestation	Hypothyroidism	Hyperthyroidism
Arthralgia, myalgia, achiness, and stiffness	PMR-like manifestation Delayed resolution	Seen at onset Resolves with treatment
Arthritis	Polyarticular MCP, MTP involvement	Acropachy, clubbing
Cutaneous	Raynaud phenomenon	Pretibial myxedema
Myopathy	Proximal, resolves slowly EMG: sensorimotor axonal neuropathy Rarely, "pseudohypertrophy"	Proximal, resolves quickly Sensorimotor axonal neuropathy
Carpal tunnel syndrome	Improves with treatment	Not observed
Vasculitis	Not observed	Rarely seen with the use of propylthiouracil
Bone metabolism effects	Not observed	Increased bone turnover and bone loss
ANA positivity	Occasionally seen	Occasionally seen

ANA, antinuclear antibody; EMG, electromyogram; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PMR, polymyalgia rheumatica.

associated with elevated levels of serum thyroid-stimulating hormone (TSH) receptor antibodies; it has been suggested that TSH receptors in affected skin may serve as antigens driving this immune response.²¹ In some patients with untreated hyperthyroidism, Raynaud phenomenon may be observed.²²

Thyroid acropachy is an unusual manifestation of hyperthyroidism that is always seen in the context of the dermopathy and ophthalmopathy. It is characterized by clubbing of the fingers and toes. The overlying skin may be swollen and tight. Rarely, radiographic evidence of a periosteal reaction involving the distal digital bones may be present.²³ However, unlike pulmonary osteoarthropathy, which it resembles, the bony reaction has a spiculated lacy appearance and is limited to the midportion of the diaphysis with sparing of the long bones.

Myopathy may be present in about 20% of patients in the early stages of hypothyroidism. Patients may complain of proximal weakness, and electromyographic studies have demonstrated a sensorimotor axonal neuropathy.¹⁹ Unlike the myopathy seen with hyperthyroidism, these signs and symptoms resolve immediately with correction of the hypothyroidism. Patients with hypothyroidism also have increased bone turnover and net loss of bone mineral density,²⁴ which resolves with therapy. The drug propylthiouracil, which is often used to treat hyperthyroidism, has been associated with the development of an antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis.²⁵ ANCA titers are generally markedly elevated and show a perinuclear (p-ANCA) staining pattern. The vasculitis usually resolves with discontinuation of treatment with the drug, although several reports of patients requiring systemic immunosuppressive therapy have been published.²⁶

HYPERPARATHYROIDISM

Primary hyperparathyroidism is now most commonly diagnosed before the onset of overt symptoms; clinically apparent bone disease is uncommon. Parathyroid hormone increases the rate of bone turnover, and its effects on bone may be catabolic or anabolic, depending on the age of the patient, skeletal site, and pattern of serum concentrations of the hormone over time.^{27,28} In general, persistently high serum parathyroid hormone concentrations have catabolic effects on bone, whereas intermittent mild increases have anabolic effects. On balance, the effects of mild primary hyperparathyroidism on bone seem to be slightly anabolic.²⁹ However, the disorder can cause demineralization of bone, distributed variably between cortical sites (i.e., mainly long bones) and trabecular sites (i.e., mainly vertebrae).^{30,31}

With long-standing, untreated severe forms of this disease, osteitis fibrosa cystica may develop. This condition is characterized by bone cysts, brown tumors, fractures, and skeletal deformity. The classic radiographic finding of osteitis fibrosa cystica is subperiosteal resorption of the radial aspect of the index and long fingers. Histologic abnormalities include extensive cortical resorption and tunneling defects lined with osteoclasts. Following successful parathyroidectomy, most of the manifestations of primary hyperparathyroidism, including the skeletal disease, are readily reversed.

Bone disease in patients with chronic renal disease is caused by hyperparathyroidism and other factors.³² Some patients with chronic renal disease have hyperparathyroid uremic bone disease, which is characterized by activation of osteoblasts and osteoclasts with excessive bone resorption. Other patients have an adynamic bone disease or osteomalacia. Adynamic bone disease is characterized by low activity of bone cells, no excessive accumulation of matrix, and little parathyroid hypersecretion.^{32,33} Osteomalacia in renal failure is characterized by excessive accumulation of osteoid and a minimal degree of hyperparathyroidism and has been associated with accumulation of aluminum in bone. This disorder has become less common as a result of minimization of the use of products with high concentrations of aluminum, such as found in some antacids and dialysis fluids.^{32,33} The frequency of hyperparathyroid bone disease in patients with uremia is similar to the frequency of adynamic bone disease.^{32,33} Uremic hyperparathyroid bone disease is best treated by raising serum calcium concentrations and thereby decreasing parathyroid hormone secretion. The cause of adynamic bone disease is not known, and no specific treatment is available.³⁴

Calciophylaxis, or calcific uremic arteriolopathy, is a serious complication of end-stage renal disease that is thought to be due to hyperparathyroidism. Female gender, hyperphosphatemia, and increased serum calcium phosphate product are associated with an increased risk for the development of calciophylaxis. The lesions begin as painful, symmetric violaceous discoloration and evolve into well-demarcated, nonhealing skin ulcers that become necrotic and gangrenous with eschar formation. More distal lesions have been described to involve the calves, forearms, acral areas, and genitalia. The presence of lesions more proximally located on the shoulders, trunk, buttocks, and thighs portends a worse prognosis. Skin biopsy specimens demonstrate extensive calcification of small- to medium-sized arteries or arterioles with intimal proliferation. The calcium deposition may be either segmental or circumferential, and the lumen is generally preserved. Management includes treatment of the ulcers and judicious use of antibiotics. Parathyroidectomy may improve survival.³⁴

In the classic form of pseudohypoparathyroidism (PHP), resistance to the effects of parathyroid hormone is seen in both the skeleton and kidney. The somatic features of Albright hereditary osteodystrophy may accompany the hormonal resistance.^{35,36} This peculiar phenotype, reported in subjects with PHP type Ia, is caused by mutations in the GNAS gene (guanine nucleotide-binding protein α -stimulating polypeptide), which encodes for the α subunit of the stimulatory G protein ($G_s\alpha$). Somatic features of Albright hereditary osteodystrophy, including short stature, short digits, and subcutaneous calcifications or ossifications, may be present. Brachydactyly, classically described as shortening of metacarpals III, IV, and V and distal phalanx I, is the typical and most specific sign of Albright hereditary osteodystrophy. It has been reported in 70% of individuals with PHP on routine radiologic examination.³⁶

ADRENAL DISORDERS

Cushing syndrome is a clinical disorder caused by excessive production of cortisol by the adrenal glands. Proximal lower extremity weakness may be one of the initial clinical symptoms and is generally noted on clinical examination. Electromyographic studies typically demonstrate myopathic changes. On muscle biopsy, atrophy of predominantly type II muscle fibers has been noted.³⁷

Adrenal insufficiency (Addison disease) leading to hypocortisolism has been linked with chronic fatigue and weakness.³⁸ Contractures as a consequence of tendon or skeletal muscle shortening have been reported in individuals with adrenal insufficiency.

LIPID DISORDERS

Heterozygous familial hypercholesterolemia is an autosomal dominant disorder with a prevalence of approximately 1 in 500 individuals, whereas the homozygous form is rarer and involves 1 in 1 million individuals (Table 193.3).³⁹ Abnormal or absent low-density lipoprotein (LDL) receptors cause the accumulation of cholesterol-rich LDL particles. These particles accumulate in tendons, particularly the Achilles, where they are metabolized into oxidized LDL, which is then actively taken up by macrophages within the tendon^{39,40} to form the xanthoma (Fig. 193.3). These structures are composed of lipid and collagen; detailed analysis has demonstrated that the lipid composition is similar to the core of advanced atherosclerotic plaque.³⁹ In fact, there appears to be a correlation between Achilles tendon thickness, as evaluated by ultrasonography, and carotid intima-media thickness in patients with familial hypercholesterolemia.⁴¹ Ultrasonography has fairly high

TABLE 193.3
Causes of xanthomas seen with normal lipid states

Apolipoprotein E No. 3 deficiency	Associated with high-density lipoprotein defects
Hypolipoprotein A-I variant	
Overproduction of apolipoprotein B	
Cerebrotendinous xanthomatosis	Autosomal recessive lipid storage disease
Hyper-B-cholesterolemia, rheumatoid arthritis, gout, trauma	Inherited sterol storage disease May lead to Achilles tendon thickening mimicking xanthoma on imaging studies

Adopted from Tsouli SG, Kiortsis DN, Argyropoulou MI, et al. Pathogenesis, detection and treatment of Achilles tendon xanthomas. *Eur J Clin Invest* 2005;35:236-44.



Fig. 193.3 Xanthomatosis of the Achilles tendon. (Courtesy Professor A.F. Lant.)

sensitivity in revealing subclinical xanthomas in some individuals with heterozygous familial hypercholesterolemia for which the diagnosis cannot be established by other means. Xanthomas appear as focal or confluent regions.^{39,40}

A transient polyarthritis involving the knees, ankles, and hands has been described in some patients with familial forms of hyperlipidemia.⁴² Affected patients had moderate pain and swelling and occasional redness of the affected joints. None of these patients had gout. Synovial fluid analysis demonstrated noninflammatory features, including white blood cell counts lower than 200/mm³, and no crystals were seen. The erythrocyte sedimentation rate was always normal.

Rarely, cholesterol crystals may be seen in the synovial fluid of patients with long-standing, severe rheumatoid arthritis. The synovial fluid has a characteristic milky appearance. The crystals may appear in two morphologic forms: (1) flat, rectangular, negatively birefringent plates with notched corners that range from 8 to 100 μ m long and consist of monohydrate cholesterol or (2) rod-shaped helical birefringent crystals ranging from 2 to 20 μ m long and consisting of anhydrate cholesterol.⁴³

STATIN DRUG-ASSOCIATED MUSCLE SYNDROMES

Myopathic syndromes associated with statin therapy range from myalgias to myositis to overt rhabdomyolysis, which may be accompanied by acute renal failure.⁴⁴

Experience in clinical practice suggests that muscle side effects, including those requiring discontinuation of statin therapy, are relatively common. Onset of the muscle symptoms usually takes place within weeks to months after the initiation of statin therapy but may occur at any time during treatment. The myalgia and weakness resolve and serum creatine kinase concentrations return to normal over a period of days to weeks after discontinuation of treatment with the drug.⁴⁵

Statin-induced myalgia is typically manifested as proximal, symmetric muscle weakness and soreness. Muscle tenderness and functional impairments such as difficulty raising the arms above the head, arising from a seated position, or climbing stairs may be noted. Less often the discomfort is asymmetric. Other reported symptoms include cramping and tendon pain. Clinically significant myopathy, defined as an elevation in serum creatine kinase to greater than 10 times normal in association with muscle symptoms, occurred in less than 0.5% of patients in large clinical trials.⁴⁶ The mechanism by which statins cause muscle toxicity is not well understood. They inhibit the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonic acid, which is an important early step in cholesterol synthesis. Statins can also decrease the synthesis of coenzyme Q₁₀ (ubiquinone), which plays an important role in the production of muscle cell energy. It has been speculated that the reduction in coenzyme Q₁₀ may contribute to the statin-induced muscle injury. Some studies have found that statins decrease plasma concentrations of coenzyme Q₁₀.⁴⁷

In large clinical trials, massive rhabdomyolysis with acute renal failure was not seen in patients who did not have other risk factors such as renal failure or concurrent use of cyclosporine, gemfibrozil, macrolide antibiotics, digoxin, antifungal medications, and warfarin. Other possible predisposing factors include hypothyroidism and inflammatory myopathies.⁴⁸

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194

Hemophilia and von Willebrand disease

■ JANE F. BLEASEL

HEMOPHILIA

- Hemophilia is a sex-linked inherited bleeding disorder caused by a deficiency of factor VIII (hemophilia A) or IX (hemophilia B).
- Bleeding occurs either spontaneously or with minor trauma. Recurrent hemarthroses can lead to progressive arthropathy, particularly affecting the ankles, knees, and elbows.
- Treatment involves adequate factor replacement. Prophylactic treatment from a young age is beneficial in preventing hemorrhage and preserving joint function.
- Chemical or radioactive synoviorrhesis is effective treatment of recurrent bleeding and synovitis. Joint replacement or fusion is beneficial for the treatment of chronic, severe arthritis.
- Viral transmission of blood-borne viruses is virtually eliminated with the use of recombinant factor.
- Inhibitor development occurs in about 30% of hemophilia A and 5% of hemophilia B patients and is associated with worse joint outcomes and quality of life.

VON WILLEBRAND DISEASE

- Von Willebrand disease is the most common of the bleeding disorders.
- It is caused by deficiency in von Willebrand factor and characterized by mucocutaneous bleeding.
- Severe forms are associated with hemarthroses.

HEMOPHILIA**History**

The term *hemophilia* (Greek: "love of blood") is attributed to Schönlein in 1818, although his pupil Hopf first referred to it in a dissertation.¹ The disease was well recognized and documented by Jewish religious writers in the fifth century AD because of the hazards of circumcision in hemophilic infants. Albucasis, who documented the deaths of men and boys in a certain Spanish village from uncontrollable hemorrhage after trivial wounds and bleeding, recorded the first published medical recognition of the disorder some 500 years later.

Joint disease secondary to chronic intraarticular bleeding was increasingly noted from the early 19th century onward.¹ The appearance of hemophilia in the British royal family in Queen Victoria's offspring and its transmission to several of the royal families of Europe during the late 19th and early 20th centuries spurred research. The young Czarévitch Alexei's severe hemophilia and the resultant established chronic joint disease distracted his parents and almost certainly altered the course of history in Russia leading up to the revolution of 1917. Elucidation of the underlying coagulation defect and the advent of effective clotting factor replacement during the 20th century revolutionized the management of hemophilia in general and allowed the potential prevention of joint disease and surgical correction of established deformity. Early therapeutic optimism was unfortunately diminished by the high incidence of human immunodeficiency virus (HIV) type 1 infection in patients treated with blood products between 1980 and 1985. The advent of synthetic factor VIII and IX concentrates, together with donor screening and heat treatment of naturally obtained

concentrates, has almost completely prevented this problem, but the recombinant products are still very expensive and not available in most developing countries.

Epidemiology

Hemophilia A has an incidence of 1 in 5000 male births and hemophilia B an incidence of 1 in 30,000. The distribution is generally uniform in the world, and there are no obvious associations with human leukocyte antigens.¹ Because it is X-linked recessive, it is a disease seen almost exclusively in males. However, symptomatic hemophilia may occur in females as a result of X-chromosome inactivation at an unusually early stage of embryogenesis. This will lead to low levels of factor VIII. In addition, if an affected male and a carrier female have offspring, 50% of the resultant female children will be homozygous for hemophilia.

Classification

In primary hemophilia, inherited deficiencies of any of the factors involved in hemostasis can result in bleeding disorders. The most well known are deficiencies in factors VIII (hemophilia A) and IX (hemophilia B).

In secondary hemophilia, factor deficiencies are caused by decreased synthesis, increased clearance, or destruction of clotting factors. The most common mechanism is antibodies (inhibitors) directed against factor VIII, although antibodies can develop to other factors, such as IX, X, or von Willebrand factor. In 50% of cases, no underlying pathologic process is found. Autoantibodies can develop postpartum or be associated with a range of diseases, most commonly autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue disorders. They can also occur with skin diseases, lymphoproliferative disorders, other tumors, and drugs. The clinical features are similar to those of inherited hemophilias.

Clinical features

Mild, moderate, and severe forms of the hemophilias are defined by plasma coagulation factor levels corresponding to 5% to 40%, 1% to 5%, and 1% or less of normal, respectively. Hemophilic arthropathy is the most important cause of morbidity in patients with severe hemophilia. Bleeding into muscle occurs at about one tenth the frequency of joint hemorrhages.

Some female carriers of the hemophilia genes have relatively low factor levels and may have problems during menstruation and with hemostasis during surgery and dental extractions, but bleeding into joints is exceptionally uncommon.

Acute hemarthrosis

Acute hemarthrosis is the initiating event in hemophilic arthropathy and frequently occurs spontaneously or in response to minor trauma with severe or moderate disease. Patients often describe a tingling sensation and tightness in the joint preceding the clinical signs of hemarthrosis. The joint then rapidly loses range of motion and becomes acutely painful, warm, and swollen. Rising intraarticular pressure eventually terminates the bleeding, and resolution occurs slowly, accompanied by bruising. Milder bleeding episodes may be manifested less dramatically and be limited to the subsynovium or be unrecognized, as is apparently the case when established arthritis develops in a joint without any history of bleeding.

The age at onset and the frequency of acute hemarthroses depend mainly on the severity of the factor deficiency. Levels of 5% of normal or less are almost invariably associated with recurrent hemarthroses, and established arthritis may occur less frequently with levels up to 20%.² Weight-bearing

joints on the dominant side are more commonly affected, coincident with the child beginning to walk. The joints traditionally affected in decreasing order of frequency are those of the knees, elbows, and ankles. However, prophylactic treatment induces a changing pattern of joint involvement, with the ankle surpassing the knee as the most common site of bleeding. Avascular necrosis of the femoral head as a result of hemorrhage into the hip joint may also occur, with the clinical and radiologic features resembling those of Perthes disease.

Differential diagnosis of acute hemarthroses

Occasionally, musculoskeletal hemorrhage is the first indication of the underlying condition, which if not recognized, can result in major morbidity or mortality. In this event the differential diagnosis includes other causes of hemarthrosis, such as joint trauma with intraarticular fractures, bleeding disorders such as platelet deficiencies or anticoagulant therapy, other blood dyscrasias, villonodular synovitis, acute inflammatory arthritides such as pyrophosphate arthropathy in older patients, and rarely, joint neoplasms.

Subacute arthropathy

Subacute arthropathy usually follows repeated hemarthroses and often targets one or several joints, in which bleeding is more frequent ("target joint"). A target joint is defined as a joint in which three or more spontaneous bleeding episodes have occurred within a consecutive 6-month period. A persistent boggy synovitis with synovial thickening, chronic joint effusion, and variable levels of pain in the absence of recent hemorrhage is seen. Muscle weakness and joint laxity contribute to further bleeding from the friable, thickened synovium, which results in continuing damage. The hyaline articular cartilage is progressively eroded by the inflammation associated with iron deposition. Ultimately, deep pits filled with friable blood clot occur in the cartilage, along with a surviving plateau of less damaged articular cartilage. Subarticular cyst formation is common, and cartilage collapse may result in large bony defects.

Chronic arthropathy

The end result after several months to years is a disorganized joint exhibiting bony thickening, deformity, loss of movement, and coarse crepitus as a result of the loss of articular cartilage and sclerosis of subchondral bone. Joint contracture secondary to fibrosis or ankylosis is common. Soft tissue swelling and effusions are rare at this stage, and pain is fluctuating and variable but at times severe.³

Muscle hemorrhage

Muscle hemorrhage may be potentially crippling, such as bleeding into the psoas muscle leading to hip contractures and femoral nerve palsy. Bleeding into the forearm can cause acute compartment syndromes and subsequent ischemic muscle atrophy and nerve damage. At times, large hemocysts develop within muscle (Fig. 194.1).

Hemophilic pseudotumors

Hemophilic pseudotumors may develop in bone and cause locally destructive lesions⁴; one type occurs in peripheral long bones, and the second type is observed around the pelvis. They are rare, with a frequency of about 1% in hemophiliacs. The majority of pseudotumors are due to repeated hemorrhage, either subperiosteally or into adjacent muscle. Subsequently, the hematoma becomes encapsulated and calcified with progressive enlargement. These events are postulated to be due to osmotic gradients across the fibrous capsule of the lesion. In children they tend to be situated distally and result from trauma.

The second type occurs more often in the pelvic region in adults and originates in soft tissues. They may exert pressure on intraabdominal or intrapelvic structures and can also cause bony erosion of the pelvic bones. They do not invade surrounding tissues, thus the name "pseudotumor." Complications of pseudotumors include fistulization to skin or intraabdominal organs, infection, internal bleeding, and even death.

Management depends on the size and location of the pseudotumor. Some distally situated lesions in children are treated conservatively with immobilization and adequate factor replacement. A 6-week course of treatment with factor is recommended in an attempt to shrink the pseudotumor. If this is effective, factor replacement can be continued. Alternative treatment options include surgical removal, injection of fibrin glue, embolization, or radiotherapy.

Diagnosis

The family history is important because in the majority of cases the mother will be identified as the carrier. In a third of cases no family history will be



Fig. 194.1 Hemocyst in the upper part of the left arm.

BOX 194.1 RADIOLOGIC CHANGES OF HEMOPHILIC ARTHROPATHY

Early

Periarticular soft tissue swelling
Periarticular demineralization
Increased radiodensity of thickened synovium* (Fig. 194.2)

Intermediate

Harris (growth arrest) lines
Epiphyseal widening, premature fusion, or both
Widening of the femoral and humeral intercondylar notches*
Squaring of the inferior border of the patella
Ankle deformities—tibiotalar slant (Fig. 194.3a)
Flattening of the talus
Proximal radial head enlargement* (Fig. 194.3b)

Late

Cartilage irregularity and narrowing; central and marginal erosions
Incongruity of joint surfaces
Subarticular sclerosis and osteophyte formation
Subarticular bone cysts
Subluxations, joint disorganization
Bony ankylosis

*Considered to be specific for hemophilic arthropathy.

elicited. This can be due to a spontaneous mutation in the factor VIII or IX gene or multiple generations of female carriers without an affected male. Initial screening tests such as a platelet count, bleeding time, prothrombin time (PT), and activated partial thromboplastin time (APTT) are required. A normal platelet count, normal PT, and prolonged APTT are characteristic of hemophilia A and B. Mild hemophilia B may have a normal APTT, and if there is uncertainty, factor IX assays should be performed. Specific factor assays confirm and quantify the deficiency. In previously undiagnosed cases of joint swelling, joint aspiration will almost certainly be necessary to confirm the presence of blood in the joint.

Imaging

The characteristic radiologic changes described in hemophilic arthropathy are listed in Box 194.1. Many are not specific and occur in other

arthropathies, especially those of childhood, most notably juvenile idiopathic arthritis.

The most widely used classification of the radiologic changes in hemophilic arthropathy is that of Pettersson and coworkers,⁵ with subsequent classifications including clinical criteria.⁶ When surgery is contemplated in patients with pseudotumors, computed tomography (CT) and magnetic resonance imaging (MRI) are indicated to determine the extent of bone and soft tissue involvement, and regional angiography is used to define the vascular supply to the lesion (Fig. 194.4).

MRI has the capacity not only to confirm the presence of blood within the joint cavity or subsynovium but also to detect early changes in hyaline cartilage not apparent on conventional radiographs and to assess the degree of synovial hypertrophy (Fig. 194.5). Gradient echo T2-weighted images can demonstrate iron in the synovium, a hallmark of previous joint hemorrhages. In some countries MRI is considered the method of choice to assess children for early joint changes, and a number of scoring systems for hemophilic arthropathy have been developed in an attempt to standardize reporting of the joint and soft tissue abnormalities. The expense of MRI and its lack of availability in many less affluent countries limit its potential usefulness at present.



Fig. 194.2 Radiograph showing subacute hemophilic arthropathy. Synovial thickening and radiologic density are present because of iron deposition.

Ultrasound has many advantages as it is accessible and relatively cheap. A protocol for scanning the six main target joints and a scoring system has recently been described.⁷ This provides information about cartilage as well as soft tissue structures, and may be particularly useful in assessing joints in younger patients with hemophilia.

Etiology

Bleeding in hemophilia is due to failure of secondary hemostasis. Formation of the platelet plug (primary hemostasis) is normal, but stabilization of the plug by fibrin is abnormal because of inadequate thrombin generation.⁸ Tissue factor VIIa is of critical importance in the initiation of coagulation by activating factors IX and X through the tissue factor VIIa pathway. In addition, its role in the interactions involving factors VIII and IX appears to result in a burst of thrombin generation on the activated platelet surface, which leads to effective blood clotting.

Hemophilia is inherited as an X-linked recessive trait that occurs in two forms—hemophilia A (factor VIII deficiency) and hemophilia B or Christmas disease (factor IX deficiency)—with the ratio of type A to type B being approximately 6:1. Deficiencies in other clotting factors are very rare, although described. The factor VIII gene is situated on the long arm of the X chromosome and is one of the largest genes; it constitutes 0.1% of the X chromosome. It is made up of 26 exons that span 186 kb. The factor VIII gene defects associated with hemophilia can be divided into three groups: (1) gross gene rearrangements, (2) insertions or deletions, and (3) single base substitutions resulting in amino acid replacement, premature peptide chain termination, or mRNA splicing defects. Approximately 45% of cases of severe hemophilia A are caused by a major inversion of a section of the tip of the long arm of the X chromosome, with one breakpoint occurring in intron 22, the so-called flip-tip mutation.⁹ This mutation arises almost exclusively in the male germline. It is now possible to detect the causative mutation in more than 95% of individuals with hemophilia A.

The factor IX gene is also situated on the long arm of the X chromosome and spans 33.5 kb with eight exons and seven introns. Hemophilia B is genetically heterogeneous, and most affected families have a unique (private) mutation. Two thirds of the gene mutations are missense mutations (changing amino acids), with a range of other types of mutation accounting for the other third.⁸ Sequence analysis of amplified fragments that include all eight exons of the factor IX gene can identify a mutation in more than 99% of individuals with hemophilia B. Direct sequencing is the usual approach, although several screening strategies have been used. Knowledge of the causative gene mutation has increased the accuracy of carrier detection and prenatal diagnosis within families and has made genetic counseling more accurate.

Fetal gender can be determined with polymerase chain reaction techniques to identify the Y chromosome in blood samples from the mother after 7 to 9 weeks. Alternatively, ultrasound can identify the sex after

Fig. 194.3 Hemophilic arthropathy. (a) Ankle radiograph showing tibiotalar slant. (b) Elbow radiograph showing an enlarged radial head.



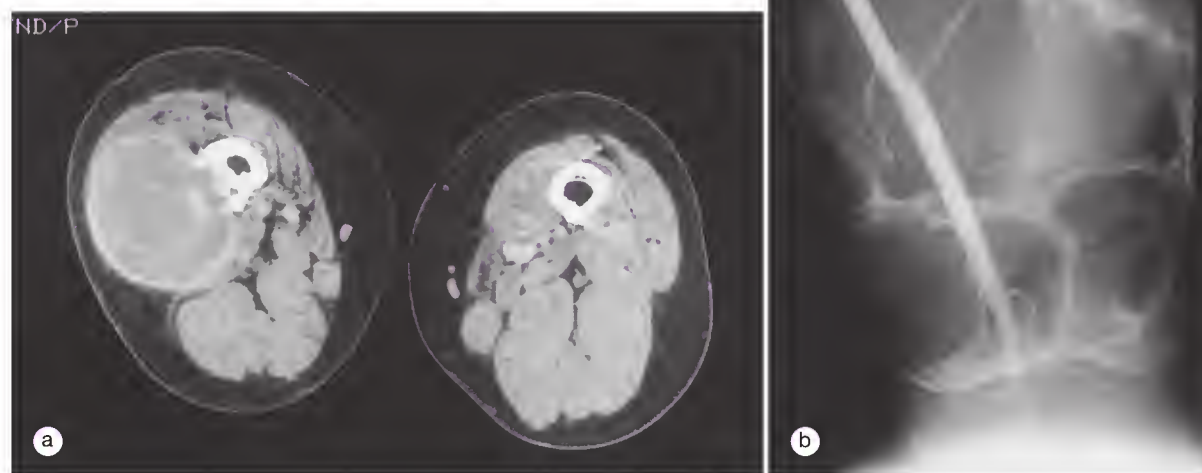


Fig. 194.4 Pseudocyst of the femur. (a) Computed tomographic scan of a pseudocyst in the right femur. (b) Femoral angiogram showing a large pseudocyst of the femur.

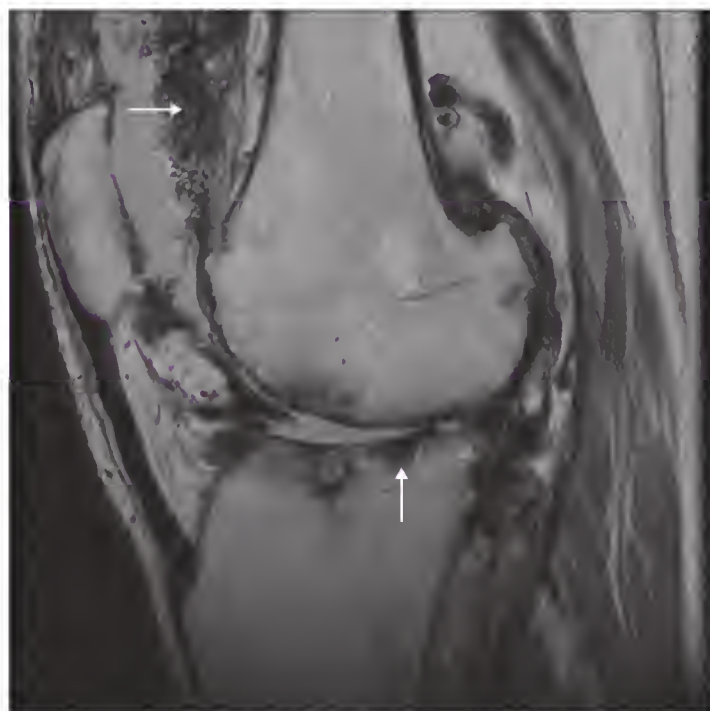


Fig. 194.5 Hemophilic arthropathy of the knee seen on a sagittal proton density-weighted magnetic resonance image. Extensive synovitis of very low signal intensity is present in the suprapatellar recess, consistent with hemosiderin from recurrent hemarthroses (horizontal arrow). In addition, full thickness cartilage loss and subchondral cysts are evident in the lateral compartment of the knee (vertical arrow).

11 weeks. Chorionic villous sampling performed between 9 and 14 weeks is the main method of prenatal diagnosis, or amniocentesis can be done at the later stage of 15 to 17 weeks. All these methods provide the option of termination if acceptable to the parents or help the family and medical specialists prepare and plan for the birth of a child with hemophilia. It is also possible to undergo *in vitro* fertilization treatment to select genetically normal embryos. Preimplantation genetic diagnosis offers families at risk the opportunity to give birth to an unaffected child.^{10,11} Despite these advances, up to 25% of cases of hemophilia occur *de novo* and are not detected by genetic screening in previously unaffected families.

Pathogenesis

The two main characteristic features of hemophilic arthropathy are chronic synovitis and cartilage degeneration. Iron deposition appears to be critical in production of the synovitis (Fig. 194-6).¹² The synovium plays a major role in absorption of blood from the joint after hemorrhage, with progressive accumulation of hemosiderin in synovial tissue leading to chronic inflammatory changes consisting of production of collagenases, proteolytic enzymes, and proinflammatory cytokines, which cause cartilage destruction. Proliferation of the synovium takes place, and neovascularization leads to inflamed, friable tissue more susceptible to bleeding. Thus, a vicious cycle is established with repeated bleeding after minimal trauma.

Blood in the joint has a direct harmful effect on cartilage by inhibiting proteoglycan synthesis and increasing degradation of the cartilage matrix. Chondrocyte apoptosis is increased via the production of toxic hydroxyl radicals induced by cytokines from mononuclear cells. Iron plays a central role in that it catalyzes the formation of oxygen metabolites. *In vivo* studies using a beagle model in which one knee was injected with blood on days 0 and 2 demonstrated that early cartilage changes appear by day 4, before the synovial inflammation is established. The cartilage of young adult dogs was more susceptible than that of older animals.¹³ When blood was injected into

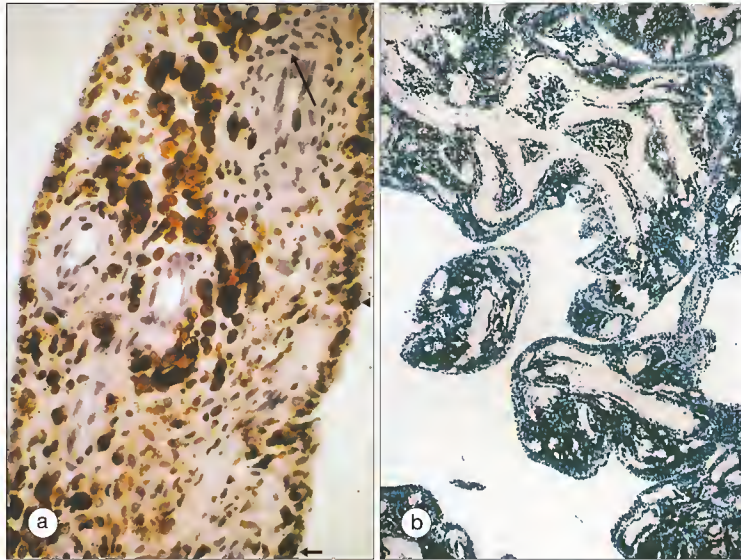


Fig. 194.6 Hemophilic synovitis. (a) Synovial hypertrophy, monocyte infiltration (long arrow, top right), heavy synovial and subsynovial deposition of hemosiderin (arrowhead, middle right margin, and arrow, lower corner), and new vessel formation (hematoxylin-eosin, original magnification $\times 100$). (b) Iron deposition (Prussian blue, original magnification $\times 100$).

the joint repeatedly and loads placed on the joint, the cartilage showed features of degeneration and synovial inflammation. Ultimately, repeated hemorrhage into a joint leads to dense fibrosis.

Management

The concept of a hemophilia center providing multidisciplinary expertise has been a major advance in hemophilia care. Such centers provide a wide spectrum of medical, nursing, surgical, and allied health professional skills.¹⁴

Prophylactic factor treatment

The idea of prophylactic factor replacement originates from the observation that chronic arthropathy rarely develops in patients with moderate hemophilia and factor levels of 1% to 4%. There is a direct relationship between the number of joint hemorrhages and joint damage, and therefore by giving factor prophylactically, joint bleeding is prevented. Prophylactic treatment with factor VIII or IX is given two to three times weekly to prevent bleeding in severe hemophiliacs. This increases their factor level to more than 1%, thereby converting them to the phenotype of moderate hemophiliacs. This should be the goal to preserve normal joint function in those with severe disease.

Prophylactic treatment can begin at an early age as either primary or secondary prophylaxis. Primary prophylaxis is defined as regular continuous treatment initiated in the absence of documented joint disease (as determined by physical examination, imaging studies, or both) and started before the second clinically evident large-joint bleeding and the age of 3 years. Secondary prophylaxis is defined as initiation after two or more bleeding episodes into large joints and before the onset of joint disease. Tertiary prophylaxis refers to continuous treatment with factor started after the onset of joint disease.

Nilsson and associates¹⁵ reported that if primary prophylaxis is begun at the age of 1 to 2 years, with factor given at high doses on alternate days (factor VIII) or twice weekly (factor IX), virtually no bleeding occurs and the boys maintain normal joints. This is considered “gold standard” therapy. Two randomized trials of prophylactic treatment with recombinant factor VIII have now been conducted and have shown a reduction in the risk for bleeding of between 48% and 82% in children with hemophilia.^{16,17} The study by Manco-Johnson and colleagues also demonstrated an 83% reduction in joint damage as assessed by MRI in the group receiving prophylactic therapy. Prophylactic treatment of severe hemophilia has been recommended by multiple health organizations worldwide. Although such management is ideal, many countries cannot afford the huge cost of this treatment.

Acute hemarthroses

Prompt and adequate treatment of acute hemarthroses is vital. Factor replacement with plasma-derived concentrates, or preferably recombinant factor VIII or IX, is essential. In developed countries such as Australia, boys

TABLE 194.1

Replacement protocols

Indication for treatment	Factor VIII* or IX [†] level (IU/dL)	Duration of therapy (days)
Hemarthrosis	40-60	1-2
Superficial muscle	40-60	2-3
Deep muscle injury with or without nerve injury		
Initial	80-100	1-2
Maintenance	30-60	3-5
Surgery—major [‡]	80-100	
Preoperative	60-80	1-3
Postoperative	40-60	4-6
	30-50	7-14

*The factor VIII dose is calculated by multiplying the patient's weight in kilograms by the factor level (IU/dL) desired, multiplied by 0.5.

[†]The factor IX dose is calculated by multiplying the patient's weight in kilograms by the factor level (IU/dL) desired.

[‡]Continuous infusions may be used to maintain factor levels of approximately 100% perioperatively if available.

with newly diagnosed hemophilia who have not previously received any human plasma products are provided with recombinant factor VIII or IX. This favorable situation is unfortunately not realized in up to 80% of the world's hemophilia patients, who do not receive adequate treatment. Replacement protocols are summarized in Table 194.1.

Although aspiration of all the blood from the affected joint would seem logical given the role of iron in the pathophysiology of hemophilic synovitis and cartilage damage, it is often impractical. Many patients have already received home-based factor replacement, and aspiration may be difficult and, for young patients, quite traumatic. Aspiration is indicated only in the following circumstances: if a tense, painful, bleeding joint shows no improvement 24 hours after conservative treatment; joint pain cannot be controlled; there is evidence of neurovascular compromise; or infection is suspected. If aspiration is required, a large-bore needle such as a 16-gauge one should be used under factor coverage for 48 to 72 hours to raise the factor level to 30% to 50% of normal.

Local treatment initially with rest, ice packs, and analgesics, followed by graduated physiotherapy and factor replacement for 48 hours, is usually effective. Isometric exercises should be started the next day, and graduated active physiotherapy should be encouraged after the first 24 hours, with prophylactic factor replacement if necessary.

Subacute hemophilic arthropathy

The subacute stage of the disease—development of a “boggy synovitis” and characteristic radiographic changes—indicates potential permanent joint damage and necessitates carefully planned management. Prompt treatment of joint bleeding is again vital, and when target joints are emerging, secondary prophylaxis with factor replacement should be initiated. The usual regimen is three-times-weekly treatments for hemophilia A and twice weekly for hemophilia B. Various protocols ranging from 15 to 40 IU/kg per dose are available for prophylaxis. This may be effective in breaking the cycle of recurrent hemarthroses and the development of synovitis and damage.

Physiotherapy to maintain strong muscles around joints is an important component of treatment to minimize bleeding. Nonsteroidal antiinflammatory drugs, specifically the cyclooxygenase-2 inhibitors, are used because they do not cause platelet dysfunction. Intraarticular corticosteroids may provide short-term benefit when total joint replacement surgery is not yet indicated.

Radionuclide synovectomy with intraarticular agents such as yttrium 90 and rhenium 186 is easy to perform and effective in reducing the frequency of intraarticular bleeding in the knee, elbow, shoulder, and ankle.¹⁸ A recent study reported the results of 156 radionuclide synovectomies in 104 joints of 78 hemophiliacs with either yttrium 90 or rhenium 186.¹⁹ Radionuclide synovectomy resulted in significant improvement in the number of hemarthroses, articular pain, range of motion, muscle strength, and degree of synovitis as measured clinically and by radiologic techniques. The number of episodes of hemarthrosis and the level of pain decreased most significantly by 70%. The ideal situation is a patient in whom a target joint with

recurrent hemorrhages and synovitis is developing but without radiologic evidence of damage. Synoviorthesis is particularly useful in patients with inhibitors because it avoids the risk of recurrent bleeding and costly consumption of factor concentrate.²⁰

Yttrium is favored for the knee and shoulder and rhenium for the elbow and ankle. One to three intraarticular injections can be given into any one joint at an interval of at least 3 months. Needle position should be confirmed with fluoroscopic arthrography if its position is at all in doubt. A corticosteroid plus local anesthetic should be injected after the radioisotope to wash out the needle track and prevent potential burn of soft tissues by the radioisotope. The joint should be rested for 24 hours after the procedure, with adequate factor coverage both before and after the procedure. This procedure can be used safely even in young patients.

Intraarticular sclerosants have been used widely in countries in which radiocolloids are not available and include rifampicin, ethanolamine (Ethamolin), and tetracyclines.

Arthroscopic synovectomy is sometimes beneficial when medical synovectomy has failed. Open surgical synovectomy is rarely performed because it is invasive and associated with a reduction in range of motion of the joint.

Chronic arthropathy

Chronic arthropathy represents failure of conservative treatment. With the advent of primary prophylaxis, the hope is that chronic arthropathy will become less of a clinical problem in the future. Pain relief with simple analgesics and nonsteroidal antiinflammatory drugs such as cyclooxygenase-2 inhibitors is essential. Stronger narcotic analgesia and involvement of a chronic pain team may be required for severe, chronic joint disease. Physiotherapy is part of the routine management of all patients with chronic joint disease to maintain muscle strength and prevent contractures. Serial casting, bracing, and orthotics are possible options for conservative management of chronic arthropathy.

Exercise and sports

Physiotherapy, exercise, and sports are essential for maintaining the physical condition and improving the quality of life of individuals with hemophilia.²¹ Improving muscle strength and stability around a joint may prevent injury and bleeding. Exercise may also prevent osteoporosis, which has been shown to be associated with hemophilia. Sporting activity that may lead to joint hemorrhage should be preceded by prophylactic therapy.

A recent prospective case-crossover study of children with hemophilia assessed the risk for bleeding related to physical activity and the use of clotting factors.²² One hundred four children between 4 and 18 years of age with moderate or severe hemophilia A or B were monitored for 4839 person-weeks. The median incidence rate (bleeding episodes per year) was 4.3 for participants receiving on-demand therapy and 3.0 for those receiving prophylaxis.

The most common sites of bleeding were the knees (15%), ankles (15%), and elbows (10%), with the frequency of bleeding highest before and after school. Not surprisingly, the study demonstrated that more vigorous activity

was associated with a transient increased risk for bleeding. When compared with inactivity or low-contact sports (e.g., swimming), the odds ratio was 3.7 for category 3 sports (e.g., wrestling) and 2.7 for category 2 activities (e.g., basketball). The risk for bleeding was reduced by approximately 2% for every 1% increase in clotting factor levels. However, the absolute increase in bleeding risk associated with physical activity was small.

Management of specific sites

The knee is commonly severely damaged in patients who have had recurrent hemorrhages followed by chronic synovitis and secondary osteoarthritis. When pain, fixed deformities, and disability interfere with the patient's life and work, joint stabilization or total joint replacement should be considered. Arthrodesis of the knee in a hemophilia patient remains a sound procedure, with predictable, lasting results and few complications.

Total knee replacement has been used successfully (Fig. 194.7), particularly in patients with severe bony changes, but it is a technically difficult operation because of soft tissue contractures, subchondral bone loss, and deformity. Continuous passive mobilization is generally begun postoperatively. Continuous intravenous infusion of factor VIII or IX before and after surgery to raise factor levels to around 100% is recommended. The improvement in range of movement after total knee replacement is not generally as significant as in nonhemophiliacs, but a reduction in the almost invariable preoperative fixed flexion deformity and a decrease in pain make this procedure very effective. The prosthesis survival rate has varied between studies, with rates of 83% and 89% reported at 10 years.^{23,24} The main reasons for prosthesis removal were infection and aseptic loosening. It has been suggested that continuous infusion of factor replacement during the preoperative, perioperative, and early postoperative phases to maintain levels close to 100% may result in better outcomes.

The ankle joint is rapidly overtaking the knee joint as a source of disability in hemophilia. The development of tibiotalar slant (see Fig. 194.3a) from medial tibial overgrowth results in valgus tilt at the ankle. Avascular necrosis of the talus may also occur and produce dome flattening and collapse, followed by advanced radiologic changes of secondary osteoarthritis. These changes are associated with severe symptoms and often occur despite few documented episodes of intraarticular bleeding. The subtalar joint is affected later in the disease process.

Conservative treatment includes the use of shock-absorbing insoles or heel pads, suitable footwear, and avoidance of sports associated with high impact on the ankle. Arthroscopic débridement or removal of osteophytes at the anterior aspect of the distal end of the tibia may have a role in patients with secondary degenerative changes. Ankle arthroplasty is available in limited units around the world with only short-term follow-up.²⁵ Ankle fusion remains the most reliable form of surgery for chronic arthritis. Usually, range of motion in the ankle at this stage is limited to a few degrees of painful movement, so pain relief at the cost of little increased disability is beneficial.

The elbow is a relatively common target joint for bleeding and chronic joint disease. It is often associated with flexion deformities, limited

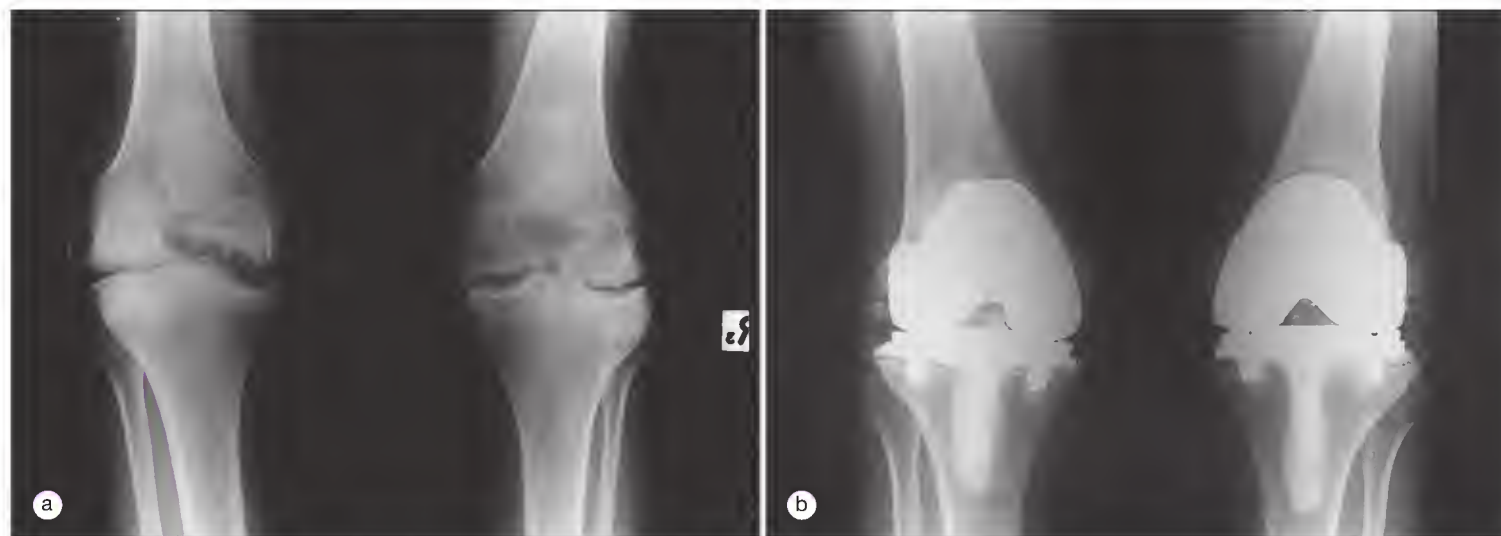


Fig. 194.7 Chronic hemophilic arthropathy. Radiographs show chronic hemophilic arthropathy and joint destruction of the knee (a) and the consequent arthroplasties (b).

pronation and supination, and marked wasting of surrounding muscles. Radionuclide synovectomy with image intensifier- or CT-guided injection is an option. Arthroscopic synovectomy of the elbow and excision or trimming of the often enlarged radial head can also be done. Total elbow replacement is the final solution for severely arthritic joints.²⁴ The hip is rarely affected (approximately 4% of patients). However, should the hip be severely arthritic, total joint arthroplasty is indicated, and good results have been reported.

Despite the potential problems with joint replacement surgery, such as bleeding, infection, and restricted range of movement, satisfaction with this procedure by hemophiliacs is high. Studies of HIV-infected patients undergoing total joint replacement have not demonstrated increased risk for prosthetic joint infection relative to HIV-negative hemophiliacs.²⁶

It is essential that orthopedic surgery in hemophilia patients be performed in major hemophilia centers by operators experienced in surgery for the condition and with the full backup of expert hematologic support, adequate laboratory facilities, and secure supplies of appropriate factor replacement.

Complications

Osteoporosis

Although periarticular demineralization is a radiologic feature of hemophilic joints, generalized osteoporosis as a result of chronic hemophilic arthropathy has been reported. An increased number of affected joints and chronic arthritis with coexistent muscle wasting are associated with lower bone density. Baseline treatment with adequate calcium and vitamin D is essential, and bisphosphonates should be used if required. Prophylactic factor treatment from an early age may prevent the development of osteoporosis.

Chronic pain

Control of the pain of chronic hemophilic arthropathy is often a significant problem. The pain can be severe and persistent, and narcotic addiction in severely affected hemophiliacs is not uncommon and best managed in a consultative situation. Cooperative effort of the pain clinic, liaison psychiatrist, social worker, family members, and most importantly, the patient is essential.

Blood product-transmitted infections

The hazards of transmission of infective agents, including HIV and hepatitis B and C viruses, via blood products are well known. With the advent of careful screening of blood products, effective virucidal techniques, and the use of recombinant factor, the risk has been almost eliminated. Management of HIV infection should be the same as in a nonhemophilic patient, and none of the currently available HIV drugs are contraindicated in people with hemophilia. Hepatitis C should be managed, if indicated, with pegylated interferon and ribavirin, and a sustained virologic response is achieved in 61% of hemophiliacs. Prion-mediated disease through plasma-derived products is also a potential risk, but no reliable screening tests are available. New synthetic factor replacements should prevent these and other rarer infective complications. It should be remembered, however, that more than 40% of countries reporting data to the World Federation of Hemophilia in 2010 indicated that they were still using cryoprecipitate from fresh frozen plasma to treat patients with hemophilia.

Coagulation factor inhibitors

Inhibitors refer to IgG antibodies that neutralize clotting factors. With the advent of modern factor replacement and viral inactivation, inhibitors represent the most severe treatment-related complication. Coagulation factor inhibitors occur in 20% to 30% of patients with severe hemophilia A and in 5% of those with hemophilia B. Inhibitors come in two varieties: low-titer inhibitors, which are often overcome by increasing the dose of factor VIII or IX, and high-titer, highly responding antibodies that react with factor VIII or IX to render it ineffective.⁸ A low-level inhibitor is defined as one that is less than 5 Bethesda units (BU), whereas a high-level inhibitor is greater than 5 BU. The presence of an inhibitor should be suspected if a patient fails to respond clinically to clotting factors. Patients with inhibitors have worse joint outcomes and quality of life than do those without inhibitors because of more joint hemorrhages and the development of chronic joint disease.

Treatment of patients with inhibitors involves two aspects: management of acute bleeding episodes and attempts to reduce inhibitor production by induction of immune tolerance. In some cases, porcine factor VIII has been effective in treating patients with inhibitors. The main avenue for treatment of bleeding episodes involves the use of agents that "bypass" the need for factor VIII or IX, such as activated prothrombin complex concentrates (APCCs). The alternative is recombinant activated factor VIIa (rFVIIa),

which avoids the use of pooled plasma. Both agents can be used for acute hemorrhages, prophylaxis, or major surgery in hemophilia A and B patients with inhibitors. The efficacy of two doses of rFVIIa and one dose of APCC for the management of joint bleeding has been demonstrated to be equivalent.²⁷ Secondary prophylaxis with rFVIIa has been shown to reduce the frequency of hemorrhages and decrease hospital admissions and days absent from work or school.²⁸

Patients with highly responding inhibitors can also undergo induction of immune tolerance with high doses of factor VIII/IX, sometimes in combination with cyclophosphamide, high-dose immunoglobulin, protein A immunoadsorption, or rituximab, with success rates of inhibitor eradication with rituximab ranging from 50% to 80%.²⁹ Induction of immune tolerance has been limited because of cost and some doubts about its long-term efficacy.

With the advent of new factor concentrates, risk for the development of inhibitors when changing from one product to another has been reported. These patients need to be monitored for inhibitor development and the new product withdrawn if required, which often leads to disappearance of the inhibitor.

Future treatment options

The ideal treatment of hemophilia would involve the *in vivo* synthesis of adequate amounts of factor VIII or IX. Genetic engineering resulting in gene insertion therapy in which suitable cells containing the appropriate portion of the normal X chromosome are introduced into the body is technically feasible but still elusive despite recent optimism. In animal studies, therapeutic levels of factor VIII and IX have been achieved in mice, dogs, and monkeys by using either mammalian cell lines or viruses as vectors to introduce appropriate genetic material.³⁰ Clinical trials have failed to achieve significant factor VIII expression in hemophilia A patients, but one trial showed transient increased expression of factor IX in hemophilia B patients.³¹

The inconvenience and hazards of repeated intravenous infusion mean that any noninvasive method of delivery would be a major advantage. The search for alternative nonvenous routes of access for coagulation proteins has a long history, but thus far novel techniques such as the oral administration of factor VIII trapped in liposomes have not proved therapeutically effective, and subcutaneous bolus injections have similarly been ineffective.

Summary

The prevalence of severe hemophilic arthropathy has decreased since the introduction of prophylactic therapy from an early age. Many issues related to the optimal treatment of hemophilic synovitis still remain unanswered, but new developments in orthopedic surgery on the elbow and ankle joints have emerged. The development of inhibitors has become an increasing issue, with worse joint outcomes and great expense involved in the use of bypassing agents.

This chapter has been written from the perspective of the treatment available in affluent, largely Western societies and paints a very favorable prognosis for young hemophilia patients in this situation. Hemophilia is distributed ubiquitously, and the reality of the situation is that probably 80% of those with the condition worldwide do not receive adequate treatment, if any, even if the diagnosis has been made.

VON WILLEBRAND DISEASE

Von Willebrand disease (VWD) is the most common of the bleeding disorders and occurs in approximately 1% of the population. Many of these individuals do not come to clinical attention because they fall into the mild end of the disease spectrum. VWD is caused by a deficiency in von Willebrand factor (VWF), which has an important role in both primary hemostasis and formation of the fibrin plug. VWF binds to both platelets and the endothelium at sites of injury and forms an important bridge to aid in platelet clotting. It is also bound to factor VIII as a carrier protein. In the absence of VWF, factor VIII has a markedly reduced half-life with decreased measurable factor VIII levels.

VWD occurs in males and females at a frequency of 1 in 1000, with variable inheritance patterns depending on the subtype. The clinical features of VWD are primarily due to mucocutaneous bleeding. Certain more severe forms of VWD can also result in joint hemorrhages indistinguishable from those in patients with hemophilia A and B.

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Joint and bone lesions
in hemoglobinopathies

■ KARLENE HAGLEY ■ KAREL DE CEULAER

- Hemoglobinopathies result from a defect in the synthesis and structure of hemoglobin.
- Rheumatic manifestations in hemoglobinopathies are found mostly in sickle cell disease, usually in homozygous hemoglobin SS disease, hemoglobin SC disease, and S- β -thalassemia.
- Sickle cell trait does not cause rheumatic disease.
- Hemolytic anemia is present along with systemic and rheumatologic manifestations.
- Specific bone and joint lesions include painful crises, dactylitis, and osteonecrosis.
- Other features include osteomyelitis and gout.

INTRODUCTION

Of the known hemoglobinopathies, specific rheumatic complaints are caused mostly by the spectrum of sickle cell disease (SCD). Other hemoglobinopathies (e.g., thalassemias, hemoglobin CC) cause joint disease rarely, mainly through hemochromatosis. Homozygous SCD (SS), the most common phenotype, results from a single nucleotide substitution in each β -globin gene (the normal codon GAG at position $\beta 6$ has been replaced by GUG); this results in substitution of valine for glutamic acid (Glu). When lysine replaces Glu at $\beta 6$ in one chain, hemoglobin C is formed. β -Thalassemia results from synthetic defects in one or more β units of hemoglobin, which causes the clinically significant thalassemia major and intermedia and typical bone marrow deformities.

Under various conditions, hemoglobin S forms liquid crystals that deform erythrocytes into rigid sickle-shaped cells. Vasoocclusion of the microvasculature caused by sickled red blood cells may lead to a variety of joint and bone abnormalities, among which painful crises, dactylitis, and osteonecrosis are the most common. Other major complications include osteomyelitis and gout. Though most frequent in SS disease, all these complications may also occur in other sickle hemoglobinopathies, such as S- β -thalassemia and sickle cell hemoglobin C (SC) disease.

In sickle cell trait, red cell sickling occurs only in nonphysiologic conditions. Therefore, rheumatic complaints should never be ascribed to the presence of sickle cell trait. Many patients with fibromyalgia or connective tissue diseases (CTDs) believe that their sickle cell trait, discovered during routine blood analysis, is the cause of their symptoms. Media reports on the frequency of sickle cell trait in various populations have contributed to this false impression.

It is a common misconception that sickle hemoglobin occurs only in people of African ethnicity. It is also found in people from southern Italy, northern Greece, southern Turkey, Saudi Arabia, and central and southern India. In cases of unexplained bone pain and avascular necrosis, screening with the sickle cell test should be performed on a wide variety of patients. If positive, it should be followed by hemoglobin electrophoresis.

PATHOGENESIS

Polymerization of hemoglobin S in a deoxygenated state leads to decreased red blood cell deformability¹ and sickled cells and is influenced by various

factors, including the intracellular concentration of hemoglobin S, the concentrations of hemoglobin F and C, the presence of β -thalassemia, and the ameliorating presence of α -thalassemia. Other factors are the oxygen saturation of blood, pH, ionic strength, temperature, plasma viscosity, and 2,3-diphosphoglycerate. Alterations in the vascular endothelium (VCAM-1, E-selectin) interact with sickled cells (expressing VLA-4, ICAM-1) and several activated blood cells (certain young red blood cells or "stress reticulocytes," leukocytes, platelets) via an inflammatory reaction, and several cytokines are generated, thus further promoting sickling.² Hemolysis depletes nitric oxide, which reduces vasodilating capacity and results in a subsequent imbalance with endothelin-1 and its vasoconstricting role. All these factors tend to be compounded, and once a sufficient number of rigid sickled cells with polymerized hemoglobin are created, microvascular occlusion will occur with subsequent hypoxia and damage to the tissues supplied. The impact on affected bone is increased intramedullary pressure, bone pain, and potential bone infarction with necrosis.

The increased incidence of *Salmonella* osteomyelitis in SS disease seems to be affected by organism endemicity, asplenia with defective opsonization, and bone necrosis.

Hyperuricemia and gout are caused by decreased renal tubular excretion of urate rather than by urate overproduction secondary to increased purine turnover. Hyperuricemia may contribute to the decreased renal function observed in sickle cell patients older than 40 years.

CLINICAL FEATURES

Painful crisis

Painful crises are the most characteristic musculoskeletal complication of sickle cell hemoglobinopathies³ and account for the majority of all visits for acute medical care and hospital admissions. The event is caused by vasoocclusion in bone marrow. Pain occurs most frequently in the juxtaarticular areas of long bones, but also in the back, ribs, and occasionally the abdomen. Acute low back pain may be the only feature. Frequently, multiple sites are involved, sometimes in a symmetric fashion; the pain may spread from one area to another in an additive or migratory pattern. Localized swelling may be pronounced, especially at the tibial epiphysis. Rib involvement causes pleuritic chest pain. During the painful crisis one or more joints may become inflamed.⁴ The duration of painful crises varies from 10 minutes to several weeks, but persistence of pain beyond 2 weeks is rare with uncomplicated painful crises.

A severe painful crisis usually consists of four distinct clinical phases. During the prodromal phase, the patient becomes restless and experiences vague feelings of being unwell. The second phase (initial phase) is characterized by sudden pain of increased intensity that reaches its maximum during the established phase. Clinical evidence of increased jaundice may be noted. During the resolving phase the pain gradually decreases, and by 2 weeks a steady state is restored in most patients.

Factors precipitating painful crises include dehydration, infections, exposure to cold, pregnancy, emotional stress, and traveling at high altitude. Painful crises are less frequent in female than in male patients; in the latter, a strikingly steep increase in incidence is seen between the ages of 15 and 25 years (Fig. 195.1). Pain frequency correlates with high total hemoglobin levels and low fetal hemoglobin.⁵ SS patients older than 20 years with a high frequency of painful crises have higher mortality than do SS patients with a fewer number of painful episodes.⁵ Occasionally, myonecrosis and myofibrosis have been observed.

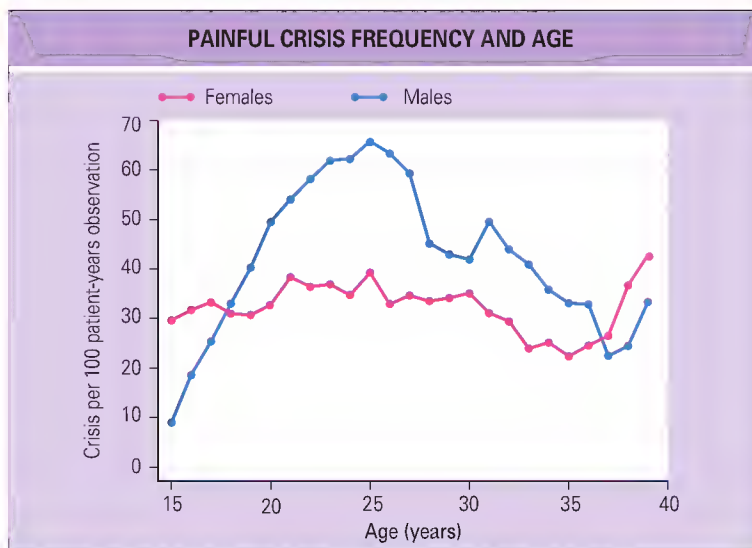


Fig. 195.1 The figure shows the incidence of painful crises according to age in male patients and nonpregnant female patients. In female patients there is little age-related change, whereas in male patients the incidence increases dramatically between 15 and 25 years of age and falls again after the age of 32 years. (Adapted from Baum KF, Dunn DT, Maude GH, Serjeant GR. The painful crisis of homozygous sickle cell disease. *Arch Intern Med* 1987;147:1231-4.)



Fig. 195.2 Shortened fingers as a result of premature fusion of the epiphyses of two metacarpal bones. Careful examination of the position of the metacarpophalangeal joints will reveal which bone is affected.

Dactylitis

In young children, vasoocclusion frequently occurs in the bones of the hands and feet and leads to dactylitis (also called *hand-foot syndrome*). This complication typically occurs between 6 months and 2 years, but cases have been described in children up to 7 years of age. Clinical examination reveals acute, painful, nonpitting swelling of hands and feet. The symptoms may improve after 1 week, but recurrences are common. The dactylitis usually heals without sequelae, but occasionally, necrosis of the central part of the epiphysis may lead to premature fusion and shortened digits (Fig. 195.2). This results in disruption of the continuity of alignment of the metacarpophalangeal joints.

Osteonecrosis

Osteonecrosis of the femoral head develops in up to 20% of patients with SS disease and has been diagnosed as early as 5 years of age. At onset the pain is indistinguishable from a painful crisis, but the symptoms do not disappear after 2 weeks and usually worsen with walking and at night. With continued weight bearing the pain increases because of progressive collapse of the femoral head. The final outcome is related to the age of the patient, the timing of diagnosis, and subsequent management. Children may retain

normal hip function despite flattening of the femoral head, whereas adults tend to show progressive deterioration in joint function. Initially, hips affected by osteonecrosis may be asymptomatic. However, 91% of these asymptomatic hips become painful and 77% show collapse. Therefore, early surgical treatment and physiotherapy should be recommended.⁶ Osteonecrosis of the femoral head secondary to hemoglobinopathy is virtually absent in patients with SC disease and S- β -thalassemia who are younger than 15 years. In contrast, the rate of osteonecrosis in older patients (older than 35 years) with SC disease is strikingly similar to that in SS disease.

Osteonecrosis is not limited to the hip joint. Shoulders affected by osteonecrosis tend to show limited function rather than pain because of the absence of weight bearing. Multifocal osteonecrosis may occur in more than 25% of patients. It is therefore important to obtain radiographs or perform magnetic resonance imaging (MRI) of any symptomatic joint in a patient with osteonecrosis of the hip. It is also good practice to order radiographs and MRI scans of the hips in any sickle cell patient in whom joint osteonecrosis is diagnosed.⁷

Osteomyelitis and septic arthritis

Osteomyelitis, when it occurs, usually follows a painful crisis episode. It should be suspected if the patient's temperature exceeds 38° C, when bone pain is present and swelling affects one single site, or if the painful crisis lasts longer than 2 weeks.⁸ A corrected white blood cell count greater than 15,000 also tends to be present. Less commonly, multiple sites of involvement may occur and be manifested in a symmetric pattern. Soft tissue swelling and persistent pyrexia are noted frequently. Osteomyelitis may be complicated by osteonecrosis of the adjacent joint, adhesive capsulitis of the shoulder, and pathologic fractures. The development of chronic osteomyelitis (Fig. 195.3) significantly increases the morbidity of affected patients. *Salmonella* remains the most common organism causing osteomyelitis in SS disease.⁹ The second most frequently seen organism is *Staphylococcus aureus*, with *Pseudomonas aeruginosa* being third.¹⁰ It is possible that chronic sickling of the intestine's vasculature predisposes the devitalized bowel to invasion by enteric bacteria.

Septic arthritis is uncommon in SS disease. It may occur in the presence of acute osteomyelitis, but more commonly it occurs secondary to hematogenous spread, both in children and in adults. In a review of adult patients with SCD, 3% had septic arthritis, 95% of whom had hemoglobin SS¹¹; hip infections predominated (61%) and 88% of all septic arthritis cases appeared to have been blood-borne. Gram-negative infections predominate, especially *Salmonella* in children, but *S. aureus* is also common. Because of recurrent episodes of bone pain and occasionally associated osteonecrosis, septic arthritis may proceed for days without early diagnosis despite marked joint swelling and tenderness. A high index of suspicion in patients with known hip osteonecrosis who experience fever and a sudden increase in hip pain and disability, as well as in those with overt swelling of other peripheral joints, is essential, and such patients should be investigated.

The diagnosis of tuberculous arthritis of a hip affected by avascular necrosis is particularly difficult because of its insidious onset and the radiographic changes associated with the preexisting disease. A positive skin test for tuberculosis may be suggestive, but synovial biopsy and culture are mandatory when the diagnosis is suspected.

Gout

Gouty arthritis is rare in SS disease¹² despite the fact that hyperuricemia occurs in more than 40% of these patients. In contrast to primary gout, involvement of the big toe is less frequently seen than arthritis of the knees, wrists, and small finger joints. Tophaceous gout is extremely uncommon.

Miscellaneous

Chronic arthritis with rapid chondrolysis of the hip may be related to the increased phagocytic activity in some sickle cell patients.¹³ Occasionally, chronic synovitis with pronounced lymphocytic and plasma cell infiltration of the synovium and early cartilage destruction has been noted. Bilateral protrusio acetabuli may result from osteoporosis because of the expanded marrow. Arthritis of the ankle may develop in association with an ischemic ulcer at the medial or lateral malleolus⁴ and tends to occur at the early stages of impending leg ulceration, when the skin surface is still intact but the tissues look shriveled and hyperpigmented. Gait is impaired, and nonsteroidal antiinflammatory drugs (NSAIDs) result in fast improvement of function. If left untreated, the pain and dysfunction of the ankle lessen when the leg ulceration develops, but persistent limitation is common as long as the ulcer persists.



Fig. 195.3 (a and b) Chronic osteomyelitis with periosteal reaction, sclerosis, and sequester. Some sclerosis may be due to previous ischemic crises.



Fig. 195.4 Rheumatoid erosion of the lateral condyle of the knee in a patient with sickle cell disease.

Thalassemia major symptoms usually occur before 3 years of age, whereas thalassemia intermedia manifests later in life. Poor development of the musculature, growth retardation, and skeletal changes, such as long-bone deformities of the legs and craniofacial changes (skull bossing, prominence of the malar eminences, nasal bridge depression, and maxillary hypertrophy), occur.¹⁴ These features are more marked in thalassemia major.

Rheumatoid arthritis rarely develops in patients with hemoglobinopathies, but it has been reported in those with β -thalassemia and SS disease¹⁵ (Fig. 195.4). It is not clear whether this is due to early mortality or factors preventing synovial proliferation. One report noted two patients with SCD (SS) and juvenile idiopathic arthritis¹⁶; a chronic asymmetric seronegative oligoarthritis may also develop in SS patients and needs to be defined. The coexistence of SS disease and systemic lupus erythematosus (SLE) does not occur frequently enough to allow speculation about complement abnormalities in SS disease leading to the development of SLE. High titers of autoantibodies with various immunofluorescence patterns have been reported,¹⁷ but this has not been shown to have a significant association with clinical autoimmune disease and may reflect only immune dysfunction.

INVESTIGATIONS

A complete blood count and reticulocyte count should be obtained with every painful crisis because of possible associated aplastic crisis. Aplastic crisis can be caused by concomitant parvovirus infection. Determination of white blood cell counts by Coulter counter methods should always be followed by a corrected white blood cell count because any immature nucleated red blood cells detected are read as leukocytes. An increasing erythrocyte sedimentation rate (ESR) and leukocytosis with a left differential shift suggest local or systemic infection, possibly osteomyelitis. In uncomplicated SS patients the ESR is usually low because of the unique rheology of sickled red blood cells, but it may rise during the resolving phase of the painful crisis and to a greater extent if infection is present. Determination of C-reactive protein is more reliable than the ESR when monitoring an inflammatory process.

No radiographic changes are typical of uncomplicated painful crises, but periosteal reaction can be seen. Blood cultures should be performed if the patient's temperature exceeds 38° C. Joint aspiration is necessary for painful crisis with associated arthritis. In uncomplicated arthritis, the synovial fluid is noninflammatory, straw colored, and sterile. Blood cultures are always indicated for dactylitis because *Salmonella* infections have been documented in patients with this complication.¹⁸

Radiographs of affected bones are not helpful in the early stages of osteomyelitis, and such changes are apparent only after weeks of illness. Plain radiographs and bone scans are unable to differentiate between painful crises and osteomyelitis. At present, soft tissue ultrasound and gadolinium-enhanced MRI are the best imaging techniques to suggest bone infection, although the exact specificity of these investigations is not yet clear. With ultrasound, a 4-mm depth or more of subperiosteal fluid is highly suggestive of osteomyelitis.¹⁹ On gadolinium-enhanced MRI, acute infarcts demonstrate thin, linear rim enhancement, whereas osteomyelitis shows more geographic and irregular marrow enhancement.²⁰ Patients with osteonecrosis of the femoral head can be staged radiographically by the Steinberg classification system.²¹ In the early stages findings on plain radiographs are normal, but the hip is symptomatic with groin or thigh pain, which is worse at night (Steinberg stage 1). However, MRI can detect abnormalities at this stage, even where bone scans fail. Because of an overall reported sensitivity of 91%, MRI should be performed if avascular necrosis is suspected. Stage 2 hips show sclerosis and radiolucent areas on radiographs (Fig. 195.5), with the symptoms being similar to those in stage 1. In stage 3, plain films show a lucent subchondral line, followed by a cortical discontinuity (crescent sign); it appears only after several weeks of illness. At this stage the pain and limitation have increased and ambulation may be possible only with a cane. Stage 4 is characterized by segmental flattening of the femoral head without radiologic evidence of acetabular involvement (Fig. 195.6). Stage 5 shows progressive destruction of the hip joint with joint space narrowing, cyst sclerosis, and osteophytes (Fig. 195.7). Stage 6 includes advanced degenerative joint disease with extreme narrowing or obliteration of the joint space. It is important to recognize that correlation between the clinical symptoms and radiologic features of osteonecrosis is poor.

The diagnosis of gouty arthritis should be made only after identification of urate crystals in joint fluid. Indeed, hyperuricemia is common in uncomplicated SS disease and therefore cannot be used as a criterion for the presence of gouty arthritis.

DIFFERENTIAL DIAGNOSIS

A painful crisis can mimic attacks of rheumatic fever, which typically starts as a migratory polyarthritis. In both diseases, cardiac murmurs are extremely common (SS patients often have left ventricular hypertrophy and flow murmurs as a result of chronic anemia), and mild elevations in antistreptolysin O are seen frequently. Of note, these conditions may also coexist, especially in developing countries where rheumatic fever is not uncommon.



Fig. 195.5 Very early osteonecrosis of the femoral head (Steinberg stage 2). The femoral head shows sclerotic and radiolucent areas.



Fig. 195.6 Osteonecrosis of the femoral head (Steinberg stage 4). Mild flattening of the superolateral part of the femoral head is present despite long-standing disease.

A chronic destructive synovitis has been described in SS disease and needs to be differentiated from rheumatoid arthritis.

Despite a lack of evidence of an increased frequency of SLE in SS disease, SS patients may frequently be positive for low-titer antinuclear and antiphospholipid antibodies. It needs to be established whether the latter antibodies are contributing to the acute chest syndrome, strokes, and recurrent miscarriages, which are common complications of SS disease.



Fig. 195.7 Advanced osteonecrosis of the femoral head (Steinberg stages 5 and 6). Gross destruction and remodeling of the femoral head are evident. The osteoarthrotic changes are significant.

MANAGEMENT

Management of an acute painful crisis depends on the patient's response to analgesics during previous crises, the severity and extent of the painful episode, and the presence of complications such as acute chest syndrome and paralytic ileus.²²

Because of associated dehydration, administration of large amounts of fluid intravenously at 3 to 4 L/24 hr and unlimited amounts orally have been the standard. However, it has been shown that the majority of uncomplicated painful crises can be managed effectively by oral hydration and analgesia alone. Mild painful crises respond to simple analgesics such as acetaminophen (paracetamol), but with a severe crisis, narcotic analgesics are necessary. In those with normal gastrointestinal motility, oral, controlled-release morphine is a reliable, noninvasive, and preferred alternative.²³ Narcotic analgesics should be prescribed at full therapeutic doses at regular 2- to 4-hour dosing intervals to relieve pain and not be restricted to an as-needed basis. Smaller additional doses should be prescribed for breakthrough pain. The severity of the pain and its response to treatment should be reassessed frequently. NSAIDs, sedatives, antiemetics, and antihistamines may reduce the amount of narcotics needed for the treatment of a painful crisis and can be used in combination with narcotics. Tramadol, a centrally acting analgesic that is administered orally, induces minimal respiratory depression and is useful in the outpatient management of vasoocclusive crises. Antisickling agents and pentoxifylline have shown disappointing results once the pain has begun.

With the recurrent nature of the pain, sickle cell patients may be at risk for addiction and drug dependence, but such risk is much lower than expected. Paranoia about this issue has often led to suboptimal treatment of painful sickle cell crises with unnecessary suffering by patients. Reluctance of hospital staff to prescribe and administer narcotic analgesics is seen by patients as a sign of indifference and perpetuates a lack of confidence in caregivers.

Although in the past most patients with moderate or severe painful crises were treated as inpatients in the hospital, recent studies have shown that daycare centers may provide an adequate alternative way of treating patients with SS crisis.²⁴ Hospitalization has been suggested because of concern for undetected infection and SS-related complications and because of the perception that adequate pain relief can rarely be achieved on an outpatient basis. However, a specialized daycare unit will be able to assess patients more rapidly and titrate the analgesia to individual needs. It may avoid the suboptimal treatment that commonly occurs on hospital wards. However, when systemic infection is suspected, the patient should be admitted for

intravenous antibiotic treatment, in addition to analgesic medication. Another indication for hospitalization is extensive associated chest syndrome, in which early exchange transfusion could be life-saving.

Attention should be paid to prevention of painful crises, including life-style changes (avoidance of stress, alcohol, overexertion, swimming, getting caught in the rain, high altitudes) and medications. Hydroxyurea increases the concentration of hemoglobin F, along with a moderate reduction in neutrophils, reticulocytes, and young, low-density SS red blood cells. Clinically, hydroxyurea has been shown to reduce the frequency of painful crises in adult SS patients and is cost-effective.²⁵

If osteonecrosis of the femoral head is documented, the patient should be maintained on complete bed rest and totally avoid weight bearing. In children this can be achieved by casting with the knee immobilized at a 30-degree angle. Another option to avoid bearing weight is crutches. Only when severe chronic hip pain is not controlled by medical treatment and when the femoral head is severely damaged (Steinberg stage 5 or 6) is a total hip replacement indicated. Indeed, the results of total hip replacement in SS patients are much less favorable than in patients with osteoarthritis. Apart from perioperative complications, loosening of the prosthesis and infection cause poor long-term replacement outcomes when compared with primary degenerative hip disease.^{26,27} However, in a more recent study, the rate of postoperative infections was reduced to 3% and long-term loosening of the prosthesis to 8% for the cup and 5% for the stem.²⁸ Despite an improved outcome with total hip arthroplasty, attention should be directed to detection of osteonecrosis at an early stage and prevention of progression with conservative treatment or core decompression. The latter, however, is superior to conservative treatment only in early osteonecrosis (Steinberg stage 1).²⁶ Physical therapy alone seems to be as effective as core decompression followed by physical therapy in reducing the need for total hip replacement, at least in the short term.²⁹ If a total hip replacement has become unavoidable, non-cemented hip arthroplasty, preferably with custom-made stems, is probably the best current choice.²⁷

When osteomyelitis is suspected, traditional treatment tended to include the use of ampicillin or trimethoprim-sulfamethoxazole because *Salmonella* is the main cause of this complication. However, emerging resistance is

decreasing its potential efficacy, and the spectrum of causative organisms is widening. Newer β -lactams and third-generation cephalosporins, sometimes in combination with an aminoglycoside, may be suitable alternatives.¹⁰ Quinolones are relatively contraindicated in children because of their potential for chondrotoxicity, arthropathy, and tendon rupture. Resistance to ciprofloxacin has already been described.³⁰ With established osteomyelitis, antibiotic therapy is usually continued for at least 3 months.

Septic arthritis needs early surgical drainage, antibiotics (as for osteomyelitis and guided by culture when available), débridement, and splinting to prevent ankylosis. This complication carries a poor prognosis.³¹

Recurrent gouty arthritis is treated with NSAIDs or cyclooxygenase-2-selective inhibitors and serum urate-lowering drugs such as allopurinol. Patients with SS disease and gout are likely to have renal impairment and challenged liver function. Therefore, checks of renal and liver function every 3 to 4 months are indicated.

When SS disease is associated with rheumatoid arthritis and other CTDs, the classic treatment may lead to severe and possibly life-threatening complications.³² Antiinflammatory drugs may cause acute renal failure. Corticosteroids have been associated with avascular joint necrosis, as well as with painful bony crisis with oral and intraarticular corticosteroids. There is concern regarding the use of weekly methotrexate and leflunomide. Hepatotoxicity is difficult to monitor in SS patients, who invariably have abnormal liver function. In those with active CTD, corticosteroids and methotrexate have been associated with more severe SCD-related outcomes, including more severe infections and a 20% overall patient mortality rate because of sepsis, stroke, or acute chest syndrome.³² Antimalarial therapy seems to be the least toxic disease-modifying antirheumatic drug therapy, but chronic use of such therapy is precluded by possible retinopathy. Sulfasalazine may be effective in reducing both the rheumatoid inflammation and the sickling process.³³

Tumor necrosis factor (TNF) is important in the pathophysiology of both vasoocclusive crises and rheumatoid arthritis. Experience with anti-TNF therapy and rituximab for SS disease is limited, but promising; good efficacy and tolerance are suggested in patients with SS disease and CTDs.³²

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Hemochromatosis

■ ELENA M. MASSAROTTI

- Hemochromatosis refers to a general increase in body iron stores with resultant tissue damage that is most often the result of a genetically inherited defect with abnormal iron absorption caused by mutations of the *HFE* gene on chromosome 6.
- Treatment by phlebotomy can prevent organ damage but does not appear to affect hemochromatosis-related arthropathy.
- The severity of the disease varies. Asymptomatic disease, detected on routine screening demonstrating elevated iron levels, is the most common manifestation. Symmetric arthropathy may also be an early feature.
- The classic clinical picture of diabetes, bronze skin, liver disease, and arthropathy is found in only a small fraction of homozygotes.

HISTORY

The term *hemochromatosis* was first used by von Recklinghausen in 1889 for a condition initially described by Trousseau in 1865. In 1927 Sheldon¹ suggested that the disease was the result of an inborn error of metabolism. By 1955 Finch and Finch² showed that classic hemochromatosis was caused by abnormal iron absorption. These authors also confirmed that the excess iron could be removed by phlebotomy. In 1976 it was reported that the gene defect was related to HLA,³ and the mutant gene *HFE* was identified in 1996.⁴ A new diagnostic test was thus available; it replaced liver biopsy for the diagnosis of hemochromatosis and simplified family studies and screenings of populations.

GENETICS AND EPIDEMIOLOGY

Epidemiologic data for hemochromatosis are shown in Table 196.1. It was postulated that the genetic defect should be found on chromosome 6 close to the HLA locus.³ This mutant gene, *HFE*, was then identified 5 Mb distal to the HLA-A locus (Fig. 196.1).⁴ One mutation resulted in a cysteine-to-tyrosine substitution at amino acid 282, C282Y, and another caused a histidine-to-aspartic acid substitution at position 63, H63D. More than 90% of patients with hereditary hemochromatosis in northern Europe are homozygous for C282Y, and 5% are heterozygous with C282Y/H63D.¹ These compound heterozygotes have a very mild phenotypic expression.

The original mutation occurred in a person who lived in northern Europe about 2000 years ago⁵ (even if more recent studies have suggested an older age).⁶ This ancestor carried HLA-A3, and about half the descendants still carry the same conserved haplotype in linkage with the mutation (Fig. 196.2). Others carry different HLA marker haplotypes resulting from recombinations between HLA-A and *HFE*. The C282Y mutation is common (≈10%) and reaches its highest prevalence in Ireland, Brittany, the United Kingdom, Norway, Denmark, and Sweden,^{6,7} as well as in emigrants from these regions.⁸⁻¹⁰ The geographic distribution suggests early migration with the Vikings.¹¹ The prevalence declines, like that of nutritional iron deficiency of the past,^{2,11} as one travels south across Europe and is absent from the original populations of Australia, Asia, and so on.⁶ A selective advantage might explain the commonness of the mutation in former iron-deficient areas.

CLINICAL FEATURES

Hereditary hemochromatosis is an autosomal recessively inherited disease characterized by iron overload caused by abnormal iron absorption. Iron overload can also be caused by multiple blood transfusions, iron injections, and prolonged oral iron intake.¹² The classic picture of “bronze diabetes” is not a representative description of hemochromatosis today; instead, this rare manifestation should be regarded as a diagnostic failure. Some evidence suggests that earlier diagnosis and treatment have led to the perception that the frequency and extent of organ damage may be changing with time.¹³ The arthropathy associated with hemochromatosis¹⁴ is a much more common manifestation than skin pigmentation, diabetes, hypogonadism, or cardiomyopathy^{15,16} and can be the initial symptom (Fig. 196.3). Screening studies with phenotypic iron tests have shown that mildly affected cases are common,^{11,17} with observations confirmed in large genotype screenings.^{8,9} Penetrance is low, and 1 in 400 to 500 northern Europeans express the disease.

Signs and symptoms usually appear between the ages of 40 and 60 years. A rare fraction express a more “malignant” form, with the full-blown clinical picture developing at 20 years of age. This juvenile hemochromatosis is caused by mutations in the hepcidin gene (*HAMP*) on chromosome 19 or in the hemojuvelin gene (*HJV*) on chromosome 1.¹

Hemochromatosis is an “a” disorder, with asthenia, arthropathy, and alanine aminotransferase elevations being the most common manifestations.¹⁵ Asthenia, though nonspecific,⁸ paradoxically may lead to diagnosis, with iron tests being performed because of suspected iron deficiency.

Asymptomatic liver abnormalities are the most constant manifestation.^{8,9,15,18} All patients with “transaminitis” should be considered for investigation of iron overload to enable early diagnosis before the establishment of liver cirrhosis.¹⁸ Treatment started in the precirrhotic stage often results in an excellent prognosis; however, those with cirrhosis have an increased risk for the development of hepatocellular carcinoma.^{1,2}

The skin pigmentation is seldom diagnostic. Diabetes is a late and rare manifestation, like cardiomyopathy caused by iron overload. Hypogonadism with decreased libido, impotence, amenorrhea, and sparse body hair is caused by gonadotropic insufficiency and is usually a late manifestation of iron overload.

Arthropathy

Arthropathy can be the first manifestation of the iron-loading process (see Fig. 196.3), although more often it occurs later, even after treatment.¹⁴ Most joints can be affected, but osteoarthritis (OA)-like changes of the metacarpophalangeal joints of the second and third fingers are the most characteristic (Figs. 196.4 and 196.5).¹⁹⁻²¹ The disease can also affect other joints¹⁹ and may be a prominent factor affecting quality of life.²² Sometimes acute episodes of inflammatory arthritis occur as a result of deposition of calcium pyrophosphate dehydrate (Fig. 196.6).^{20,23}

The reported frequencies of arthropathy associated with hemochromatosis are variable^{12,20,22,24} and probably influenced by biased ascertainment. Its specificity has been questioned in three large screening studies using controls.^{8,9,17}

In one study of 65,238 Norwegians, 16% of men with hemochromatosis had OA as compared with 7.6% of controls.¹⁷ In a California genotype study of 41,038 individuals, self-reported arthropathy was present in 36% of C282Y homozygotes and 42.9% of C282Y/H63D heterozygotes, no different from controls at 41.6%.⁸ A genotype study of 99,711 participants in the United States and Canada gave similar results; self-reported arthritis in C282Y homozygotes was not different from controls.⁹ A small follow-up interview study²⁵ of 17 of 124 (13.7%) C282Y homozygotes from the California study⁸ seemed to indicate a higher frequency of symptoms in the

TABLE 196.1
Epidemiology of hemochromatosis

Peak age (yr)	40-60
Sex distribution (F:M)	1:4
Prevalence	10-60/10,000
Annual incidence	1-4/100,000
Geographic distribution	Most prevalent in northern European populations
Genetic associations	Most cases caused by a point mutation, C282Y, of the <i>HFE</i> gene on chromosome 6, distal to the HLA-A locus

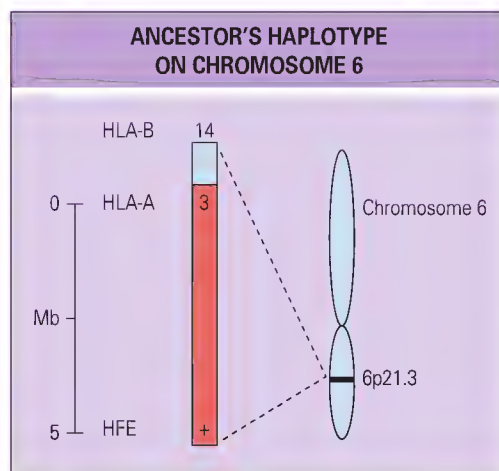
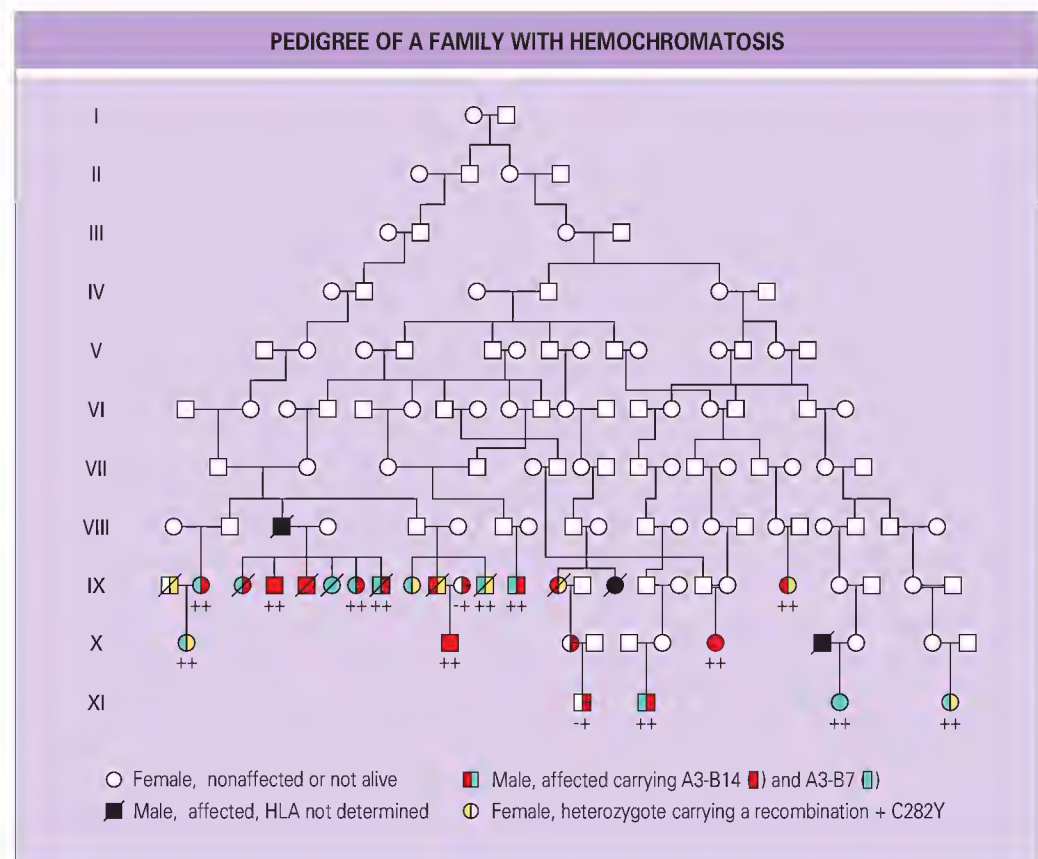


Fig. 196.1 The ancestor's haplotype starts centromeric of the HLA-A locus and extends telomerically for more than 5 Mb, including *HFE* and its mutation C282Y (+). The ancestor probably carried A3-B7 or A3-B14.³

Fig. 196.2 Ten "unrelated" families with hereditary hemochromatosis were found to have the ancestor's HLA-A3 in common (red). A family investigation had fortunately been done and revealed that all the patients could be traced to common ancestors 11 generations earlier in the late 17th century. Homozygosity for the *HFE* mutation C282Y is marked with ++ below the individuals. Black symbols indicate affected members not available for *HFE* genotype testing. Half-filled symbols are heterozygotes (they carry only one mutation). Filled symbols indicate homozygotes or carriers of two haplotypes. Those with A3-B14 are shown in a red and those with A3-B7 in teal. (Adapted from Ritter B, Safwenberg J, Olsson KS. HLA as a marker of the hemochromatosis gene in Sweden. *Hum Genet* 1984;68:626; and Raha-Chowdhury R, Gruen JR. Localization, allelic heterogeneity and origins of the hemochromatosis gene. In: Barton JC, Edwards CQ, editors. *Hemochromatosis*. Cambridge: Cambridge University Press; 2000, p. 75-90.)



fingers and hands in C282Y homozygotes. Reviews of arthritis in hemochromatosis have been published.^{16,26}

Slight bony swelling and an inability to extend and flex the second and third metacarpophalangeal joints may be seen. Erythema or increased warmth is seldom present, the erythrocyte sedimentation rate is often normal, and rheumatoid factor is negative. Anti-citrullinated peptide antibodies were absent in the sera of patients with hereditary hemochromatosis.²⁷ Some hereditary hemochromatosis sufferers who have had arthropathy for several years have reported being reassured that "this is not rheumatoid arthritis" (RA), and the correct diagnosis was not considered.

Radiographs may show cystic lesions with sclerotic walls, joint space narrowing, sclerosis, osteophytes, and osteoporosis (see Fig. 196.5); these features are similar to those seen in idiopathic OA.^{20,28}

Although the arthropathy is most often noninflammatory, it is a prominent clinical feature that affects the quality of life of a person with hemochromatosis.²²

INVESTIGATIONS

Diagnosis of hereditary hemochromatosis is simple, provided that it is considered. The screening tests are transferrin saturation, expressed as the serum iron concentration divided by the iron-binding capacity multiplied by 100, which is elevated (>45%), in combination with an increased serum ferritin concentration (>200 µg/L in males, >100 µg/L in females). If an inflammatory condition is superimposed, percent transferrin saturation drops (Fig. 196.7). If the screening test results are abnormal, they should be followed by the *HFE* genotype test. A finding of homozygosity for C282Y or compound heterozygosity for the two mutations C282Y/H63D confirms the diagnosis. If the liver test results are abnormal and serum ferritin signals severe iron overload (>1000 µg/L), liver biopsy is recommended.¹ Once the diagnosis is established, all first-degree relatives should be screened with genotype and iron tests.¹ Population screening is no longer recommended because of the low penetrance of the genotype.^{1,8,9}

DIFFERENTIAL DIAGNOSIS

Secondary iron overload, which sometimes produces arthropathy, is excluded by a history that does not include blood transfusions, parenteral

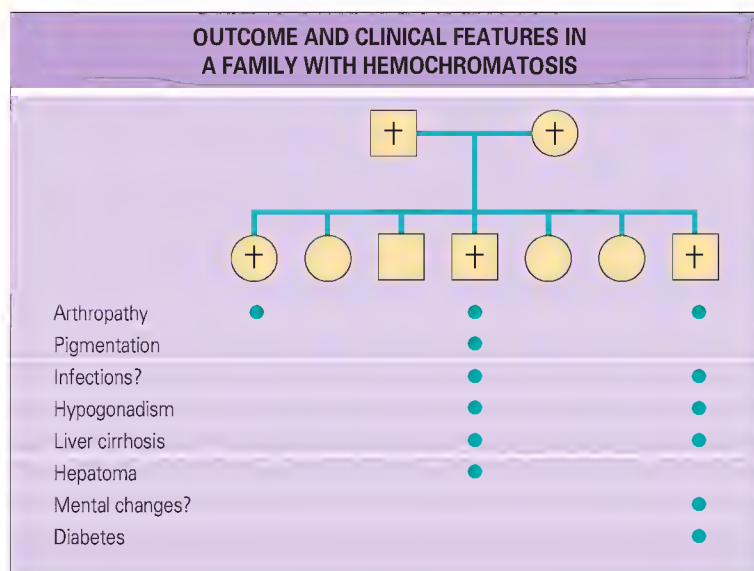


Fig. 196.3 A record from 1936 showed that the father (VIII:3 on Fig. 196.2) had suffered from "polyarthritis" from the age of 48. He died at 49 years of "diabetes bronze and myocarditis" proven by autopsy. Fifty years later, arthropathy developed in his eldest daughter and she underwent total hip replacement. Child No. 4, a son, died of a hepatoma. Child No. 7, the youngest son, has had arthropathy from the age of 26, abdominal pain from the age of 30, a diagnosis of "seronegative polyarthritis" at age 39, hypogonadism at age 44, and the diagnosis of "hemochromatosis with cirrhosis" at age 46. Children Nos. 3, 5, and 6 were mainly free of symptoms despite being homozygous. (Adapted from Ritter B, Safwenberg J, Olsson KS. HLA as a marker of the hemochromatosis gene in Sweden. *Hum Genet* 1984;68:626.)



Fig. 196.4 The hands of a patient with hemochromatosis. The bony swelling of the metacarpophalangeal joints is apparent.



Fig. 196.5 Radiograph of the hand of a 45-year-old man with hemochromatosis. Cystic lesions of the metacarpal heads, joint space narrowing, and osteophytes at the second and third metacarpophalangeal joints are present.

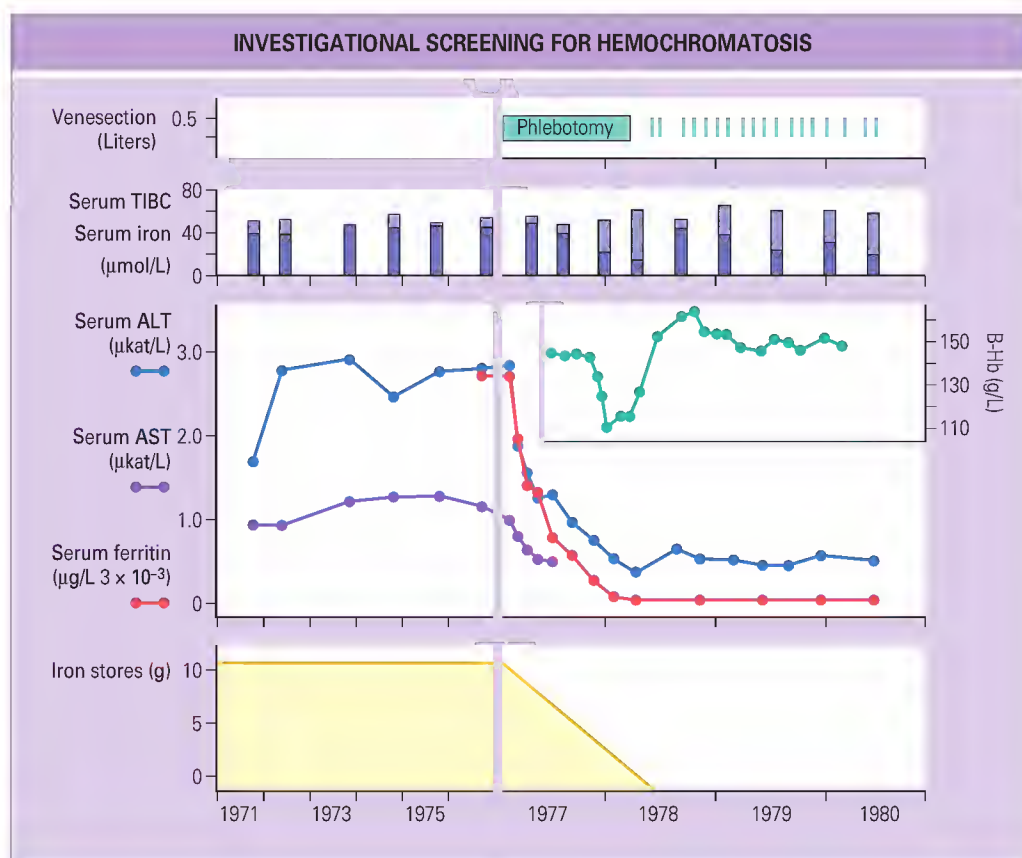


Fig. 196.6 Findings from a broad biochemical laboratory profile show constantly abnormal transferrin saturation and elevated transaminase levels in a 44-year-old man with pseudogout as the initial symptom. Liver biopsy confirmed the diagnosis of hemochromatosis in the cirrhotic stage. The effect of phlebotomy is obvious. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; TIBC, total iron-binding capacity.

CHANGES IN TRANSFERRIN SATURATION INDUCED BY AN INFLAMMATORY REACTION

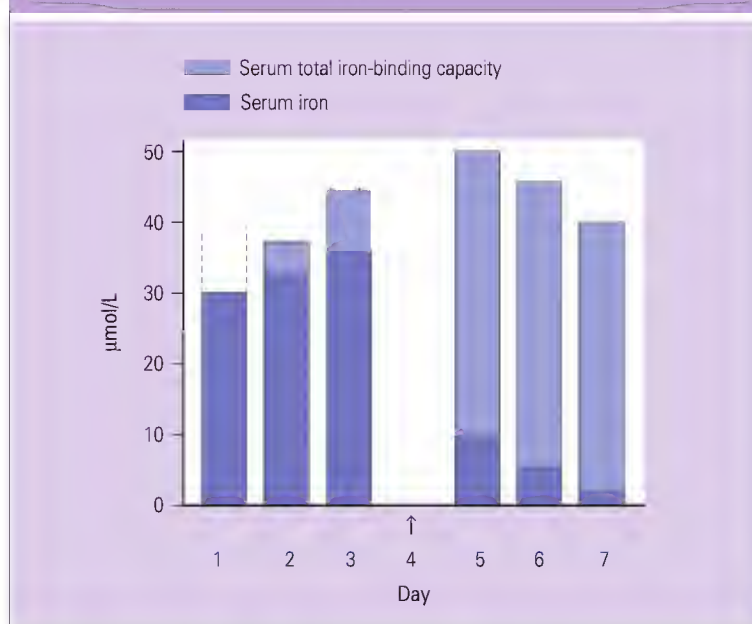


Fig. 196.7 The patient, aged 69, suffered a myocardial infarction on day 4 (arrow) while hospitalized because of hemochromatosis. The remarkable drop in plasma iron is probably an effect of increased hepcidin activity.^{1,24}

iron administration, and anemia (β -thalassemia, sideroblastic anemia). Porphyria cutanea tarda is also manifested as elevated percent transferrin saturation, increased serum ferritin concentration, and abnormal liver test results. However, these patients have more intense pigmentation, skin fragility, blisters, and hirsutism.¹ Interestingly, the C282Y mutation has been found in 40% of patients with porphyria cutanea tarda.²⁹

Alcoholic liver disease might be associated with an increased serum ferritin concentration and elevated transferrin saturation. Abstinence often results in a rapid drop in these parameters.

PATHOGENESIS

In hemochromatosis, absorption of iron from the diet is increased. Because iron excretion is minimal, the result is progressive iron loading of parenchymal tissues, particularly the liver.¹ Studies have identified several new genes along the iron pathway through the major cell types involved (Fig. 196.8).³⁰ The iron hormone hepcidin has a central role in regulating the influx of iron into plasma from red cell breakdown in macrophages and iron-absorbing gut cells. With low hepcidin expression, plasma iron increases as in hemochromatosis. When inflammation takes place, hepcidin activity increases and plasma iron is reduced (see Fig. 196.7). Hemochromatosis thus seems to be the opposite condition of anemia of chronic disease. How the defective C282Y protein interacts with hepcidin is not yet clear.

Within the cell, extra iron is stored in lysosomes as ferritin and hemosiderin. Iron may be toxic to the cell by inducing free radical production, which causes lipid peroxidation and weakening of lysosomal membranes. An iron load of no more than 3 g (only four times normal) can induce liver cells to release transaminases.¹⁸ Knowledge of the joint pathology seen in hemochromatosis has been derived largely from joint replacement surgery.¹⁶ In contradistinction to secondary hemochromatosis, in which iron deposition is noted in the sublining areas of the synovium or synovial stroma, iron deposition in primary hemochromatosis occurs in the synovial lining cells.^{16,31} The histopathology of hemochromatosis-

IRON DELIVERY TO PLASMA FROM THE ENTEROCYTE AND THE MACROPHAGE IS REGULATED BY THE IRON HORMONE HEPcidIN PRODUCED BY THE HEPATOCYTE

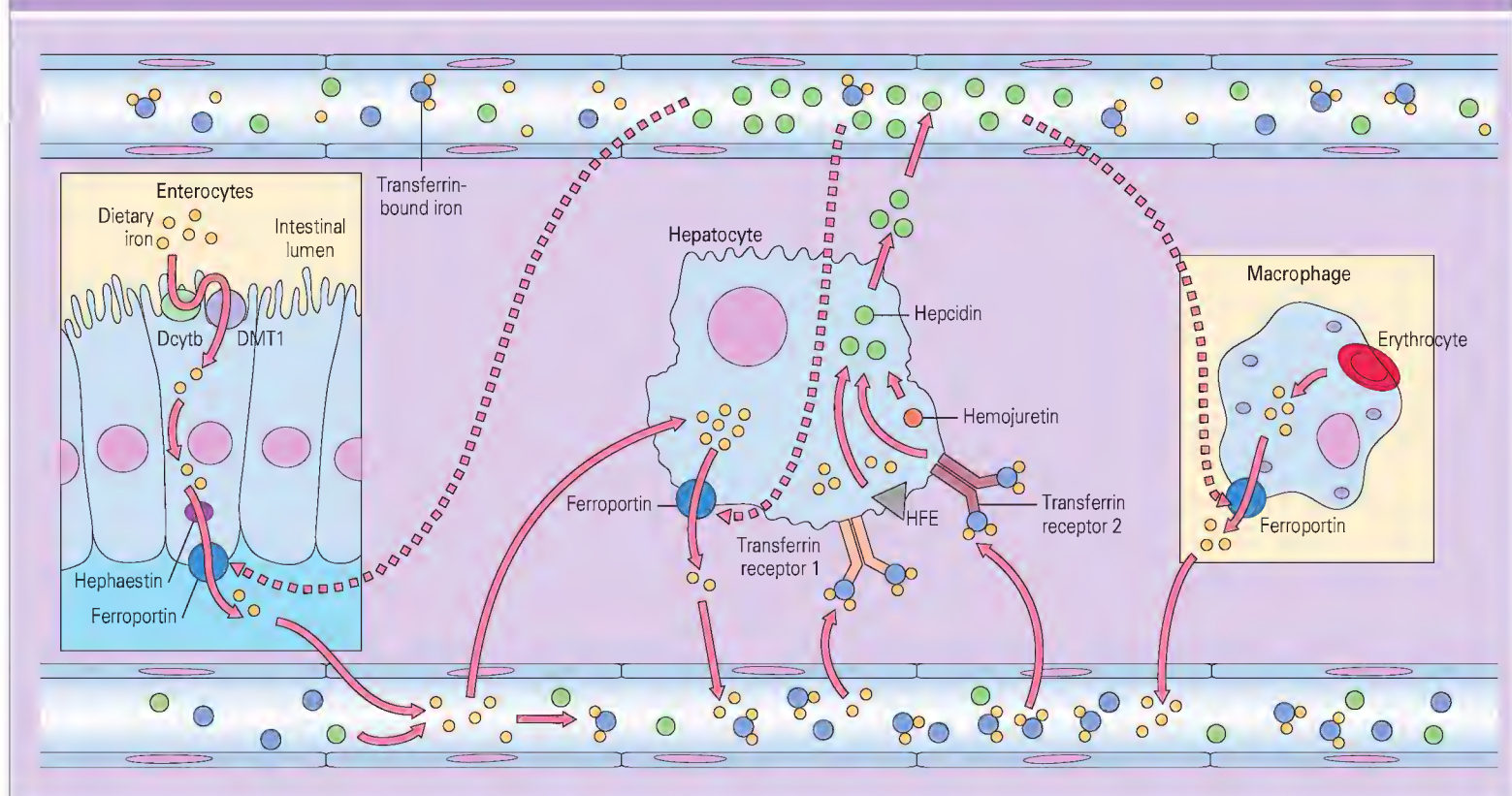


Fig. 196.8 When the hepcidin activity is inappropriately low, plasma iron increases as in hemochromatosis. The opposite situation is seen with inflammation (see Fig. 196.6) and the anemia of chronic disease. (From Fleming RE, Bacon BR. Orchestration of iron homeostasis. *N Engl J Med* 2005;352:1741-4.)

related arthropathy lies between that of OA and RA.^{27,32} Synovial infiltration of macrophages and neutrophils is more pronounced in hemochromatosis than in OA. Hemosiderin deposition is not found in RA or OA but can be found in hemochromatosis-related arthropathy. However, B and T cells, which are present in RA synovium, are not seen in hemochromatosis-related arthropathy. No clear relationship has been found between iron load and effect on the synovium.^{19,20,32} Biopsy specimens have demonstrated hemosiderin granules in type B synovial cells rather than in macrophage-like type A cells, as seen in RA and hemarthrosis. Synovial inflammation is scarce.¹⁴ Ferritin particles have been identified in intact chondrocytes together with calcium pyrophosphate dehydrate crystals in cartilage.³² The osteoporosis associated with hemochromatosis is usually a late manifestation.

Environmental factors

Several factors other than age can influence phenotypic expression of the disease, such as blood donation and menstrual blood loss. Dietary factors, such as high intake of dairy products, may explain why patients in Scandinavia with hereditary hemochromatosis are less iron loaded than their genetic relatives living in Germany, Australia, or other, more fertile areas.^{15,19,22} Excessive alcohol intake has an additive influence on the liver damage, and iron tablets may worsen the phenotype.

MANAGEMENT

Excess iron is removed from the body by weekly phlebotomy. Each unit of blood (450 cm³) contains 200 to 250 mg of iron, and this quantity is mobilized from storage sites to compensate for the blood loss. Bloodletting is well tolerated and is continued until the serum ferritin level indicates iron depletion (30 to 40 mg/L). Maintenance phlebotomy three to six times a year is then required to prevent iron reaccumulation. Dietary restrictions are not needed. Liver function improves during phlebotomy (see Fig. 196.6), the abdominal pain disappears, and general well-being is increased. Even the cardiomyopathy is reversible, but diabetes and hypogonadism are not usually affected by iron removal.

Arthropathy does not generally improve with phlebotomy.¹⁹ Treatment with nonsteroidal antiinflammatory drugs is helpful in the majority of patients.

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METABOLIC BONE DISEASE

197

Epidemiology and classification of osteoporosis

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- Osteoporosis is a systematic skeletal disorder characterized by low bone mass, microarchitectural deterioration of bone tissue, and susceptibility to fracture. It can be divided into primary and secondary forms.
- The most widely used definition of osteoporosis is that of the World Health Organization: bone mineral density (BMD) greater than 2.5 standard deviations or greater below the young normal mean.
- Even though BMD and bone strength are strongly correlated, other factors may weaken bone independently of BMD; hence, there has recently been a move toward assessing an individual's 5- or 10-year risk for osteoporotic fracture. An example of such a model is the FRAX tool.
- Risk factors for low BMD relate to either inadequate bone formation during growth or excessive bone loss thereafter, but the underlying pathogenesis remains somewhat obscure.
- Fractures, the clinical manifestation of osteoporosis, increase dramatically with aging and are more frequent in women than in men and in whites than in other races.
- Hip fractures are most devastating in terms of mortality, morbidity, and cost, but other types of fracture contribute substantially to the social burden of osteoporosis.
- Because of the dramatic growth in the elderly population worldwide, the number of osteoporotic fractures will increase substantially in future years unless cost-effective control programs can be implemented.

INTRODUCTION

Osteoporosis is a systematic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue that increases the fragility of bone and hence susceptibility to fracture. It is increasingly being recognized as a global concern and remains the most common metabolic bone disease; osteoporosis affects both sexes and all races. Osteoporotic fractures are not only common but may also have devastating consequences. They represent a major public health problem because they increase patient morbidity and certain fractures (e.g., hip and vertebral fractures) are associated with increased mortality. The public health burden of the disease is likely to rise in future generations, in part because of an increase in life expectancy and a growing elderly population. Understanding the epidemiology of the disease is crucial in trying to develop strategies to help reduce this load.

HISTORY

Historically, the term *osteoporosis* first entered medical terminology in France in the 19th century. Jean Lobstein, a French pathologist, used the

term to emphasize the porosity of the histologic appearance of aged human bone (porosis = porous bone). Around the same time, Sir Astley Cooper, an English surgeon, suggested that certain types of fractures may occur as a result of the age-related reduction in bone mass or quality.¹ He described the classic epidemiologic hallmarks of these fractures: incidence rates that increase with age, rates that are higher in women than in men, and fractures that are associated with only moderate trauma at sites containing large amounts of trabecular bone. Little attention was paid to the disease until the 1940s, when Fuller Albright, an American endocrinologist, attributed the disease to loss of estrogen after menopause. Unfortunately, at that time a reliable test for the diagnosis of osteoporosis was not available, so most patients came to medical attention only after a fracture. It was not until the 1960s, with the introduction of bone densitometry, that greater understanding of the association between osteoporosis and certain fractures was achieved and the potential public health burden of the condition became apparent. Since the 1980s, much progress has been made in terms of therapeutic developments for prevention of osteoporosis with the introduction of bisphosphonates and other agents.

OSTEOPOROSIS

Definition

The definition of osteoporosis remains difficult. Dual-energy x-ray absorptiometry is currently the "gold standard" tool for measuring bone mass, and from this, bone mineral density (BMD) can be obtained. BMD and the strength at which bones break *in vitro* are strongly correlated; however, BMD does not completely explain the architectural changes in bone that lead to skeletal fragility. Nonetheless, it is recognized that BMD is highly predictive of fracture risk. In 1994, an expert panel convened by the World Health Organization (WHO) established the most widely used definition that encompasses both BMD and previous fracture.² They defined osteoporosis as a state in which BMD in women falls more than 2.5 standard deviations below the young adult mean. This definition, however, takes into account only deterioration in bone mineralization and does not consider any of the microarchitectural changes that may weaken bone independently of any effect on BMD. More recently, there has been a move toward assessing an individual's absolute risk for osteoporotic fracture, an example of which is the FRAX tool.³

Classification

Osteoporosis can develop as a primary disorder or be secondary to other factors such as associated medical diseases, surgical procedures, or medications known to accelerate bone loss. It is important to note that both categories are not completely independent of each other and may on occasion be additive; for example, in individuals with primary osteoporosis, secondary causes may further aggravate the bone loss and increase the risk for fractures.

BOX 197.1 SECONDARY CAUSES OF OSTEOPOROSIS

- Immobilization
- Malignancy
- Chronic renal failure
- Gastrointestinal disease:
 - Malabsorption syndrome
 - Liver disease
 - Inflammatory bowel disease
- Rheumatologic disease:
 - Rheumatoid arthritis
 - Systemic lupus erythematosus
- Genetic conditions:
 - Cystic fibrosis
 - Osteogenesis imperfecta
 - Ehlers-Danlos syndrome
 - Glycogen storage diseases
 - Prolonged weightlessness
- Chronic obstructive pulmonary disease
- Endocrine disease:
 - Cushing disease
 - Hyperparathyroidism
 - Hyperthyroidism
 - Hypogonadism
 - Hyperprolactinemia
 - Diabetes mellitus (type 1)
- Drugs:
 - Corticosteroids
 - Ethanol
 - Antiepileptics
 - Heparin
 - Tobacco

Primary osteoporosis accounts for more than 95% of cases of osteoporosis in women and 70% to 80% in men. In general, it occurs in postmenopausal women and older men. *Idiopathic osteoporosis* is included in this category and is used to describe the uncommon forms of osteoporosis found in children and young adults with normal gonadal function and no detectable secondary cause. The pathogenesis of this type remains unclear. *Secondary osteoporosis* accounts for less than 5% of cases of osteoporosis in women but up to 20% in men. Its causes are listed in Box 197.1.

Assessment of fracture risk

Since 1994, osteoporosis has been defined in terms of BMD. In general, clinical development of pharmacologic agents has focused on the selection of patients on the basis of low BMD with or without prevalent vertebral deformities for inclusion into trials of efficacy. Thus guidance on whom to treat has emphasized assessment of BMD. Use of T-scores has many benefits because it is simple and widely used, is strongly correlated with risk for fractures, and can detect some high-risk patients.² However, shortcomings include lack of standardization regarding which skeletal sites to study, lack of generalization to the nonwhite population, and the fact that it evaluates BMD as the only risk factor for fracture.

Given the increasing evidence now suggesting that T-scores alone are insufficient predictors of fracture risk, the WHO convened a scientific group to develop more accurate ways of assessing fracture risk. The use of clinical risk factors together with age and BMD increases the sensitivity of fracture prediction still further without sacrificing specificity. From this, multivariate models have been created that allow the 10-year probability of hip and other fractures to be predicted. An example of such a model is the FRAX tool³ developed in the United Kingdom by the WHO. Clinicians can easily input clinical data to estimate the 10-year probability of hip and major osteoporotic fractures (which includes forearm, hip, spine, and humerus fractures) in men and women between 40 and 90 years of age. The estimate can be used alone or with BMD to enhance fracture risk prediction. The 10-year probability of fracture was preferred over lifetime risk for several reasons, namely, treatments are not given for a lifetime, the 10-year interval accommodates the clinical trial experience of interventions, and the long-term prognostic value of some risk factors may decrease with time. If an individual's life expectancy is less than 10 years, the probability produced by FRAX equals the remaining lifetime risk for fracture. In addition, the FRAX tool does not simply adjust for mortality risk based on average mortality rates for the population but also accommodates for the fact that many risk factors that predict fracture risk also influence mortality (older age, previous fracture, low body index, smoking).

Using cost-effectiveness analysis, intervention thresholds for use in clinical practice within the United Kingdom concerning when to commence treatment (or perform BMD testing if not yet done) have also been added to the model. These thresholds are in accordance with recent U.K. National Osteoporosis Guideline Group guidance and are set by age and sex and based on a fracture probability equivalent to that of women with a history of a previous osteoporotic fracture. For example, the intervention threshold for treatment at the age of 50 years corresponds to a 7.5% 10-year probability of sustaining a major osteoporotic fracture. This figure rises progressively with age to 30% at the age of 80 years; assessment thresholds for BMD

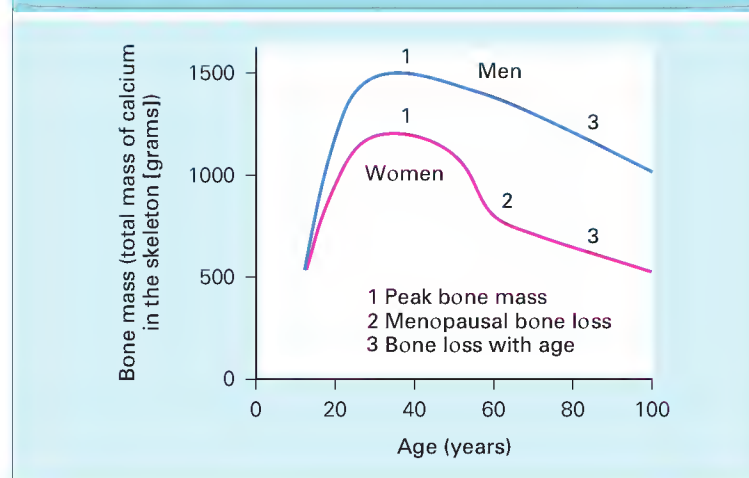
CHANGES IN BONE MASS OVER TIME IN WOMEN AND MEN

Fig. 197.1 Changes in bone mass over time in women and men.

testing also rise with age (6% to 9% at 50 years rising to 18% to 36% at the age of 80 years).⁴

The FRAX model has now been calibrated to the epidemiology of 44 other countries. It is important to note that any intervention thresholds developed in one country may not be applicable to other countries. For instance, intervention thresholds have also been developed in the United States by the National Osteoporosis Foundation and suggest that persons with a 10-year risk for major osteoporotic fracture of 20% or higher or a 10-year risk for hip fracture of 3% or higher should receive pharmacologic treatment to reduce this risk.

Risk factors

Constitutional and lifestyle risk factors for low BMD are numerous, although none have high enough sensitivity to confirm or exclude the diagnosis of osteoporosis. Factors that influence BMD exert their effect in two ways—through either inadequate development of peak bone mass or an excessive rate of bone loss (or a combination of the two). Genetic factors are thought to be very important in the attainment of peak bone mass; family studies have examined parent-offspring and sibling-sibling correlations in BMD and found correlation coefficients of 0.28 to 0.59,^{5,6} and twin studies have shown much closer concordance of bone density in monozygotic than in dizygotic twins.⁷ However, environmental factors such as hormonal status, physical activity, and calcium intake are also important in attaining peak bone mass. Environmental influences are thought to be more important than genetic factors in determination of bone loss.

Increasing age is an important risk factor for osteoporosis. Peak bone mass is achieved in men and women by the mid-20s. It then plateaus for around 10 years before falling at a rate of 0.3% to 0.5% each year. At menopause the rate of bone loss in women accelerates to around 3% to 5% per year for 5 to 7 years before returning to the previous rate of decline (Fig. 197.1). This accounts for the increasing incidence of osteoporosis with age. Female gender is also important; men naturally have higher bone mass than women and do not have an accelerated rate of bone loss corresponding to that in women around menopause. Other risk factors include low body weight and weight loss, late age at menarche, early age at menopause, physical inactivity, low dietary calcium intake, smoking, and increased alcohol and caffeine intake. A previous fracture and a maternal history of fracture are further risk factors. In individuals with a maternal history of fracture, the risk for hip fracture is doubled.⁸ Protective factors for osteoporosis include greater height, weight, and muscle strength; increased dietary calcium; greater physical activity; later age at menopause; and postmenopausal estrogen use.

Prevalence and incidence

The prevalence of osteoporosis in the European Union in 2010 was estimated to be 27.6 million. Furthermore, it has been estimated that 10 million Americans older than 50 years have osteoporosis and that a further 34 million are at risk for the disease. This figure is likely to increase to more than 14 million in 2020.⁹ Epidemiologic studies from North America have

estimated that the remaining lifetime risk for an osteoporotic fracture is 40% in white women 50 years of age (Table 197.1); the risks are 17.5% for hip fracture, 15.6% for clinically diagnosed vertebral fracture, and 16% for distal forearm fracture. Corresponding risks in men are 6%, 5%, and 2.5% (13.1% overall risk for osteoporotic fracture). Data from the General Practice Research Database in the United Kingdom (which includes 6% of the U.K. population)¹⁰ have indicated that the risk is similar in the United Kingdom. In women, the 10-year risk for any fracture increases from 9.8% at 50 years of age to 21.7% at 80 years, whereas in men the 10-year risk remains fairly stable with advancing age (Table 197.2). Our knowledge of the epidemiology of childhood fractures in the United Kingdom has recently been expanded by interrogation of the same database; at their childhood peak, the incidence of fractures (boys, 3%; girls, 1.5%) is surpassed only at 85 years of age in women and never in men (Fig. 197.2).

Health impact of osteoporotic fracture

All osteoporotic fractures are associated with significant morbidity, but both hip and vertebral fractures are also associated with excess mortality. It has been estimated that around 740,000 deaths take place per year worldwide as a result of hip fracture, with 21,000 occurring in the European Union within the first year of fracture. Worldwide, osteoporotic fractures account for 0.83% of the global burden of noncommunicable disease and 1.75% in Europe, where osteoporotic fractures account for more disability-adjusted life years than many other chronic noncommunicable diseases do.¹¹

Mortality

There is clear evidence of excess mortality associated with hip and vertebral fracture in both sexes. It has been estimated that only 25% of deaths from hip fracture are due to the fracture itself or to complications such

as infection, thromboembolism, and subsequent surgery.¹² The rest of the mortality reflects coexisting morbidity from underlying disease. In individuals sustaining a vertebral fracture, these comorbid conditions probably play an even larger role in mortality rates. Fractures of the forearm tend to not be associated with increased mortality except in elderly men, in whom slightly excess mortality has been observed.

It has been estimated that 8% of men and 3% of women older than 50 years die while hospitalized for their hip fracture. Mortality rates after hip fracture continue to rise over the subsequent months and peak at 1 year, with a rate of 36% for men and 21% for women.¹³ Mortality rates then tend to decline after the first year. Recent data from the Dubbo Epidemiology Study of community-dwelling women and men 60 years and older suggest that the elevated mortality persists for up to 10 years for hip fracture.¹⁴

After a vertebral fracture the excess mortality appears to remain in effect for up to 5 years in both sexes.¹⁴ This has been observed both in studies using clinically diagnosed vertebral fractures and in those using radiologic morphometric approaches to classify vertebral deformity. Impaired survival is more pronounced for vertebral fractures that follow moderate trauma rather than severe trauma, only 8% of which are actually attributable to osteoporosis. Five-year survival appears to be worse for men (5-year survival rate of 72%) than for women (5-year survival rate of 84%). In women, as the number of vertebral fractures increases, increased risk for death from cardiovascular and pulmonary disease has been observed.¹⁵

Overall, the four main predictors of higher mortality after fragility fractures appear to be male sex, increasing age, coexisting illness, and poor prefracture functional status. Smoking and low BMD may also be predictors in women.¹⁴

Morbidity

In 2004 a Swedish study weighted osteoporotic fractures according to morbidity (in terms of cumulative loss of quality of life) in an attempt to obtain an accurate determination of the true burden of osteoporotic fracture.¹⁶ Thus for a man between 50 and 54 years of age the disability caused by osteoporotic fractures is 4.5 times that accounted for by hip fracture alone; for women of the same age, the disability caused by osteoporotic fractures is 6 times that accounted for by hip fractures alone. The cumulative loss of quality of life tends to decrease with age. Four vertebral fractures appear to have the same morbidity as one hip fracture.

In the United States, about 7% of survivors of all types of fragility fractures have a degree of permanent disability and 8% require long-term nursing home care. Overall, after any type of fracture, a 50-year old white American woman has a 13% chance of experiencing attributable functional decline.¹⁷ Hip fracture invariably requires hospitalization, and patients are susceptible to the development of acute complications such as pressure sores, bronchopneumonia, and urinary tract infections. The degree of functional recovery after hip fracture depends on age. Recent data from the multinational Global Longitudinal Study of Osteoporosis in Women

TABLE 197.1
Lifetime risk for osteoporotic fracture at 50 years of age

	Women	Men
United Kingdom	53.2	20.7
Sweden	46.4	22.4
Australia	42.1	
United States	39.7	13.1

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TABLE 197.2
Estimated risk for fracture at various ages

	Current age (yr)	Any fractures	Radius/ulna	Femur/hip	Vertebra
Lifetime risk					
Women	50	53.2%	16.6%	11.4%	3.1%
	60	45.5%	14.0%	11.6%	2.9%
	70	36.9%	10.4%	12.1%	2.6%
	80	28.6%	6.9%	12.3%	1.9%
Men	50	20.7%	2.9%	3.1%	1.2%
	60	14.7%	2.0%	3.1%	1.1%
	70	11.4%	1.4%	3.3%	1.0%
	80	9.6%	1.1%	3.7%	0.8%
10-year risk					
Women	50	9.8%	3.2%	0.3%	0.3%
	60	13.3%	4.9%	1.1%	0.6%
	70	17.0%	5.6%	3.4%	1.3%
	80	21.7%	5.5%	8.7%	1.6%
Men	50	7.1%	1.1%	0.2%	0.3%
	60	5.7%	0.9%	0.4%	0.3%
	70	6.2%	0.9%	1.4%	0.5%
	80	8.0%	0.9%	2.9%	0.7%

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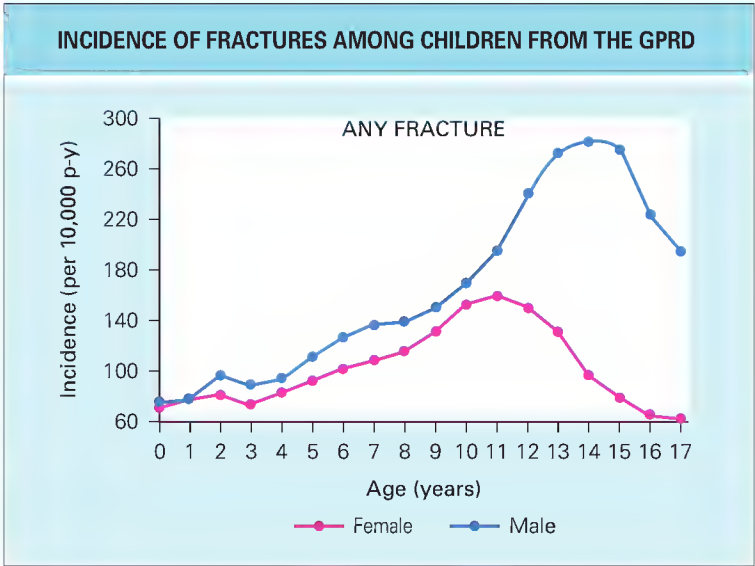


Fig. 197.2 Incidence of fractures in children from the General Practice Research Database in the United Kingdom. (Reproduced with permission of John Wiley & Sons, Inc. Cooper C, Dennison EM, Leufkens HG, Bishop N, von Staa TP. Epidemiology of childhood fractures in Britain: a study using the General Practice Research Database. J Bone Miner Res 2004;19:1976-81.)

(GLOW) cohort showed that 134 patients who sustained a hip fracture over the 1-year follow-up accounted for 1306 days of hospitalization and 1650 days of rehabilitation or nursing home care.¹⁸

Hip fracture has a significant effect on an individual's ability to walk; 40% are still unable to walk independently 1 year after hip fracture, with 60% requiring assistance in at least one essential activity of daily living (e.g., dressing, bathing); 80% are unable to perform at least one instrumental activity of daily living, such as driving or shopping.¹³

Despite only a minority of vertebral fractures coming to clinical attention, they account for around 52,000 hospital admissions in the United States and more than 2000 in England and Wales each year in patients 45 years or older. The impact of a single vertebral fracture can often be low, but multiple fractures lead to progressive loss of height and kyphosis and severe back pain in both the acute and chronic stages.¹⁵ The resultant loss of mobility can further exacerbate the underlying osteoporosis and lead to an increased risk for further fractures.¹⁶ The psychological impact of functional loss can result in depression and social isolation, as well as loss of self-esteem. Participants in the European Prospective Osteoporosis Study (EPOS) with a radiologically identified vertebral fracture at baseline had radiographs repeated 3 years later. Women who had suffered a further fracture during this period experienced substantial levels of disability along with impairment in key physical functions of independent living.¹⁹

Wrist fractures do not seem to increase mortality. They may have an impact on some activities such as writing or meal preparation, but few patients are completely disabled. More than 50%, however, still report only fair to poor function at 6 months, often because of complications such as reflex sympathetic dystrophy, neuropathy, and posttraumatic arthritis.¹⁵

Bone mineral density and fracture

Several prospective epidemiologic studies have shown that BMD is a strong predictor of fracture independent of age. Risk for osteoporotic fracture increases continuously as BMD declines, with a 1.5- to 3-fold increase in risk for fracture for each standard deviation fall in BMD.² There is no convincing evidence of a threshold in the relationship between BMD and fracture; the relationship appears to be continuous. In the Rotterdam study, a prospective population-based cohort study of 7806 men and women 55 years or older, the age-adjusted hazard ratio for all nonvertebral fractures per standard deviation decrease in femoral neck BMD was 1.5 for women and 1.4 for men.²⁰ For hip fractures, hazard ratios were 2.1 for women and 2.3 for men. A meta-analysis of prospective studies from 1996 found that for each standard deviation decrease in hip BMD, the risk for hip fracture increases by 2.6-fold.²¹

Some evidence also suggests a definite inverse correlation between BMD and the severity of fracture. Recent data from the United Kingdom on distal radial fractures revealed an increased rate of early instability, malunion, and carpal malalignment after fractures in patients with reduced BMD.²²

Although it has its limitations, measurement of bone density is currently the best available method of predicting future fracture. Appropriate cutoff

values have been defined by the WHO so that intervention can be directed toward "at-risk" individuals (Table 197.3). The relationship between BMD and osteoporosis can be compared with that between blood pressure and stroke. Although hypertension is a risk factor for stroke, stroke can occur in individuals with normal blood pressure. Likewise, fractures can occur in the absence of osteoporosis. Of note in the Rotterdam study, only 44% of nonvertebral fractures occurred in women with a T-score lower than -2.5 (the WHO definition of osteoporosis); in men this percentage was even lower at 21%. This highlights the presence of other known risk factors for fracture that are independent of BMD: family history of fracture, cigarette smoking, excess alcohol consumption, and low body weight. Thus BMD alone cannot reliably discriminate between individuals who will sustain a fracture and those who will not.

FRACTURE EPIDEMIOLOGY

It is estimated that 3.5 million fragility fractures occur every year in the European Union.²³ Fracture incidence in the community is bimodal, with a peak in the young and in the elderly. In young people, fractures are usually associated with substantial trauma, occur in the long bones, and are seen more frequently in males than in females. In this group the question of bone strength rarely arises. Osteoporotic fractures characteristically occur in areas of the skeleton with a high amount of trabecular bone after low or moderate trauma. The "classic" osteoporotic fragility fractures are hip, vertebral, and wrist fractures, although prospective studies have shown increased risk for almost any type of fracture. The frequency of fracture increases with age in both sexes because of a combination of lower bone density and the increased tendency to fall in the elderly (Fig. 197.3).

TABLE 197.3
Diagnostic categories for osteoporosis based on World Health Organization criteria

Category	Definition
Normal	BMD not more than 1 SD below the young adult mean value
Low bone mass (osteopenia)	BMD lying between 1 and 2.5 SD below the young adult mean value
Osteoporosis	BMD more than 2.5 SD below the young adult mean value

BMD, bone mineral density; SD, standard deviation.
From World Health Organization data, 1994.

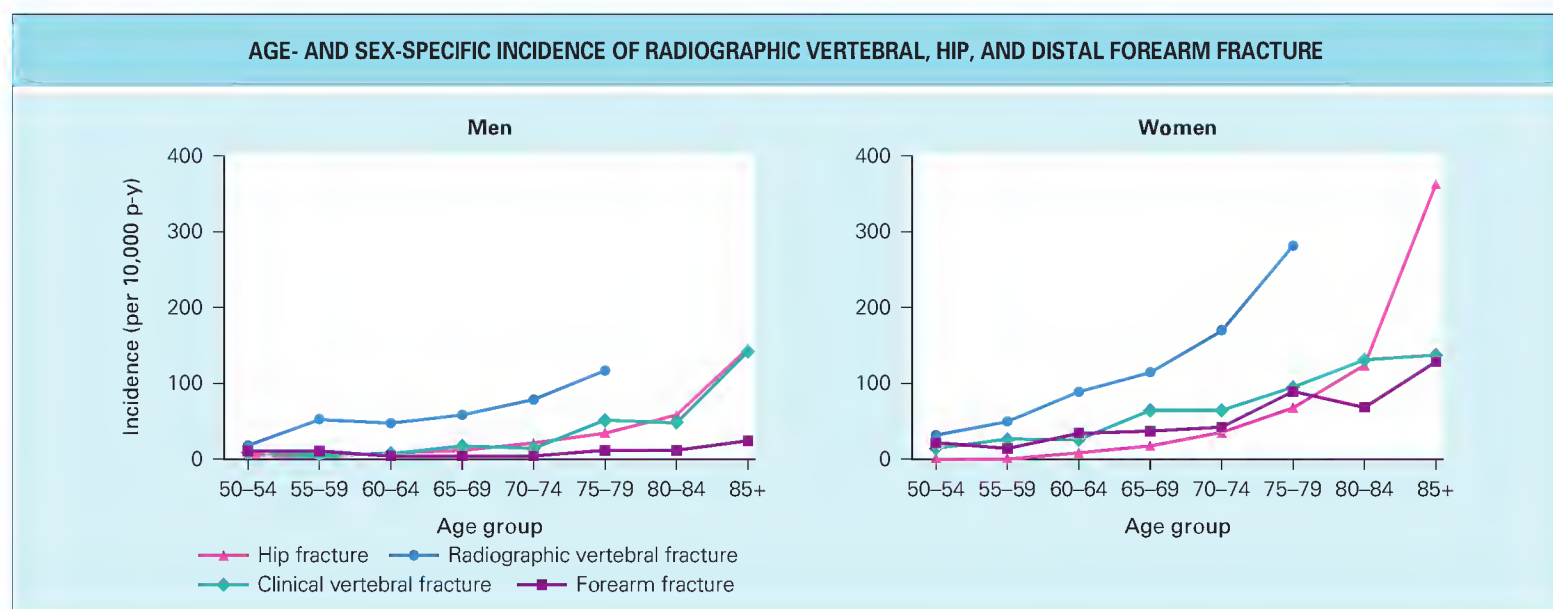


Fig. 197.3 Age-specific incidence of common fractures in men and women. (Modified from Sambrook P, Cooper C. Osteoporosis. Lancet 2006;367:2010-18.)

Hip fracture

Hip fracture is the most devastating consequence of osteoporosis. It has been estimated that worldwide, around 1.7 million hip fractures occurred in 2000, 1,197,000 in females and 463,000 in males.²⁴ In individuals older than 50 years in Western populations, there is a female preponderance of hip fracture with a female-to-male incidence ratio of approximately 2:1. Overall, 90% of hip fractures occur in people older than 50 years, and 80% occur in women (because there are more elderly women than men).²⁵ Hip fractures are seasonal, with an increase in winter in countries in a temperate climate. They occur mainly indoors, thus suggesting that the increase is not caused by slipping on icy pavement. It may be related to slowed neuromuscular reflexes and lower sunlight in winter, as well as to seasonal changes in vitamin D levels and bone turnover.

Incidence rates of hip fracture vary considerably; in general, individuals who live in latitudes farther from the equator have a higher incidence of fractures, as do those who live in urban rather than rural areas. Racial differences have clearly been observed, with lower fracture rates in black than in white or Asian populations. Incidence rates also vary considerably according to geographic area (Table 197.4) and may differ widely even within the same country in populations of a given sex and race. In a study of the 10-year probability of hip fracture standardized for gender and age across 29 countries, a greater than 10-fold variation in risk for hip fracture between countries was observed, with the highest rates in Scandinavia and low rates in Africa and South America.²⁶ Figure 197.4 illustrates the variation in hip fracture incidence throughout the world.

In Europe, hip fracture rates vary sevenfold between northern and southern countries. The highest rates of hip fracture are seen in whites living in northern Europe, especially Scandinavians. A recent systematic review of hip fractures worldwide found the highest rates in Denmark (574/100,000),

closely followed by Norway (563/100,000) and Sweden (539/100,000).²⁶ The rates are intermediate in people from China, and Kuwait and lowest in black populations.²⁷ Data from Middle Eastern and African countries are limited because of the absence of fracture registries. A study of hip fractures in Morocco suggested that fragility fractures occur in North Africa less frequently than in most European, North American, and Asian countries but more frequently than in sub-Saharan African countries.²⁸ Many of the lower incidence rates seen in these developing countries can be partially explained by lower life expectancy in Latin America, with only 5.7% of the population being older than 65.

It is likely that the differences in hip fracture rates are a combination of genetic and environmental factors. However, the factors studied thus far, such as alcohol consumption, smoking, activity levels, obesity, and migration status, have not explained these trends. The differences may be related to differences in risk for falling because BMD measurements are similar in white and nonwhite women and men after correction for bone size. Further research is clearly needed to explain these important environmental factors.

Secular trends in hip fracture

Trends in hip fracture rates over time in many countries have also been reported. From the 1930s until the mid-1980s, age- and sex-specific hip fracture incidence rates rose across the United Kingdom and Scandinavia. In the United States, data from Rochester, Minnesota, showed a similar trend in age-adjusted rates for men, whereas in women the rate increased until the 1960s and then plateaued until the 1980s.²⁹ Since then the age-adjusted incidence rate of hip fracture has fallen across most of northern Europe and North America, more than counteracting the effects of the aging population and resulting in a decline in the annual number of hip fractures. This phenomenon may reflect the implementation of osteoporosis screening and treatment programs, among other factors. In the United Kingdom the rate fell by 0.5% between the years 1992 and 1998,³⁰ and in the United States the rate fell by 1.4% over the years 1980 to 2006.³¹ The rate in southern Europe and parts of Asia continues to rise, however, with observed increases of 3% and 3.8% in age-adjusted hip fracture incidence rates in Spain and Japan, respectively (Fig. 197.5). These discrepancies in secular trends by race, gender, and age are likely to represent a combination of genetic and environmental factors. Many of these factors remain poorly elucidated, but with improved understanding it is hoped that novel public health measure may be identified. The relationship between socioeconomic status and fracture risk remains unclear, although a recent systematic review has suggested that BMD in women is positively associated with educational attainment.³²

Vertebral fracture

Only a fourth of vertebral fractures result from falls, and most are precipitated by routine daily activities such as bending or lifting light objects. Until recently, accurate epidemiologic studies of vertebral fracture had been limited, partly because of the often asymptomatic nature of the fracture, as well as a lack of consensus regarding the techniques that should be used to define vertebral deformity. However, the advent of morphometric and semi-quantitative visual techniques has now enabled a number of studies to report on the prevalence of vertebral fractures. Only about a third of all vertebral deformities noted on radiographs come to medical attention, and less than 10% necessitate admission to a hospital.³³ Data from the United States (Rochester, Minnesota) suggest that the prevalence of any vertebral

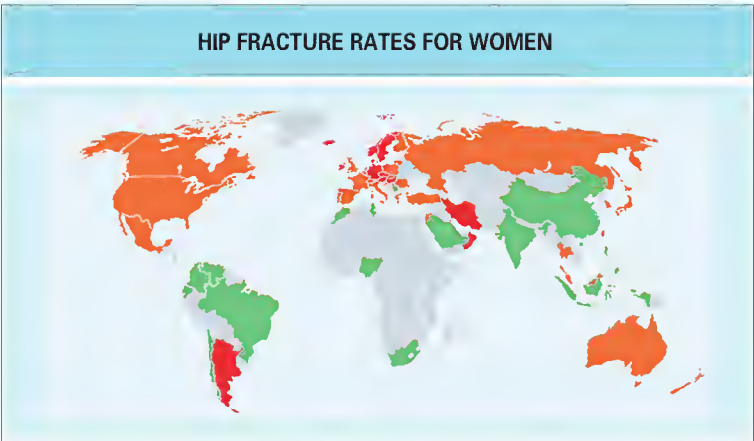


Fig. 197.4 Categorization of hip fracture rates for women in different countries by risk. Where estimates are available, countries are color-coded red (annual incidence >300/100,000), orange (200 to 300/100,000), or green (<200/100,000). (Reproduced with permission from Kanis JA, Odén A, McCloskey EV, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int* 2012;23:2239-56.)

TABLE 197.4
Estimated number of osteoporotic fractures in men and women older than 50 years in 2000 by World Health Organization region

WHO region	Expected number of fractures by site (thousands)				All osteoporotic fractures	
	Hip	Spine	Proximal humerus	Forearm	No.	%
Africa	8	12	6	16	75	0.8
Americas	311	214	111	248	1406	15.7
Southeast Asia	221	253	121	306	1562	17.4
Europe	620	490	250	574	3119	34.8
Eastern Mediterranean	35	43	21	52	261	2.9
Western Pacific	432	405	197	464	2536	28.4
Total	1627	1417	706	1660	8959	100

From Jahnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726-33.

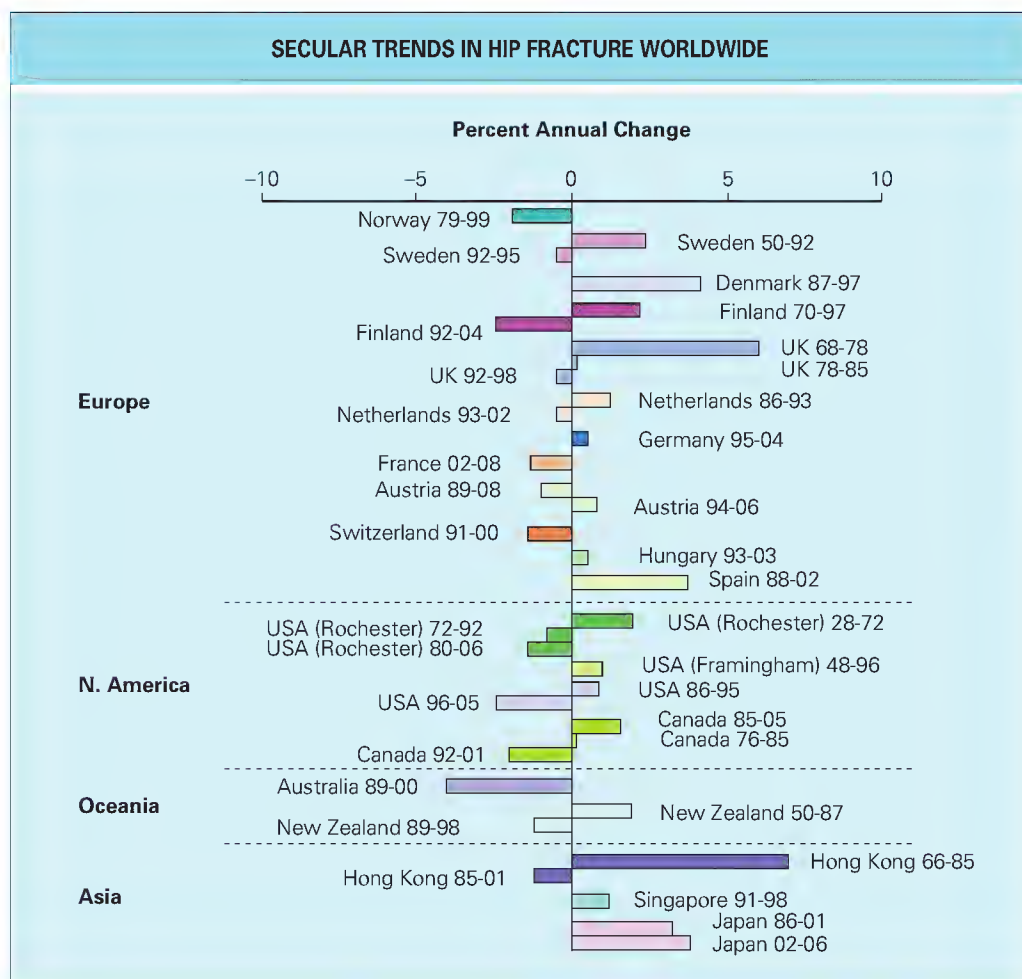


Fig. 197.5 Annual change in age- and sex-adjusted hip fracture incidence. (Reproduced from Cooper C, Cole ZA, Holroyd CR, et al. Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporos Int* 2011;22:1277-88.)

deformity is 25.3% per 100 women 50 years and older, and the incidence of a new deformity in this group is estimated to be 17.8 per thousand person-years.³⁴ By contrast, in the European Vertebral Osteoporosis Study, one in eight women and men 50 years and older had evidence of a vertebral deformity.³⁵ The prevalence of vertebral deformity increased steadily with age in both sexes, although the gradient was steeper for women. There is a threefold variation in the occurrence of deformity across Europe and up to a twofold variation in centers within individual countries, perhaps reflecting a combination of environmental and genetic factors. The risk for vertebral deformity in men was significantly elevated in those with high levels of physical activity, thus suggesting the importance of trauma (possibly occupational) as a cause. By contrast, women with higher levels of customary physical activity may have a reduced risk for deformity.³⁶

The prevalence of vertebral fractures varies less across regions than the prevalence of hip fractures does. For example, the risk for vertebral fractures in postmenopausal women in Beijing is only 25% lower than that in women in the United States despite much lower hip fracture rates in the former.³⁷ Recent data from the EPIDOS (Epidémiologie de l'Ostéoporose) study have yielded estimates of the prevalence of vertebral fractures: 19% of women aged 75 to 79 years, 21.9% of women aged 80 to 84 years, and 41.4% of those 85 years and older would be expected to sustain a vertebral fracture. These observations are broadly in keeping with estimates from other populations.³⁸

Wrist fracture

Distal forearm fracture almost always results as a consequence of a fall from standing height onto an outstretched hand. These fractures show a steep rise in incidence during the perimenopausal period in women but tend to plateau thereafter. In men, the incidence remains constant between 20 and 80 years of age. A much stronger sex ratio exists for this fracture than for most others, and it has been estimated to be 4:1 in favor of women. Recent data from Dorset in the United Kingdom showed that in women, the incidence of distal radius fracture rose from a premenopausal baseline of 10 per 10,000 of the population per year to a peak of 120 per 10,000 of the population per year older than 85 years.³⁹ Although geographic variation exists, a

partial explanation may be methodologic considerations of case ascertainment because less than 20% of patients with a forearm fracture are hospitalized. A winter peak is again demonstrated, but unlike hip fractures, this peak is probably due to falls outside on icy surfaces. The plateau with age in women may be due to the mode of falls because later in life a woman is more likely to fall onto a hip than onto an outstretched hand because of deterioration in neuromuscular coordination.

Clustering of fractures

Several epidemiologic studies have shown that patients with fragility fractures are at increased risk for the development of additional osteoporotic fractures, both at the same site and at other locations. In general, the presence of previous vertebral deformities has been shown to increase the risk for subsequent vertebral deformities by 7- to 10-fold.⁴⁰ This is comparable to the increase in risk for a second hip fracture observed in those who have already sustained a first hip fracture. In a retrospective cohort study of 1288 residents of Rochester, Minnesota, a distal forearm fracture occurring when 35 years or older was associated with a 1.4-fold increased risk for subsequent hip fracture in women (95% confidence interval [CI], 1.1 to 1.8) and a 2.7-fold increased risk for hip fracture in men (95% CI, 0.98 to 5.8).⁴¹ Excess risk in women was confined to individuals who sustained their first forearm fracture at 70 years or older. By contrast, a previous distal forearm fracture increased the risk for vertebral fracture across all ages, with a 5.2-fold (95% CI, 4.5 to 5.9) increased risk in women and a 10.7-fold (95% CI, 6.7 to 16.3) increased risk in men. This increased risk was more marked in subjects with vertebral deformities associated with moderate or minimal trauma than with severe trauma.

Regarding vertebral fracture data from EPOS,⁴⁰ prevalent vertebral deformity was seen to predict incident hip fracture at a rate ratio of 2.8 to 4.5, and this figure increases with the number of vertebral deformities. In the United States, data from the Study of Osteoporotic Fractures (a prospective study of 9704 U.S. women 65 years or older) demonstrated that prevalent vertebral deformity was associated with a 5-fold increased risk for sustaining a further vertebral deformity; the risk for hip fracture was increased 2.8-fold (95% CI, 2.3 to 3.4) and the risk for any nonvertebral fracture was increased

1.9-fold (95% CI, 1.7 to 2.1) after adjustment for age and calcaneal BMD.⁴² Despite a small increased risk for wrist fracture, it was not significant after adjustment for age and BMD. In the United Kingdom, a study has recently shown that 25% of patients with a new low-trauma nonvertebral fracture had evidence of a previous vertebral fracture.⁴³ The greatest risk for a subsequent fracture appears to occur soon after a fracture, particularly in the first year, with the incidence of a new vertebral fracture being 19.2%.⁴⁴ This increased risk for virtually all clinical fractures may persist for up to 10 years.⁴⁵

Some evidence suggests that individuals 50 years or older who sustain a rib fracture (as recalled from memory) have an increased risk for future limb fracture. The predictive risk was particularly marked for subsequent hip fracture (relative hazard [RH], 7.7; 95% CI, 2.5 to 25.9) and humerus fracture (RH, 4.5; 95% CI, 1.4 to 14.6).⁴⁶

Economic cost

The first-year direct cost per hip fracture in the United Kingdom was recently estimated to be between €11,055 and €20,359.⁴⁷ Worldwide, the combined direct and indirect annual costs for hip fracture have been predicted to rise to US \$131.5 billion by 2050 (at a cost of \$21,000 per patient).⁴⁸ A recent analysis estimated that patients with osteoporosis-related fractures incurred nearly US \$10,000 in excess direct health care costs in the 6 months after fracture when compared with patients with no fracture.⁴⁹ The costs associated with other fractures have also recently been calculated. In the United States, the cost of osteoporotic fractures in 2005 was estimated to be \$19 billion.⁵⁰ More recently, the cost of osteoporosis, including pharmacologic intervention in the European Union, was estimated to be €37 billion²³; in the United Kingdom alone the annual cost to the health care system for osteoporotic fractures was €5.5 billion.⁴⁷ Hip fractures account for more than a third of the total figure. Expenditures are rising faster than the general rate of inflation and are a major source of concern to governmental leaders. Much research is currently focusing on the cost-effectiveness of treatment programs for osteoporosis. At present this still remains difficult to assess, and in addition, the widespread use of expensive drugs may not be affordable in many countries. The cost of various fractures in the United Kingdom is illustrated in Table 197.5.

FUTURE PROJECTIONS

Osteoporotic fractures represent a significant public health burden that will rise in future generations because of an aging population. Life expectancy is increasing around the globe, and the number of elderly individuals is rising within every geographic region. The world population is expected to increase from the current 323 million individuals 65 years or older to more than 1.5 billion by the year 2050. These demographic changes alone can be expected to increase the number of hip fractures occurring worldwide. The

TABLE 197.5
First-year costs of osteoporotic fracture in the United Kingdom

Site	Cost (€)
Hip (first year)	11,055
Forearm	1,263
Clinical vertebral fracture	2,756
Other fractures	7,910

Data from Ström O, Borgström F, Kanis JA et al. Osteoporosis: burden, health care provision and opportunities in the EU. Arch Osteoporos 2011;6:59-155.

incidence is estimated to rise from 1.66 million in 1990 to 6.26 million in 2050.⁵¹ On the basis of current trends, assuming a constant age-specific rate of fracture, hip fractures would be expected to increase in the United Kingdom from 46,000 in 1985 to 117,000 in 2016. Likewise, in the United States, as the population older than 65 increases from 32 million in 1990 to 69 million in 2050, the number of hip fractures is expected to triple. In the United States in 2005, the total number of estimated incident fractures was higher than 2 million, with 72% of the cost being accounted for by hip fractures alone. By 2025, annual fractures and cost were predicted to rise by almost 50%, with the most rapid growth seen in the 65- to 74-year-old group (87% increase) and in Hispanic and other nonwhite subpopulations (175% increase).⁵⁰

Currently, roughly half of all hip fractures in elderly people occur in Europe and North America; however, by 2050 the increasingly elderly population in Latin America and Asia could lead to a shift in the geographic distribution of hip fractures, with only a fourth occurring in Europe and North America.⁵¹

CONCLUSION

Osteoporosis is a disease that has a huge effect on public health because of its association with fracture. The impact of osteoporotic fractures is far-reaching, not only for the individual but also for the health service, economy, and population as a whole. Osteoporotic fractures are expected to rise in subsequent generations because of an increase in life expectancy and a higher proportion of elderly individuals in most countries; however, rates have fallen in many Western countries, possibly as a result of improved public screening and treatment programs. Recently, several of the risk factors for this disease have been elucidated and models have been developed to allow more accurate assessment of fracture risk in patients so that preventive and therapeutic measures can be implemented appropriately.

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Clinical features of osteoporosis

■ JONATHAN H. TOBIAS

- The clinical manifestations of fractures, which are the expression of failure of bone to resist breaking, differ between fracture locations. Almost all non-spine-related fractures occur in the context of trauma and have the acute signs and symptoms of a fracture. In contrast, most osteoporotic vertebral fractures are not the result of overt trauma, and their diagnosis is frequently delayed.
- Clinical risk factors for fractures include those related to intrinsic bone strength, including low bone mineral density, and those related to the frequency, severity, and impact of falls and other types of trauma.
- Clinical risk factors can be integrated into case-finding strategies to calculate an individual's 10-year risk for a first or subsequent fracture (with or without the results of bone densitometry), thereby facilitating informed treatment decisions.
- The clinical outcome of fractures includes increased morbidity, increased risk for subsequent fractures, and increased mortality, all of which are highest within the first few years after a fracture.

INTRODUCTION

Fractures result from failure of bone to withstand external forces applied to it and occur because of intrinsic weakness of the skeleton, excessively high extrinsic force, or a combination of the two. They are associated with increased morbidity, mortality, and risk for subsequent fractures, thereby resulting in a vicious cycle of further fractures and worsening morbidity (Fig. 198.1 and Table 198.1).

Osteoporosis may be diagnosed on the basis of the presence of either a hip or vertebral fracture or low bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DXA). Risk factors for osteoporotic fractures consist of those related to low intrinsic bone strength (i.e., osteoporosis) and those related to the frequency, severity, and impact of falls. The multitude of clinical risk factors for osteoporosis and fractures reflects their multifactorial etiology, and this has formed the basis of clinical algorithms intended to quantify fracture probability with the aim of facilitating treatment decisions. Recognizing these features is important for case finding, diagnosis, and treatment.

Clinical findings differs between fractures. In contrast to non-spine-related fractures, vertebral and stress fractures often lack the signs and symptoms of an acute fracture. They are therefore underdiagnosed and their clinical significance is frequently underestimated. The clinical outcome of fractures consists of short- and long-term increases in morbidity, mortality, and risk for subsequent fractures, and depends on the location, number, and severity of the presenting fracture. Patients with a fracture require immediate attention to optimize long-term outcomes.

CLINICAL FEATURES OF FRACTURES

Although osteoporosis is associated with increased risk for fractures throughout the skeleton, three sites, namely, the spine, distal end of the radius, and hip, have received the greatest attention to date. Nonetheless, fractures at other sites, including the pelvis, upper and lower parts of the leg, shoulder, upper part of the arm, knee, and elbow, make important contributions to the morbidity related to osteoporotic fractures.¹

Non-spine-related fractures

A cardinal feature of non-spine-related osteoporotic fractures is that although they occur in association with a defined injury, the level of trauma needed is relatively low because of the reduced intrinsic strength of the skeleton. This has led to use of the term “minimal/low-trauma fracture” in describing fractures in which underlying osteoporosis is thought to have made a major contribution.

Typically, a low-trauma fracture occurs following an event such as a fall from standing height or less when the individual is standing or walking. Certain characteristics of falls are associated with a risk of sustaining a fracture at specific sites. For example, hip fractures are thought to be related to a sideways fall, which may be more common in older subjects, thus helping explain the relatively high prevalence of hip fractures in this age group.² Falls from a greater height such as falling off a step or downstairs or falls involving greater energy, such as when running, skiing, skating, or playing sports, do not meet this definition of low trauma. However, this distinction is by no means absolute, and it seems clear that reduced intrinsic bone strength contributes to fracture risk even in the context of higher levels of trauma.³

Vertebral fractures

Radiographically evident vertebral fractures are the most common fractures in men and women.⁴ Although vertebral fractures may be seen acutely, most are clinically silent and do not have the signs and symptoms of an acute fracture. Consequently, the majority of vertebral fractures go undetected; of radiographically evident vertebral fractures, only about a third are diagnosed clinically.^{5,6} However, identification of vertebral fractures is clinically relevant because such fractures, whether clinically apparent or silent, are associated with increased morbidity,^{7,8} increased mortality,⁹ and increased risk for subsequent vertebral and nonvertebral fractures.^{10,11}

Patients with acute osteoporotic vertebral fractures often have no clearly defined preceding injury. Instead, a trivial precipitating event such lifting a heavy load may have occurred.¹² Consequently, osteoporotic vertebral fractures may be manifested as apparently unexplained new mid or low back pain. Conversely, vertebral fractures occurring after clearly defined trauma are less likely to be osteoporotic in origin. For example, vertebral fractures occurring after a fall from standing height directly onto the back generally represent traumatic rather than osteoporotic fractures.

The pain associated with acute vertebral fractures has several clinical features that may aid in diagnosis. Back pain is often very intense, exacerbated by weight bearing, and relieved by lying flat, which leads to patients spending prolonged periods in bed. Back pain secondary to vertebral fractures has also been found to have a relatively rapid onset, with many describing a sudden onset.¹² The pain can be sufficiently severe to cause breathlessness, pallor, nausea, and vomiting and is also exacerbated by coughing or sneezing. The pain frequently radiates laterally along the dermatomal distribution and is often accompanied by spasms of the paraspinal muscles. Episodes of acute, severe pain usually subside gradually within 2 to 6 weeks but can persist longer after severe fractures.

Patients with osteoporotic vertebral fractures may have a history of previous fractures or other risk factors for osteoporosis (see later). In addition, patients with vertebral fractures may report loss of height from when they were young adults. Even though a certain degree of loss of height occurs with normal aging, loss of greater than 3 cm in men and 4 cm in women may be suggestive of underlying vertebral fractures.¹³ Accurate height measurements form an essential component of the clinical assessment of patients with vertebral fractures, both to evaluate loss of height and to provide a baseline for future measurements.

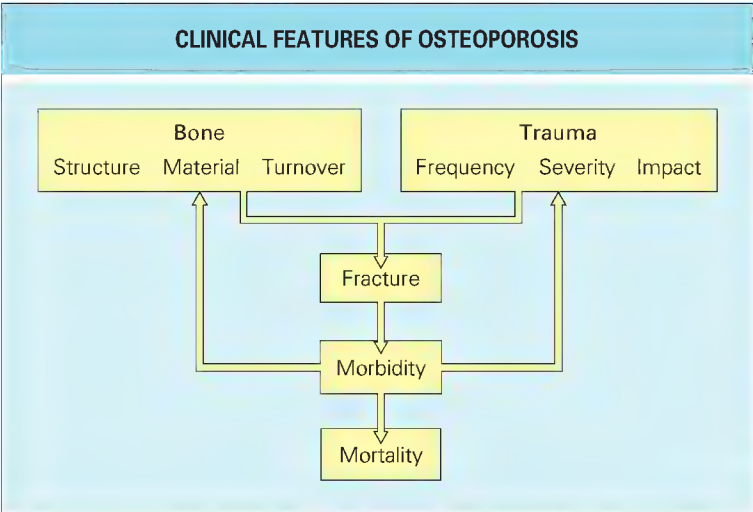


Fig. 198.1 Clinical features of osteoporosis include a clinical bone- and fall-related predisposition for osteoporosis and fractures (clinical risk factors), clinical signs of fractures, and the clinical consequences of fractures (clinical outcome). The clinical consequences of fractures in survivors include physical and functional limitations, reduced quality of life, and increased risk for subsequent fractures, thereby resulting in a vicious circle of new fractures and increasing morbidity.



Fig. 198.2 Dowager's hump. (a) Marked thoracic kyphosis secondary to multiple osteoporotic fractures in an elderly woman. (b) Corresponding radiograph.

TABLE 198.1
Clinical consequences of hip, vertebral, and wrist fractures

	Hip	Vertebrae		Wrist
		Clinical	Radiographic	
Excess mortality	+	+	+	–
Increased fracture risk	+	+	+	+
Pain				
Acute	+	+	+ or –	+
Chronic	–	+	+ or –	+
Functional decline				
Short term	+	+	+	+
Long term	+	+	+	+
Psychosocial decline	+	+	+	–
Quality of life	+	+	+	+

+, yes; –, no.

BOX 198.1 CAUSES OF VERTEBRAL DEFORMITY

- Vertebral fracture due to trauma
- Vertebral fracture due to osteoporosis
 - Generalized
 - Idiopathic juvenile osteoporosis
 - Osteoporosis of pregnancy
 - Localized
 - Pathologic fracture due to malignancy
 - Multiple myeloma
 - Skeletal metastases
 - Pathologic fracture due to metabolic bone disease
 - Osteomalacia
 - Primary hyperparathyroidism
 - Pathologic fracture due to osteomyelitis
- Paget disease
- Spondylosis
- Scheuermann disease
- Artifactual (scoliosis)

On clinical examination, variable degrees of kyphosis of the thoracic spine can be found in individuals with a thoracic vertebral fracture (Fig. 198.2), and flattened (reduced) lumbar lordosis is evident in those with a lumbar vertebral fracture. Loss of spinal height may be evident as a reduced distance between the bottom of the rib cage and the iliac crest, which can be quantified as finger breadths.¹⁴ Preferential loss of trunk height may also be evident by comparing standing height with arm span (measurements of which are generally equivalent). Tenderness may be elicited over the affected vertebrae and paraspinal muscles, although it is sometimes diffuse and not localized to the fractured vertebra. Mobility of the spine is restricted and movements are painful. Very restricted movements raise the possibility of a pathologic fracture related to infection or malignancy.

When an acute vertebral fracture is suspected, radiography is required to confirm its presence. Although physicians may be unwilling to refer patients with back pain for radiologic investigation, new onset of unexplained back pain in older patients should always be investigated. The investigation of choice depends on local resources but most commonly consists of a spinal radiograph. It is essential to obtain both lateral and anteroposterior views and to image both the lumbar and thoracic spine; even if a patient complains of back pain localized to one site, vertebral fractures may be present elsewhere, detection of which may be important in making management decisions. In the presence of scoliosis, lateral films in isolation may convey the mistaken impression of vertebral deformity.

Rarely, magnetic resonance imaging may be performed as the initial investigation or, more commonly, as a secondary study, depending on the results of the initial radiographs. It may be helpful in documenting the timing of the vertebral fracture based on the presence of marrow edema; confirmation that a specific fracture is recent may be important when considering interventions such as kyphoplasty. Magnetic resonance imaging may also be helpful in investigating other causes of vertebral fracture, such as malignancy. In terms of further investigations, DXA is helpful in confirming the presence of underlying osteoporosis (with the proviso that vertebrae affected by height loss be excluded from the analysis because they cause an artifactual elevation in BMD).

Vertebral deformities evident on imaging have a relatively wide differential diagnosis (Box 198.1). Those related to osteoporosis typically show characteristic wedge-shaped deformities or loss of height (see Fig. 198-2). If these findings are present and the patient has other characteristics in keeping with osteoporosis, including low BMD, it may be reasonable to accept this diagnosis. However, in certain circumstances it may be prudent to arrange further investigations to exclude other possible diagnoses; arguably, the most important of these are osteomalacia and multiple myeloma.

Conversely, minor vertebral deformities are common, particularly at the thoracolumbar junction, and can be mistaken for osteoporotic vertebral fractures, especially in the presence of other disorders such as spondylosis and particularly Scheuermann disease.¹⁵ Further evaluation of minor

vertebral deformities (e.g., by arranging for a DXA scan) may be advisable to exclude underlying osteoporosis and to reassure the patient and clinician that treatment with a bone-protective agent is not required.

From the preceding it is clear that careful evaluation of radiographs is essential to ensure that vertebral deformities are detected and that those likely to be related to osteoporotic vertebral fractures are identified correctly and reported. However, radiographic vertebral fractures are often overlooked in daily clinical practice. For example, a survey of 934 hospitalized older women with an available chest radiograph was used to evaluate the frequency with which vertebral fractures were identified and treated by clinicians.¹⁶ Moderate to severe vertebral fractures were identified in 132 (14.1%) of the study subjects, 50% of whom had a fracture recorded in the radiology report but only 17% of whom had a fracture noted in the medical record or discharge summary.

The most widespread method of evaluating spinal radiographs for the presence of vertebral deformities is the Genant semiquantitative method.¹⁵ Advantages of this method include the fact that it is relatively simple to perform and little training is required. In addition to being used in clinical research, this approach has also been recommended for use in routine clinical reporting.¹⁷ However, one limitation of this method is that patients with mild deformities (i.e., 20% to 25% loss of height) may be incorrectly labeled as having clinically significant vertebral fractures but instead may have a normal variant (i.e., “short vertebral height”).¹⁸ To overcome this shortcoming, an alternative method has been developed, the algorithm-based qualitative assessment, which uses a more specific definition based on identification of vertebral endplate fractures.¹⁹ However, the latter method requires specific training, is relatively time-consuming, and to date has not been routinely adopted into clinical practice.

Detection of vertebral fractures in patients with osteoporosis but without back pain represents a further challenge. Several attempts have been made to develop algorithms for identifying patients at highest risk for prevalent vertebral fracture, in whom spinal radiographs are most likely to be beneficial; such algorithms are based on the presence of risk factors, including age, gender, history of fracture, and loss of height.^{20,21} Some evidence suggests that implementation of such a strategy has a positive impact in targeting drug therapy in patients with vertebral fractures.²²

Vertebral fracture assessment (VFA), in which vertebral fractures are identified by inspection of lateral DXA scans, represents a further way of detecting vertebral fractures in asymptomatic individuals. The International Society for Clinical Densitometry recommends performing VFA in a number of different clinical scenarios associated with increased risk for vertebral fracture.²³ The optimal method for detecting vertebral fractures with this approach remains to be established; although current guidance proposes the application of semiquantitative methods as developed for analyzing spinal radiographs,²³ this may be overly sensitive.²⁴

Stress fractures

Stress fractures, which can also be difficult to diagnose, are a particular manifestation of fractures related to fatigue damage in bone whereby propagation of microcracks outstrips repair. *Fatigue fractures* occur in normal healthy bone repeatedly subjected to high-level stress. Such fractures are seen most commonly in track and distance runners, athletes who take part in field sports, gymnasts, dancers, and military recruits.²⁵ The most commonly affected sites include the tibia, metatarsals, and femur.²⁵ *Insufficiency fractures* occur in bone subjected to normal strain that is intrinsically weak because of osteoporosis or other metabolic bone diseases. In addition to the sites just described, insufficiency fractures commonly affect the sacrum as well. Stress fractures are often difficult to diagnose clinically and are frequently not readily recognizable on plain radiographs. Other imaging techniques, such as nuclear bone scintigraphy, computed tomography, or magnetic resonance imaging, may be needed to identify stress fractures.

CONSEQUENCES AND OUTCOME OF FRACTURES

The clinical consequences of fractures are related to the short- and long-term outcomes and differ according to fracture location (see Table 198.1) and patient characteristics. Clinical consequences include morbidity (which results in medical, hospital, and institutional care), mortality, and risk for subsequent fractures. This refracture risk is driven by a threefold to fivefold increase in risk in the years immediately after a first fracture, followed by gradual waning later (Fig. 198.3).^{10,11,26-28} The clinical consequences of hip and vertebral fractures, which are associated with substantially greater morbidity and mortality than fractures at other sites, are discussed in more detail in the following sections.

Hip fractures

Hip fractures are the most serious consequence of osteoporosis in terms of disability, mortality, and need for hospital and institutional care.²⁹ The number of hospital bed days for patients with hip fractures is higher than that for patients with stroke, diabetes, or myocardial infarction.³⁰ The combined cost of hospitalization and medical care during the 12 months after a hip fracture is approximately three times higher than that for patients without hip fractures.³¹ Patients with a hip fracture are particularly prone to complications. General (cardiovascular, pulmonary, and cerebral events and infection) and local complications (wound and problems with the implant such as dislocation, fixation failure, and infection) affect more than 30% of patients within 4 months of the hip fracture.³²

Mortality after hip fracture

In-hospital mortality ranges between 1% and 9%^{33,34} but can be as high as 55% in patients with end-stage dementia or pneumonia.³⁵ Twenty percent to 25% of patients die within the first year after a hip fracture.³⁰ After adjustment for other predictors of hip fracture, women with a hip fracture are still more than two times more likely to die than women without a fracture.¹⁰

Morbidity after hip fracture

Hip fracture has a substantial impact on morbidity and leads to reduced function and loss of independence. One study reported that after 3 months, physical performance had decreased by 51%, vitality by 24%, and social function by 26% in comparison to prefracture levels.³⁶ After 6 months, only 24% of patients had returned to their prefracture walking competence and just 43% had returned to their prefracture basic activities of daily living.³⁷ Little further improvement occurred after 1 year.^{32,38}

Of women who could dress independently before fracture, only 60% were able to do so after a hip fracture, and only two thirds were able to resume independent transfers (from bed to chair or standing from a chair).³⁹ The proportion of women who could walk across a room independently dropped from 75% before the hip fracture to 15% 6 months after the fracture. Similarly, the proportion of women able to walk one-half mile decreased from 41% before fracture to 6% 6 months after fracture, and the proportion of women able to climb stairs fell from 63% to 8%.³⁹ Only 38% of women reporting independence in several activities of daily living and basic mobility measures (including transfer from bed to chair and toilet, putting on socks and shoes, and indoor walking) recovered independence in all functions after a hip fracture.⁴⁰ Further limitations were found in cooking, performance of housework, use of transportation, grocery shopping, carrying items, taking medication, visiting friends, managing finances, and engaging in community activities.⁴¹

Indirect evidence for morbidity comes from a prospective case-control study of survivors of hip fracture.³¹ Medical and nonmedical needs were significantly higher in fracture patients than in age- and sex-matched controls. These needs were reflected in an increased number of physician contacts, increased use of physiotherapy, more days of new hospitalization and home care, and a longer stay in nursing homes.³¹

The outcome of hip fracture depends largely on preexisting comorbidity and level of function. Mortality is higher in patients living in an institution than in other patients.³⁸ In a study that adjusted for known risk factors, mortality at 6 months after hip fracture was significantly associated with prefracture mobility, health status, and the use of paid help at home.³⁴ Longer hospital stay is associated with older age, male sex, and poorer general health.³³ Patients living in an institution have a higher risk for pressure sores, surgical complications, and pulmonary and urinary infections than do patients living independently before the fracture.³⁸

Vertebral fractures

Although the back pain caused by acute vertebral fractures is generally self-limited, there is a high risk for additional vertebral fractures; such risk is increased even further in those with multiple fractures and can ultimately result in rapidly progressive disease. Patients with a prevalent (pre-existing) vertebral fracture have an approximately four times greater risk for further vertebral fractures than do patients without a prevalent fracture,²⁷ as well as twice the risk for hip and other nonvertebral fractures.¹⁰ The risk for additional vertebral fractures is extremely high in patients with multiple past vertebral fractures. For example, the risk for an additional vertebral fracture is 12 times higher in women with two or more vertebral fractures at baseline than in those without an existing vertebral fracture.⁴² After experiencing an initial vertebral fracture, 20% of postmenopausal women with osteoporosis sustain an additional vertebral fracture within 1 year.²⁷

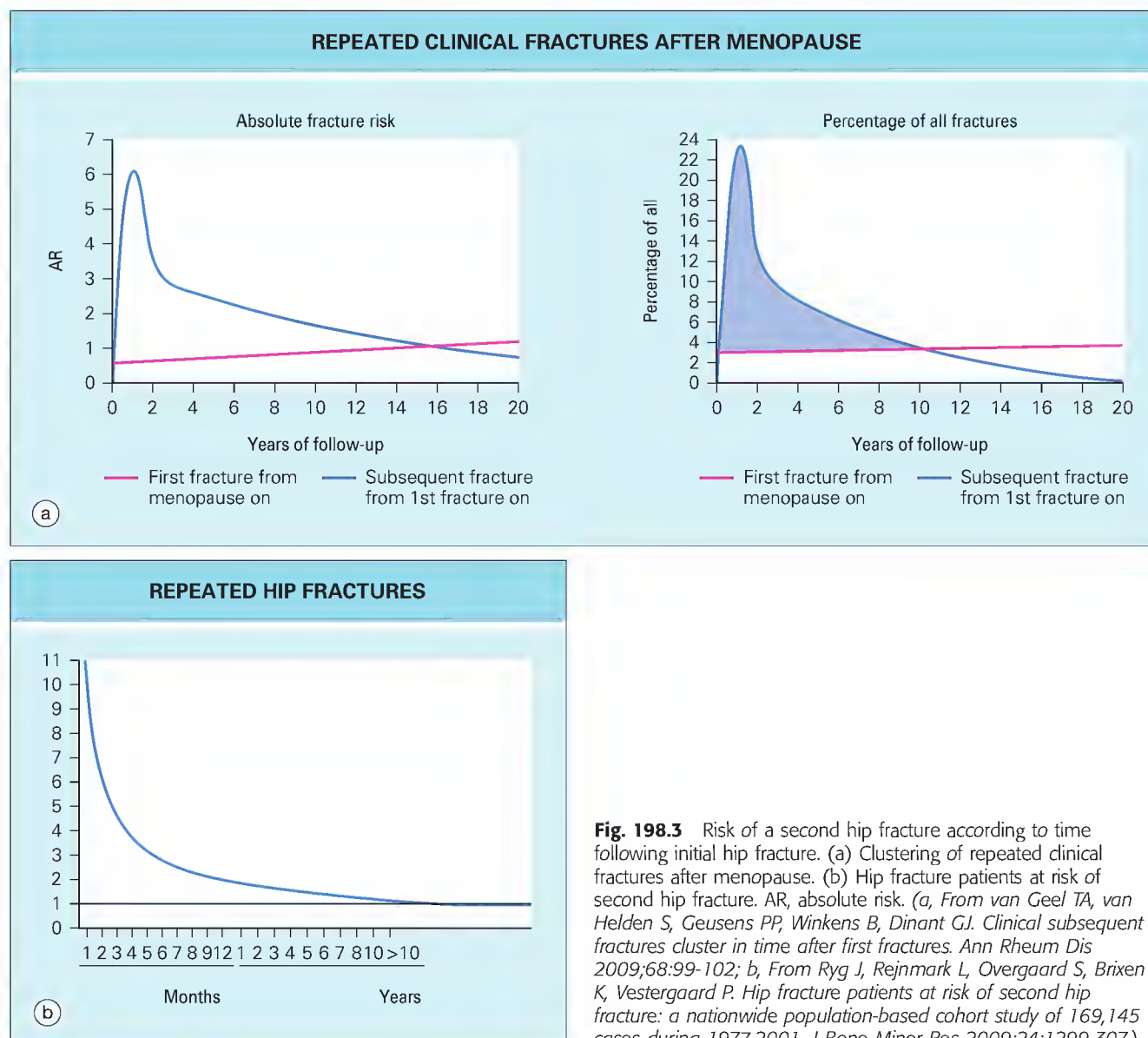


Fig. 198.3 Risk of a second hip fracture according to time following initial hip fracture. (a) Clustering of repeated clinical fractures after menopause. (b) Hip fracture patients at risk of second hip fracture. AR, absolute risk. (a, From van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. *Ann Rheum Dis* 2009;68:99-102; b, From Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P. Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. *J Bone Miner Res* 2009;24:1299-307.)

Mortality after vertebral fracture

Mortality is higher in people after vertebral fractures than in those without vertebral fractures. The age-adjusted relative risk of dying after a vertebral fracture is as high as 8.6,⁴³ and this increase persists for at least 5 years.⁴⁴ The rate of death in patients with vertebral fractures is highest in those with multiple vertebral fractures⁴⁵ and in those who required hospitalization because of vertebral fractures.²⁶

Morbidity after vertebral fracture

Although only a third of vertebral fractures result in an acute pain episode, even vertebral fractures without acute symptoms contribute to attendant chronic morbidity.⁴⁶

Back pain

Patients with vertebral fractures are at increased risk for back pain, particularly in the lateral waist area.⁴⁷ In contrast to patients with chronic low back pain without fractures, chronic back pain after a vertebral fracture is more effectively relieved by lying down, aggravated by doing housework, and restricted to physical activity.⁴⁸ No specific circadian rhythm of pain is found. The chronic phase of back pain after an acute pain episode can last for many years, although its intensity may, but not always, decrease over time.^{48,49} In one study, half of patients with symptomatic clinically diagnosed vertebral fractures reported slight to moderate chronic pain after 4 years; the other half reported severe to intolerable pain.⁴⁸ In clinical cases, chronicity of the back pain is related to the number and severity of vertebral fractures.^{48,50,51} In other studies, pain was related to the degree of kyphosis⁵² and loss of height.⁵³ In a large cross-sectional study involving around 13,000

men and women, a positive relationship was observed between the number of vertebral deformities and back pain, irrespective of the type of deformity (i.e., wedge, biconcave, or crush fracture).¹³ However, in the latter study the strength of the relationship was relatively weak (odds ratios below 2), possibly because of the frequency of back pain in the general population.

Loss of height and kyphosis

Vertebral fractures are associated with kyphosis, which results in the typical clinical feature of a "dowager's hump" (see Fig. 198.2) and loss of height.^{13,21} During a follow-up period of 8 years, standing height decreased by approximately 1 cm with each new wedge or crush vertebral fracture but not with endplate fractures.⁵⁴ Significant loss of height has also been described in women with postmenopausal osteoporosis in control groups of clinical trials and was nearly 2.5-times greater (4.6 mm/yr) in women with new vertebral fractures than in those without vertebral fractures (1.8 mm/yr).⁵⁵

Kyphosis and loss of height also reduce the distance between the iliac crest and ribs,^{14,48} thereby resulting in problems with digestion and a protruding abdomen that makes fitting clothes difficult and detracts from appearance.⁵⁶ Loss of spinal mobility because of a vertebral fracture has been associated with difficulty dressing, standing, lying down, moving in bed, doing housework, walking, climbing stairs, washing, bathing, using the toilet, and getting to the floor.^{48,51,56} Lung function progressively decreases with increasing number of vertebral fractures and degree of kyphosis, perhaps as a result of increased abdominal pressure.⁵⁷

Physical function and quality of life

Pain, loss of height, and kyphosis secondary to vertebral fractures cause a spiraling decline in physical function, mobility, and muscle strength.^{51,52}

which affects measures of general health status and activities of daily living.^{12,48,58,59} Postural stability, which is related to the risk of falls and appendicular fractures, may also be affected.⁶⁰ Physical performance measures such as functional reach, mobility skills, 6-minute walk, and muscle strength are all significantly decreased.⁵⁹ This results in increased dependency and need for help in self-care, which is associated with moderate and severe vertebral fractures.^{12,58}

In general, the same physical and functional outcomes as in clinical cases are reported in population and case-control radiographic surveys. For example, in the Study of Osteoporotic Fractures, the odds of impaired function (difficulty in more than two activities of daily living) was 2.3 times higher in elderly women with a history of a clinically diagnosed vertebral fracture.⁶¹ New vertebral fractures, even those not recognized clinically, are associated with substantial functional limitation because of back pain in older women.⁷

A multidimensional and validated osteoporosis-targeted quality-of-life questionnaire (QUALEFFO) has been used in a population study to assess the impact of vertebral fractures.⁶² Patients with a vertebral fracture had a higher QUALEFFO score than did patients with low BMD without a vertebral fracture. The total score and its subdomains (pain, physical function, general health, and physical mobility) correlated with the number of vertebral fractures.⁶² Lumbar vertebral fractures led to greater impairment of physical function than did thoracic vertebral fractures and were associated with lower physical function, lower general health, and a lower total QUALEFFO score.⁶²

RISK FACTORS FOR OSTEOPOROSIS AND FRACTURES

In addition to the sequelae related to fractures, the clinical features of patients with osteoporosis include clinical risk factors for osteoporotic fractures, such as risk factors related to low intrinsic bone strength and risk factors for falls. These risk factors can be integrated to provide an overall estimate of fracture risk, which can be helpful in making decisions about further investigation and treatment. Osteoporosis may also occur in the context of other diseases in which osteoporosis is a secondary phenomenon and in patients found to have low BMD after DXA scanning in the absence of a recognized cause.

Clinical risk factors

Although DXA-based measurements of BMD are widely used to evaluate osteoporosis and fracture risk, many clinical risk factors for osteoporotic fracture are recognized, some of which act via BMD whereas others are thought to act independently. This has led to use of the term *bone quality* as an umbrella term for the many characteristics of bone that contribute to bone's resistance to fracture, including its structural and material components and bone turnover, some of which are clinically measurable (e.g., BMD, cortical bone size, vertebral deformities, bone turnover markers) but many of which are not (e.g., material properties).⁶³

A proposed list of major clinical risk factors for osteoporotic fractures is presented in Box 198.2.⁶⁴ Age and female sex are the strongest risk factors, consistent with the well-established descriptive epidemiology of osteoporotic fractures.⁶⁵ Other risk factors used clinically have generally been confirmed in meta-analyses of large cohorts. Previous fracture and glucocorticoid therapy were associated with approximately a doubling of risk for hip fracture as assessed in approximately 60,000 individuals¹¹ and 42,000 individuals,⁶⁶ respectively. Smoking and excessive alcohol use were associated with approximately a 50% and 100% excess risk for hip fracture, respectively, in 59,000 individuals.^{67,68} Parental hip fracture was associated with a 50%

excess risk for hip fracture in approximately 35,000 individuals.⁶⁹ Low body mass index (BMI) was associated with an increased risk for hip fracture in a meta-analysis of approximately 60,000 individuals.⁷⁰ However, the relationship between BMI and fracture risk may be complex, with recent evidence suggesting that high BMI may increase the risk for fractures at other sites such as the ankle.⁷¹ A history of falls has also been reported to be associated with an increased risk for hip fracture, although estimates vary according to study and method of adjustment.⁶⁴

Causes of secondary osteoporosis

Clinical risk factors for osteoporosis also include other disorders or treatments that are thought to cause bone loss and lead to increased risk for osteoporotic fracture. With the exception of glucocorticoid therapy, the level of evidence relating these other factors to risk for osteoporotic fracture is relatively weak. This is partly because of the relatively small number of patients involved, which prevents similar large-scale meta-analyses as those examining the relationship with glucocorticoid use. Nonetheless, although smaller numbers of individuals are affected, when causes of secondary osteoporosis are present, their impact on fracture risk may be as strong or stronger than the other clinical risk factors described earlier.

Sex hormone deficiency due to menopause is an important contributing factor in the great majority of women who develop osteoporosis. In contrast, andropause, depending on its definition, is found only in a subgroup of men with osteoporosis.⁷² Hypogonadism resulting from the treatment of breast and prostate cancer is recognized as an emerging clinical problem.⁷³ Cancer treatment-induced bone loss as a result of adjuvant endocrine therapy with an aromatase inhibitor or androgen deprivation can be considered a risk factor for the development of low BMD, osteoporosis, and bone fracture, which can be mitigated by appropriate bisphosphonate therapy.⁷³

A more complete list of causes of secondary osteoporosis, including rarer causes, is presented in Box 198.3.⁶⁴ In addition, a number of drugs have been suggested to impair bone metabolism, which may represent further risk factors for osteoporotic fractures; such drugs include anticonvulsants, selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors, and antiretroviral drugs.

Fracture risk calculators

In evaluating an individual's fracture risk, as well as identifying specific risk factors and causes, it is useful to integrate these measures to provide an estimate of absolute fracture risk. The latter is helpful in making decisions

BOX 198.2 MAJOR CLINICAL RISK FACTORS FOR OSTEOPOROTIC FRACTURE

Age
Gender
Previous fragility fracture
Glucocorticoid therapy
History of falls
Family history of hip fracture
Other causes of secondary osteoporosis
Low body mass index
Smoking
High alcohol intake

BOX 198.3 CAUSES OF SECONDARY OSTEOPOROSIS

Endocrine

- Hypogonadism in either sex, including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy
- Hyperthyroidism
- Hyperprolactinemia
- Cushing disease
- Diabetes

Gastrointestinal

- Celiac disease
- Inflammatory bowel disease
- Chronic liver disease
- Chronic pancreatitis
- Other causes of malabsorption

Rheumatologic

- Rheumatoid arthritis
- Other inflammatory arthropathies

Hematologic

- Multiple myeloma
- Hemoglobinopathies
- Systemic mastocytosis
- Chronic heparin treatment

Respiratory

- Cystic fibrosis
- Chronic obstructive pulmonary disease

Metabolic

- Homocystinuria
- Chronic renal disease
- Immobility

about starting treatment because it can be used to define risk thresholds above which a given therapy is likely to prove cost-effective. In addition, assessment of fracture risk based on clinical risk factors may be helpful in identifying individuals whose fracture risk is close to an intervention threshold, in whom use of DXA to provide more detailed assessment of fracture risk may be warranted.

The fracture risk tools that have been developed permit the clinician to enter information about a series of predefined risk factors on a simple Web-based platform, from which absolute fracture risk is generated. Precisely how a given risk factor is entered will depend on how the variable was handled in previous analyses underpinning the calculator; because risk factors are often reduced to binary exposures, they can often be entered only as yes/no rather than a continuous variable. It also needs to be recognized that although interactions may exist between certain risk factors, they have not been modeled in previous data sets, and thus risk calculators are unable to reflect these interactions.

Risk calculators provide an absolute estimate of fracture risk for a given individual over a fixed period. Risk for fracture is calculated for either hip fractures or major osteoporotic fractures combining the hip, spine, humerus, and distal end of the radius. The time window over which fracture risk is estimated has been subject to much debate, but calculators such as FRAX (see below) use a 10-year time window. A further uncertainty is whether the output should be rendered as fracture risk or as probability; the latter adjusts the output for survival, which has a major impact on results in older subjects, in whom 10-year fracture probability starts to fall with increasing age despite the fact that their absolute risk for fracture increases. Consequently, caution should be exercised in using assessments of 10-year fracture probability in patients older than 80 years because short-term fracture risk is likely to be underestimated.

Several fracture risk calculation tools have been developed, and they differ in a number of ways, including the strength of evidence on which they are based, how robustly their performance has been replicated in an independent data set, their ease of use, and availability. FRAX,⁷⁴ which is discussed further in the following sections, was developed at the University of Sheffield, United Kingdom, on behalf of the World Health Organization and is the leading tool internationally because it has been calibrated separately for many different countries. However, other valid tools have also been developed. For example, the QFracture risk assessment tool was based on data from approximately 2 million patients collected in the QResearch database, which is a large primary care database for England and Wales.⁷⁵ QFracture is available in the United Kingdom as a Web-based assessment tool⁷⁶ and has been reproduced successfully in an external validation study.⁷⁷ One disadvantage in comparison to FRAX is that there is no opportunity in QFracture to integrate clinical risk factors with BMD results. However, an advantage over FRAX is that a history of falls can be input as a risk factor for fracture. Unlike FRAX, which produces a 10-year probability of fracture, the output from QFracture is 10-year risk for fracture not adjusted for survival. Moreover, the output from QFracture can be adjusted to provide shorter fracture risk periods.

FRAX

The FRAX tool is based on meta-analyses of the large-scale population-based studies described earlier and includes age, sex, BMI, a history of fracture, parental hip fracture, current smoking, excessive alcohol intake, rheumatoid arthritis, glucocorticoid use, and other forms of secondary osteoporosis (Box 198.4).⁷⁴ Several studies have validated this tool in independent populations. In a study based on the Canadian FRAX tool, reasonably good agreement was observed between predicted and observed 10-year risk for hip and major osteoporotic fracture.⁷⁸ Conversely, a second independent study based on this tool found that FRAX noticeably underestimated 10-year fracture risk in higher-risk men.⁷⁹ In a further study aimed at calibrating the U.K. FRAX tool in a New Zealand population, risk for major osteoporotic fractures appeared to be overestimated, particularly when combined with BMD.⁸⁰

Application of FRAX

The 10-year fracture risk generated by FRAX can be used to decide whether to commence therapy for osteoporosis according to whether the result is above or below a predefined intervention threshold (see Chapter 197). FRAX can be calculated from clinical risk factors alone, and if the result falls within an intermediate zone, it may be an indication to arrange a DXA scan and then recalculate FRAX with BMD. In the version available in the United Kingdom, this intermediate zone has been defined by the National Osteoporosis Guideline Group in relation to their proposed age-varying intervention threshold (Fig 198.4), and links directly with the FRAX website.⁸¹ Other groups such as the National Osteoporosis Foundation have proposed age-independent intervention thresholds.⁸²

BOX 198.4 CLINICAL RISK FACTORS INCLUDED IN THE FRAX CASE-FINDING ALGORITHM

- Age (50 to 90 years)
- Sex
- Weight (in kg) and height (in cm). Body mass index is automatically computed from height and weight
- Previous fragility fracture (yes/no)
- Parental history of hip fracture (yes/no)
- Current tobacco smoking (yes/no)
- Long-term use of oral glucocorticoids ever (yes/no)
- Rheumatoid arthritis (yes/no)
- Daily alcohol consumption of 3 or more units daily (yes/no)
- Other causes of secondary osteoporosis (yes/no)
- Untreated hypogonadism in men and women (e.g., bilateral oophorectomy or orchiectomy, anorexia nervosa, chemotherapy for breast cancer, hypopituitarism)
- Inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis)
- Prolonged immobility (e.g., spinal cord injury, Parkinson disease, stroke, muscular dystrophy, ankylosing spondylitis)
- Organ transplantation
- Type 1 diabetes
- Thyroid disorders (e.g., untreated or overtreated hypothyroidism)

From World Health Organization. WHO risk fracture assessment tool. Available at www.shef.ac.uk/FRAX.

BOX 198.5 GROUPS IN WHOM FRACTURE RISK SHOULD BE ASSESSED

- Women 65 years and older and all men 75 years and older
 Women younger than 65 years and men younger than 75 years in the presence of risk factors, for example:
- Previous fragility fracture
 - Current use or frequent recent use of oral or systemic glucocorticoids
 - History of falls
 - Family history of hip fracture
 - Other causes of secondary osteoporosis
 - Low body mass index (<18.5 kg/m²)
 - Smoking
 - Alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

From Osteoporosis: fragility fracture risk. National Clinical Guideline Centre, 2012.

The National Clinical Guideline Centre has recently published guidelines for the use of fracture calculators such as FRAX.⁶⁴ Fracture risk assessment with such tools is recommended for all women 65 years and older and all men 75 years and older and in younger patients with risk factors (Box 198.5). It is suggested that fracture risk not be routinely assessed in people younger than 50 years unless they have major risk factors (e.g., current or frequent use of glucocorticoids, untreated premature menopause, or previous fragility fracture) because they are unlikely to be found to be at high risk. It is also recommended that fracture risk be recalculated after a minimum of 2 years if the original calculated risk was in the region of the intervention threshold for a proposed treatment or when a change has occurred in the person's risk factors. The FRAX algorithm was developed for use within a specific age range (i.e., between 40 and 90 years of age). In patients younger than 40 years, it is suggested that BMD be measured in those with a major risk factor, such as a history of multiple fragility fractures or current or recent use of high-dose steroids.⁶⁴ Patients older than 90 should be considered to be at high risk.⁶⁴

Use of FRAX is limited by the variables that are available for entry into the algorithm, which in turn reflects the available evidence base. In many clinical scenarios the characteristics of a given patient are not reflected accurately by the FRAX output, thus requiring the use of clinical judgment on a case-by-case basis. Interpretation and use of FRAX in clinical practice have been reviewed in detail.⁸³ Some of the issues that need to be considered are discussed below (Box 198.6).

Many of the FRAX risk factors, such as alcohol intake, smoking, and glucocorticoid therapy, are likely to exert dose-dependent effects on fracture risk, but they can be entered only as present or absent in the algorithm. A

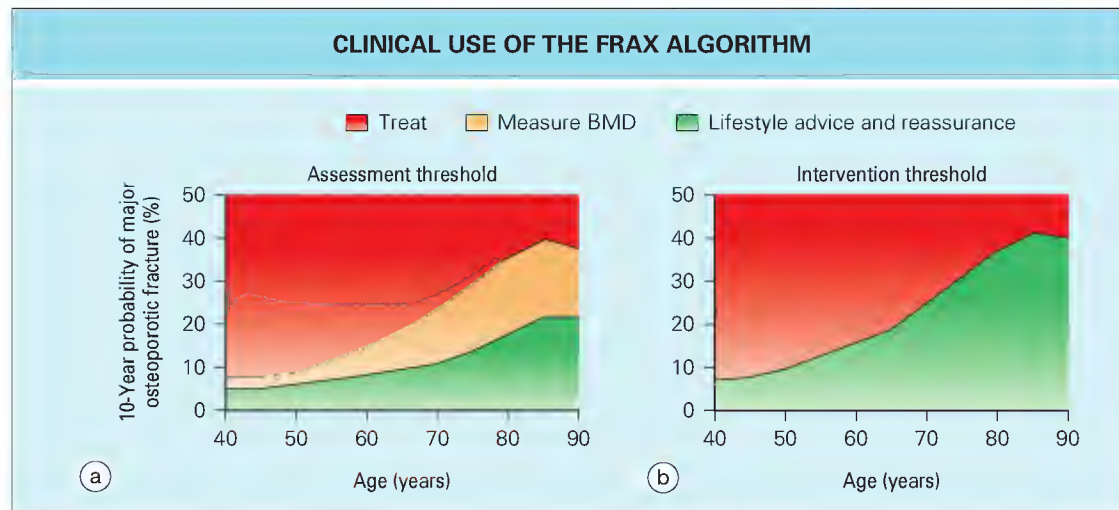


Fig. 198.4 (a) After assessment of risk for fracture by using the clinical risk factors of the FRAX in the absence of bone mineral density (BMD) values, the patient may be classified as being at low, intermediate, or high risk. (b) After recalculation of fracture probability with the additional input of femoral neck BMD, the individual's risk may lie above or below the intervention thresholds for major osteoporotic fracture, hip fracture, or both. (Data from World Health Organization. WHO risk fracture assessment tool. Available at www.shef.ac.uk/FRAX.)

BOX 198.6 PRACTICAL ISSUES IN THE USE OF FRAX

Ten-year fracture risk with mortality adjustment leads to underestimation of short-term fracture risk in older patients
 No account of the dose dependency of risk factors such as alcohol, smoking, and steroid therapy
 No account of isolated reductions in spinal bone mineral density
 Uncertain performance in patients already being treated for osteoporosis
 Results need to be treated with caution in those with secondary osteoporosis
 Exclusion of fall-related risk factors
 Does not account for multiple fractures or vertebral fractures

TABLE 198.2

Percent adjustment in the 10-year probability of a hip fracture or a major osteoporotic fracture by age according to the dose of glucocorticoid

Dose	Prednisone equivalent (mg/day)	Age (yr)						
		40	50	60	70	80	90	All ages
Hip fracture								
Low	<2.5	-40	-40	-40	-40	-30	-30	-35
Medium*	2.5-7.5							
High	≥7.5	+25	+25	+25	+20	+10	+10	+20
Major osteoporotic fracture								
Low	<2.5	-20	-20	-15	-20	-20	-20	-20
Medium*	2.5-7.5							
High	≥7.5	+20	+20	+15	+15	+10	+10	+15

*No adjustment.

From Kanis JA, Johansson H, Oden A, McCluskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. *Osteoporos Int* 2011;22:809-16.

refinement of FRAX has recently been published: when the entering the prednisolone dose, the result can be adjusted according to whether the dose is higher or lower than 2.5 or 7.5 mg (Table 198.2).⁸⁴ How to adjust for doses beyond 7.5 mg, which are used frequently to treat inflammatory rheumatologic disorders, remains uncertain. Moreover, although long-term use of oral glucocorticoids at any time is used as a FRAX risk factor, substantial and rapid recovery of BMD occurs after the use of glucocorticoids is discontinued,⁸⁵ thus suggesting that current steroid use represents a stronger risk factor for fracture than does previous use, but there are no means of differentiating between the two in the algorithm.

OFFSET OF FRAX RESULTS

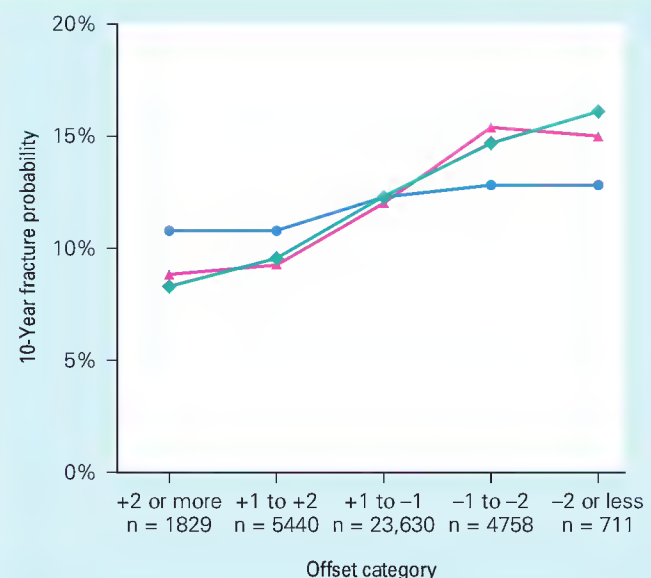


Figure 198-5 Offset of FRAX results according to whether lumbar spine BMD is above or below that of the hip. The FRAX estimate for a major fracture should be increased or decreased by a 10th for each rounded T-score difference between the lumbar spine and femoral neck. (From Leslie WD, Lix LM, Johansson H, et al. Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. *Osteoporos Int* 2011;22:839-47.)

When using FRAX, only hip BMD is entered, and therefore a further question is how to deal with a patient whose spine BMD is considerably lower than that in the hip. Based on a study comparing observed and predicted fracture risk according to the discrepancy between hip and spine BMD, it is recommended that the FRAX estimate for a major fracture be altered by a 10th for each rounded T-score difference between the lumbar spine and femoral neck (Fig. 198.5).⁸⁶

Another question is how well FRAX performs in patients already receiving treatment, because it may be useful to repeat the fracture risk assessment sometime after therapy has commenced. Treatment effects were evaluated in 3047 women with high adherence to at least 5 years of bisphosphonate use. On comparing observed fractures with the risk predicted by FRAX,

good agreement was observed for major osteoporotic fractures, whereas incident hip fractures in those in the highest-risk tertile were significantly overestimated (observed-predicted ratio, 0.61).⁸⁷

A further issue on using FRAX is how patients with osteoporosis secondary to other causes are dealt with in the algorithm. In patients with "other causes of secondary osteoporosis" as listed in Box 198.4, the estimated fracture probability is increased if no BMD score is available. In many instances the evidence base used to weight fracture risk in persons with secondary osteoporosis is relatively weak, and these weightings are likely to change in the future as more evidence becomes available. Fracture risk in those with secondary osteoporosis is generally assumed to be mediated by reduced BMD, except in the case of patients with rheumatoid arthritis or those who have used oral glucocorticoids, in whom fracture risk is assumed to be increased independently of BMD. Consequently, when using FRAX in patients with low BMD scores, those receiving glucocorticoids for rheumatoid arthritis are frequently shown to have a relatively high risk for fracture in comparison to patients with other causes of secondary osteoporosis.

One limitation of FRAX is that unlike QFracture, fall-related risks are excluded despite the fact that a history of falls is a major risk factor for future fracture. For example, in an integrated bone- and fall-related risk evaluation tool for estimation of the 5- and 10-year absolute risk for fracture in patients taking glucocorticoids, a history of falls had a greater impact on fracture risk than did any other evaluated risk, and its contribution to fracture risk was similar to—and independent of—the use of high-dose glucocorticoids.⁸⁸

A further issue with FRAX is that fracture risk may be underestimated in patients with multiple fractures or vertebral fractures because a history of a previous fragility fracture is entered as being present or absent, irrespective of the number of previous fractures or site. For example, although a history of a previous fracture is associated with an approximately twofold increase in subsequent fracture risk,¹¹ fracture risk is increased approximately fourfold in those with a vertebral fracture.^{27,42}

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Pathophysiology of osteoporosis

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- Osteoporosis is a disease characterized by reduced bone strength and increased susceptibility to fractures. The reduction in bone strength is a function of reduced bone mass and abnormal bone quality. Determinants of bone quality include bone microarchitecture, geometry, turnover, mineralization, and osteocyte viability.
- Peak bone mass is highly heritable, with genes controlling 60% to 85% of the variance at different skeletal sites. Small contributions from each of at least 60 genes contribute to this heritability. Genes identified as having an impact on bone mass include those involved in bone formation through the Wnt pathway (e.g., low-density lipoprotein receptor–like protein 5), bone resorption through the RANK-RANKL-OPG pathway, steroid hormone receptors (e.g., estrogen, vitamin D), bone proteins (e.g., type 1 collagen, bone morphogenetic protein), growth factors (e.g., insulin-like growth factor-1, transforming growth factor- β), and cytokines (e.g., interleukin-6).
- Vitamin D deficiency (defined variably as serum 25-hydroxyvitamin D levels <20 ng/mL [Institute of Medicine] or <30 ng/mL [Endocrine Society]) plays a strong role in osteoporosis, both as a result of increasing rates of bone loss and possibly by contributing to muscle weakness, impaired balance, and increased risk for falling.
- Bone remodeling describes the process by which old bone is continuously replaced by new. Net gain or loss of bone at a particular skeletal site is determined by the balance between bone resorbed by osteoclasts and bone formed by osteoblasts.
- Osteoclasts are activated by membrane signaling through RANK, the cognate receptor for RANKL, which is a member of the family of tumor necrosis factor ligands expressed on marrow stromal cells (including osteoclast precursors) and osteoblasts. The RANKL/RANK interaction promotes the differentiation of osteoclast precursors and increases the activity and life span of mature osteoclasts.
- Although aging and hypogonadism are universal risk factors for bone loss, many other factors play an important role, including chronic diseases, genes, medications, lifestyle, and environmental factors.

INTRODUCTION

Osteoporosis is a disease characterized by reduced bone strength and increased susceptibility to fracture. The reduction in bone strength is a function of both reduced bone mass and abnormal bone quality. Determinants of bone quality include bone microarchitecture, geometry, turnover, damage accumulation, mineralization, and osteocyte viability. Osteoporosis is generally asymptomatic until clinical sequelae (fractures) occur. Osteoporotic fractures are associated with increased mortality and morbidity, including pain, disability, and deformity. The ability to measure bone mass with increasing detail by noninvasive means and progress in understanding the genes related to bone formation and fracture have shed significant light on the pathogenesis of osteoporosis. Osteoporosis is a complex disease with multiple genetic, hormonal, and environmental influences. This chapter briefly reviews the role of these factors in the development of osteoporosis.

DETERMINANTS OF BONE MASS

Bone mass at any time in life is the integral of the amount of bone accrued during growth and consolidation (peak bone mass) and the inevitable loss of bone with aging. Both factors contribute to risk for fractures.

Peak bone mass

Bone mass peaks by the early 20s in women and mid-20s in men and is determined principally by genetic factors. Lifestyle and environmental factors are also important, as are gene-environment interactions. At skeletal maturity, men have 5% to 10% greater bone mass than women do because of sexual dimorphism in periosteal bone apposition at puberty.¹ In boys, higher androgen levels cause greater periosteal apposition; in girls, estrogen inhibits this process.²

Genetic factors

Genes influence not only peak bone mass but also bone loss with aging.³ Genome-wide association studies (GWASs) using meta-analyses of population-based databases of up to 70,000 individuals have identified more than 60 genes related to bone health, thus expanding our knowledge of bone physiology.^{4,5} Genes identified include those related to (1) the Wnt pathway, which is critical for bone formation; (2) the RANK-RANKL-OPG (receptor activator of nuclear factor κ B and its ligand, osteoprotegerin) pathway, which activates osteoclasts to resorb bone; and (3) endochondral ossification, which is important for the formation of long bones. In addition, GWASs have confirmed the contribution of genes related to vitamin D and parathyroid function. Each gene identified contributes no more than 3% of the total genetic influence on bone health. In conglomerate, identified genes explain less than 30% of the total genetic influence on bone health. Identification of genes related to bone turnover has directly led to new drugs for osteoporosis, such as denosumab, a human monoclonal antibody to RANKL.⁶ In addition, antibodies to sclerostin (SOST)⁷ and cathepsin K⁸ are currently in clinical trials for osteoporosis. Sclerostin, produced by osteocytes, inhibits the Wnt pathway; conversely, inhibition of sclerostin stimulates the Wnt pathway, thereby increasing bone formation. Cathepsin K, produced by osteoclasts, is an enzyme that dissolves bone matrix.

Identification of genes causing monogenetic disorders of osteoporosis has given great insight into the pathogenesis of osteoporosis. For example, in 2001 a rare syndrome of childhood osteoporosis and congenital blindness, osteoporosis pseudoglioma syndrome, was found to be due to inactivating mutations in *LRP5* (protein product low-density lipoprotein receptor–like protein 5), a key regulator of the Wnt pathway.⁹ Activating mutations in *LRP5* cause nonsyndromic high bone mass.¹⁰ In the general population, *LRP5* has been shown to be important for mechanosensation of bone and mediates the response of bone to physical activity.¹¹

The effects of genes are modulated by hormonal factors, which in themselves are genetically regulated. For example, 33% of the variance in peak bone mass can be explained by variations in endogenous growth hormone production, even after adjustment for height.¹²

There are also racial differences in peak bone mass and fracture risk, with blacks having 5% to 10% greater bone mass than whites and lower fracture risk. This is despite lower serum 25-hydroxyvitamin D (25[OH]D) levels, lower average calcium intake, and higher parathyroid hormone (PTH) levels in blacks than in whites. This discrepancy can be explained by the resistance

of the skeleton in blacks to the bone-resorbing effects of PTH, presumably an adaptive response to reduced cutaneous vitamin D production.¹³

Nutrition

Several nutrients play a key role in skeletal development, including calcium, phosphorus, and vitamin D. Greater lifetime dietary calcium intake is directly related to peak bone mass and indirectly to hip fracture rate.¹⁴ In 2011, the Institute of Medicine (IOM) set the recommended daily intake of calcium at 700 mg for children 1 to 3 years of age, 1000 mg for those 4 to 8 years of age, 1300 for those 9 to 18 years of age, 1000 mg for adults 19 to 50 years of age, 1000 mg for men 51 to 70 years of age, 1200 mg for women older than 50 years, and 1200 mg for men older than 70 years.¹⁵ The IOM report also recommended daily vitamin D intake of 600 IU for those aged 1 to 70 years and 800 IU for those older than 70 years, an increase from previous recommendations. Although sunlight exposure allows skin to produce vitamin D endogenously, use of sunblock and increasing avoidance of sun exposure are contributing to an epidemic of vitamin D inadequacy in the young and old.

Exercise

According to Wolff's law, bone adapts to the load applied to it, and the higher mechanical load experienced during exercise leads to an increase in bone density, particularly during childhood. High-impact exercise appears to confer the greatest benefit. Participation in weight-bearing sports during childhood has a positive influence on peak bone mass,¹⁶ and the positive effects persist into adulthood. Among different active sports participants, gymnasts have greater bone density than runners do, whereas swimmers and cyclists have the lowest bone density.¹⁷ School-based exercise interventions have been found to improve bone mass in children,¹⁸ particularly those that include jumping.

Gonadal function

Ovarian and testicular dysfunction can adversely affect peak bone mass. In women with amenorrhea as a result of excessive exercise, anorexia nervosa, and hyperprolactinemia, the deficit in bone mass is partially reversible if normal ovarian function is resumed, but the longer the duration of amenorrhea, the less bone mass can be regained.¹⁹ In men, hypogonadism as a result of Klinefelter syndrome and androgen receptor mutations has been associated with low bone mass.²⁰

Bone loss

Age-related bone loss is a universal phenomenon that occurs at almost all skeletal sites, in all races and cultures, and in both men and women. The rate of age-related bone loss is influenced by genetic, endocrine, and environmental factors.

Nutrition: calcium and vitamin D

Adequate calcium intake, by calcium supplementation if necessary, retards bone loss in postmenopausal women. Some, but not all studies have shown that calcium plus vitamin D supplementation reduces fracture risk; reduction of the risk for hip fractures requires a vitamin D dose of at least 800 IU daily.²¹ The serum level of 25(OH)D that defines vitamin D deficiency is controversial—20 ng/mL according to the IOM¹⁵ and 30 ng/mL according to the Endocrine Society.²² The discrepancy is primarily due to different interpretations of data related to 25(OH)D and bone health. Given the higher level of 25(OH)D considered to be normal by the Endocrine Society, it is not surprising that higher vitamin D intake is recommended (than by the IOM), up to 2000 IU daily for adults at risk for vitamin D deficiency.²² Vitamin D deficiency also contributes to muscle weakness, impaired balance, and increased risk for falls,^{23,24} thereby increasing the risk for fracture.²⁵ Low levels of 25(OH)D have been associated with numerous diseases besides osteoporosis, including cancer, diabetes, autoimmune diseases, and cardiovascular disease.²⁶ However, large prospective, controlled studies are needed to confirm that correcting vitamin D deficiency reduces the risk for these diseases.

Nutrition: other dietary factors

Patients with hip fractures are frequently malnourished, with inadequate protein intake, and protein supplementation has been found to reduce complications after hip fracture.²⁷ Dietary phosphate or magnesium deficiency may both accelerate bone loss.²⁸ Similarly, several studies have shown that vitamin C and K deficiencies may increase fracture risk.²⁹⁻³¹ By contrast, excess vitamin A may cause bone loss and increased risk for hip fractures.³² Elevated serum homocysteine levels have been associated with bone loss and fracture risk only in women.³³

Alcohol and smoking

High alcohol consumption (more than two servings in women and more than four servings in men daily) inhibits bone formation and results in an increase in hip fracture risk.³⁴ Safe daily alcohol intake for bones is one serving for women and two for men.³⁵ Smoking increases the risk for fracture,³⁶ delayed fracture healing, and postoperative complications.³⁷ Smoking exerts a toxic effect on osteoblasts, leads to earlier menopause, and reduces the production while accelerating the degradation of estrogen. In men, smoking is associated with increased levels of both testosterone and estradiol, as well as increased risk for osteoporosis and fracture.³⁸

Physical activity

Immobilization results in rapid and profound bone loss. In contrast, weight bearing and resistance exercises improve bone mass, slow bone loss,³⁹ and reduce fracture risk.⁴⁰

Chronic diseases and medications

Many chronic diseases and disorders are associated with enhanced bone loss and increased risk for osteoporosis (Table 199.1). Numerous medications (Table 199.2) are known to have detrimental effects on the skeleton, including glucocorticoids, which inhibit bone formation by promoting osteoblast and osteocyte apoptosis, reducing gastrointestinal absorption of calcium and

TABLE 199.1
Medical conditions associated with osteoporosis

System	Disease
Cardiac	Congestive heart failure
Endocrine and metabolic	Acromegaly
	Adrenal insufficiency
	Cushing syndrome
	Diabetes mellitus
	Glycogen storage diseases
	Homocystinuria
	Hyperparathyroidism (primary and secondary)
	Hyperprolactinemia
	Hyperthyroidism
	Hypogonadism
Gastrointestinal	Celiac sprue
	Chronic liver disease
	Gastrectomy
	Inflammatory bowel disease
	Malabsorption syndromes
	Malnutrition
	Pernicious anemia
Hematologic/oncologic	Amyloidosis
	Ectopic parathyroid hormone secretion (malignancy)
	Hemochromatosis
	Hemophilia
	Leukemia
	Lymphoma
	Systemic mastocytosis
	Multiple myeloma
	Thalassemia
Musculoskeletal	Ehlers-Danlos syndrome
	Marfan syndrome
Neurologic	Multiple sclerosis
	Muscular dystrophy
	Stroke
Psychiatric	Alcoholism
	Anorexia nervosa
Pulmonary	Chronic obstructive pulmonary disease
	Cystic fibrosis
	Sarcoidosis
Renal	Chronic kidney disease
	Hypercalciuria
Rheumatologic	Ankylosing spondylitis
	Rheumatoid arthritis
	Scoliosis

increasing renal calcium excretion.⁴¹ Anticonvulsants decrease bone mass primarily by increasing vitamin D catabolism and increasing bone resorption; thiazolidinediones⁴² decrease bone mass by promoting maturation of bone marrow stromal cells into adipocytes rather than osteoblasts.

PATHOGENESIS OF BONE LOSS

The effects of these risk factors on increasing bone loss are mediated through changes in the bone-remodeling cycle.

Bone remodeling

Bone remodeling describes the process by which resorption of old bone is continuously replaced by the formation of new bone. The balance between resorption and formation determines whether there is net loss or gain of

bone tissue at a particular skeletal site. Bone remodeling is accomplished by osteoclasts, osteoblasts, osteocytes, and other accessory cell types, referred to as bone-remodeling units (BRUs).⁴³ The three-dimensional geometry of the newly modeled bone occurs in discrete entities called osteons or packets. The structures of cortical and cancellous bone are distinctly different (Figs. 199.1 to 199.3), but the cellular processes are essentially the same.

Osteoclast activation and resorption

The first event in the cycle is activation. During activation, mononuclear osteoclast precursors, derived from circulating monocytes or bone marrow macrophage precursors, fuse on the bone surface to form multinucleated osteoclasts. Evidence is mounting that activation is triggered by the death or disruption of nearby osteocytes, with the resultant microdamage serving as a target for bone remodeling.⁴⁴ Differentiated osteoclasts degrade the organic and inorganic components of the bone matrix. In cancellous bone and on the endosteal and periosteal surfaces of cortical bone, osteoclasts move along the bone surface. In cortical bone they tunnel through the bone and make a cylindric hole.

The formation, activation, and activity of osteoclasts are regulated by local cytokines, including RANKL, interleukin-1 (IL-1) and IL-6, colony-stimulating factors, and systemic hormones such as PTH, 1,25-dihydroxyvitamin D₃, and calcitonin.⁴⁵ Osteoclast resorption is achieved by signaling through RANKL/RANK interaction⁴⁶ (Fig. 199.4).

Reversal and formation, osteocytes

The resorption phase is followed by the reversal phase. Osteoclasts die by apoptosis and are replaced by osteoblasts, thereby initiating the formation phase.⁴⁷ On bone surfaces, osteoblasts refill the resorption pits (cancellous bone) and tunnels (cortical bone) with new units of lamellar bone, referred to as osteon or packets (see Fig. 199.2).

In the formation phase, osteoblasts are buried in matrix and become osteocytes. Osteocytes communicate with one another via a large, three-dimensional, functional lacunocanalicular network that can “sense” a change in the mechanical properties of the surrounding bone and communicate this information to osteoblasts and osteoclasts to regulate bone remodeling.^{48,49} With bone unloading, osteocytes produce more sclerostin, which suppresses bone formation.⁵⁰ Mutations in the gene for sclerostin (SOST) lead to the sclerosing bone disorder sclerosteosis/Van Buchem disease.⁵¹ Other factors involved in the crosstalk among bone cells include IL-33 (produced by osteoblasts), which inhibits osteoclast formation, and the cytokine cardiotrophin-1 (produced by osteoclasts), which stimulates osteoblast bone formation.⁵²

TABLE 199.2 Medications associated with osteoporosis	
System	Medication
Endocrine	Aromatase inhibitors (e.g., anastrozole)
	Excess thyroxine replacement
	Glucocorticoids
	Gonadotropin-releasing hormone agonists
	Ovarian-suppressing drugs (e.g., medroxyprogesterone acetate)
Gastrointestinal	Thiazolidinediones
	Proton pump inhibitors
Hematologic	Heparin
	Warfarin
Infectious disease	Antiretroviral therapy
Immunosuppressant	Cyclosporine
	Cytotoxic drugs
	Tacrolimus
Neurologic	Anticonvulsants—phenytoin, phenobarbital, carbamazepine
Psychiatric	Selective serotonin reuptake inhibitor
Renal	Loop diuretics (e.g., furosemide)

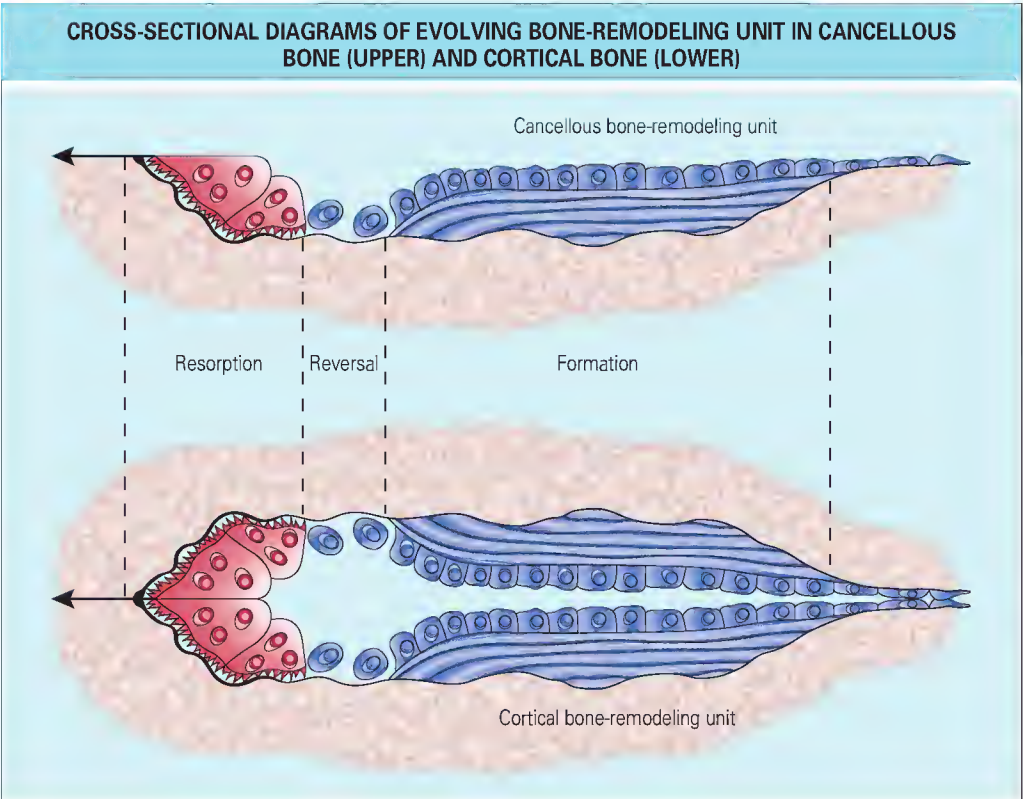


Fig. 199.1 The arrows indicate the direction of movement through space. Note that the cancellous bone-remodeling unit (BRU) is essentially half the cortical bone-remodeling unit. (From Dempster DW. *New concepts in bone remodeling*. In: Seibel MJ, Robins SP, Bilezikian JP, editors. *Dynamics of bone and cartilage metabolism*. San Diego: Academic Press; 1999, p. 261-73.)

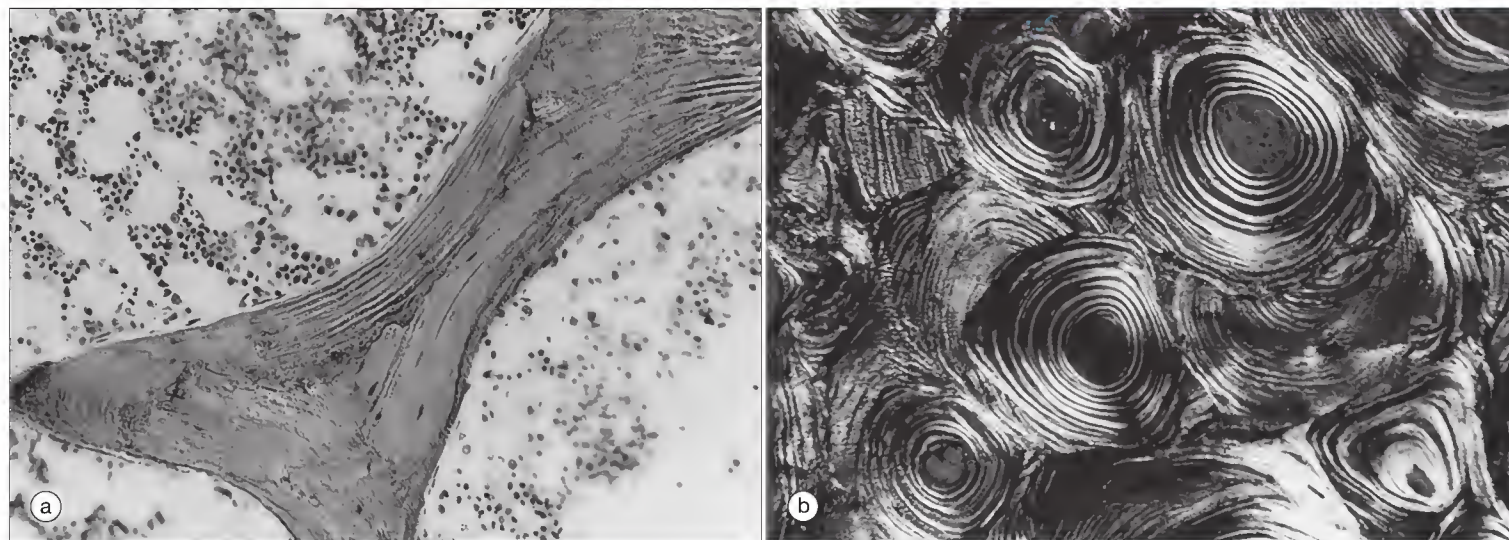


Fig. 199.2 Intact bone packet in human cancellous bone (a) and intact haversian system in human cortical bone (b). Note the osteons that have been partially replaced by prior remodeling events. (From Dempster DW. Bone remodeling. In: Coe FL, Favus MJ, editors. *Disorders of bone and mineral metabolism*. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 2002, p. 315-43.)

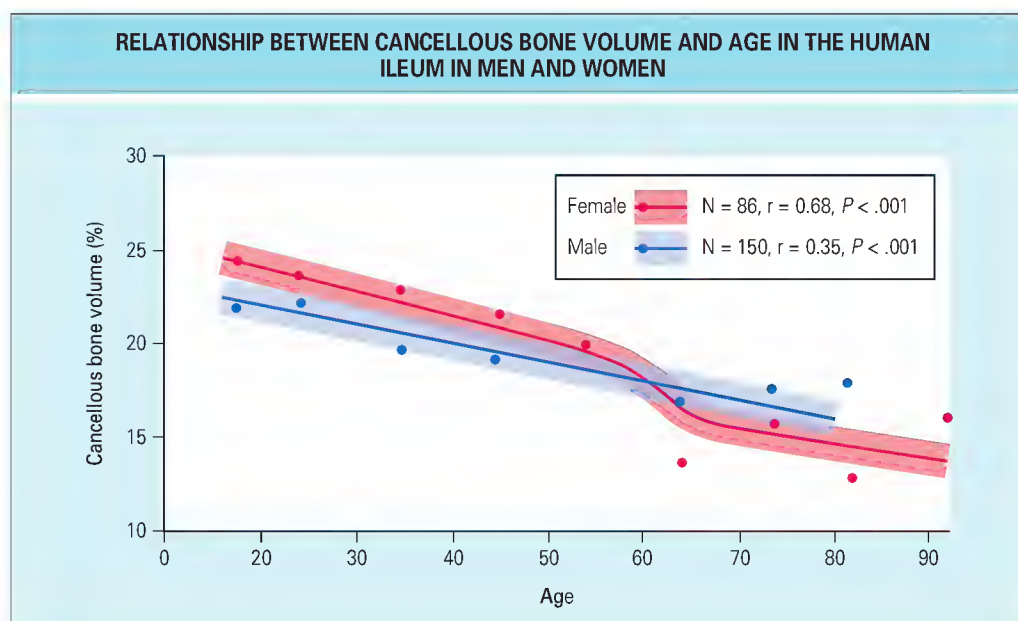


Fig. 199.3 (From Meunier P, Courpron P, Edouard C, et al. *Physiological senile involution and pathological rarefaction of bone: quantitative and comparative histological data*. *Clin Endocrinol Metab* 1973;2:239-56.)

Gender and other influences on remodeling

Women lose more bone with age than men do. By 90 years of age, women have lost 25% of their peak cortical bone mass versus 18% in men and 55% of their trabecular bone (in central sites) versus 46% in men.⁵³ In both sexes, the reduction in serum estradiol with age is an important mediator of bone loss.⁵³ In men, aging results in a gradual decrease in osteoblast function, decreased thickness of cancellous bone packets, trabecular thinning, and a linear reduction in cancellous bone volume with age (see Fig. 199.3). Trabecular connectivity is better preserved in men than in women.⁵⁴

At menopause women have an abrupt acceleration in the rate of bone loss for 5 to 10 years (see Fig. 199.3), primarily because of enhanced osteoclast activity via increased RANKL production.⁵⁵ RANKL production is further increased with aging as a result of secondary hyperparathyroidism caused by renal insufficiency, vitamin D deficiency, and a reduction in activation of vitamin D.⁵⁶ Osteoclasts ultimately remove many trabeculae. The reduced trabecular number decreases bone strength much more than trabecular thinning does.⁵⁷

Strong bidirectional links have been shown between bone and energy metabolism. Osteoblasts and adipocytes share a common progenitor cell, the mesenchymal stem cell (MSC). Although bone volume decreases with age, marrow adiposity increases.⁵⁸ Factors that control differentiation of MSCs into osteoblasts include lamin A/C (nuclear protein important for

gene expression), RUNX2 (transcription factor), and the bone morphogenetic protein, Wnt, and Notch signaling pathways.^{59,60} Age-related changes in lamin A/C and RUNX2 expression lead to bone loss. Secretion of leptin by adipocytes reduces bone production, and secretion of osteocalcin by osteoblasts improves insulin sensitivity.⁶¹ Adding further complexity, the sympathetic nervous system has an effect on bone remodeling. Patients taking β -blockers have higher bone mass and fewer fractures.⁶²

Strength of cancellous bone

At weight-bearing sites, struts of trabeculae are aligned in the direction of the primary load axis and are supported by trabeculae oriented perpendicular to the load axis (serving as cross-ties). With aging and osteoporosis, there is preferential loss of cross-ties.⁶³ According to Euler's theorem, the buckling load of a weight-bearing trabecula decreases inversely with the square power of its unsupported length. Thus loss of two cross-ties will triple the effective length of the trabecula to which it was connected, but the load that the trabecula can support will decrease by a factor of 9. Loss of cross-ties and other architectural changes that compromise bone quality have been demonstrated in patients with hip fractures.⁶⁴⁻⁶⁷

Effects on long bones

With aging, long bones increase in diameter and their cortex thins because of small imbalances in bone resorption and formation in each remodeling

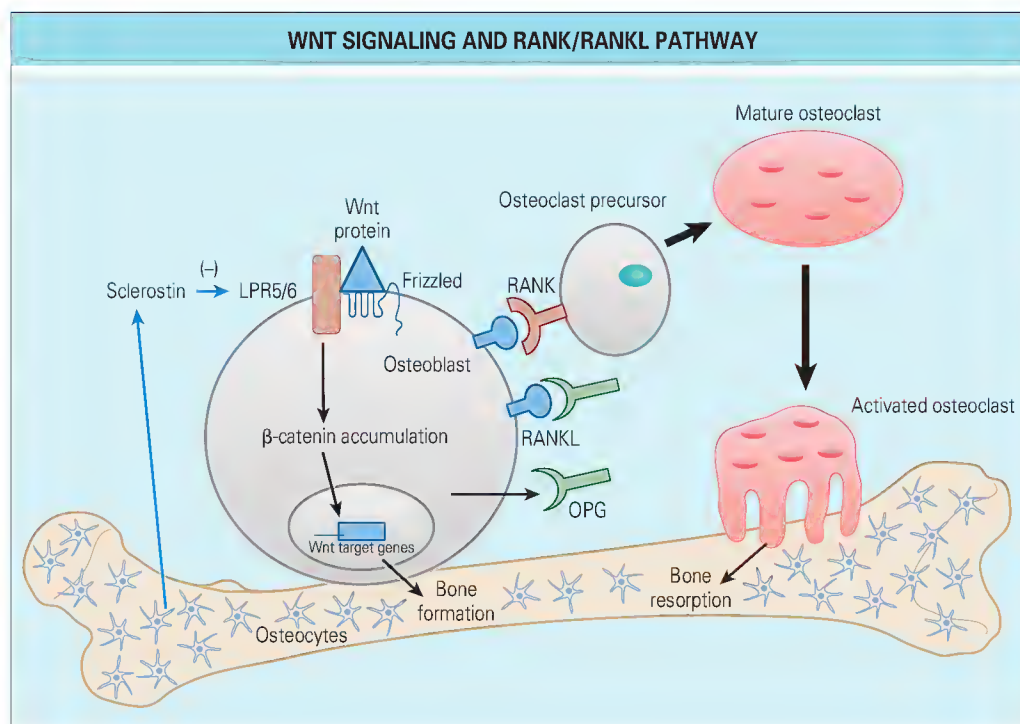


Fig. 199.4 Crosstalk between bone cells. The balance between bone formation and resorption is largely regulated by the Wnt pathway (bone formation), receptor activator of nuclear factor κ B (RANK)/RANK ligand (RANKL) pathway (osteoclast activation), and sclerostin (negative regulation of bone formation). Osteoblasts express the cell surface receptors RANK and also secrete a soluble decoy receptor, osteoprotegerin (OPG), a member of the superfamily of tumor necrosis factor receptors. Wnt protein binds the coreceptors Frizzled and low-density lipoprotein receptor-like proteins 5 and 6 (LRP5/6), which leads to stabilization of β -catenin and its translocation to the nucleus to regulate target genes, thereby resulting in increased bone formation. In the absence of OPG, RANKL on the osteoblast surface is available to bind the RANK present on osteoclast precursors. Binding of RANK/RANKL leads to osteoclast maturation and resorption of bone. Sclerostin, secreted by osteocytes, inhibits Wnt from binding LRP5.

cycle. The balance is negative on the inner, endosteal surface and positive on the outer, periosteal surface. Women lose more bone from the endosteal surface than men do,⁶⁸ which results in greater loss of the cross-sectional moment of inertia with age in women and greater fracture risk. Within the

cortex, women have more age-related declines in the area occupied by circumferential lamellar bone, greater increases in haversian canal diameter, and greater decreases in osteon wall thickness than men do, all leading to greater cortical porosity and higher risk for fracture.⁶⁹

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200

Biochemical markers in bone disease

■ KIM E. NAYLOR ■ RICHARD EASTELL

- Specific and sensitive assays are available for the measurement of biochemical markers of bone turnover.
- The International Osteoporosis Foundation recommends that serum PINP and CTX-I be used as reference analytes in clinical and research studies to allow comparison of results.
- Bone turnover markers that have shown reliable performance in studies of osteoporosis are bone alkaline phosphatase, total osteocalcin, PINP, CTX, and NTX.
- Markers can reflect posttranslational modification of collagen.
- Bone turnover markers are clinically useful for monitoring the efficacy of antiresorptive therapy in women with postmenopausal osteoporosis.

INTRODUCTION

Bone remodeling is a continuous process that contributes to the preservation of skeletal health and regulation of calcium homeostasis. It is normally a coupled process that occurs in local areas called bone multicellular units (BMUs)^{1,2} and is regulated by systemic hormones and local factors. During the bone resorption phase, bone tissue is broken down by osteoclasts, which produces a resorption cavity (Fig. 200.1). This cavity is then filled with new bone synthesized by osteoblasts during the bone formation phase. Bone remodeling and the number of BMUs are normally in steady state; however, an imbalance can occur, for example, with changes in age, hormonal status, or mobility or with disease or medications.³ In some diseases, such as postmenopausal osteoporosis, the increase in bone resorption is greater than the increase in bone formation, thereby resulting in net bone loss (see Chapter 199). In glucocorticoid-induced osteoporosis, on the other hand, bone loss is due to a reduction in osteoblast function leading to a decrease in bone formation (see Chapter 202).

Biochemical markers of bone turnover provide a noninvasive method of assessing changes in bone metabolism.⁴⁻⁷ They are divided into markers of bone formation and bone resorption (Box 200.1). In disease states in which bone turnover remains coupled and changes in the same direction, both bone formation and bone resorption markers will reflect the rate of bone turnover. Not all markers of bone turnover are specific to bone because some can be found in other tissues. Type I collagen accounts for approximately 90% of the organic matrix of bone.⁸ Several bone turnover markers are based on byproducts of type I collagen synthesis or degradation. Other bone markers include markers of enzymatic activity or bone matrix proteins that are released into the circulation during bone remodeling. Bone turnover markers reflect the whole-body net changes in the skeleton and cannot discriminate between changes in turnover in a specific skeletal envelope. New markers are emerging, including regulators of bone turnover (Box 200.2).

Bone markers are useful for assessment of metabolic bone disease; however, they are most widely used in women with postmenopausal osteoporosis. Several studies have assessed the use of bone markers to predict fracture and their role in monitoring the efficacy of treatments. This chapter reviews recent developments in the methodology and use of bone markers for the management of metabolic bone disease.

BIOCHEMICAL MARKERS OF BONE TURNOVER

Bone resorption

Bone resorption markers include products of osteoclast activity and type I collagen degradation. Bone resorption markers are predominantly based on type I collagen degradation products. Hydroxyproline was one of the first markers of bone resorption but lacked specificity for bone. More specific markers were developed with assays for the measurement of type I collagen cross-links (pyridinoline [PYD] and deoxypyridinoline [DPD]) in urine by high-performance liquid chromatography.^{9,10} Free DPD can also be measured by enzyme-linked immunosorbent assay.¹¹ More recently, the telopeptides of type I collagen have been established as bone resorption markers.^{12,13} These telopeptides are nonhelical peptide fragments of type I collagen that contain the following cross-linking regions: the N-terminal cross-linked telopeptide of type I collagen (NTX)^{13,14} and the C-terminal telopeptide of type I collagen (CTX) generated by cathepsin K.¹⁵ Assays have also been developed for the C-telopeptides generated by metalloproteinase (CTX-MMP or ICTP).¹⁶

Because reference markers for bone turnover have not been established, it is difficult to directly compare published results from clinical studies. The International Osteoporosis Foundation (IOF) has recommended CTX as the reference marker for bone resorption.^{17,18} However, because CTX is reduced by feeding, it is recommended that samples be collected after an overnight fast. Urine NTX measurements can be made on second-void morning samples collected before attendance at the clinic, which makes them more convenient for some patients.

An interesting property of type I collagen telopeptides is nonenzymatic posttranslational modification of the (1209)AHDGGR(1214) sequence of CTX, which is thought to reflect bone matrix maturation (Fig. 200.2). The native α form of the C-telopeptide of type I collagen (α -CTX) is found in newly synthesized type I collagen. The carboxyl group in position α of aspartic acid is involved in a peptide bond with the adjacent glycine residue. As maturation of the collagen occurs, it undergoes β -isomerization with spontaneous translocation of the peptide bond to the carboxyl group in position β of the aspartic acid (D) residue within the C-telopeptides of the α 1 chains.^{12,19} The resulting β -CTX isomerized sequence alters the three-dimensional conformation of type I collagen. The native (α) and isomerized (β) CTX are measured with specific immunoassays, available as both manual assays and assays by automated analyzers.

Other bone resorption markers include osteoclastic enzymes such as tartrate-resistant acid phosphatase (TRAcP) and cathepsin K. Sensitive immunoassays are available for TRAcP type 5b, which is expressed by osteoclasts^{20,21} and mainly reflects osteoclast number. Cathepsin K can be measured by immunoassay, but further evaluation of its use as a marker of bone resorption is required.²²

Bone formation

Type I collagen is synthesized in the early phase of bone formation. During this process the amino and carboxy propeptides of type I procollagen (PINP, PICP) are released into the circulation.^{23,24} The IOF selected PINP as the reference marker for bone formation because of its robust nature and dynamic response to treatment.^{17,18}

Bone alkaline phosphatase is an enzyme associated with matrix maturation and accounts for around half of the total alkaline phosphatase in the circulation.²⁵ Total alkaline phosphatase is a suitable marker for assessment of metabolic bone diseases associated with large changes in bone turnover, such as Paget disease of bone. However, the bone isoenzyme of alkaline

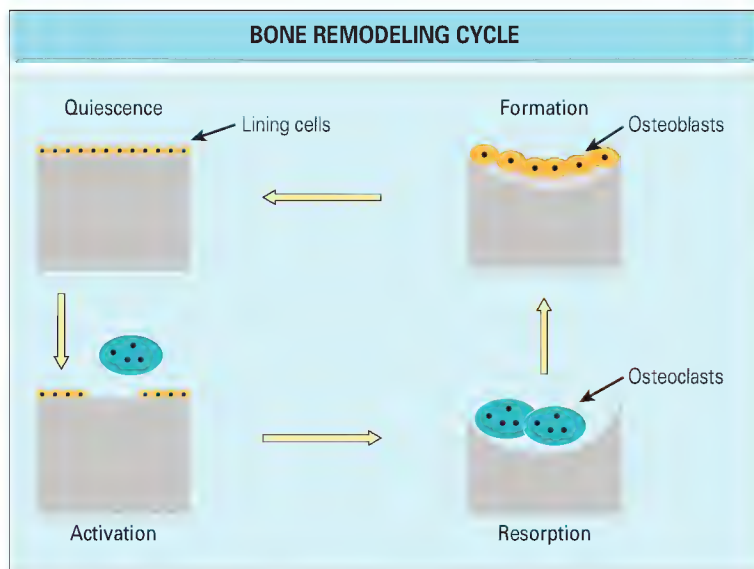


Fig. 200.1 Local and systemic factors initiate activation of the bone-remodeling cycle. Osteoclasts break bone down during the resorption phase, which creates a cavity. Mononuclear cells signal the initiation of bone formation by osteoblasts. New bone replaces the bone removed from the erosion cavity. A period of quiescence occurs before the next remodeling cycle begins.

BOX 200.1 BIOCHEMICAL MARKERS OF BONE TURNOVER

Bone resorption markers

Collagen degradation products

Pyridinoline (PYD), deoxypyridinoline (DPD)

Telopeptides of type I collagen:

C-terminal (α / β -CTX, ICTP, or CTX-MMP)

N-terminal (NTX)

Osteoclast enzymes

Tartrate-resistant acid phosphatase 5b (TRAcP-5b)

Bone formation markers

Collagen synthesis byproducts

Type I procollagen C-terminal and N-terminal propeptides (PICP, PINP)

Matrix proteins

Intact and total osteocalcin (OC)

Osteoblast enzymes

Total alkaline phosphatase (total ALP)

Bone alkaline phosphatase (bone ALP)

BOX 200.2 NOVEL BIOCHEMICAL MARKERS OF BONE METABOLISM

Regulators of osteoclast-osteoblast differentiation/activity

OPG/RANKL Wnt signaling molecules (Dkk-1/sFRP)

Sclerostin

Noncollagenous proteins

Bone sialoprotein

Osteopontin

Periostin

Urinary midmolecule osteocalcin

Osteoclast enzymes

Cathepsin K

Markers of bone matrix properties

Nonenzymatic glycation-mediated modifications of collagen, (e.g., pentosidine, vesperlysine, carboxymethyllysine)

Carboxylation and isomerization of osteocalcin

Type I collagen C-telopeptide isomerization (α / β -CTX ratio)

Dkk-1, Dickkopf-1; sFRP, soluble Frizzled-related protein; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κ B ligand.

phosphatase is more specific and can detect more subtle changes in bone turnover.

Osteocalcin is a bone matrix protein produced by osteoblasts and is expressed at the mineralization phase of bone formation. Osteocalcin is incorporated into the bone matrix, and a small fraction is released into the circulation both as intact molecules and as fragments. Assays are available that measure the intact molecule and the large N-terminal midfragment.²⁶ It has been suggested that osteocalcin fragments could be released during bone resorption.²⁷

Vitamin K is required for γ -carboxylation of the three glutamic acid residues necessary for the mineral-binding ability of osteocalcin. Undercarboxylated osteocalcin is a measure of vitamin K insufficiency,²⁸ and increased levels are associated with risk for hip fracture.²⁹ It has been proposed that this form of osteocalcin has a role in energy metabolism by stimulating insulin secretion and increasing insulin sensitivity.³⁰

REGULATORS OF BONE TURNOVER

The osteoprotegerin (OPG)/receptor activator of nuclear factor κ B (RANK)/RANK ligand (RANKL) system is one of the key mediators of osteoclast differentiation and action.³¹ Imbalances in this pathway are associated with postmenopausal bone loss. Circulating OPG and RANKL have been shown to be affected by different diseases; however, conflicting data have been reported in clinical studies.³² OPG inhibits osteoclastogenesis, thereby resulting in a decrease in bone resorption. Circulating OPG was not associated with the reported change in bone markers in some studies.^{33,34} Circulating OPG levels are higher in patients with osteoporosis than in controls.³⁵ The clinical utility of OPG and RANKL as bone turnover markers remains to be fully evaluated.

Novel markers

The Wnt signaling pathway is central to the regulation of bone metabolism; it plays a pivotal role in osteoblast cell growth, differentiation, and apoptosis.³⁶ The Wnt ligands primarily signal through the seven-transmembrane receptor complex of the Frizzled family. The Frizzled-related proteins (FRPs) each interact with the low-density transmembrane lipoprotein receptor-related protein-5/6 (LRP-5/6). The Wnt signaling pathway is inhibited by proteins that prevent ligand receptor binding such as Dickkopf-1 (Dkk-1) and soluble FRPs. Alterations in the Wnt signaling pathway have been associated with conditions of abnormal bone turnover and bone loss. Elevated Dkk-1 has been associated with conditions characterized by suppressed bone formation and osteolysis (e.g., multiple myeloma, bone metastasis, and rheumatoid arthritis). Treatment with bisphosphonate anti-resorptive therapy results in a decrease in Dkk-1.³⁷

Sclerostin

Sclerostin is a protein containing 188 amino acids with two N-glycosylation sites.³⁸ It is secreted by osteocytes and inhibits the genesis of osteoblasts, thereby resulting in a decrease in bone formation. Circulating sclerostin levels are higher in postmenopausal than in premenopausal women.³⁹⁻⁴¹ Sclerostin was found to be modestly associated with bone mineral density (BMD) and bone turnover in a population-based study of postmenopausal women.⁴²

Elevated sclerostin is associated with a greater risk for hip fractures in older women, particularly those with low BMD (Fig. 200.3).⁴³

Measurement of sclerostin is not yet suitable for use in clinical practice because the assays need to be optimized and standardized since the data from different assays are discordant.⁴⁴ The circulating molecular forms have not been characterized (intact or fragments). The kinetics still needs to be determined. It is unclear what percentage of sclerostin enters the circulation from bone, whether the rate of production is related to bone mass, and what the clearance mechanism is. Even though sclerostin levels are increased in those with chronic kidney disease, the increase in sclerostin with age is not explained by the decline in the estimated glomerular filtration rate.⁴⁵

Sources of variability also need to be explored. Levels of sclerostin are reported to be higher in men than in women, as well as higher in older people. Sclerostin levels are increased for up to 48 weeks following fracture of a long bone.⁴⁶ Variability could be altered in metabolic bone diseases with a high bone turnover state such as Paget disease of bone and prostate cancer with bone metastases. Further studies are required to determine the effects of other sources of variability, such as circadian rhythm, effect of meals, day-to-day and seasonal variability, ethnicity, race, and geographic location.

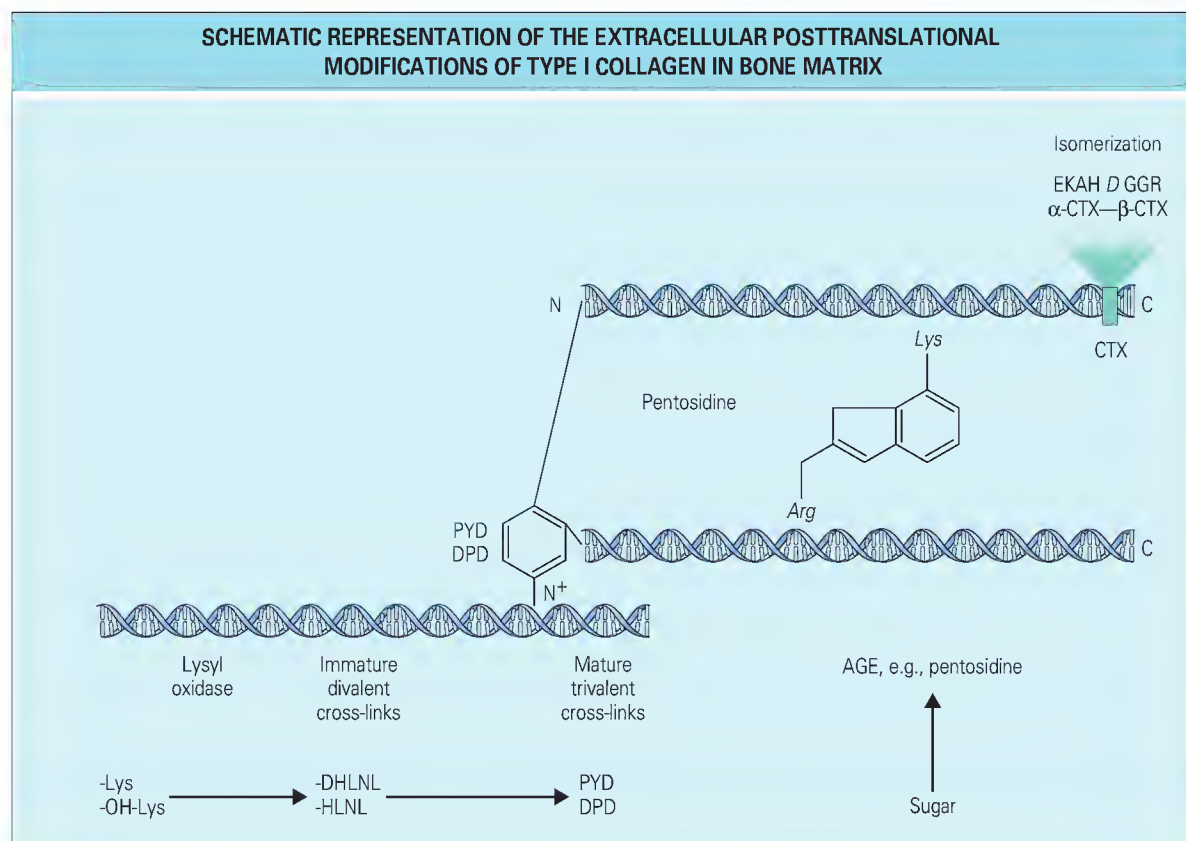


Fig. 200.2 Type I collagen is formed by the association in a triple helix of two α_1 and one α_2 chains except for the two ends (N- and C-telopeptides). In bone matrix, type I collagen is subjected to different posttranslational modifications: the mature trivalent cross-links, including pyridinoline (PYD), deoxypyridinoline (DPD), and pyrrole, that make bridges between two telopeptides and the helicoidal region of another collagen molecule. These molecules result from the maturation of divalent cross-linking molecules (dihydroxylysinoxonoreucine [DHLNL] and hydroxylysinoxonoreucine [HLNL]) whose synthesis requires an enzymatic process (lysyl oxidase); the advanced glycation end products (AGEs) are formed by nonenzymatic glycation when sugar (e.g., glucose) is present in the extracellular matrix. Some AGEs, such as pentosine, are cross-linking molecules, although their precise location remains to be determined; the nonenzymatic isomerization of aspartic acid (D) occurs in the C-telopeptides of α_1 chains. CTX, C-terminal telopeptide of type I collagen.

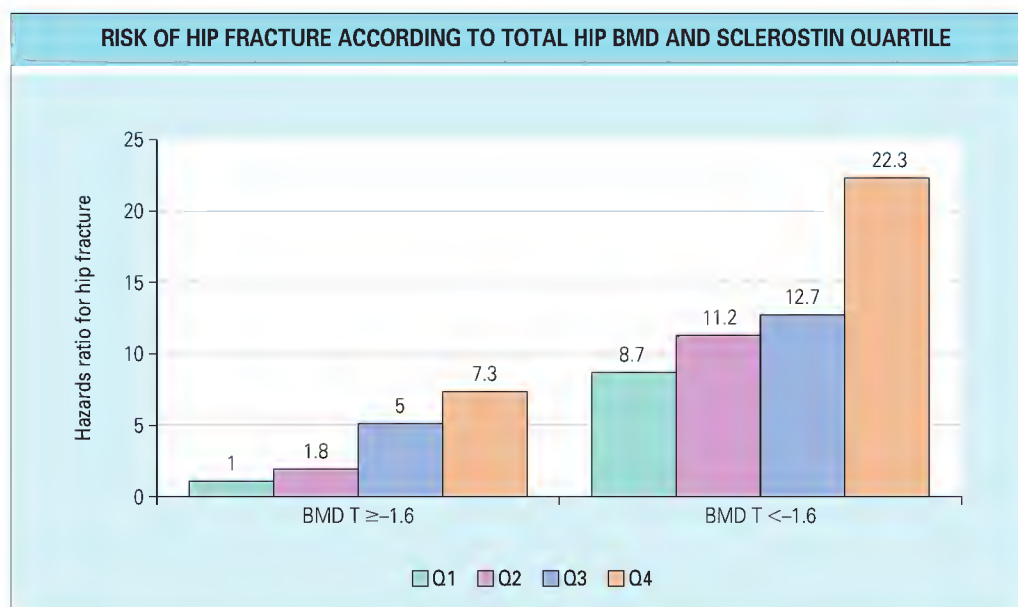


Fig. 200.3 The median bone mineral density (BMD) (0.742 g/cm^2 ; T-score, -1.6) was chosen as a cutoff point. Lower BMD is defined as less than 0.742 g/cm^2 and higher BMD as 0.742 g/cm^2 or higher. Serum sclerostin quartiles are as follows: quartile 1, 209 pg/mL; quartile 2, 210 to 267 pg/mL; quartile 3, 268 to 353 pg/mL; and quartile 4, higher than 353 pg/mL. The hazard ratio (HR) for the risk for hip fracture (95% confidence intervals) as compared with higher BMD/quartile 1 are as follows: higher BMD/quartile 2, HR = 1.8 (0.4 to 7.3); higher BMD/quartile 3, HR = 5.0 (1.3 to 18.7); higher BMD/quartile 4, HR = 7.3 (2.0 to 26.3); lower BMD/quartile 1, HR = 8.7 (2.4 to 31.3); lower BMD/quartile 2, HR = 11.2 (3.1 to 41.0); lower BMD/quartile 3, HR = 12.7 (3.5 to 45.9); and lower BMD/quartile 4, HR = 22.3 (5.8 to 86.3). (Data from Arasu A, Cawthon PM, Lui LY, et al. Serum sclerostin and risk of hip fracture in older Caucasian women. *J Clin Endocrinol Metab* 2012;97:2027-32.)

When sclerostin is low, it would be expected that BMD and bone formation would be high and vice versa. Glucocorticoid-induced osteoporosis fits this model with high sclerostin, low bone formation, and low BMD. Postmenopausal women have higher sclerostin than premenopausal women do, but with high bone formation markers and low BMD. With estrogen therapy there is a decrease in sclerostin and a relative decrease in bone formation.⁴¹ In a study of immobilization in young men, sclerostin was increased in response to 90 days of bed rest. Bone resorption but not bone formation was increased with a decrease in parathyroid hormone and BMD.⁴⁷

Preliminary data are inconclusive, and this is an area for future development. Regulators of bone turnover, including sclerostin and Dkk-1, are promising targets for anabolic therapies for metabolic bone disease. Clinical trials are evaluating antibodies against sclerostin and Dkk-1 for the treatment of bone loss.⁴⁸

Periostin

Periostin is an osteoblast-specific factor that was renamed periostin because of its preferential location in the periosteum. Periostin has a role in bone biology, possibly in the regulation of bone formation.⁴⁹ It is expressed in collagen-rich fibrous connective tissues such as bone, heart valves, tendons, and periodontal ligaments, as well as by some tumors. The role of periostin in connective tissue disease has yet to be determined. In metastatic bone disease, periostin is increased in breast and prostate cancer with bone metastases.⁵⁰ Periostin could be an early marker of bone metastasis or periosteal apposition, but further studies are required.

Pentosidine

Advanced glycation end products (AGEs) are formed by nonenzymatic glycosylation of protein amino groups. AGEs have been observed in bone tissue and associated with a decrease in the mechanical properties of bone. Pentosidine is one of the most studied AGEs; it forms cross-links between collagen molecules, which potentially alters their structure and function. Pentosidine increases with aging, and high levels of pentosidine have been identified as a risk factor for fracture in older adults with diabetes.⁵¹ However, pentosidine is not specific to bone tissue, and further identification of tissue-specific AGEs would be beneficial in studying their effects on the structural properties of bone.

VARIABILITY IN BIOCHEMICAL MARKERS OF BONE TURNOVER

Automated assays are now available for many of the established bone markers. They provide fast, high-volume sample throughput with high analytic precision.^{52,53}

Sources of variability in the measurement of biochemical markers of bone turnover should be considered and controlled,^{54,55} including preanalytic and analytic variability.⁵⁶ There are both modifiable and nonmodifiable sources of variability, some examples of which are presented in Table 200.1. Preanalytic variability includes uncontrollable factors such as age, gender, ethnicity, geographic location, medications, diseases, and other conditions that can affect bone markers such as pregnancy, immobilization, and fracture.⁵⁷⁻⁶¹ These factors cannot be controlled; however, it is important to be aware of their influence on clinical interpretation of bone turnover marker results.

Sources of preanalytic variability that are controllable include circadian rhythm, effect of meals, menstrual cycle, diet, and exercise.^{62,63} These factors can be controlled by standardization of timing and conditions for collection of samples. Bone markers decrease following a meal, which can be controlled by collecting samples following an overnight fast.^{64,65}

Analytic variability should be minimized by controlling for parameters identified in assay protocols such as correct sample collection, processing, and storage and assay conditions such as temperature monitoring.⁶⁶

CLINICAL UTILITY OF BIOCHEMICAL MARKERS OF BONE TURNOVER

Bone markers are useful tools for understanding the mechanism of action of therapeutic agents on bone in clinical trials. In a clinical setting they are useful for monitoring response to treatment and identifying possible causes of secondary osteoporosis (e.g., myeloma, chronic kidney disease). Bone markers do not have a role in the diagnosis of osteoporosis; this is routinely assessed by measuring BMD with dual-energy x-ray absorptiometry.

TABLE 200.1

Sources of preanalytic variability to be considered for interpretation of results from bone turnover marker (BTM) measurements

Source of variability	Comment
Uncontrollable	
Age, pubertal stage	High BTMs in children. Use appropriate reference interval
Gender	Use male/female reference intervals
Geographic location	Use appropriate reference interval
Ethnicity	Use appropriate reference interval
Menopause	Increased BTMs
Oral contraceptive	Lower values of BTMs
Pregnancy and lactation	Elevated BTMs
Recent fracture	BTMs elevated for up to 1 year
Metabolic bone disease	Usually cause an increase in BTMs
Renal/hepatic function	Increase in BTMs
Medications	Record the medical/drug history
Controllable	
Circadian rhythms	Collect samples at the same time of day during each visit
Meals	Because BTMs decrease after food, take fasting samples
Diet	Because BTMs decrease after Ca supplementation, take fasting samples
Seasonal	Repeat visits in the same season
Exercise	Effect is dependent on type and duration
Menstrual cycle	Collect samples in the early phase of the cycle

Proposed applications of biochemical markers of bone turnover include (1) prediction of increased risk for fracture, (2) prediction of whom will benefit from treatment, (3) assessment of the efficacy of treatment, and (4) promotion of adherence to treatment.

Markers of bone turnover for prediction of bone loss and fracture risk

There is a strong association between bone density measurements and risk for fracture; however, assessment of fracture risk by measurement of BMD lacks sensitivity because up to half of patients who sustain a nonvertebral fracture do not have osteoporosis (BMD T-score of -2.5 or less).^{67,68}

Bone markers are elevated in metabolic bone diseases and other conditions associated with accelerated bone loss. Bone turnover is increased in postmenopausal women and is higher in those with lower bone mass.^{69,70} Although high levels of bone markers are associated with accelerated rates of bone loss, the predictive value at an individual patient level is uncertain.⁷¹ It is possible that the deterioration in bone architecture caused by increased bone turnover may have a greater effect on bone strength and fracture risk than the decrease in bone mass does. Vasikaran and colleagues reviewed prospective studies that examined the association of bone turnover markers with subsequent fracture.¹⁷ Some of the limitations identified included inconsistent results for individual bone markers, different methodologies and sample collection procedures, use of multiple statistical approaches, and heterogeneity in the fracture types identified.

Bone markers for identification of patients who will benefit from treatment

Bone markers may be useful for identifying patients who are the most likely to have the best response to treatment. Some studies have shown that participants with higher pretreatment bone turnover markers have a greater increase in bone density in response to treatment with antiresorptive agents.^{72,73} The Fracture Intervention Trial reported that participants treated with alendronate who had higher pretreatment bone formation markers had a greater reduction in nonvertebral fractures than did those with lower bone turnover.⁷⁴ However, the association between pretreatment bone markers and response to treatment is modest and variable. The use of bone markers to identify patients for specific types of treatment warrants further study.

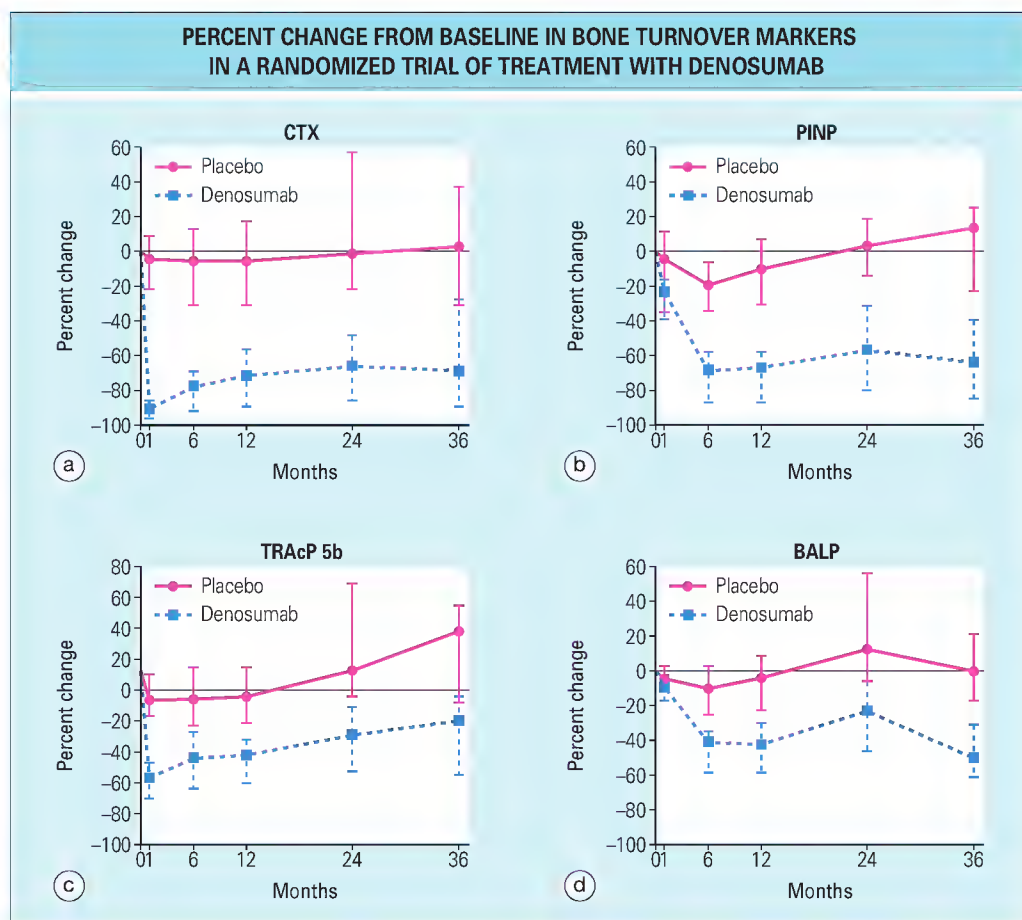


Fig. 200.4 Percent change from baseline in bone turnover markers—(a) C-terminal telopeptide of type I collagen (CTX); (b) PINP; (c) tartrate-resistant acid phosphatase 5b (TRAcP-5b); (d) bone alkaline phosphatase (BALP)—in a randomized trial of treatment with denosumab (FREEDOM Trial). The horizontal line represents no change, and each point and error bar represent the median percent change and interquartile range, respectively. Samples were measured before the next injection, with the exception of months 1 and 36, at which time the dose was not administered. * $P < .000$. (From Eastell R, Christiansen C, Grauer A, et al. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. *J Bone Miner Res* 2011;26:530-7.)

Bone markers for monitoring treatment of bone disease

The aim of treatment of metabolic bone disease is to reduce the risk for fragility fractures.⁷⁵ To monitor treatment efficacy, bone density measurements have been used as surrogate markers for fracture in many clinical trials. It is assumed that a change in bone density brought about by treatment reflects a change in the clinical endpoint, occurrence of fracture.

The change in BMD in response to treatment is relatively small, and in individual patients in clinical practice it is necessary to wait at least 2 years to determine whether a treatment is effective. Biochemical markers of bone turnover generally respond more rapidly and with greater magnitude of change than BMD does.⁷⁶ This is useful for managing the treatment of patients, particularly those who show no change in bone markers. Good adherence to risedronate treatment was associated with greater changes in bone markers and a reduction in fracture risk.⁷² The influence on adherence to treatment by feedback of information to patients regarding the change in bone markers is inconclusive.⁷⁷⁻⁷⁹

A modest or no change in bone markers with osteoporosis treatments may identify poor compliance or, less commonly, a lack of response. Other conditions may be the cause of persistently elevated bone turnover markers, such as fracture or comorbid conditions.

Response of bone markers to treatment

Clinical trials of antiresorptive treatments of postmenopausal osteoporosis have shown bone turnover markers to decrease after the start of treatment. The aim of treatment is to reduce bone turnover to the lower half of the premenopausal reference range.⁸⁰ Those in the lower half of the reference range have the lowest risk for fracture. The magnitude, onset, and duration of response are dependent on the study population, treatment, and bone marker measured. Treatment with bisphosphonates prompts a rapid decrease in bone resorption markers. Alendronate treatment causes a significant decrease in bone resorption within 3 months, followed by a decrease in bone formation around 6 to 12 months.^{21,81,82} Similar decreases have been reported in men.⁸³⁻⁸⁷ Bone resorption markers remain suppressed for up to 5 years after cessation of alendronate treatment.⁸⁸

Intravenous bisphosphonates such as zoledronic acid produce a more rapid decrease in bone turnover, within 1 month for bone resorption and 3 months for bone formation.^{89,90} Denosumab is a monoclonal antibody that mimics OPG by targeting RANKL to inhibit bone loss. Denosumab treatment produces a large and rapid decrease in bone resorption followed by a slower decrease in bone formation (Fig. 200.4).^{91,92}

Bone markers have also been used to study the anabolic effect of teriparatide. The bone formation marker PINP doubled after 1 month of treatment and reached a maximum response after 6 months.^{93,94} These changes were more dynamic than those of other bone formation markers.

Bone markers can provide useful information in drug development by providing data on different dosing regimens. Antiresorptive treatments such as the bisphosphonate ibandronate produce a dose-dependent decrease in bone resorption,⁹⁵ whereas anabolic agents induce increases in bone formation markers.⁹⁶ Cathepsin K inhibitors suppress bone resorption by a greater magnitude than they do bone formation.⁹⁷ It has been suggested that bone markers are possible candidates as surrogate endpoints for fracture in clinical trials of osteoporosis.⁹⁸

SUMMARY

Well-established markers of bone turnover that have proved useful in monitoring treatment are available. Bone markers may be useful to establish an optimal dose for new treatments of osteoporosis. More work is needed to standardize assays so that results can be compared between studies and centers. Further data are needed on the clinical utility of bone markers. New markers are emerging that may provide a better understanding of the local regulation of bone turnover and changes in the quality of bone. Further information on the circulating molecular forms and kinetics of these analytes is required.

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201

Management of osteoporosis

■ CHAD L. DEAL ■ ABBY G. ABELSON

- A woman's lifetime risk for fracture is 40%, so strategies to evaluate and treat women at risk are critical to reduce fracture burden.
- Effective evaluation and treatment include a workup for secondary causes of low bone mass, lifestyle modification, fall prevention, calcium and vitamin D supplementation, and when appropriate, therapy with an antiresorptive or anabolic agent.
- Antiresorptive agents include the bisphosphonates, which are available in oral and intravenous forms; denosumab, a monoclonal antibody against RANKL; raloxifene, an estrogen agonist-antagonist; and strontium ranelate, available outside the United States. The only anabolic agent approved in the United States is teriparatide (recombinant human parathyroid hormone 1-34).
- The appropriate duration of antiresorptive therapy is an important issue that should be decided by weighing the benefits of fracture prevention and potential long-term side effects.

INTRODUCTION

A comprehensive management plan for osteoporosis should include assessment of fracture risk, interventions that reduce the risk for future fractures, and treatment of patients with acute fractures. Assessment of fracture risk is critical for making cost-effective treatment decisions in individual patients. A woman's lifetime risk for fracture is 40% and for hip fracture, 16%.¹

Low bone mass increases fracture risk; risk factors that are independent of bone mass also contribute to fracture risk, including older age and falls. This chapter focuses on the management of osteoporosis and covers guidelines for treatment; pretreatment evaluation, including exclusion of secondary causes of low bone mass; nonpharmacologic therapies, including exercise; fall prevention; calcium and vitamin D supplementation; drug therapies; emerging therapies; and treatment of fractures. Identification of subjects at risk for fracture based on bone mineral density (BMD) and clinical risk factors is discussed in Chapter 198.

RECOMMENDATIONS FOR TREATMENT

In February 2008 the World Health Organization (WHO) published FRAX, a fracture risk assessment tool (<http://www.shef.ac.uk/FRAX/>), and the National Osteoporosis Foundation (NOF) released new guidelines for the prevention and treatment of osteoporosis in the United States. Previous guidelines from the NOF and American Association of Clinical Endocrinologists were based on previous fracture, BMD T-score, and risk factors but were limited in that they addressed only postmenopausal women, not men; lacked weighting of risk factors; did not adequately account for the effect of age on risk for fracture; and expressed future fracture risk as increased relative, not absolute risk. Because at least 50% of all fractures occur in individuals who have low BMD but not osteoporosis, the addition of risk factors to BMD is a method for selecting higher-risk patients within this category who need treatment.

The 2008 NOF guidelines ("Clinician Guide to Prevention and Treatment of Osteoporosis," available at http://www.nof.org/professionals/Clinicians_Guide.htm) are based on the FRAX calculator, which expresses fracture risk as a 10-year probability of fracture and uses an economic analysis for cost-effective treatment thresholds.²

Treatment is recommended if the BMD T-score is less than -2.5 at the hip or lumbar spine, if the patient has had a hip or vertebral fracture, or if the T-score is between -1.0 and -2.5 at the hip or spine and the 10-year fracture risk by FRAX is 3% or higher for hip or 20% or higher for a major osteoporosis-related fracture (humerus, forearm, hip, or clinical vertebral fracture). The WHO FRAX tool allows individual assessment for ethnicity in the United States and in more than 40 country-specific databases and calculates fracture risk on the basis of gender, height, previous fragility fracture as an adult, parental history of hip fracture, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol use. The NOF guidelines and FRAX are applicable to previously untreated postmenopausal women and men older than 50 years (Fig. 201.1).

The FRAX model has limitations.³ Nonetheless, FRAX and the 2008 NOF treatment guidelines for osteoporosis offer a significant advance by providing health care personnel with treatment recommendations on the basis of BMD (or body mass index if BMD has not been measured) and clinical risk factors and by predicting absolute, not relative fracture risk.

EVALUATION FOR SECONDARY OSTEOPOROSIS

Management of a patient with osteoporosis requires attention to possible secondary causes. Many individuals with low bone mass have diseases (Table 201.1) or take medications that affect bone metabolism (Table 201.2). Switching medications to alternatives that do not adversely affect bone quality or providing preventive therapy should be considered. Laboratory investigation in patients with low bone mass is recommended since up to 50% have underlying disorders such as vitamin D deficiency or hypercalciuria. Routine laboratory tests to identify common causes of secondary osteoporosis include a complete blood count, sedimentation rate, chemistry profile, 25-hydroxyvitamin D, thyroid-stimulating hormone, parathyroid hormone (PTH), and 24-hour urine for measurement of calcium excretion (Box 201.1). Correction of the underlying cause may have a substantial impact on BMD and fracture risk and needs to be done before institution of any pharmacologic therapy.

TREATMENT: NONPHARMACOLOGIC THERAPY

This section focuses on evidence-based approaches or, in the absence of evidence, general consensus.

Patient and physician education

Education on risk for falls, exercise programs, dietary advice including adequate calcium and vitamin D intake, and other lifestyle modifications are an important first step for those at risk. Assessment of propensity for falls and modification of such risk factors through effective intervention when possible should be undertaken. Use of assistive devices and a multidisciplinary team approach for prevention of falls have been shown to be efficacious and should be considered for appropriate individuals. Such measures, coupled with careful observation and reassurance, may be all that is necessary for many individuals with low BMD who are thought to have low absolute risk for fracture and who do not have osteoporosis or a previous fracture.

Exercise

The molecular mechanisms that result in skeletal mechanotransduction are complex. Regular exercise increases bone strength by creating small gains in bone mass.⁴

Country: US (Caucasian)

Name / ID:

About the risk factors ⓘ

Weight Conversion

pound:

convert

Height Conversion

inch:

convert

Questionnaire:

1. Age (between 40-90 years) or date of birth

Age Date of birth Y: M: D:

2. Sex

☐ Male ☐ Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture

☐ No ☐ Yes

6. Parent fractured hip

☐ No ☐ Yes

7. Current smoking

☐ No ☐ Yes

8. Glucocorticoids

☐ No ☐ Yes

9. Rheumatoid arthritis

☐ No ☐ Yes

10. Secondary osteoporosis

☐ No ☐ Yes

11. Alcohol 3 or more units per day

☐ No ☐ Yes

12. Femoral neck BMD (g/cm²)

GE-Lunar

Select DXA

GE-Lunar

Hologic

Norland

T-Score

Calculate

Fig. 201.1 FRAX questionnaire.

TABLE 201.1
Secondary causes of low bone mass

Category	Specific examples
Inflammatory diseases	Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis
Malabsorption syndromes	Celiac disease Short bowel syndrome Cystic fibrosis
Endocrine diseases	Hypogonadism Hyperthyroidism (exogenous and endogenous)
Deficiency states	Vitamin D deficiency Malnutrition Excessive weight loss
Renal diseases	Renal insufficiency Renal osteodystrophy Renal tubular acidosis Idiopathic hypercalciuria
Bone marrow disorders	Multiple myeloma Thalassemia
Genetic diseases	Osteogenesis imperfecta Ehlers-Danlos syndrome Turner syndrome
Prolonged immobilization	Stroke Quadriplegia Space flight

TABLE 201.2
Medications known to cause or accelerate bone loss

Category	Name
Steroids	Glucocorticoids
Endocrine/hormonal therapies	Depo-Provera, GnRH analogues, LHRH analogues, excessive thyroid hormone replacement
Diuretics	Furosemide
Chemotherapy	Cyclosporine, methotrexate, tacrolimus
Transplant	Cyclosporine
Aromatase inhibitors	Exemestane, anastrozole
Seizure medications	Phenytoin, phenobarbital
Psychotropic	Lithium, neuroleptics
Other	Heparin

GnRH, gonadotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone.

BOX 201.1 RECOMMENDED LABORATORY INVESTIGATIONS FOR INDIVIDUALS WITH OSTEOPOROSIS

Recommended screening in all patients

Serum calcium, albumin, phosphorus*^{†,‡,§}
Serum creatinine*^{†,‡,§}
Liver function tests*
Bicarbonate*
Complete blood count*
24-Hour urinary calcium level*^{†,‡,§}
25-Hydroxyvitamin D level*^{†,‡,§}
Thyroid-stimulating hormone level*^{†,‡,§}

Other testing if appropriate

Biochemical markers of bone turnover*^{†,‡,§}
Cortisol levels*[†]
Protein electrophoresis*^{†,§}
Parathyroid hormone level*^{‡,§}

*American Association of Clinical Endocrinologists guidelines.

[†]National Osteoporosis Foundation Physician's Guide.

[‡]U.S. Surgeon General's report.

[§]American College of Obstetricians and Gynecologists.

Exercise in children, especially when combined with calcium intake, appears to be most effective before attainment of peak bone mass. Moderate, regular weight-bearing exercise is essential for skeletal health, both for direct effects on bone strength and for prevention of falls. Intensive regular weight-bearing exercise increases BMD, at least transiently, although the effect tends to wear off after cessation of such a regimen. Devices that deliver a specific mechanical stimulation (vibration plates) may also have a similar effect.⁵

Exercises to increase muscle strength result in better conditioning and balance, thereby helping reduce risk for falls. Although regular weight-bearing exercise has been shown to increase or preserve BMD in young and middle-aged individuals, exercise alone does not prevent postmenopausal bone loss. Combining exercise programs with calcium supplementation or other therapeutic interventions may be more effective in maintaining bone mass than either intervention alone.⁶

Smoking, alcohol, and caffeine

Smoking is directly toxic to bone cells, and population studies have shown that smokers have lower BMD, a greater annual rate of bone loss, and a higher prevalence of osteoporosis than nonsmokers do. Current smokers have been shown to have an increased risk for hip fracture relative to never smokers. Although limited data are available on the benefits of smoking cessation, discontinuation of tobacco use has resulted in favorable effects on bone metabolism in some small trials. The Nurses' Health Study found that fracture risk fell, but only after 10 or more years of abstinence from smoking.⁷

Although alcohol in moderation may have a positive effect on BMD, three or more drink equivalents per day should be discouraged given its association with an increased propensity for falls and risk for fracture. A meta-analysis demonstrated a J-shaped relationship between alcohol consumption and risk for hip fracture, with persons consuming less than one or more than two drinks per day having a higher risk for hip fracture.⁸

Excessive caffeine use has been associated with decreased intestinal calcium absorption and lower dietary calcium intake. Because caffeine may induce hypercalciuria and has been linked to an increased risk for fracture, moderation or cessation of intake is required in those at risk. However, all studies linking caffeine intake as a risk factor for osteoporosis have involved populations with suboptimal calcium intake.

Calcium and vitamin D

Recent studies have resulted in conflicting recommendations about the optimal intake of calcium and vitamin D. The Institute of Medicine (IOM) emphasized the limitations of the existing studies on the benefits and risks of calcium and vitamin D supplementation (see Chapter 203 for current IOM recommendations).⁹

A 2011 meta-analysis conducted for the U.S. Preventive Services Task Force demonstrated the complexity of the analyses, with the impact of

TABLE 201.3
Recommended supplementation of calcium and vitamin D

Individual age categories	Elemental calcium	Vitamin D*
Birth to 6 mo	400 mg	200 IU
6-12 mo	600 mg	200 IU
1-10 yr	800 mg	200 IU
11-24 yr	1200-1500 mg/day	400 IU
Women and men 25-65 yr: premenopausal or postmenopausal taking estrogen	1000 mg/day	400-600 IU
Postmenopausal woman, no estrogen	1500 mg/day	400-600 IU for men and women >65 yr
Pregnant and lactating women	1200-1500 mg/day	400 IU
National Osteoporosis Foundation guidelines	1200 mg	800-1000 IU

*These recommendations are guidelines and may be sufficient for healthy individuals with normal 25-hydroxyvitamin D levels. In many circumstances, however, they are insufficient.

supplementation on fracture risk being smaller in community dwellers and in institutionalized individuals.¹⁰

Current recommendations for supplementation of calcium and vitamin D are presented in Table 201.3; however, in some instances larger doses of vitamin D may be necessary. Assessment of vitamin D status by measuring serum 25-hydroxyvitamin D levels is required before initiation of pharmacologic therapy.¹¹

Serum 25-hydroxyvitamin D levels should be rechecked after about 8 to 12 weeks of replacement therapy.¹²

Adequate correction of vitamin D deficiency (normal vitamin D, alkaline phosphatase, PTH, and 24-hour urine calcium) should be undertaken before institution of pharmacologic therapy for osteoporosis. Striking gains in BMD may be seen within months in individuals in whom severe deficiency is corrected. Skeletal muscle also has receptors for vitamin D, and evidence suggests that elderly institutionalized subjects randomized to supplemental vitamin D significantly lower their risk for falls. In some situations such as renal osteodystrophy, more extensive evaluation and complex replacement therapy with calcium and vitamin D may be necessary (see Chapter 205).

Both calcium and vitamin D stabilize BMD, have favorable effects on biochemical markers of bone turnover, and reduce the risk for fracture. Chapuy and colleagues¹³ demonstrated in two large randomized, placebo-controlled trials that elderly institutionalized individuals with osteoporosis randomized to a combination of calcium and vitamin D supplementation significantly reduced their risk for vertebral, nonvertebral, and hip fractures.

Recent studies have questioned the true efficacy of this therapy in some populations; however, it is unclear whether adherence was adequate in these studies.¹⁴

A meta-analysis of the effect of oral vitamin D on prevention of nonvertebral fractures concluded that its efficacy for fractures is dose dependent, with higher doses reducing fractures by at least 20%.¹⁵

Prevention of falls

Almost a third of persons older than 70 years will sustain a fall each year, with higher numbers being reported in women, older individuals, and nursing home residents. Falls are a major source of morbidity and increased mortality, and about 5% result in a fracture. Nursing home residents are three times more likely to fall, in part because of their increased frailty, and they sustain a higher number of hip fractures and have a poorer prognosis after fracture than do community dwellers. In the Dubbo Osteoporosis Epidemiology Study, falling in the previous year was the factor that most highly correlated with risk for incident hip fracture in more than 1600 nonosteoporotic men and women observed for 15 years (hazard ratio [HR], 1.9 and 2.1, respectively).¹⁶

Most falls are predictable, with readily identifiable risk factors (Box 201.2). Studies have shown that risk for falls is related to a history of falls; use of medications or conditions that predispose to falls, including cognitive, visual, or auditory impairment; decreased muscle strength; increased body sway; and poor balance. Such conditions are more prevalent in older

BOX 201.2 FACTORS PREDISPOSING TO FALLS

Chronic conditions

Arthritis and other musculoskeletal disorders
Visual impairment
Hearing impairment
Proprioceptive impairment
Previous history of falls
Poor gait
Poor balance
Dementia or confusion

Acute conditions

Infection
Stroke/cardiovascular events
Medications—sedatives, psychotropics, and other drugs including alcohol
Postural hypotension
Stairs, restraints, lack of support rails
Poor lighting
Delirium
Wet floors or uneven surfaces

individuals, and the propensity to fall increases as the number of risk factors rises.^{17,18}

Thorough evaluation of the risk for falls and careful clinical assessment of medications and conditions that may contribute to such risk or bone loss can readily be performed in the office by a trained health care provider. Dissemination of evidence about fall prevention, along with interventions to affect clinical practice, may reduce fall-related injuries. Assessing all factors that influence the propensity for falls may be better accomplished with more comprehensive methods, and a multidisciplinary team approach can be effective.¹⁹

Controlled studies evaluating tai chi have shown that this particular type of exercise reduces falls and fear of falling and improves muscle strength and activity in elderly persons.²⁰

Hip pads and other assistive devices

Hip protectors have been shown to prevent hip fractures in compliant subjects at significant risk for falling.²¹ A study involving 18 nursing homes randomized patients to hard or soft hip protectors and showed a 60% reduction in hip fractures in patients using protectors.²² However, not all devices are the same and not all studies show an effect. Although compliance is poor and the effectiveness remains unclear, high-risk individuals who wear hip pads may reduce their risk for proximal femoral fracture. Given the benign nature of this intervention, it is worth considering in elderly osteoporotic patients at increased risk for falls.

PHARMACOLOGIC INTERVENTIONS

Hormone replacement therapy

The major cause of postmenopausal osteoporosis is estrogen deficiency. With declining levels of estrogen in postmenopausal women, bone turnover increases, the rate of bone resorption exceeds the rate of bone formation, and bone density decreases.²³

A meta-analysis of 57 randomized placebo-controlled trials reported significantly increased bone density in patients receiving hormone therapy.²⁴

Estrogen therapy decreased the risk for hip fractures by 25% to 30% and the risk for vertebral fractures by approximately 50% in observational studies.²⁵

In the Women's Health Initiative (WHI) trial in which women unselected for osteoporosis were randomized to treatment with estrogen plus progestone or placebo, the incidence of all fractures decreased by 24% and hip fractures were reduced by 33% when compared with placebo.²⁶

In the WHI trial of unopposed estrogen in postmenopausal women with a previous hysterectomy unselected for osteoporosis, the women receiving unopposed estrogen demonstrated a reduction in the risk for hip fracture by 39% and risk for vertebral fracture by 38%. The reduction in fracture risk associated with hormone therapy diminishes after it is stopped. In the National Osteoporosis Risk Assessment observational cohort, women who used hormone therapy for 5 to 10 years after menopause and then

discontinued its use had no greater bone density at the heel or radius at the age of 70 than did women who never used hormone therapy.²⁷

Worldwide patterns of estrogen use have changed radically since publication of results from the WHI raised concern regarding increased risk for cardiovascular disease, stroke, pulmonary embolism, and breast cancer with estrogen.²⁸

Several randomized controlled trials (RCTs) have documented additional risks associated with hormone therapy, including stroke and venous thromboembolism and possibly gallbladder disease.²⁹⁻³¹

The effect of hormone therapy on risk for cardiovascular disease is currently controversial because the differences observed in the results of previous randomized trials may be related to the type of progestin used in the trials.³²

Additional studies on cognitive dysfunction, ovarian cancer, and other conditions have yielded inconsistent results. A recent statement on menopausal hormone therapy for the U.S. Preventive Services Task Force recommended against the use of combined estrogen and progesterone for prevention of chronic health conditions in postmenopausal women who have undergone hysterectomy.³³

Estrogen agonist-antagonists

Although estrogen therapy has been demonstrated to increase BMD and decrease fracture risk, recognition of the risks and toxicities of estrogen therapy has directed research on compounds that can selectively act as either agonists or antagonists on various estrogen target tissues. Estrogen agonist-antagonists are compounds that possess tissue specificity and bind to estrogen receptors. These agents represent a group of compounds that can inhibit bone resorption through mechanisms similar to estrogens without stimulating other tissues such as breast or uterine tissue.³⁴ The mechanisms for these differential effects on estrogen receptors that result in tissue specificity can be explained by differential gene expression in a given target tissue, differential estrogen-receptor conformation on ligand binding, and differential expression and binding of coregulator proteins to the estrogen receptor.

Several agents such as clomiphene and tamoxifen were developed for the treatment of nonskeletal conditions. Tamoxifen, for example, is currently used for the treatment and prevention of breast cancer and acts as an estrogen receptor antagonist in breast tissue, but it was recognized to possess estrogen agonist effects on the endometrium and weak estrogen agonist activity in bone, although the increases in bone density in patients treated with tamoxifen are minimal (Table 201.4) and the effects on fracture risk are variable.³⁵⁻⁴³

Raloxifene was specifically developed to have antiresorptive effects on bone in postmenopausal women. A reduction in risk for vertebral fractures was demonstrated in the Multiple Outcomes of Raloxifene Evaluation (MORE) study. In this study, raloxifene was shown to decrease markers of bone turnover and increase bone density at several skeletal sites, including the spine and femoral neck. The incidence of vertebral fracture decreased

by 30% in subjects with a prevalent fracture and by 55% in subjects without a prevalent fracture. However, the incidence of nonvertebral fractures, including hip fracture, did not differ significantly between the treatment and placebo groups. A *post-hoc* analysis from MORE show a decreased risk for nonvertebral fracture at 3 years only in subjects with severe vertebral fractures (semiquantitative grade 3) at baseline.⁴⁴

The women receiving raloxifene had a higher risk for venous thromboembolism, leg cramps, and hot flashes than did those given placebo. Of interest, women in the treatment group exhibited a lower incidence of invasive breast cancer (relative risk, .4; $P < .001$).⁴⁵

The Continuing Outcomes Relevant to Evista (CORE) trial assessed the effects of raloxifene on breast cancer for 4 additional years beyond the original 4-year MORE trial. After 8 years of follow-up, the risk for invasive breast cancer was reduced by 66% in women treated with raloxifene. The incidence of nonvertebral fractures was similar in the placebo and raloxifene groups.⁴⁶

Raloxifene is approved for reduction in risk for invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.⁴⁷ Comprehensive reviews of the use of raloxifene for prevention of breast cancer and clinical efficacy and safety have been published.^{48,49}

The third-generation estrogen agonist-antagonists lasofoxifene and bazedoxifene are approved in the European Union but not in the United States for the treatment of osteoporosis in women at increased risk for fracture.⁵⁰ A 5-year trial of lasofoxifene demonstrated a 31% and 42% reduction in vertebral fractures (dose, 0.25 and 0.5 mg). The 0.5-mg dose also reduced the risk for nonvertebral fractures at 5 years ($P = .002$).⁵¹

A 3-year trial of bazedoxifene 20 or 40 mg, raloxifene 60 mg, or placebo showed a 42% reduction in new vertebral fractures with bazedoxifene 20 mg and raloxifene. The treatment effect of both drugs was similar in subjects with or without prevalent fractures. A *post-hoc* analysis in women with a femoral neck T-score of -3.0 or lower and moderate or severe vertebral fractures found a lower incidence of nonvertebral fractures with bazedoxifene than with raloxifene or placebo (44% and 50% reduction, $P = .05$ and $.02$, respectively).⁵²

Calcitonin

Calcitonin, a naturally occurring 32-amino acid polypeptide hormone produced by parafollicular "C" cells of the thyroid, pituitary, and neuroendocrine system, is secreted in response to high plasma ionized calcium levels. Salmon calcitonin, administered parenterally or as a nasal spray, is used as treatment of postmenopausal osteoporosis, as well as Paget disease of bone and hypercalcemia. It is an antiresorptive agent that inhibits bone resorption by binding to receptors on osteoclasts. A number of studies suggest that it is effective for spinal osteoporosis by maintaining or slightly increasing BMD, and one study showed that intranasal calcitonin at a dose of 200 IU/day reduced incident vertebral fractures in women with prevalent vertebral fractures.⁵³

TABLE 201.4
Randomized controlled trials of estrogen agonist-antagonists and bone density

Trial	Study subjects	Duration (mo)	Change in bone density as compared with placebo group (%)		
			Total-body bone mineral	Lumbar spine	Proximal femur
Tamoxifen (20-30 mg/day)					
Love et al. ³⁵	140 postmenopausal women with breast cancer	24	—	1.6*	—
Grey et al. ³⁶	57 normal late postmenopausal women	24	0.5†	2.1†	0.6
Powles et al. ³⁷	179 healthy women in chemoprevention trial for breast cancer				
	54 postmenopausal women	36	—	4.7*	3.6†
	125 premenopausal women	36	—	−2.6*	−4.3†
Raloxifene (60 mg/day)					
Delmas et al. ³⁸	302 normal postmenopausal women	24	2.0*	2.4*	2.4*
Lufkin et al. ³⁹	143 postmenopausal women with osteoporosis and vertebral fractures	12	−0.1	1.8†	1.0†
Ettinger et al. ^{40,41}	5140 postmenopausal women with osteoporosis	36	—	2.6*	2.1*
Johnston et al. ^{42,43}	576 health early postmenopausal women	36	1.7*	2.6*	2.5*

* $P < .05$ for comparison with placebo.

† $P < .005$ for comparison with placebo.

Calcitonin may have analgesic effects on bone pain in patients with osteoporosis, which has been noted in clinical trials and has led to a reduction in conventional analgesia and a decrease in disability.⁵⁴

Bisphosphonates

Bisphosphonates are the pharmacologic agents most commonly used for the treatment of osteoporosis. Both oral and intravenous preparations of bisphosphonates are currently approved by the Food and Drug Administration for the prevention and treatment of osteoporosis. Their efficacy is based on their ability to both bind avidly to bone and inhibit osteoclast function. The relative potency of the different bisphosphonates is a function of differences in side chain structure among the compounds.⁵⁵

Bisphosphonates are stable synthetic analogues of pyrophosphate (Fig. 201.2). Their primary effect is to suppress osteoclast-mediated bone resorption. They bind avidly to bone, a property that is primarily related to the R1 side chain (Table 201.5) (an OH group for nitrogen-containing bisphosphonates), which functions as a “bone hook.” The R2 side chain determines the compound’s potency as an antiresorptive agent and contains the nitrogen group common to all potent bisphosphonate compounds. The nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronate) interfere with the mevalonate pathway by inhibiting the enzyme farnesyl pyrophosphate (Fig. 201.3). This prevents protein prenylation, or attachment of a lipid anchor in the membrane, which inhibits osteoclast recruitment, differentiation, formation of the ruffled border, and acid production and induces apoptosis.

Suppression of osteoclasts decreases bone turnover, thereby reducing the number and activity of bone-remodeling units (BMUs). Bone remodeling sites are a source of trabecular perforations, as well as microcracks and stress risers, weak areas that can propagate in bone and result in increased fragility and fractures. The decrease in bone resorption with bisphosphonate therapy occurs within 1 month. Because of the coupling of formation and resorption, inhibition of resorption results in a decrease in bone formation. Inhibition of resorption before formation allows the “remodeling space,” or the cavities created by BMUs, to fill, which increases bone mass. The increase in bone mass created by this uncoupling of bone resorption and formation results in a brisk rise in BMD in the first 1 to 2 years of therapy. Subsequent increases in BMD occur at a slower rate, approximately 0.8% per year through 10 years for alendronate, and are the consequence of an increase in matrix mineralization, a result of the decrease in turnover that allows

more complete secondary mineralization of bone, as well as a decrease in cortical porosity.

It is estimated that approximately 25% of the observed reduction in fracture risk is related to increases in BMD. Other factors that may be important include decreased bone turnover, altered microarchitecture, changes in mineralization, and other cellular effects.

Pharmacologic properties

Orally administered bisphosphonates are poorly absorbed, with less than 0.7% of the administered dose being absorbed into the bloodstream. Food and liquids (except plain water) inhibit bisphosphonate absorption within the first 120 minutes after dosing. Absorption of alendronate is 40% to 50% less when food is consumed 30 to 60 minutes after a dose than when it is consumed 120 minutes after dosing. A meal 2 hours before dosing also results in poor absorption, so it is recommended that these agents be taken after an overnight fast with no food or liquid other than water for a minimum of 30 minutes. For alendronate, approximately 50% of the dose is retained in the skeleton and the remainder is excreted unchanged in urine. Patients with impaired renal function and creatinine clearance lower 30 mL/min retain a greater amount of the dose in the skeleton. This could reduce turnover to a degree that would impair the ability to repair microdamage. Analysis of risedronate in patients with various degrees of renal impairment concluded that no adjustment in dose was needed with a creatinine clearance higher than 30 mL/min.⁵⁶

Similar data for other orally administered nitrogen-containing bisphosphonates, including alendronate and ibandronate, are reviewed in Chapter 205. Intravenous zoledronic acid is contraindicated in patients with a creatinine clearance lower than 35 mL/min.

After 3 months of oral bisphosphonate therapy, bone turnover is reduced to the middle to lower range of normal premenopausal turnover. With continued treatment and incorporation into the skeleton, no further reduction in turnover occurs, thus suggesting that the accumulated drug is buried in bone and becomes inactive. In the vast majority of patients, bone turnover is not reduced to such a level that accumulation of microdamage occurs, which might increase risk for fractures. Histomorphometric data sometimes show marked inhibition of skeletal turnover with these drugs, but biopsy data in a small number of patients treated for up to 10 years with alendronate and 5 years with risedronate are available and do not show significant

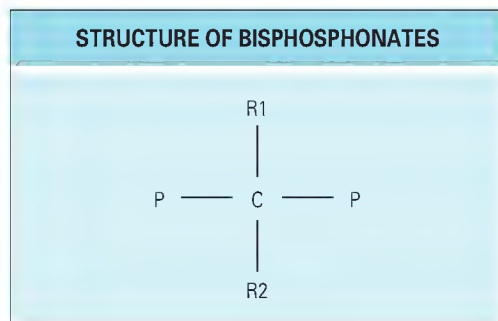


Fig. 201.2 Structure of bisphosphonates.

TABLE 201.5
Chemical formula for bisphosphonates

Bisphosphonate	R1	R2
Non-nitrogen containing		
Etidronate	OH	CH
Clodronate	Cl	Cl
Tiludronate	H	SC ₆ H ₅ Cl
Nitrogen containing		
Pamidronate	OH	CH ₂ CH ₂ NH ₂
Alendronate	OH	CH ₂ CH ₂ CH ₂ NH ₂
Risedronate	OH	CH ₂₃ -PYRIDINYL
Zoledronate	OH	CH ₂ C ₃ N ₂ H ₃
Ibandronate	OH	(CH ₂) ₂ N(CH ₃)(CH ₂) ₅

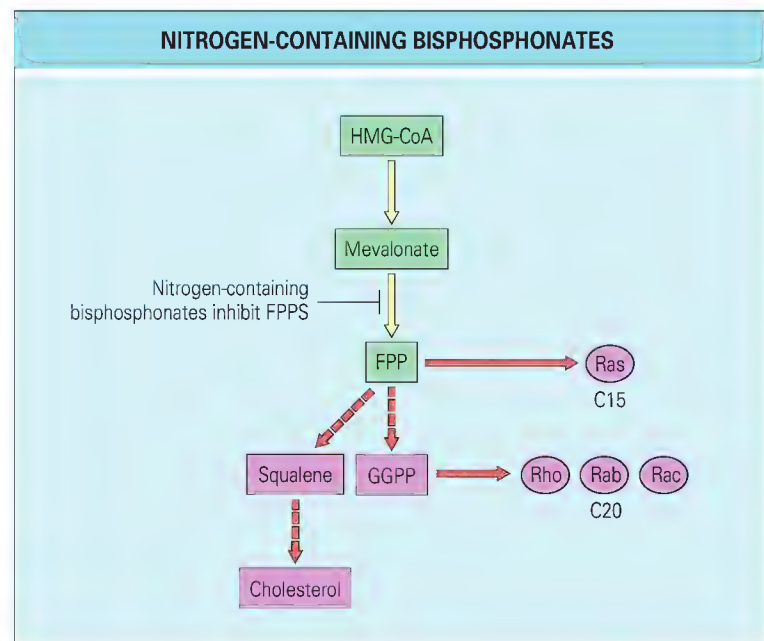


Fig. 201.3 Nitrogen-containing bisphosphonates such as risedronate sodium, zoledronic acid, disodium pamidronate, alendronic acid, and ibandronic acid work predominantly by inhibiting the enzyme FPPS, which catalyzes a step in the mevalonate pathway and inhibits protein prenylation. Protein prenylation involves the transfer of a farnesyl or geranylgeranyl isoprenoid lipid group onto the C-terminus of small GTPases. GTPases are critical for osteoclast proliferation, apoptosis, membrane ruffling, and membrane trafficking. Loss of these prenylated proteins in cell membranes results in loss of osteoclast function. FPP, farnesyl pyrophosphate; FPPS, farnesyl pyrophosphate synthase; GGPP, geranylgeranyl diphosphate; GTPase, guanine triphosphatase; HMG-CoA, hydroxyl-3-methylglutaryl coenzyme A.

TABLE 201.6
Bisphosphonate pivotal trials

Bisphosphonate	Trial	No. patients	Previous fracture	Duration	Fracture reduction
Vertebral fractures					
Alendronate	FIT-VFA	2027	Y	3 yr	47%
	FIT-CFA	4432	N	4 yr	44%
Risedronate	VERT-NA	1628	Y	3 yr	41%
	VERT-MN	814	Y	3 yr	49%
Etidronate		423	Y	2 yr	56%
Ibandronate	MN, NA	2946	Y	3 yr	62%, 50%*
Zoledronate	Horizon	7765	Y/N	3 yr	70%
Zoledronate	RFT	2127	Y/N	3 yr	46%
Hip fractures					
Alendronate	FIT-VFA	2027	Y	3 yr	51%
	FIT-CFA	4432	N	4 yr	56%†
Risedronate	HIP	9331		3 yr	30%‡
		5455		3 yr	40%§
		1128		3 yr	60%
		3886		3 yr	20%¶
Zoledronate	Horizon	7765		3 yr	41%

*Combined multinational, North American, daily and intermittent dosing.

†Post-hoc analysis hip T-score lower than -2.5.

‡Intention-to-treat analysis.

§Age 70 to 79 years, hip T-score lower than -2.5.

||Post-hoc analysis with vertebral fracture.

¶Older than 80 years with risk factors.

FIT-CFA, Fracture Intervention Trial, Clinical Fracture Arm; FIT-VFA, Fracture Intervention Trial, Vertebral Fracture Arm; HIP, Hip Intervention Program; RFT, Recurrent-Fracture Trial; VERT-MN, Vertebral Efficacy with Risedronate Therapy, Multinational; VERT-NA, Vertebral Efficacy with Risedronate Therapy, North America.

accumulation of microdamage. Bone biopsy specimens from alendronate-treated patients versus placebo-treated patients demonstrate decreased cortical porosity (7.5% with placebo and 4% with alendronate) and increased uniformity of mineralization with a slight increase in mineral per unit volume.⁵⁷

Because the cortical shell provides most of the bending strength of bone, this observed reduction in porosity could account for a portion of the anti-fracture efficacy of alendronate.

Clinical trials

Clinical trial experience with bisphosphonates is summarized in Table 201.6. Bisphosphonates decrease fracture risk in patients at high risk for fracture, including those with prevalent vertebral fractures or osteoporosis.

Etidronate

Etidronate is the oldest bisphosphonate in use and is approved for the treatment of postmenopausal osteoporosis in numerous countries, though not in the United States. Trials have demonstrated a reduction in the incidence of vertebral fractures in high-risk populations.⁵⁸ The weight of the evidence supports its efficacy in reducing vertebral fractures in patients with osteoporosis; a meta-analysis reported a 37% reduction in vertebral fractures.⁵⁹

Etidronate is given at a dose of 400 mg/day for 14 days every 3 months instead of continuously to avoid a mineralization defect. It has not been shown to reduce the incidence of nonvertebral fractures, including hip fractures.

Alendronate

Alendronate was approved for the prevention and treatment of osteoporosis in the United States in 1995. It was shown to increase BMD in a dose-dependent fashion in postmenopausal women without osteoporosis. Current practice is to use weekly doses of 35 or 70 mg for prevention and treatment, respectively, which were shown to result in increases in BMD equivalent to 5 or 10 mg/day. In postmenopausal women with low BMD (femoral neck T-score of -1.6 and below) and prevalent vertebral fractures (Fracture Intervention Trial, Vertebral Fracture Arm [FIT 1]) treated for 3 years, alendronate significantly reduced vertebral, hip, and wrist fractures by approximately 50% and multiple vertebral fractures by 89%.^{60,61}

In women without vertebral fractures but with low BMD treated for 4 years (FIT Clinical Fracture Arm [FIT 2]), a 44% reduction in vertebral fractures was noted ($P = .001$).⁶²

A preplanned, *post-hoc* analysis of patients with either prevalent vertebral fractures or a femoral neck BMD T-score of -2.5 or below showed a significant 36% reduction in clinical osteoporotic fractures and a 50% reduction in risk for hip fractures.⁶³

Rapid onset of fracture reduction was demonstrated in the Fosamax International Trial (FOSIT). Patients with a T-score lower than -2.0 had a significant 47% reduction in clinical nonvertebral fractures by 12 months and, in *post-hoc* analysis, a significant reduction in clinical vertebral fractures at 12 months in women with a previous vertebral fracture or femoral neck T-score lower than -2.5.⁶⁴

In a meta-analysis of several alendronate trials, clinical vertebral fractures were reduced at 1 year and hip fractures by 18 months. Treatment with alendronate for 7 years resulted in a continuous increase in bone mass during the 7 years; however, the effect on fractures beyond 3 years could not be assessed because of the lack of a placebo control group beyond that interval.

FLEX (FIT long-term extension trial) enrolled 1099 women treated with alendronate for an average of 5 years into a 5-year placebo-controlled extension. In patients treated for 5 years, BMD in the spine was stable, whereas hip BMD declined for up to 5 years after discontinuation of alendronate. No difference in hip, nonvertebral, or morphometric vertebral fractures was seen in patients taking alendronate for 5 years versus those taking it for 10 years; however, clinical vertebral fractures decreased in those who remained taking alendronate for a total of 10 years.^{65,66}

In men treated for 2 years with 10 mg of alendronate, bone mass increased in both the spine and hip, and a significant reduction in new vertebral fractures was demonstrated.⁶⁷

Risedronate

Risedronate was approved for the prevention and treatment of osteoporosis in the United States in 2000. In the pivotal placebo-controlled clinical trials in postmenopausal women with previous vertebral fractures treated with 5 mg/day for 3 years, incident vertebral fractures were reduced by 41% and 49% and nonvertebral fractures were reduced by 33% ($P = .06$) and 39% ($P = .02$), respectively, in the North American and multinational studies (Vertebral Efficacy with Risedronate Therapy [VERT]-NA and VERT-MN).^{68,69}

In an extension of the VERT-MN trial in which patients (with a placebo control) were monitored for an additional 2 years (5 years total), a 50% reduction in vertebral fractures in years 3 to 5 was demonstrated.⁷⁰ A further 2-year extension without a placebo group showed an 11.5% increase in BMD over the 7-year period.

An RCT with hip fracture as a primary endpoint showed a significant 30% reduction in hip fractures.⁷¹ In those aged 70 to 79 with osteoporosis, a significant 40% reduction was seen, whereas in those older than 80 who were enrolled primarily on the basis of risk factors for falling (not BMD), a nonsignificant 20% reduction in hip fractures was seen. A 1-year observational study in which men were randomized to risedronate or alfacalcidol showed that risedronate reduced new vertebral fractures by 60% relative to alfacalcidol.

Ibandronate

The BONE (Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe) trial assessed the effect of 2.5 mg oral ibandronate (and 20 mg every other day for 12 doses every 3 months). After 3 years, new morphometric vertebral fractures were significantly reduced by 62% in the group receiving 2.5 mg/day. Clinical vertebral fractures were also significantly reduced; however, nonvertebral fractures, including hip fractures, were not reduced in comparison to placebo.⁷²

Ibandronate is approved for postmenopausal osteoporosis orally in doses of 2.5 mg/day and 150 mg/mo on the basis of a bridging study in which it was shown that the 150-mg dose increased bone density in the lumbar spine and total hip significantly more than 2.5 mg daily did. The Dosing Intravenous Administration (DIVA) trial compared ibandronate 2 mg given every 2 months, 3 mg every 3 months, and 2.5 mg/day for 1 year. Increases in lumbar spine BMD were significantly greater with the intravenous doses than with the oral dose.⁷³

The doses used in the clinic were either 150 mg orally per month or 3 mg intravenously every 3 months.

Zoledronate

Intravenous zoledronic acid was approved in 2007 for (1) treatment of postmenopausal osteoporosis, (2) treatment and prevention of glucocorticoid-induced osteoporosis in patients expected to be taking glucocorticoids for

at least 12 months, (3) men with osteoporosis to increase bone mass in a once-yearly dosing regimen, and (4) treatment of osteopenia in a biannual dosing regimen.

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT), women taking zoledronate had a significantly lower rate of new morphometric vertebral fractures (relative risk reduction [RRR], 70%), nonvertebral fractures (RRR, 25%), and hip fractures (RRR, 41%), along with a 6.7% increase in lumbar bone density over a 3-year period.⁷⁴

In the first RCT that examined the post-hip fracture population, the HORIZON Recurrent-Fracture Trial (HORIZON-RFT), patients treated with zoledronic acid once yearly had a significantly reduced risk for new clinical vertebral fracture (RRR, 46%) and any clinical fracture (RRR, 35%). In addition, all-cause mortality was reduced by 28% in this post-hip fracture population.⁷⁵

No impairment in fracture healing occurred when zoledronic acid was administered within 90 days of hip fracture. A *post-hoc* analysis divided treatment timing into 2-week intervals (calculated from surgical repair to the first infusion); patients who received the infusion in the first 2 weeks did not show a significant reduction in fractures or mortality. Combined results of the HORIZON-PFT and HORIZON-RFT showed that zoledronic acid reduced the risk for all clinical fractures by 12 months (HR, 0.75), with reductions at years 2 and 3 being greater than those at year 1.^{76,77}

It is unclear whether dosing at less frequent intervals would be as efficacious as once-yearly dosing. The HORIZON-PFT extension trial randomized women who received 3 yearly doses of zoledronic acid to receive either 3 additional yearly doses or 3 years of placebo. Femoral neck BMD declined only 1.04% after 3 years with placebo, whereas biochemical markers of bone turnover rose only slightly but were still substantially lower than before treatment. The incidence of morphometric vertebral fractures was lower in women treated with 6 years versus 3 years of zoledronic acid. No significant differences were seen in nonvertebral, clinical vertebral, hip, or all clinical fractures. The study suggests that some patients may discontinue treatment after 3 years for up to 3 years; however, since patients did have an increase in morphometric fractures, those at highest risk for future vertebral fractures may benefit from continued therapy.⁷⁸

Almost 20% of subjects who received intravenous zoledronate experienced an acute-phase reaction characterized by low-grade fever, myalgia, headache, arthralgia, bone pain, and nausea, with symptoms generally resolving within 3 days of dosing but possibly lasting up to 7 to 14 days. An acute-phase reaction is more likely to occur in patients who have not previously been exposed to bisphosphonates and is less likely to recur with subsequent dosing.⁷⁹

Zoledronic acid should be considered in patients who are not candidates for oral bisphosphonates, such as those with esophageal strictures or swallowing dysfunction, those who are unable to remain upright, or those in whom oral bisphosphonate therapy has failed. Vitamin D should be replenished before the zoledronate infusion, and patients should be monitored for hypocalcemia. Both serum creatinine and calcium should be measured before each infusion; use of the drug is contraindicated in patients with a creatinine clearance lower than 35 mL/min.

Denosumab

A critical breakthrough in the understanding of bone remodeling came with unraveling of the essential pathways and critical interactions occurring at the cellular level. Receptor activator for nuclear factor- κ B ligand (RANKL), a member of the tumor necrosis factor (TNF) family, is an important mediator of bone remodeling and is expressed by a number of cell types, including osteoblasts, synovial fibroblasts, and activated T cells. RANKL binds to RANK, a receptor on osteoclast membranes, and induces differentiation, activation, and survival of osteoclasts. A regulator of the RANK-RANKL interaction is the soluble cytokine osteoprotegerin (OPG). OPG is a naturally occurring member of the TNF receptor family that functions as a decoy receptor by competing for binding to RANK (Fig. 201.4). Failure of RANKL to bind to RANK results in apoptosis of osteoclast precursors. Murine models with genetic alterations in their RANKL gene or OPG-deficient mice have severe osteoporosis, which can be prevented or reversed by administration of OPG. Excessive OPG can result in an osteopetrotic phenotype.

Denosumab, a fully human monoclonal IgG2 antibody that binds selectively and with high affinity to RANKL and mimics the effect of OPG on RANKL, was approved for use in the United States in 2010. The pivotal phase 3 trial randomized postmenopausal women with osteoporosis to receive subcutaneous denosumab 60 mg every 6 months or placebo.⁸⁰

Subjects treated with denosumab demonstrated a significant 68% reduction in spine fractures, 40% reduction in hip fractures, and 20% reduction

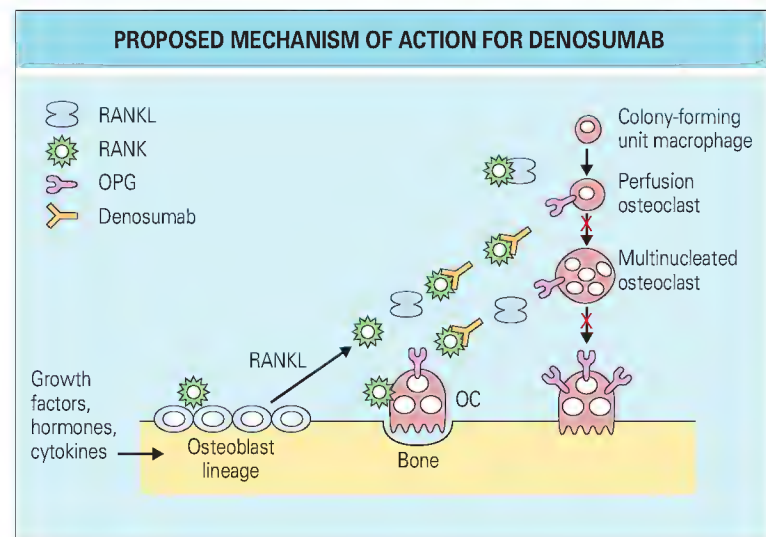


Fig. 201.4 Denosumab is a fully human monoclonal antibody that binds with high affinity to and inhibits the activity of human RANKL, a key mediator of osteoclast activity. RANKL is an essential mediator of the formation, activation, and survival of osteoclasts. OC, osteoclast; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor- κ B; RANKL, RANK ligand.

in nonvertebral fractures. The pharmacodynamics of denosumab differs from that of the bisphosphonates; bone turnover markers decline rapidly, as soon as 12 hours, after an injection and exhibit more rapid recovery after discontinuation. The drug does not accumulate in bone, in contrast to the bisphosphonates. Several of the trials of denosumab reported numeric increases in infections and malignancies. Bone biopsy data revealed an absence of tetracycline labeling in 30% of tested subjects (www.fda.gov).

Side effects of antiresorptive agents

Shortly after the release of alendronate, numerous reports of severe gastrointestinal (GI) side effects were published, primarily esophageal erosions and stricture. RCTs, however, suggest little or no increase in risk for upper GI tract problems if oral bisphosphonates are administered properly. Patients with esophageal motility disorders are at greater risk for toxicity. Rechallenge placebo-controlled studies with both alendronate and risendronate have shown no difference in the occurrence of GI symptoms. With the highest level of evidence, generic alendronate became available in the United States in 2008. A study that compared gains in bone density at 1 year with branded versus generic alendronate showed that gains in lumbar spine BMD were 40% to 50% less, GI adverse events were greater, and persistence was lower with generic than with branded alendronate.

Administration of intravenous bisphosphonates is associated with an influenza-like illness characterized by fever, myalgia, arthralgia, and nausea for 24 to 48 hours after the infusion. Rapid infusion of zoledronic acid has been reported to cause renal failure. Some patients may suffer severe bone pain with bisphosphonates that may be related to the small decrease in serum calcium and subsequent rise in PTH values. Osteonecrosis of the jaw (ONJ) with bisphosphonates was first reported in 2003, initially in cancer patients treated with high doses of intravenous bisphosphonates. No definition of ONJ is universally accepted, but it usually appears as an area of exposed alveolar bone in the mandible or maxilla that does not heal within 8 weeks. A systematic review in 2006 revealed 368 reported cases of ONJ (many cases are not reported); 94% occurred with intravenous bisphosphonates, usually in patients with multiple myeloma or metastatic cancer.⁸¹

About 65% were in the mandible, a third were painless, 60% occurred after a tooth extraction or other surgery, and the rest developed spontaneously. Although the incidence of ONJ with oral bisphosphonates is much less, by mid-2006, approximately 30 cases had been reported in patients receiving oral bisphosphonates. The American Society for Bone and Mineral Research (ASBMR) task force identified 57 cases of ONJ in patients treated with bisphosphonates for osteoporosis and 7 cases in patients who had Paget disease. Risk for ONJ in patients without cancer is estimated to be less than 1 in 100,000.⁸²

A Canadian consensus practice guideline for patients treated for osteoporosis did not recommend dental examination before therapy in those who maintained good oral hygiene, stopped smoking, and had limited alcohol intake.⁸³

No published data support the recommendation that bisphosphonate therapy be discontinued once ONJ develops, but most patients are likely to stop therapy for at least several months.⁸⁴

"Atypical" subtrochanteric fractures of the femur have been associated with long-term bisphosphonate use.^{85,86} Review of radiographs is required since these fractures have a characteristic appearance in that they are transverse or short oblique with a thickened cortex and have a periosteal elevation or beak on the lateral cortex. The ASBMR task force has published a report on this topic.⁸⁷

Parathyroid hormone

Anabolic therapy with teriparatide (recombinant human PTH [rhPTH] 1-34) has been available in the United States since 2002 and is also available in the European Union, as is the full-length rhPTH 1-84. Subjects in the pivotal trial with the full 84-amino acid rhPTH molecule had a higher than expected incidence of hypercalcemia, and the trial program was discontinued in the United States.

Teriparatide was evaluated in an RCT of postmenopausal women with at least one moderate or two mild previous vertebral fractures and a T-score in the hip or spine lower than -1.0 .⁸⁸ Subjects were randomized to 20 or 40 μg daily of rhPTH 1-34 or placebo. Treatment averaged 19 months in the three groups. When compared with placebo, BMD significantly increased by 9.7% and 13.7% in the lumbar spine and by 2.8% and 5.1% in the femoral neck in the 20- and 40- μg groups. The incidence of vertebral fractures was reduced by 65%, and the risk for two or more fractures was decreased by 77% with the 20- μg dose. The incidence of moderate and severe vertebral fractures was reduced by 90%.⁸⁹ Women in the 20- μg treatment group were 35% (all nonvertebral) and 53% (traumatic nonvertebral) less likely to have one or more new nonvertebral fractures. Reanalysis of the original radiographs via quantitative morphometric methodology showed an 84% reduction in vertebral fractures and a 94% reduction in multiple fractures.⁹⁰

In an 11-month RCT in men with osteoporosis, patients were randomized to placebo or treatment with 20 or 40 $\mu\text{g}/\text{day}$ of rhPTH 1-34; the relative risk for new vertebral fractures was 0.5 for the combined 20- and 40- μg PTH-treated group.⁹¹

Teriparatide is indicated for postmenopausal women and men at high risk for fracture. Although the indications give general guidelines for patient selection, they leave the physician with a large amount of discretion and many questions about which patients are most appropriate. Patients with one or more of the following characteristics are appropriate for teriparatide therapy:

- Those who have a significant decline in BMD during antiresorptive therapy
- Those who are unable to take antiresorptive agents because of side effects
- Those who sustain a fracture during antiresorptive therapy
- Patients who are treatment naive and at high risk for fracture

Few data directly comparing bisphosphonates with teriparatide in women with postmenopausal osteoporosis are available; none of the studies report fracture outcomes. McClung and colleagues⁹² compared the BMD response to teriparatide 20 μg and alendronate 10 mg daily. At 18 months, areal BMD increased 10.3% in the teriparatide group and 5.5% in the alendronate group. Volumetric density (quantitative computed tomography [QCT]) increased 19% in the teriparatide group and 3.8% in the alendronate group. Finite element analysis of QCT scans of the L3 vertebral body showed a significantly greater increase in compressive strength at 18 months in patients treated with teriparatide (21.1% vs. 3.7%).⁹³

The effect of simultaneous use of PTH 1-84 and alendronate was examined in the PaTH trial.^{94,95} BMD in the spine increased 6.3% in the PTH group, 6.1% in the combination group, and 4.6% in the alendronate group. Volumetric density (QCT) increased 25.5% in the PTH group, 10.5% in the alendronate group, and 12.9% in the combination group. The authors concluded that there is no evidence of synergy between PTH and alendronate and that concurrent use of alendronate may reduce the anabolic effect of PTH. No data are available on the most important outcome, fracture reduction.

Teriparatide (rhPTH 1-34) plus raloxifene versus teriparatide alone has been evaluated and showed that raloxifene did not inhibit the anabolic effect of teriparatide on the basis of bone density or markers of bone turnover.⁹⁶

Several trials have examined the use of sequential PTH followed by alendronate. In the PaTH trial, PTH for 1 year followed by alendronate for 1 year increased volumetric BMD by 31% (QCT) as compared with 14% in PTH-placebo patients. Treatment with an antiresorptive agent is required to maintain the gains in bone mass with PTH.

The effect of previous treatment with an antiresorptive agent on response to PTH was evaluated by Ettinger and colleagues⁴⁰ in an open-label, non-randomized study comparing the effects of teriparatide following 18 to 36 months of therapy with either raloxifene or alendronate in postmenopausal women with a T-score of -2.0 or lower. After 18 months, patients previously treated with raloxifene had a greater increase in lumbar spine BMD in response to teriparatide than did patients previously treated with alendronate (10.2% vs. 4.1%, respectively). These findings suggest that blunting of the anabolic effect of teriparatide may occur not only with concomitant therapy as illustrated in the PaTH trial but also with sequential therapy in which teriparatide is administered after alendronate. It did not appear that raloxifene blunted the BMD response to teriparatide. No data on fracture reduction are available from this study.

The OPTAMISE study examined the effect of previous risedronate or alendronate on response to PTH and showed that previous alendronate therapy blunted both the bone density and bone marker response to PTH significantly more than previous risedronate therapy did.⁹⁷ After 12 months of therapy with teriparatide, subjects who previously received risedronate showed a 76% significantly greater increase in the density of trabecular bone at the spine as measured by QCT than did those who previously received alendronate (24% vs. 13.7%).

A prospective randomized, double-blind, placebo-controlled trial compared the BMD response to teriparatide in postmenopausal women with osteoporosis who previously received a bisphosphonate versus those who were bisphosphonate naive. After 24 months of treatment with teriparatide, lumbar spine BMD increased significantly more in the treatment-naive group than it did in inadequate responders to bisphosphonate. Although previous bisphosphonate therapy blunts the response to PTH, treatment with teriparatide for 24 months was associated with robust and statistically significant increases in BMD regardless of previous bisphosphonate therapy.⁹⁸

PTH results in periosteal bone formation and a change in bone size. This geometric effect increases strength by increasing diameter and is likely to explain a portion of the effect of PTH on reduction of fractures. The earlier rise in markers of bone formation than in markers of resorption with PTH treatment provides a rationale for the observed increases in bone density. Formation markers peak at 1 month, whereas resorption markers peak at 6 months, thus indicating early osteoblast stimulation and bone formation with a delayed effect on osteoclasts and bone resorption.

Side effects

In the pivotal phase 3 fracture prevention trial using rhPTH 1-34, the only significant side effects were dizziness and leg cramps. Mild hypercalcemia was common (11%), but treatment was discontinued only rarely. Uric acid levels increased 13% to 25% during treatment with rhPTH 1-34, but no gout attacks occurred. Uric acid levels returned to baseline at the end of treatment. The planned 36-month pivotal rhPTH 1-34 trial was terminated early because of the development of osteosarcoma in rat studies.⁹⁹

Osteosarcoma has been reported in one patient treated with PTH (not greater than the expected background incidence of osteosarcoma). Teriparatide should not be prescribed to populations at higher risk for osteosarcoma, including patients with Paget disease of bone, patients with previous radiation therapy involving the skeleton or with implants that deliver radiation, and pediatric populations (and young adults) with open epiphyses. Elevations of alkaline phosphatase should be evaluated before using teriparatide because of the possibility of Paget disease and bone tumors. Patients who have bone metastases or a history of skeletal malignancies should not be treated with teriparatide. Patients with hypercalcemia should be evaluated, and those with hyperparathyroidism and bone metastases should not receive teriparatide. It would also be prudent to check serum calcium levels after starting teriparatide but avoid measurement in the first 16 hours after a dose. The approved lifetime duration of therapy with teriparatide is 24 months.

Strontium ranelate

Strontium occurs naturally as a nonradioactive element and was first isolated in 1808. Strontium competes with calcium for intestinal absorption and, once absorbed, for incorporation into bone and dental tissues. At low doses, strontium ranelate results in uncoupling of bone turnover by stimulating osteoblastic activity and decreasing osteoclastic activity. This would appear to make it different from other antiresorptive agents by increasing formation and reducing resorption of bone. Human and animal studies of strontium ranelate demonstrate it to be an effective therapy for the treatment of osteoporosis.

Two large multicenter, randomized, placebo-controlled trials of postmenopausal osteoporotic women treated with oral strontium ranelate at a

dose of 2 g daily have been published: the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial and the Treatment of Peripheral Osteoporosis (TROPOS) study.^{100,101}

Both showed that strontium ranelate significantly increased bone formation and decreased bone resorption, increased BMD, and significantly reduced the risk for vertebral fractures by between 39% and 45% after 3 years. In TROPOS, patients treated with strontium had a small but significant 16% reduction in non-spine-related fractures. A *post-hoc* analysis demonstrated a significant 36% reduction in the risk for hip fracture in those considered to be at high risk: age older than 74 years and femoral neck T-score of -3 or lower. A preplanned *post-hoc* analysis that pooled data from SOTI and TROPOS showed significant reductions in vertebral, nonvertebral, and symptomatic fractures in women 80 to 100 years old.¹⁰² Strontium has also been shown to reduce the risk for vertebral fractures in postmenopausal women with osteopenia in the spine.¹⁰³

As a result, strontium ranelate (Protelos) received approval for use in more than 90 countries as of 2009 at a dose of one 2-g sachet to be taken before bedtime at least 2 hours after eating along with an 8-oz glass of water; however, it is not approved in either the United States or Canada. In SOTI the most frequent adverse events were nausea and diarrhea, most common in the first 3 months of therapy. A few cases of hypersensitivity syndrome with rash, fever, eosinophilia, and hepatic and renal impairment have been reported.

Summary

The use of antiresorptive therapy has proven benefits in reducing recurrent vertebral fractures by about 40% to 50% when added to a background of calcium and vitamin D supplementation; it does not eliminate the risk for new vertebral fractures, however. Hormone therapy and the nitrogen-containing bisphosphonates alendronate, risedronate, and zoledronic acid, as well as denosumab, have been shown to reduce the risk for nonvertebral fractures, including hip fractures. PTH has been shown to reduce both vertebral and nonvertebral fractures. Such evidence of antifracture efficacy for non-spine-related sites is not available for raloxifene, calcitonin, or ibandronate. The most appropriate patients for PTH treatment are likely to be those with previous fractures, those with very low BMD, and those who lose bone mass and suffer fractures while being treated with antiresorptive therapy. It appears that sequential use of PTH followed by a bisphosphonate will result in a larger increase in BMD than with either agent alone, but whether the increase in bone mass will translate into great reduction of fractures is not known.

The duration of treatment may depend on the initial bone mass, prevalent and incident fractures, other factors that contribute to fracture risk, and the drug used for treatment. The optimal duration of therapy with bisphosphonates is an area currently being debated. Bisphosphonates have a long skeletal half-life and an antiresorptive effect that may persist for years after drug discontinuation. This is not the case with raloxifene and estrogen because their skeletal half-life is short and bone loss would be likely to occur immediately after discontinuation. The off time for denosumab is rapid, and markers of bone resorption will increase to levels higher than pretreatment values 9 to 12 months after the last dose. The implications of discontinuation of denosumab are very different from those for discontinuation of a bisphosphonate.

MANAGEMENT OF VERTEBRAL FRACTURES

The acute pain after a vertebral fracture usually resolves in 4 to 6 weeks. Standard measures of pain relief are used, including analgesics, muscle relaxants, calcitonin, short periods of bed rest, and physical therapy. Spinal orthotics are three-point hyperextension contact braces (sternum, pubic symphysis, lumbar spine; e.g., Jewett and Cash orthoses) and may be helpful. Postural training support devices are designed to decrease kyphosis, move the center of gravity backward, and encourage use of the extensor muscles of the back. No long-term controlled studies of these devices have been conducted.

Operative management

Two percutaneous treatment options for painful vertebral compression fractures, vertebroplasty and kyphoplasty, involve the injection of polymethylmethacrylate (PMMA) into a compressed vertebral body. Studies show that the procedures may restore vertebral height, especially if performed within 6 to 12 weeks of the fracture, and that treated vertebral bodies have increased stiffness and load-bearing capacity, all mechanical advantages that could relieve pain and reduce the risk for additional fracture. Kyphoplasty uses a balloon tamp to create a cavity into which the PMMA is injected. When compared with vertebroplasty, which does not use a balloon, kyphoplasty allows greater filling of the vertebral body and greater height restoration with lower risk for extravasation of PMMA (the balloon creates a cortical shell that impedes extravasation, and the PMMA is injected under lower pressure). The mechanism of pain relief is not known, but reduction in the micromotion of fractured vertebral bodies after the procedure has been hypothesized.

Complications include extravasation of PMMA (up to 30% with vertebroplasty and 10% with kyphoplasty), which can result in neurologic sequelae and embolization to the vertebral venous plexus and to distant sites. Some but not all studies have shown an increased rate of adjacent fractures, and one suggested an increased incidence of subsequent fractures in patients with steroid-induced osteoporosis but not in those with primary osteoporosis. Although kyphoplasty appears to be most effective if performed soon after fracture, a nonrandomized trial in patients with painful vertebral fractures longer than 12 months in duration showed increased vertebral height, reduced pain, and improved mobility when compared with medical management alone.¹⁰⁴

A randomized controlled trial at 21 sites in 8 countries in which 300 patients were randomized to receive kyphoplasty or nonsurgical care documented a mean 36-item Short-Form Health Survey (SF-36) physical component score that improved by 7.2 points in the kyphoplasty group at 1 month with only a 2.0 point improvement in the nonsurgical group. The frequency of adverse events did not differ between groups.¹⁰⁵

A prospective, comparative, randomized trial comparing vertebroplasty and kyphoplasty showed little difference between the two procedures and recommended vertebroplasty on the basis of the higher cost of kyphoplasty.¹⁰⁶

Two recently published high-quality trials compared vertebroplasty with sham procedures and found no beneficial effect on pain and pain-related disability at any time points up to 3 to 6 months.^{107,108}

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Glucocorticoid-induced osteoporosis

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- Glucocorticoids are effective agents for a number of inflammatory conditions, but prolonged use can cause rapid bone loss, particularly in trabecular-rich sites such as the spine and ribs.
- Bisphosphonates and teriparatide are efficacious in treating and preventing glucocorticoid-induced bone loss.
- A significant care gap exists in the screening, prevention, and treatment of glucocorticoid-induced osteoporosis.

INTRODUCTION

Oral glucocorticoids are commonly prescribed for a variety of medical conditions, particularly in the field of rheumatology. They are very useful in controlling inflammation in the short term and serve as an important immunosuppressive agent. However, despite many clinical benefits, their use is associated with significant morbidity and mortality. One of the most significant adverse effects is glucocorticoid-induced osteoporosis (GIOP) and resultant fractures. The association between glucocorticoid excess and osteoporosis has been recognized for more than 80 years. Glucocorticoid therapy is the most common cause of secondary osteoporosis.¹

PATHOPHYSIOLOGY OF GLUCOCORTICOID-INDUCED BONE LOSS

Glucocorticoids affect bone metabolism through a variety of mechanisms (Fig. 202.1). GIOP affects mainly areas rich in cancellous bone, particularly the lumbar spine and proximal end of the femur. Both bone formation and bone resorption processes are affected, and it is the combination of these processes that leads to a significant decline in bone mineral density (BMD) and increased risk of fractures. Bone loss in GIOP occurs in a biphasic pattern. An early transient phase of increased bone resorption occurs in the first year of glucocorticoid use, with a large rapid decline in BMD (6% to 12%) ensuing within the first 12 months, but with long-term therapy, the rate of decline in BMD slows significantly (3% per year) after the rapid resorption phase.²

The reduction in bone formation is probably the most important process in GIOP that contributes to the large reduction in BMD. Glucocorticoids have a direct effect on the osteoblast lineage that leads to decreased new bone formation. Apoptosis of osteoblasts and osteocytes is crucial in the pathophysiology of GIOP.¹ Even low doses of glucocorticoids are sufficient to significantly suppress markers of osteoblast activity, including the propeptide of type 1 N-terminal procollagen (P1NP) and the propeptide of type 1 C-terminal procollagen (P1CP).³ With glucocorticoid use, the caspase-3 pathway is activated, which in turn promotes apoptosis of both osteoblasts and osteocytes. The reduction in number of osteoblasts and osteocytes has been confirmed in histomorphometric studies of patients with GIOP.^{4,5} Osteocyte apoptosis has been associated with a decrease in vascular endothelial growth factor, which in turn reduces skeletal angiogenesis.^{6,7} This disruption of the osteocyte-canalicular circulation contributes to the reduction in biomechanical strength of the affected cancellous bone. This process also plays an important role in the repair of damaged bone.^{6,7} Given the role of the osteocyte-canalicular circulation, disruption of this network may also account for the loss of bone strength, which occurs before a decline in BMD is seen in patients who take glucocorticoids⁸ (Fig. 202.2).

In addition to promoting osteoblast apoptosis, glucocorticoid use also leads to a subsequent decrease in osteoblastogenesis through downregulation of the Wnt signaling pathway. The Wnt signaling pathway is downregulated by Dickkopf-1 (Dkk-1) and sclerostin, both of which are upregulated with glucocorticoid use.^{9,10} Dkk-1 and sclerostin suppress the binding of Wnt to lipoprotein receptor-related proteins-5/6 (LPR-5/6), which in turn limits the ability of β -catenin to be stabilized. Loss of β -catenin from pre-osteoblasts causes a shift in fate of these cells from the osteoblast lineage to the adipocyte lineage, thus leading to a reduction in osteoblastogenesis.¹¹

Peroxisome proliferator-activated receptor- γ 2 (PPAR- γ 2) is also upregulated with long-term glucocorticoid use, which also contributes to a decrease in osteoblastogenesis. When PPAR- γ 2 is upregulated, undifferentiated bone marrow stromal cells are more likely to differentiate into the adipocyte lineage rather than the osteoblast lineage, which accounts for its effect in decreasing osteoblastogenesis. Overall, a combination of an increase in osteoblast apoptosis and a decrease in osteoblastogenesis leads to a decline in new bone formation.

In contrast to its effects on osteoblasts, osteoclastogenesis is promoted and the rate of osteoclast apoptosis is suppressed with glucocorticoid use. This effect is probably due to increased expression of receptor activator of nuclear factor κ B ligand (RANKL) and macrophage colony-stimulating factor by osteoblastic cells.^{1,12} Osteoprotegerin (OPG) is also downregulated, which increases osteoclastogenesis and reduces rates of osteoclast apoptosis.¹³

Aside from its effects on the osteoblast and osteoclast lineages, glucocorticoids also exert indirect effects on bone metabolism. Glucocorticoids reduce intestinal calcium absorption and increase renal calcium clearance.¹ Glucocorticoid use also reduces sex steroid production, which has an influence on bone formation.¹

Risk for fracture is higher in elderly patients with glucocorticoid use. The activity of the 11 β -hydroxysteroid dehydrogenase (11 β -HSD) system may play an important role in this observation. Two isoenzymes, 11 β -HSD1 and 11 β -HSD2, catalyze the conversion between hormonally active and inactive forms of glucocorticoids.¹⁴ The 11 β -HSD1 enzyme serves as an activator, whereas the 11 β -HSD2 enzyme serves as an inactivator. With aging comes an increase in 11 β -HSD1 activity and thus more conversion of glucocorticoids to a hormonally active form.¹⁵

EPIDEMIOLOGY

Glucocorticoids are widely prescribed in medical practice. It is estimated that 2.5% of the elderly population (70 to 79 years of age) are prescribed oral glucocorticoid therapy at any given time.¹⁶ Of these patients, about 22% are prescribed a dose higher than 7.5 mg/day for long-term (>6 months' duration) use.¹⁶ Epidemiologic data from Iceland revealed that osteoporosis developed in an estimated 26% of patients treated long-term with oral glucocorticoids (>6 months' duration).¹⁷

With increasing daily doses, risk of fracture also increases.¹⁸ This was assessed with data derived from the U.K. General Practice Research Database, a large retrospective cohort study that included 244,235 oral corticosteroid users and 244,235 controls. This study revealed that in patients taking higher doses of oral glucocorticoids (at least 7.5 mg of prednisolone or equivalent), the relative risk (RR) for development of a clinical vertebral fracture was 2.83 (95% CI, 2.35 to 2.40), the RR for development of a hip fracture was 2.21 (95% CI, 1.85 to 2.64), and the RR for development of a nonvertebral fracture was 1.44 (95% CI, 1.34 to 1.54).¹⁹ Even a low daily dose of oral glucocorticoids (2.5 to 7.5 mg/day of prednisolone or equivalent) has been shown to increase the risk for vertebral fractures (RR, 1.54; 95% CI, 1.29 to 1.84) and nonvertebral fractures (RR, 1.18; 95% CI, 1.11

to 1.26) (Fig. 202.3).¹⁹ With discontinuation of glucocorticoid therapy, fracture risk declines. However, it is unclear whether the risk returns back to baseline values. A case-control study demonstrated that longer than 1 year of discontinuation of oral glucocorticoids is required before fracture risk returns to levels in the background population.²⁰

Furthermore, patients receiving intermittent high-dose oral glucocorticoids (≥ 15 mg/day and cumulative exposure of ≤ 1 g) have a small increase in fracture rates but no effect on hip fractures. However, in patients receiving doses of 30 mg/day or higher with a cumulative dose of 5 g or greater, the RR for an osteoporotic fracture was 3.63 (95% CI, 2.54 to 5.20), the RR for a hip fracture was 3.13 (95% CI, 1.49 to 6.59), and the RR for a vertebral fracture was 14.42 (95% CI, 8.29 to 25.08).²¹

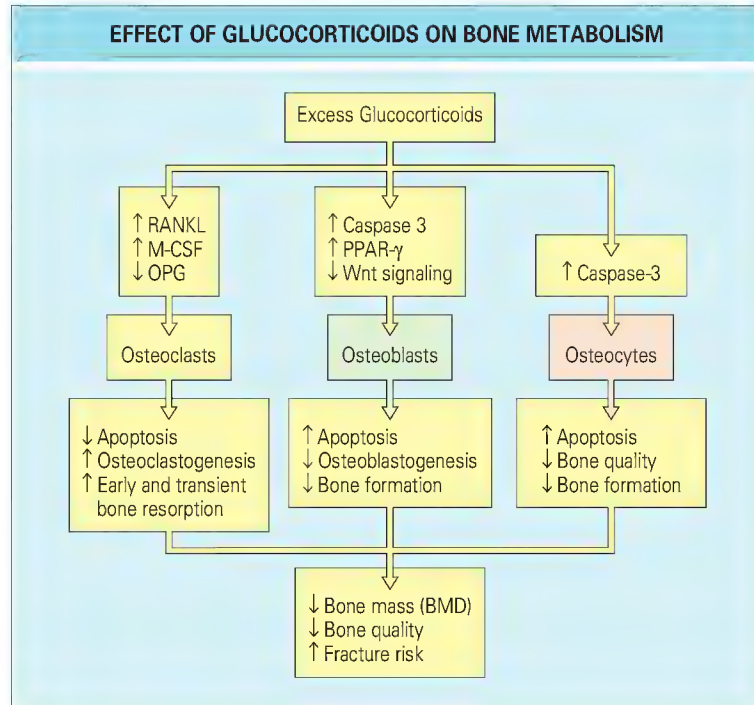


Fig. 202.1 Glucocorticoids lead to a subsequent decrease in bone quantity and quality and an overall increased risk for fractures. BMD, bone mineral density; M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; PPAR- γ , peroxisome proliferator-activated receptor- γ ; RANKL, receptor activator of nuclear factor κ B ligand. (Adapted from Compston J. Management of glucocorticoid-induced osteoporosis. *Nat Rev Rheumatol* 2010;6:82-8.)

High doses of inhaled glucocorticoids have also been associated with a decline in BMD.²² There are reports of increased fracture rates (hip and vertebral) in both adults and children treated with inhaled glucocorticoids. However, similar fracture rates were seen in those treated with inhaled nonsteroidal bronchodilators, which suggests that the increase in fracture risk may be due to the underlying respiratory disease rather than the inhaled glucocorticoid treatment.^{23,24}

INVESTIGATIONS

Bone mineral density

Bone strength depends on both the quantity and quality of the bone. The most commonly used quantitative imaging measure in osteoporosis is BMD measured by dual-energy x-ray absorptiometry (DEXA). The effects of glucocorticoids on BMD can be measured accurately with DEXA of the lumbar spine, hip, and distal end of the forearm. In GIO, the earliest changes in BMD are often seen at the lumbar spine because of its high content of trabecular bone. A rapid decline in BMD usually occurs within the first 3 months of glucocorticoid use. This rapid decline peaks at about 6 months and is followed by a period of slower, but steady decline with continued use.²⁵

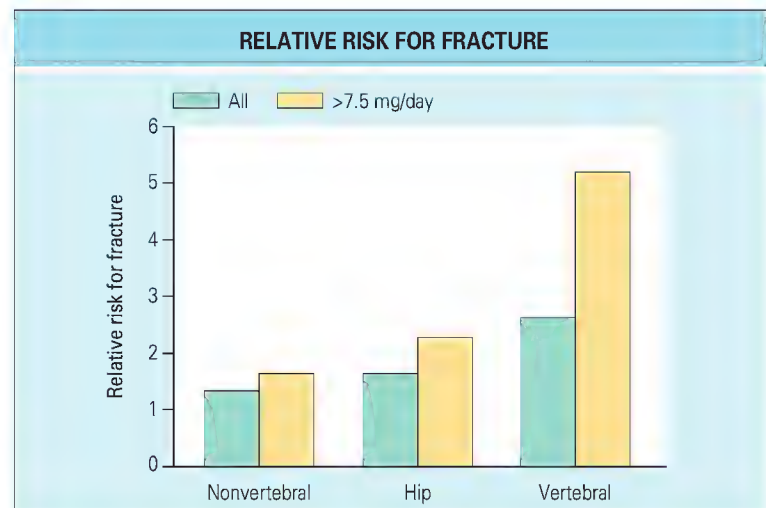
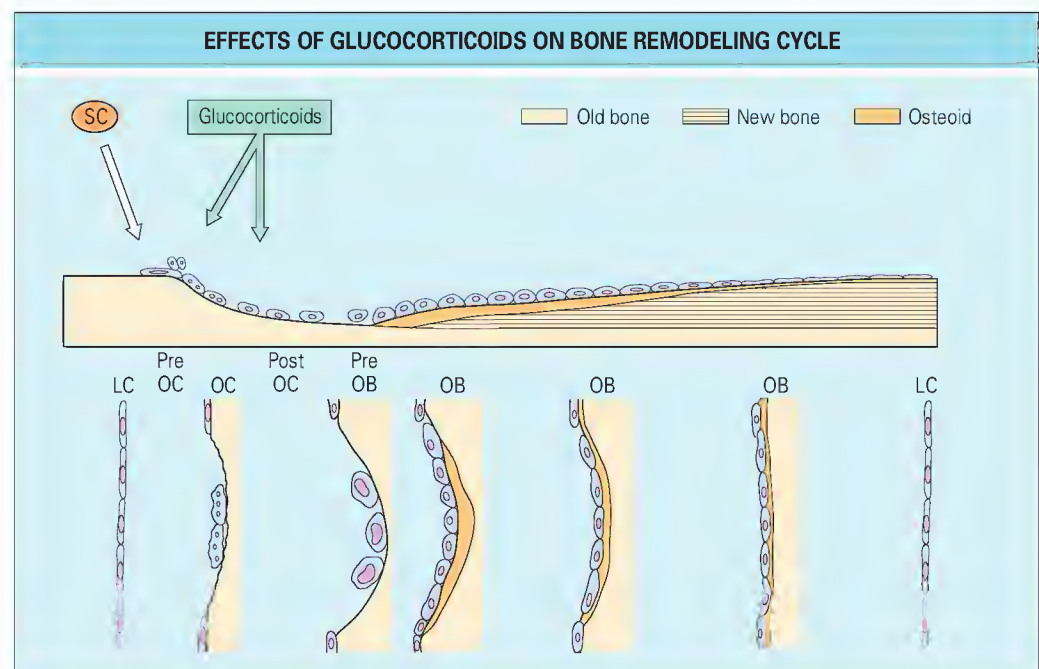


Fig. 202.3 Relative risk for different types of fractures in patients with long-term glucocorticoid use. (Adapted from Van Staa TP, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:993-1000.)

Fig. 202.2 A trabecular basic multicellular unit is depicted in the top panel. Selected transverse sections are depicted in the lower panels. Successive stages of quiescence, activation, resorption, formation, and quiescence are depicted. Glucocorticoids may enhance activation early but later delay the interval between completion of resorption and onset of formation. Histomorphometric studies reveal an increase in resorptive surfaces, which is due to decreased recruitment of osteoclast precursors and an increase in osteoblast apoptosis. LC, lining cell; OB, osteoblast; OC, osteoclast; SC, stem cell.



However, the decline in BMD does not completely account for the increase in fracture risk.²⁶ This indicates that glucocorticoids have an effect on not only the quantity of bone but also on the quality of bone produced.

Advanced imaging

Fractures in patients treated with oral glucocorticoids occur at a higher BMD than in those not treated with glucocorticoids.²⁷ Advanced imaging techniques that provide insight into the quality of the bone produced are available. These techniques can provide information regarding the effect of glucocorticoids on the microstructural and macrostructural features of the underlying bone.

The macrostructure of bone can be assessed quantitatively with volumetric quantitative computed tomography (QCT) and high-resolution computed tomography. Low BMD as measured by volumetric QCT of the lumbar spine, total hip, and all hip subregions was significantly associated with prevalent vertebral fractures in postmenopausal women treated long-term with glucocorticoids.²⁸ One study suggested that BMD of the lumbar spine measured by QCT, but not by DEXA, was an independent predictor of vertebral fractures in postmenopausal women receiving glucocorticoids.²⁹

The microstructure of bone can be assessed with micro-magnetic resonance imaging and high-resolution magnetic resonance imaging (hrMRI). An hrMRI study showed changes in trabecular bone in patients receiving glucocorticoids in the setting of organ transplantation. This study showed an increase in fracture rate (vertebral and peripheral) in patients with structural changes seen on hrMRI.³⁰

Biochemical markers

Profound changes in biochemical markers of bone turnover occur in the setting of glucocorticoid treatment. Like other markers of bone formation, serum osteocalcin levels fall within even a few hours of glucocorticoid treatment. With long-term glucocorticoid use, serum osteocalcin levels fall to as low as 30% of their pretreatment levels.

MANAGEMENT

Risk stratification

Glucocorticoid use is an important risk factor for fractures. The decision to intervene with an anti-osteoporotic agent should be based on the patient's absolute fracture risk. FRAX is a fracture risk assessment tool developed by the World Health Organization. It can be used to calculate the 10-year probability of fracture by using a number of clinical risk factors, with or without BMD testing.³¹ Given its importance, glucocorticoid therapy is one of the risk factors included in the FRAX algorithm. FRAX can provide an estimated 10-year fracture risk in patients receiving a daily dose of 2.5 to 7.5 mg of prednisolone (or equivalent). For patients receiving higher doses of glucocorticoids (>7.5 mg/day), the 10-year fracture risk can be adjusted upward to account for the dose-related risk.³²

Current recommendations

Given the high risk for fractures in this population, there is a large emphasis on initiating anti-osteoporotic therapy in patients being treated long-term with oral glucocorticoids. The American College of Rheumatology (ACR), in its latest recommendations (2010), suggested risk stratification of patients taking oral glucocorticoids based on FRAX. The ACR recommended that patients at low to medium risk for fracture (<10% and 10% to 20% probability of a major osteoporotic fracture, respectively) start anti-osteoporotic therapy if the daily dose of oral glucocorticoid equals or exceeds 7.5 mg/day of prednisolone (or equivalent). For high-risk patients (>20% probability of a major osteoporotic fracture), the ACR recommended initiation of anti-osteoporotic therapy for anyone treated with glucocorticoids for longer than 1 month (at any dose) or for anyone treated with daily oral glucocorticoids at a dose of 5 mg/day or higher of prednisolone (or equivalent), even if the duration is less than 1 month.

Similar to the ACR, the International Osteoporosis Federation (IOF) and the European Calcified Tissue Society (ECTS) published a joint guideline for the management of GIOP.³³ The IOF-ECTS developed an algorithm to risk-stratify and treat patients older than 50 years who had been taking oral glucocorticoids for at least a 3-month duration. The committee recommended FRAX assessment in women and men 50 to 70 years of age who were exposed to oral glucocorticoids for a 3-month or longer duration but

with a daily dose of less than 7.5 mg/day (of prednisolone or equivalent). In patients considered to be at high risk for fracture (previous fracture, age >70 years, or daily doses ≥ 7.5 mg/day of prednisolone or equivalent for more than 3 months' duration), the IOF-ECTS recommended initiation of anti-osteoporotic therapy.³³

Calcium and vitamin D

Physiologically, glucocorticoid use exerts an effect on calcium metabolism by decreasing calcium absorption through the gastrointestinal tract. Several trials have assessed the use of calcium supplementation as primary prevention in patients treated with low-dose oral glucocorticoids. However, despite primary prevention with calcium supplementation, there was still a significant decline in BMD,³⁴ which suggests that calcium supplementation alone is insufficient to prevent a decline in BMD in the setting of glucocorticoid use.

The combination of vitamin D with calcium supplementation has been evaluated in a number of trials in the GIOP population. This combination was assessed in both the primary and secondary prevention settings. An early study evaluated the combination of calcium 500 mg/day and vitamin D 50,000 U/wk in patients treated long-term with glucocorticoid therapy. This trial showed a significant increase in BMD, but only BMD of the radius was assessed in this study.³⁵

The combination of calcium and vitamin D was assessed in the primary prevention setting by Adachi and colleagues. Only patients starting high-dose oral glucocorticoid therapy were included. Patients taking oral glucocorticoids were randomized to 1000 mg of elemental calcium per day and 50,000 units of vitamin D per week versus placebo over a 3-year follow-up duration. BMD of the lumbar spine was evaluated. No difference was found in lumbar spine BMD between the calcium/vitamin D combination and the placebo groups over the follow-up period.³⁶

A secondary prevention trial assessed the combination of calcium and vitamin D supplementation in patients treated long-term with glucocorticoids. Patients were randomized to receive calcium (1000 mg/day) and vitamin D₃ (500 U/day) versus placebo. This trial reported a 2.0% annual decline in lumbar spine BMD in the placebo group versus a 0.7% increase with the calcium/vitamin D combination.³⁷

Supplementation with active vitamin D metabolites has been assessed in a number of trials. The two most commonly used forms of activated vitamin D are calcitriol (1,25-dihydroxyvitamin D) and alfacalcidol (1 α -hydroxyvitamin D). One study evaluated the effect of calcium, calcitriol, or calcitonin in 103 patients starting therapy with oral glucocorticoids.³⁸ At the 12-month follow-up, a statistically significant decline in lumbar spine BMD was noted in the calcium-treated group (4.3% decline over a 12-month period) when compared with the calcitriol group (1.3% decline) and the calcitonin group (0.2% decline). Another randomized controlled trial compared alfacalcidol treatment with calcium supplementation alone in 145 patients starting glucocorticoid therapy.³⁹ At the 12-month follow-up period, a 0.4% increase in lumbar spine BMD occurred in the alfacalcidol group versus a 5.7% decline in the calcium group. Furthermore, a meta-analysis showed the beneficial effect of active vitamin D metabolites. When compared with no treatment or with calcium supplementation alone, treatment with active vitamin D metabolites resulted in a greater increase in BMD and a statistically significant reduction in vertebral fractures.⁴⁰ However, a meta-analysis performed by the same group showed that active vitamin D metabolites were not as effective as bisphosphonates in preventing loss of BMD in the lumbar spine (2.1% increase in the alendronate group vs. a 1.9% decline in the alfacalcidol group).⁴¹

Calcitonin

Calcitonin was assessed in both primary and secondary prevention trials. In two primary prevention trials, addition of calcitonin to active vitamin D metabolites (alfacalcidol and cholecalciferol) resulted in no significant improvement in BMD or vertebral fracture rates.^{34,42}

Bisphosphonates

Bisphosphonates act by binding to hydroxyapatite crystals in bone and have an inhibitory effect on osteoclasts. Overall osteoclast activity is inhibited by decreasing osteoclast maturation, increasing osteoclast apoptosis, and decreasing the activity of mature osteoclasts. The decrease in osteoclast numbers and activity results in an overall anti-resorptive effect. The mechanism by which bisphosphonates exert their protective effect in the setting of GIOP is still unclear. A period of rapid bone resorption occurs soon after initiation of glucocorticoid therapy. Inhibition of this process

may account for the early improvement in BMD seen after the initiation of bisphosphonate therapy. It is suggested that bisphosphonates reduce the rate of glucocorticoid-induced apoptosis of osteocytes, which is an important factor in the pathogenesis of GIOP.⁴³

A number of trials have assessed the efficacy of bisphosphonates in the setting of GIOP. These trials evaluated the use of bisphosphonates in both primary and secondary prevention settings. A primary prevention trial randomized 141 patients initiating glucocorticoid therapy to receive cyclic etidronate and calcium supplementation of 500 mg versus placebo. At the 12-month follow-up period, BMD of the lumbar spine and the greater trochanter was significantly increased (increase of $0.6\% \pm 0.54\%$ and $1.46\% \pm 0.67\%$, respectively) in comparison to the control group (decrease of $3.23\% \pm 0.60\%$ and $2.74\% \pm 0.66\%$, respectively).⁴⁴ There were also significantly fewer new vertebral fractures in the etidronate groups than in the placebo group.⁴⁴

Two randomized, placebo-controlled trials assessed the use of alendronate as prophylaxis in patients starting glucocorticoid therapy. The combined results of the two trials included 477 patients randomized to either alendronate or placebo treatment. Patients in the alendronate group received either 5 or 10 mg/day. In addition, patients in both groups received 800 to 1000 mg of elemental calcium and 250 to 500 IU of vitamin D daily. The alendronate group had a mean increase in BMD in the lumbar spine of $2.1\% \pm 0.3\%$ and $2.9\% \pm 0.3\%$, respectively, for the 5- and 10-mg groups. The placebo group had a decrease of $0.4\% \pm 0.3\%$, which was a statistically significant difference ($P < .001$). Similarly, femoral neck BMD increased by $1.2\% \pm 0.4\%$ and $1.0\% \pm 0.4\%$ in the 5- and 10-mg alendronate groups, respectively ($P < .01$) and decreased by $1.2\% \pm 0.4\%$ in the placebo group ($P < .01$).⁴⁵ After completion of the trial, a 12-month extension was performed to evaluate the efficacy of alendronate over a 24-month duration. In 208 patients who continued in the 12-month extension, those randomized to receive alendronate preserved bone mass in the lumbar spine, femoral neck, and greater trochanter, in contrast to the placebo group, in which bone mass was not preserved. Over the 24-month follow-up period, fewer new vertebral fractures occurred in the alendronate groups combined than in the placebo group (0.7% vs. 6.8% , $P = .026$).

Risedronate is another oral bisphosphonate that has been evaluated in the setting of GIOP. In a primary prevention trial, 224 patients newly initiated to long-term glucocorticoid therapy were randomized to receive either risedronate (2.5 or 5 mg) or placebo daily over a 12-month follow-up duration.⁴⁶ Patients in both groups also received 500 mg of elemental calcium daily. The results were similar to those in the two prior primary prevention studies using either etidronate or alendronate. At the 12-month follow-up period, lumbar spine BMD increased by $0.6\% \pm 0.5\%$ in the 5-mg group and decreased by $0.1\% \pm 0.7\%$ in the 2.5-mg risedronate group. In the placebo group, lumbar spine BMD decreased by $2.8\% \pm 0.5\%$. The mean difference in BMD between the 5-mg risedronate and placebo groups was $3.8\% \pm 0.8\%$ ($P < .001$) at the lumbar spine, $4.1\% \pm 1.0\%$ ($P < .001$) at the femoral neck, and $4.6\% \pm 0.8\%$ ($P < .001$) at the greater trochanter. At the 12-month follow-up mark there was also a trend toward a reduction in incident vertebral fractures in patients treated with 5 mg risedronate daily versus placebo (5.7% vs. 17.3% , $P = .072$).⁴⁶ The effects of risedronate were evaluated in patients treated long-term with glucocorticoids (>7.5 mg of prednisone or equivalent). Reid and colleagues randomized 290 men and women treated long-term with glucocorticoids to receive either risedronate (2.5 or 5 mg/day) or placebo daily for a 12-month duration. At the 12-month follow-up mark, a statistically significant difference in BMD was noted between the risedronate and placebo groups at the lumbar spine ($P < .001$), femoral neck ($P = .004$), and trochanter ($P = .01$).⁴⁷ Although it was not powered to show efficacy in preventing fractures, there was a reduction in the incidence of vertebral fractures by 70% in the combined risedronate groups versus placebo ($P = .042$).⁴⁷

In addition to oral bisphosphonates, intermittent intravenous bisphosphonates have also been tested in the setting of GIOP. A randomized, double-blind, double-dummy noninferiority trial was conducted in which 833 patients starting glucocorticoid therapy were randomized to receive either zoledronic acid (5 mg intravenously once yearly) or risedronate (5 mg orally daily).⁴⁸ Patients were stratified into a prevention subgroup (those who received glucocorticoid treatment for less than 3 months) and a treatment subgroup (those who received glucocorticoid treatment for more than 3 months). At 12 months, zoledronic acid was found to be noninferior to risedronate in terms of an increase in lumbar spine BMD in the treatment subgroup (mean difference, 1.36% ; 95% CI, 0.67 to 2.05 ; $P = .0001$). Furthermore, zoledronic acid was superior to risedronate with respect to an increase in lumbar spine BMD in the prevention subgroup (mean difference, 1.96% ; 95% CI, 1.04 to 2.88 ; $P < .0001$).⁴⁸ In this trial the rate of new vertebral fractures was very low (five in the two zoledronic acid subgroups

combined and three in the risedronate group), with no statistically significant difference between the treatments.

A small randomized controlled trial also assessed the role of intermittent intravenous pamidronate in preventing GIOP. A total of 27 patients newly starting long-term glucocorticoid therapy were randomized to receive either pamidronate (induction infusion of 90 mg with subsequent infusion of 30 mg every 3 months) or elemental calcium alone (800 mg/day).⁴⁹ At 12 months the patients randomized to pamidronate showed a significant increase in BMD at the lumbar spine and femoral neck (3.6% and 2.2% increase, respectively), whereas a 5.3% decline in BMD occurred at both the lumbar spine and femoral neck in the calcium-only group.

Currently, the bisphosphonates alendronate, risedronate, etidronate, and zoledronic acid are all approved for patients taking glucocorticoids. They are effective in the setting of both prophylaxis and treatment of GIOP.

Parathyroid hormone

Parathyroid hormone (PTH) plays a critical role in the regulation of calcium metabolism. Intermittent pulsatile administration of PTH produces an overall anabolic effect on bone turnover. The intermittent pulse of PTH binds to the PTH-1 receptor, a G protein-coupled protein. This binding subsequently activates the cyclic adenosine monophosphate-dependent protein kinase A and protein kinase C signaling pathways, which in turn promote osteoblastogenesis and osteoblast activity.⁵⁰ Teriparatide is a recombinant human PTH (1-34) that has been shown to be effective for the treatment of osteoporosis in postmenopausal women and men. The Fracture Prevention Trial demonstrated that in postmenopausal women, teriparatide treatment resulted in a significant increase in BMD at the level of the lumbar spine, femoral neck, and total body. The trial also demonstrated a reduction in risk for both vertebral and nonvertebral fractures.⁵¹

Given that a decrease in osteoblastogenesis and an increase in osteoblast apoptosis play a critical role in the pathogenesis of GIOP, an anabolic agent such as teriparatide would be a physiologically rational agent for the treatment and prevention of GIOP. Human PTH 1-34 was first assessed in the setting of GIOP by Lane and colleagues.⁵² Fifty-one postmenopausal women with osteoporosis who were concurrently taking glucocorticoids were randomized to receive teriparatide plus estrogen versus estrogen only. At the 12-month follow-up, lumbar spine BMD increased by 11% as measured by DEXA versus no change in the estrogen-only group ($P < 0.001$). In addition, lumbar spine BMD increased by 35% as measured by QCT versus a 1.7% increase in the estrogen-only group ($P < 0.001$).⁵² At the 24-month follow-up (after the study was extended for an additional 12 months), lumbar spine BMD measured by DEXA increased by 12.6% ($P < .001$), and lumbar spine BMD measured by QCT increased by 45.9% ($P < .001$). However, no significant improvement in BMD of the femoral neck or total hip was seen.⁵³

Furthermore, the efficacy of teriparatide in the setting of GIOP was also assessed in a randomized controlled trial that included both men and women who were taking oral glucocorticoids (≥ 5 mg of prednisone or equivalent) for at least 3 months at the time of enrollment. A total of 214 patients were randomized to receive 20- μ g injections of teriparatide daily versus 10 mg of alendronate daily.⁵⁴ At the 36-month follow-up, a significant increase in BMD of the lumbar spine (measured by DEXA) occurred in the teriparatide group versus the alendronate group (increase of 11.0% vs. 5.3% , respectively; $P < 0.001$). A significant increase also occurred in femoral neck BMD (increase of 6.3% vs. 3.4% , respectively; $P < .001$) and total hip BMD (increase of 5.2% vs. 2.7% , respectively; $P < .001$) in the teriparatide group versus the alendronate group. In addition, fewer subjects sustained vertebral fractures in the teriparatide group than in the alendronate group (1.7% vs. 7.7% , respectively; $P = .007$), with most of the fractures occurring in the first 18 months.⁵⁵ No significant difference was seen between the groups in the incidence of nonvertebral fractures at the 36-month follow-up.

RANKL inhibition: denosumab

RANKL plays a critical role in the activation, differentiation, and life span of osteoclasts. Denosumab is a fully human monoclonal IgG2 antibody against RANKL. Denosumab has been shown to be effective in the treatment of osteoporosis in postmenopausal women and in men.^{56,57}

Glucocorticoid use is associated with overexpression of RANKL and suppression of OPG, which is an endogenous inhibitor of RANKL.⁵⁸ Given the underlying pathophysiology, denosumab would be an agent with biologic plausibility to be tested for the treatment and prevention of GIOP. Currently, few trials have assessed the efficacy of denosumab in this setting. One study evaluated the use of denosumab in patients with rheumatoid arthritis treated with oral glucocorticoids and methotrexate. This phase 2,

double-blind controlled trial randomized patients to receive either placebo, 60-mg injections of denosumab every 6 months, or 180-mg injections of denosumab every 6 months. The study was initially designed to evaluate the effect of denosumab on structural damage from the underlying rheumatoid arthritis.⁵⁹ However, BMD (measured by DEXA) of the lumbar spine and total hip was assessed as a secondary outcome. At the 6- and 12-month follow-up marks, a statistically significant increase in BMD of the lumbar spine and total hip occurred in the denosumab-treated groups. There was also a reduction in serum bone turnover markers (type I C-telopeptide and serum PINP) from baseline in the denosumab groups.⁶⁰

CARE GAP IN THE SCREENING, PREVENTION, AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Despite the known deleterious effects of glucocorticoids on bone and the availability of agents effective in preventing and treating GIOP, a significant care gap still exists. A retrospective chart review from an academic rheumatology practice revealed that in rheumatoid arthritis patients treated with glucocorticoids, only 25% received calcium or vitamin D (or both) and only 42% received an anti-osteoporotic agent.⁶¹ In addition, only 23% of patients had a baseline BMD measurement. Male patients and premenopausal women were less likely to be screened with a baseline BMD.

In another study conducted in an academic Veterans Administration medical center, a retrospective chart review was conducted to identify

clinicians who prescribed long-term glucocorticoids. The clinicians included primary care providers, subspecialists, and medical trainees. These identified clinicians were invited to attend a focus group and complete a questionnaire. Common barriers in the management of GIOP identified through this process included a lack of knowledge, having limited time during the clinic visit, patient nonadherence, and system problems.⁶² Potential system problems identified through provider focus group questionnaires include difficulty obtaining a DEXA scan and difficulty obtaining appropriate treatment of GIOP.

CONCLUSION

Despite the effectiveness of glucocorticoids in treating a variety of inflammatory conditions, GIOP is a significant and common adverse effect. A FRAX assessment or similar algorithm should be performed on all patients starting glucocorticoid therapy to risk-stratify those at moderate and high risk for fractures. All patients starting oral glucocorticoid therapy should be prescribed calcium and vitamin D supplementation; calcium supplementation alone is ineffective in preventing glucocorticoid-induced bone loss. Oral bisphosphonates are an effective first-line therapy for both prevention and treatment of GIOP. Intravenous zoledronic acid and subcutaneous teriparatide are both options, especially if oral bisphosphonates are contraindicated or not tolerated. Despite numerous effective therapies, there is still a significant care gap in the prevention and treatment of GIOP. Clinician and patient education is essential to ensure that GIOP is not underrecognized and undertreated.

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203

Osteomalacia and rickets

■ MICHAEL F. HOLICK

- Osteomalacia is caused by a defect in the mineralization of osteoid laid down by mature osteoblasts. Once osteoid is laid down, adequate calcium-phosphorus product in the circulation results in normal mineralization, with deposition of calcium hydroxyapatite forming mineralized bone.
- The most common causes of osteomalacia/rickets are vitamin D deficiency and calcium deficiency. Any acquired or inherited disorder that alters absorption of phosphorus in the intestine and enhances excretion of phosphorus via the kidneys will also cause osteomalacia and rickets.
- Osteomalacia cannot be distinguished from osteopenia or osteoporosis by either radiographic examination or determination of bone mineral density. Physicians should be alert for the presence of osteomalacia in adults because it is often seen in men and women with osteopenia and osteoporosis.
- Treatment of vitamin D deficiency and correction of calcium and phosphorus intake result in complete resolution of osteomalacia/rickets when caused by these nutritional deficiencies.
- Several hereditary and acquired disorders affect both calcium and phosphorus metabolism and lead to rickets and osteomalacia. Management of these disorders depends on the cause and should be based on treating the mechanism resulting in osteomalacia/rickets or removing the offending agent that may be precipitating the mineralization defect.

INTRODUCTION

Osteomalacia by definition means that osteoblasts have laid down a collagen matrix, but there is a defect in its ability to be mineralized. In children, a defect in mineralization of osteoid in long bones and failure or delay of mineralization of endochondral new bone formation at the growth plate leads to the classic skeletal deformities of rickets. However, in adults the disorder takes on a different character as a result of failure of mineralization of newly formed osteoid at sites of bone turnover in regions of periosteal or endosteal apposition. Several causes of poor or absent skeletal mineralization can lead to both rickets and osteomalacia and are reviewed in this chapter.

CALCIUM, PHOSPHORUS, AND VITAMIN D METABOLISM

The major skeletal mineral components are calcium and phosphate. Thus any alteration in the calcium-phosphate product in the circulation can result in a mineralization defect in the skeleton. Vitamin D plays a critical role in maintaining both serum calcium and phosphate concentrations.¹ Vitamin D (D represents D₂ or D₃) is obtained by exposure of the skin to sunlight or through dietary sources^{2,3} (Fig. 203.1).

Vitamin D is converted in the liver by vitamin D-25-hydroxylase (25-OHase) to form the major circulating form of vitamin D, 25-hydroxyvitamin D (25[OH]D).^{1,2} 25(OH)D is, however, biologically inert and requires hydroxylation in the kidneys on carbon 1 by 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase) to form 1 α ,25-dihydroxyvitamin D (1,25[OH]₂D), the biologically active form of vitamin D responsible for regulating calcium and phosphorus homeostasis.^{1,2} Interaction of 1,25(OH)₂D with its vitamin D nuclear receptor (VDR) in the small intestine results in an increase in the

efficiency of intestinal calcium absorption.^{1,2,4} 1,25(OH)₂D also stimulates phosphate absorption. It is the calcium $\times$ phosphate product in the circulation and in the extravascular space that plays a major role in normal mineralization of the osteoid laid down by osteoblasts.

EFFECT OF VITAMIN D ON BONE METABOLISM

It is known that vitamin D is not necessary for mineralization of the osteoid matrix.^{5,6} Patients with vitamin D-resistant rickets have a mutation in their VDR and severe rickets and osteomalacia. When these patients were infused with calcium and phosphorus to maintain a normal calcium-phosphate product, the unmineralized osteoid was mineralized.⁶

Interaction of 1,25(OH)₂D with its VDR in osteoblasts increases the expression of alkaline phosphatase, osteocalcin, and receptor activator of nuclear factor κ B ligand (RANKL).⁷ The alkaline phosphatase produced by osteoblasts is important in bone mineralization because patients with a decrease in bone-specific alkaline phosphatase, known as hypophosphatasia, suffer from a mineralization defect in osteoid.^{8,9} Osteocalcin is the major noncollagenous protein in the skeleton. Although its function is not well understood, it appears to have a role in osteoclastic activity.¹⁰

RANKL, once expressed on the surface of an osteoblast, interacts with its receptor RANK on osteoclast precursors. This intimate interaction leads to signal transduction that results in the formation of multinucleated mature osteoclasts (Fig. 203.2).^{1,7,10} These osteoclasts, under the direction of a variety of cytokines,¹⁰ increase resorption of bone by releasing hydrochloric acid to dissolve the mineral and collagenases to dissolve the matrix (Fig. 203.3).

CAUSES OF OSTEOMALACIA/RICKETS

Consequences of vitamin D deficiency on bone mineralization

When a child or adult is deficient in vitamin D, the efficiency of intestinal calcium absorption is decreased and a transient reduction in serum ionized calcium takes place. Recognition of the reduction in serum ionized calcium by the calcium sensor in the parathyroid glands results in an increase in the secretion of parathyroid hormone (PTH).^{1,2,11} PTH conserves calcium by increasing tubular reabsorption of calcium throughout the renal tubule^{12,13} and stimulates the production of 1,25(OH)₂D.^{2,13} and both PTH and 1,25(OH)₂D increase the expression of RANKL on osteoblasts, which in turn mobilizes osteoclast precursors to become mature osteoclasts so that calcium and phosphorus can be removed from the skeleton by resorption of bone.^{1,2,12,13} (see Fig. 203.2). Thus, unless there are no longer any calcium deposits in the skeleton, the blood level of calcium is usually normal or low normal in both vitamin D-deficient children and adults.^{1,2,14}

PTH also causes internalization of the sodium-dependent phosphate cotransporter (NaPi-2A), which results in loss of phosphate into urine.^{1,2,12,13} This ultimately causes the blood phosphorus level to be lowered to a degree that the calcium-phosphate product is no longer adequate to mineralize the osteoid matrix (see Fig. 203.3c).

Thus the major cause of osteomalacia is secondary hyperparathyroidism and the low normal or low serum phosphate level. The fasting biochemistry for rickets and osteomalacia is summarized in Table 203.1.^{8,14}

Definition of vitamin D deficiency and insufficiency

The concentration of 25(OH)D that needs to be achieved to maximize bone health is still being debated. The Institute of Medicine (IOM) and the Endocrine Society defined vitamin D deficiency as a serum level of 25(OH)D

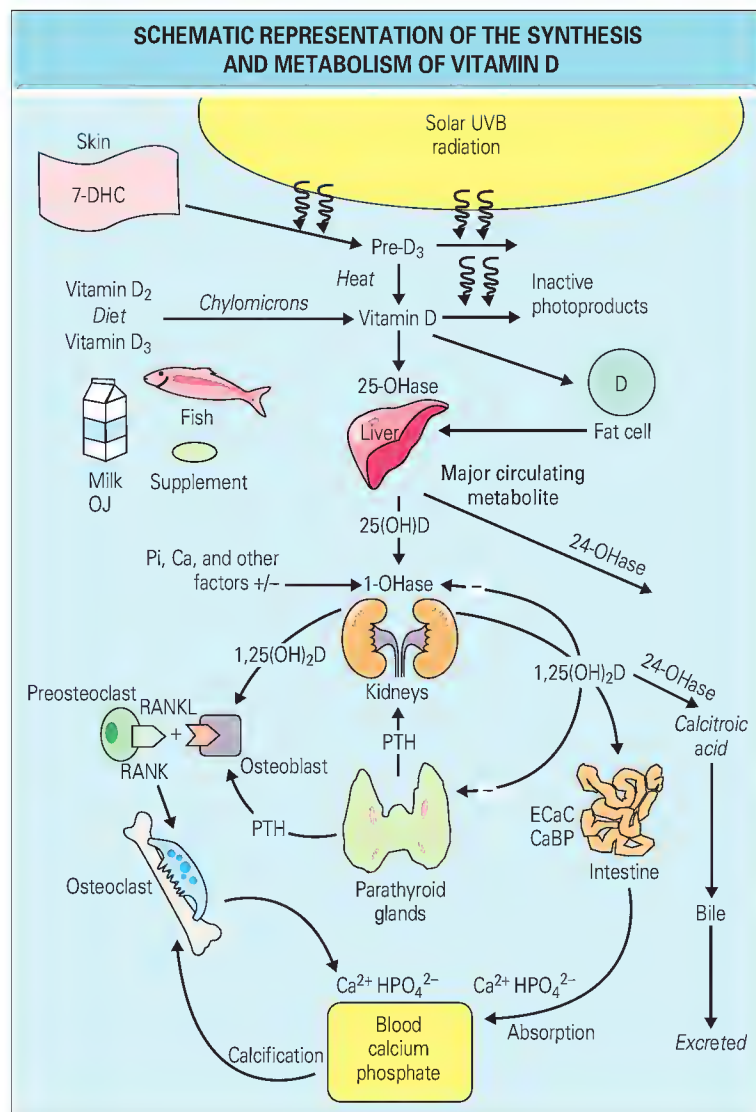


Fig. 203.1 Synthesis and metabolism of vitamin D for regulating calcium, phosphorus, and bone metabolism. During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin is converted to pre-vitamin D₃ (pre-D₃). Pre-D₃ is immediately converted by a heat-dependent process to vitamin D₃. Excessive exposure to sunlight degrades pre-D₃ and vitamin D₃ to inactive photoproducts. Vitamin D₂ and vitamin D₃ from dietary sources are incorporated into chylomicrons, which are transported by the lymphatic system into the venous circulation. Vitamin D (D represents D₂ or D₃) made in the skin or ingested in the diet can be stored in fat cells and then released from them. Vitamin D in the circulation is bound to the vitamin D-binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D (25(OH)D). This is the major circulating form of vitamin D that is used by clinicians to measure vitamin D status (although most reference laboratories report the normal range to be 20 to 100 ng/mL, the preferred healthful range is 30 to 60 ng/mL). 25(OH)D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D (1,25(OH)₂D). Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of 1,25(OH)₂D. 1,25(OH)₂D feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. 1,25(OH)₂D increases expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)₂D and 25(OH)D to the water-soluble biologically inactive calcitroic acid, which is excreted in bile. 1,25(OH)₂D enhances intestinal calcium absorption in the small intestine by stimulating expression of the epithelial calcium channel (ECaC, also known as transient receptor potential cation channel subfamily V member 6 [TRPV6]) and calbindin 9K (calcium-binding protein [CaBP]). 1,25(OH)₂D is recognized by its receptor in osteoblasts, which causes an increase in expression of receptor activator of nuclear factor κ B ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL, which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote mineralization of the skeleton and maintain neuromuscular function. OJ, orange juice; UVB, ultraviolet B. (Courtesy M.F. Holick, PhD, MD, © 2007.)

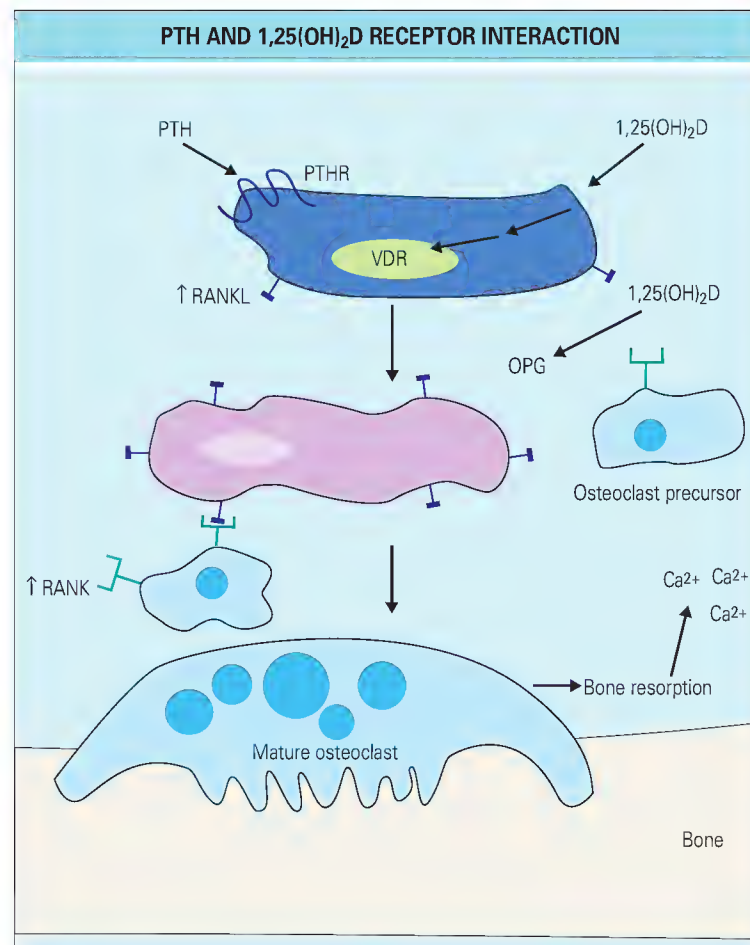


Fig. 203.2 Both 1,25-dihydroxyvitamin D (1,25(OH)₂D) and parathyroid hormone (PTH) stimulate the mobilization of calcium from the skeleton by interacting with their respective receptors on osteoblasts, which induces the expression of receptor activator of nuclear factor κ B (RANK) ligand (RANKL). RANK on the immature osteoclast's plasma membrane binds to RANKL, which causes it to mature and coalesce with other osteoclast precursors to become mature multinuclear osteoclasts. Osteoprotegerin (OPG) is a soluble decoy of RANK that binds to RANKL and inhibits osteoclastogenesis. (Courtesy M.F. Holick, PhD, MD, © 2007.)

lower than 20 ng/mL.^{15,16} Several studies have demonstrated, however, that PTH levels plateau when serum 25(OH)D is between 30 and 40 ng/mL.^{17,18} Furthermore, in a study of 675 otherwise healthy German adults who died prematurely in accidents and had bone biopsies performed and their blood collected, 26.5% of these otherwise healthy adults had evidence of osteomalacia and 36.1% had evidence of osteoidosis (buried osteoid within mineralized bone).¹⁹ The Endocrine Society noted that 21% of adults with serum levels of 25(OH)D between 21 and 29 ng/mL had evidence of osteomalacia.^{19,20} Based on this and other evidence, it was concluded that vitamin D insufficiency should be defined as a 25(OH)D level of 21 to 29 ng/mL and vitamin D sufficiency as a 25(OH)D level of 30 ng/mL or higher.¹⁶ Both the IOM and the Endocrine Society recommended that a 25(OH)D blood level of up to 100 ng/mL is safe.

Calcium deficiency

In Africa, where children are exposed to sunlight daily, rickets develops as a result of calcium deficiency.¹⁵ A diet poor in calcium will result in an increase in PTH levels, which causes hyperphosphaturia. Thus, in children living in Africa, India, and Bangladesh who ingest approximately 200 mg of calcium daily and have a diet high in phytates and oxalates, which irreversibly bind calcium in the gut and prevent its absorption, rickets and osteomalacia will develop.^{21–29}

Phosphate deficiency, heritable and acquired disorders

Nutritional phosphate deficiency is uncommon because our diet is rich in phosphate. Human breast milk, cow's milk, and infant formulas have enough phosphate to satisfy an infant's requirement. There are, however, several

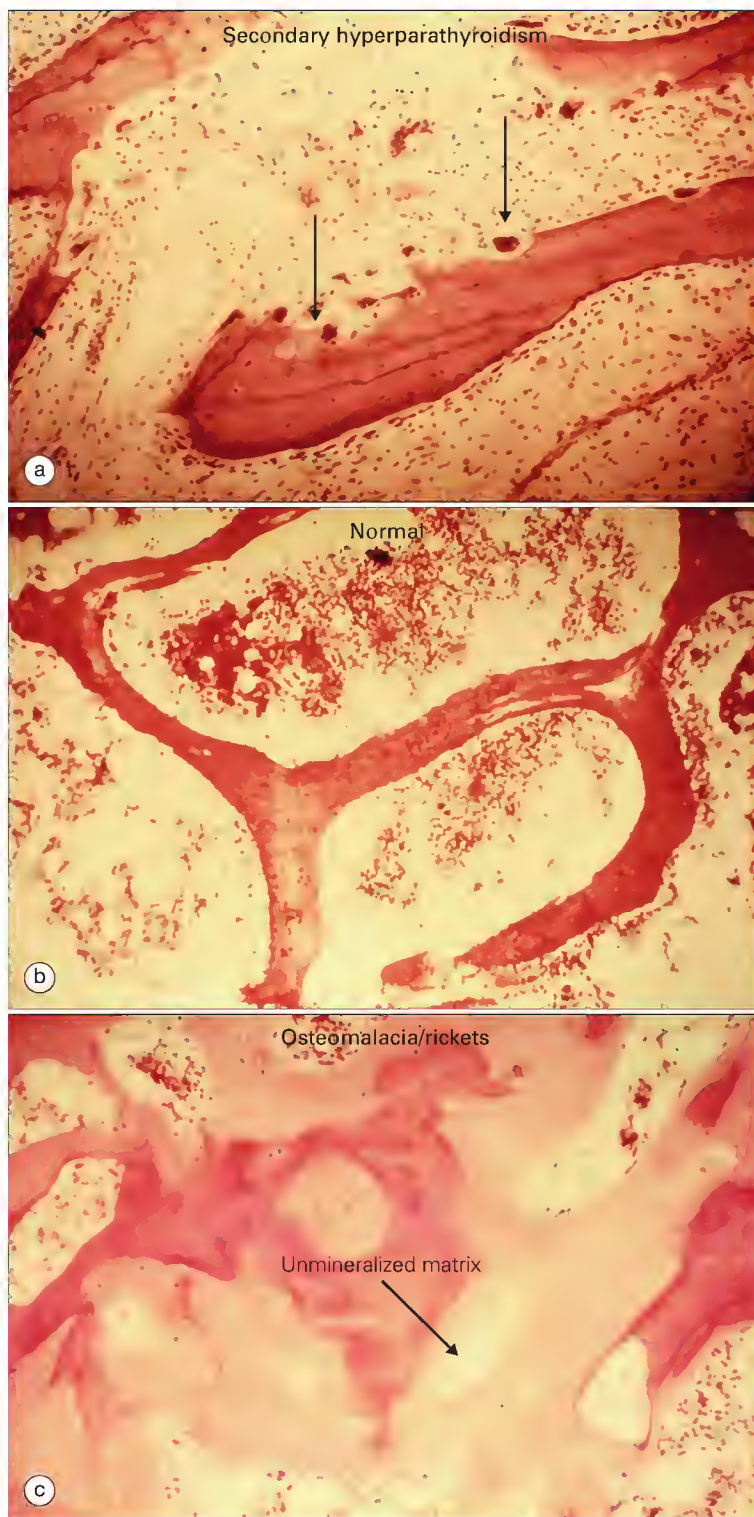


Fig. 203.3 Bone histology demonstrating (a) increased osteoclastic bone resorption (arrows) as a result of secondary hyperparathyroidism, (b) normal mineralized trabecular bone, and (c) osteomalacia with widened unmineralized osteoid matrix (lighter areas). (Courtesy M.F. Holick, PhD, MD, © 2007.)

acquired and inherited disorders that cause phosphate wasting into urine and can lead to severe hypophosphatemia and subsequent rickets and osteomalacia.

X-linked hypophosphatemic rickets and autosomal dominant phosphatic rickets are caused by either an increase in the production of fibroblast growth factor 23 (FGF-23) and other phosphatonins or a decrease in their catabolism and therefore severe phosphate wasting into urine. FGF-23, produced by osteocytes, causes internalization of the NaPi cotransporter and phosphaturia.¹⁴ In addition, the elevated blood level of FGF-23/phosphatonins inhibits the renal production of 1,25(OH)₂D, thus diminishing the efficiency of both intestinal calcium and phosphate absorption.^{14,30-33}

Oncogenic osteomalacia is due to the production of FGF-23/phosphatonins by benign or malignant tumors.³⁴ The result is severe hypophosphatemia

secondary to increased phosphate wasting into urine. Because this disease is often seen in adults, the clinical skeletal manifestations of the osteomalacia include aches and pains in the bones and muscles and signs of periosteal discomfort induced by applying pressure on the periosteum of the sternum, radius, ulna, and anterior aspect of the tibia. A radiograph of the skeleton may show osteopenia, and bone densitometry often reveals osteoporosis.^{8,35}

Fanconi syndrome and renal tubular acidosis

Fanconi syndrome is a disorder of the renal proximal tubules that results in decreased reabsorption of phosphorus, glucose, and amino acids, accompanied by metabolic acidosis secondary to proximal tubular bicarbonate wasting (type II renal tubular acidosis).^{36,37} Typically, these patients have hypophosphatemia, hyperphosphaturia, and a low tubular maximum inorganic phosphate concentration. Serum calcium is usually normal, alkaline phosphatase is elevated, PTH and 25(OH)D are normal, but serum 1,25(OH)₂D is inappropriately low or low normal.^{29,36-38} Children with Fanconi syndrome have classic radiographic evidence of rickets, whereas adults exhibit changes consistent with osteomalacia.³⁹

As noted in Box 203.1, a multitude of acquired and heritable disorders can cause Fanconi syndrome.³⁶ Patients found to have hypophosphatemia on a fasting blood specimen should be evaluated for Fanconi syndrome and the underlying cause identified and either treated appropriately or the offending agent removed.³⁶

Aluminum

The aluminum antacids used to prevent phosphate absorption in patients with chronic kidney disease can lead to the development of osteomalacia (see Chapter 203).^{15,40} Aluminum is a trivalent cation that at low concentrations stimulates osteoblastic activity but at higher concentrations inhibits the release of PTH and 1-OHase activity. It also inhibits osteoblastic activity and is deposited on the mineralization surface of the skeleton, thereby preventing further mineralization of osteoid. These patients often have little osteoblastic or osteoclastic activity, which results in a very inactive bone-remodeling state known as adynamic bone disease. A bone biopsy specimen that demonstrates stainable aluminum on the mineralization surface helps make the diagnosis of aluminum-induced osteomalacia.^{8,15,40}

Heavy metals

Several heavy metals can cause phosphaturia.^{8,15,41,42} Cadmium exposure causes Itai-Itai disease. High cadmium exposure has wide-ranging pathologic effects on the body, including damage to the glomerulus and renal tubular function. Besides leading to renal failure, it initially causes proteinuria and phosphaturia.¹⁵

Fluoride

Fluoride in low concentrations stimulates osteoblastic activity.¹⁵ However, at high concentrations fluoride becomes incorporated into the skeleton as a calcium fluorhydroxyapatite crystal. Because fluoride has a larger atomic weight than the OH that it replaces, the skeleton appears to be hyperdense on radiography and bone densitometry. Ingestion of food and water with a high fluoride content of between 3 and 16 ppm is associated with increased bone density, which leads to stiffness, rigidity, and limitation of movement at the spine and can also lead to skeletal deformities and fractures.^{8,15,43-45}

In certain populations, including children in India who are exposed to high dietary fluoride and have a low-calcium diet, severe skeletal deformities consistent with rickets develop.^{15,46-48} Histologically, biopsy specimens show widened osteoid seams, poorly mineralized new bone formation, and areas of hypermineralization.¹⁵

Drugs

A variety of drugs can cause rickets and osteomalacia.^{1,8,15} In children and adults who are institutionalized and taking several antiepileptic medications, rickets/osteomalacia often develops.^{1,14,15,49-51} It is now recognized that not only antiseizure medications but also glucocorticoids, certain antiretroviral medications, and even St. John's wort can cause vitamin D deficiency and resultant rickets and osteomalacia. These medications interact with the steroid xenobiotic receptor that binds to the retinoic acid X receptor, which leads to increased catabolism of 25(OH)D.^{1,14,51}

Osteomalacia has developed in patients with Paget disease who were treated with the bisphosphonate etidronate at a dose of 400 mg daily for more than 6 months.^{1,8,15,52} To prevent this complication, patients with Paget

TABLE 203.1
Biochemistry of osteomalacia/rickets

	Ca	PO ₄	25(OH)D	1,25(OH)D	PTH	Other
Deficiencies						
Vitamin D deficiency	≈↓ or N	≈↓ or N	↓↓	↑ or N	↑	
Calcium-deficient diet	↓	↓ or N	↓ or N	↑ or N	↑	↑ Alkaline phosphate
Kidney disease	↓	↑	N or ↓	↓ or N	↑ or N	
1 α -Hydroxylase deficiency, “vitamin D–dependent rickets” type 1	↓	↓	N	↓↓	↑	↑ Alkaline phosphate
Vitamin D resistance, “vitamin D–dependent rickets type 2”	↓	↓	N	↑↑↑	↑	↑ Alkaline phosphate
Hypophosphatemia						
X-linked hypophosphatemic rickets	N	↓↓	N	↓ or low-N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
Autosomal dominant hypophosphatemic rickets	N	↓↓	N	↓ or low-N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
Autosomal recessive hypophosphatemic rickets	N	↓↓	N	↓ or low-N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
Oncogenic osteomalacia with FGF-23 secretion	N	↓↓	N	↓ or low-N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
“Hereditary hypophosphatemic rickets with hypercalciuria,” NaPi2c mutation	N	↓↓	N	↑ or N	N	↑ Urine calcium ↑ Urine phosphate
Renal phosphate loss (including Fanconi syndrome, Dent disease, cadmium toxicity, heavy metal poisoning)	N	↓↓	N	N or low-N	N	↑ Urine phosphate ↑ Urine amino acids ↑ Urine bicarbonate ↑ Alkaline phosphate
Toxicities						
Fluoride	N	N	N	N	N	↑ Fluoride in bone biopsy specimens
Etidronate	N or low-N	N	N	N	N	
Parenteral aluminum	N	N	N	N or ↓	N or ↑↓	Aluminum-staining bone biopsy specimen
Hypophosphatasia	N	N	N	N	N	↓↓ Alkaline phosphate
Acidosis	N	N	N	N or low-N	Low N	↓ Bicarbonate in urine

FGF-23, fibroblast growth factor 23; N, normal.

BOX 203.1 DISORDERS ASSOCIATED WITH FANCONI SYNDROME

Acquired

Vitamin D deficiency
 Multiple myeloma
 Lymphoma
 Light-chain nephropathy
 Amyloidosis
 Sjögren syndrome
 Nephrotic syndrome
 Renal transplantation
 Balkan nephropathy
 Paroxysmal nocturnal hemoglobinuria
 Interstitial nephritis/uveitis syndrome
 Renal vein thrombosis

Heritable

X-linked hypophosphatemic rickets
 Autosomal dominant hypophosphatemic rickets
 Cystinosis
 Lowe syndrome
 Hereditary fructose intolerance
 Tyrosinemia
 Galactosemia
 Glycogen storage disease
 Wilson disease
 Cytochrome oxidase deficiency
 Subacute necrotizing encephalomyelopathy
 Alport syndrome
 Leigh syndrome
 Fanconi-Bickel syndrome

Dent disease
 GRACILE syndrome
 Rod-cone dystrophy, sensorineural deafness, and renal dysfunction
 Pearson syndrome

Drugs

Ifosfamide
 Methy-3-chromone
 6-Mercaptopurine
 Gentamicin
 Valproic acid
 Streptozocin
 Isophthalanilide
 Cephalothin
 Outdated tetracycline

Heavy metals

Cadmium
 Lead
 Mercury
 Uranium
 Platinum
 Copper
 Bismuth

Other

Paraquat
 Lysol
 Toluene inhalation

GRACILE, metabolic disorder characterized by **g**rowth **r**etardation, **a**minoaciduria, **c**holestasis, **i**ron overload, **l**actacidosis, and **e**arly death.



Fig. 203.4 (a) Anteroposterior (AP) views of the lower extremities of a 2-month-old white girl show mild irregular sclerotic changes in the tibial and fibular metaphyses, distal more than proximal (arrows). (b) AP views of the forearms demonstrate transverse lucency with sclerotic borders of the right distal radial metadiaphysis and transverse sclerotic changes in the same location on the distal end of the left radius (i.e., Looser zones, arrows). (Modified from Keller K, Barnes P. Rickets versus abuse: a national epidemic. *Pediatr Radiol* 2008;38:1210-6.)

disease took the medication for several months, stopped taking it for several months, and then restarted it again to control the Paget disease but prevent the side effect of osteomalacia.^{8,15}

The newer class of aminobisphosphonates is very effective in treating Paget disease when given either daily, weekly, or monthly, without any evidence of osteomalacia based on bone biopsy specimens (see Chapter 206). These potent bisphosphonates are also used for the prevention and treatment of osteoporosis and do not cause osteomalacia (see Chapter 201).

Ifosfamide, used to treat solid tumors, has been associated with renal Fanconi syndrome and hyperphosphaturia.^{53,54} Saccharated ferric oxide injected intravenously can cause transient proximal renal tubular damage that leads to phosphaturia.⁵⁵ A wide variety of other drugs have been associated with hypophosphatemia, osteomalacia, and rickets^{8,15} (see Box 203.1).

RADIOGRAPHIC AND BIOCHEMICAL MANIFESTATIONS OF OSTEOMALACIA AND RICKETS

It is not possible to distinguish osteomalacia from osteopenia and osteoporosis either by radiographic examination or by bone densitometry. The only exception is if the radiographic examination reveals Looser zones (Fig. 203.4). These zones are radiolucent lines penetrating through the cortex perpendicular to the shaft and are most often seen in the medial cortices of the femurs and in the pelvis and ribs. In children, rickets/osteomalacia is easily detected because the epiphyseal plates have not closed. There is widening of the physis along with fraying, cupping, and splaying of the metaphyses (Fig. 203.5). The diaphyses of the long bones often appear to be less dense (i.e., osteopenic) and show thinning of the cortices with periosteal new bone formation.^{8,15}

In utero, vitamin D deficiency can cause infantile rickets.⁵⁶ A decrease in mineralization of the fetal skeleton can increase the infant's risk for sustaining a variety of skeletal fractures during birth that often go undetected and heal quickly. If solely breastfed, the infant will not receive sufficient vitamin D because human breast milk on average contains just 25 IU of vitamin D per liter unless the mother is ingesting at least 4000 IU of vitamin D daily.⁵⁷ Therefore the infant's skeleton remains fragile, and handling of the infant can lead to nontraumatic fragility fractures of long bones and the rib cage. A radiograph of the long bones or chest may reveal a fracture or radiographic findings that appear to be a fracture but may be a consequence of rickets (see Fig. 203.4). A skeletal survey is often performed and reveals multiple

fractures in various stages of healing. The child may be removed from the parents' care and given to the child protection agency and the parents possibly prosecuted for child abuse. However, more careful analysis of the radiographs deemed to show multiple fractures in various stages of healing can also reveal that these "fractures" have been overinterpreted and misread as fractures caused by trauma (see Fig. 203.4).⁵⁸

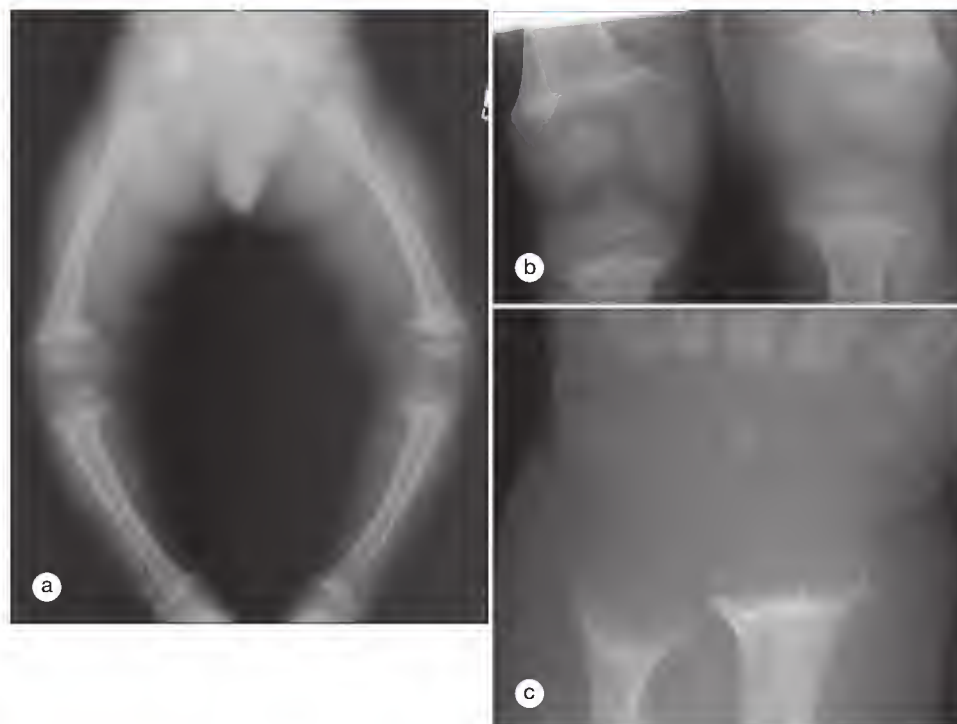
Rickets and osteomalacia are associated with a variety of abnormalities in blood biochemistry (Box 203.2).^{1,8,15} However, it is often the initial symptoms or manifestations of osteomalacia that will prompt the diagnosis before any biochemical abnormalities are appreciated. The reason for this is that the abnormal biochemical findings can vary depending on the cause. For example, a child with severe vitamin D deficiency will have low normal or low serum calcium; low normal or low fasting serum phosphorus; elevated alkaline phosphatase, PTH, and 1,25(OH)₂D; and a 25(OH)D level lower than 15 ng/mL. If the child has been deficient in vitamin D for a prolonged period or has very little calcium intake, the biochemical manifestation is often hypocalcemia associated with all of the other biochemical abnormalities. An adult with vitamin D deficiency will have normal or low normal serum calcium, low normal or low serum fasting phosphorus, normal alkaline phosphatase, elevated PTH, normal or elevated 1,25(OH)₂D, and a 25(OH)D level lower than 20 ng/mL. However, if the cause is due to an acquired disorder that results in severe phosphate wasting into urine, these patients will have normal or low normal serum calcium, elevated PTH, low serum phosphorus, elevated alkaline phosphatase, low or low normal 1,25(OH)₂D, and normal 25(OH)D.

CLINICAL FINDINGS

Children with rickets often have skeletal abnormalities, including a rachitic rosary, bowed or knocked knees, frontal bossing, soft fontanelles, and severe muscle weakness (Fig. 203.6). Frequently, children with rickets have other subtle symptoms as noted in Box 203.3.

In adults, osteomalacia is not associated with any overt skeletal signs. However, patients with osteomalacia complain of throbbing, aching bone discomfort. They often note that the bone discomfort is worse when sitting or lying in bed. They also have proximal muscle weakness and aching in their muscles.^{1,8,15,29,50} To make the diagnosis, pressing with the thumb or forefinger with some force on the sternum, radius, ulna, and anterior aspect of the tibia will often result in wincing bone discomfort. Frequently, physicians conclude that discomfort when pressing on the skeleton is consistent

Fig. 203.5 Classic radiographic findings in a child with severe vitamin D deficiency and rickets. (a) Skeletal deformities of the legs. (b) Distal ends of the femurs and proximal ends of the right tibia and fibula from a rachitic child. (c) Radiograph of the wrist of this rachitic child. (Courtesy M.F. Holick, PhD, MD, © 2007.)



BOX 203.2 CLINICAL MANIFESTATIONS OF RICKETS

Restlessness/irritability
Sweating of the head
Skeletal signs in about 6 to 9 months
Head somewhat square
Fontanelles opened/frontal bossing
Osseous borders soft (craniotables)
Teething delayed
Enlargement of costochondral junctions
Muscles flabby
Upper respiratory tract infections
Anemia (Von Jaksch–Luzet syndrome)

with a tender point and the diagnosis of fibromyalgia. In many cases these patients are suffering from periosteal bone discomfort consistent with osteomalacia.⁵⁹

Although the exact cause of the muscle weakness and bone discomfort is not fully understood, it is thought that because the major cause of osteomalacia is vitamin D deficiency and skeletal muscle has VDRs, the lack of $1,25(\text{OH})_2\text{D}$ interacting with skeletal muscle VDRs increases the muscle weakness. Collagen matrix laid down by osteoblasts on a periosteal surface with no mineralization provides little structural support for the periosteal covering, which is heavily innervated with sensory fibers. Thus the deformation caused by pressing on the periosteal covering leads to immediate bone discomfort. In addition, the collagen matrix acts like gelatin dessert and, once hydrated, expands. As a result, application of outward pressure on the periosteal covering leads to the sensation of throbbing, aching bone discomfort.⁵⁹

STRATEGIES FOR THE TREATMENT AND PREVENTION OF OSTEOMALACIA

Vitamin D deficiency is defined as a serum $25(\text{OH})\text{D}$ concentration lower than 20 ng/mL. However, to maximize intestinal calcium absorption and to minimize circulating PTH levels, it is desirable to maintain a $25(\text{OH})\text{D}$ level higher than 30 ng/mL.^{1,16} Most children and adults have a circulating blood $25(\text{OH})\text{D}$ level of between 15 and 25 ng/mL. For every 100 IU of vitamin D_2 or vitamin D_3 ingested, the blood level of $25(\text{OH})\text{D}$ increases by approximately 1 ng/mL.^{60,61} Thus, to achieve a blood $25(\text{OH})\text{D}$ level higher than 30 ng/mL, it has been recommended by the Endocrine Society that neonates during the first year receive 400 IU of vitamin D per day and that children older than 1 year and all adults receive 600 to 1000 IU and 1500 to 2000 IU of vitamin D per day, respectively.¹⁶ For obese children and adults, the



Fig. 203.6 Child with rickets demonstrating the bowed-leg deformity and rachitic rosary. The child is being held up because of severe muscle weakness. (Courtesy M.F. Holick, PhD, MD, © 2007.)

amount of vitamin D ingested should be increased by twofold to threefold.^{1,2,16}

These recommendations differ from the IOM's recommendations in part because of the fact that the IOM based its recommendations on a population model in which it was assumed that children and adults have sufficient vitamin D^{15} (Table 203.2). However, because it is now recognized that vitamin D deficiency is common worldwide,¹⁹ it is reasonable to follow the recommendations of the Endocrine Society, which used a medical model to recommend vitamin D intake for the treatment and prevention of vitamin D deficiency.¹⁶

BOX 203.3 CAUSES OF OSTEOMALACIA/RICKETS

Vitamin D deficiency
 Calcium deficiency
 Hypophosphatemia
 Fanconi syndrome
 Pseudovitamin D deficiency rickets, vitamin D–dependent rickets type 1
 Vitamin D–resistant rickets, vitamin D–dependent rickets type 2
 X-linked hypophosphatemic rickets
 Autosomal dominant hypophosphatemic rickets
 Oncogenic osteomalacia
 Hypophosphatasia
 Malabsorption syndrome
 Hypokalemic distal renal tubular acidosis
 Wilson disease
 Renal failure, chronic
 Cystinosis
 Phenytoin
 Glucocorticoids
 Highly active antiretroviral therapy
 Etidronate
 Glutethimide
 Heavy metals
 Cancer drugs

To treat vitamin D deficiency, 50,000 IU of vitamin D₂, which is the major pharmaceutical form of vitamin D available in the United States, once a week for 12 weeks or twice a week for 6 weeks will often raise the blood level above 30 ng/mL.⁶² Patients who are severely vitamin D deficient with a 25(OH)D level of less than 10 ng/mL, patients who are taking medications that would enhance vitamin D destruction, and obese patients may require an additional 12 weeks of therapy with 50,000 IU of vitamin D₂. Once the blood level of 25(OH)D is higher than 30 ng/mL, vitamin D sufficiency can be maintained by taking 50,000 IU of vitamin D once every 2 weeks.⁶³ An alternative is to treat with a vitamin D supplement, 5000 IU of vitamin D per day for 2 months followed by 2000 IU of vitamin D per day.¹⁶ The American Academy of Pediatrics recommended that all infants and children receive 400 IU of vitamin D per day, which will prevent rickets in children.⁶⁴

Children and adults who have rickets or osteomalacia caused by calcium deficiency should be treated with the adequate intake recommended for calcium, which is 800 mg/day for children younger than 12 years, 1300 mg/day for teenagers, 1000 mg for adults 19 to 50 years of age, and 1200 mg/day for adults older than 50. They should also be taking an adequate amount of vitamin D to maximize the benefit of the calcium.^{15,65}

Patients with phosphate wasting need to take either Neutra-Phos or sodium phosphate in amounts of 250 to 500 mg three to five times per day along with 0.5 to 1.0 mg of 1,25(OH)₂D₃ (calcitriol) twice per day.^{1,15,30} It should be noted that more frequent dosing of phosphate at lower doses to help maintain serum levels of phosphate is desirable for two reasons. The

TABLE 203.2
Vitamin D dietary reference intakes

Life stage group	IOM recommendations				Committee [†] recommendations	
	AI	EAR	RDA	UL	Daily allowance (IU/day)	RUL (IU)
Infants						
0-6 mo	400 IU (10 µg)	—	—	1000 IU (25 µg)	400-1000	2000
6-12 mo	400 IU (10 µg)	—	—	1500 IU (38 µg)	400-1000	2000
Children						
1-3 yr	—	400 IU (10 µg)	600 IU (15 µg)	2500 IU (63 µg)	600-1000	4000
4-8 yr	—	400 IU (10 µg)	600 IU (15 µg)	3000 IU (75 µg)	600-1000	4000
Males						
9-13 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600-1000	4000
14-18 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600-1000	4000
19-30 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
31-50 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
51-70 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
>70 yr	—	400 IU (10 µg)	800 IU (20 µg)	4000 IU (100 µg)	1500-2000	10,000
Females						
9-13 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600-1000	4000
14-18 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600-1000	4000
19-30 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
31-50 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
51-70 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
>70 yr	—	400 IU (10 µg)	800 IU (20 µg)	4000 IU (100 µg)	1500-2000	10,000
Pregnancy						
14-18 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600-1000	4000
19-30 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
31-50 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
Lactation*						
14-18 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600-1000	4000
19-30 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000
31-50 yr	—	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500-2000	10,000

*Mother's requirement: 4000 to 6000 IU (mother's intake for an infant's requirement if the infant is not receiving 400 IU/day).

[†]The Endocrine Society Practice Guidelines Committee.

AI, adequate intake; EAR, estimated average requirement; RDA, recommended dietary allowance; RUL, recommended upper intake level; UL, tolerable upper intake level.

first is that maintenance of a more normal calcium phosphate product will help in the mineralization of osteoid. Second, taking large amounts of phosphate orally results in a transient decrease in serum ionized calcium, which

stimulates the parathyroid glands to produce and secrete PTH. Chronic stimulation of the parathyroid glands by transient hypocalcemia can result in tertiary hyperparathyroidism.⁶⁶

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Primary hyperparathyroidism: rheumatologic manifestations and bone disease

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- Primary hyperparathyroidism is diagnosed on the basis of an elevated serum calcium concentration and a parathyroid hormone level that is either elevated or inappropriately normal.
- “Classic” primary hyperparathyroidism was associated with rheumatologic manifestations.
- Primary hyperparathyroidism is now generally an asymptomatic disorder with rheumatologic manifestations seen only rarely and as the subject of case reports.
- The incidence of gout and calcium pyrophosphate crystal deposition or pseudogout was previously found to be increased in patients with primary hyperparathyroidism.
- Pseudogout was also described in the past in patients with primary hyperparathyroidism after successful parathyroid surgery.
- Metabolic conditions such as primary hyperparathyroidism, though uncommon, should be considered in patients with pyrophosphate arthropathy before the age of 65 and can occur, though rarely, in patients older than 65.
- Skeletal involvement in primary hyperparathyroidism is detected with dual energy x-ray absorptiometry, with preferential involvement of cortical sites such as the distal third of the radius.
- Parathyroidectomy is indicated in patients with primary hyperparathyroidism who meet the accepted surgical criteria.
- Cinacalcet is approved by the Food and Drug Administration for the medical treatment of advanced primary hyperparathyroidism.

INTRODUCTION AND HISTORY

The effects of parathyroid hormone (PTH) on its major target organs the skeleton and kidneys gave rise to the original description of primary hyperparathyroidism more than 70 years ago as a disease of “bones, stones and groans.”^{1,2} The classic bone disease, osteitis fibrosa cystica, included degranulation of the skull (or “salt-and-pepper skull”), distal tapering of the clavicles, subperiosteal bone resorption (particularly in the phalanges), brown tumors, and bone cysts. In addition to these skeletal manifestations, rheumatologic manifestations of primary hyperparathyroidism were described commonly.³ Gout⁴ and pseudogout were appreciated as classic manifestations of primary hyperparathyroidism.^{5,6} Gout or pseudogout occasionally developed even after successful parathyroid surgery.^{7,8} Patients also periodically complained of nonspecific arthralgias. A neuromuscular disorder with atrophy of type II muscle fibers was sometimes featured as a major manifestation of the disease.⁹ These aspects of primary hyperparathyroidism were consistent with the traditional idea that PTH in excess can affect organ systems besides the skeleton and kidneys.

Over the past 30 years, however, this classic description of primary hyperparathyroidism has been replaced by one that is primarily asymptomatic. The shift in manifestation from a symptomatic to an asymptomatic clinical phenotype has been due to the widespread use of multichannel autoanalyzers, which typically include serum calcium measurement.^{10,11}

CURRENT PROFILE OF HYPERPARATHYROIDISM

Most patients with primary hyperparathyroidism are women in their postmenopausal years.¹²⁻¹⁴ The serum calcium concentration is typically within 1 mg/dL above the upper limit of normal, and the PTH concentration is usually 1.5 to 2 times the upper limit of normal.^{2,12,14} Hypercalciuria is seen in approximately 40% of patients. Hypophosphatemia, reflecting the physiologic actions of PTH to induce phosphaturia, is seen in less than 25% of patients. Overt hyperparathyroid bone disease with specific radiologic findings is vanishingly rare. The incidence of kidney stones has diminished to approximately 15% to 20% of all patients, although it remains the most common clinical complication of primary hyperparathyroidism.¹⁵ Consistent with this modern manifestation, patients rarely have overt neuromuscular disease but may still complain of vague muscle weakness and easy fatigability. Rheumatologic manifestations that can be ascribed specifically to the articular system and that are reviewed here are uncommon and have been relegated to case reports. These manifestations can be divided into the impact on crystal-related arthropathies (gout and pseudogout) and nonspecific effects on bones and joints.

CRYSTAL ARTHROPATHIES

Gout

The incidence of gout appears to be increased in patients with primary hyperparathyroidism who have hyperuricemia.¹⁶⁻¹⁸ Rather dramatic radiologic manifestations can sometimes be seen, as in the case report of an individual with a lytic lesion that was initially assumed to be a brown tumor but found on joint aspiration to contain urate deposits.¹⁹ A possible explanation for the association of gout and primary hyperparathyroidism is the increased levels of serum uric acid that have been described in some,⁴ but not all¹⁵ cohorts of patients with primary hyperparathyroidism. Data on serum uric acid in primary hyperparathyroidism are limited. However, in one study, 53 subjects with primary hyperparathyroidism had significantly higher serum uric acid levels, along with a reduction in the clearance of uric acid,⁴ than did age- and sex-matched control subjects. Within 6 months after successful parathyroid surgery in 26 subjects, serum uric acid levels declined significantly. It has been suggested that PTH might inhibit uric acid excretion in the proximal renal tubule. Pseudohypoparathyroidism, a disease associated with renal resistance to PTH, was found in one kindred to be associated with hypouricemia and an increase in the fractional excretion of uric acid, thus suggesting an important role of PTH in the renal handling of uric acid.²⁰

Calcium pyrophosphate crystal deposition disease (pseudogout)

Primary hyperparathyroidism and calcium pyrophosphate crystal deposition (CPPD) disease, now named pyrophosphate arthropathy, have been associated in numerous reports.^{5,21-27} As is the case for CPPD in general, aging confers greater risk for radiographic evidence of CPPD in primary hyperparathyroidism. Mechanisms other than chronic hypercalcemia might be particularly relevant to the process of CPPD in the joints of subjects with primary hyperparathyroidism. It has been speculated that the function of proteoglycans that normally inhibit calcium pyrophosphate crystallization²⁸ might be impaired by the elevated calcium in serum and joint fluid.^{24,26} It

has also been postulated more recently that hyperparathyroid patients with CPPD exhibit abnormal local cartilage metabolism of pyrophosphate.²⁹ The nucleoside triphosphate pyrophosphohydrolase enzymes, which normally catalyze the production of pyrophosphate, appear to be overactive.³⁰ Excessive nucleoside triphosphate pyrophosphohydrolase activity could promote the formation and ultimate deposition of calcium- and pyrophosphate-containing material in the joints.³¹

A clinical attack of pseudogout is an uncommon complication of CPPD disease, although this is true for patients both with and without primary hyperparathyroidism. Metabolic conditions such as primary hyperparathyroidism, though an uncommon cause, should be considered in patients in whom CPPD occurs before 65 years of age and can be considered in those older than 65.^{32,33} Interestingly, pseudogout has been described in patients with primary hyperparathyroidism after successful parathyroid surgery when the serum calcium level has returned to normal.^{7,8,21,24,34-37} In one series in which 20 patients with primary hyperparathyroidism and pseudogout were described,³⁸ CPPD had previously been diagnosed in 8, whereas the diagnosis was made in the remainder after parathyroidectomy. In another report, three hyperparathyroid patients with radiographic CPPD received immediate, aggressive vitamin D treatment after parathyroidectomy in an attempt to prevent postoperative pseudogout,³⁹ and indeed, pseudogout did not develop after parathyroidectomy in these patients. However, without a control group, one cannot be certain that the attacks would have occurred if they had not been treated with vitamin D.

The occurrence of pseudogout after parathyroid surgery appears to be triggered by the fall in serum calcium.^{21,24} As the serum calcium concentration falls, it is presumed that the synovial fluid calcium concentration also falls, thus rendering the pyrophosphate crystals more soluble and allowing their release into the synovial space.^{22,40} The idea that a rapid reduction in serum calcium is primarily responsible for an attack of CPPD and not the primary hyperparathyroidism *per se* comes from other reports in which pseudogout has been precipitated after medical treatment that leads to hypocalcemia. One report described a case of pseudogout in the setting of mithramycin treatment of hypercalcemia⁴¹ and another in the setting of hypocalcemia after pamidronate treatment.⁴² Similarly, injection of hyaluronate into the joint space can precipitate pseudogout, possibly because the phosphate in the hyaluronate preparation may lower intraarticular calcium concentrations and lead to crystal shedding.⁴³

PRIMARY HYPERPARATHYROIDISM AND THE SKELETON

There is evidence that excessive PTH may have an adverse effect on joints in addition to the specific situations mentioned earlier. These rheumatologic effects are consistent with the classic notion that PTH is catabolic at skeletal sites. However, our understanding of the skeletal effects of PTH has changed along with the evolving clinical profile of primary hyperparathyroidism. Thus, in the series of Silverberg and colleagues,⁴⁴ less than 2% of patients with primary hyperparathyroidism had specific skeletal manifestations of hyperparathyroidism noted on conventional x-ray examination. Along with the rarity of overt skeletal disease in primary hyperparathyroidism, other less common target organs of the primary hyperparathyroid state, including the articular system, have also become rare manifestations. The effects of mild primary hyperparathyroidism on the skeleton are therefore the key consequence to be considered.

Skeletal effects of mild primary hyperparathyroidism

With primary hyperparathyroidism now commonly manifested as an asymptomatic disorder, it has been possible to address a more subtle but critically important question: do patients with asymptomatic primary hyperparathyroidism have evidence of skeletal involvement? Using dual-energy x-ray absorptiometry (DXA), Silverberg and coworkers⁴⁴ provided evidence that skeletal involvement does occur in patients with asymptomatic primary hyperparathyroidism, although it is site specific. Bone mineral density (BMD) is reduced in the distal third of the radius, a site that contains mainly cortical bone. In the lumbar skeleton, which is enriched in cancellous bone, skeletal mass is relatively well preserved in patients with primary hyperparathyroidism, with only small reductions from age- and sex-specific norms.^{44,45} BMD of the hip region, which contains a more even admixture of cortical and cancellous elements, is intermediate between that of cancellous and cortical sites (Fig. 204.1).

Even though DXA has provided valuable information, high-resolution peripheral quantitative computed tomography (HRpQCT) of the radius and

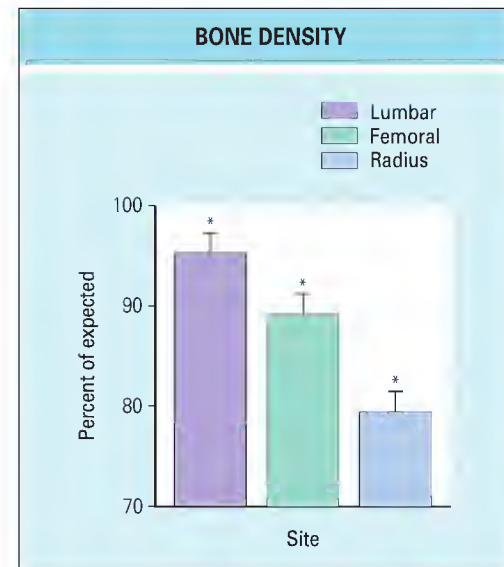


Fig. 204.1 Bone densitometry in primary hyperparathyroidism. Data are shown in comparison to age- and sex-matched normal subjects. Divergence from expected values is different at each site ($P = .0001$). (Reprinted with permission from Silverberg SJ, Shane E, de la Cruz L, et al. *Skeletal disease in primary hyperparathyroidism*. *J Bone Miner Res* 1989;4:283-91.)

tibia has allowed examination of the skeleton in greater detail.^{46,47} HRpQCT has confirmed that cortical bone is affected at both sites, but it has also demonstrated that cancellous bone may also be affected.

Fracture data in patients with primary hyperparathyroidism are not clear because virtually all information comes from retrospective or cross-sectional studies.⁴⁸⁻⁵⁴ A Mayo Clinic study⁵¹ of more than 400 patients showed an increase in both vertebral and nonvertebral fractures. In a review of several studies, Mosekilde⁵⁴ reported that the incidence of fractures was increased in primary hyperparathyroidism. By classifying patients according to disease severity, Vignali and associates⁵⁵ observed an increased incidence of vertebral fractures in both symptomatic and asymptomatic patients.

Parathyroid hormone therapy and joint manifestations

It is also important to consider the rheumatologic consequences of “medical” hyperparathyroidism as a consequence of therapy with PTH. Teriparatide [recombinant human PTH(1-34)] increases BMD and reduces the incidence of fractures in postmenopausal women with osteoporosis (Fig. 204.2).^{56,57} Teriparatide also increases BMD in men with primary or hypogonadal osteoporosis.⁵⁸ When compared with alendronate, it has a greater effect in reducing vertebral fractures in patients with glucocorticoid-induced osteoporosis.⁵⁹ As opposed to primary hyperparathyroidism, in which exposure to elevated PTH is continuous, once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical surfaces by preferential stimulation of osteoblast activity.⁶⁰ Although it is theoretically possible that adverse rheumatologic effects, formerly seen frequently in primary hyperparathyroidism, could be experienced in some PTH-treated patients, this has not been noted clinically. Clinical trials have shown that treatment with teriparatide results in 3% of patients having serum uric acid concentrations above the upper limit of normal as opposed to 1% of placebo-treated patients. However, the hyperuricemia did not result in an increase in episodes of gout.^{56,58,59} Moreover, gout attacks were not increased in patients with mild or moderate renal impairment whose uric acid concentration increased.⁶¹

Transient increases in the serum calcium concentration have been noted in controlled trials, but articular cartilage calcification has not been reported as an adverse event.^{56,58,59,62-64} The incidence of pseudogout in patients treated with teriparatide is not increased over that in patients treated with placebo. Much less information is available about PTH(1-84), the full-length recombinant human PTH molecule, in part because of the fact that it is not approved in the United States. The experience in Europe, where it is approved in many countries for the treatment of postmenopausal osteoporosis, does not suggest that the data reviewed earlier with regard to rheumatologic manifestations are any different from that of teriparatide.^{65,66}

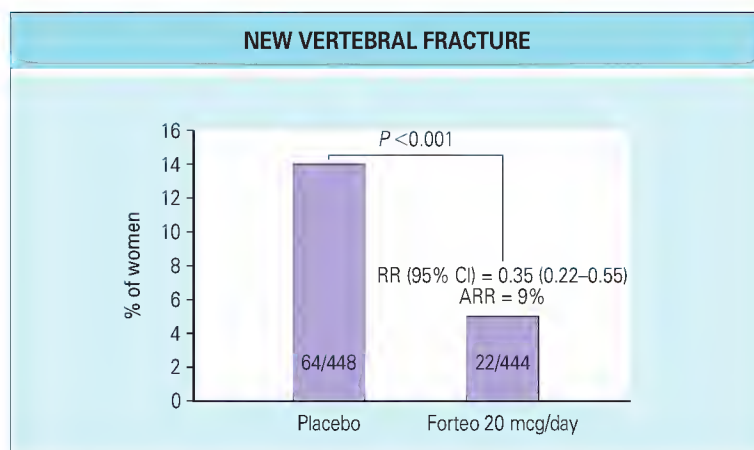


Fig. 204.2 Reduction in the risk for new morphometric vertebral fractures in postmenopausal women with severe osteoporosis after PTH(1-34) [Forteo] 20 mcg/day over a median treatment period of 19 months versus placebo. ARR, absolute risk reduction; RR, relative risk. (Data from Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone [1-34] on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001;344:1434-41.)

DIAGNOSIS AND TREATMENT OF PRIMARY HYPERPARATHYROIDISM

Diagnosis of primary hyperparathyroidism is based on an elevated serum calcium concentration and a PTH level that is either elevated or inappropriately normal. When the PTH level is elevated in a patient with hypercalcemia, the differential diagnosis includes the use of thiazide diuretics or lithium, familial hypocalciuric hypercalcemia, and tertiary hyperparathyroidism associated with end-stage renal disease. Malignancy-associated hypercalcemia should not be a consideration when the PTH level is high because the hypercalcemic agent in this condition, PTH-related protein, is not detected by the currently available immunoradiometric assays for PTH.

Surgical treatment

Surgery is indicated for patients with overt symptoms of classic disease (i.e., kidney stones, osteitis fibrosa cystica). In patients with few if any symptoms, guidelines to aid in clinical decision-making are based on the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (Table 204.1).⁶⁷⁻⁷² Patients who successfully undergo parathyroidectomy show rapid normalization of serum calcium and PTH levels. Improvement in BMD at the spine and hip follows over a 3- to 4-year period after surgery.¹⁵ Most patients who are asymptomatic and do not meet the surgical criteria do well without evidence of progressive disease. However, approximately a third of patients will experience progressive disease.¹⁴ Only age appears to be predictive of progression: patients younger than 50 years are significantly more likely than those older than 50 to experience worsening disease.⁷³

Medical treatment

Development of a medical approach to asymptomatic primary hyperparathyroidism has been of considerable interest. The calcimimetic agent

TABLE 204.1

Criteria for parathyroid surgery in patients with asymptomatic primary hyperparathyroidism

Variable	Surgical criteria*
Serum calcium	1.0 mg/dL (0.25 mmol/L) greater than the upper limit of normal
Creatinine clearance	Reduced to <60 mL/min (calculated)
Bone mineral density	T-score less than -2.5 at any site [†] and/or previous fragility fracture
Age	<50 yr

*Surgery is also indicated for patients in whom medical surveillance is neither desired nor possible.

[†]Lumbar spine, total hip, femoral neck, or distal third of the radius.

From Bilezikian JP, Khan AA, Potts JT Jr; Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 2009;94:335-9.

cinacalcet (Sensipar) is the only medical therapy approved for primary hyperparathyroidism in the United States. It is indicated for individuals with advanced disease. Cinacalcet is a calcimimetic that binds to a region of the calcium receptor that increases its affinity for calcium. The subsequent increase in intracellular calcium in parathyroid cells leads to a reduction in the synthesis and secretion of PTH. Cinacalcet has been shown to normalize serum calcium levels for more than 5 years in patients with primary hyperparathyroidism.⁷⁴⁻⁷⁶ PTH levels fall modestly but not usually into the normal range. Bone density does not increase with cinacalcet. Gout and pseudogout have not been reported with this treatment.

Estrogen therapy in postmenopausal women with primary hyperparathyroidism is associated with small reductions in the serum calcium concentration and increases in bone density, along with stable PTH levels.⁷⁷ Raloxifene, a selective estrogen receptor modulator, is a potential alternative that has shown calcium-lowering effects similar to estrogen in a small pilot study of postmenopausal women with primary hyperparathyroidism.⁷⁸ Bisphosphonates have also been considered as a possible medical approach to primary hyperparathyroidism. Alendronate has been shown to increase lumbar spine BMD in patients with primary hyperparathyroidism by approximately 4% to 6%.⁷⁹⁻⁸¹ In most studies, serum calcium and PTH levels do not change significantly.

CONCLUSION

In the past, symptomatic primary hyperparathyroidism was associated with abnormalities in the articular system. Now that primary hyperparathyroidism is generally asymptomatic in the United States and in most of the developed world, rheumatologic manifestations are mainly of historic interest. Primary metabolic conditions such as primary hyperparathyroidism, though uncommon, should be considered in patients with CPPD occurring before the age of 55 years and can be considered in those older than 55. In patients with rheumatologic manifestations along with primary hyperparathyroidism, a search for other conditions should be undertaken before concluding that they might be unusually affected in this manner by the hyperparathyroid state.

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205

Renal osteodystrophy

■ PAUL D. MILLER

- Renal osteodystrophy is a heterogeneous group of metabolic bone disorders that accompany chronic kidney disease (CKD). The derangements in mineral metabolism begin even in early CKD (stages 1 to 3: glomerular filtration rate [GFR] between 90 and 30 mL/min).
- A specific diagnosis of the type of renal bone disease is made most objectively by double tetracycline-labeled quantitative bone histomorphometry (biopsy).
- All forms of renal osteodystrophy may feature low bone mineral density (BMD) or fragility fractures. The World Health Organization criteria, well accepted for the diagnosis of osteoporosis in postmenopausal women and elderly men, cannot be used to diagnose osteoporosis in individuals with CKD (stage 4-5/5D: GFR <30 mL/min or 15 mL/min with or without dialysis [D]) but can be used to make the diagnosis in early (stages 1 to 3) CKD.
- The diagnosis of osteoporosis in patients with stage 4-5/5D CKD is made by excluding other forms of renal osteodystrophy in the setting of low BMD or fragility fractures.
- Specific approaches are used to treat specific forms of renal osteodystrophy (e.g., hyperparathyroidism, aluminum bone disease, chronic metabolic acidosis).
- Based on *post-hoc* analysis, oral bisphosphonates in doses approved by the U.S. Food and Drug Administration for the treatment of postmenopausal, glucocorticoid-induced, or male osteoporosis seem to be safe in patients with stage 4 CKD, at least for a 2- to 3-year period of use. No data are available on the efficacy or safety of bisphosphonates for stage 5/5D CKD. Intravenous bisphosphonates are safe in the usual doses for stages 1 to 3 CKD; slowing the infusion time to 30 to 60 minutes seems to be safe for off-label use of zoledronic acid in stage 4-5/5D CKD. Intravenous ibandronate does not appear to require a slower rate of injection in stage 4-5/5D CKD. Denosumab has no GFR registration restrictions because it is not cleared by the kidney.
- More data are needed to define the relationship between low BMD and fracture risk in the various heterogeneous forms of renal osteodystrophy and whether bisphosphonates or denosumab can reduce fracture risk in osteoporotic patients with severe stage 5/5D CKD or in those with severe secondary hyperparathyroidism.
- Bisphosphonates are contraindicated in patients with osteomalacia and adynamic renal bone disease. In adynamic bone disease there remains the possibility that reducing bone turnover by any antiresorptive pharmacologic agent may be associated with an increase in the risk for vascular calcification.

INTRODUCTION

Renal osteodystrophy is the term used to define the heterogeneous group of metabolic bone disorders that accompany a declining glomerular filtration rate (GFR) (Box 205.1).^{1,2} Although one of these forms of renal bone disease may be present in patients with different stages of chronic kidney disease (CKD), patients may also move from one form to another, either as a process of the natural biology of renal bone disease or as a result of the treatments used to manage a specific form of renal bone disease. Recently, the Kidney Disease Improving Global Outcome (KDIGO) working group has defined the bone diseases that accompany CKD as systemic diseases in that they are associated with vascular calcification and abnormalities in bone turnover, a

condition termed chronic kidney disease–mineral and bone disorder (CKD-MBD).³ Even though no distinct methods are available to make a diagnosis of CKD-MBD, the abnormalities in bone turnover that universally accompany CKD are often associated with vascular calcification. The presence of elevated levels of parathyroid hormone (PTH) or serum phosphorus may suggest the presence of CKD-MBD in patients with CKD. The Disease Outcome Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) has classified the degrees of CKD according to the GFR in patients with known intrinsic renal disease (Table 205.1).⁴ The NKF divided the broad category of stage 3 CKD (GFR, 30 to 60 mL/min) into two categories—stage 3A (45 to 60 mL/min) and 3B (30 to 45 mL/min)—and added quantitative levels of proteinuria to the classification because recent data have linked the level of proteinuria to the prognosis for progression of CKD. Proteinuria (>300 mg/g creatinine or >500 mg/24 hr) serves as a cut point that adds a risk factor for progression of CKD over and above a low GFR *per se*.⁵ In addition, aging is associated with a reduction in GFR even without any known intrinsic renal disease. The Third U.S. National Health and Nutrition Examination Survey reported that 25% of otherwise healthy adults have GFR levels lower than 25 mL/min.⁶ It is not known whether bone metabolism differs in patients whose GFR is reduced because of intrinsic parenchymal damage as opposed to age-related reductions in GFR without another specific intrinsic renal diagnosis.

At each level of CKD a specific form of renal osteodystrophy may be detected by quantitative bone histomorphometry. The earliest form of renal bone disease (secondary hyperparathyroidism) may be defined by quantitative histomorphometry or biochemical profiling (elevated 1-84 intact PTH) as early as stage 3 CKD (GFR, 30 to 60 mL/min). Even though there is an exponential relationship between the declining level of GFR and the height of endogenous PTH, elevated PTH levels (secondary hyperparathyroidism) may also be seen in patients with various forms of osteoporosis from other causes that may not be related to a reduced GFR (e.g., low 25-hydroxyvitamin D levels, calcium malabsorption, hypercalciuria). Only after correcting other reversible factors that may also lead to secondary hyperparathyroidism can the elevated serum PTH level be attributed to the reduction in renal function.

The KDOQI guidelines (based on both opinion and evidence) provide suggestions concerning the management of secondary hyperparathyroidism when attributable to intrinsic renal damage.⁴ In addition, suggestions have been published for the management of patients with postmenopausal, male, and glucocorticoid-induced osteoporosis who have secondary hyperparathyroidism not related to a reduction in renal function.⁷⁻¹⁵

The other forms of renal bone disease (osteomalacia, mixed renal osteodystrophy, adynamic renal bone disease, and aluminum bone disease) are less common until stage 5 CKD (end-stage renal disease [ESRD] with a GFR lower than 15 mL/min or undergoing dialysis). These forms of renal bone disease are most objectively defined by double tetracycline-labeled quantitative histomorphometry, and quantitative histomorphometric criteria for classifying the specific form of renal bone disease (standardized nomenclature) have been published.^{16,17} Hence, the means by which renal osteodystrophy is first defined is divided into quantitative bone histomorphometry, then biochemical profiling, and finally, clinically. In addition, the challenge of defining osteoporosis, a common metabolic bone disease in the CKD population, is discussed. Finally, the therapeutic options that are available to treat specific forms of renal bone disease and osteoporosis associated with CKD are presented.

QUANTITATIVE BONE HISTOMORPHOMETRY

Double tetracycline-labeled quantitative bone histomorphometry is the “gold standard” for defining the specific forms of renal osteodystrophy.^{1,2,17,18}

BOX 205.1 HISTOMORPHOMETRIC FORMS OF RENAL BONE DISEASE**High or normal bone turnover**

Osteitis fibrosa cystica: increased osteoclast and osteoblast activity and peritrabecular fibrosis

Bone biopsy: increased bone turnover, increased number and activity of osteoblasts and osteoclasts, and variable amounts of peritrabecular fibrosis; increased osteoid with a “woven” pattern (as opposed to a normal “lamellar” pattern)

Etiology: secondary hyperparathyroidism

Low bone turnover

Osteomalacia: defective mineralization of newly formed osteoid

Bone biopsy: increased osteoid seam width, increased trabecular surface covered with osteoid, and decreased bone mineralization

Etiology:

Vitamin D related:

Vitamin D deficiency

Resistance to vitamin D

Non-vitamin D related:

Chronic metabolic acidosis: excess H^+ ions are buffered by bone HCO_3^- , which leads to release of calcium and a gradual reduction in bone calcium stores, subsequent bone demineralization, and eventually osteopenia; it is associated with an increased risk for recurrent fractures

Aluminum accumulation: most commonly related to aluminum-containing phosphate binder therapy and, recently, aluminum-containing antacids

Phosphate depletion

Adynamic or aplastic bone disease: most commonly seen in patients undergoing continuous ambulatory peritoneal dialysis; though characterized by low bone turnover, as in osteomalacia, there is no increase in osteoid formation

Bone biopsy: normal or decreased osteoid volume and reduced bone formation rate, reduced numbers of osteoblasts and osteoclasts

Etiology:

Sustained:

Total parathyroidectomy

Corticosteroid-induced osteoporosis

Diabetes mellitus: in patients with type 1, plasma parathyroid hormone levels tend to be lower than normal, which probably accounts for the lower than normal bone formation rate (speculative); lack of insulin may contribute by diminishing bone turnover in the uremic setting

Reversible:

Calcitriol and vitamin D analogues used to suppress the production of parathyroid hormone

Possibly oversuppression of parathyroid hormone production by cinacalcet

Exogenous calcium loading

Immobilization

Aluminum toxicity

Strontium

Diagnosis: aluminum loading must be excluded; bone biopsy is definitive.

Low to high bone turnover

Mixed uremic osteodystrophy

Calcific uremic vasculopathy

Dialysis-related β_2 -microglobulin amyloidosis (not exactly a metabolic bone disease)

Posttransplant bone disease

Osteoporosis

Age related

Hypogonadism

Corticosteroids

Heparin

Chronic acidosis

Poor nutrition

Vitamin D deficiency

Calcineurin inhibitors

TABLE 205.1
Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage with a normal or increased GFR	>80
2	Kidney damage with a mildly decreased GFR	80-60
3	Kidney damage with a moderately decreased GFR	60-30
4	Kidney damage with a severely decreased GFR	30-15
5	Kidney failure	<15 (or dialysis)

GFR, glomerular filtration rate.

From Massry SG, Calum JW. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42(suppl 3):S10-135.

Several comprehensive atlases of renal bone disease have been published that describe in depth the normal bone remodeling process as measured by histomorphometry and then provide examples of bone biopsy specimens with a detailed descriptive analysis of each form of renal osteodystrophy.^{1,2} In addition, these atlases deal with histomorphometric data in post-renal transplantation bone disease and also provide histologic and clinical guidance for the diagnosis of osteoporosis in patients with CKD.

The KDOQI was the first attempt to provide broad guidelines for management of the abnormalities in calcium, phosphorus, PTH, and bone that accompany CKD,⁴ and more recently, a working group of the KDIGO expanded our understanding of the association of bone turnover, mineralization, and volume with the systemic vascular calcification that leads to the most prevalent cause of death in CKD patients: CKD-MBD.¹⁹

Bone biopsy should be considered in the following special clinical circumstances in patients with CKD^{1,2,10-12,18,19-25}.

- In those with fragility fractures because patients with all forms of renal osteodystrophy may sustain fractures and making the correct diagnosis is paramount in choosing the correct treatment. The diagnosis of osteoporosis, a very prevalent metabolic bone disease in patients with CKD, cannot be made in patients with stage 4-5/5D CKD by the bone mineral density (BMD) (World Health Organization [WHO]) criteria established for postmenopausal osteoporosis, nor by the presence of fragility fractures.^{9-12,20}
- In patients with an unexplained elevation in bone-specific alkaline phosphatase (BSAP) to exclude osteomalacia.
- In patients with severe secondary (e.g., tertiary) hyperparathyroidism before parathyroidectomy to be certain that no aluminum is present in bone. Parathyroidectomy before aluminum is removed will mitigate the ability of deferoxamine (DFO) to chelate and remove aluminum from bone.
- Before initiating DFO chelation to remove aluminum from bone in patients with suspected aluminum renal bone disease to be absolutely certain that aluminum is present in bone. Serum aluminum levels may not always reflect the presence of aluminum in bone.
- In patients with suspected adynamic renal bone disease based on biochemical profiles (hypercalcemia, low BSAP levels, lower intact PTH levels [<100 to 150 pg/mL], or a ratio of 1-84 to 7-84 [scantibodies] PTH <1.0).^{21,26,27}
- Before treating patients with stage 5/5D (dialysis) CKD with osteoporosis-specific pharmacologic agents for suspected osteoporosis because both osteomalacia and adynamic renal bone disease are diseases for which bisphosphonates or denosumab are not recommended. This opinion is based on the theoretic concept that it might be harmful to further reduce bone turnover in states of low bone turnover. Data would be needed to establish that antiresorptive agents may provide additional benefit for bone (further reduction in fracture risk) in patients with preexisting adynamic bone disease before these osteoporosis agents can be recommended.

TABLE 205.2
Relationship between biochemical profiles and key quantitative histomorphometrics in renal osteodystrophy in certain groups of patients

	iPTH	ALP/BSAP	BFR/BS	OV/BV	O.Th
High bone turnover					
	>10 times normal	Normal to increased	Increased	Variable, <15%	Normal to increased
	>3 times normal				
Low bone turnover					
Osteomalacia	Variable	Variable, increased	Reduced	>15%	Increased
Adynamic bone disease <2 times to reduced	Normal to reduced	Reduced to absent	<15%	Normal to reduced	
Mixed	Variable increased	Variable increased	Variable	>15%	Normal to increased
Osteoporosis	Normal (variable)	Normal (variable)	Normal	<15%	Normal

ALP, alkaline phosphatase; BFR, bone formation rate; BS, breaking strength; BSAP, bone-specific alkaline phosphatase; BV, bone volume; iPTH, intact parathyroid hormone; O.Th, osteoid thickness; OV, osteoid volume.
From Miller PD, Lerner E. Renal bone diseases. In: Kleerekoper M, Siris E, McClung M, editors. The bone and mineral manual. Vol II. San Diego: Academic Press; 2004.

BIOCHEMICAL PROFILING

The laboratory tests that should be performed routinely in patients with renal disease, especially from stage 3 CKD onward, include serum calcium, phosphorus, PTH, BSAP, creatinine, chloride, carbon dioxide, and 25-hydroxyvitamin and 1,25-dihydroxyvitamin D levels.^{4,19,28-30}

Biochemical tests are performed for two distinctly separate reasons: (1) in an attempt to predict the histomorphometric findings in patients with CKD and (2) to make clinical management decisions to prevent the development of hyperphosphatemia, metabolic acidosis, and hyperparathyroidism.²²⁻²⁵

The use of biochemical profiling for characterizing the type of renal bone disease as defined by histomorphometry has value in groups of patients but loses both sensitivity and specificity in individual patient management. Table 205.2 condenses the generalities of the biochemical findings in CKD.²⁸ Previous publications have defined these biochemical-histologic relationships in much greater detail.^{4,19}

In general, patients with intact PTH (1-84) levels six times the upper limit of normal have a high probability of osteitis fibrosa cystica being present. In turn, patients who have low levels of PTH and BSAP have a higher probability of renal-related very low bone turnover or even adynamic or aluminum bone disease or low-bone turnover osteoporosis.^{4,22,30} Hence, although biochemical profiles are helpful in groups of patients, there is enough overlap that they may not accurately reflect bone histology in individual patients sufficiently to make bone biopsy unnecessary. For example, although PTH levels are ordinarily lower (<150 pg/mL) in patients with adynamic renal bone disease,^{4,19} published data suggest that patients with biopsy-proven adynamic renal bone disease may have intact PTH levels greater than 500 pg/mL.²¹ These situations may be associated with higher levels of catabolic PTH (7-84 PTH) and a 1-84:7-84 ratio of less than 1.0, although these ratios have been inconsistent in their discriminatory value.³¹ Even though it is biologically reasonable to assume that a patient with a 1-84:7-84 PTH ratio of less than 1.0 and a low BSAP has a high probability of having adynamic renal bone disease, data validating this are lacking, and thus biopsy is a necessity before major management decisions are made.

There are nonmodifiable as well as modifiable causes of adynamic bone disease (see Box 205.1).³² If the clinician suspects that the adynamic renal bone disease may be due, for example, to oversuppression of PTH by a vitamin D analogue or cinacalcet, it may be simpler to discontinue or reduce the dosage of the vitamin D analogue or cinacalcet and allow endogenous PTH levels to increase. However, clinical questions still remain unanswered if these modifications are made to allow the PTH level to rise. For example, does the increase in PTH translate into an improvement in bone turnover or a reduction in fracture risk in patients with iatrogenically induced adynamic renal bone disease? Bone histomorphometry, with measurement of bone formation rates and mineral apposition rates both before and after modification of factors that might be associated with adynamic bone disease, might be the most objective means by which to monitor the influence of any modification designed to alter rates of bone turnover.³³

Patients with renal osteodystrophy may move from one form of renal bone disease to another, and accompanying these transitions are distinct biochemical and histomorphometric changes that reflect the transition.^{19,28-30} For example, as CKD progresses through stages 3 to 5, there is progressive

development of secondary hyperparathyroidism that often resolves after renal transplantation and may then return again if the transplant is rejected and the patient returns to dialysis.^{19,22,30} Management decisions surrounding renal transplantation have been the topic of recently published texts.^{29,34}

The use of biochemical tests to manage individual derangements in chemical values that develop during the progression of CKD is a common means by which clinical nephrologists attempt to prevent the consequences of the development of hyperphosphatemia, metabolic acidosis, hyperparathyroidism, osteomalacia, and aluminum bone disease. The reader is referred to previously published details on management of the metabolic derangements that are seen in the progressive stages of CKD.^{4,19,22,30}

HYPERPHOSPHATEMIA AND HYPERPARATHYROIDISM

Hyperphosphatemia develops as the GFR declines because of the restricted capacity of the renal tubule to increase absolute urinary phosphorus excretion. Tubular reabsorption of phosphorus (TRP) decreases as the filtered phosphorus load decreases in an attempt to maintain the absolute urine phosphorus excretion rate and prevent hyperphosphatemia. Mediators of the decrease in TRP are the rising PTH and osteocyte-derived fibroblast growth factor-23 (FGF-23) levels.^{35,36} However, TRP can decline to only a limited degree even though serum PTH and FGF-23 levels continue to rise.

In the original description of the “trade-off hypothesis,” one of the causes of the progressive rise in endogenous PTH as GFR declines is retention of phosphorus and the subsequent adaptation to maintain a normal serum phosphorus level (to keep the calcium × phosphorus product normal and mitigate soft tissue calcification). The trade-off is the development of progressive secondary hyperparathyroidism.²⁵ Hence, in an ideal CKD management scenario, one restricts dietary phosphorus intake at certain levels of GFR to prevent the subsequent development of secondary hyperparathyroidism (which is now known to be related to multifactorial cascades: hypocalcemia, reduced renal production of 1,25-dihydroxyvitamin D, and a direct effect of elevated serum phosphorus and FGF-23 levels in reducing PTH production). Restriction of dietary phosphorus is difficult because phosphorus is ubiquitous in the food chain. In addition, serum phosphorus concentrations may vary because of the cellular shifts in phosphorus that occur after a glucose load or change in acid-base status. Thus mild and intermittent hyperphosphatemia may not be recognizable in stages 1 to 3 CKD. Persistent elevation of serum phosphorus may be seen only in stages 4 to 5 CKD, yet increased FGF-23 and secondary hyperparathyroidism precede this development. Hence, in both the KDOQI and KDIGO guidelines, the recommendation is to restrict dietary phosphorus and, if this is ineffective, to use one of the vitamin D analogues to suppress PTH values in stages 3 and 4 CKD when PTH levels rise to higher than 70 pg/mL (stage 3 CKD) or 110 pg/mL (stage 4 CKD) on more than two consecutive measurements. The purpose is to mitigate the effects of chronic elevation of PTH on skeletal health.

Suppression of PTH in patients with stage 5/5D CKD with the use of vitamin D analogues or cinacalcet has greater consensus in the nephrology community than does suppression of PTH in those with stage 3 or 4 CKD.^{37,38} Use of the pharmacologic modalities designed to suppress PTH levels in

patients with CKD is probably best directed by either nephrologists or specialists with a keen interest in metabolic bone disease. In patients with CKD, before or during the use of vitamin D analogues it is also very important to maintain the serum phosphorus concentration in a normal range to mitigate the potential for soft tissue calcification. A potential advantage of using cinacalcet as opposed to vitamin D analogues to suppress PTH levels is the finding that cinacalcet does not increase serum phosphorus or calcium levels in CKD patients.³⁹

Cinacalcet (initially at a dose of 30 mg/day with the dosage titrated to achieve an intact PTH level <250 pg/mL) normalized serum calcium and BSAP levels and, in contrast to the hyperphosphatemia that may be seen with the use of vitamin D analogues, lowered serum phosphorus concentrations as well.³⁹ Careful monitoring of PTH values is important if inhibitors of PTH production are used in patients with ESRD and severe secondary hyperparathyroidism. Although current guidelines suggest reducing PTH levels to less than 250 pg/mL in ESRD patients, there is a concern that oversuppression of bone turnover may lead to the development of adynamic bone disease if PTH levels are reduced too low.^{32,33} Currently, no universal consensus about the safe level of reduction of PTH has been reached. The KDIGO guidelines suggest watching the trend of PTH rather than making a clinical decision based on a single determination.

Surgical parathyroidectomy is indicated in patients with stage 5 CKD who have severe hyperparathyroidism that is not manageable with vitamin D analogues or cinacalcet. Parathyroidectomy is suggested in ESRD patients with persistent elevations in PTH levels greater than 800 pg/mL associated with persistent hypercalcemia, bone fractures, soft tissue calcification, or hyperphosphatemia.^{4,8,19}

OSTEOMALACIA

Osteomalacia, another form of low bone turnover, may also be seen in patients with CKD and has a variety of causes (Fig. 205.1). Even though accumulation of aluminum on the surfaces of osteoid is one of the reversible causes of osteomalacia, this disease may also be seen in the absence of aluminum accumulation and be related to either deficiency or insufficiency of 25-hydroxyvitamin D levels, low 1,25-dihydroxyvitamin D levels, chronic hypophosphatemia, or chronic metabolic acidosis.

Specific quantitative histomorphometric criteria have been established for the classification of osteomalacia.^{1,17,18} Although low bone turnover may be seen in a variety of disease states, including osteoporosis, osteomalacia *per se* has very specific diagnostic criteria.

Because all forms of osteomalacia have a distinct treatable etiology, the correct diagnosis is essential for effective therapy. Fragility fractures may develop in patients with osteomalacia and osteoporosis. As will be discussed, bisphosphonates are contraindicated in patients with osteomalacia. Thus it becomes especially important to differentiate osteoporosis from osteomalacia, especially in a patient with ESRD and fragility fractures. Here, too, double tetracycline-labeled bone biopsy is the single most objective means of making the differential diagnosis.

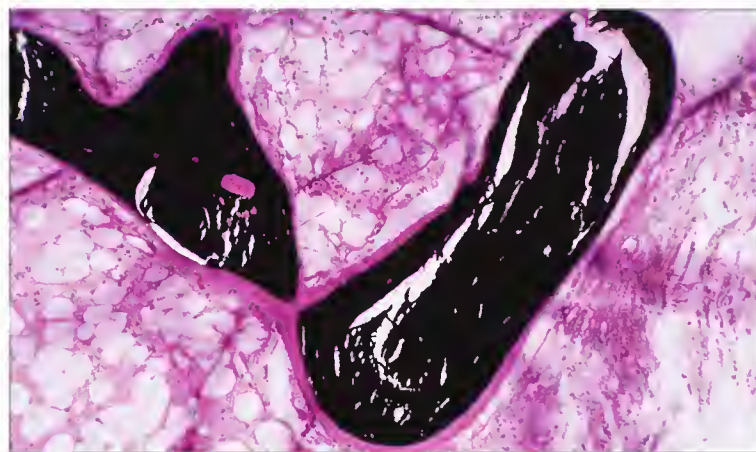


Fig. 205.1 Osteomalacia: osteoid (pink) surface greater than 80%, osteoid thickness greater than 12 μ m, and mineralization lag time longer than 100 days. (From Miller PD, Huffer W. Renal osteodystrophy. In: Schrier RW, Bennett W, editors. *Essential atlas of nephrology and hypertension*. 2nd ed. Philadelphia: Current Medicine; 2004.)

Osteomalacia caused by very low levels of 25-hydroxyvitamin D can be treated by vitamin D supplementation, which leads to an increase in 25-hydroxyvitamin D levels to greater than 30 ng/mL; this will be accompanied by a reduction in and ultimately normalization of the serum BSAP level. To increase vitamin D levels to normal in the elderly population, 50,000 units of vitamin D₂ or D₃ may be required once or twice per week for a protracted time to be effective. Monitoring BSAP, 25-hydroxyvitamin D, PTH, and serum calcium levels must be done periodically, with the vitamin D replacement titrated accordingly.

Although the prevalence of aluminum bone disease has decreased with the less frequent use of aluminum-containing phosphate binders, it is still surprisingly common. The KDOQI guidelines suggest maintaining the aluminum concentration in dialysate fluid at less than 10 mg/L. In addition, the KDOQI guidelines recommend treating symptomatic ESRD patients with either basal serum aluminum levels greater than 60 mg/L or a rise in serum aluminum of 50 mg/L or more after a DFO challenge test. Treatment of aluminum bone disease is long-term (4 to 6 months), with DFO doses of 5 mg/kg administered intravenously over a period of 1 hour before hemodialysis, one to two times per week.

Before therapy with DFO, one should be as certain as possible that aluminum bone disease is present. Here again, bone biopsy with aluminum staining is diagnostic. In addition, repeating bone biopsy after completion of the DFO treatment course is the most sensitive way to be certain that the aluminum has been removed. It is not uncommon to have normal basal and post-DFO challenge serum aluminum levels and yet still have abundant aluminum covering the osteoid surfaces.

ADYNAMIC RENAL BONE DISEASE

Adynamic renal bone disease is an increasingly prevalent form of renal osteodystrophy that may be associated with fragility fractures, low BMD, and variable biochemical profiles (Fig. 205.2).^{18,19,21,30,33} Adynamic bone disease was initially seen predominantly in diabetic ESRD patients being treated with peritoneal dialysis, even in those who had not received interventions to reduce PTH levels. However, the prevalence of this disease seems to be increasing.

Although some forms of adynamic bone disease have no apparent cause, there may be modifiable as well as nonmodifiable forms.³² It is probable that oversuppression of PTH, whether by vitamin D analogues, cinacalcet, or parathyroidectomy, may lead to some forms of adynamic bone disease. In theory, forms of adynamic bone disease that are induced by pharmacologic suppression of PTH may be reversible once the agent responsible is removed. However, in some situations, adynamic bone disease is seen without an identifiable etiology, and these forms are very problematic because severe fragility fractures develop in many of these patients.^{40,41} In addition, biochemical profiling may not be sensitive or specific enough to make a diagnosis of adynamic bone disease in an individual patient. Thus bone histomorphometry becomes a necessity in these patients.

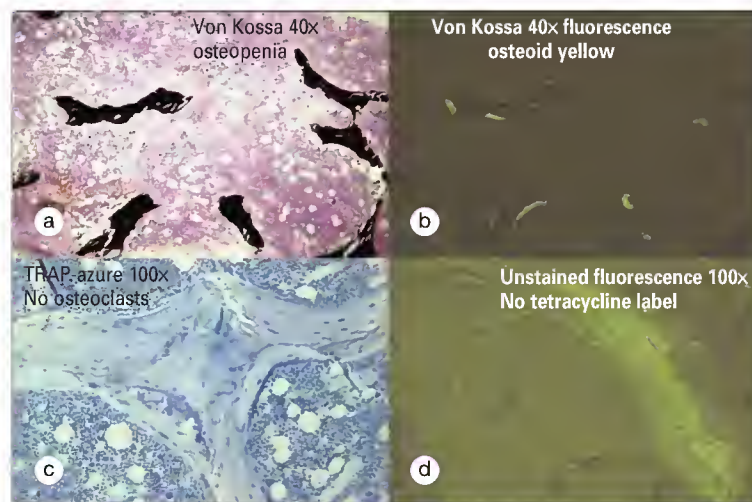


Fig. 205.2 (a to d) Adynamic renal bone disease. (From Miller PD, Huffer W. Renal osteodystrophy. In: Schrier RW, Bennett W, editors. *Essential atlas of nephrology and hypertension*. 2nd ed. Philadelphia: Current Medicine; 2004.)

In patients with severe CKD who are experiencing fractures and have low BMD and clinical reasons suggesting osteoporosis, biopsy is often a necessity before initiating bisphosphonate treatment or, for that matter, any antiresorptive agent to reduce fracture risk. Use of an agent that reduces bone turnover in patients who already have preexisting low bone turnover could possibly be detrimental.^{42,43} Oversuppression of bone turnover leading to bone fragility has been suggested by anecdotal data but remains an unproven hypothesis.⁴²⁻⁴⁵ It is also plausible that bisphosphonates can mitigate vascular calcification.⁴⁶⁻⁴⁸ However, in ESRD patients in whom adynamic bone disease is defined by quantitative bone histomorphometry, bisphosphonates should not be given to augment bone strength.^{19,49,50}

METABOLIC ACIDOSIS

Metabolic acidosis, most commonly caused by the accumulation or reduced excretion of organic anions, may develop in patients with CKD. It is seen most often when the GFR reaches less than 30 mL/min. A non-anion gap metabolic acidosis (renal tubular acidosis [RTA]) may be seen at any level of GFR and in patients without any reduction in renal function. Either proximal (rare) or distal (common) RTA can lead to either osteomalacia or osteoporosis.⁵¹⁻⁵³ In patients with CKD, the serum bicarbonate level should be measured and, if necessary, maintained at a level higher than 22 mmol/L with alkali salts. However, it is important to not use citrate as the alkali salt because it enhances the intestinal absorption of aluminum.

OSTEOPOROSIS

Although osteoporosis is not listed in the literature as a form of renal osteodystrophy, the consideration that some form of osteoporosis rather than a renal-related metabolic bone disease is causing fractures will take on more significance in clinical practice. Osteoporosis may develop in patients with CKD for many reasons.^{10-12,15} As patients with CKD live longer, more will also have an increased risk for the development of osteoporosis.

How does one make the diagnosis of osteoporosis in patients with CKD? All forms of renal bone disease may be associated with fragility fractures or low BMD. The recent KDIGO working group does support use of the WHO criteria for the diagnosis of osteoporosis in stages 1 to 3 CKD.¹⁹ However, neither fractures nor the WHO criteria (BMD T-score of -2.5 or below) can be used with certainty to make a diagnosis of osteoporosis in patients with stage 4-5/5D CKD. Because biochemical profiling cannot clearly discriminate among the various forms of renal osteodystrophy with certainty, it also cannot be used to make a diagnosis of osteoporosis. Hence, it becomes a necessity to differentiate between the renal osteodystrophies and osteoporosis by quantitative bone histomorphometry, especially if the physician thinks that the patient has osteoporosis and is contemplating using osteoporosis-specific pharmacologic agents designed to improve bone strength and reduce the risk for fracture.²⁴ Although hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), and calcitonin can reduce fracture risk in postmenopausal women, older men, and patients with glucocorticoid-induced osteoporosis, they may have limitations in patients with CKD. HRT and SERMs increase the risk for venous thrombosis, and there is no evidence that calcitonin reduces the risk for nonvertebral or hip fractures. These latter forms of fragility fractures are common in patients with CKD. Thus physicians caring for patients with CKD who also have fragility fractures, especially ones associated with high mortality, often ask about the use of bisphosphonates or even teriparatide (recombinant human 1-34 PTH) for patients with CKD.

The Food and Drug Administration (FDA) advised against using bisphosphonates in patients with a creatinine clearance lower than 30 to 35 mL/min. This warning is not a contraindication to the use of bisphosphonates in patients with stages 4 to 5 CKD but is based mostly on the lack of evidence of safety in patients with more severe CKD and on data from animal studies indicating that high oral doses of bisphosphonates may induce a renal lesion and reduced GFR. The exception is intravenous zoledronic acid (Reclast), which is contraindicated in those with a GFR lower than 35 mL/min.

Recent *post-hoc* pooled analyses obtained from the risedronate clinical trial data set indicate that daily doses of risedronate (5 mg/day) are safe (do not alter serum creatinine concentrations) and effective (reduction in incident vertebral fracture risk) in patients with GFR levels between 15 and 30 mL/min.⁵⁵ In addition, a *post-hoc* analysis from the alendronate postmenopausal registration trials also demonstrated that the daily formulations of alendronate are also safe and effective in reducing all clinical fractures in women with an estimated GFR as low as 15 mL/min.⁵⁶ Similar *post-hoc* data have also been reported from the raloxifene postmenopausal registration trial.⁵⁷ These *post-hoc* analyses need to be confirmed by prospective studies; however, the data do suggest that FDA-approved doses of oral bisphosphonates are safe and effective even in patients with stage 4 CKD.⁵⁸ These data may not apply to patients with stage 5/5D CKD, those with ESRD, or the post-renal transplant population.

Intravenous bisphosphonates, zoledronic acid, and ibandronate may have a greater potential for inducing abrupt and mostly short-term changes in renal function and, for these reasons, should be avoided even off-label in patients with a GFR lower than 35 mL/min.⁵⁹ Intravenous zoledronic acid is now contraindicated for use in patients with a GFR lower than 35 mL/min because of postmarketing reports of 25 cases of acute renal failure.⁶⁰ In contrast, in a prospective analysis of patients at high risk for renal failure, intravenous ibandronate given as the registered injection or a slower 5-minute infusion did not induce acute renal failure.⁵⁹ A clinical question often arises about what dose of oral bisphosphonate should be considered off-label in patients with stage 5 or 5D CKD who have osteoporosis. Here we have no evidence and only opinion exists. Because of the known pharmacokinetics of oral bisphosphonates, using 50% of the dose prescribed for patients with stage 4 CKD and a normal GFR seems reasonable while recognizing that bone affinities, bone retention time, and bone accumulation may be very different in those with GFR values lower than 15 mL/min or even among the various oral bisphosphonates.

What about the use of teriparatide in patients with CKD? There should be no reason why teriparatide should not be effective in reducing the risk for both nonvertebral and vertebral fractures in patients with stages 1 to 3 CKD. Even in elderly women and men with osteoporosis, who often have secondary hyperparathyroidism because of vitamin D insufficiency, teriparatide appears to be effective. Most clinicians do not measure PTH levels at baseline before initiating teriparatide, yet elevations are common in the elderly, who often also have reductions in the GFR. Indeed, recent *post-hoc* data from the teriparatide fracture prevention trial suggested that it is also safe and effective down to GFR levels of 30 mL/min.⁶¹ It is certainly not suggested that patients with stage 4-5/5D CKD should receive teriparatide for severe osteoporosis. In the author's opinion, in patients with these severe degrees of CKD, bisphosphonates should be used only in those with osteoporosis and fractures.

CONCLUSION

Renal osteodystrophy is a heterogeneous group of metabolic bone diseases associated with declining GFR values. There are many causes and clinical manifestations that often cannot be distinguished from one another without quantitative bone histomorphometry, especially in patients with stage 4-5/5D CKD. Once the diagnosis is clear, all forms of renal osteodystrophy have many reversible causes; some remain "idiopathic," however. Newer therapies such as vitamin D analogues or cinacalcet can mitigate one form of renal osteodystrophy: secondary hyperparathyroidism. Osteoporosis also occurs in patients with CKD and is associated with clinical findings not easily indistinguishable from those of "renal bone disease," fractures, and low bone mass. Nevertheless, osteoporosis does occur in CKD and may be amenable to interventions designed to reduce fracture risk in patients with osteoporosis and normal renal function. The recent KDIGO report has expanded the relationships between bone mineralization, turnover, and volume to link the bone derangements in CKD to systemic vascular calcification (CKD-MBD). Physicians need guidance on how to diagnose and treat osteoporosis in their CKD patients, especially those with stage 4-5/5D CKD, for which evidence-based data are nearly nonexistent.

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■ MARGARET SETON

- Paget disease of bone is a focal disorder of bone remodeling characterized by accelerated bone resorption coupled to formation that results in enlargement and deformity of bone.
- The disease may occur in one or more bones; has a predilection for the skull, spine, pelvis, and lower extremities; and is a disease of the adult skeleton that increases in prevalence with aging and is marked by a slight male preponderance.
- Familial and sporadic cases are reported. Geographic prevalence of the disease varies throughout the world.
- The pathogenesis is unknown; although genetic determinants have now been recognized, the environmental triggers remain undefined.
- Clinical complications include pain, deformity, fracture, and nerve compression syndromes; metabolic consequences are reported. Rarely, an osteosarcoma arises in pagetic bone.

HISTORY

In 1876, Sir James Paget presented a paper titled "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)" in which he detailed the progressive, crippling deformity of bone that would be called Paget disease of bone.¹ That it existed before this time is evidenced by paleoarcheologic findings of thickened skulls consistent with Paget disease in some Neanderthal remains and by excavations of early Anglo-Saxon graveyards in northern England.²

EPIDEMIOLOGY

Paget disease of bone is a disorder of the adult skeleton and is not seen in children. This observation was confirmed in autopsy series in Germany and England in which pagetic bone was identified only in persons older than 40 years; its prevalence ranged from 3.0% to 3.7%. Population studies undertaken since that time to determine the prevalence of this disease have depended largely on screening radiographs and questionnaires. Because of its predilection for the axial skeleton and proximal end of the femurs, radiographs of the kidney/ureter/bladder, taken as routine admission films or for other indications such as abdominal pain or kidney stones, formed the basis of many population studies to determine prevalence. Using this protocol in England, the radiographic prevalence of Paget disease was 5.4% in persons aged 55 and older.³ In the United States, using the First National Health and Nutrition Examination Survey database, the prevalence of radiographic Paget disease of the pelvis in the population aged 55 to 74 years was reported to be around 2% and was more frequent in residents of northeastern states and in whites.⁴ In a 1982 postal survey across western Europe, Detheridge and colleagues⁵ mapped the prevalence of Paget disease from 1416 replies; they noted it to be most prevalent in Great Britain, where geographic clusters occurred. In addition, Paget disease is common in regions of France, Spain, Italy, and other western European countries and in Australia and New Zealand. It is unusual in Norway and Sweden and rarely reported in India and the Far East. The prevalence of Paget disease increases with age. Between 10% and 40% of persons with Paget disease report a family history of this disorder. Males are affected slightly more than females at a ratio of 1.4:1.^{6,7} More recent epidemiologic data suggest a decline in both the prevalence and severity of this disease.^{8,9}

PATHOGENESIS

Etiology

Paget disease is thought to reflect a genetic disorder that is autosomal dominant in transmission with variable penetrance. The most prevalent mutation accounting for both familial and sporadic Paget disease is in the gene *sequestosome 1* (*SQSTM1*), with more than 20 mutations now described in or proximal to the ubiquitin-associated (UBA) domain of the protein product p62.¹⁰ Polymorphisms in the genes affecting osteoclast-signaling pathways are also thought to play a role in facilitating the expression of Paget disease in bone. Because Paget disease exists in many persons without the *SQSTM1* mutation and the mutation is reported in persons without evidence of Paget disease, other environmental determinants such as viruses, toxins, trauma, and rural exposures have been explored as predisposing factors.¹¹

Genetic factors

In 2002, scientists studying a French-Canadian cohort of patients with Paget disease described a mutation in the gene *SQSTM1* on chromosome 5q35 that occurred in 46% of patients with familial Paget disease and in 16% of patients with sporadic Paget disease.¹² The most common mutation, P392L, occurred in the UBA domain of p62 and was confirmed in patients with Paget disease in other countries, albeit at lower rates.¹³ These *SQSTM1* mutations seem to occur in a limited number of shared haplotypes, thus suggesting a founder effect.¹⁴ This observation is consistent with the epidemiology of Paget disease and the European origins of this disorder. Unresolved is whether sporadic Paget disease of bone, in which the prevalence of germline mutations in *SQSTM1* is low, may be due to a somatic mutation.¹⁵

Work is under way to understand how these mutations in *SQSTM1*/p62 affect ubiquitin binding and result in osteoclast activation and bone resorption.¹⁰ Increasingly, autophagy is postulated to play a role in Paget disease, and evidence of inclusion bodies in pagetic osteoclasts points toward this mechanism of disease, both in animal models and in humans.¹⁶

Insight into this has been gleaned from a rare degenerative disease, IBMPFD (inclusion body myopathy, Paget disease, and frontotemporal dementia), in which mutations in the valosin-containing protein (VCP) gene result in disruption of the ubiquitin-proteasome degradation pathways.¹⁷ However, the etiology of these inclusion bodies and their identify remain controversial.¹⁸

In the clinical realm, efforts to correlate genotype with phenotype suggest that truncating mutations in patients with Paget disease may result in more severe disease characterized by earlier onset and more affected bones. The *SQSTM1* mutation by itself does not seem to predict an earlier age at onset or a particular phenotype.^{19,20}

Environmental factors

A number of environmental factors have been proposed to be of importance in Paget disease of bone. The most persuasive of these factors is exposure to paramyxoviruses, specifically canine distemper virus and measles. Despite evidence that measles virus nucleocapsid can promote a pagetic phenotype in osteoclasts and to some degree in mouse models,²¹ there is no proof that these viruses are causative. Still, work from Kurihara and colleagues²² elucidated a mechanism whereby infection can augment osteoclast activity, perhaps by increasing local interleukin-6 production. The marrow itself may provide a microenvironment permissive of Paget disease.²³ Pet ownership, exposure to well water, urban versus rural upbringing, and sibship size are proving inconsistent determinants of Paget disease at this time.²⁴

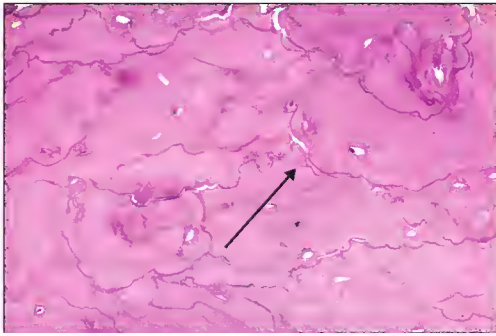


Fig. 206.1 Histopathology of pagetic bone. Irregular cement lines (arrow) formed by the disorganized deposition of bone result in a characteristic mosaic pattern.

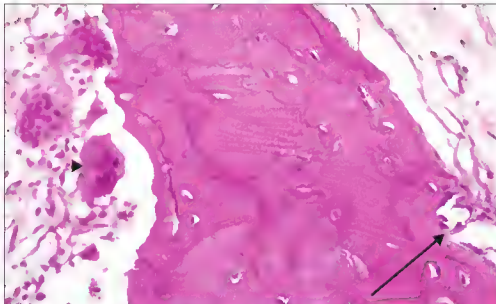


Fig. 206.2 Histopathology of pagetic bone. Note the numerous, large multinucleated osteoclasts (arrowhead) active in bone resorption, whereas osteoblasts (arrow) respond with bone formation. Highly vascular fibrous connective tissue is present, replacing normal marrow.

Histopathology

Paget disease of bone is mediated largely by abnormal osteoclasts. Evidence that the osteoclast plays a pivotal role in the pathogenesis of Paget disease is based on the following:

- Pagetic osteoclasts express a bizarre phenotype, contain intranuclear inclusions, and are hypersensitive to physiologic amounts of vitamin D.
- The earliest clinical lesion is lytic.
- Treatment of the osteoclast is sufficient to restore normal rates of bone remodeling.

The accelerated rate of bone resorption seen in patients with Paget disease is accompanied by bone formation, a process that results in pagetic bone that is thickened but structurally compromised. This structural incompetence is due to the abnormal deposition of both woven and lamellar bone. The woven bone is weaker than normal; although the units of lamellar bone increase bone mass, they are deposited in an architectural pattern that is biomechanically unsound. Histologically, this is manifested as randomly arranged units of lamellar bone delineated by cement lines that form the pathognomonic “mosaic” pattern (Fig. 206.1). Other secondary changes include increased vascularity, peritrabecular fibrosis, and loss of normal marrow elements over time (Fig. 206.2). Despite large fluxes of calcium in and out of bone, there tend to be no perturbations in the measured serum calcium or phosphate concentrations in otherwise healthy individuals.

CLINICAL FEATURES

Signs and symptoms

Sir Paget wrote, “It begins in middle age or later, is very slow in progress, may continue for many years without influence on the general health, and may give no other trouble than those which are due to the changes of shape, size and direction of the diseased bones.”¹ Many patients with Paget disease of bone are asymptomatic and the diagnosis is made incidentally because of an isolated elevation in the serum alkaline phosphatase level or because pagetic bone is noted on a screening radiograph ordered for another reason. Other patients with Paget disease may suffer crippling deformities of bone (Fig. 206.3), disfigurement (Fig. 206.4), pain, fracture, nerve compression

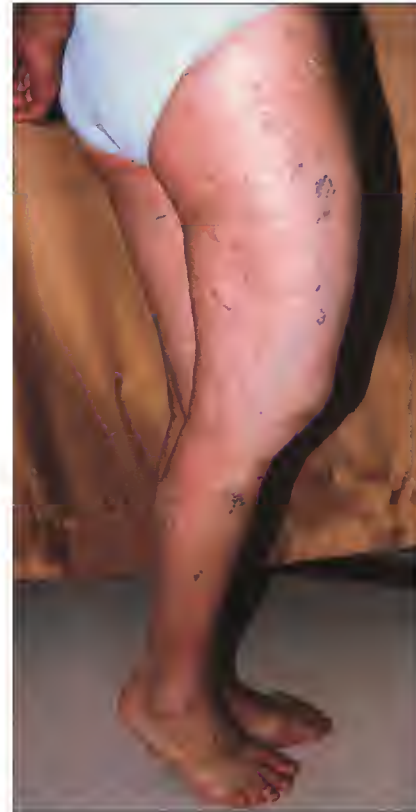


Fig. 206.3 Bowing of the right femur leading to shortening of the right lower limb.



Fig. 206.4 Paget disease of the maxilla resulting in the characteristic facial deformity known as leontiasis ossea. Note also hypertrophy of the right temporal artery, which can potentially be mistaken for temporal arteritis.

syndromes, and impaired quality of life, depending on the bones affected. Pain in patients with Paget disease of bone is derived from several sources: from the bone itself, from the consequence of encroachment on proximal structures, and from secondary osteoarthritis of joints provoked or in part driven by overgrowth of the pagetic bone.²⁵

Skeletal sites

Paget disease may affect any bone and may be monostotic or polyostotic. It has a predilection for the skull, lumbosacral spine, pelvis, and femur but is commonly noted in other bones of the appendicular skeleton as well. When the disease affects the skull, hearing loss, headache, and visual disturbance may ensue; the skull may “settle” and soften in a “tam-o-shanter” shape that can result in basilar invagination, cord compression, and hydrocephalus (Fig. 206.5). Vertebral involvement with overgrowth of bone or compression fractures (or both) may be manifested as spinal cord lesions, isolated radiculopathy, spinal stenosis, and cauda equina syndromes (Fig. 206.6). The heightened vascularity of bone has also been reported to cause vascular steal syndromes (Fig. 206.7). When Paget disease involves bone proximal to a joint, patients usually have pain, limitation of motion, and early osteoarthritic changes at that site (Fig. 206.8). The consequence of the bowing deformities of limbs is frequently degenerative changes at multiple sites as a result of misalignment of joints and altered weight bearing. The clinical consequences of these problems include instability of gait, falls, and fracture.

IMAGING

Radiography and bone scintigraphy record the abnormal bone turnover and selective bony involvement so characteristic of Paget disease. Bone



Fig. 206.5 This magnetic resonance image shows a grossly thickened pagetic skull with evidence of basilar invagination and compression of the lateral ventricle of the brain.

scintiscans are particularly useful in defining the extent of disease (Fig. 206.9), whereas conventional radiographs define important information about the anatomy of the pagetic bone. Classic radiographic features of Paget disease include thickened cortical bone and mixed lytic-sclerotic lesions that evolve over time with subsequent distortion and overgrowth of affected bone. Lesions usually begin in the subchondral area and are continuous (progressing without skip lesions through that bone); cortical tunneling and trabecular thickening may be present (Fig. 206.10).²⁶ Plain films are diagnostic in most instances and are useful in assessing the complications of Paget disease and in evaluating whether the disease is in its incipient lytic phase or has progressed (Fig. 206.11). As the weight-bearing bones bow, small fissure fractures may occur in cortical bone (Fig. 206.12). These fractures usually occur on the convex portion of the femur, in contradistinction to the pseudofractures of osteomalacia (Looser zones), which occur on the concave portion. Paget disease of bone does not cross normal articular surfaces, although it may bridge bony calluses. It does not metastasize, and it is distinctly unusual to identify new bone involvement with Paget disease over time. The environmental or genetic determinants of this remain unclear. Serial bone scintiscans and radiographs have been reported to show



Fig. 206.7 Paget disease producing a right deformity of the skull, deafness (see the hearing amplifier device in the right ear), and apathy as a result of vascular steal syndrome.

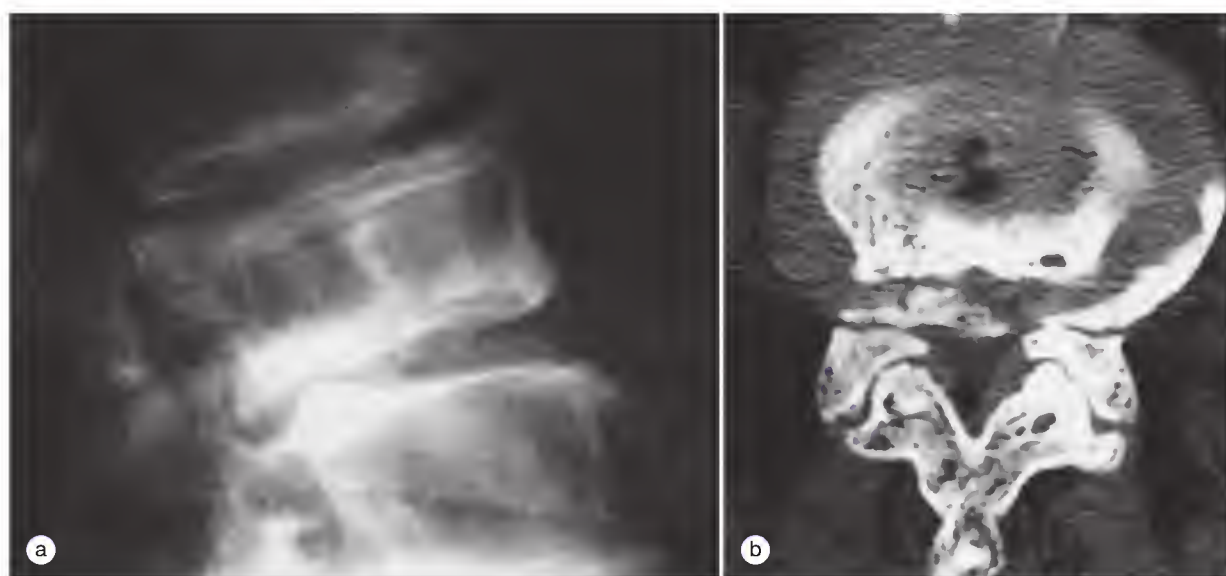


Fig. 206.6 Paget disease of the spine. (a) Slipped pagetic vertebra narrowing the neural foramen. (b) Bulging of an intervertebral disk leading to spinal stenosis; the stenosis is less severe at the level of the pagetic vertebra.



Fig. 206.8 Standing anteroposterior radiograph of the knees taken in a flexed position. Marked pagetic involvement of the left tibia has resulted in end-stage degenerative changes in that knee. Note the thickened bone, mixed lytic and sclerotic lesions, and heightened trabecular markings. The right lower extremity and left fibula are unaffected.

improvement with treatment of Paget disease of bone and may be useful in monitoring some patients with pagetic lesions and normal biochemical parameters and those with predominantly lytic lesions of bone (Fig. 206.13).

LABORATORY FINDINGS

Serum alkaline phosphatase is a useful measure of active Paget disease of bone when its origin has been identified as bone. Although historically an elevated serum alkaline phosphatase level reflected the extent and activity of skeletal disease, increasingly patients are being found to have normal alkaline phosphatase levels.²⁷ This is attributed to a decrease in the prevalence and severity of Paget disease being reported²⁸ and an increase in monostotic disease.²⁹ Some patients with long-standing Paget disease will have little or no elevation in the serum alkaline phosphatase value or uptake by bone scintigraphy, thus suggesting end-stage Paget disease that is sclerotic and biochemically quiescent. Recent studies suggest that other markers of bone formation, including bone-specific alkaline phosphatase and procollagen type I N-terminal propeptide, may prove useful in screening for pagetic activity and in monitoring therapy with the bisphosphonates and that markers of bone resorption such as urinary N-telopeptides may reveal early (e.g., 10 to 14 days) and late responses to therapy. However, investigations over the years have failed to demonstrate any marker of bone turnover that is superior to serum alkaline phosphatase in most patients.³⁰

DIFFERENTIAL DIAGNOSIS

Paget disease is usually well defined by the clinical picture and the classic findings on bone scans, radiographs, and computed tomography. In the age group affected by this disease, osteoporosis and cancer are also prevalent, and it is prudent to remember that these diseases may coexist and affect skeletal health. Because of the variable manifestations of Paget disease in both the lytic and blastic phases, there are a few circumstances in which tissue biopsy may be required to prove the diagnosis. New lesions noted on bone scintiscan at any site, not present or suspected on earlier bone scans, require further evaluation. Metastases rarely occur at sites of pagetic bone, so comparison of a new bone scintiscan with a baseline bone scintiscan may prove useful. In cases in which the diagnosis of Paget disease of bone remains unclear and in cases in which a pagetic osteosarcoma is suspected on the basis of increasing pain and soft tissue swelling, magnetic resonance imaging may better define the soft tissue anatomy and address whether effacement of normal marrow or structures or cortical disruption by a mass is present.

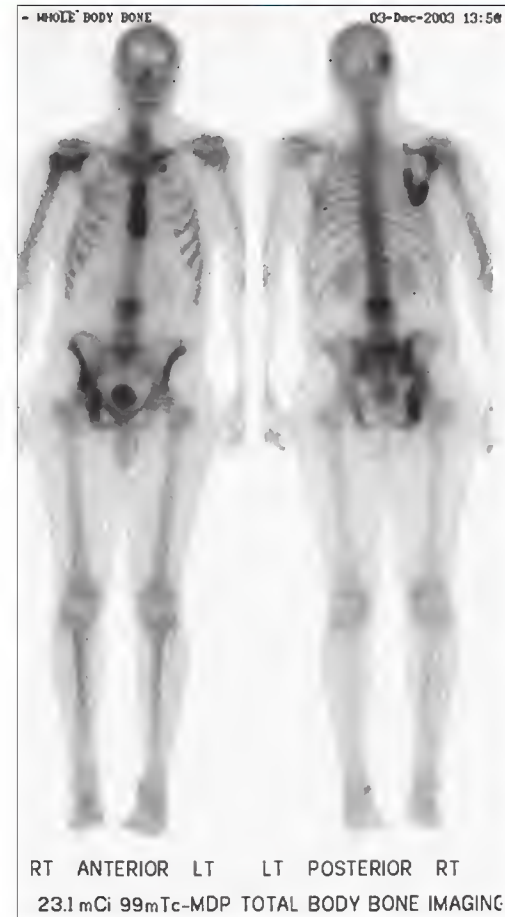


Fig. 206.9 A technetium-99m MDP (methylenediphosphonate) bone scan shows polyostotic Paget disease involving the sternum, right scapula, two lumbar vertebral bodies, and right hemipelvis. Early pagetic disease may be involving the right side of the skull as well.

COMPLICATIONS AND NATURAL HISTORY

The most devastating long-term complication of Paget disease of bone is osteosarcoma. This complication is rare and occurs in less than 1% of persons with known disease; it carries a distinct genetic signature and accounts for many of the sarcomas in the elderly.³¹ Outcomes are usually poor. Other complications of Paget disease result from the overgrowth and deformation of bone and include neurologic compression syndromes, disfigurement or periodontal complications as a result of pagetic bone affecting the mandible or maxilla, vascular steal syndromes, high-output heart failure, headache, and hearing loss. In addition, patients with Paget disease seem to be more vulnerable to osteoarthritis and its attendant morbidity, hyperparathyroidism, renal stones, and gout.³² Anecdotal reports suggest that angiod streaks and Peyronie disease may be more common in persons with Paget disease. A study from the United Kingdom suggested that all-cause mortality in patients with Paget disease may be increased in comparison to age-matched controls,³³ although this finding was not corroborated in the United States.³⁴

TREATMENT

Treatment should be undertaken with the aim of easing pain, preventing progression of the disease, and improving the quality of bone. Treatment is indicated in patients with polyostotic Paget disease who require prolonged bed rest or are immobilized in a cast for other reasons, a state that may exacerbate the lytic lesions in bone. Treatment is also indicated for metabolic complications of Paget disease such as high-output cardiac failure and for hypercalcemia or nerve compression syndromes, as well as for patients in whom surgery on pagetic bone is anticipated. Treatment options and regimens are listed in Table 206.1.



Fig. 206.10 Lateral radiograph of the lower extremity. Classic changes of Paget disease are present in the bowing deformity of the tibia, marked cortical thickening, and mixed lytic and sclerotic lesions. The fibula is spared.



Fig. 206.11 This lateral radiograph of the skull shows the early, lytic phase of Paget disease known as osteoporosis circumscripta (arrows mark the leading edge).

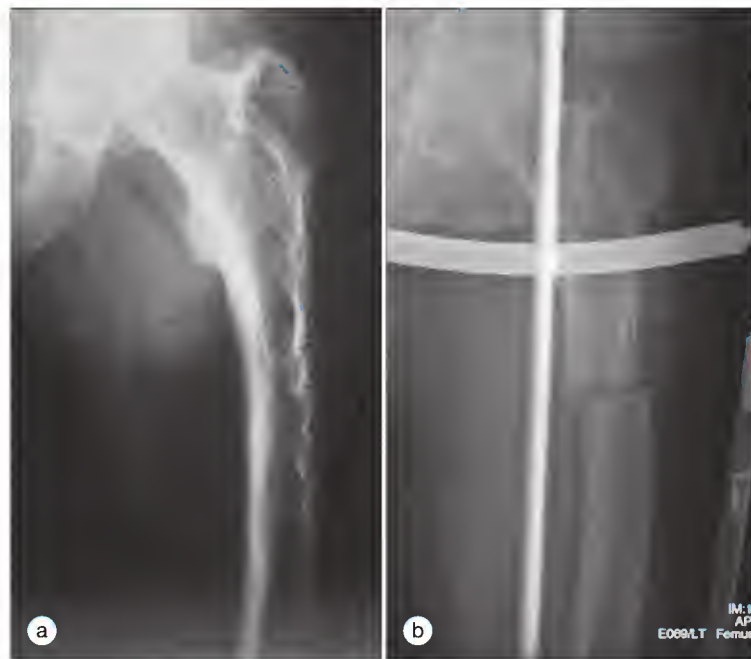


Fig. 206.12 Lateral radiographs of the left femur before (a) and after (b) fracture. (a) Cortical incongruities or fissure fractures are present on the convex surface of this pagetic femur. They were asymptomatic for 15 years and showed no resolution with bisphosphonate treatment. (b) In 2005 the patient suffered an atraumatic fracture at this site. The fracture is a classic "chalk stick" fracture characteristic of Paget disease.

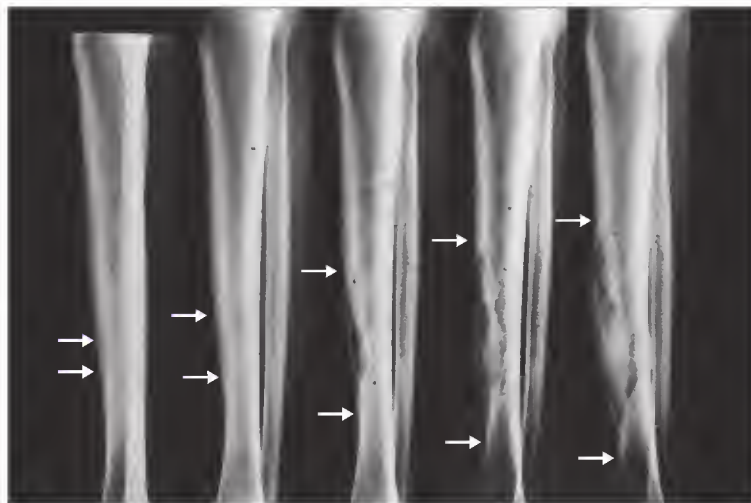


Fig. 206.13 Sequential radiographs of a pagetic tibia demonstrating the natural progression of the advancing osteolytic fronts within the bone.

Bisphosphonates

With development of the bisphosphonates and their promise of sustained clinical remission, these drugs have become the agents of choice for the treatment of Paget disease. The newer generation nitrogen-containing bisphosphonates reflect a trend toward more potent suppression of bone resorption without impairment of mineralization at therapeutic doses. The mechanism of action is inhibition of farnesyl diphosphate synthase, an enzyme in the mevalonate pathway critical in the prenylation of small proteins that facilitate cytoskeletal reorganization and bone resorption.³⁵ Tiludronate and clodronate are also bisphosphonates that work through another mechanism of action to promote osteoclast apoptosis and inhibit bone resorption; they are less potent, yet effective in treating Paget disease. These bisphosphonates are variably accessible in countries around the world, their distribution determining in large part choice and utilization.

Zoledronic acid is the most effective bisphosphonate for the treatment of Paget disease of bone; it secured a durable remission in patients as measured by suppression of serum alkaline phosphatase levels and biochemical

TABLE 206.1
Medications for the treatment of Paget disease of bone*

Medication	Dose and regimen	RCT	Reference
Calcitonin	50-100 IU subcutaneous daily Comments: Well tolerated with mild nausea and flushing expected. Eases pain often, but no sustained efficacy; nasal spray is not FDA approved in the USA but may be effective at 400 IU daily	No	J Clin Invest 1971;50:1927-40 Calcif Tissue Int 1991;49:164-7
Etidronate	5 mg/kg daily by mouth for 6 mo Comments: Osteomalacia, fractures, worsening lytic lesions, and pain	Yes	N Engl J Med 1973;289:1379-84
Alendronate	40 mg daily on rising by mouth for 6 mo Comments: CVS ProCare pharmacy distributes this, often at cost to the patient and excessive time to the physician (888-900-1500)	Yes	J Clin Endocrinol Metab 1996;81:961-7 Bone 2004;34:747-54
Tiludronate	400 mg daily by mouth for 3 mo Comments: Less potent than the nitrogen-containing bisphosphonates	Yes	Arthritis Rheum 1995;38:851-8 Postgrad Med J 1997;73:496-502
Risedronate	30 mg daily on rising by mouth for 2 mo Comments: Readily available, well tolerated	Yes	Am J Med 1999;106:513-20 Calcif Tissue Int 2004;75:189-96
Pamidronate	30 mg daily IV over a 4-hour period on 3 consecutive days (90 mg total dose) Comments: Infusion time may be shortened; regimens vary widely worldwide	Yes	Bone 2004;34:747-54 Clin Rheumatol 1994;13:39-44
Zoledronate	5 mg IV over a 15-minute period Comments: Reassessment rather than annual infusions are encouraged	Yes	N Engl J Med 2005;353:898-908 Ther Clin Risk Manag 2007;3:913-8 J Bone Miner Res 2007;22:142-8

*These are approved by the FDA; in other countries, clodronate, ibandronate, neridronate, and alpadronate are available for the treatment of Paget disease. FDA, U.S. Food and Drug Administration; IV, intravenously; RCT, randomized controlled trial.

markers of bone turnover into the normal range. It is given once at a dose of 5 mg by infusion over a 15-minute period, is well tolerated, and seems to be more effective in patients who have previously been treated with other bisphosphonates or have shown resistance to them.

In Paget disease, for which treatment is intermittent and confined mostly to the population older than 55 years, complications of treatment are infrequent and the benefits tend to be measurable.³⁶

Whether bisphosphonate treatment will prove useful in terms of long-term outcomes in the lives of patients with Paget disease is less unclear. In the PRISM trial in England in which aggressive versus symptomatic treatment of patients with Paget disease was studied,³⁷ no difference was found in outcomes in the two groups as measured by fracture rate, quality of life, or other complications of the disease. Perhaps this should have been anticipated inasmuch as treatment cannot restore the structural integrity of a deformed pagetic limb, reverse the evolution of arthritis in a pagetic joint, or restore hearing once the skull is overgrown. Treatment can, however, ease neurologic syndromes, diminish blood flow through pagetic sites, enhance the deposition of more normal bone, and ease pain; it may prevent disease progression, promote healing of radiographic lesions in some, and normalize serum alkaline phosphatase in many. Patients should be treated with vitamin D and calcium concurrently.

Other drugs

Calcitonin has been used widely for the treatment of Paget disease since the 1970s. Its waning efficacy over time, the absence of durable remission, and the discomfort of the injection limit more extensive use of this drug. Calcitonin is relatively safe, eases pain, and improves bone lesions, so it continues to have a role in infirm geriatric patients who are intolerant of or have contraindications to bisphosphonates and in whom transient relief from Paget disease is sought. There is a case report of the use of denosumab for the treatment of a patient with Paget disease.³⁸

Supportive therapy

Failure of the bisphosphonates to ease pain may not signify resistance to the drug but may indicate pain originating from other sources.²⁵ Many patients afflicted with Paget disease of bone are elderly and suffer from arthritic pain, loss of hearing, sciatica, and instability of gait from other causes. Analgesics, bracing, gait training, and walking aids may be beneficial

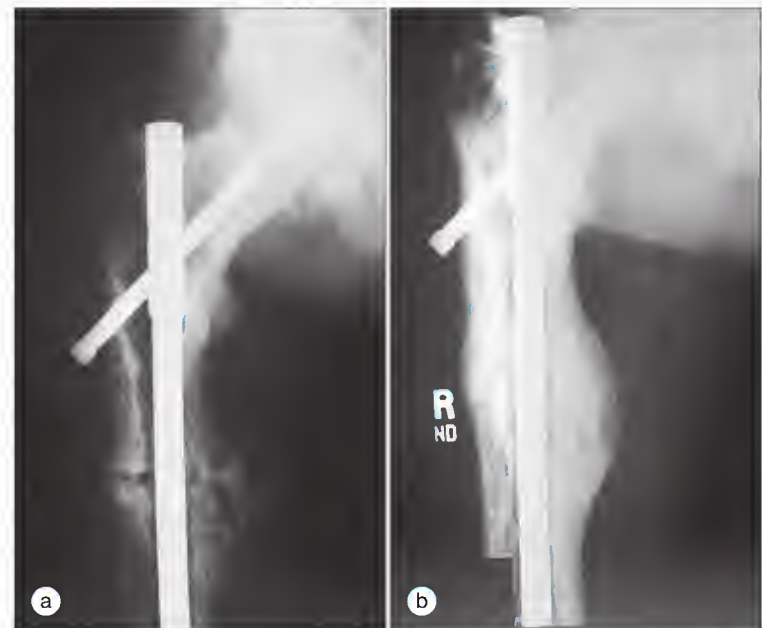


Fig. 206.14 Lateral radiographs of the right femur before (a) and after (b) bisphosphonate therapy. (a) Postoperative lytic lesions are seen in the pagetic bone around the rod placed to stabilize the fracture site. (b) Note the radiographic evidence of healing after therapy with alendronate.

when treatment of the pagetic bone fails to ease their distress. Hearing aids and glasses are prescribed when appropriate. Physical therapy and therapy aimed at the psychosocial issues of aging may also prove useful.

Surgery

When end-stage osteoarthritis of the hip or knee occurs, orthopedic surgery may prove beneficial in restoring independence and easing pain. Paget disease has distinct orthopedic issues, including the quality and vascularity

of bone, the bowing deformity in the long limbs, or distortion of the acetabulum with or without protrusio. Anticipating surgery by pretreating patients with bisphosphonates is thought to improve outcomes by diminishing the vascularity of bone, restoring normal lamellar bone formation, and preventing postoperative lysis of bone (Fig. 206.14). Clinical data are sparse, and no randomized controlled trials have evaluated blood loss, healing, or bony ingrowth in patients pretreated with bisphosphonates versus controls. Heterotopic bone formation may be more common in patients with Paget disease undergoing total hip replacement, but the outcomes are generally excellent for both total hip and total knee replacement. Satisfaction with corrective osteotomies for severe limb deformity in Paget disease is less consistent, but the surgery may be beneficial for some.³⁹

CONCLUSION

Paget disease of bone is a focal disorder of the aging skeleton that may be expressed as a familial or sporadic disease and may affect one or many bones in a given person. The geographic and familial clusters of the disease have led to the identification of environmental and genetic determinants of Paget disease. No cure is available, but there is effective treatment that will ease the pain and nerve compression syndromes caused by pagetic bone, normalize the serum alkaline phosphatase level in many, and hopefully prevent progression of early Paget disease. Therapeutic advances in the past 25 years have made these goals feasible.

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HERITABLE DISEASE AND TUMORS
OF BONE AND CONNECTIVE TISSUE

207

Gaucher disease

■ PHILIPPE ORCEL ■ ROSE-MARIE JAVIER

- Gaucher disease results from the accumulation of glucosylceramide in organs and tissues throughout the body in characteristic storage cells, namely, "Gaucher cells."
- The most common inherited glycolipid storage disease, Gaucher disease is a heterogeneous disorder with three clinical phenotypes:
 - Type 1, the adult, nonneuronopathic chronic form, is characterized by organomegaly, hematologic disorders secondary to hypersplenism, bone lesions attributable to medullary infiltration by Gaucher cells, and no central nervous system involvement.
 - Type 2, the infantile, neuronopathic acute form, is manifested as early involvement of the brain and cranial nerves and is fatal by 2 years of age.
 - Type 3, the juvenile, neuronopathic subacute form, consists of involvement of visceral organs, bone, and the central nervous system, with neurologic symptoms appearing later and being less severe.

EPIDEMIOLOGY

Type 1 is the most common form of Gaucher disease (Table 207.1). Type 1 Gaucher disease (GD1) is more frequent in persons of Ashkenazi Jewish heritage but is pan-ethnic. Types 2 and 3 are rarer and affect predominantly non-Jewish individuals. A genetic isolate of type 3 has been identified in northern Sweden (so-called Norrbottnian Gaucher disease). No family has been reported with more than one type of the disease, thus suggesting that the three types of Gaucher disease are genetically distinct. Each type is inherited as an autosomal recessive trait without any sex preponderance. The peak age at onset is variable: any age from birth to elderly for type 1, usually before 6 months of age for type 2, and juvenile (teenage) for type 3.^{1,2}

An international registry database organized by the International Collaborative Gaucher Group has presently enrolled around 6000 patients worldwide.²⁻⁷ It provides a genotype reference resource and several clinical investigations on different aspects of the disease (e.g., evaluation of bone response by densitometry, dose schedule for enzyme replacement therapy, pulmonary involvement).

ETIOLOGY

Biochemistry

Gaucher disease arises from an inherited deficiency of the activity of acid β -glucosidase (EC.3.2.1.45; lysosomal glucocerebrosidase), a membrane-associated monomeric glycoprotein with a molecular weight of 65 kDa.^{1,2}

This enzyme hydrolyzes β -glucosidic ester bonds and is specialized for complex lipid substrates. Impairment of its activity results in the accumulation of glucosylceramide, linked by a β -glucosidic bond. Glucosylceramide is at the end of the glycosphingolipid catabolic pathway and is normally catabolized into ceramide and glucose by glucocerebrosidase.¹ The compounds that contribute to the pool of glucosylceramide are derived from the degradation of membranes, particularly those of white blood cells (Fig. 207.1).

Molecular biology and genetics

More than 300 discrete mutant alleles have been identified in the β -glucocerebrosidase gene (*GBA1*).² There is also a pseudogene that is about 96% homologous with the active gene and may complicate the pattern of mutations.² Mutations include both insertional and point mutations, as well as crossover mutations with the pseudogene. Four common mutations are found in 96% to 98% of the Ashkenazi Jewish population^{1,2}; the most common is an A→G point mutation at nucleotide 126, which results in substitution of serine for asparagine (370), decreased catalytic activity of the enzyme, and a mild phenotype. This mutant allele is not observed in patients with the neuronopathic type 2 or 3 forms. Other common mutations include (1) insertion of a guanine at nucleotide 84, which induces a shift in the reading frame with no enzyme production and a severe phenotype; (2) a T→C mutation at nucleotide 1448 in which proline is substituted for leucine (444), which causes severe loss of activity and a severe phenotype (homozygous patients have a neuronopathic form); and (3) a G→A mutation at nucleotide 1604, which results in substitution of histidine for arginine (496) and produces a very mild phenotype.¹

PATHOGENESIS

Physical crowding or impairment of blood flow secondary to the massive accumulation of storage cells has been hypothesized to explain some tissue alterations such as bone ischemia.¹ On the other hand, macrophage activation with alterations in macrophage function and the local release of lysosomal enzymes, chemokines, and cytokines may have deleterious effects on neighboring cells in the spleen, liver, bone, or central nervous system.²

However, these mechanisms do not explain the entire spectrum of the clinical phenotype in GD1, and recent observations in an animal model suggest an effect of *GBA1* deficiency on other cell types such as osteoblasts, thymic T cells, and dendritic cells.⁸ Conditional *GBA1* deletion in mice recapitulates most of the features of GD1 and shows that the skeletal abnormalities could result mainly from a defect in osteoblast differentiation and function. An imbalance in bone remodeling caused by decreased bone formation is also suggested in patients with GD1, as shown in a recent retrospective cohort study and review of the literature.⁹ A decreased osteocalcin level is present in about 50% of patients and correlates with the severity of bone involvement.

TABLE 207.1**Epidemiology of Gaucher disease type 1**

Peak age	Any age from birth to old age
Sex distribution	1 : 1
Prevalence rate (per 100,000), incidence, geography	15–40 in Ashkenazi Jews, rare (<1) in other populations; about 1 in 800 live births; panethnic
Genetic association	Association of sporadic Parkinson disease with heterozygous variants in the glucocerebrosidase gene
Transmission	Autosomal recessive

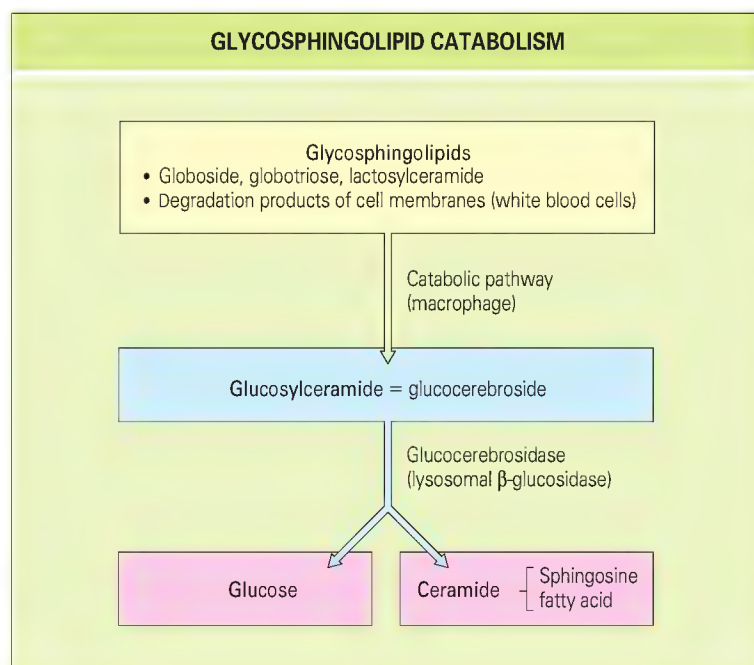


Fig. 207.1 The impaired activity of the lysosomal enzyme glucocerebrosidase results in the accumulation in macrophages of glucosylceramide, which is normally catabolized into ceramide and glucose.

CLINICAL FEATURES

GD1, the most common form of the disorder (Mendelian Inheritance in Man [MIM] No. 230800), is very heterogeneous as far as age at diagnosis and severity of clinical expression are concerned.

Hematologic manifestations and other extraskeletal disorders

The principal initial feature is splenomegaly, which is usually painless. Splenic rupture is rare, but infarction may occur, sometimes as the initial complaint. Primary hypersplenism with thrombocytopenia, anemia, and leukopenia occurs frequently. In most patients these abnormalities are not life-threatening and may go unrecognized for many years. Hepatomegaly is also common but occurs later in the course of the disease. A moderate increase in cholestatic enzymes is frequent; cytotoxicity, however, is rare but, when present, may be associated with the development of irreversible fibrosis. Liver failure has been reported in a few patients with portal hypertension and extensive fibrosis.

Several other extraskeletal disorders have been described in patients with GD1, especially pulmonary involvement in the form of interstitial lung disease or pulmonary vascular disease (severe pulmonary hypertension or hepatopulmonary syndrome). Several authors and a recent report from the Gaucher registry have mentioned an association of sporadic Parkinson disease with heterozygous variants of the glucocerebrosidase gene¹⁰ or with GD1. The relationship between GD1 and cancer was controversial for a long time, but a recent report showed that the number of cancers identified in patients in the international registry was comparable to that expected in the

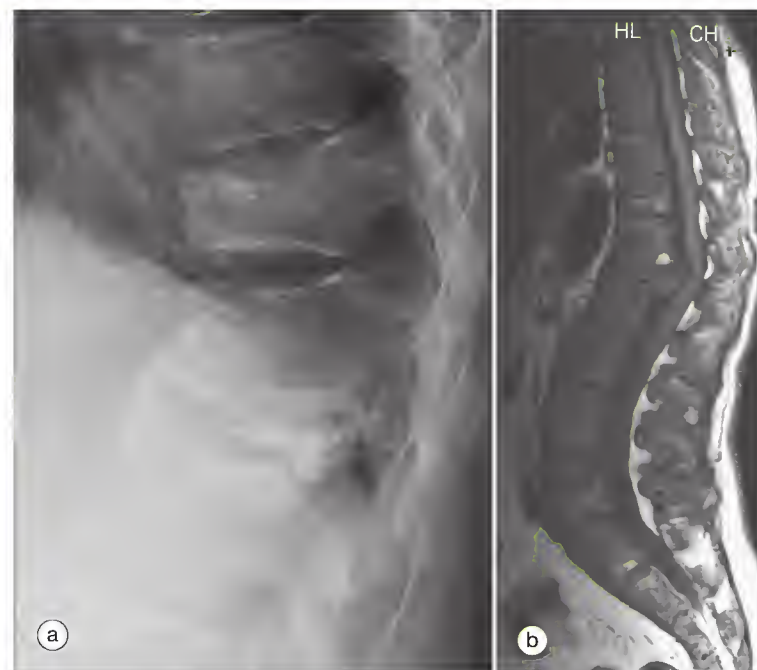


Fig. 207.2 (a) Severe compression fracture of the T12 vertebra with subsequent hyperkyphosis. The T10 vertebra is also crushed and has a grade 2 fracture. (b) In the same patient, magnetic resonance imaging of the spine shows spinal cord compression and angulation, although the patient remained free of neurologic complications, and diffuse heterogeneous low-intensity signal of all vertebrae on this T1-weighted sequence.

reference population, except for multiple myeloma (estimated relative risk, 5.9; 95% confidence interval, 2.8 to 10.8).⁶ A 16% prevalence of monoclonal gammopathy in 107 patients was observed recently.¹¹

Bone involvement

Skeletal involvement, which is the major complication of GD1 that leads to pain and disability, affects 50% to 85% of patients with type 1, and up to 20% of patients have impaired mobility.^{12,13} Although it is the consequence of bone marrow infiltration, bone involvement correlates only poorly with visceral and hematologic disease.^{4,7} Even though bone features (in particular, avascular osteonecrosis [AVN]) have been found to be worsened after splenectomy in some studies, only anemia was associated with increased risk for AVN.^{7,14}

Before any treatment, 63% of patients complain of bone pain in the back, hips, legs, and shoulders.³ Osteopenia, present in 42% of cases,³ is characterized by decreased bone mineral density (BMD, as assessed by osteodensitometry)^{15,16} and thinning of the cortices. Fractures may occur, most frequently in the vertebral spine (36.4% of all fractures), followed by the lower extremities.⁷ Neurologic compression and thoracic hyperkyphosis have been reported as being consequences of severe or multiple vertebral fractures (Fig. 207.2).¹³ Low bone density in the lumbar spine were reported to be a strong risk factor for fractures of the spine and femur in a large retrospective study of 5894 patients from the International Collaborative Gaucher Group Registry.⁷

Failure of modeling during growth is the most characteristic skeletal abnormality.¹² It develops progressively throughout the period of rapid skeletal growth and is evident in about 80% of adults with the disease. Expansion of the contours of long tubular bones results in cortical thinning and loss of the normal concavity of the bony outline, particularly medially (Fig. 207-3). The so-called Erlenmeyer flask deformity is very suggestive of GD1, though not pathognomonic (see “Differential Diagnosis” and Box 207.1). Vertebral bodies sometimes show steplike depressions in the superior and inferior margins. This deformity, which has been termed *H vertebra*, is identical to that observed in sickle cell anemia.

Osteonecrosis and bony infarctions are the most common bone complications in GD1 and the most frequent cause of chronic pain and limitation of function. Both are the consequences of sudden ischemia in an infiltrated bone area and result in acute-onset episodes (bone crisis). All bones may be involved, including flat bones. Symptoms include acute pain, tenderness, and fever, similar to the symptoms of osteomyelitis or septic arthritis.¹²

Epiphyseal osteonecrosis frequently occurs at multiple sites and affects the femoral heads, humeral heads (see Fig. 207.4a and b), and less commonly, the femoral condyles and tibial plateaus. Radiographic changes are similar to those seen in other forms of osteonecrosis.¹² Secondary cartilage destruction often appears subsequently and results in a disabling arthropathy that may require total arthroplasty.¹² The typical radiographic appearance of bony infarctions consists of serpiginous osteosclerotic areas, which correspond to the calcified scar of the perimeter of ischemia, located nearby or within lytic lesions and associated with periostitis (see Fig. 207.4c). In the cortex, an inner layer of new bone formation that does not merge with the overlying cortical bone produces cortical splitting or a “bone-within-bone” appearance.



Fig. 207.3 Typical distal femoral deformity of the Erlenmeyer flask type on a radiograph of the distal end of the femur and proximal end of the tibia of a 31-year-old man. Note the expansion of the contour of the long tubular bones with convexity of the osseous margins, typical but not pathognomonic for Gaucher disease.

Increased susceptibility to bone infections has been reported. Septic arthritis is rare but osteomyelitis occurs in less than 5% of affected patients.¹⁵ The clinical features may simulate those of bone crisis. Bacteriologic findings, short-term repeated bone scintiscans, tomodensitometry, and magnetic resonance imaging (MRI) facilitate making the proper diagnosis.

BOX 207.1 DIFFERENTIAL DIAGNOSIS OF THE RADIOLOGIC FEATURES OF TYPE 1 GAUCHER DISEASE

Diffuse or localized osteopenia

Osteoporosis (idiopathic, corticosteroid induced)
Hyperparathyroidism
Hemoglobinopathies
Neoplastic disorders (multiple myeloma)

Osteosclerosis

Osteosclerotic skeletal metastasis
Phakomatosis (tuberous sclerosis)
Osteopetrosis
Mastocytosis
Osteomyelofibrosis
Hodgkin disease
Hemoglobinopathies

Osteonecrosis

Hemoglobinopathies (sickle cell anemia)
Hypercorticism
Caisson disease
Collagen vascular disorders
Hyperlipemia
Pancreatitis

Erlenmeyer flask deformity

Niemann-Pick disease
Pyle disease
Fibrous dysplasia
Hyperthyroidism
Hemolytic anemias (thalassemia)
Leukemia
Osteopetrosis (Albers-Schönberg disease)
Heavy metal poisoning
Rachitism sequelae
Fracture sequelae

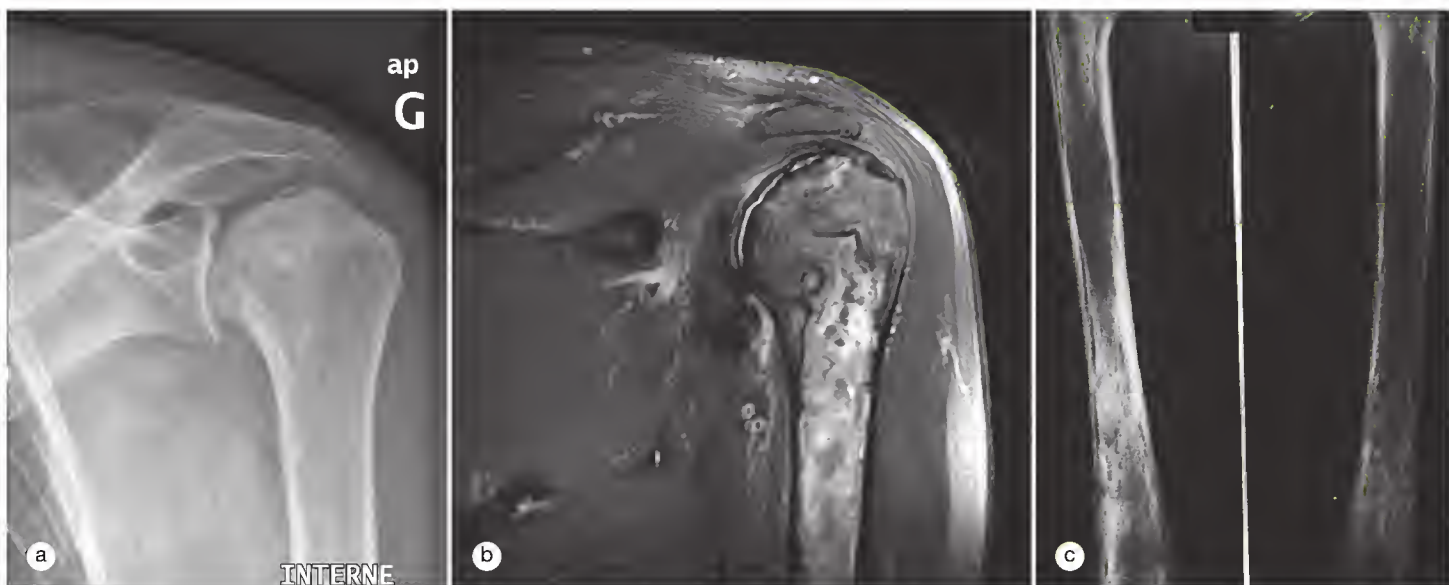


Fig. 207.4 Typical features of ischemic bone complications in Gaucher disease. A standard radiograph (a) and T2-weighted magnetic resonance image (b) of the proximal end of the humerus show osteonecrosis of the left humeral head. (c) Radiograph of the right humeral diaphysis of a second patient shows bony infarction with heterogeneous condensation of the diaphyseal bone and a cortical reaction producing cortical splitting, the so-called bone-within-bone appearance.

INVESTIGATIONS

Biochemical studies

Current recommendations for the initial assessment of individuals with GD1 include confirmation of acid β -glucosidase deficiency and measurement of biochemical markers of the disease. Enzyme activity could be measured in circulating lymphocytes or on fibroblast cultures. Biochemical markers reflecting overloading of activated macrophages, such as plasma tartrate-resistant acid phosphatase, angiotensin-converting enzyme, ferritin, chitotriosidase, and more recently, chemokine CCL18/PARC, are useful for evaluating disease activity and monitoring response to therapy.^{2,17}

Imaging

Radiologic bone manifestations are found in more than 95% of patients, with features and frequency depending on the imaging method used.

Plain radiology makes it possible to view the basic lesions. As a result of infiltration of bone marrow by Gaucher cells, radiographs show increased radiolucency of bone and cortical scalloping and thinning. These abnormalities involve predominantly the axial skeleton and proximal long bones, where they are often symmetric. They are prominent in the distal portion of the femur and tibia (Fig. 207.5). In some cases they appear as limited massive osteolytic lesions in a metaphysis resembling a tumor or aneurysmal bone cyst and are called a “gaucheroma.”

The extent and severity of the disease vary and are poorly evaluated by radiography, computed tomography (CT), or bone scintigraphy. MRI has been shown to be the most sensitive technique for detecting early bone marrow changes and for assessing the extent and severity of marrow involvement.^{18,19} Many sites in the marrow are characterized by a signal of abnormally low intensity on both T1- and T2-weighted sequences (see Fig. 207-2b). The distribution of the abnormality is heterogeneous; vertebrae are consistently involved, but in the lower extremity the femoral areas are affected more frequently than the tibial sites. The epiphyses are generally spared unless the involvement of bone is extensive. Quantification of the infiltrate with scoring systems involving conventional MRI or experimental MRI techniques are now being developed.¹⁹ MRI allows early detection of ischemic bone lesions with a high-intensity signal on T1-weighted sequences at the time of clinical bone crisis. A decrease in BMD has been reported to correlate with the severity of skeletal involvement and may be useful for monitoring bone changes.¹⁵ Combining CT and technetium Tc99m



Fig. 207.5 Radiograph of the right tibial diaphysis of a 52-year-old man showing osteopenia, osteolytic lesions, cortical thinning, and scalloping.

methylene diphosphonate bone scintigraphy helps in the differential diagnosis between osteonecrosis and osteomyelitis in the clinical setting of sudden bone crisis. The presence of a necrotic soft tissue swelling adjacent to the affected bone is suggestive of an infectious complication. Increased uptake on a bone scintiscan performed a few days after the onset of a bone crisis suggests acute osteomyelitis, whereas its absence makes an ischemic bone crisis more likely.

Histology

Demonstration of Gaucher cells in bone marrow biopsy specimens is key to the diagnosis¹ but is not required in most patients when the clinical and biochemical features are characteristic. These large mononucleated or multinucleated cells have characteristic cytologic features with a typical “wrinkled tissue paper” appearance of the cytoplasm (Fig. 207.6). Bone tissue alterations are highly variable.

DIFFERENTIAL DIAGNOSIS

The bone features of GD1 are not specific and may be observed in other disorders (see Box 207.1), particularly the hemoglobinopathies (see Chapter 195). The diagnosis should be considered in a patient with hepatosplenomegaly who exhibits widespread osteopenia with a coarsened trabecular pattern, focal osteosclerosis, osteonecrosis of the proximal femoral epiphyses, and Erlenmeyer flask deformities of the distal portions of the femur.

MANAGEMENT

Current recommendations for the initial evaluation (Box 207.2) and monitoring of type 1 Gaucher disease in adult patients have been elaborated by the Gaucher registry coordinators.²⁰

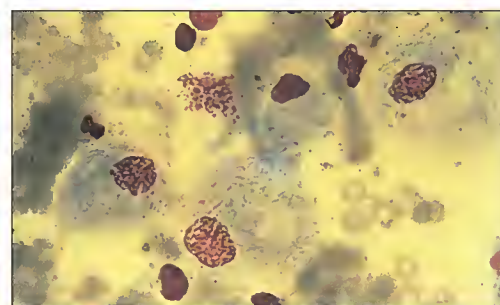


Fig. 207.6 Light microscopy of Gaucher cells in bone marrow. Note the typical “wrinkled tissue paper” appearance of the cytoplasm (May-Grünwald-Giemsa stain; original magnification $\times 160$). (Prepared by Dr. Mallarmé.)

BOX 207.2 INITIAL ASSESSMENT OF PATIENTS WITH TYPE 1 GAUCHER DISEASE

1. History and pedigree
2. Comprehensive physical examination
3. Quality-of-life questionnaire
4. β -Glucocerebrosidase activity and genotyping
5. Primary blood tests: hemoglobin, platelet count
6. Biochemical markers of the disease: chitotriosidase, angiotensin-converting enzyme, TRAP
7. Additional blood tests: white blood cell count, hemostasis testing, serum immunoelectrophoresis, liver enzymes, calcium and phosphorus values
8. Assessment of visceral involvement: spleen and liver volume (MRI or CT)
9. Assessment of skeletal involvement:
 - a. Radiographs of the femora (posteroanterior view) and spine (lateral view)
 - b. MRI of the entire femora (coronal T1- and T2-weighted images)
 - c. Dual-energy x-ray absorptiometry of the lumbar spine and hip
10. Assessment of pulmonary involvement: electrocardiogram, chest radiograph, Doppler echocardiogram for measurement of right ventricular systolic pressure

CT, computed tomography; MRI, magnetic resonance imaging; TRAP, tartrate-resistant acid phosphatase.

Therapeutic goals

Following a consensus conference held in Amsterdam in October 2003, therapeutic goals have been proposed for each specific involvement of the disease.²¹ The following goals for skeletal involvement are recommended:

- Lessen or eliminate bone pain within 1 to 2 years.
- Prevent bone crises.
- Prevent osteonecrosis and subchondral joint collapse.
- Improve BMD—for pediatric patients, attain normal or ideal peak skeletal mass and increase cortical and trabecular BMD by year 2; for adult patients, increase trabecular BMD by 3 to 5 years.

Enzyme replacement therapy

Three forms of macrophage-targeted glucocerebrosidase are now available: recombinant glucocerebrosidase produced by DNA technology (imiglucerase [Cerezyme], Genzyme Corporation, Cambridge, Mass), human glucocerebrosidase produced in a human cell line with gene activation technology (velaglucerase alfa [VPRIV], Shire Human Genetic Therapies, Inc., Cambridge, Mass), and a carrot cell-expressed human recombinant β -glucocerebrosidase (taliglucerase alfa [Elelyso], Protalix Biotherapeutics, Carmiel, Israel). Glucocerebrosidase infusions reverse the hematologic complications and hepatosplenomegaly within 12 to 20 weeks,^{18,20,22,23} although bone response requires a longer period.²⁰ Bone pain and bone crises statistically decrease rapidly, with improvement at 3 months continuing progressively and the reduction being maintained for at least the first 3 years with a significant positive impact on quality of life.^{2,4,24-26} Risk for AVN is reduced in patients who initiated enzyme replacement therapy within 2 years of diagnosis.¹⁴ Imaging features improve after 1 to 2 years with an increase in BMD.^{4,15,22,25} Currently recommended therapeutic regimens start with 2-hour intravenous infusions of 60 IU/kg every 2 weeks.^{1,17} Even if there is a dose-response relationship for enzyme replacement therapy in GD1, optimal management is not well defined, and some patients experienced ongoing bone disease despite increased doses.^{2,27} Low-dose or intermittent-dosing regimens fail to achieve sustained improvement of the bone lesions or symptoms, and treatment for 2 to 3 years (lifelong in severely affected patients) is currently recommended. Because imiglucerase results in amelioration of osteopenia in all age groups, with the greatest improvements noted in younger patients, early treatment is recommended to attain better peak bone mass.¹⁶ MRI scores have recently been proposed for evaluating the therapeutic response.¹⁹ Chitotriosidase activity in serum is useful as an indicator of the efficacy of enzyme replacement therapy and as an early indicator of relapse after dose reduction or therapeutic interruption.²¹

Substrate reduction therapy

Miglustat is an iminosugar that decreases substrate synthesis. It has been shown to reduce hepatic and splenic volume and the incidence of bone pain

and to increase platelet counts.²⁸ It is approved by the U.S. Food and Drug Administration and European Medicines Agency for patients with mild to moderate GD1 who are intolerant of imiglucerase or unwilling to take enzyme replacement therapy. Eliglustat tartrate, an investigational substrate reduction drug and a specific inhibitor of glucosylceramide synthase, is currently in phase 3 trials.²⁹

Symptomatic treatments

Bone remodeling–targeted treatments and vitamin D

Antiresorptive therapy with high-dose alendronate in addition to enzyme replacement therapy increases BMD at 24 months without radiologic modification of focal lesions.³⁰ The effect on risk for fractures is unknown. The recent finding that osteoblast formation is impaired in patients with GD1 may suggest that bone anabolic agents could be explored as a treatment option. Because vitamin D deficiency seems to be frequent in patients with GD1, optimization of the vitamin D level is recommended.³¹

Splenectomy

Enzyme replacement therapy has considerably limited the indications for splenectomy because glucocerebrosidase infusions commonly reverse the hematologic disorders associated with hypersplenism¹⁷ and splenectomy has been shown to accelerate skeletal involvement.

Orthopedic treatments

Relief of bone and joint pain may necessitate the use of strong analgesics. Osteonecrosis or pathologic fractures often require surgery. Improved surgical techniques have increased the probability of good results and decreased the postoperative complications that were reported in historical series: bleeding, infection, and prosthetic loosening. For example, the first hip arthroplasty takes place at 43.8 years, 20 years earlier than in the general population and with as good results.^{32,33} Because of the frequency of atypical organisms, infectious complications (e.g., osteomyelitis) require both careful bacteriologic studies and prolonged antibiotic therapy.

Experimental therapies

Marrow transplantation has been shown to be curative in some patients, but the risks, which increase with the severity of the disease, do not justify this procedure in patients with relatively mild disease, especially since the development of enzyme replacement therapy.² An exception may be patients with neuronopathic disease. Somatic cell gene therapy is currently under investigation.

Management of Gaucher disease is a rapidly growing area. It now appears possible to prevent and reverse some of the most devastating and disabling complications of this disease, but initial evaluation plus monitoring of multiple compartments is necessary to better achieve more therapeutic goals. Prevention and treatment of bone complications will lead to much higher quality of life for all patients with GD1.

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■ MARWAN A.S. BUKHARI

- Mucopolysaccharidoses are lysosomal storage diseases.
- The lysosomal defect is responsible for the deficient degradation of glycosaminoglycans.
- This complex group of mucopolysaccharidoses has several well-defined types; the most frequent forms are Hurler disease (type I) and Morquio disease (type IV).
- The main clinical features of the most common mucopolysaccharidosis (type I) are facial dysmorphism, visceral and corneal storage abnormalities, and skeletal disorders (dysostosis multiplex). Neurologic abnormalities are present in several types.

HISTORY

In 1917, Hunter¹ reported two brothers with coarse facies, mental retardation, and bone disorders. However, the first detailed description of mucopolysaccharidosis was by Gertrud Hurler² in 1919, who was inspired by Pfaundler. In 1929, Morquio and Brailsford gave a precise description of type IV mucopolysaccharidosis, and in 1963, Sanfilippo defined type III disease and Maroteaux and Lamy defined type VI disease.³⁻⁷

In 1952, Brante⁸ reported that the material stored in these patients was mucopolysaccharides. Dorfman and Lorincz documented increased urinary excretion of mucopolysaccharides, and Van Hoof and Hers demonstrated that mucopolysaccharides are stored in lysosomes.^{9,10} The corrective factors were then purified and their enzyme functions identified (Table 208.1). In 1962, Scheie and colleagues described a patient with corneal clouding, skeletal dysplasia, and coarsening of the features, and this was initially referred to as mucopolysaccharidosis V until it was discovered that it was a milder form of type I.^{11,12}

CLINICAL FEATURES

Type I

Hurler disease (mucopolysaccharidosis type IH) is the most typical of these disorders. It is usually apparent by 2 years of age and is characterized by facial dysmorphism, dorsal kyphosis, or mental retardation. The craniofacial morphology is typical, with macrocephaly, broad nasal bridge, full cheeks, thick lips, enlarged tongue, coarse hair, and hirsutism (Fig. 208.1). Joint movements are limited, and clawhand is common (Fig. 208.2). Lumbar kyphosis occurs frequently. The abdomen is protuberant, with hepatosplenomegaly and hernias. Corneal opacities are visible on slit-lamp examination. Cardiomyopathies have also been reported.¹³ Progressive mental and physical deterioration leads to death, often between 10 and 15 years of age.

Scheie disease (mucopolysaccharidosis type IS) is detected later, usually in childhood, and has a slow evolution.^{11,12} Joint stiffness, clawhand, heart murmurs, and corneal clouding are the main clinical manifestations of this form. Intermediate manifestations are frequently called Hurler/Scheie disease.¹⁴ Some of the milder forms of disease are usually detected only later in life because patients can have normal features and may report just Achilles tendon shortening or joint contracture.¹⁴

Radiographic features

Radiographs show macrocephaly, sagittal craniosynostosis, and an enlarged sella turcica. The ribs are wide, with an "oar-shaped" deformity. The

vertebral bodies are ovoid, and hooklike dysplasia is visible at the apex of the gibbus (Fig. 208.3). The midshafts of long bones are enlarged, with typical tilting of the distal ends of the radius and ulna toward each other, together with coxa valga. The epiphyses and carpal and tarsal bones are small and irregular. The iliac wing is small, and subluxation of the femoral head occurs frequently. The phalanges and metacarpal bones are shortened and enlarged, and the pointed proximal end of the metacarpals gives the characteristic "sugar loaf" appearance.¹⁵

Type II

Mucopolysaccharidosis type II is an X-linked recessive disorder. Its clinical and radiologic manifestations are similar to those of Hurler disease but are often more slowly progressive (Fig. 208.4), and the cornea is clear.

Type III

In mucopolysaccharidosis type III (Sanfilippo disease), the facial features and skeletal deformities are much milder than those in Hurler syndrome (Fig. 208.5). However, the mental and motor deterioration is precocious and severe.

Type IV

In type IV (Morquio disease), dwarfism is severe, with a short trunk, kyphosis at the thoracolumbar junction, pectus carinatum, and knock-knees (Fig. 208.6). Intelligence is normal, and no visceral storage is observed (only minimal corneal clouding). Universal platyspondyly with small odontoid processes, coxa valga, irregularities of the epiphyses and metaphyses, small and irregular carpal bones, and pointed proximal ends of the metacarpals are the more typical radiologic manifestations. The spinal cord compression secondary to atlantoaxial dislocation must be prevented by surgical intervention. Morquio type B syndrome is similar but has milder deformities.

Type VI

In type VI the facies is less grotesque than in Hurler disease. The cornea is cloudy, but mental development remains normal. Skeletal changes and dwarfism are variable but often severe.

Type VII

Mucopolysaccharidosis type VII (Sly disease) is very rare. It is associated with considerable phenotypic and bone deformity variations.¹⁶

HISTOLOGIC MANIFESTATIONS

In type I and type II disease, vacuolated lymphocytes are found with metachromatic inclusions in the vacuoles (Gasser cells). In addition, reticular cells of the bone marrow contain inclusions that vary from moderately coarse to very thick black-violet (type II Gasser cells).¹⁷ In type II, lymphocytes have also been described with pink-ringed vacuoles.¹⁸ In mucopolysaccharidosis type III, Gasser cells are more numerous, and plasmacyte cells containing vacuoles with metachromatic inclusions (Buhot cells) are found in the bone marrow. Alder anomaly is seen in type VI and is evident as coarse, dense granules in granulocytes, monocytes, and a large proportion of lymphocytes.

TABLE 208.1
Summary of the main types of mucopolysaccharidosis

	Skeletal dysplasia	Corneal opacities	Mental degradation	Inheritance	Urinary glycosaminoglycans	Enzymatic deficiency	Gene localization
Type IH (Hurler disease)	+	+	+	Autosomal recessive	Heparan sulfate Dermatan sulfate	α -L-Iduronidase	4p16.3
Type IS (Scheie disease)	$\pm$	+	–	Autosomal recessive	Heparan sulfate Dermatan sulfate	α -L-Iduronidase	4p16.3
Type II (Hunter disease)	–	+	$\pm$	X-linked recessive	Heparan sulfate Dermatan sulfate	Iduronidate-2-sulfate sulfatase	Xq27.3q28
Type III (Sanfilippo disease)	$\pm$	–	++	Autosomal recessive Autosomal recessive Autosomal recessive Autosomal recessive	Heparan sulfate	(a) Heparan sulfatase (b) <i>N</i> -acetyl-b-glucosaminidase (c) α -glucosaminide <i>N</i> -acetyltransferase (d) <i>N</i> -acetylglucosamine-6-sulfate sulfatase	17q25.3 17q21.1 14p13 12q14
Type IV (Morquio disease)	++ (a) + (b)	+	–	Autosomal recessive Autosomal recessive	Keratan sulfate	(a) <i>N</i> -acetylglucosamine-6-sulfate sulfatase (b) β -Galactosidase	16q24.3 3p21p33
Type VI (Maroteaux-Lamy)	+ / ++	+	–	Autosomal recessive	Dermatan sulfate	Arylsulfatase B	5p11p13
Type VII (Sly)	+	+	+	Autosomal recessive	Chondroitin sulfate	β -Glucuronidase	7q11.21q11.22

–, absent; $\pm$, could be present; +, mild; +/++, moderate; ++, severe.

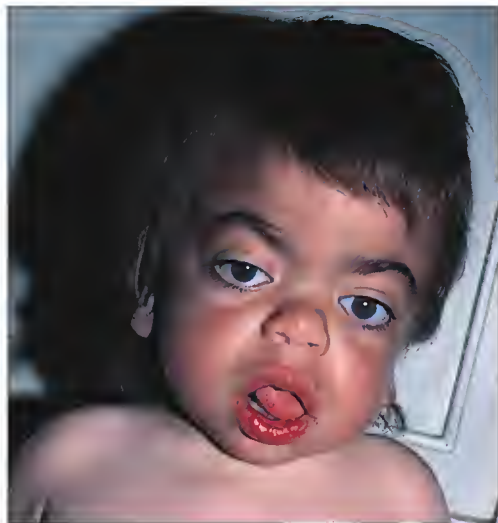


Fig. 208.1 Hurler disease. Typical facial dysmorphism.



Fig. 208.3 Hurler disease. Note the hooklike deformity of the second lumbar vertebral body.

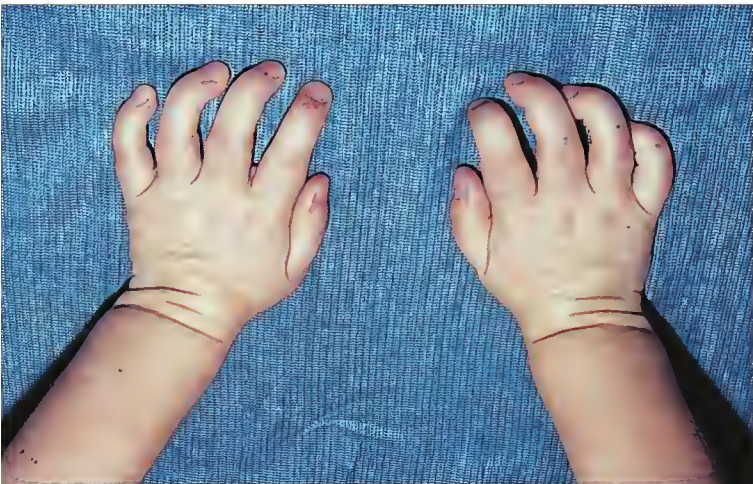


Fig. 208.2 Hurler disease. Clawhand is a common feature.



Fig. 208.4 Hunter disease. Note that the facial dysmorphism is milder than in Hurler disease.



Fig. 208.5 Sanfilippo disease. Mild coarsening of the facial features is apparent.

BIOCHEMICAL MANIFESTATIONS

Urinary elimination of dermatan sulfate and heparan sulfate is increased in type I and type II disease. Heparan sulfate is elevated in type III, keratan sulfate in type IV, and dermatan sulfate in type VI. These diseases arise from an inherited deficiency of the activity of lysosomal enzymes. For example, type I is characterized by an inherited deficiency of α -L-iduronidase (see Table 208.1).



Fig. 208.6 Morquio disease in a brother and sister. Note the short trunk with pectus carinatum and knock-knees.

PATHOGENESIS

The mucopolysaccharidoses are caused by a deficiency of specific lysosomal enzymes that catabolize glycosaminoglycans into shorter subunits for reuse or excretion. Deficiency of these enzymes results in intracellular accumulation and increased urinary excretion of the products of incomplete catabolism. As a result, cellular function is altered in cartilage, connective tissue, the heart, and the central nervous system.

The genes for these deficient enzymes have been mapped and cloned (see Table 208.1). Each gene has several mutations. The mutation 1113F is common and produces a severe phenotype, whereas the mutation T312S is found in patients with milder disease.¹⁹ However, significant interpopulation variation is observed.²⁰

MANAGEMENT

Management of all the mucopolysaccharidoses involves a multidisciplinary team approach that includes a neurologist; ear, nose, and throat and orthopedic surgeons; physiotherapists; and an experienced physician coordinating care.²¹ Advances have recently been made in disease-specific treatments, and these are summarized per disease and involve either enzyme replacement therapy (ERT) or hematopoietic stem cell transplantation (HSCT).

Mucopolysaccharidosis I: ERT for this disease is in the form of laronidase (0.58 mg/kg/wk). Laronidase is more effective in early disease.^{22,23}

HSCT for type I has been associated with a 3-year survival rate of 77%.²⁴

Mucopolysaccharidosis II: ERT for type II disease is in the form of idursulfase at a dose of 0.5 mg/kg/wk.²⁵ Trials of HSCT have been less successful.²⁶

The only other form of ERT to have been published is galsulfase for type VI.²⁷ HSCT has been used for the other diseases with variable results.²¹

New therapies are emerging, including a small-molecule approach, a gene therapy approach, and intrathecal drugs, all in early-phase experimentation.

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209

Heritable connective tissue disorders

■ JOAN C. MARINI

OSTEOGENESIS IMPERFECTA

- Osteogenesis imperfecta is a genetic collagen-related syndrome characterized by abnormal bone matrix and secondary osteoporosis. Most cases (85%) are caused by autosomal dominant inheritance of defects in the genes coding for type I collagen, *COL1A1* or *COL1A2*, whereas rare recessive forms are caused by deficiency of proteins that interact with type I collagen posttranslationally for folding or modification, including the three components of the prolyl 3-hydroxylation complex (CRTAP, P3H1, CyPB) and two separate peptidyl-prolyl isomerases (HSP47 and FKBP10).
- Osteogenesis imperfecta is a generalized connective tissue disorder with variable nonosseous features, including abnormal scleral hue, hearing loss, dentinogenesis imperfecta, short stature, macrocephaly, joint laxity, and easy bruising.
- "Brittle bone disease" is susceptibility to fractures as a result of mild trauma.
- Forms of osteogenesis imperfecta range from those lethal in the perinatal period to those barely detectable.
- Treatment with bisphosphonates improves vertebral strength and geometry in children, but long-term detrimental effects on bone quality should limit use to 3 to 5 years.

EHLERS-DANLOS SYNDROME

- Ehlers-Danlos syndrome (EDS) is a genetic condition that affects joints, skin, and blood vessel walls.
- It is a heterogeneous group of generalized connective tissue disorders associated with multiple modes of inheritance and abnormalities of (predominantly) type III collagen in vascular EDS and type V collagen in hypermobility EDS, as well as some cases with defects in type I collagen and fibronectin, enzyme deficiencies, or abnormal copper metabolism.
- Joint involvement may include hyperextensibility of large or small joints and joint dislocations. Skin involvement may include a soft velvety texture, hyperextensibility, and fragility with stretched or "cigarette paper" scars.
- Vascular and visceral involvement ranges from easy bruising to life-threatening arterial rupture and rupture of the colon or uterus.

MARFAN SYNDROME

- Marfan syndrome is a genetic syndrome with abnormalities in the musculoskeletal, cardiovascular, and ocular systems.
- It is a generalized connective tissue disorder with variable clinical expression caused by defects in the fibrillin-1 gene, an extracellular matrix protein found in microfibrils. The overlapping conditions congenital contractural arachnodactyly and Loeys-Dietz syndrome are caused by defects in fibrillin-1 and subunits of the transforming growth factor- β receptor.
- Skeletal signs include tall stature, dolichostenomelia (long extremities), arachnodactyly, scoliosis, and chest deformities. Ocular signs include lens dislocation or subluxation.
- Cardiovascular manifestations include aortic root dilation and ascending aortic aneurysm. Treatment with β -blockers is the currently accepted standard; children who received the angiotensin receptor blocker losartan had a decreased rate of aortic root growth.

CHONDRODYSTROPHIES

- The chondrodystrophies are a large and strikingly heterogeneous group of heritable skeletal dysplasias with abnormal proportions of the limbs, trunk, and/or skull and often short stature.
- Disorders are classified according to the Paris nomenclature of 1976.
- Some chondrodystrophies have abnormal type II collagen. However, in most chondrodystrophies the abnormality in extracellular matrix is unknown.
- Skeletal involvement may include short or disproportionate stature and joint and skull abnormalities. Nonskeletal involvement may include abnormalities of the cardiac, ocular, or auditory systems.
- Achondroplasia, the most common chondrodystrophy, is evident at birth because of rhizomelic shortening of the limbs, large calvaria with a prominent forehead, trident hand, and lordosis.
- Stickler syndrome is characterized by ocular, facial, and joint involvement.

INTRODUCTION

In the past 20 years, dramatic progress has been made in understanding the molecular genetics of heritable connective tissue disorders. Various types of osteogenesis imperfecta (OI) have been shown to be caused by abnormalities in type I collagen or deficiency of proteins involved in collagen modification. Some types of Ehlers-Danlos syndrome (EDS) have been shown to be caused by abnormalities in types I, III, or V collagen. Some chondrodystrophies have been associated with abnormal type II collagen, whereas Marfan syndrome, long classified as a "collagen disorder," is caused by mutations in fibrillin-1 (*FBN1*), a component of the extracellular matrix.

These discoveries have served to highlight the basic principles that distinguish these disorders. First, they are primary connective tissue disorders with a primary heritable defect in a component of matrix. In contrast, the "collagen vascular" disorders exert their effect on connective tissue indirectly; a defect in one allele can inactivate 93% of the total product of both alleles. Second, metabolic disorders are usually symptomatic only when both alleles of a gene are defective. Third, connective tissue disorders display variability in the phenotype of individuals with the same mutation and genetic heterogeneity, because mutations in different genes can cause the same phenotype in different individuals.

OSTEOGENESIS IMPERFECTA**History**

The term *osteogenesis imperfecta* was first used by Vrolik in 1849. Since 1979, some form of the Sillence genetic classification has been in use.¹ In the early 1980s, Prockop demonstrated that OI was caused by abnormalities in type I collagen.^{2,3} Recently, discoveries have identified causes of recessive OI,³ namely, deficiency of proteins involved in collagen prolyl 3-hydroxylation or of two separate collagen peptidyl-prolyl *cis-trans* isomerases (PPIases) or deficiency of *SERPINF1/PEDE*. Dominant type V OI was shown to be caused by a single mutation in *IFITM5/BRIL*.

Epidemiology

The overall frequency of OI identifiable at birth is about 1 per 20,000 to 30,000.³ The frequency of mild type I OI has been estimated to be 1 in 30,000 in Australia.³ The overall prevalence and severity are not influenced by gender, race, or ethnic origin. However, a west African *LEPRE1* recessive founder mutation is carried by about 1.5% of contemporary Ghanians and Nigerians and also occurs in mid-Atlantic African Americans.⁴ Recessive OI accounts for 5% to 7% of OI cases overall.

Clinical features

Sillence classification

The modified Sillence classification of OI (Table 209.1)^{1,3} is based on genetic, clinical, and radiographic data. Type II OI is lethal in the perinatal period. The overwhelming majority of cases are associated with new dominant mutations; 10% of affected offspring of clinically normal parents are a result of germline mosaicism in one parent. Type III, the most severe form compatible with long-term survival, has a natural history characterized by extremely short stature, progressive scoliosis, and deformity of long bones. Type IV consists of moderately severe skeletal features with significantly short stature; this form is compatible with assisted ambulation. Individuals with type I OI have mild skeletal disease and frequently have blue sclerae.

The Sillence classification has been extended to types V to XI.³ Types V and VI were classified by their distinctive bone histology; their etiology has recently been identified as being due to a dominant mutation in *IFITM5* and recessive mutations in *SERPINF1*, respectively. Types VII, VIII, and IX have recessive inheritance. They are caused by null mutations in the genes encoding cartilage-associated protein (CRTAP), prolyl 3-hydroxylase-1 (P3H1), and cyclophilin B (CyPB),³ components of the collagen prolyl 3-hydroxylation complex. Types VII and VIII have a severe to lethal phenotype that clinically overlaps with that of types II and III and distinctive features, especially white sclerae. Types X and XI are recessive forms caused by deficiency of the collagen chaperone/PPIases HSP47 or FKBP10.³ The one patient with type X exhibited partial enzyme deficiency and early childhood demise, whereas FKBP10 deficiency causes a moderate to severe phenotype that incorporates congenital contracture disorders, Bruck syndrome, and Kuskokwim disease.³

Skeletal dysplasia

The skeletal system in OI is characterized by osteoporosis secondary to abnormal matrix, bowed long bones, compressed vertebrae, and triangular facies. Individuals with type II OI (Fig. 209.1a) have prenatal fractures of ribs and long bones and severe limb shortening and deformity. Relative macrocephaly, a soft membranous skull, and wormian bones are also features. Individuals with type III OI (see Fig. 209.1b) experience frequent fractures, progressive scoliosis, long-bone deformity, and metaphyseal flaring with “popcorn” formation. In type IV (see Fig. 209.1c and d) and type I, the long bones are generally well modeled, though relatively osteoporotic. Fractures usually occur after ambulation, are related to trauma, heal with minimal deformity, decrease dramatically in number after puberty, and recur after menopause.³ The skeletal dysplasia of recessive OI is extremely severe, with dual-energy x-ray absorptiometry (DEXA) z scores below –6 and the development of metaphyseal “popcorn” in midchildhood. Type V overlaps clinically with moderate OI but adds the triad of hypertrophic callus, ossification of the interosseous membrane, and dense metaphyseal bands, whereas patients with type VI have severe progressive deforming OI with wide osteoid seams and a slow mineralization time, as well as a “fish scale” pattern of lamellar bone under polarized light.³

Ocular features

Blue sclerae, caused by decreased scleral thickness, is common in classic dominant OI and occurs especially in types I and II. Some individuals with dominant OI have white sclerae. However, white sclerae in patients with severe or lethal OI are strongly associated with the recessive forms.

Dental features

Dentinogenesis imperfecta with grayish opalescent or brown-yellow dentition may be present and sometimes leads to crumbling of teeth. The permanent dentition is less severely affected.

Other systems

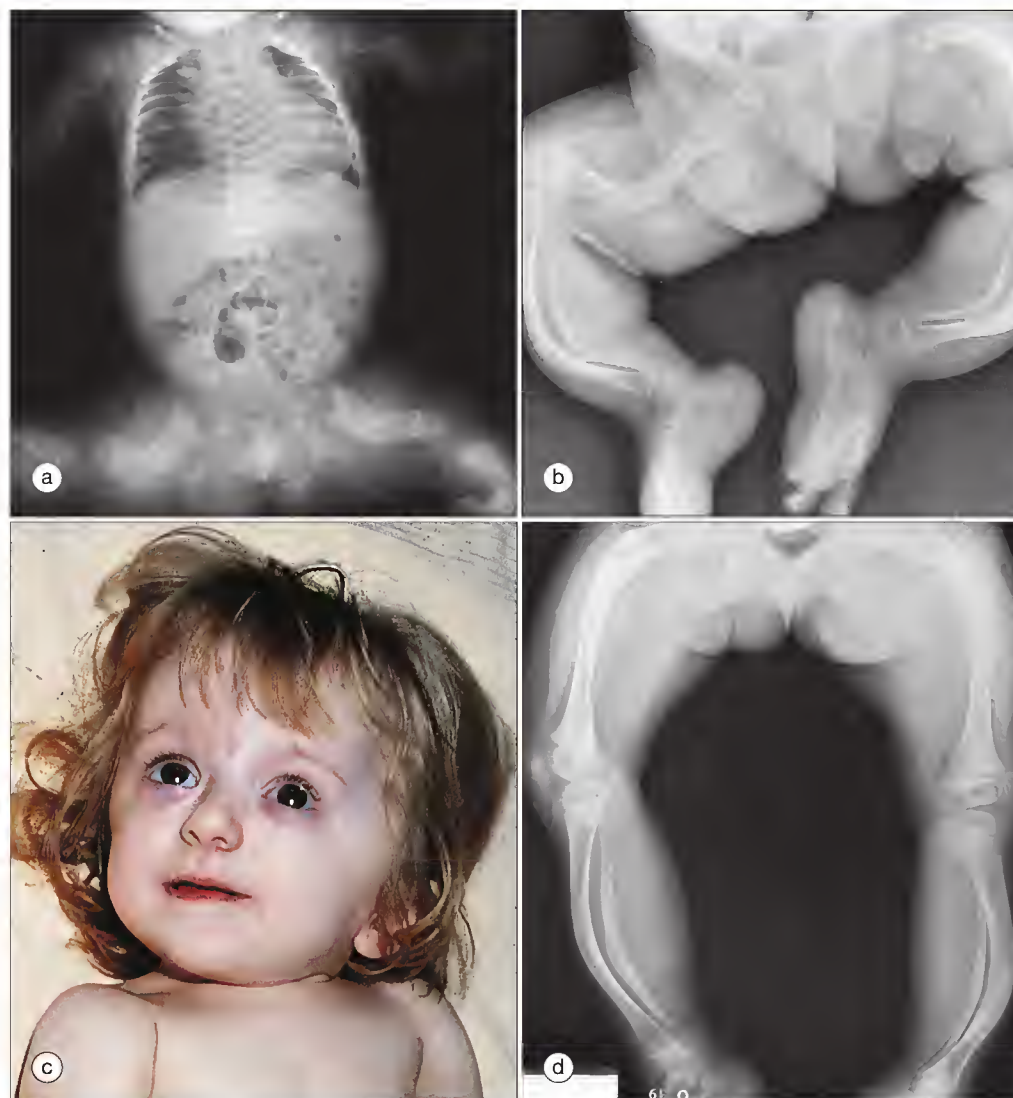
Hearing loss is a common feature of OI that occurs in about 50% of patients over their lifetime and is especially prevalent with type I.⁶ It is manifested as conductive or mixed hearing loss and develops in the early adult years. Pulmonary complications may be a significant source of morbidity and mortality.³ Infants with type II OI generally die of respiratory insufficiency.

TABLE 209.1
Modified Sillence classification of osteogenesis imperfecta

Type	Genetics	Description
I	Autosomal dominant	Mildest form of OI Mild to moderate bone fragility without deformity Associated with blue sclerae, early hearing loss, easy bruising May have mild to moderate short stature Type IA: dentinogenesis imperfecta absent Type IB: dentinogenesis imperfecta present Null mutations in <i>COL1A1</i>
II	Autosomal dominant	Perinatal lethal or recessive Extreme fragility of connective tissue, multiple <i>in-utero</i> fractures, usually intrauterine growth retardation Soft, large cranium Micromelia, long bones crumpled and bowed, ribs beaded Mutations in <i>COL1A1</i> or <i>COL1A2</i>
III	Autosomal dominant	Progressive deforming phenotype Severe fragility of bones, usually <i>in-utero</i> fractures Severe osteoporosis Relative macrocephaly with triangular facies Fractures heal with deformity and bowing Associated with white sclerae and extremely short stature, scoliosis Mutations in <i>COL1A1</i> or <i>COL1A2</i>
IV	Autosomal dominant	Skeletal fragility and osteoporosis more severe than in type I Associated with bowing of long bones; light sclerae with or without moderate short stature and moderate joint hyperextensibility Type IVA: dentinogenesis imperfecta absent Type IVB: dentinogenesis imperfecta present Mutations in <i>COL1A1</i> or <i>COL1A2</i>
V	Autosomal dominant	Moderate fragility Hypertrophic callus Dense metaphyseal bands Ossification of interosseous membranes “Meshlike” bone histology Mutation in <i>IFITM5</i> (BRIL)
VI	Autosomal recessive	Moderate to severe osteopenia secondary to a mineralization defect “Fish scale” lamellae on bone histology Mutations in <i>SERPINF1</i> (PEDF)
VII	Autosomal recessive	Perinatal lethality or severe dysplasia Caused by null (lethal) or hypomorphic (surviving) defects in CRTAP
VIII	Autosomal recessive	Perinatal lethality or severe bone dysplasia West African founder mutation, 1%-2% prevalence Caused by null mutations in <i>LEPRE1/P3H1</i>
IX	Autosomal recessive	Lethal to moderate Mutations in <i>PPIB</i> (CyPB)
X	Autosomal recessive	Severe deforming OI Blue sclerae and dentinogenesis imperfecta Mutation in <i>SERPINF1</i> (HSP47)
XI	Autosomal recessive	Moderate to severe deforming OI Variable congenital contractures (Bruck syndrome type I) White sclerae, normal teeth Mutations in <i>FKBP10</i> (FKBP65)

OI, osteogenesis imperfecta.
Data from Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979;16:101-16; and Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. *Nat Rev Endocrinol* 2011;7:540-57.

Fig. 209.1 Features of osteogenesis imperfecta. (a) Type II: short, crumpled long bones and rib fractures. (b) Type III: progressive deformity and osteoporosis of long bones. (c and d) Type IV: triangular facies, frontal bossing, shallow orbits, and long bones with moderate deformity and osteoporosis.



In types III and IV OI, pectoral deformities, scoliosis, and flaring and softness of the rib cage may predispose to frequent pneumonia or eventually cor pulmonale. Mitral valve prolapse may be present. Growth impairment³ affects virtually 100% of patients with types III and IV and is unrelated to fracture frequency or location. Patients with type I are shorter than their family members. Neurologically, children with types III and IV often have ventriculomegaly and sulcal prominence, even without macrocephaly. This does not indicate hydrocephalus and is not associated with intellectual impairment.

Investigations

The diagnosis of OI is usually apparent from the clinical and radiologic findings. The initial radiologic survey should also include lateral views of the skull and vertebrae. Normal or elevated serum alkaline phosphatase, calcium, and phosphate concentrations rule out metabolic mineralization disorders. In moderate and severe OI, periodic radiographs of the lower extremity long bones and vertebral bodies are useful for surgical and rehabilitative management. DEXA is useful for monitoring the progression of osteoporosis. Audiologic evaluation and pulmonary function tests every other year starting in childhood allow anticipatory management.

Prenatal detection of types II and III OI is possible with ultrasound. Analysis of collagen from chorionic villi has been accurate in detecting types II, III, and IV OI and allows diagnosis by 12 to 15 weeks' gestation.⁷ Cultured amniotic fluid cells may yield false-positive biochemical diagnoses.

Identification of the specific *COL1A1*, *COL1A2*, *CRTAP*, *LEPRE1/P3H1*, *PP1B/CyPB*, *IFITM5/BRIL*, *SERPINF1/PEDE*, *SERPINH1/HSP47*, or *FKBP10* mutation is useful for accurate genetic counseling and for establishing the diagnosis in ambiguous or mild cases. Biochemical analysis of fibroblast collagen is less sensitive for detection of mutations in the amino third of the α chains. It is most useful for detecting type I OI. Biochemical analysis

of collagen in recessive types VII, VIII, and IX OI shows full overmodification of collagen chains, as occurs with collagen mutations toward the COOH end of the helix.³ Direct sequencing at the DNA or complementary DNA (RNA) levels is more sensitive for the most common structural changes in collagen associated with types II, III, and IV OI. Overall, diagnostic tests demonstrate a type I collagen abnormality in about 85% of patients with OI. Recessive OI accounts for 5% to 7% of the total OI cases; the dominant type V OI may be as prevalent as 5% of OI cases in North Americans.

Etiology and pathogenesis

Structure and function

Dominant OI has been associated with defects in the structure or synthesis of type I collagen (Fig. 209.2).^{2,3,8} Type I collagen² is the major protein in human extracellular matrix and plays a crucial scaffolding role in bone, skin, ligaments, tendons, sclerae, and blood vessel walls. This wide distribution accounts for the generalized nature of OI.

Type I collagen is a heterotrimer composed of two $\alpha 1(I)$ chains and one $\alpha 2(I)$ chain twisted around each other in a right-handed helix. Each chain is synthesized as a propeptide with globular extensions at both ends and a central helical domain of 1014 amino acids. The helical domain is composed of repeating Gly-X-Y triplets, in which X and Y are often proline and hydroxyproline, respectively. Each exon begins with a glycine and ends with a Y codon.

The three chains of the helix initially associate through the globular carboxyl extension. Helix formation then proceeds linearly toward the N-terminus, with glycine residues occupying the core positions inside the helix. Concomitant with synthesis and helix formation, lysine residues are hydroxylated and glycosylated and proline residues are 4-hydroxylated. This modification occurs in multiple residues in the helical region; once the chains are in the triple-helical configuration, they are no longer accessible

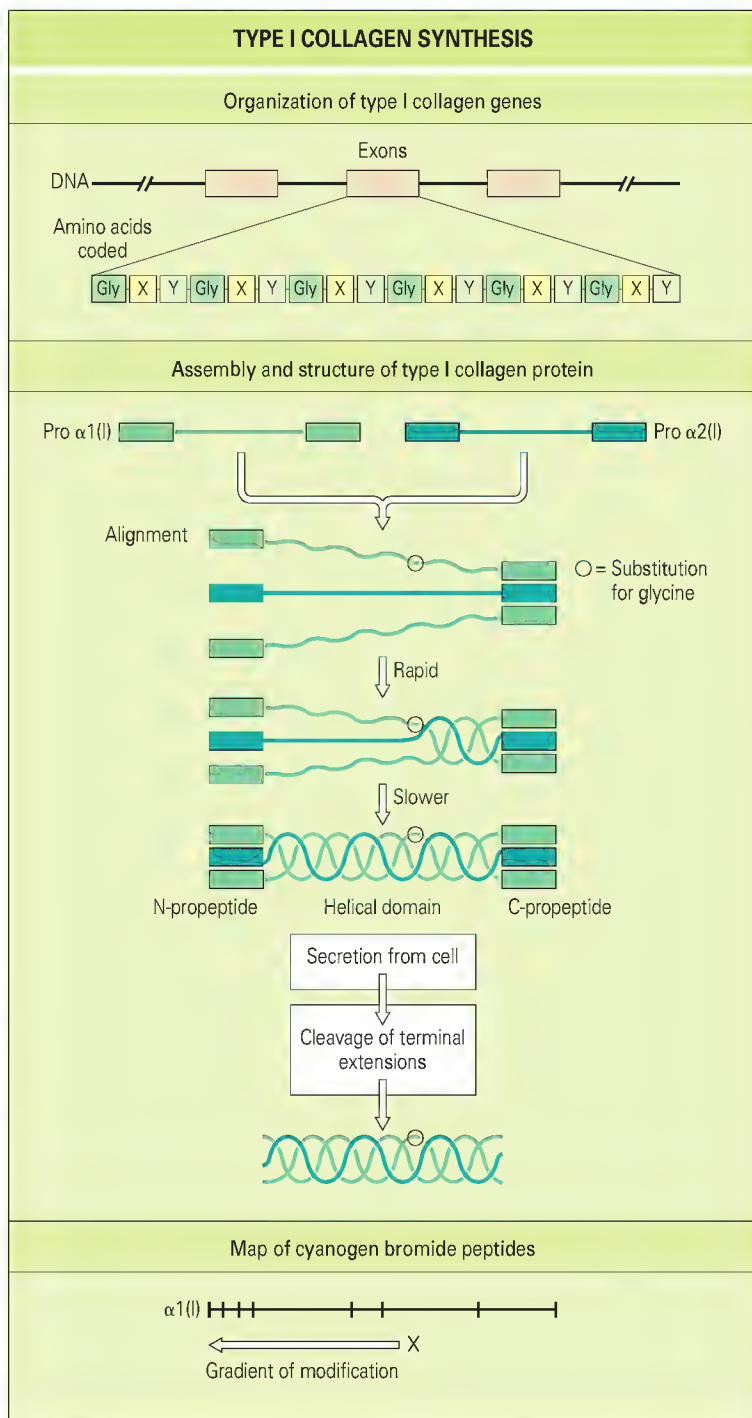


Fig. 209.2 Organization of type I collagen genes and protein. Assembly of a heterotrimer containing a mutant chain, its effect on glycosylation, and cyanogen bromide mapping are shown.

to these modifying enzymes. Substitution of a charged or a polar amino acid for a glycine residue in one chain will result in a temporal delay in helix propagation. The portions of all three chains in the helix that are N-terminal to the substitution will then be exposed to the modifying enzymes for a longer period, and a greater proportion of potential sites will be glycosylated. Thus overmodification is a helical process and does not identify the mutant chain.

Some cases of recessive OI are caused by defects in a second collagen modification system.⁵ The prolyl 3-hydroxylation complex in the endoplasmic reticulum 3-hydroxylates a single residue (Pro986) on each $\alpha 1(I)$ chain. Deficiency of any of the components of this complex, CRTAP, P3H1, or CyPB, causes the severe or lethal recessive forms of OI.

Types X and XI OI are caused by defects in two collagen-related chaperones/PPIases, HSP47 and FKBP10.³ HSP47 is crucial for folding of the three α chains into a collagen monomer. FKBP10 deficiency does not have a significant effect on helix folding but instead affects hydroxylation of the collagen telopeptide lysine.

The terminal extensions of the procollagen helix are cleaved by specific peptidases in the extracellular space. The mature collagen molecules subsequently assemble into fibrils driven by hydrophobic and hydrostatic forces and are then stabilized by cross-link formation. Absent or diminished telopeptide hydroxylation in patients with FKBP10 deficiency is associated with a diminished ability to cross-link collagen into fibrils and results in sparse and disorganized matrix.³

Finally, types V and VI OI,³ for which the genes were identified only recently, appear to have their pathology at the level of matrix mineralization. PEDF, a potent antiangiogenic factor, is known to bind to collagen in matrix, and this interaction is crucial for its vascular effect. Investigation into the mechanisms of these types is just beginning.

Molecular defects and phenotypic correlations

The full range of OI phenotypes, from lethal to mild, is associated with defects in type I collagen. They can be broadly divided into quantitative and structural defects. Type I OI, the mildest form, is caused by quantitative defects⁹; that is, patients secrete about half the normal amount of type I collagen but their collagen is structurally normal. Usually, this is caused by nonsense or frameshift mutations in one allele of *COL1A1* that lead to premature chain termination.

Types II, III, and IV OI are caused by structural defects in either the $\alpha 1(I)$ or $\alpha 2(I)$ chains of type I collagen.⁸ Most (80% to 85%) of these structural defects consist of substitutions of another amino acid for one of the invariant glycine residues that occur in every third position along the chain. Fifteen percent to 20% of defects involve splice junctions. The genotype-phenotype relationships of mutations in the two α chains are complex. Mutations in the $\alpha 1(I)$ and $\alpha 2(I)$ chains are lethal in a third and a fifth of cases, respectively. No correlation has been found between the severity of bone dysplasia and the extent of collagen helix overmodification. Modeling of lethal and nonlethal mutations in the two chains reveals different correlations, thus supporting a distinct role for each chain in the extracellular matrix. Although most collagen mutations occur *de novo*, 5% to 7% of dominant cases are caused by parental germline mosaicism.³ This factor should be considered in genetic counseling and molecular testing.

Some patients previously classified as having type IV OI have been shown to have distinctive bone histology and were subsequently classified as having types V and VI OI. Type V OI is an autosomal dominant form characterized by hypertrophic callus formation, calcification of the interosseous membrane of the forearm, and a radiodense metaphyseal band.³ A mutation in *IFITM5/BRIL* in which five residues are added to the amino end of BRIL has been identified in type V OI, and this unique mutation appears to cause all cases of type V OI.¹⁰

Finally, recessive OI is genetically heterogeneous, with mutations in six different genes and more to come. In one group of recessive patients, OI is caused by deficiency of one of the posttranslational modification systems of collagen (see earlier). These patients have null mutations in *CRTAP*, *P3H1*, or *PPIB* and clinically have an extremely severe or lethal form of OI.⁵ Patients in whom recessive OI is suspected can be screened for gene expression by real-time polymerase chain reaction or sequencing. Risk for the recessive form is increased in African Americans who may have inherited a west African founder mutation. Type VI OI is caused by null mutations in *SERPINF1*, which causes nearly total absence of PEDF.³ Interestingly, absence of this antiangiogenic factor results in a mineralization defect with wide osteoid seams on bone histology and a prolonged mineralization lag time. Recessive types X and IX OI result from a deficiency of collagen chaperone/PPIases.³ For type X, only one proband has been described with deficiency of HSP47, not surprising given the importance of HSP47 in embryonic development. Type XI OI has an interesting phenotypic heterogeneity—the same mutations in *FKBP10* can also cause Bruck syndrome (OI with congenital contractures), even in siblings,³ thus showing that contractures are a variable manifestation of the mutation. An additional *FKBP10* mutation in which a single tyrosine residue is deleted causes a congenital contracture syndrome, Kuskokwim disease, which is associated with mild incidental skeletal findings in some patients.

Management Rehabilitation

The goal of physical rehabilitation in OI is to attain age-appropriate physical skills as a child and to retain them as adults. The specific goals range widely with age and severity and include independent or assisted ambulation, transfer ability, and wheelchair-assisted mobility.

Active physical therapy with a therapist experienced in OI should begin in infancy.¹¹ To prevent deformities and assist respiratory effort, severely

affected infants may require a custom-molded seating insert for proper positioning. Hydrotherapy¹¹ should begin in the bath in infancy and continue through life as swimming and water exercises. This improves general conditioning, as well as muscular strength for head and trunk control and independent extremity movements.

Children who are not expected to walk should be provided with a powered wheelchair for independent mobility in the preschool years. Children with ambulation potential should receive regular physical therapy to strengthen their abdominal, pelvic girdle, and lower extremity musculature and prevent contractures.¹¹ Some children may require surgical correction of lower limb deformities before weight bearing is attempted. When ready to pull to a standing position, they progress through ambulation aids such as walkers and crutches to independent ambulation.

Orthopedic management

An orthopedic surgeon experienced in treating OI is essential for a successful physical outcome. Even in severely affected individuals, fractures should not be allowed to heal without proper alignment and reduction. Fracture healing is generally normal in patients with OI; the period of immobilization should be minimized to avoid worsening osteoporosis secondary to disuse.

Intramedullary placement of rods in the long bones via the multiple osteotomy procedure of Sofield and Millar³ is used to interrupt refracture sequences, correct deformity, and support the bone for weight bearing. Extensible telescoping rods such as the Bailey-Dubow and, more recently, the Fassier-Duval models are used most often. They have the advantage of extending with bone growth. Unfortunately, however, they have a high rate of migration into a joint space. Furthermore, because the rod is much stiffer than normal bone, it bears a disproportionate share of the gravity load, which causes significant cortical atrophy. To circumvent the problems of rod migration and bone atrophy, a straight Sofield rod or a Rush rod with a crook may be used to stabilize a healing osteotomy in the lower limb. Generally, rods require replacement several times during childhood. The use of plates and screws to stabilize an osteotomy has resulted in increased osteoporosis of bone and poorly healed screw holes and cannot be recommended.

The scoliosis associated with moderate and severe OI is not responsive to Milwaukee bracing. When the scoliosis exceeds 40 degrees, spinal fusion with Harrington instrumentation generally provides good stabilization.

Management of generalized connective tissue symptoms

Bisphosphonate drugs have come into widespread use for OI based on observational trials. The consensus of three recent controlled trials involving children with OI¹² is that bisphosphonates are more beneficial for vertebrae than for long bones. Treatment for 1 to 2 years increases L1-L4 DEXA scores and, more importantly, improves vertebral compressions and area, which may prevent or delay the scoliosis of OI. The relative risk for long-bone fractures is somewhat decreased, in agreement with the increased load until fracture occurs in animal studies. However, such treatment weakens the material properties of long bones and increases the risk for osteotomy

nonunion. The consensus of the controlled trials is that bisphosphonate treatment does not affect muscle strength, ambulation status, or bone pain. Maximum benefit may be obtained with 2 to 3 years of treatment in mid-childhood; the benefits appear to persist for several years after treatment stops.

Growth deficiency is the most consistent secondary feature of OI. In a treatment trial of recombinant growth hormone for types III and IV OI in children,³ half the children (mostly with type IV OI) responded with more than a 50% increase in their linear growth rate, increased vertebral bone mineral density, and positive changes in bone histology.

Severely affected infants may have multiple bouts of pneumonia in the first years of life and should be treated promptly with antibiotics. To forestall the development of pulmonary hypertension and cor pulmonale, older patients with OI should be given oxygen when signs of desaturation appear.

The high-frequency hearing loss characteristic of OI can usually be overcome with amplification. If the conductive hearing loss is severe, stapedectomy can be performed but requires an OI-experienced surgical team to avoid fracturing the stapes or creating a "floating footplate."

EHLERS-DANLOS SYNDROME

History

Ehlers and Danlos each made a contribution to the associations of this syndrome shortly after 1900. Defects in types III, V, and I collagen, as well as in tenascin-X, lysyl hydroxylase, and the zinc transporter gene *SLC39A13*, have been identified in patients with EDS.^{13,14} The Villefranche nosology groups EDS into six types and eliminates rare forms.¹⁵

Epidemiology

The genetic inheritance and incidence of EDS vary widely with type.¹⁵ Fortunately, severe type IV EDS is rare and occurs in less than 1 in 100,000 births; the diagnosis is often made in childhood. Milder dominant forms of EDS are much more common, with an estimated prevalence of 1 in 20,000 for EDS type I.

Clinical features

The different types of EDS and their main clinical features¹⁵ are listed in Table 209.2.

Types I and II are the classic forms. Type I EDS is the gravis variant. Patients have velvety and hyperextensible skin, marked joint extensibility, "cigarette paper" scars, and easy bruisability (Fig. 209.3). Many are born prematurely or have mitral valve prolapse.

Type II EDS is a less severe manifestation of the type I clinical associations, except that premature degenerative arthritis may develop. In type III

Fig. 209.3 Features of Ehlers-Danlos syndrome. (a) Hyperextensibility of small joints. (b) Cigarette paper scarring. (Courtesy Dr. D. K. Grange.)



■ TABLE 209.2

Villefranche classification of Ehlers-Danlos syndrome

Former type	New classification	Genetics	Etiology	Clinical features
EDS I (gravis) EDS II (mitis)	Classic type	AD	90% of cases caused by mutations in <i>COL5A1</i> or <i>COL5A2</i>	Soft skin with scars Hypermobile joints Easy bruising Mitis less severe than gravis
EDS III	Hypermobility type	AD	Unknown	Soft skin without scars Marked mobility of large and small joints
EDS IV (arterial-ecchymotic)	Vascular type	AD	Defects in type III collagen	Translucent skin Marked bruising Ruptured arteries, uterus, bowel Normal joint mobility
EDS VI (ocular-scoliotic)	Kyphoscoliosis type	AR	Defects in lysyl hydroxylase	Skin soft and extensible Scoliosis Ocular fragility Hypermobile joints
EDS VIIA, VIIB (arthrochalasia multiplex congenita)	Arthrochalasia type	AD	$\alpha 1(I)$ $\Delta E6$ $\alpha 2(I)$ $\Delta E6$	Congenital hip dislocation Skin soft without scars Hypermobile joints
EDS VIIC (human dermatosparaxis)	Dermatosparaxis type	AR	Deficient procollagen N-proteinase	Congenital hip dislocation Skin soft without scars Hypermobile joints

AD, autosomal dominant; AR, autosomal recessive.
Data from Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. *Am J Med Genet* 1998;77:31-7.

EDS, joints dislocate repeatedly and are associated with degenerative joint disease. Scars form normally.

Type IV EDS, the severest form, includes complications that reduce adult life expectancy (median survival, 48 years), such as rupture of arterial walls, colon, or pregnant uterus. Patients have a characteristic facies with large eyes and thin nose and lips, as well as marked bruisability, an aged skin appearance of the hands and feet, and small-joint hypermobility.

The arthrochalasia type of EDS is manifested predominantly as joint symptoms, beginning with congenital hip dislocations, usually bilateral, and continuing with striking joint laxity and multiple dislocations. Patients may have moderate short stature and dysmorphic cigarette paper scars.

Diagnostic studies

Biochemical and molecular studies of types V, III, and I collagen from fibroblasts are important to establish the genetics of EDS and to identify patients with type IV EDS for anticipatory management. Fibroblast lysyl hydroxylase deficiency and reduction of collagen cross-links in urine can be demonstrated in EDS type VI.¹⁶

Differential diagnosis

The features of EDS overlap with those of other connective tissue disorders, especially marfanoid hypermobility syndrome, cutis laxa, and mild OI. Neuromuscular disorders and Menkes syndrome are included in the differential diagnosis of some childhood EDS features.

Etiology and pathogenesis

Type III collagen

Type III collagen is a homotrimer encoded by a gene on chromosome 2q31. The $\alpha 1(III)$ chains have the Gly-X-Y repeats typical of fibrillar collagen. Type III collagen is located in skin, blood vessel walls, and pleuropertitoneal lining; bone has a minimal amount of type III collagen.

Molecular defects in types I, III, and V collagen

The most consistent molecular correlations in EDS have been type IV EDS with defects in type III collagen and type VII EDS with defects in type I collagen. Type IV EDS results from defects in the structure or synthesis of type III collagen. Some defects involve glycine substitutions or splice site defects. All cases are dominant heterozygous lesions, consistent with the fact that a mutation in one allele will result in 93% of homotrimers containing at least one mutant chain.

The arthrochalasia type of EDS involves defects in processing of the N-propeptide of type I collagen.¹⁷ The defective pN-collagen forms abnormal fibrils. Most cases are dominant structural defects involving skipping of exon 6 of type I collagen, which contains the N-proteinase cleavage site. More recently, the human equivalent of dermatosparaxis has been documented. This recessive form of EDS type VII is characterized by deficiency of the N-terminal proteinase.

Classic EDS (formerly types I and II EDS) involves defects in type V collagen, a quantitatively minor fibrillar collagen in skin, in more than 90% of patients.¹⁸ About half are null mutations in *COL5A1* that cause haploinsufficiency. The remainder are structural defects in *COL5A1* or *COL5A2* that result in reduced availability of type V collagen.

There is additional genetic heterogeneity in EDS. Defects in tenascin-X interfere in the deposition of collagen and elastin fibrils in dermis and cause a recessive form of classic EDS. Some cases of classic EDS are caused by defects in type I collagen, specifically, homozygous defects resulting in total absence of the $\alpha 2(I)$ collagen chain and heterozygous defects resulting in Arg-to-Cys substitutions in the helical region of $\alpha 1(I)$. Persons with classic OI caused by defects in type I collagen may also have a range of vascular problems.

Management

Sports that hyperextend or otherwise stress joints should be discouraged in childhood. Joint surgery may be performed for pain, instability, or poor range of motion. Success in terms of joint stability and relief of pain is limited in about half of cases.¹⁹ Joint effusions and hemarthrosis may occur as a result of cumulative minor trauma and require intervention to maintain ambulation.

The skin fragility in patients with EDS necessitates particular attention to closure after even minor surgical procedures. Sutures should be closely spaced and left in place for a longer period than normal.

Patients with a diagnosis of type IV EDS should communicate all vascular and visceral symptoms to their physician. The natural history of type IV EDS necessitates prompt evaluation of even vague complaints in pertinent systems, with echocardiography, computed tomography, or laparoscopy being performed as indicated.^{20,21} If pregnancy is attempted, elective cesarean section through the lower uterine segment is essential because the uterus will be stressed less than with spontaneous vaginal delivery and delivery-related tears can be prevented. The classic and hyperextensibility types of EDS are associated with premature rupture of membranes and preterm labor; obstetric management for determination of the delivery route and treatment of potential bleeding complications is considered on a case-by-case basis.¹³

MARFAN SYNDROME

History

This syndrome, initially reported by Marfan in 1896, was the first heritable disorder of connective tissue to be described. Marfan syndrome type 1 is caused by heterozygous mutations in *FBNI*, which encodes the matrix protein fibrillin-1. A mouse model that has been useful for translational studies was generated by Ramirez.²² Cumulative survival probability has increased from 48 years in 1972 to 72 years in 1995 because of surgical advances in prophylactic repair of the dilated aortic root, and survival has improved further by treatment with losartan.

Epidemiology

Marfan syndrome has an autosomal dominant inheritance and approximate prevalence of 1 in 5000 to 10,000.¹⁸ It is not associated with any racial or gender bias in prevalence.

Clinical features

Skeletal features

Musculoskeletal features,²² such as stature greater than the 95th percentile and limbs disproportionately long for trunk size (arachnodactyly), may first bring the patient to medical attention. Other skeletal aspects of Marfan syndrome include scoliosis, pectus excavatum (Fig. 209.4) or carinatum, and high-arched narrow palate, and laxity of joints, including flat feet.

Ocular features

Nonprogressive subluxation of the lens is present in about 60% of patients. It is most commonly bilateral, with the lens being displaced upward. Myopia is frequent and may be severe because of increased axial length of the globe.

Cardiovascular features

Mitral valve prolapse and dilation of the ascending aorta are the most common cardiovascular findings. Mitral or aortic regurgitation may develop. Histologically, the aorta demonstrates cystic medial necrosis. Dilation of the aortic root occurs in 60% to 80% of adults with Marfan syndrome, and ascending aortic aneurysms are the most common cause of morbidity and mortality.

Infantile Marfan syndrome

Marfan syndrome also has a severe perinatal subset. Progressive cardiovascular abnormalities and pulmonary disease cause increased morbidity and mortality in the childhood years.



Fig. 209.4 Marfan syndrome: pectus excavatum. (Courtesy Dr. K. Rosenbaum.)

Ghent nosology

The diagnostic criteria for Marfan syndrome were revised to include the diagnosis of Marfan syndrome in relatives of affected patients and the contribution of molecular diagnosis.²³ The Ghent nosology (Box 209.1) uses skeletal features as major criteria if at least four of eight typical skeletal features are present. A diagnosis of Marfan syndrome in the index case requires meeting the major criteria in at least two organ systems (skeletal, ocular, cardiovascular, skin, family history) and having involvement of a third system. Relatives of a confirmed case require major criteria in one system and involvement of a second system.

Prognosis

In the past, cardiovascular complications reduced the mean life span of patients with Marfan syndrome. With aggressive and anticipatory drug and surgical management of aortic root dilation, the majority of patients have a life span in the 50- to 70-year range.²⁴

Diagnostic studies

Studies essential for establishing a diagnosis of Marfan syndrome include a slit-lamp examination with fully dilated pupils and echocardiography focused on the mitral valve and aortic root. A radiographic skeletal survey should include the limbs, spine, skull, and chest. Detection of a fibrillin mutation contributes to the diagnosis, especially in children, but the diagnosis is primarily made clinically.

Differential diagnosis

Loeys-Dietz syndrome (LDS),²⁵ characterized by the triad of hypertelorism, cleft palate or bifid uvula, and aortic aneurysms or arterial tortuosity, is caused by mutations in *TGFBR1* and *TGFBR2*. LDS lacks ocular involvement. Homocystinuria has similar ocular and skeletal manifestations as Marfan syndrome but a positive urine cyanide nitroprusside test and downward lens dislocation. Congenital contractural arachnodactyly,²⁶ caused by mutations in *FBNI*, shares the Marfan skeletal traits. In “marfanoid” hypermobility syndrome, the lens and aorta are normal, and the skin and joints are more extensible than in Marfan syndrome. In vascular EDS, skeletal proportions are normal.

BOX 209.1 GHENT NOSOLOGY OF MARFAN SYNDROME

For an index case: diagnosis requires major criteria in at least two different organ systems and involvement of a third organ system.

For a relative of an index case: diagnosis requires a major criterion in one organ system and involvement of a second organ system.

Major criteria, skeletal system (4 or more):

- Pectus carinatum
- Pectus excavatum
- Span-to-height ratio >1.05
- Wrist and thumb signs
- Scoliosis >20 degrees
- Elbow extension <170 degrees
- Pes planus
- Protrusio acetabuli

Dura

- Lumbosacral dural ectasia evident on computed tomography or magnetic resonance imaging

Ocular system

- Ectopia lentis

Cardiovascular system

- Dilation of the ascending aorta involving at least the sinuses of Valsalva
- Dissection of the ascending aorta

Family/genetic history

- First-degree relative with Marfan syndrome
- Presence of an *FBNI* mutation

Etiology and pathogenesis

Classic Marfan syndrome is caused by mutations in fibrillin-1, a glycoprotein abundant in the aortic tunica media, ciliary zonules, periosteum, and skin. Mutation screening for the *FBN1* gene is available.²⁷ A genotype-phenotype comparison has been done in more than 1000 patients. *FBN1* mutations producing premature termination cause a more severe skeletal and skin phenotype than do in-frame mutations. Mutations causing severe neonatal Marfan syndrome or high cardiac risk usually occur in the epidermal growth factor–like sequences in exons 24 to 32, whereas mutations in the last seven exons are associated with milder phenotypes. Patients with a missense mutation producing cysteine have a higher probability of ectopia lentis. The pathophysiology of the disorder involves dysregulation of transforming growth factor- β signaling.

Management

Patients with Marfan syndrome are best managed at a tertiary center. Cardiovascular care includes annual echocardiography and electrocardiography until the aortic root exceeds 40 mm and more frequently thereafter. Prophylactic aortic surgery is usually performed when the aortic root diameter is about 50 mm. The Bentall procedure, which uses a composite graft to replace the aortic valve, root, and proximal ascending aorta, is associated with a survival rate higher than 90% but a lifelong need for anticoagulation.²⁴ In the early 1990s a valve-sparing approach was developed and achieved excellent results. Treatment with β -adrenergic blockers is standard preventive treatment, but their effect on aortic dilation or dissection is controversial.²⁸ The angiotensin II receptor blocker losartan restored the cardiovascular phenotype in the Marfan mouse model, and early results in children are encouraging.²⁹ A long-term losartan trial is ongoing through the National Heart, Lung and Blood Institute, as is a controlled combination trial of losartan and β -blockers (the Ghent Marfan Trial).³⁰ Risk for a catastrophic cardiovascular event during and after pregnancy is high, even for women with moderate aortic dilation. Management also includes annual ophthalmology and semiannual orthopedic evaluation. Because the deformity may recur, correction of pectus is best postponed until growth stops.

CHONDRODYSTROPHIES

The chondrodystrophies are classified according to the Paris nomenclature of 1976, which used clinical and radiographic criteria, such as different parts of the long bones involved (epiphyses, metaphyses, or diaphyses) and the presence of spinal involvement (Box 209.2).³¹ The genetic defects responsible for these conditions are wide ranging and include signaling defects and involvement of matrix structural proteins.³²

BOX 209.2 PARIS NOMENCLATURE OF CHONDRODYSTROPHIES

Osteochondrodysplasias

- I. Defects in the growth of tubular bones, the spine, or both
- II. Disorganized development of cartilage
- III. Abnormalities in the density of the cortical diaphyseal structure, metaphyseal modeling, or both

Dysostoses

- I. With cranial and facial involvement
- II. With predominantly axial involvement
- III. With predominant involvement of the extremities

Idiopathic osteolysis

Primary metabolic abnormalities

- I. Calcium, phosphorus, or both
- II. Complex carbohydrates
- III. Lipids
- IV. Nucleic acids
- V. Amino acids
- VI. Metals

From Rimoin DL, Lachman RS. The chondrodysplasias. In: Emery AE, Rimoin DL, editors. Principles and practice of medical genetics. Edinburgh: Churchill Livingstone; 1983, p. 703-735.

Stickler syndrome is characterized by ocular, facial, and joint involvement and commonly results from mutations that cause premature termination codons and haploinsufficiency in the gene that encodes type II collagen. About 25% of patients with Stickler syndrome have mutations in the genes encoding type XI collagen. Manifestations of the syndrome include myopia, retinal detachment, midface hypoplasia, midline clefting, and hearing loss, but their expression is highly variable. Progressive osteoarthritis of large joints may develop in the third or fourth decade.

History

Several studies have revealed the familial nature³² and the underlying molecular defects in this group of disorders. These advances have led to an attempt to classify the disorders (see Box 209.2).

Epidemiology

Achondroplasia, the most common chondrodystrophy, occurs in about 1 per 40,000 live births. McKusick-type metaphyseal dysplasia is relatively common in the Old Order Amish.

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Hypermobility syndrome

■ RODNEY GRAHAME ■ ALAN J. HAKIM

- Joint hypermobility syndrome is now considered by most authorities to be a heritable disorder of connective tissue that is indistinguishable from, if not identical to, the hypermobility type of Ehlers-Danlos syndrome.
- Far from representing a mild (some say trivial) rheumatologic disorder occurring in healthy individuals, it is now seen as a multisystemic disorder of connective tissue that is responsible for chronic widespread pain (often mislabeled fibromyalgia), gastrointestinal dysmotility, anxiety and phobic states, and dysautonomias, thus adding additional tiers of symptoms to the already wide panoply of the musculoskeletal sequelae of joint pain and instability and a predisposition to soft tissue trauma.
- Effective treatment is now available and consists of physical rehabilitation adapted to the needs of patients with lax and fragile tissues combined with effective pain management such as cognitive-behavioral therapy. Analgesics are often ineffective.
- Failure to institute effective treatment leads to progressive loss of function, self-efficacy, and quality of life. Untreated patients become physically disabled—some immobile, dependent, depressed, and desperate. Joint hypermobility syndrome is frequently overlooked and misdiagnosed and is the cause of much needless suffering.

INTRODUCTION

Hypermobility denotes an increased range of joint movement. Joint mobility is pronounced at birth but declines thereafter. It is greater in females and people of Asian or African descent. Hypermobility syndrome, also now known as (benign) joint hypermobility syndrome (JHS), is a common disorder. Originally defined as “the occurrence of symptoms in otherwise healthy hypermobile individuals,”¹ it is now seen as a complex genetic disorder with manifestations that permeate well beyond the confines of the musculoskeletal system. Most authorities regard it as being the same as the hypermobility type of Ehlers-Danlos syndrome (EDS-HT), formerly EDS type III (see Chapter 210).²

MOLECULAR BASIS, HERITABILITY, PATHOGENESIS, AND EPIDEMIOLOGY

Hypermobility is strongly “heritable”; one twin study showed 70% of its variance to be accounted for by genetic factors.³ Racial differences in prevalence also implicate genetic influences. Asian and Afro-Caribbean populations have a higher prevalence of hypermobility than whites do. The heritability of JHS has not been determined; however, anecdotal observations suggest dominant inheritance with variable penetrance. Both hypermobility and JHS are three times more common in females than in males. Hormonal influences may play a role, although the mechanisms have not been identified. Anecdotally, individuals with JHS observe that their symptoms are often worse immediately before menstruation, a point when serum estrogen levels peak in the cycle.

Collagen is abundant in virtually all connective tissue. Ultrastructural abnormalities in collagen fibrils and mutations in collagen-modifying enzymes have been found in all subtypes of EDS with the exception of EDS-HT. Like EDS-HT, mutations involved in the pathology of JHS remain obscure. Linkage analysis in two large families with JHS failed to show any

association with *COL1*, *COL3*, *COL5*, or *COL6* as causative genes.⁴ Other candidate genes for proteins involved in collagen fibrillogenesis, in particular, the family of small leucine-rich proteoglycans (SLRPs), have also not shown associations. Of note, deficiency in tenascin-X, an extracellular matrix glycoprotein, results in a phenotype similar to that of classic EDS. Haplo-insufficiency of the gene for tenascin-X has been found to account for some of the disorder's presence in families with EDS-HT and may in part explain the nature of the molecular disturbance in JHS.⁵

The epidemiology of JHS is in its infancy. However, surveys conducted in the United Kingdom and Chile suggest that the JHS phenotype may be identifiable in more than 40% of patients attending routine community hospital rheumatology clinics.⁶

RECOGNITION, DIFFERENTIAL DIAGNOSIS, DIAGNOSTIC CRITERIA

Various scoring systems for hypermobility have been devised. The most widely used is the 9-point Beighton scale (Table 210.1).⁷ Introduced in 1973, it has stood the test of time. However, it is an “all or none” criterion that gives no indication of severity. Because only five body sites are sampled, hypermobility may be missed, especially the pauciarticular variety. Hypermobility may be uncovered by a person's response to a validated 5-point questionnaire. Two affirmative answers would suggest an 85% chance of being hypermobile (Box 210.1).⁸ Hypermobility syndrome is diagnosed with the 1998 “Brighton criteria,”⁹ in which relevant symptoms, a low Beighton score, and other phenotypic features are included (Box 210.2).

Patients with JHS also often display increased skin stretchiness, a marfanoid habitus (complete or incomplete), and other manifestations that overlap with other heritable disorders of connective tissue. Rheumatologists need to be aware of the distinctive features of true Marfan syndrome and the other major forms of EDS, notably the classic form (EDS type I/II) and the life-threatening vascular form (EDS type IV), and be ever vigilant of their possible appearance. In this regard, the Ghent¹⁰ and Villefranche¹¹ criteria for Marfan syndrome and EDS, respectively, are essential reading.

CLINICAL FEATURES

Musculoskeletal

Once perceived as a trivial ailment causing minor joint and spinal pain after exercise with the occasional occurrence of joint dislocation predisposing in some cases to premature osteoarthritis, it is now regarded as a *forme fruste* of heritable disorders of connective tissue with features overlapping other types of such disorders. In practice, JHS may be manifested as (1) almost any soft tissue injury or overuse lesion affecting a ligament, tendon, muscle, enthesis, or joint; (2) recurrent joint instability, subluxation, or dislocation; (3) chronic noninflammatory joint or spinal pain without apparent structural abnormality; and (4) secondary osteoarthritic or spondylotic changes in peripheral or spinal joints, respectively. What sets patients with JHS apart from others is the range and frequency of the manifold varieties of acute and chronic painful episodes occurring over the course of their lives, with the intensity of pain seemingly increasing inexorably over time from childhood to adolescence and through adult life. Avoidance of (painful) movement as a strategy to avoid pain (described as kinesiphobia) inevitably leads to muscle deconditioning, the development of adverse postures, and loss of function, which serve only to aggravate a fraught situation and diminish the ability to lead a normal active life with a reasonable quality of life.

TABLE 210.1
Nine-point Beighton hypermobility score

Ability to	Right	Left
1. Passively dorsiflex the fifth metacarpophalangeal joint to $\geq 90^\circ$	1	1
2. Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1
3. Hyperextend the elbow to $\geq 10^\circ$	1	1
4. Hyperextend the knee to $\geq 10^\circ$	1	1
5. Place the hands flat on the floor without bending the knees	1	
Total	9	

One point may be gained for each side for maneuvers 1 to 4 such that the hypermobility score will have a maximum of 9 points if all are positive.
 From Beighton PH, Solomon L, Sankolne CL. Articular mobility in an African population. *Ann Rheum Dis* 1973;32:413-7.

BOX 210.1 FIVE-PART QUESTIONNAIRE FOR IDENTIFYING HYPERMOBILITY

- Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- Can you now (or could you ever) bend your thumb to touch your forearm?
- As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
- Do you consider yourself double-jointed?

Affirmative answers to two or more questions suggest hypermobility with a sensitivity of 80% to 85% and a specificity of 80% to 90%.
 From Hakim AJ, Grahame R. A simple questionnaire to detect hypermobility: an adjunct to the assessment of patients with diffuse musculoskeletal pain. *Int J Clin Pract* 2003;57:163-6.

BOX 210.2 1998 BRIGHTON REVISED DIAGNOSTIC CRITERIA FOR BENIGN JOINT HYPERMOBILITY SYNDROME

Major criteria

1. A Beighton score of 4 of 9 or greater (either currently or historically)
2. Arthralgia for longer than 3 months in four or more joints

Minor criteria

1. A Beighton score of 1, 2, or 3 of 9 (0, 1, 2, or 3 if older than 50 years)
2. Arthralgia in one to three joints or back pain, spondylosis, or spondylolysis/spondylolisthesis
2. Dislocation in more than one joint or in one joint on more than one occasion
3. Three or more soft tissue lesions (e.g., epicondylitis, tenosynovitis, bursitis)
4. Marfanoid habitus (tall, slim, span greater than height; upper segment–lower segment ratio <0.89 , arachnodactyly)
5. Skin striae, hyperextensibility, thin skin, or abnormal scarring
6. Eye signs: drooping eyelids, myopia, or antimongoloid slant
7. Varicose veins, hernia, or uterine/rectal prolapse

Benign joint hypermobility syndrome (BJHS) is diagnosed in patients with two major criteria, one major and two minor criteria, or four minor criteria. Two minor criteria will suffice in those with an unequivocally affected first-degree relative. BJHS is excluded by the presence of Marfan syndrome or Ehlers-Danlos syndrome (other than the hypermobility type of Ehlers-Danlos syndrome [EDS], formerly EDS III), as defined by the Ghent 1996¹⁰ and Villefranche 1998¹¹ criteria, respectively. Major and minor criteria 1 and 2 are mutually exclusive.
 From Grahame R, Bird HA, Child A, et al. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* 2000;27:1777-9.

Extraarticular manifestations

Mechanical failure of connective tissue beyond the locomotor system will be expected to be evident clinically. The dermis of the skin, being 70% collagen by dry weight, is abnormal in JHS. Its texture is soft or silky, its thickness is palpably reduced, it may be visibly transparent, and skin stretching is increased. Scar formation is impaired, which gives rise to characteristically

paper-thin scars. Stretch marks (striae atrophicae) as a result of internal slippage of dermal collagen bundles usually appear around the time of puberty, and by contrast, striae gravidarum are often paradoxically absent (Fig. 210.1).

Visceral complications arise from weakness affecting supporting structures such as the diaphragm, abdominal wall, and pelvic floor. Thus, hiatal hernias (with the closely associated gastroesophageal reflux) and abdominal wall hernias occur. In later life, uterine or rectal prolapse, rectocele, or cystocele (with or without stress incontinence) may develop in parous women with JHS. Varicose veins are also a common occurrence in JHS. Mitral valve prolapse and spontaneous pneumothorax are rarer manifestations.

Depression and anxiety are frequent accompaniments of the chronic pain in JHS, but the connection may be more fundamental. A link between hypermobility and panic attacks and phobias secondary to a chromosomal duplication has been postulated but thus far unconfirmed.¹²

Pain, fatigue, and dysautonomia

Pain, fatigue, depression, and anxiety are common in JHS. Pain is both acute and chronic. The chronic pain of JHS is best likened to that seen in patients with widespread chronic pain syndrome or fibromyalgia. Fatigue is often a severely disabling complaint, but its cause remains elusive.

Perhaps most surprising is the recent observation that up to 60% of patients with JHS have symptoms suggestive of an autonomic disturbance, including presyncope, syncope, and palpitations as a consequence of orthostatic hypotension, orthostatic intolerance, and postural orthostatic tachycardia syndrome. Bowel disturbance akin to irritable bowel syndrome is also reported.^{13,14} Vascular disturbance may be related to the increased reactivity of α - and β -adrenoreceptors in the vasculature and vagal hyperactivity.¹³ Recent studies have shown a significant association between JHS and the occurrence of gastrointestinal symptoms such as bloating, reflux, constipation, and diarrhea. Functional studies on individual patients reveal pan-intestinal dysmotility, which may result from laxity of intestinal connective tissue.¹⁵

The combination of all these symptoms is encountered commonly in the clinic. It is likely that their interactions are linked in a complex manner, each potentially “fueling” the other, as is depicted in Figure 210.2. Here, injury can lead to pain and maladaptive function, both physical and psychological. Likewise, primary psychological triggers may lead to anxiety and fatigue. Both these phenomena interact with each other and may also account for the secondary autonomic symptoms. In patients with a primary autonomic disturbance, the scene is set for a cycle of insults, each driving other components in the pyramid.¹⁶

MULTIDISCIPLINARY MANAGEMENT

Drug treatment

Simple analgesics and antiinflammatory drugs have an important place in the management of acute and acute-on-chronic pain from soft tissue injuries and degenerative disease, as with any other condition. The majority of patients, however, report that these agents are of little benefit in the control of chronic pain.

Local injection of corticosteroid may also be of value in treating isolated soft tissue lesions. Theoretically, despite the lack of an evidence base to favor or refute it, the risk for tendon rupture may be greater in patients with JHS than in the general population. Corticosteroid inhibits fibroblast formation, and this may add to the risk for delayed or poor healing of soft tissue already inherent in JHS.¹⁷ The clinician should also be aware of the poor efficacy of local anesthetics. Up to 60% of patients with JHS report failure or the need for additional local anesthetic. The mechanisms behind this are unclear.¹⁸

Patients with JHS are similar to those with fibromyalgia and widespread chronic pain with respect to the phenomenon of chronic pain amplification in the absence of chronic tissue injury. Serotonergic and noradrenergic agents can be used in this context, although no randomized controlled trials of the use of these agents for JHS have been conducted. It is speculative how much such agents influence central pain processing, mood, and consequent behavior and how much they influence stimulation of the spinal column descending inhibitory pain pathways. Similarly, such agents may have a place in patients with JHS in controlling autonomic disturbances of the bowel.

β -Blockade may relieve the symptoms of postural orthostatic tachycardia syndrome. Nonpharmacologic interventions such as attention to salt and fluid balance are likely to be most effective in managing orthostatic hypertension and orthostatic intolerance in these patients.



Fig. 210.1 (a and b) Skin stretching in an individual with joint hypermobility syndrome (JHS). (c) Papyraceous scar after a patellar tendon operation. (d) Lumbar region of a patient with JHS showing the characteristic striae atrophicae together with a papyraceous scar from spinal surgery.

THE POTENTIAL ASSOCIATION BETWEEN HYPERMOBILITY, ANXIETY, FATIGUE, CHRONIC WIDESPREAD PAIN, AND AUTONOMIC DYSFUNCTION

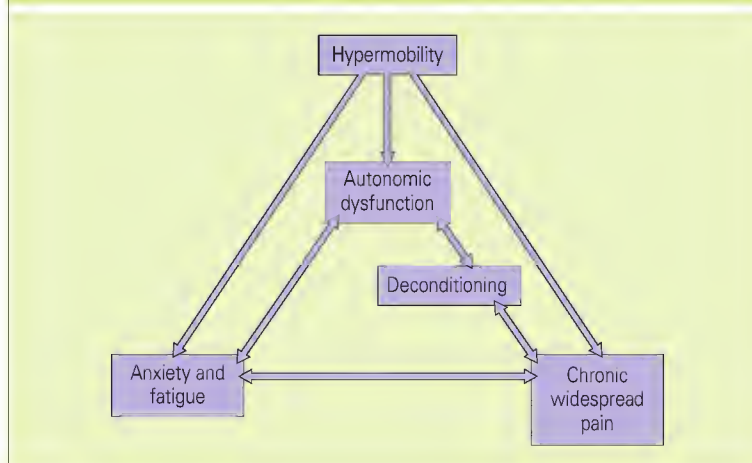


Fig. 210.2 Primary autonomic disturbance may add to anxiety and fatigue. Secondary autonomic disturbance may be a consequence of anxiety driven by pain and disability. (Reproduced by kind permission of the publishers of *Best Practice & Research. Clinical Rheumatology*.)

New physiotherapeutic approaches

Conventional physiotherapy has often been deemed unhelpful (or counterproductive) by patients with JHS. However, a new approach has been developed in which physiotherapeutic methods are adapted to the needs of patients with lax tissues who lack the normal tensile strength by

- Seeking to build up the muscles responsible for joint and core stability
- Restoring diminished proprioceptive acuity, with several studies showing that proprioception is impaired in hypermobile joints and can be improved by exercise and training¹⁹
- Avoiding harmful postures (e.g., resting at the end of the hypermobile range)
- Applying mobilizing techniques to restore to the natural hypermobile range those areas (e.g., the dorsal spine) that tend to stiffen up to the detriment of the non-stiffened hypermobile segments²⁰
- Working with clinical psychologists to enable patients with chronic pain to acquire pain management techniques such as pacing, relaxation, and so on
- Educating patients about JHS and encouraging self-management

Occupational therapy and podiatry

Occupational therapists provide splints to protect unstable finger joints and advice on joint protection in general. Specific devices (e.g., fat pen handles) can be an invaluable aid in writing.

Flatfoot on weight bearing (which disappears when not weight bearing) is a common finding in JHS, as is forefoot pronation and hindfoot valgus deformity. These deformities can produce discomfort and difficulty walking. A podiatrist can provide molded orthoses (insoles) capable of relieving such symptoms in patients with JHS.

Self-management

The nature and impact of JHS are not well appreciated by the medical community at large, and for this reason patients often remain undiagnosed and untreated for years and are forced to rely, to a large extent, on their own devices. It is not surprising that patient self-help groups have been formed and run by people who are also sufferers. In the United Kingdom, self-help groups play an important role in providing information and support for their

members by distributing leaflets, books, and newsletters; holding study days; and maintaining interactive websites. In the United Kingdom, active groups include the Hypermobility Syndrome Association, the Ehlers-Danlos Support Group, and the Marfan Association. Details are available through the Internet.

FUTURE TRENDS IN RESEARCH

Much remains to be understood about this common and debilitating condition. Identification of causative genes will lead to greater understanding of

the pathogenesis of the condition. Neurophysiologic mechanisms leading to impaired proprioception, autonomic disturbance, local anesthetic failure, and pain amplification also warrant further investigation.

At a therapeutic level, randomized controlled trials of pharmacologic, physical, and psychology techniques are lacking. Before such trials can be conducted, however, good objective, subjective, and patient-centered outcome measures need to be identified.

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Skeletal dysplasias

■ CLAIR A. FRANCOMANO

- Skeletal dysplasias are a heterogeneous group of inherited disorders associated with structural abnormalities of the skeletal system. They can affect the bones of the spine, as well as those of the appendicular skeleton; most patients have short stature.
- Skeletal dysplasias are classified on the basis of clinical, radiographic, and molecular features.
- Achondroplasia, the most common skeletal dysplasia, is caused by a mutation in the gene encoding fibroblast growth factor receptor 3.
- Medical management is largely symptomatic.
- Surgical management has significantly improved functional ability and quality of life in patients with skeletal dysplasias.

INTRODUCTION

The term *skeletal dysplasias* refers to a clinically and molecularly heterogeneous group of inherited disorders primarily associated with structural anomalies of the skeletal system. More than 450 developmental disorders of the skeletal system have been described.¹ If one includes the broader spectrum of disorders in which multisystem abnormalities are present, including bone, joint, and limb malformations, more than 500 distinct syndromes are known.² This chapter presents an overview of the skeletal dysplasias, including molecular abnormalities, their translation into skeletal structural abnormalities, the role of imaging in defining the syndromes and assessing clinically significant deformities, and discussion of specific syndromes that have a high incidence of rheumatologic sequelae.

The skeletal dysplasias have a high frequency of rheumatologic complications involving both the axial and appendicular skeleton. Patients with disorders characterized by angular deformities of the long bones, joint surface irregularities, joint contractures, and joint instability are at particularly high risk for rheumatologic complications. Patients with disorders characterized by structural anomalies of articular cartilage are at high risk for the development of secondary osteoarthritis.

CLASSIFICATION

Skeletal dysplasias have been recognized since antiquity, primarily because many are associated with profound short stature. Efforts at categorizing these conditions began in the mid-20th century. Classification criteria have been based on clinical, radiographic, and molecular approaches. Early clinical distinctions were made between “short-limbed” dwarfism and “short-trunk” dwarfism. Radiographic classification has centered on the anatomic location of the radiographic anomalies, for example, epiphyseal, metaphyseal, diaphyseal, or in the spine. A number of disorders are defined by these localized affected regions, such as multiple epiphyseal dysplasia, the Schmid type of metaphyseal dysplasia, and Camurati-Engelmann diaphyseal dysplasia.

Recent advances in identifying the molecular pathogenesis of the skeletal dysplasias have led to a molecular classification of these disorders.^{1,3} Increasingly, the skeletal dysplasias are defined molecularly, according to the relevant molecular pathway.

MOLECULAR ASPECTS OF LIMB MORPHOGENESIS

The characteristic histologic appearance of the developing limb from the limb bud stage to skeletal maturation has been known for more than a century. Increasing knowledge of the timing and anatomy of gene expression in long-bone, epiphyseal, and joint development has resulted in a deeper understanding of the molecular events driving the complex processes involved.

Molecular analysis of the skeletal dysplasias has taught us much about the role of specific genes in skeletal development. The most recently published international nosology and classification of constitutional disorders of bone describes 456 conditions placed into 40 groups defined by molecular, biochemical, or radiographic criteria (or any combination of these criteria).¹ Box 211.1 outlines some of the mutations detected in skeletal dysplasia syndromes. New information is accumulating rapidly.^{4,5} Many aspects of craniofacial, axial, and appendicular skeletal growth and development can now be correlated with expression of genes encoding specific molecules such as growth factors and structural proteins. The complex process of bone growth at the epiphyses has been dissected at the molecular level. Multiple different molecular abnormalities can lead to disruptive effects on the timing of development and shape of the epiphyses and thereby result in angular deformity and joint incongruity. Other mutations affect the structural integrity of the articular cartilage and lead to increased risk for early osteoarthritis.

HISTOPATHOLOGY

Histopathologic analysis of the skeletal dysplasias is challenging because of the difficulties inherent in sectioning and staining cartilage and calcified bone. As a result, pathologic analysis has not played a prominent role in classification and clinical diagnosis of the skeletal dysplasias. Nonetheless, many studies show specific chondrocyte and matrix pathology in animal models and human tissue from patients with a variety of skeletal dysplasias.

At the ultrastructural level, changes in chondrocyte endoplasmic reticulum include massive dilation with retention of electron-dense homogeneous material (as in osteogenesis imperfecta and spondyloepiphyseal dysplasia), alternating electron-dense and electron-lucent whorled lamellae (as in pseudoachondroplasia),⁶ and alternating electron-dense and electron-lucent parallel lamellae (as in multiple epiphyseal dysplasia) (Fig. 211.1).⁷ These changes are reflective of abnormal intracellular protein processing. Matrix studies have shown early abnormal aggregation of type II collagen fibrils within the cartilage matrix in diastrophic dysplasia (Fig. 211.2).⁸ An overview of these features has been presented elsewhere.⁹

IMAGING

All the most frequently used imaging modalities currently available play a major role in assessment of patients with a skeletal dysplasia.

Ultrasonography

Ultrasonography is particularly valuable for intrauterine assessment in the fetal period.¹⁰ Fetal ultrasound evaluation may identify angular deformity or

BOX 211.1 PARTIAL LISTING OF MUTATIONS IN SKELETAL DYSPLASIA SYNDROMES

1. Fibroblast growth factor receptor (FGFR) mutation group
 - a. *FGFR3*
 - Thanatophoric dysplasia, types I and II
 - Achondroplasia
 - Hypochondroplasia
 - b. *FGFR2*
 - Crouzon syndrome
 - Apert syndrome
 - Jackson-Weiss syndrome
 - Pfeiffer syndrome
 - c. *FGFR1*
 - Pfeiffer syndrome
2. Collagen mutation group
 - a. Type I collagen
 - COL1A1*
 - Osteogenesis imperfecta
 - COL1A2*
 - Osteogenesis imperfecta
 - b. Type II collagen
 - COL2A1*
 - Achondrogenesis type II
 - Hypochondrogenesis
 - Spondyloepiphyseal dysplasia congenita (SEDC)
 - Kniest dysplasia
 - Stickler syndrome type I
 - Spondyloepimetaphyseal dysplasia (SEMD)
 - Strudwick dysplasia
 - c. Type IX collagen
 - COL9A2*
 - Multiple epiphyseal dysplasia type 2
 - COL9A3*
 - Multiple epiphyseal dysplasia type 3
 - d. Type X collagen
 - COL10A1*
 - Schmid metaphyseal dysplasia
 - e. Type XI collagen
 - COL11A1*
 - Otospondylomegaepiphyseal dysplasia, dominant and recessive
 - COL11A2*
 - Stickler syndrome type II
3. Diastrophic dysplasia sulfate transporter (DTDST) mutation group
 - Achondrogenesis type 1 B
 - Atelosteogenesis type 2
 - Diastrophic dysplasia
4. Arylsulfatase gene mutation family (ARSE)
 - Chondrodysplasia punctata, X-linked recessive
5. Lysosomal enzyme gene mutation family
 - Mucopolysaccharidoses (MPS I to VI)
 - Mucopolidoses
6. Cartilage oligomeric matrix protein (COMP) mutation group
 - Multiple epiphyseal dysplasia type I (EDM 1)
 - Pseudoachondroplasia
7. Parathyroid hormone/parathyroid hormone-related peptide receptor (PTHrPR) mutation group
 - Jansen metaphyseal dysplasia
 - Blomstrand lethal chondrodysplasia
8. SOX mutation family (SOX9)
 - Camptomelic dysplasia
9. Short-stature-homeobox (SHOX)-containing mutation family
 - Leri-Weill dyschondrosteosis
 - Langer mesomelic dysplasia
10. Cartilage-derived morphogenetic protein (CDMP1) mutation family
 - Grebe dysplasia
 - Hunter-Thompson dysplasia
 - Brachydactyly type C
11. Cell-surface heparan sulfate proteoglycan mutation group (EXT1, EXT2)
 - Hereditary multiple exostoses

See [reference 1](#) for a full list of 456 recognized genetic skeletal disorders and their grouping by clinical and radiographic features and molecular pathogenesis.



Fig. 211.1 An electron micrograph of an iliac crest chondrocyte from a biopsy specimen from a 10-year-old boy with multiple epiphyseal dysplasia shows dilated rough endoplasmic reticulum (arrow) containing parallel lamellae of alternating electron-dense and electron-lucent material. Also note the pathologic presence of a circular fat inclusion. Studies identified a mutation in the $\alpha 3$ chain of type IX collagen. The material in the rough endoplasmic reticulum represents abnormally processed protein.

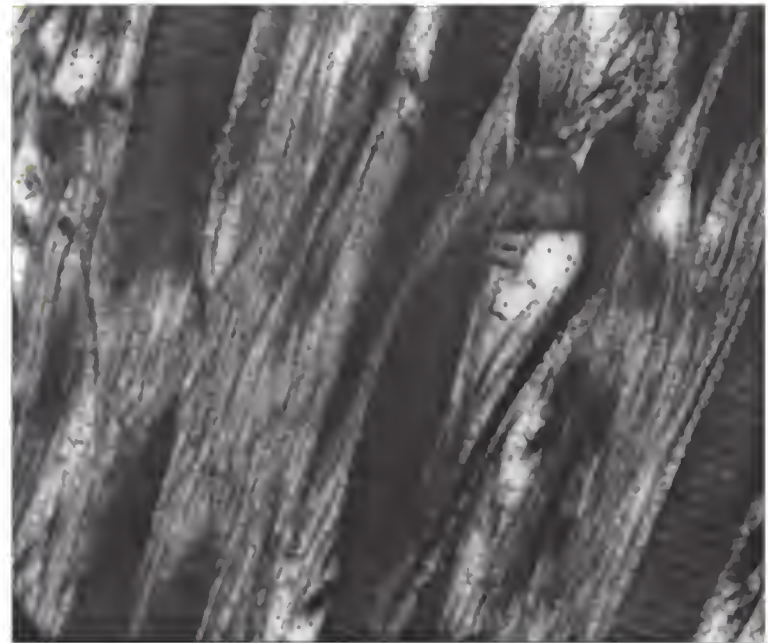


Fig. 211.2 Electron micrograph of iliac crest cartilage from a skeletally immature patient with diastrophic dysplasia. Large accumulations of abnormally thickened and aggregated type II collagen can be seen. The cross-banding was due to the thickened type II because no type I was identified on testing. Type II collagen is normally present in the cartilage matrix as thin, 10- to 15-nm-wide fibrils, but the molecular abnormalities in cartilage with diastrophic dysplasia allowed fibrils to aggregate.

the presence of missing or extra digits. Ultrasonography is especially of value in diagnosing lethal perinatal dysplasias in the second trimester because of the severity of the rib and long-bone abnormalities in this group. In the post-natal period, ultrasonography is helpful in evaluating the position and shape of the cartilaginous epiphyses before the formation of secondary ossification centers and in assessing the size of the cerebral ventricles in an infant.

Plain radiography

Plain radiography remains the most frequent and important method for evaluating a patient with a suspected skeletal dysplasia.¹¹ The skeletal survey, including radiographs of the skull, chest, spine, pelvis, and upper and lower extremities, can be diagnostic based on characteristic radiographic changes in specific bones. Such a survey will also assess the extent of deformity of the spine or appendicular skeleton and indicate the presence of osteoarthritis or inflammatory arthritis in specific joints. Radiographs of the cervical spine in flexion and extension are used to assess cervical stability, which may be compromised by odontoid hypoplasia.

Computed tomography

Computed tomography (CT) is most valuable for evaluating three-dimensional relationships in the skeleton. These relationships can be significantly altered, for example, in the hip, where acetabular dysplasia, subluxation, protrusio acetabuli, and coxa vara can occur, and in the cervical spine, where C1-C2 subluxation is common in disorders affecting odontoid development. CT may also be used as a quicker alternative to magnetic resonance imaging (MRI) when there is a question of enlarged cerebral ventricles.

Magnetic resonance imaging

MRI is of extreme importance in evaluating patients with skeletal dysplasias because of its ability to detect and differentiate soft tissue components such as muscle, fibrous connective tissue, cartilage, and blood vessels.¹² Joint structure, which is often abnormal in the dysplasias, can be assessed in terms of articular cartilage integrity, ligamentous continuity, capsular position, meniscal pathology, and even the vascularity of the epiphyseal cartilage through the use of gadolinium enhancement.

MRI may also be used to assess the impact of skeletal deformity on other organ systems, most commonly the central nervous system. In young children with achondroplasia, a small foramen magnum may impinge on the cervicomedullary junction and cause a high cervical myelopathy. Cine-MRI for evaluation of cerebrospinal fluid flow through the foramen magnum is a crucial tool in assessing the need for surgery in these children.

SPECIFIC REGIONAL SKELETAL ABNORMALITIES

Abnormalities of the spine (axial abnormalities)

Cervical spine

The possibility of spinal abnormalities should always be considered when evaluating a patient with skeletal dysplasia. Cervical abnormalities may easily lead to neurologic compromise. Anesthesiologists in particular must bear this in mind because of the extreme head and neck manipulation often needed for intubation. Abnormalities of the cervical spine were reported to occur in approximately 35 of the 150 defined dysplasia syndromes recognized in 1997.¹³ Symptoms generally develop slowly and often do not appear until adulthood even though the deformity has been present since birth. The clinical findings are typically those of a high cervical myelopathy.

Maldevelopment of the odontoid process with atlantoaxial instability¹⁴ predisposes to subluxation of the first cervical vertebra onto the second (C1-C2 subluxation) with spinal cord compression (Fig. 211.3). Treatment is generally posterior C1-C2 fusion or occiput-C2 fusion. This finding is frequently seen in Morquio disease (mucopolysaccharidosis type IV [MPS IV]) and is also very common in the type II collagenopathies (see Box 211.1).

Midcervical kyphosis is seen commonly with diastrophic dysplasia and occasionally with some of the type II collagenopathies. Some cases resolve with growth in the first few years of life, but those that do not may lead to progressive deformity. Other complications involving the cervical spine include cervical spina bifida occulta, cervical spinal cord stenosis (usually accompanied by foramen magnum stenosis in achondroplasia), and nerve root compression by exostoses in hereditary multiple exostoses.



Fig. 211.3 Lateral cervical radiograph from a patient with spondyloepiphyseal dysplasia congenita with quadriplegia showing C1 subluxation anteriorly (arrow) on C2.

Thoracolumbar spine

The thoracolumbar spine is affected in many of the skeletal dysplasias, with findings of scoliosis, kyphosis, or combined kyphoscoliosis. Flattening or irregularity of the vertebrae or intervertebral disks may be observed. Affected persons may require spinal fusion in childhood or adolescence. If untreated by surgery, the spinal deformity may increase in adulthood, unlike the idiopathic scoliosis observed in persons of average stature, which usually stabilizes once adult height is reached. Mid- to late-life osteoporosis may exacerbate this process.

Lumbar spine

Lumbar spinal stenosis may lead to nerve root compression compounded by intervertebral disk herniation in midadult life. In achondroplasia, caudal narrowing of the interpedicular distance often results in symptomatic spinal stenosis in adulthood (Fig. 211.4). Two other common skeletal dysplasias, diastrophic dysplasia and pseudoachondroplasia, are also typified by symptomatic spinal stenosis.

Abnormalities of the extremities (appendicular abnormalities)

Abnormalities of the extremities are practically universal in the skeletal dysplasias, even in conditions in which the trunk is more profoundly involved than the limbs. Shortening of the long bones is common, and most children with skeletal dysplasias come to medical attention because of short stature. In most dysplasias the shortening is symmetric, and one of four clinical patterns generally predominates.

Thus the shortening may be:

- Micromelic, in which all segments of the limb are short
- Rhizomelic, in which there is proportionally greater proximal shortening (humerus and femur)
- Mesomelic, in which shortening is concentrated in the midlimb regions (radius, ulna, tibia, fibula)
- Acromelic, in which the most marked shortening is distally in the hands and feet

Lower extremity length discrepancy with asymmetric shortening does occur, for example, in Ollier enchondromatosis and hereditary multiple exostosis. Other types of extremity deformity include angular bone deformity because of asymmetric physal involvement leading to varus, valgus, flexion, extension, or rotational malposition; limb deformity secondary to unequal growth rates of paired long bones in the forearm and leg; and joint



Fig. 211.4 Anteroposterior radiograph of the knee in a patient with pseudoachondroplasia illustrating the severe structural abnormalities that can occur in some dysplasias. Note the irregular surfaces of the distal end of the femur and proximal end of the tibia, varus angulation with lateral subluxation of the tibia and fibula, and irregular ossification of the medial tibial secondary ossification center and adjacent metaphysis (arrow). The lateral view showed a small, irregularly shaped patella, underdevelopment or overdevelopment of condylar cartilage shape, cruciate ligament and meniscal abnormalities, and capsular laxity. A tendency toward lateral patellar subluxation or full dislocation, often with underdevelopment of the lateral femoral condyle, may be observed.

contractures, instability, or articular or epiphyseal cartilage malformation, all of which can predispose to early osteoarthritis as a result of abnormal weight bearing.

Abnormalities of the hip

Many skeletal dysplasias are accompanied by hip abnormalities, which predispose to early osteoarthritis. Some pediatric orthopedic centers perform femoral and acetabular osteotomies during the growing years in an effort to forestall the degenerative changes. These surgeries often improve the structural relationship of the hip bones and gait. However, the skeletal pathology frequently affects the shape of the femoral head, including the articular surface and the structure of the cartilage matrix, so premature osteoarthritis is likely to develop. Structural defects of the hip in skeletal dysplasias with a known predisposition to osteoarthritis include congenital hip dislocation, acetabular dysplasia, coxa vara, hip contractures, and primary lack of sphericity of the femoral head. Multiple epiphyseal dysplasia, one of the most common of the skeletal dysplasias, frequently leads to hip and knee joint arthroplasty. Mutations in the type II collagen gene *COL2A1* have been found in several families with isolated osteoarthritis.¹⁵

Abnormalities of the knee

The knee is another joint commonly affected by the skeletal dysplasias, and early degenerative changes often develop (see Fig. 211.4). As in the hip, both structural abnormality leading to abnormal weight bearing and inherent cartilage abnormality in shape and molecular matrix composition predispose to arthritic changes. Genu varum or genu valgum deformity is common in many syndromes and frequently has associated rotational and flexion-extension components. These are due to epiphyseal abnormalities

in the distal end of the femur or proximal end of the tibia or both, including asymmetric growth plate involvement, underdevelopment or overdevelopment of condylar cartilage shape, cruciate ligament and meniscal abnormalities, and capsular laxity.

Ankle and foot abnormalities

Ankle and foot abnormalities are common in some dysplasias but in general are not as problematic as hip or knee involvement. Some disorders, such as hereditary multiple exostosis, have unequal growth of the distal ends of the tibia and fibula, with the shorter fibula leading to an ankle valgus that may require surgical correction. The equinovarus deformity of diastrophic dysplasia is notoriously difficult to correct surgically. In many syndromes the bones of the feet are affected by the dysplastic process and result in a foot that is shorter and wider than normal. This can make it difficult to find shoes that fit appropriately.

Upper extremity abnormalities

The upper extremities are the site of structural bone defects in many dysplasias, but the symptoms are often less frequent or severe than in the lower extremities because of the lack of weight bearing. As in the lower extremities, osteoarthritis is a common complication of conditions in which the underlying gene defect affects the structural integrity of articular cartilage. The type II collagenopathies are the most widely represented in this group. Patients may also have pain in the finger joints, elbow, and wrist because of asymmetric bone segment growth or ligamentous laxity. In hereditary multiple exostosis there can be dislocation of the radial head at the elbow and dorsal prominence and shortening of the distal part of the ulna with ulnar angulation of the hand (Madelung deformity). Wrist and hand involvement runs a wide gamut of possibilities, including shortened fingers (brachydactyly), shortened metacarpal bones, nail dysplasias, and loose or stiffened interphalangeal and metacarpophalangeal joints.

MANAGEMENT

Medical management

Despite recent advances in understanding the molecular pathogenesis of the skeletal dysplasias, management is still limited to symptomatic treatment and surgical correction of disabling deformities. It is important to know whether the disorder in question affects the articular cartilage surface either directly or indirectly. In many disorders, such as achondroplasia, which is the most common of the dysplasias, arthritis is rarely ever present because the epiphyseal ends of the bone are of normal shape and the articular cartilage has no molecular matrix abnormalities. In other conditions, such as diastrophic dysplasia, secondary osteoarthritis is almost invariable in all joints, and the combination of epiphyseal malformation, flattening and irregularity of the articular cartilage surface, fibrosis of the cartilage, and joint contractures renders many patients either nonambulatory or ambulatory with extreme difficulty by their late teenage years, even with intensive orthopedic management. The type II collagenopathies and multiple epiphyseal dysplasias are commonly associated with early-onset osteoarthritis. Preventive measures in persons at high risk for early joint disease include an emphasis on low-impact aerobic exercise, such as aquatic aerobics and elliptical trainers. Treatment of the painful joint or joints in patients with a skeletal dysplasia includes conservative measures such as decreased use, rest, crutches, splints, and antiinflammatory medications. Enzyme replacement is under active investigation for patients with mucopolysaccharidoses.

Surgical treatment

Surgical treatment of the extremities can be of great help even in the years before skeletal maturity. Such procedures include osteotomies to restore anatomic bone alignment, patellar realignment, and arthroscopy or open arthrotomy to remove degenerative debris from affected joints. On the other hand, it is not generally advisable to operate on joints that appear to be structurally abnormal but are asymptomatic in the hope of preventing or retarding osteoarthritic changes. Many patients with dysplasia tolerate apparently abnormal structure for decades because the surrounding musculature and soft tissues have developed in that position from the fetal period onward and are often stressed pathologically by radical surgical repositioning.

Total joint arthroplasty is a frequent intervention for patients with these disorders in the adult years. Orthopedists are generally reluctant to insert prosthetic joints in young and even middle-aged adults because the likelihood of replacement of a prosthesis increases the longer that it is in place.

These decisions are based on patient tolerance for ongoing pain, physical dysfunction, and reduced health-related quality of life, as well as current practice standards. The initial results are generally favorable because the bone tissue is normal and the patients are otherwise healthy.

The most commonly indicated spinal surgery in this population is laminectomy, which is performed for correction of lumbar stenosis in persons with achondroplasia. Those taking care of any patient with a skeletal dysplasia when general anesthesia is being given must bear in mind the high incidence of cervical C1-C2 abnormalities, which are often asymptomatic, even into adulthood. Extreme neck movements in an anesthetized patient may cause neurologic damage. Some centers perform lateral neck radiographs in patients with skeletal dysplasia before general anesthesia even if no symptoms have been elicited by the history.

Over the past 2 decades the practice of distraction osteotomies, or limb-lengthening procedures, has become more widely accepted as an approach to increasing height in persons of short stature. There has been considerable controversy about the advisability of adopting this procedure as a standard of care, and extensive experience has been achieved in only a few of the most common skeletal dysplasias, such as achondroplasia.¹⁶

OVERVIEW OF COMMON SKELETAL DYSPLASIAS

Achondroplasia

Achondroplasia, the most common of the skeletal dysplasias, is caused by a mutation in the gene expressing fibroblast growth factor receptor 3 (FGFR3).¹⁷ In more than 98% of cases the mutation causing achondroplasia is a glycine-to-arginine substitution at amino acid 380. The diagnosis is frequently made in the first few days of life by an astute pediatrician or radiologist. An anteroposterior radiograph of the spine and pelvis characteristically shows a progressively narrowed interpedicular distance from L1 to S1 (Fig. 211.5), a horizontal acetabulum, and a small sciatic notch. Genu varum requiring tibial osteotomies is common in childhood. A thoracolumbar gibbus deformity is not uncommon in infancy but usually resolves with weight bearing. Extreme lumbar lordosis is common. There is little evidence of osteoarthritis, even in adult life.



Fig. 211.5 Anteroposterior radiograph of the lumbar spine in a patient with achondroplasia showing progressive narrowing of the interpedicular distance from L1 above to S1 below. The distance should normally increase with each descending level.

Limb lengthening involving bilateral femoral and tibial distraction osteotomies may add up to 12 inches to adult height. Patients with achondroplasia are usually good candidates for this procedure because their cartilage is normal.

Other disorders caused by mutations in the *FGFR3* gene include the lethal thanatophoric dysplasia and the much milder hypochondroplasia.

Multiple epiphyseal dysplasia

This disorder has many subtypes in clinicoradiographic classifications, and not surprisingly, a number of different genes have been found to underlie it. Although the condition is a true skeletal dysplasia, not all patients are of short stature and many with severe joint involvement are normal to tall in terms of overall height. Those with multiple epiphyseal dysplasia represent the most common diagnostic group that undergoes total joint arthroplasty. The pattern of joint involvement varies in the different subtypes of multiple epiphyseal dysplasia. Involvement is often limited to the hips, and it tends to be bilateral. The radiographic appearance in those with hip involvement in the first decade superficially resembles the appearance in Legg-Calvé-Perthes disease, but there are several notable differences. In contrast to Legg-Calvé-Perthes disease, children with multiple epiphyseal dysplasia are usually minimally symptomatic or asymptomatic, range of motion is good, and the bilateral appearance is close to symmetric. In Legg-Calvé-Perthes disease, however, bilateral involvement develops in only about 20%, with second-side involvement occurring 18 to 24 months later than the first side. Molecular abnormalities in multiple epiphyseal dysplasia include mutations in genes encoding cartilage oligomeric protein (COMP) and collagen type IX.

Spondyloepiphyseal dysplasia

Radiographic features, including involvement of the epiphyses and flattening of the vertebrae, typify this class of dysplasia, which has a wide range of severity. Mutations in type II collagen are seen in the autosomal dominant forms of this condition. The more severe variants have extremely short stature with a short trunk and relatively long arms and legs. There is a high incidence of bilateral coxa vara and C1-C2 subluxation because of odontoid hypoplasia (see Fig. 211.3), along with increased risk for neurologic deficits. Cleft palate is observed in a minority of affected persons. Nonskeletal features include vitreoretinal degeneration with retinal detachment and progressive sensorineural hearing loss.

Kniest dysplasia

This disorder is also associated with mutations in type II collagen and tends to be on the more severe end of the spectrum of type II collagenopathies. Profound skeletal abnormalities are evident at birth. Craniofacial features include a depressed nasal bridge and cleft palate. In many patients, hearing problems develop in the second decade, and severe eye problems develop in others, including myopia, glaucoma, and retinal detachment, which may lead to blindness. The skeletal deformity is marked and progressive. Moderate to severe kyphoscoliosis is seen. The joints are characterized by dramatic widening of the epiphyses. Contractures can develop, and by the late second or early third decade, marked clinical and radiographic osteoarthritis may be present. The hips, knees, and ankles have considerable involvement. Procedures such as realignment osteotomy, patellar realignment, and knee joint débridement are helpful in alleviating the symptoms.

Diastrophic dysplasia

This disorder is one of the most deforming of the skeletal dysplasias, with severe short stature exacerbated by scoliosis, kyphosis, and fixed flexion contractures of the hips, knees, and feet and ankles (equinus and metatarsus adductus). The incidence of posterior cervical spina bifida is high; it is usually asymptomatic but must be recognized if cervical fusion is performed. Many patients become nonambulatory by the end of the second decade.

Correction of deformity often requires osteotomy, but even this can be followed by relentless recurrence. The disorder is further worsened by osteoarthritis with degeneration of articular cartilage because of misshapen epiphyses and inherent structural abnormality of the cartilage matrix, which is excessively fibrotic, thus limiting normal growth and function.

Diastrophic dysplasia is due to a mutation in the gene encoding the diastrophic dysplasia sulfate transporter (DTDST), which also causes two lethal dysplasias, atelosteogenesis type 2 and achondrogenesis type 1B. Growth plate cartilage is characterized histologically by increased deposition of fibrous tissue.

Morquio disease

Morquio disease (MPS IV) is the most common MPS syndrome compatible with longevity. The major enzyme deficiency involves galactose-6-sulfatase, which leads to imperfect processing of keratan sulfate. Patients are mentally normal and physically healthy but suffer from severe short stature, marked bilateral hip coxa vara, and acetabular dysplasia with a waddling gait, genu valgum, and a shortened spine with platyspondyly. Frequently, odontoid hypoplasia leads to C1-C2 instability with cervical myelopathy. Surgical stabilization of the C1-C2 junction is often required.¹⁸

Hereditary multiple exostoses

In this autosomal dominant disorder, multiple exostoses, or osteochondromas, are present at the periphery of the growth plates and metaphyses. They grow from cartilage caps via the endochondral sequence, and the bone of the exostosis is contiguous with metaphyseal bone with no interposition of cortical bone.

Three genes have been associated with multiple exostoses: *EXT1*, *EXT2*, and *EXT3*. *EXT1* and *EXT2* are proteins with glycosyltransferase activities needed for the synthesis of heparan sulfate, a proteoglycan present both on cell surfaces and in the extracellular matrix. Growth of the exostoses is normally controlled such that it ceases when the adjacent physeal growth stops. Recurrence of growth in adulthood in any of the osteochondromas is usually a sign of malignant transformation of persisting cartilage, generally a chondrosarcoma. The frequency of malignant transformation has been estimated to be approximately 5%.¹⁹

The osteochondromas themselves can cause discomfort, especially at or near skeletal maturation, when involution of the cartilage cap exposes bone tissue to surrounding tendon. Surgical excision is often indicated.

Asymmetric growth of paired long bones because of the presence of osteochondromas can contribute to the angular deformation leading to genu valgum, ankle tilt into valgus, dislocation of the radial head at the elbow, and wrist deformation with a dorsally displaced and shortened ulna (Madelung deformity). Complications occurring toward the end of growth and early in the adulthood may include pain and swelling behind the knee secondary to pseudoaneurysm of the popliteal artery caused by a pointed posteromedial exostosis, weakness of the foot and ankle secondary to stretching of the peroneal nerve by osteochondroma of the fibula, and radicular nerve symptoms secondary to an intraspinal osteochondroma growing against a nerve root.

CONCLUSION

This brief overview of the skeletal dysplasias has highlighted the increasing knowledge gained from genetic and molecular findings in the various syndromes. Awareness of the clinical complications associated with these disorders is important because most have a negative impact on the musculoskeletal system and many compromise neurologic function as well. Osteoarthritis, a common feature of many dysplasias, is frequently responsive for a considerable time to nonsurgical management, but many patients with progressive osteoarthritis eventually benefit from arthroplasty. The disorders represent a highly active field of investigation concerning the interplay between molecular and clinical pathology.

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Bone tumors

■ EDWARD F. MCCARTHY

- Any adult older than 50 years with a new bone lesion should be considered to have metastatic carcinoma until ruled out, which requires biopsy.
- Multiple myeloma also occurs in older adults and should be considered after metastatic carcinoma is ruled out.
- Primary bone tumors generally occur in adolescents and young adults.
- More than 60 subtypes of primary bone tumors are recognized.
- Classification of primary bone tumors is based on what bone-related tissue they reproduce.
- Most primary bone tumors are benign.
- Many benign primary bone tumors have diagnostic radiographic features and need not undergo biopsy.
- Malignant bone tumors are low grade and high grade. Low-grade neoplasms require margin-free excisions. High-grade malignant bone neoplasms require chemotherapy in addition to excision.

INTRODUCTION

Bone tumors may be divided into three categories: metastatic tumors in bone, hematologic malignancies involving bone, and primary bone tumors. The first category, metastatic tumors in bone, are most common in middle-aged and older patients. Metastatic lesions in bone may have a wide variety of radiographic appearances. Because they are the most common cause of bone lesions in older patients, any patient older than 50 years with a radiographic bone lesion should be considered to have metastatic carcinoma until proved otherwise. Metastatic carcinomas generally indicate stage IV of the patient's disease. Because cure is not possible, it is the job of the treating physician to manage pain and preserve the structural stability of the skeleton.

The second category, hematologic malignancies in bone, also tend to favor older adults. These tumors include multiple myeloma and malignant lymphoma of bone. Multiple myeloma, though not as common as metastatic carcinoma in bone, should also be considered when any older patient has a bone lesion. Multiple myeloma has a wide range of radiographic features, and older patients with bone lesions should also have serum studies performed to rule out myeloma. Malignant lymphoma of bone is often a manifestation of a stage IV lymphoma that began, as lymphomas usually do, in the lymph nodes. However, malignant lymphomas may occasionally begin primarily in bone. In this setting the prognosis is often good.

Primary malignant bone tumors, the third category, are tumors that begin in bone and differentiate along tissue lines that are normally associated with bone, such as cartilage, fibrous tissue, and osteoid. Primary bone tumors are most common in adolescents and young adults. They can be both benign and malignant. More than 60 subtypes are recognized on the basis of tissue differentiation. Many primary bone tumors have diagnostic radiographic features. If benign, biopsy may not need to be performed, and some may be managed by observation. In contrast, biopsy is needed for primary malignant bone tumors to ensure proper treatment.

METASTATIC CARCINOMA IN BONE

Although carcinomas in any organ can spread to bone, the most common are carcinomas of the lung, breast, prostate, kidney, and thyroid. Primary

carcinoma of these organs is the most common of all cancers and accounts for half of the 1.3 million new cases of cancer each year in the United States.¹ Although the incidence of bone metastases in all patients dying of cancer is reported to be as high as 70%, it is probably higher. Therefore, because about 525,000 Americans die of cancer each year, diagnosis and management of bone metastases are an enormous clinical burden.

In men, the most common metastatic tumors are from the lung and prostate. Formerly, before widespread screening for prostate-specific antigen (PSA), almost a third of patients already had bone metastases when the diagnosis of prostate cancer was made.² With PSA screening, this incidence is falling. In patients with lung carcinoma, bone marrow involvement is present in 5% to 21% of patients at diagnosis. Small cell carcinoma is the most common type of tumor to metastasize.

In women, in contrast, breast carcinoma is the most common type of tumor to metastasize. As many as 21% of patients will have bone marrow metastases at the time of diagnosis,³ and probably all of the 45,000 women who die of breast cancer each year in the United States have bone metastases.

Carcinomas usually metastasize within 2 years, so a destructive bone lesion is easily connected to the primary cancer diagnosis. However, some cancers may not metastasize until years after primary therapy. For example, a metastasis from a breast carcinoma may develop 20 years after mastectomy. Usually, a patient has more than one bone lesion. Even though only one lesion may be symptomatic, a technetium bone scan will, in 90% of cases, demonstrate other sites of involvement. Occasionally, however, only a single metastatic focus is present.

Metastatic carcinoma in bone is remarkable for its wide range of plain radiographic patterns. In contrast to most primary bone tumors, which have distinctive, often diagnostic plain radiographic features, metastatic carcinoma can look like anything. Lesions may be radiolytic or radiodense; they may be permeative or well defined; or they may periosteal, intracortical, or intramedullary. The only distinctive feature of metastatic carcinoma in bone is its predilection for the axial skeleton, particularly the spine.

Certain metastatic carcinomas, however, produce consistent radiographic patterns. For example, metastatic prostate cancer usually produces radiodense lesions—so-called osteoblastic metastases. Sometimes, the osteoblastic metastases of prostatic carcinoma are widely distributed throughout the entire skeleton. Breast carcinoma can also be osteoblastic, but the lesions are often mixed osteolytic and osteoblastic (Fig. 212.1).

Metastatic lung carcinoma, by contrast, almost always produces radiolytic lesions (Fig. 212.2). Lesion can be permeative or well defined, and cortical destruction is often present.

Histologically, the characteristic feature of metastatic carcinoma in bone is an organoid growth pattern of neoplastic cells (Fig. e212.1). The cells are grouped in tight clusters or lines separated by a fibrous stroma. Frequently, the clusters assume a glandular shape, a pattern suggestive of adenocarcinoma. Pathologists have more than 100 immunohistochemical stains that can be used to determine the primary site of the carcinoma in most cases.

HEMATOLOGIC MALIGNANCIES

Multiple myeloma

Multiple myeloma is a malignant manifestation of plasma cell dyscrasia that results in bone lesions.⁴ Although plasma cells do not normally reside in bone marrow, multiple myeloma is regarded as a primary bone tumor. Other malignant plasma cell dyscrasias include solitary myeloma of bone, osteosclerotic myeloma, and amyloidosis of bone.



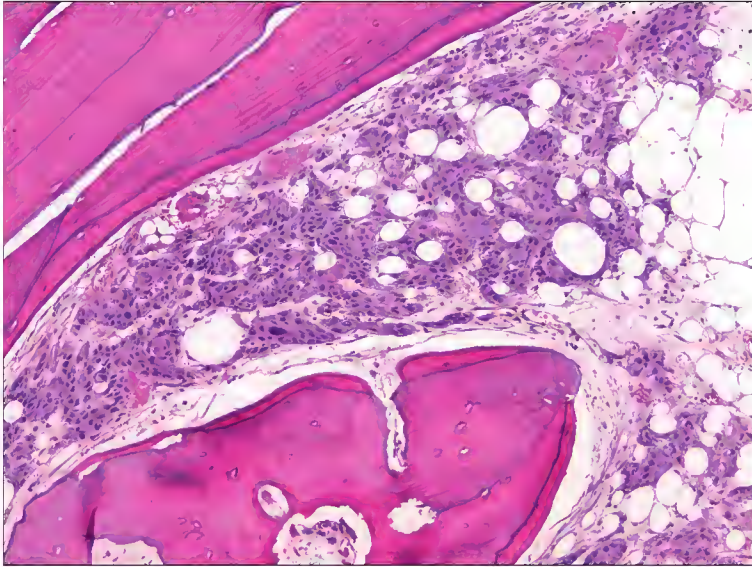


Fig. e212.1 Photomicrograph ($\times 40$) of metastatic carcinoma in bone. An organoid growth pattern is present where the cells cluster in small groups. This represents metastatic lung carcinoma.

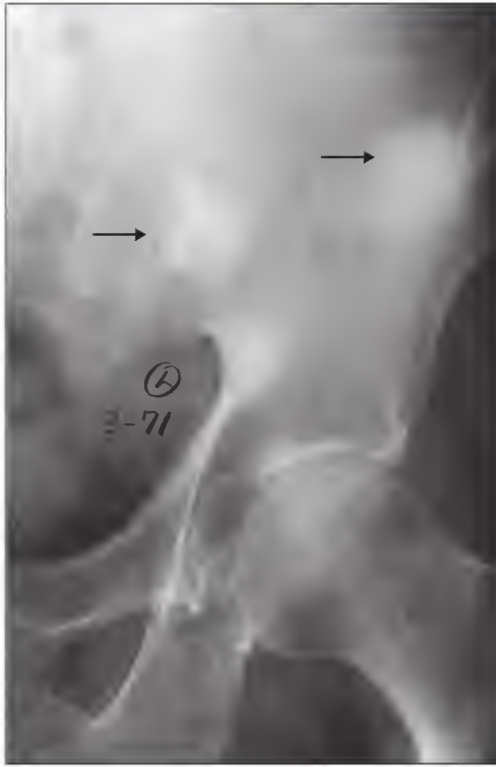


Fig. 212.1 Radiograph of a pelvis showing poorly defined radiodense lesions (arrows). These lesions are osteoblastic metastases from metastatic breast carcinoma.



Fig. 212.2 Radiograph of the proximal end of a femur showing a poorly defined lytic lesion involving the greater trochanter (arrow). This is a focus of osteolytic metastatic lung cancer.

Multiple myeloma accounts for approximately 1% of all malignancies in the United States each year, with an annual incidence of about 13,000 cases.⁵ This disease is twice as common in blacks and more common in males than in females (1.6:1.0). It is second in incidence only to Hodgkin disease among the nonleukemic hematologic malignancies. Multiple myeloma is a

disease of older adults and is generally discovered between the ages of 50 and 80 years. Therefore it should be considered in the differential diagnosis of all lytic bone lesions in patients in this age range. Less than 2% of cases occur in patients younger than 40. The etiology of myeloma is not known, although genetic, racial, occupational, and environmental factors have been implicated in some studies.⁶ Myeloma often has the most insidious and nonspecific manifestation. Pain, present in two thirds of patients, is the most common symptom.⁴ Back and chest pain (secondary to rib fractures) occur commonly. Unlike the pain of metastatic bone disease, which is worse at rest and at night, the pain of multiple myeloma is precipitated by movement. The pain is often sudden in onset, and many patients remember the exact date and time that it began.

The most common radiographic changes of myeloma, however, are multiple discrete punched-out lytic bone lesions. They are most commonly seen in the skull, spine, pelvis, and proximal end of the femur or humerus. Lesions vary in size from 3 to 4 mm to 5 to 10 cm. They have well-defined borders and lack a sclerotic rim. In long bones a circular or elliptic lytic area may be seen on the endosteal bone surface.⁷ Larger lesions cause extensive cortical destruction (Fig. e212.2). Histologically, myeloma is composed of sheets of atypical plasma cells (Fig. e212.3).

Malignant lymphoma

Malignant lymphomas may secondarily involve bone marrow as a manifestation of disseminated disease. For example, bone marrow may be involved in disseminated small lymphocytic lymphomas and in many small cleaved cell lymphomas. In these low-grade lymphomas, bone involvement does not necessarily carry a poor prognosis, and plain radiographs often do not show osseous abnormalities. In addition, secondary bone involvement may occur in patients with stage IV, high-grade lymphomas. However, bone involvement in these patients indicates a poor prognosis.

In contrast to secondary osseous involvement, a malignant lymphoma may involve bone without evidence of nodal or visceral disease. Patients with this disease, known as *primary malignant lymphoma of bone*, have a more favorable prognosis than do those with secondary bone involvement. Primary malignant lymphoma of bone may occur at any age; patients range in age from 1.5 to 86 years, with a mean of 46 years.⁸ Any bone may be involved, and 29% of patients have multiple osseous sites of involvement. The mandible, maxilla, femur, pelvis, and spine are the most common locations. Patients have pain, often for longer than a year's duration. Some patients with a lymphoma at the epiphyseal end of a bone have a joint effusion secondary to neoplastic involvement of joint structures.

Malignant lymphomas are characteristically diffusely permeative lytic lesions that often involve a large segment of the affected bone. Lesions have varying amounts of intraosseous reactive bone, which imparts a mottled appearance (Fig. e212.4).

Malignant lymphomas of bone are usually diffuse, large cell, noncleaved lymphomas. The neoplastic cells are generally uniform with a large round nucleus and clumped chromatin; cytoplasm is scant (Fig. e212.5). However, some osseous lymphomas have cells with cleaved or even multilobed nuclei. Also, in rare cases the cells may be pleomorphic and have abundant cytoplasm, a pattern consistent with immunoblastic lymphoma. Osseous lymphomas in children may be of the lymphoblastic type and have small cells with round nuclei and fine chromatin.

Malignant lymphomas of bone are almost always B-cell neoplasms. Lymphoid origin is confirmed with a CD45 (leukocyte common antigen) stain, and B-cell lineage is confirmed with a CD20 stain. The latter stain differentiates neoplastic cells from the inflammatory infiltrate, which usually consists of many T lymphocytes.

Lymphomas of bone, without nodal or visceral disease, have a favorable prognosis. Generally, younger patients do better. Irradiation plus adjuvant chemotherapy yields a 5-year survival rate of 50% to 88%. Patients with multifocal osseous disease but without soft tissue involvement also do well, with 40% surviving for 5 years.

PRIMARY BONE TUMORS

Bone-forming neoplasms

Bone island

A bone island, also known as an *enostosis*, is a focus of dense compact bone within the medullary cavity. This nonneoplastic lesion most probably results from a remodeling error during skeletal growth. Although it is a developmental abnormality, a bone island may be mistaken radiographically for a neoplasm. Patients are asymptomatic. Therefore a bone island is almost



Fig. e212.2 Radiograph of an expansile lytic lesion of the proximal end of the radius. This is an example of a large focus of plasma cell myeloma.

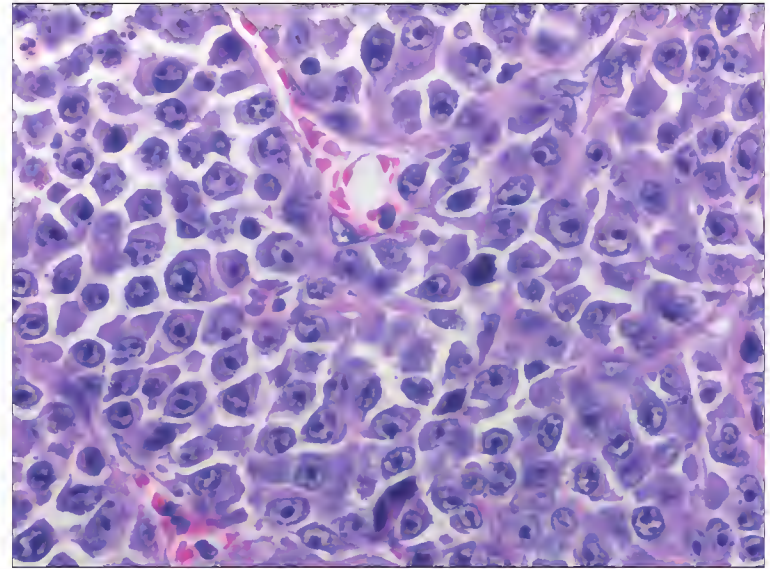


Fig. e212.3 Photomicrograph (x40) showing sheaths of atypical malignant plasma cells.



Fig. e212.4 Radiograph of the knee of a patient with primary malignant lymphoma of the proximal end of the tibia. A poorly defined osteolytic area is located adjacent to a radiodensity (arrow).

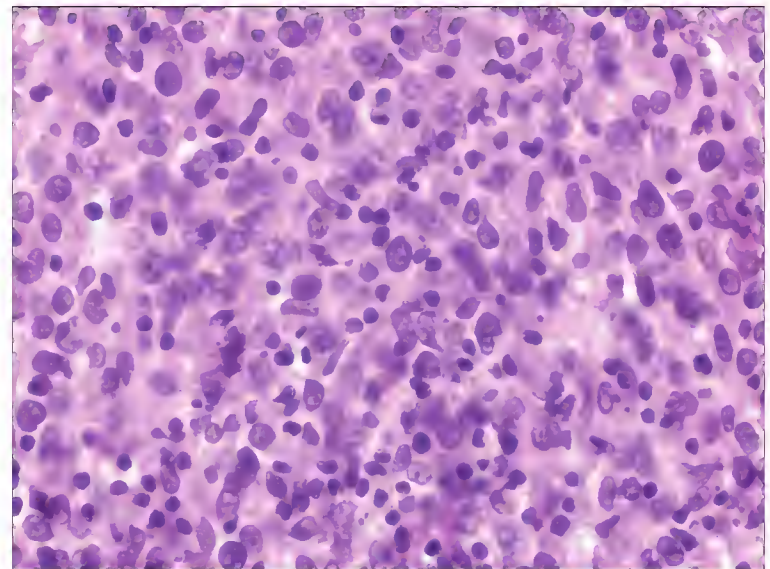


Fig. e212.5 Photomicrograph (x60) of a large B-cell lymphoma from the patient in [Figure e212.4](#).



Fig. 212.3 Radiograph of a bone island in the proximal end of the humerus with sharp margins. This patient was asymptomatic. A well-defined radiodensity is apparent.

always discovered incidentally when a radiograph taken for other reasons. A bone island can occur in any bone, and occasionally, several bones may be involved.

A bone island can usually be diagnosed with certainty by plain radiography. A well-defined round or oval radiodensity is present in the medullary canal, usually in the metaphysis (Fig. 212.3). The degree of radiodensity is comparable to the cortex. The size varies, but most are 1 mm to 2 cm in diameter. The margins of a bone island are generally sharply circumscribed.

Histologically, a bone island is a well-defined island of lamellar compact bone identical to the cortex. Also, mature haversian canals are usually present.

Osteoid osteoma

Osteoid osteomas are benign osteoid-producing neoplasms with three important characteristics: small size, self-limited growth, and a tendency to cause extensive reactive changes in adjacent tissues. The lesional tissue of an osteoid osteoma, known as a *nidus*, is almost always only 1 cm or less in diameter. Despite its small size, the lesional tissue causes intense pain and provokes an exuberant periosteal reaction, a reaction that often obscures the small nidus.⁹

Like most other primary bone tumors, osteoid osteomas affect children and young adults. Most cases occur between the ages of 10 and 35, with the average being 19 years. Rarely, children younger than 5 years or adults older than 35 may be affected.¹⁰ Patients invariably complain of pain. Characteristically, the pain is worse at night and dramatically relieved by aspirin. This feature is present in more than 75% of cases and is an important diagnostic clue.

In addition to pain, the highly irritative nature of osteoid osteomas affects adjacent tissues. These local effects may be due to the prostaglandin synthesis demonstrated in some osteoid osteomas. For example, a lesion in the spine can cause scoliosis, and a lesion near a growth plate can stimulate lengthening of the extremity. Also, an intraarticular lesion may cause an intense synovitis. These intraarticular osteoid osteomas, particularly inside the hip or elbow capsule, may be difficult to diagnose because the bone inside a joint capsule lacks a periosteum and therefore lesions in these locations cannot stimulate the typical periosteal reaction. Another local effect of some osteoid osteomas is significant edema in adjacent soft tissues. A final effect of some osteoid osteomas is muscular atrophy and osteopenia in the involved extremity.

Osteoid osteomas may occur in any bone, but lesions in the femur and tibia account for 50% of cases. Other sites of predilection include the posterior elements of the spine (the vertebral body is a very rare location), the humerus, and the small bones of the hands and feet.

Osteoid osteomas have a very characteristic radiographic appearance. A small radiolucent nidus is surrounded by dense reactive bone. The nidus may be subperiosteal, intracortical, or subcortical (Fig. e212.6). On rare occasion the nidus is deep in the medullary canal. Occasionally, the reactive bone may be so dense that it obscures the nidus. In this situation, the small radiolucent focus in the center of the radiodense area can usually be identified with computed tomography (CT) or magnetic resonance imaging (MRI).

Histologically, osteoid osteomas are characterized by thin interconnecting seams of osteoid or woven bone lined by osteoblasts (Fig. e212.7). The osteoid seams are separated by loose fibrous stroma with prominent vascularity. This lesional tissue is sharply demarcated from the dense surrounding bone.

Osteoblastoma

Osteoblastomas are benign bone-forming neoplasms that share many histologic features with osteoid osteomas. However, these neoplasms differ in several important ways. First, osteoblastomas are rare neoplasms, unlike osteoid osteomas, which are relatively common. Second, osteoblastomas are larger than osteoid osteomas. Third, unlike the self-limited growth of osteoid osteomas, osteoblastomas grow progressively.

Osteoblastomas may occur at any age; however, 80% occur between the ages of 10 and 25. Patients usually have pain, and some have local swelling and tenderness. Any bone may be involved, including the calvaria and the small bones of the hands and feet. The spine, however, is the most common location and accounts for about a third of reported cases. In this location the vertebral posterior elements are the principal site of involvement, but occasionally the vertebral body may also be involved. Osteoblastomas almost never involve the vertebral body alone. All portions of the spine, including the sacrum, are equally affected. In the appendicular skeleton, the diaphysis or metaphysis of long bones, particularly the femur or tibia, is the most common location.

Radiographically, osteoblastomas are expansile, lytic lesions with variable amounts of fluffy mineralization (Fig. e212.8). Reported lesions have ranged from 1 to 11 cm. Most are well circumscribed, and occasionally they have a sclerotic rim. Many osteoblastomas expand the cortex and are bounded by a thin shell of reactive bone. Histologically, osteoblastoma is identical to osteoid osteoma, although the lesions are larger (Fig. e212.9).

Osteosarcoma

Osteosarcomas are malignant bone tumors whose cells have the ability to synthesize osteoid. Osteosarcoma is the most common primary malignant bone tumor. They have a wide range of histologic and radiographic patterns that can be subdivided into numerous osteosarcoma variants. Such variants include conventional osteosarcoma, parosteal and periosteal osteosarcoma, telangiectatic osteosarcoma, well-differentiated osteosarcoma, and others. These variants have characteristic radiographic and histologic features. The most common type of osteosarcoma is a high-grade interosseous osteosarcoma known as conventional osteosarcoma.

Conventional osteosarcoma accounts for 90% of all osteosarcomas.¹¹ It begins in the medullary canal and sometimes penetrates the cortex and invades the adjacent soft tissues. Most patients with conventional osteosarcoma are adolescents or young adults. About 85% of patients are younger than 30 years, with the peak incidence occurring at 20 to 25 years of age. This neoplasm is extremely rare in children younger than 10 years. Conventional osteosarcoma may also develop in older adults, although many have predisposing factors such as Paget disease or previous radiation therapy. In younger patients, conventional osteosarcoma most commonly occurs around the knee, with the distal end of the femur accounting for a third of all cases. By contrast, osteosarcoma develops in older patients more commonly in the flat bones. Pain, tenderness, and swelling, rarely present for more than a few months, are the usual initial symptoms.

The radiographic features of conventional osteosarcoma are diagnostic in two thirds of cases. The lesion has poorly circumscribed medullary lucency with mottled areas of radiodensity (Fig. 212.4). Occasionally, a lesion may be entirely radiodense. Cortical destruction is usually present, and there is often a focally mineralized soft tissue mass. Benign, periosteal reactive bone forms a Codman triangle adjacent to the soft tissue mass. In the long bones, conventional osteosarcoma is usually centered in the metaphysis.

Conventional osteosarcoma cells synthesize abundant osteoid. Seams or sheets of eosinophilic osteoid are distributed in a sarcomatous stroma



Fig. e212.6 Computed tomography scan of an osteoid osteoma in the talus. A well-defined lytic area contains a focal radiodensity characteristic of osteoid osteoma.

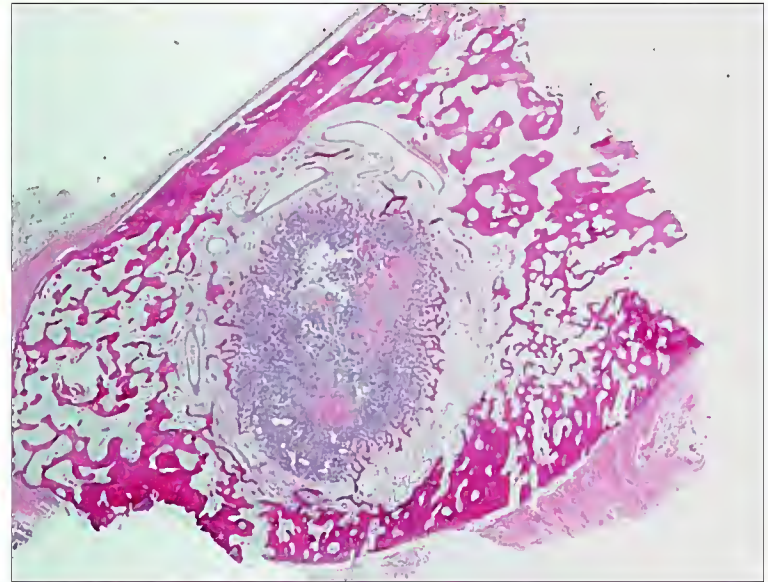


Fig. e212.7 Macrophotomicrograph of an osteoid osteoma in the medullary canal of bone.



Fig. e212.8 Axial computed tomography scan of a cervical vertebra showing an expansile radiolytic lesion in the pedicle of the vertebrae. This pattern is characteristic of osteoblastoma.

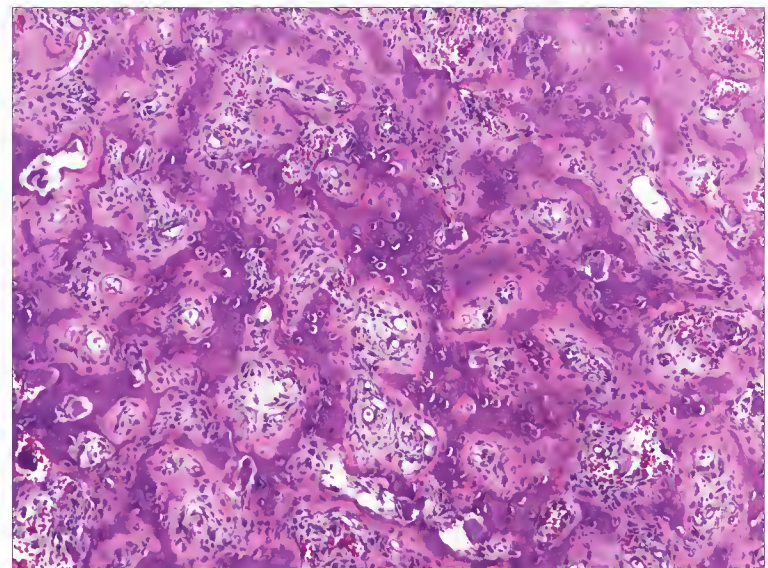


Fig. e212.9 Medium-power photomicrograph (x60) of an osteoblastoma showing seams of mineralized osteoid in a loose fibrovascular stroma.



Fig. 212.4 Radiograph of an osteosarcoma of the distal femoral metaphysis. A poorly defined radiolytic lesion with associated radiodensity is present. Extraosseous spread of radiodensity and a Codman triangle proximally (arrow) can be seen.

(Fig. e212.10). The stromal cells of conventional osteosarcoma are usually high grade. They show varying degrees of atypia and numerous mitotic figures. The pattern and distribution of osteoid are often variable. In some areas, osteoid is deposited in fine lacelike seams.

Parosteal osteosarcoma is the most common osteosarcoma variant after conventional osteosarcoma. This neoplasm is a low-grade fibroblastic osteosarcoma that is limited to the surface of bone. Radiographically, an irregular bony protrusion projects from the bone surface like a multilobulated door knob (Fig. 212.5). Only in rare circumstances is the medullary canal of the bone involved. The posterior aspect of the distal end of the femur is the most common location. Histologically, parosteal osteosarcoma shows interlacing seams of osteoid in a low-grade fibroblastic stroma (Fig. e212.11). This neoplasm has low potential to metastasize and does not require chemotherapy. Lesions can be cured by *en bloc* resection with tumor-free margins.

Cartilage neoplasms

Chondroblastoma

Chondroblastoma is a rare benign neoplasm of fetal-type cartilage differentiation. Though reported in patients ranging in age from 3 to 72 years, more than 50% of lesions develop in patients between the ages of 15 and 25. Approximately 70% of chondroblastomas occur in the long bones, most commonly the proximal end of the humerus, followed by the distal end of the femur and proximal end of the tibia.¹² In the long bones, the center of the lesion is almost always the epiphysis. Other bones commonly involved are the proximal end of the femur, the small bones of the feet, and the temporal bone of the skull. Patients generally complain of pain. In addition, because of epiphyseal involvement, joint symptoms, such as stiffness or effusion, are common.

Radiologically, chondroblastoma is usually a well-circumscribed lytic lesion that when in a long bone, involves the epiphysis (Fig. 212.6). About 50% of lesions extend into the metaphysis, a feature usually seen only when the epiphyseal plate is closed. Most lesions lack a sclerotic rim. Varying degrees of stippled calcification are present in 40% of lesions, the remainder being completely lucent. Chondroblastomas average 4.3 cm in maximum dimension, but they may be as large as 19 cm. Occasionally, they expand or destroy the cortex.



Fig. 212.5 Radiograph of a parosteal osteosarcoma of the posterior aspect of the distal end of the femur. An irregular bony mass projects from the bone surface.



Fig. 212.6 Radiograph of a chondroblastoma of the proximal femoral epiphysis. The lesion is a well-defined lytic area with a circumferential zone of reactive bone.

Histologically, chondroblastoma is composed of sheets of stromal cells, scattered multinucleated giant cells, and varying amounts of chondroid matrix (Fig. e212.12). The stromal cells, resembling fetal chondroblasts, are distinctive. They are round with abundant cytoplasm and generally have distinct cytoplasmic membranes. The nuclei are also round and are located in the center of the cytoplasm, thus giving the cells a “fried egg” appearance. The nuclei have faintly clumped chromatin and often have a grooved or folded membrane.

Chondromyxoid fibroma

Chondromyxoid fibroma, when in a long bone, is a metaphyseal lesion that usually abuts against one cortex. Occasionally, lesions involve a portion of the epiphysis if the plate is closed. In all locations, chondroblastomas are radiographically well-circumscribed lytic lesions and often have a sclerotic

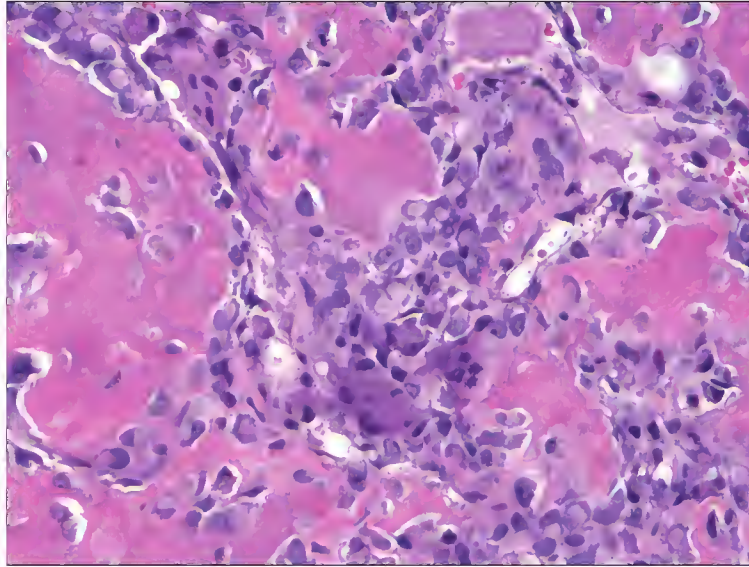


Fig. e212.10 Medium-power photomicrograph (x60) of an osteoblastic osteosarcoma showing sheets of malignant osteoid amid atypical rounded sarcoma cells.

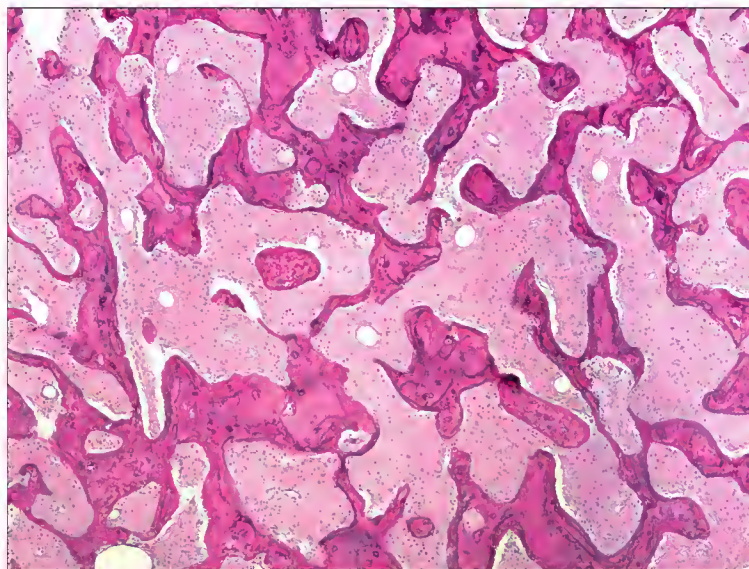


Fig. e212.11 Low-power photomicrograph (x20) of a parosteal osteosarcoma showing interlacing strands of osteoid in a bland fibrous tissue background.

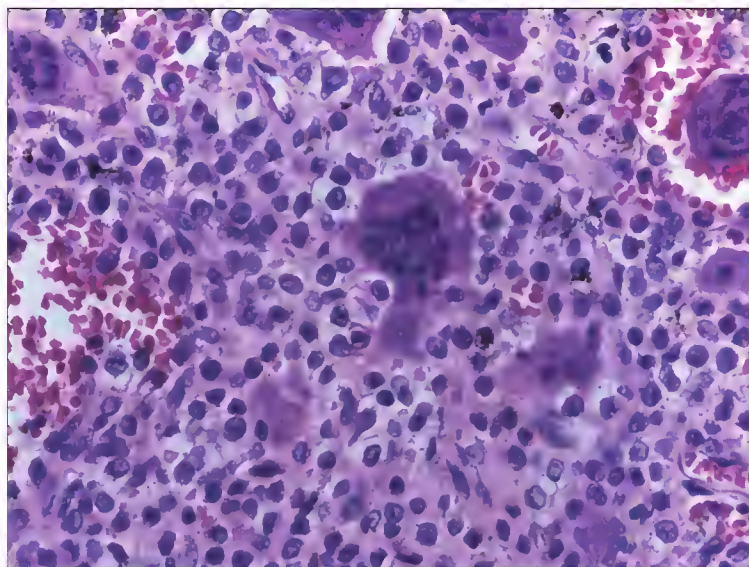


Fig. e212.12 Medium-power photomicrograph (x60) of chondroblastoma showing rounded stromal cells and numerous multinucleated giant cells.



Fig. 212.7 Radiograph of a chondromyxoid fibroma of the proximal femoral metaphysis. This well-defined lytic lesion has a sclerotic margin.

margin (Fig. 212.7). Some lesions, particularly in the pelvis, have a multiloculated, “soap bubble” appearance, and some have a scalloped margin. Lesions range in size from 2 to 10 cm in maximum dimension.

Chondromyxoid fibroma has distinctive histologic features. Elongated or stellate cells are present in an abundant extracellular chondroid matrix (Fig. e212.13). Two important low-power features are a lobular growth pattern and sharp demarcation from surrounding bone. Cellularity is variable, but each lobule tends to be more cellular at the periphery. The peripheral cells are more spindle shaped and appear to separate the lobules by fibrous bands. The fibrous bands contain blood vessels and, frequently, osteoclast-like giant cells.

Enchondroma

An enchondroma is a hamartomatous proliferation of mature hyaline cartilage in the medullary canal of the metaphysis or metadiaphysis. The origin of this lesion is thought to be due to a portion of the epiphyseal plate becoming entrapped in the metaphysis during bone growth. These lesions are common. Approximately 2% of all people have a small cartilaginous island in the medullary canal of the femur, presumably caused by this entrapment mechanism. These rests are undoubtedly present in other bones as well. The cartilaginous islands, subject to the same growth factors as epiphyseal plate cartilage, cease to grow in adulthood.

Enchondromas most commonly involve the tubular bones of the hands and feet. In fact, enchondromas are the most common bone tumor of the hand. The long bones are also frequent sites, particularly the tibia, distal end of the femur, and proximal end of the humerus. Rarely, the pelvis is involved.

Enchondromas in adulthood are generally asymptomatic; they are discovered incidentally on radiographs or bone scans obtained for other reasons. Large enchondromas or enchondromas in the hand may, however, produce pain from a stress fracture. Enchondromas may be discovered at any age, but most are found in persons between the ages of 15 and 40.

Enchondromas show the characteristic mineralization pattern of hyaline cartilage—radiodense rings and stipples (Fig. 212.8). Occasionally, the mineralization is very dense. Characteristically, the clusters of ringlike and stippled mineralization are well defined and can be traced in a continuous line. In adults, enchondromas vary in size from 1 cm to almost 10 cm in maximum dimension. Histologically, islands of hyaline cartilage are present (Fig. e212.14).

Osteochondroma

Osteochondromas are hamartomatous proliferations of bone and cartilage that arise from the cortex and project into soft tissue (Fig. 212.9). They are



Fig. 212.8 Radiograph of an enchondroma of the proximal end of the tibia showing stippled and ring-shaped calcifications. This patient was asymptomatic, and the lesion was found incidentally.



Fig. 212.9 Radiograph of an osteochondroma of the proximal end of the tibia arising from the metaphysis. A “ring and stippled” radiodensity in the head of the lesion is present, consistent with cartilage.

thought to develop from islands of epiphyseal plate cartilage entrapped beneath the periosteum during skeletal growth. The cartilage rests grow and ossify at the same rate as adjacent bone. When skeletal maturity is reached, osteochondromas stop growing. Osteochondromas are probably the most common tumorous process of bone. The true incidence cannot be calculated because many are asymptomatic. Some are discovered incidentally on radiographs taken for other reasons. Most osteochondromas are solitary. Symptomatic lesions usually occur before 30 years of age. Large osteochondromas are manifested clinically as firm subcutaneous masses. Pain may be caused by fracture of the stalk, nerve impingement, or inflammation of an overlying bursa. Osteochondromas may arise from any bone formed in cartilage, but the distal end of the femur, proximal end of the tibia, proximal end of the humerus, and pelvis are the most common sites.

Histologically, an osteochondroma consists of a cartilage cap overlying a stalk of cortical and trabecular bone (Fig. e212.15). The cartilage cap is bounded by a well-defined perichondrium that separates the lesion from the surrounding soft tissue. Often, particularly in large osteochondromas, islands of partially calcified and ossified cartilage are present inside the stalk, indicative of cartilage entrapment during growth.

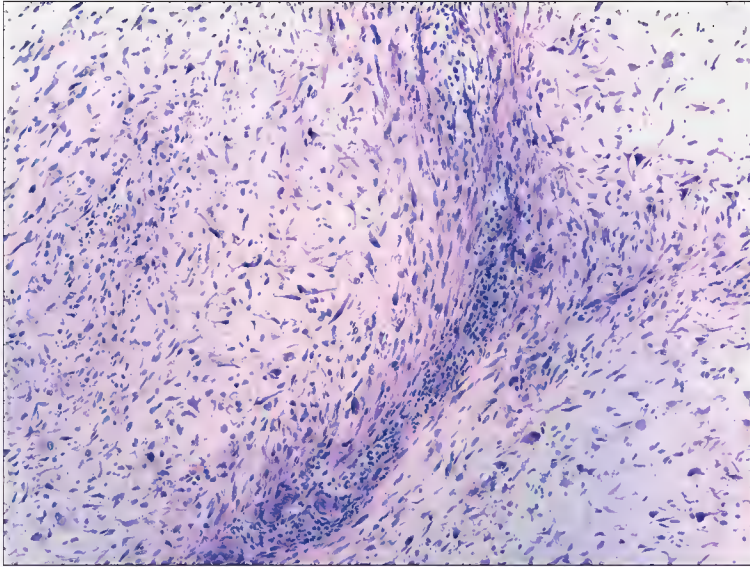


Fig. e212.13 Photomicrograph (×20) of a chondromyxoid fibroma showing a lobulated proliferation of myxoid cells in a faint chondroid background.

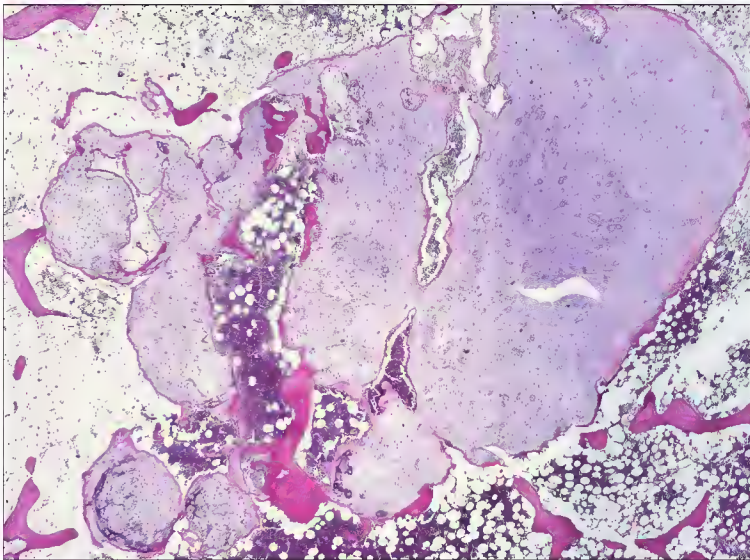


Fig. e212.14 Lower-power photomicrograph of an enchondroma (×10) in the medullary canal showing well-defined lobules of cartilage that are surrounded by reactive bone.

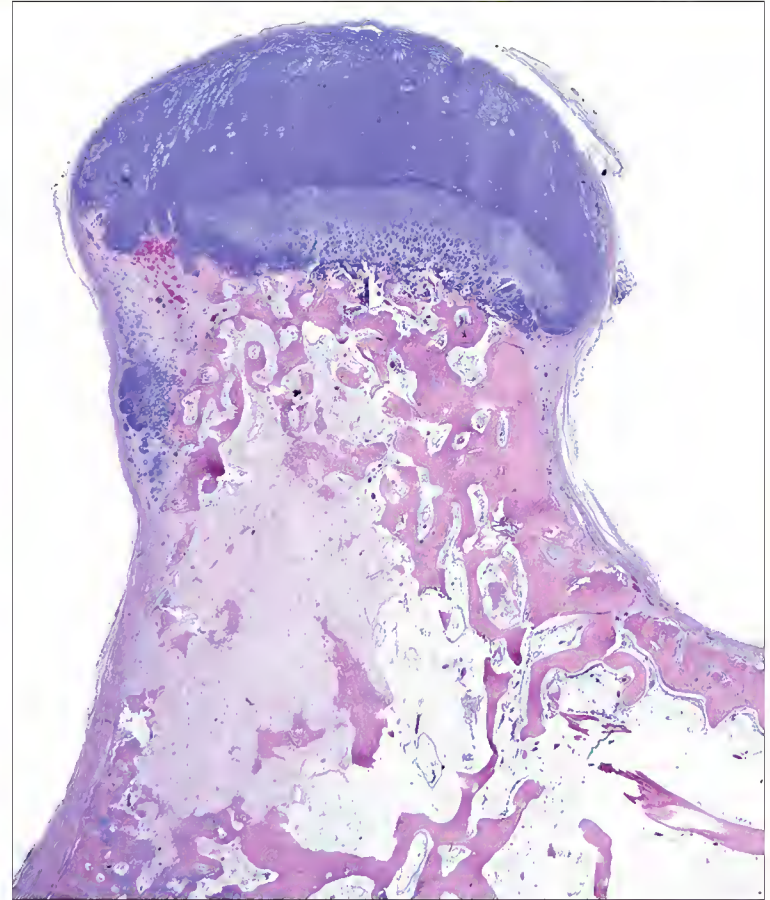


Fig. e212.15 Lower-power photomicrograph of a small osteochondroma (×5) showing a well-defined basophilic cartilage cap.



Fig. 212.10 Radiograph of a periosteal chondroma of the proximal end of the humerus. A well-defined zone of lucency is seen in the proximal end of the humerus along with margin buttresses suggestive of a surface lesion.

Periosteal chondroma

Periosteal chondroma, also known as juxtacortical chondroma, is a benign proliferation of hyaline cartilage on the bone surface beneath the periosteum. Lesions range in size from 1 to 5 cm in diameter and may involve any bone in the appendicular skeleton, although the proximal or distal ends of the femur and the proximal end of the humerus are the most common sites. Patients are generally between the ages of 10 and 30 years, and they have usually have pain, often for longer than a year.

Radiologically, periosteal chondromas, unlike osteochondromas, lack a bony stalk. In a periosteal chondroma, a well-demarcated aggregate of ring-like and stippled densities is directly adjacent to the cortex (Fig. 212.10). The cortex is intact under the cartilaginous mass, although it is usually scalloped or cratered. Buttresses of reactive bone are occasionally present at the margins of the lesion.

Histologically, periosteal chondromas show lobules of hyaline cartilage on the external surface of the cortex beneath the periosteum (Fig. e212.16). Frequently, networks of reactive and endochondral bone separate the hyaline cartilage lobules. The cartilage is mildly cellular, and sometimes the nuclei are plump and hyperchromatic. Occasionally, the cartilage matrix shows myxoid changes.

Periosteal chondromas are best treated by *en bloc* excision of the cartilage, including the overlying perichondrium and the underlying cortex. Recurrence after complete removal is rare.

Chondrosarcoma

Chondrosarcomas are malignant neoplasms of cartilage-producing cells. After osteosarcoma, chondrosarcoma is the second most common primary malignant bone tumor. Unlike most other primary bone tumors, chondrosarcomas tend to occur in older patients and have a predilection for the axial skeleton.

Chondrosarcomas may be divided into two major categories: *central chondrosarcomas* (Fig. e212.17) and *surface chondrosarcomas* (Fig. 212.11). They occur with equal frequency. Central chondrosarcomas are centered in the medullary canal and occasionally penetrate through the cortex. By contrast, surface chondrosarcomas, also known as peripheral chondrosarcomas, arise on the bone surface and grow into the adjacent soft tissue.

Chondrosarcomas show a wide range of aggressiveness. Some lesions, though locally aggressive, grow slowly and rarely metastasize. By contrast, other chondrosarcomas are very destructive and metastasize readily. Fortunately, most chondrosarcomas (about 75%) grow slowly. In general, the aggressiveness of a chondrosarcoma can be predicted by its cellularity and degree of nuclear atypia, features known as “histologic grade.” High-grade lesions permeate through the marrow cavity (Fig. e212.18).

The higher the grade of the chondrosarcoma, the poorer the prognosis. Grade 1 chondrosarcomas have a low incidence of metastasis and can often



Fig. 212.11 Radiograph of a surface chondrosarcoma of the pubic symphysis showing a mass of rings and stippled calcifications consistent with a chondrosarcoma.

be cured by local incision. Wide radical incision is required for higher-grade chondrosarcomas. Generally, chondrosarcomas do not respond to chemotherapy or radiotherapy.

Fibrous neoplasms

Nonossifying fibroma

Nonossifying fibromas are common developmental proliferations of fibrous tissue that occur in the metaphyseal region of long bones. Although the cause of these lesions is unknown, they are probably due to exaggerated subperiosteal osteoclastic resorption during metaphyseal remodeling. This exaggerated resorptive process often begins at the site of tendon insertions.¹³ Small lesions, known as fibrous cortical defects, result from the same process. Though forming in the metaphysis, lesions migrate into the diaphysis as the bone grows.

Nonossifying fibromas most commonly involve the distal end of the femur and the distal or proximal end of the tibia, sites that account for 80% of lesions. The flat bones, the small bones of the hands and feet, the spine, and the craniofacial skeleton are not affected. Many nonossifying fibromas are asymptomatic and discovered incidentally on radiographs obtained for other reasons. Undoubtedly, many are never diagnosed. Large nonossifying fibromas may cause pain, and some are diagnosed after a pathologic fracture. Symptoms, when present, usually develop when patients are in their mid-teens. Development of a nonossifying fibroma before 5 years of age is extremely rare.

Radiographically, nonossifying fibromas are lytic metaphyseal lesions. Characteristically, the lesions are eccentric in the medullary canal and are juxtaposed to one cortex (Fig. 212.12). In addition, the margins are scalloped and a sclerotic rim is usually present. Small lesions, from 1 to 2 cm, are regarded as fibrous cortical defects. Alternatively, some lesions reach 7 cm in maximum diameter and cause cortical expansion.

Histologically, nonossifying fibromas consist of a spindle cell stroma with scattered small multinucleated giant cells, although the giant cells may be scarce. Characteristically, the spindle cells are arranged in a whorled or storiform pattern. Occasionally, the stroma is very cellular and the spindle cells often have plump hyperchromatic nuclei.

Small asymptomatic nonossifying fibromas need no therapy. Most heal spontaneously over a period of several years. Larger lesions, particularly those that expand the cortex or are accompanied by pathologic fractures, should be treated by curettage and bone grafting. Recurrence after treatment is very rare.

Fibrous dysplasia

Fibrous dysplasia is a common skeletal lesion characterized by a hamartomatous proliferation of fibroosseous tissue in the medullary canal. This tissue proliferates during skeletal growth and, in some cases, continues to grow during adulthood. The bone involvement in fibrous dysplasia exhibits a wide spectrum of severity. In about 80% of cases only a small focus of one bone is affected, a condition known as monostotic fibrous dysplasia. Multiple bones are involved in the remainder of patients, the so-called

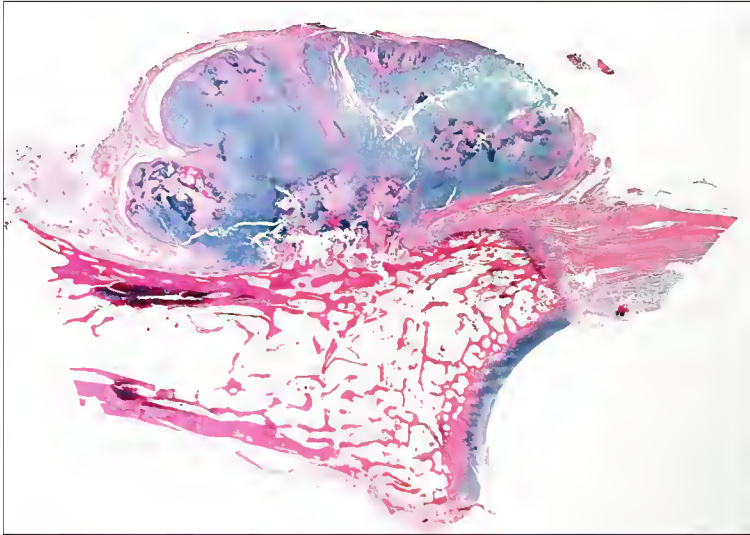


Fig. e212.16 Lower-power photomicrograph of a periosteal chondroma (x2) showing a well-defined island of cartilage sitting on the bone surface. The medullary canal is not involved.



Fig. e212.17 Radiograph of a high-grade central chondrosarcoma. There are rings and stipules characteristic of cartilage associated with a poorly defined lucency and destruction of the lateral cortex of the tibial metaphysis.

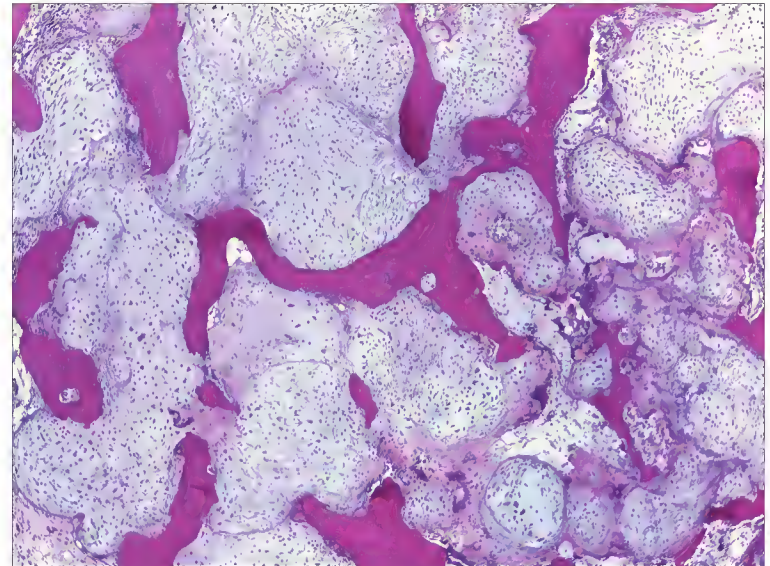


Fig. e212.18 Photomicrograph (x40) of a chondrosarcoma showing basophilic cartilage infiltrating throughout the marrow spaces.



Fig. 212.12 Radiograph of a nonossifying fibroma of the distal tibial metaphysis. A well-defined lytic area is surrounded by a sclerotic rim. The lesion is centered on the cortex.

polyostotic fibrous dysplasia. In this form, fibrous dysplasia may involve long segments of bone, and it may cause significant cortical expansion. Occasionally, polyostotic fibrous dysplasia involves only one extremity.

Fibrous dysplasia may occur in any bone. In the axial skeleton, the craniofacial bones and ribs are the most common sites. The tibia and proximal end of the femur are the preferred sites in the appendicular skeleton. Fibrous dysplasia is often asymptomatic—lesions are discovered on plain radiographs taken for other reasons. Although lesions develop during skeletal growth, 25% of cases are not diagnosed until after 30 years of age.

Some patients with severe polyostotic fibrous dysplasia also have pigmented skin lesions and endocrine abnormalities. Patients with this condition, known as McCune-Albright syndrome, have severely deformed bones and are usually symptomatic before 10 years of age. In McCune-Albright syndrome the skin lesions are often confined to one extremity. Some patients with this syndrome also have soft tissue myxomas. McCune-Albright syndrome is now known to be a genetic mutation caused by a mosaic state of an activating mutation in the *GNAS1* gene. This gene codes for an adenosine diphosphate-dependent G protein.¹⁴

The radiologic features of fibrous dysplasia are often diagnostic. In the appendicular skeleton, fibrous dysplasia is typically an elongated lesion with symmetric cortical thinning and expansion—the characteristic “long lesion in a long bone” (Fig. 212.13). Although most lesions have a “ground-glass” texture, some may be entirely radiolytic; others may be radiodense. In severely involved weight-bearing bones, deformity is common because of multiple fractures. Histologically, fibrous dysplasia shows irregular seams of woven new bone in a cellular fibrous stroma. The seams of bone are thin and disconnected and are arranged in curved shapes reminiscent of “Chinese letters” or “alphabet soup” (Fig. e212.19).

Malignant fibrous histiocytoma

Malignant fibrous histiocytomas are high-grade sarcomas with fibrohistiocytic differentiation. Some pathologists refer to this neoplasm as high-grade undifferentiated pleomorphic sarcoma. In addition to occurrence in bone as a primary lesion, this neoplasm is the most common sarcoma to complicate preexisting osseous lesions such as radiation damage, Paget disease, and cartilaginous neoplasms. Moreover, malignant fibrous histiocytomas may, on rare occasion, occur as a complication of a bone infarct.¹⁵ In this situation the sarcoma probably develops in the reparative granulation tissue at the margin of the infarct.



Fig. 212.13 Radiograph of a typical lesion of fibrous dysplasia in the fibula (arrow) showing a long lesion in a long bone with a characteristic “ground-glass” appearance.

Primary malignant fibrous histiocytomas may involve any bone.¹⁶ However, the femur is the most common site (one third of cases), followed by the tibia and humerus. Patients range in age from 6 to 81 years, but more than 50% of cases occur in individuals older than 40 years. Patients have pain, and 67% have swelling or a mass. Some patients are initially found to have a pathologic fracture.

Radiographically, malignant fibrous histiocytomas are poorly defined radiolytic lesions, often with extensive cortical destruction, and periosteal new bone reaction is unusual (Fig. e212.20). MRI often shows an associated soft tissue mass. Malignant fibrous histiocytoma most commonly involves the metaphyseal region of bone. However, secondary involvement of the epiphysis is common.

Malignant fibrous histiocytomas are composed of spindle cells, histiocytic cells, or an intermingled combination of the two in varying proportions (Fig. e212.21). The spindle cells are arranged in a storiform pattern, the most characteristic feature of malignant fibrous histiocytoma. The nuclei are oval and vesicular with mild to moderate pleomorphism.

Giant cell tumor

Giant cell tumor of bone, sometimes referred to as conventional giant cell tumor, is a benign locally aggressive neoplasm that usually affects young adults; about two thirds of patients are between the ages of 20 and 40. Giant cell tumors may occasionally occur in the elderly—a patient 74 years old has been documented.¹⁷ However, these neoplasms are extremely rare in growing children. Less than 2% of giant cell tumors affect patients younger than 15 years.

Giant cell tumors occur most commonly in the distal end of the femur, proximal end of the tibia, and distal end of the radius. These locations account for about 65% of cases. Other common locations include the pelvis, vertebral bodies, and proximal end of the femur. Patients almost always have pain and a few have a pathologic fracture.

Giant cell tumors, when they occur in long bones, have a diagnostic radiographic pattern. A well-defined lytic lesion involves both the epiphysis and the metaphysis and almost always extends to subchondral bone (Fig. 212.14). The epiphyseal plate is almost always closed. At least one cortex is thin and may also be expanded or destroyed. In the flat bones, giant cell tumors are also well-defined lytic lesions without a sclerotic rim.

Histologically, giant cell tumors consist of multinucleated giant cells admixed with mononuclear stromal cells (Fig. e212.22). The stromal cells are polygonal or slightly elongated. Mitotic figures are numerous in the

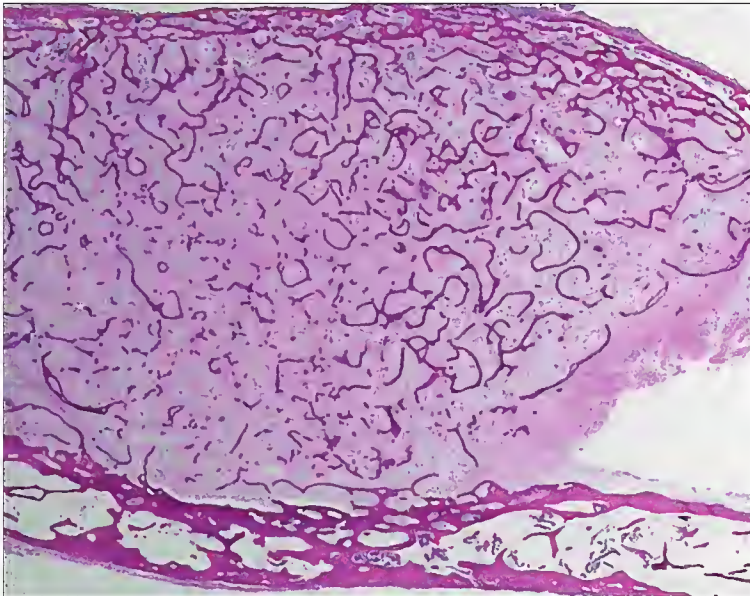


Fig. e212.19 Lower-power photomicrograph (x2) of fibrous dysplasia showing a fibrous lesion with many curved deposits of osteoid assuming a "Chinese letter" pattern.



Fig. e212.20 Radiograph of a malignant fibrous histiocytoma of the proximal end of the femur. A poorly defined radiolytic lesion (arrow) in the intertrochanteric lesion extends into the diaphysis.

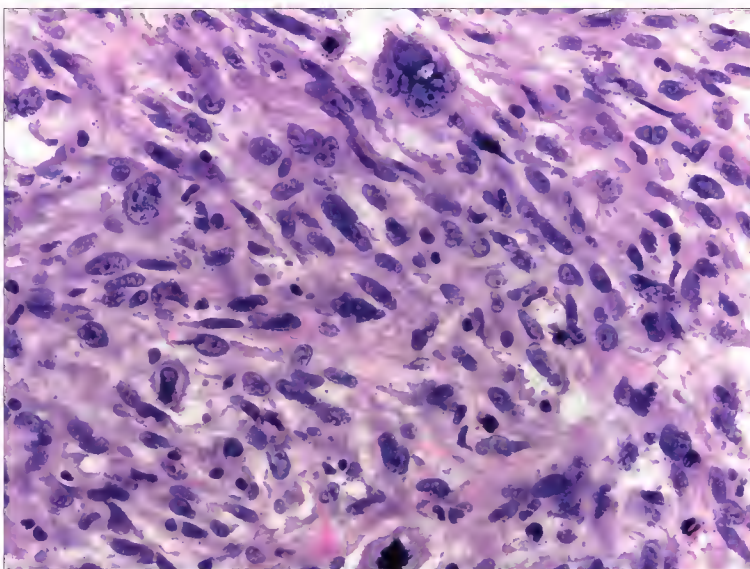


Fig. e212.21 High-power photomicrograph (x60) of a high-grade pleomorphic sarcoma characteristic of malignant fibrous histiocytoma.

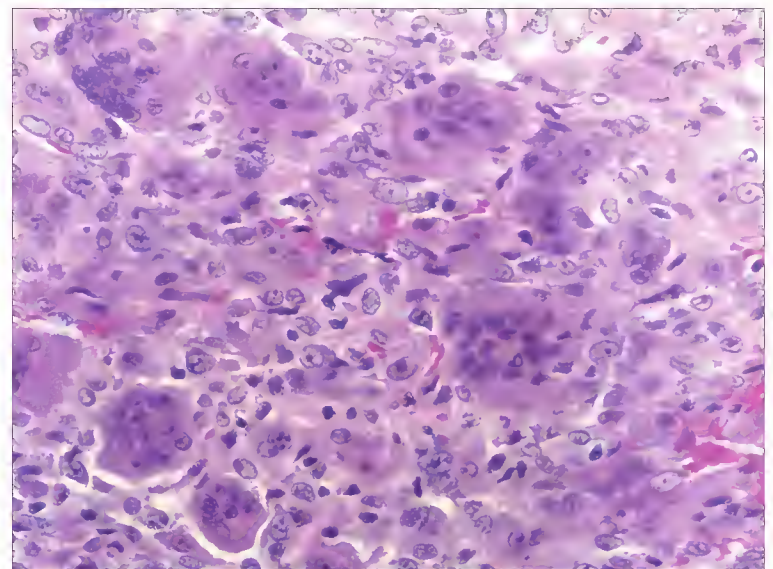


Fig. e212.22 High-power photomicrograph (x40) of a giant cell tumor showing multinucleated giant cells with a background of mononuclear stromal cells.



Fig. 212.14 Radiograph of a giant cell tumor. A well-defined lytic lesion involving the metaphyseal and epiphyseal zones of the distal end of the femur (arrow) is present.

stromal cells. The multinucleated giant cells, often numerous, resemble osteoclasts.

Ewing sarcoma

Ewing sarcoma and its differentiated subtype peripheral neuroectodermal tumor (PNET) of bone are the most malignant of all the primary bone tumors. They are the most common tumors in the group called “small round blue cell tumors.” Other neoplasms in this group are primary lymphoma of bone, small cell osteosarcoma, and mesenchymal chondrosarcoma. A genetic abnormality that distinguishes Ewing sarcoma from other neoplasms is the characteristic chromosomal translocation $t(11;22)(q24;q12)$.¹⁸ Other small round blue cell tumors, such as embryonal rhabdomyosarcoma and neuroblastoma, are not primary osseous tumors but may involve bone secondarily.

Ewing sarcoma is not uncommon. It accounts for as many as 15% of all primary malignant bone tumors and is the fourth most common bone malignancy after myeloma, osteosarcoma, and chondrosarcoma.¹⁹ Ewing sarcoma occurs in patients younger than those with all other primary malignant bone tumors. Although patients range in age from 5 months to 47 years, 8% are between the ages of 5 and 20 years.²⁰ Any bone may be affected, but involvement of the femur and pelvis account for a third of cases. A characteristic feature of both Ewing sarcoma and PNET is a very large soft tissue mass adjacent to the involved bone. Patients have pain, and many have signs and symptoms that mimic acute osteomyelitis: fever, leukocytosis, and an elevated sedimentation rate. Occasionally, patients have a pathologic fracture.

The very aggressive growth of Ewing sarcoma and PNET is evident radiographically. Both neoplasms show a highly permeative growth pattern with a periosteal new bone reaction (Fig. e212.23). The periosteal reaction may be of the “onion skin” or the “sunburst” pattern. The diaphysis of bone is the usual location; however, the metaphysis is also sometimes affected. The intraosseous component of some lesions may be so highly permeative that plain radiographs may be interpreted as normal. In such cases, a minimal periosteal reaction may be the only clue to the presence of a neoplasm. MRI or a bone scan, however, reveals long segments of marrow involvement. In addition, MRI often shows an adjacent soft tissue mass.

Histologically, Ewing sarcoma and PNET consist of broad fields of small uniform round cells with scant cytoplasm (Fig. e212.24). The nuclei are round and contain fine chromatin. Nucleoli are usually inconspicuous.

Osteofibrous dysplasia/adamantinoma

Osteofibrous dysplasia and adamantinoma are two lesions at either end of a spectrum of neoplasms that involve only the tibia. Osteofibrous dysplasia is a benign fibroosseous process, and adamantinoma is a low-grade malignant neoplasm. It is possible that an adamantinoma is a malignant version of osteofibrous dysplasia. However, it is extremely rare for a lesion of osteofibrous dysplasia to transform into an adamantinoma.

Osteofibrous dysplasia is a fibroosseous proliferation that affects the bones of children, almost always before they are 10 years old. The distinctive feature of this lesion is its predilection for one site—the anterior cortex of the tibia (Fig. e212.25).

Histologically, osteofibrous dysplasia is characterized by irregular new bone trabeculae amid cellular fibrous tissue, a pattern reminiscent of fibrous dysplasia. However, unlike the trabeculae of fibrous dysplasia, which seem to appear *de novo* in the fibrous stroma, the trabeculae of osteofibrous dysplasia are lined by plump osteoblasts.

Osteofibrous dysplasia is a nonneoplastic, self-limited process. Lesions grow slowly until skeletal maturity, and thereafter they stabilize. Small lesions are sometimes asymptomatic and disappear spontaneously. Large lesions, even those that have resulted in architectural deformity, stop growing. Therefore surgical removal of these lesions should be avoided. Curettage during the proliferative phase is almost always followed by recurrence. Surgery should be reserved for lesions causing severe deformity or pseudarthrosis.

Adamantinoma, at the malignant end of the spectrum, is a very rare neoplasm. Patients range in age from 3 to 72 years, but most are in their 20s and 30s. Almost all lesions occur in the midshaft of the tibia, and in 10% of cases the ipsilateral fibula is involved. On rare occasion, other long bones, such as the femur, humerus, and ulna, may be involved. This neoplasm has also been reported in the pretibial soft tissues.²¹ Patients usually complain of pain and swelling, often of long duration. Approximately a third of patients have had symptoms for longer than 5 years. One patient was reported to have symptoms for 50 years.²²

Adamantinomas share some radiologic features with osteofibrous dysplasia. For example, adamantinomas are also cortical-based lesions, and 90% of cases involve the diaphysis. In addition, like osteofibrous dysplasia, adamantinomas show multiloculated lytic areas surrounded by dense reactive bone. Frequently, the lesions appear multifocal and involve long segments of the tibial shaft. However, two radiographic features help distinguish adamantinomas from osteofibrous dysplasia. The first, seen in 10% of cases, is cortical penetration and involvement of soft tissues. Second, most cases of adamantinoma have one or more foci of medullary canal involvement, a feature not usually seen in osteofibrous dysplasia (Fig. e212.26).

Histologically, adamantinomas consist of various patterns of epithelial cells in a fibrous and fibroosseous stroma.

Adamantinomas are low-grade malignant neoplasms. They should be treated by wide segmental resection or amputation. Metastases develop in about 25% of patients after surgical ablation. Metastasis may occur as late as 16 years after surgery.²³

Vascular neoplasms

The nomenclature of vasoformative bone lesions has been confusing. Terms such as “epithelioid hemangioma” and “hemangioendothelial sarcoma” create artificial categories that can possibly lead to improper therapy. Vascular lesions of bone are best subdivided into three major categories: hemangioma, epithelioid hemangioendothelioma, and angiosarcoma.

Hemangiomas in the skeleton may be solitary or multiple. Solitary hemangiomas usually affect a vertebral body or the calvaria (Fig. e212.27). Small lesions can be found at autopsy in 11% of carefully examined spines.²⁴ Most spinal hemangiomas are asymptomatic and discovered incidentally on radiographs obtained for other reasons. Some patients, however, have back pain because of a compression fracture. Hemangiomas of the calvaria are usually manifested as a slowly growing mass. They may be discovered at any age, but most patients are in their 40s.²⁵

Radiographically, vertebral hemangiomas are lytic lesions with coarse vertical striations, the so-called jail bar pattern. These dense striations on cross-sectional CT scans appear as spots of dense bone. Lesions in the calvaria bulge the outer cortical table and have a “sunburst” appearance of reactive bone.

Epithelioid hemangioendotheliomas are indolent neoplasms characterized by the proliferation of plump, histiocytoid endothelial cells.²⁶ Most epithelioid hemangioendotheliomas of bone are diagnosed in patients between the ages of 10 and 30, although this lesion may also develop in older individuals. The femur, pelvis, and tibia are the most common sites.



Fig. e212.23 Radiograph of Ewing sarcoma of the fibular diaphysis showing a poorly defined surface lesion on the medial border of the fibula with a periosteal reaction (arrow).



Fig. e212.25 Radiograph of osteofibrous dysplasia of the midshaft of the anterior aspect of the tibia. The lesion is lobulated and has a sclerotic rim.

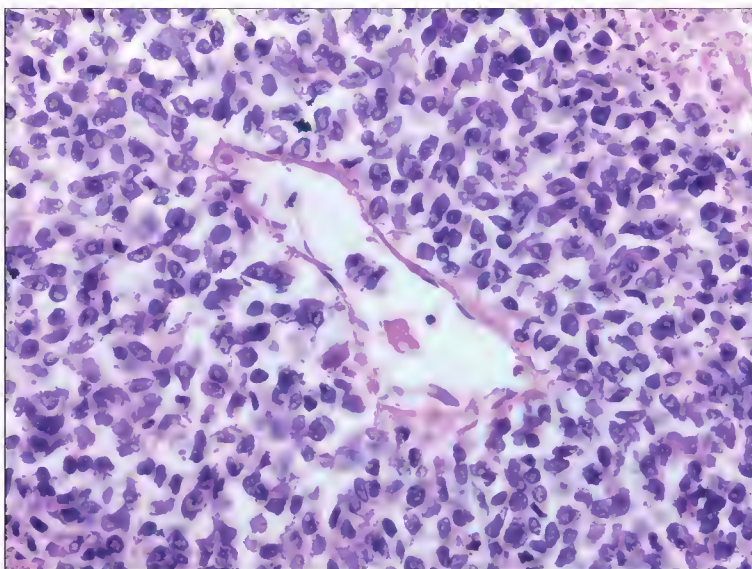


Fig. e212.24 Medium-power photomicrograph (×60) of a small round blue cell tumor consistent with Ewing sarcoma.



Fig. e212.26 Radiograph of an adamantinoma in the posterior aspect of the tibia showing a poorly defined lytic lesion with involvement of the medullary canal.

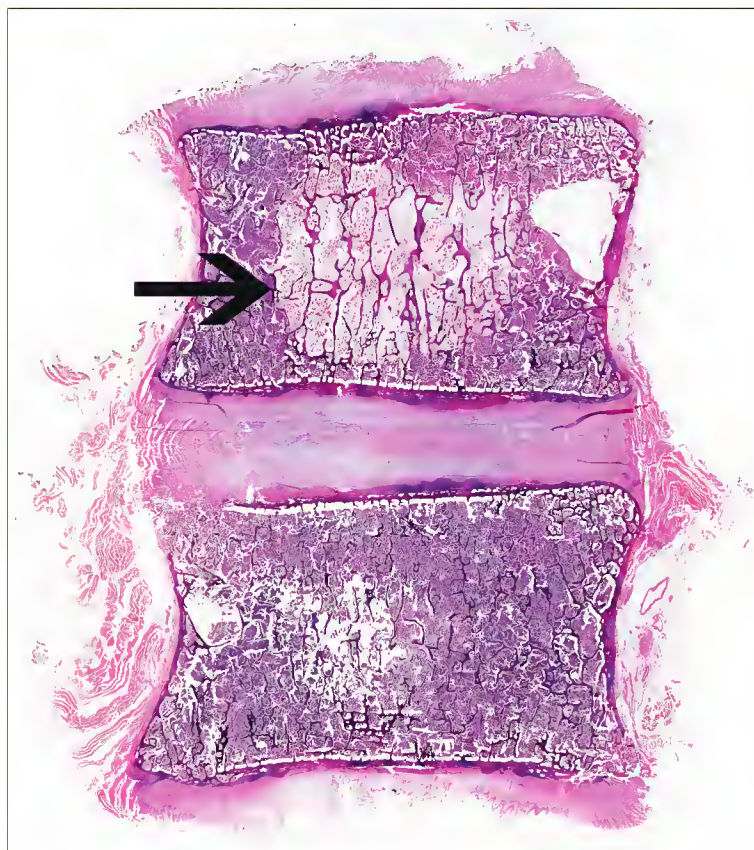


Fig. e212.27 Macrophotograph of a specimen of two vertebrae showing a hemangioma in the medullary canal with infiltration of the trabecular spaces (arrow).

Patients usually have pain or a pathologic fracture. A distinctive feature of epithelioid hemangioendothelioma, present in 64% of patients, is involvement of multiple sites. Curiously, multicentric lesions tend to involve the bones of one extremity. Although any bone may be involved, the bones of the lower extremity are favored sites.

Epithelioid hemangioendothelioma of bone is usually a well-circumscribed radiolytic defect ranging in size from 2.5 to 15 cm in maximum dimension. A mildly sclerotic border is occasionally present. Sometimes this neoplasm is multifocal in the adjacent bones (Fig. e212.28). On rare occasion the lesions may be predominantly sclerotic. Cortical expansion and extension into the soft tissue may occur occasionally.

Epithelioid hemangioendotheliomas of bone are characterized by nests, cords, or sheets of plump, round, or polygonal cells with abundant eosinophilic cytoplasm. Their nuclei are round and moderately hyperchromatic. These “histiocytoid” cells, which show little pleomorphism, often contain intracytoplasmic lumina that may coalesce with similar structures in an adjacent cell (Fig. e212.29). Frequently, the cell nests form well-developed vascular lumina that contain red cells. In some areas the clusters of histiocytoid endothelial cells are separated by a fibrovascular stroma containing lymphocytes, plasma cells, and often many eosinophils.

Epithelioid hemangioendotheliomas of bone are slow-growing neoplasms with a protracted clinical course. Lesions should be removed totally, either by complete curettage or by limb-sparing resection. Radiotherapy may be of value if complete excision is impossible. Lesions with more than mild mitotic activity may be more aggressive. Patients with epithelioid hemangioendothelioma should be evaluated for multifocal lesions. These patients have an equally good and perhaps better prognosis.

Angiosarcomas of bone are very rare, highly malignant neoplasms that develop in patients from the ages of 10 to 70. Most, however, are older than 30 years. Pain of several weeks' to a few months' duration is the usual symptom prompting evaluation. Angiosarcomas most commonly involve the femur and tibia.

Angiosarcomas of bone have the radiographic pattern of an aggressive, high-grade malignant bone tumor. Lesions are radiolytic with poorly defined margins, and cortical expansion and cortical destruction are usually present (Fig. e212.30).

Histologically, these lesions have anastomosing blood-filled clefts and slits. These spaces are lined by large cells with abundant eosinophilic cytoplasm. Unlike the uniform cells of epithelioid hemangioendotheliomas, the cells of angiosarcomas show marked pleomorphism. Large, bizarre, hyperchromatic nuclei are common, and mitotic figures are numerous. Papillary tufts of the pleomorphic cells often project into the neoplastic vascular lumina (Fig. e212.31).

Chordoma

Chordomas, thought to arise from notochordal rests, are slow-growing malignant neoplasms that occur exclusively along the spinal axis.²⁷ The two ends of the spinal axis, inside the skull and the sacrococcygeal region, are the most common locations. Half of all chordomas arise in the sacrococcygeal region, where they are associated with pain and occasionally bladder dysfunction. At the other end of the spine, intracranial chordomas, which account for 40% of lesions, involve bones at the base of the skull. When chordomas occur in this region, patients have headache and neurologic impairment. The remaining 10% of chordomas involve the vertebral column. These locations correlate with the distribution of notochordal rests found



Fig. 212.15 Magnetic resonance image of a chordoma consisting of a large well-defined mass anterior to the sacrum.

by meticulous study of adult and developing spines.²⁸ Most patients with a chordoma are older than 40, although intracranial lesions occur in some—what younger patients.

Radiologically, sacral chordomas are intraosseous destructive lesions that often expand into soft tissues. Sometimes these neoplasms consist of midline paraspinal or intrapelvic masses with minimal or no bone destruction (Fig. 212.15). Chordomas are best studied with CT. Intracranial chordomas may destroy the sella turcica, and they frequently invade the petrous or sphenoid bone. Occasionally, intracranial chordomas calcify, a feature rarely present in chordomas of the sacrum and spine.

The histologic features of chordomas are distinctive. On low power, a lobular growth pattern, similar to cartilage neoplasms, is apparent. Cords and sheets of cells are embedded in an abundant, pale extracellular matrix. Higher-power study reveals two types of cells. One is a square to oblong cell with a round central nucleus and an eosinophilic cytoplasm. The other type contains a round nucleus but has bubbly cytoplasm (physaliferous cell) (Fig. e212.32). Chordomas show little nuclear pleomorphism, and mitotic figures are rare. They are epithelial neoplasms and are strongly positive for cytokeratin. Stains for epithelial membrane antigen and S-100 protein are also positive. However, the stain for S-100 protein is usually only weakly positive.

Chordomas are aggressive neoplasms that can rarely be excised completely. Removal often requires sacrifice of the cauda equina. Palliative debulking followed by radiation therapy is the most common therapy. Typically, patients suffer multiple recurrences. Metastasis, usually to the lungs, skin, or bones, occurs in 3% of sacral or vertebral chordomas.²⁹ More than 90% of patients die within 10 years.

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Fig. e212.28 Radiograph of an epithelioid hemangioendothelioma involving multiple foci in the tibia and fibula.



Fig. e212.30 Radiograph of an angiosarcoma of the distal femoral metaphysis. The lesion is poorly circumscribed. An asymptomatic incidental nonossifying fibroma of the proximal tibial metaphysis (arrow) is also present.

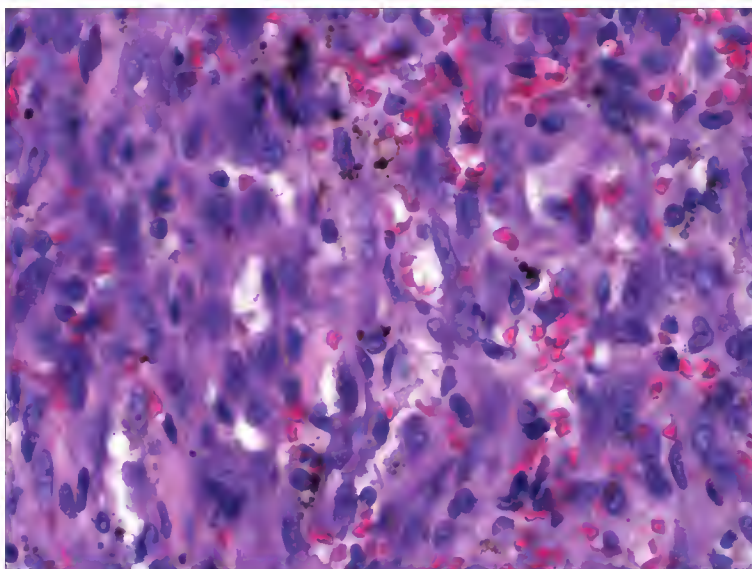


Fig. e212.29 Photomicrograph (x60) of an epithelioid hemangioma showing rounded epithelioid endothelial cells with numerous small blood vessels and red blood cells.

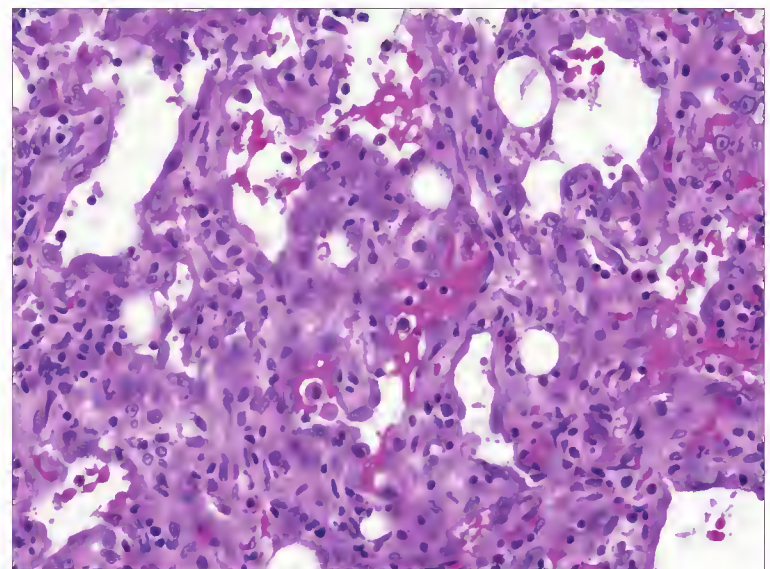


Fig. e212.31 Medium-power photomicrograph (x60) of an angiosarcoma showing atypical endothelial cells creating blood-filled spaces.

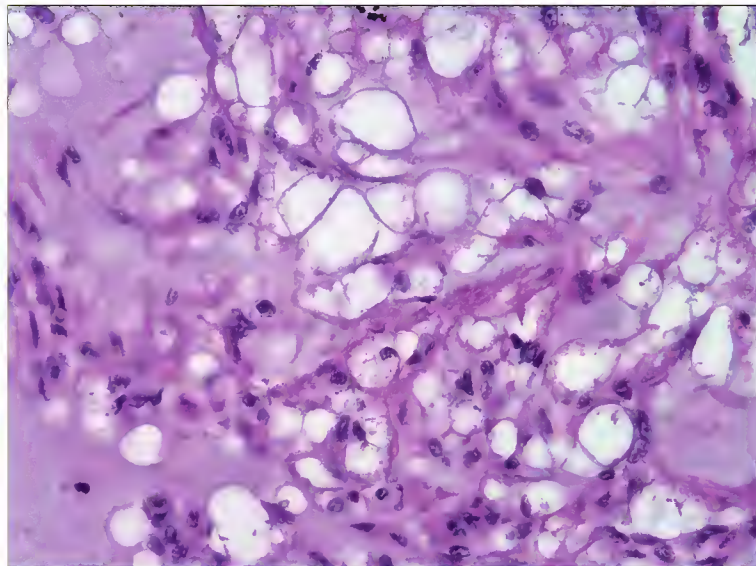


Fig. e212.32 Photomicrograph of a chordoma showing numerous bubbly neoplastic cells, the so-called physaliferous cells (x60).

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